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A CLINICAL STUDY TO EVALUATE THE EFFICACY OF A NEW NEUTRACEUTICAL COMBINATION BASED ON RESVERATROL, BERBERISAND ASTRALAGUS EXTRACTS IN COMPARISIONTO A FORMULATION CONTAININGRED YEAST RICE (MONACOLIN K) IN PATIENTS WITH MODERATE DYSLIPIDEMIA

PanicoAnnalisa*[1], Lupoli Gelsy Arianna[1], Roberto Marcantonio[2], BarbaLivia, Cacciapuoti Marianna[1], MessinaGiovanni[3] & Lupoli Giovanni[1].

[1]Dipartimento di Medicina Clinica e Chirurgia-Sezione Endocrinologia-Università degli Studi di Napoli "Federico II"

[2]Dipartimento di Sanità Pubblica-Università degli Studi di Napoli "Federico II"

[3]Dipartimento di Medicina Clinica e Sperimentale- Università di Foggia

Keywords:

Hyperlipidemia, Berberis, Resveratrol, HDL-cholesterol, LDL-Cholesterol and Cardiovascular risk.

Abstract

Background: Treatment strategies of dyslipidemia include pharmacologic and non-pharmacologic interventions though recently a relevant role has been shown for nutraceutical compoundsor specific functional ingredients in combination rather then in monotherapy.

Objectives: The aim of this study was tocompare, in a randomized trial, the effects of two nutraceutical combinations on the control of glico-lipidic metabolism in patients with hypercholesterolemia not on statins and to evaluate the efficiency of a new nutraceutical combination based on Berberis, Resveratrol and Astragalus.

Subjects: Fifty patients with a first diagnosis of moderate dyslipidemia were included in a 6-week open-label, randomized, parallel-group controlled clinical trial. At study start patients were given dietary counseling and were randomized into two groups treated with either; Combination A(RYR extract containing 10 mg of monacolin k and 160 mg of improved form of highly bioavailable resveratrol (REVIFAST) or Combination B (160mg of REVIFAST, 500 mg of Berberis and 40 mg Astragalus extracts.

Results: Compared to baseline values, both treatments reduced significantly total and LDL-cholesterol, systolic blood pressure, and glycemic parameters (Fasting insulinaemia, glucose and HOMA-index). Both combinations reduced total and LDL cholesterol below 5,4mmol/L and 3,12 mg/dL respectively, when compared though, combination B lead to a greater reduction in TC and LDL (p\0.05) while increased HDL. Fasting insulinaemia and HOMA-index improved both nutraceutical treated groups. Thus, both treatments led to comparable and results in reduced glico-lipidic metabolic parameters with significant differences in further ameliorating lipidic parameters among treated patients with combination B.

Conclusions: Treatment with the novel neutraceutical combination based on resveratrol, berberis and Astragalus extracts is superior to combinationcontaining monacolin Kover the 6 week treatment period. Cholesterol, triglycerides and HOMA index had a greater reduction in patients treated with this combination. Both treatments were efficacious, safe, and well tolerated among patients. The absence of monacolin k does not affect the overall efficacy of the novel composition in treatment of dyslipidemia, thus could represent an efficient alternative therapy.

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Introduction

Cardiovascular diseases still today is the leading cause of death globally(1). The risk of cardiovascular disease is influenced by a variety of risk factors, including high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) (2-4). In particular, elevated LDL-C plays a pivotal role in impairing endothelial function, in atheromatous plaque development and in progression and rupture of the plaque which causes most of the acute symptoms of acute coronary heart disease (4). Many randomized trials including > 40,000 subjects, showed that decreasing serum cholesterol levels with cholesterol-lowering drugs or dietary modification slows or reverses the progression of coronary atherosclerosis. In this regard, cholesterol-lowering substances in functional foods or in supplements across Europe, namely plant sterols and stanols, monacolin K found in red yeast rice, berberine and beta-glucans have been widely studied(5). Currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5 to 25%, either alone or in combination (6).

One of the most used cholesterol-lowering nutraceutical ingredient on the market to date is Red yeast rice (RYR), because they contain a family of naturally occurring statins (monacolins), one of which is monacolin K/lovastatin, a well-known inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase (7). In meta-Analysis, placebo-controlled trials showed the lowering effects on TC, TG and LDL-C of RYR, as well as demonstrating the lack of serious side effects in all trails (8).Monacolin K food supplements can vary in the quality and quantity of their components (9), with the daily MK dose ranging from 2.5 to 10 mg. The European Food Safety Authority (EFSA) defined 10 mg of MK as the daily intake dose that effectively contributes to the maintenance of the blood cholesterol level (10).

Resveratrol (trans-3,5,4'-tri-hydroxic-stilbene) has also been demonstrated to have effects on metabolic health. First emerged after the discovery that resveratrol was linked to cardiovascular benefits associated with the consumption of red wine (11). It has been demonstrated that in healthy obese human subjects that treatment with trans-resveratrol reduces glucose, triglycerides and levels of inflammation markers with an effect similar to the one induced by caloric restriction (12). The combination of resveratrol with monocolin K has also proven to be effective (13), possibly given the highly bioavailable ingredient of natural resveratrol from (Polygonumcuspidatum, 98%) supported on magnesium hydroxide ("Revifast™") used (14).The mechanism of action of resveratrol has yet not been completely even if recently its effects, have been associated to the increase of cyclic adenosine monophosphate's levels (cAMP) resulting from the inhibition of type IV phosphodiesterase (PDE4) caused by resveratrol (15). However, resveratrol is poorly bioavailable because of reduced absorption linked mainly to its low solubility (16).However, there are many formulative strategies on the market in order to increase its bioavailability. REVIFAST a formulation of natural resveratrol from (Polygonumcuspidatum, 98 %) supported on magnesium hydroxide (below referred to as "RevifastTM") demostrated that the absorption of resveratrol contained in REVIFAST versus Polygonumcuspidatum is about 3 times more bioavailabile and the blood profile is better in terms of amplitude and duration of peak plasma, a behavior demonstrating a sustained chemical formulation of the compound (unpublished).

Berberisaristata(tree turmeric) known as an Indian medicinal plant, which belongs to the family Berberidaceae; The shrub containes the quaternary ammonium salt berberine which is useful as antipyretic, antibacterial, antimicrobial, antihepatotoxic, antihyperglycemic, anticancer, antioxidant and antilipidemic agent (17).Berberinehas been also demonstrated to improve glucose and lipid metabolism disorders, and to reduce atherogenesis and endothelial inflammation in diabetic patients, with clinical effects similar to those of metformin (18,19). Berberine upregulates LDL-receptor (LDL-R) expression independent of sterol regulatory element binding proteins but dependent on extracellular signalregulated kinases and c-Jun N-terminal kinase activation leading to total cholesterol (TC) and LDL-C reduction of about 30 and 25%, respectively. This up-modulation occurs through a post-transcriptional mechanism that stabilizes themRNA and makes berberine a cholesterol-lowering drug endowed with a mechanism of action different from that of statins (20). Along with its cholesterol-lowering properties, berberinereduces triglycerides (TG) as well by about 35% and overall has positive effects on lipid metabolism, results observed both in animals and in humans (20).

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Another herbal extract which has documented effects on lipid and glicemic parameters is Astragalus polysaccharides (APS), an extract of Radix Astragali, the dried root of the leguminous plant Astragalusmembranaceus (Fischer) Bge. var. mongolicus (Bge.) Hsiao. According to traditional Chinese medicine, Radix Astragali is an important and commonly used traditional Chinese medicine for strengthening healthy energy and tonifying (22). Astragalus polysaccharide (APS) is the primary active ingredient of Radix Astragali and previous pre-clinical studies have demonstrated it to have a variety of pharmacological effects. It has been demonstrated the APS is efficent in lowering plasma lipids in hypercholesterolemia hamsters by up-regulating cholesterol-7α-hydroxylase and LDL-receptor gene expressions and these findings identify APS working through mechanisms distinct from statinsand thus could be a proposed as a potential natural cholesterol lowering agent (23).

Recently, a new nutraceutical formulation containing berberine 500 mg from Berberisaristata, highly bioavailable resveratrol (REVIFAST), Astralagus extract became available. This combination was aimedto have a synergic effect on lipid and metabolic profile. In this context, we planned to carry out a randomized study to evaluate the efficacy and safety of a nutraceutical agent in comparison to a formulation based on resveratrol (REVIFAST) and monacolin K, with a documented efficiency compared to RYR alone.

The main objective of the present study was the evaluation of the synergic association of the novel nutraceutical combination based on Berberisaristata, Resveratrol and Astralaguson a set of biomarkers associated with the cardiometabolic risk in patients with moderate dyslipidemia and the comparison of its efficacy with formulation of resveratrol associated with RYR.

METHODS

Study design and population

The study was performed at the department of Clinical Medicine and surgery of University of Naples (Federico II) from Januaryto March 2018 and was designed as an Open-label, randomized, parallel-group controlled clinical trial. The study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from each subject. Fifty patients with a first diagnosis of moderate dyslipidemia were included in a 4-week open-label, randomized, parallel-group controlled clinical trial. At study start patients were given dietary counseling and were randomized into two groups treated with either; Combination A(RYR extract containing 10 mg of monacolin k and improved form of highly bioavailable resveratrol 160 mg REVIFAST containing 48 mg resveratrol)or combination B(160mg of (REVIFAST) containing 48 mg of resveratrol, 500 mg of Berberis 97%s e.s. tit and 40 mg Astragalus extracts e.s. tit 70% .

Fifty patients, 35 men and 15 females were selected and completed the study. The inclusion criteria were patients of both sexes, aged 18 years or older (up to 60), diagnosis hypercholesterolemia not on statin therapy, with LDL-C within the range of 115 to 165 mg/dL. The exclusion criteria were presence of chronic liver disease, renal disease, or severe renal impairment treated with antidiabetic medications or insulin; untreated arterial hypertension; obesity (body mass index; calculated as weight divided by height squared; kg/m2] pharmacologic treatments known to interfere with the study treatment and pregnancy (Table 1). Clinical and laboratory data were obtained at the beginning (baseline) and after the end of the treatment period (6 weeks). Patients underwent a fasting blood sampling and a full clinical examination, including the evaluation of height, body weight, abdominal and hip circumferences, heart rate, and arterial blood pressure. Primary end point of the study was the reduction of total cholesterol, LDL-C, HDL-C and triglyceride. Secondary end points were the changes of other cardiometabolic biomarkers (glucose, insulin, HOMA index and blood pressure). REVIFAST®CARDIO (RYR, monacolin K + REVIFAST) and the REVIFAST + Berberis + Astragalus supplement were kindly provided in an anonymous packaging by S&R Farmaceutici Bastia Italy.

Biochemical, immunometric assays and Statistical analysis

TC, TGs, HDL-C, glucose, insulin and LDL-C were measured by standard enzymatic techniques. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated. Continuous variables are indicated as mean SD and all differences were assessed by Student's t test with P values .05 are considered as statistically significant. Statistical analysis was performed by using EXcell.

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RESULTS

The main baseline clinical data indicate that the study subjects showed moderate dyslipidemia (Table 2).Compared to baseline, both treatments reduced significantly total and LDL-cholesterol, systolic blood pressure, and glycemic parameters (Fasting insulinaemia, glucose and HOMA-index). Both combinations reduced total and LDL cholesterol below 5,4 mmol/L and 3,09 mg/dL respectively, but in comparing the treatments, combination B lowered TC and LDL-C by 25% (p\0.01), vs 20% and 19.8% variation towards baseline with combination A. Fasting insulinaemia and HOMA-index improved both nutraceutical treated groups(Table 2). Thus, compared to baseline values, both treatments led to comparable and results in reduced metabolic parameters with significant differences in further amelioratinglipidic parameters (TC , LDL)among treated patients with combination B.Both treatments were well tolerated by patients and no side effects were reported.The combination of Berberis, Resveratrol and Astragalusalso lead to significant improvement in HDL-C (+6,7 %), a finding that together with the improvement of LDL, glucose, insulin and HOMA-Index, indicate a positive effect on plasma and metabolic markers that predict the metabolic risk for the development cardiovascular disease.

DISCUSSION AND CONCLUSION

According to our previous observational clinical study, the addition of REVIFAST resveratrol to RYR had a positive effect on the metabolic profile and further improved the lipid profile in patients with mild/moderate hyperlipidemia in comparison to RYR alone (13). LDL reduction was about 24%,also a decrease of TC and Tg was obtained, similar to the current results.The combination proved to be superior in lowering triglycerides and ameliorating HOMA index. Thus, we can assume that, as expected, combining Resveratrol (REVIFAST) with Berberisaristata and astralagus, similar results could be expected.

Additionally, while synthetic pharmaceuticals are based on single chemicals, many nutraceutical compounds exert their beneficial effects through the additive or synergistic interactions among the different chemical compounds acting at single or multiple target sites associated with a physiological process. In this study regarding the interactions among the different components resveratrol, berberin and Astralagus may interact during lipid metabolism through different distinct and synergetic mechanisms. In detail, Berberin and Astralagus exert their lipid lowering function by up-regulating LDL-receptor (LDL-R) and cholesterol-7α-hydroxylase while resveratrol may increase the LDLC receptor binding activity and gene expression, suggesting that red wine polyphenols may regulate the major pathways involved in lipoprotein metabolism (21, 24).

Both tested products were associated with a high tolerability profile that is important to guarantee long-term compliance of the treatment. Moreover, the observed results were at least partly expected, because the components of the tested mixture are all supported by an acceptable level of clinical evidence of efficacy. The results of this study suggested that combining different hypocholesterolemic nutraceutical agents such as Berberisaristata, resveratrol and Astralagus could be effective and safe to obtain a reduction of LDL-C, Tg and ameliorating glycemic parameters, indicating overall a positive effect on plasma markers that predict the metabolic risk for the development cardiovascular disease.

This present study further confirms that the supplementation of specific nutraceutical ingredients association with a highly bioavailable form of resveratrol (Revifast^{TM}), is a synergic association that better improves lipid and glycemic profile. The combination of Berberis, Astralagusand Resveratrol is efficient, tolerable and may represent a valid approach in patients with moderate cardiovascular risk. The absence of monacolin K form RYR could be of interest since some case report studies have shown possible side effects related to RYR administration, such as muscle weakness and pain, which tend to subside upon cessation of the treatment (24)Furthermore, the association of resveratrol with berberis and astralagus can be more effective than either component alone in improving lipid profile, probably due to a synergic and multi-target effect of each of the compounds.

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Table 1
Table 2

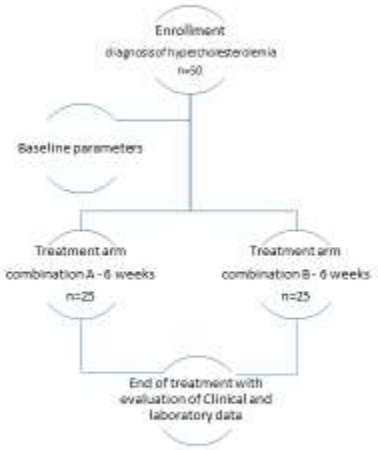

Table 1 Main baseline clinical Characteristics of the study population

Characteristics	Value
No. Of participants	50
Age, years	49.1 ± 8,
Weight	80.5 ± 15.4
BMI	28.68 ± 4,7
Smokers	18

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Table 2 Effects of the oral supplementation with Combination A (REVIFAST+ monacolin K (REVIFASTCARDIO®) or Combination B (REVIFAST + Berberis aristata + Astragalus) after 6 weeks of treatment

PARAMETER	BASELINE	Combination A: REVIFAST + Monacolin K			Combination B: REVIFAST + Berberis aristata + Astragalus			P value for Δ combination A vs B
		After 6 weeks	Variation vs baseline (%)	P value (vs baseline)	After 6 weeks	Variation vs baseline (%)	P value (vs baseline)	
Weight (Kg)	88.5 ± 13.4	88.2 ± 10,2	-5,9 %	0,79	83.1 ± 9,2	-6,1 %	0,78	ns
BMI	27,31 ± 4,7	25.68 ± 3,11	-6 %	0,18	25,65 ± 2,10	-6,1 %	0,09	ns
TC (mmol/L)	6.8 ± 0,6	5,4 ± 0,8	-20.6 %	0,05	5,1 ± 0,3	-25 %	0,01	≤0,05
HDL-C (mmol/L)	1,04 ± 0,23	1,05 ± 0,22	0,01 %	0,98	1,21 ± 0,2	+6,7 %	0.05	≤0,05
LDL-C (mmol/L)	3,89 ± 0,42	3,12 ± 0,52	- 19,8 %	0,05	2,91 ± 0,25	-25,1 %	0,01	≤0,05
TG (mg/dL)	2,39 ± 0,17	1,98 ± 0,13	-17 %	0,05	1,93 ± 0,11	-19,2%	0,05	ns
Glucose (mmol/L)	5,13 ± 0,2	4,89 ± 0,11	-4,7 %	0,05	4,76 ± 0,12	-7,2 %	0,04	ns
Insulin (mU/L)	11.2 ± 1,2	9,7 ± 1,1	-15 %	0,04	9,3 ± 0,9	-16,9 %	0,03	ns
HOMA index	2,48 ± 1,1	2,01 ± 0,41	-18,9 %	0,04	1,98 ± 0,24	-20,1 %	0,04	ns
Systolic blood pressure (mmHg)	131,9 ± 2,9	128,3 ± 1,6	-2,7%	0,05	126,9 ± 1,2	-3,8 %	0,05	ns

Figure 1