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Resveratrol improves the lipid profile promoted by red yeast rice (monacolin k) in patients with moderate dyslipidemia: An open-label, randomized, parallel-group controlled clinical trial

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Abstract

Introduction: A relevant role is now emerging for nutraceuticals and specific functional foods in the treatment of dyslipidemia. The aim of this study was to evaluate the efficacy of a nutraceutical multi-target approach in subjects with moderate cardiovascular risk and to compare it with red yeast rice (RYR) treatment alone.

Materials and Methods: Sixty patients with a first diagnosis of moderate dyslipidemia were included in a 6-week open-label, randomized, parallel-group controlled clinical trial and were treated with a nutraceutical supplement of Red Yeast Rice (RYR) extract containing 10 mg of monacolin k or its combination with 48 mg of an improved form of highly bioavailable resveratrol. The dosage of RYR was selected on the basis of its expected efficacy in reducing low-density lipoprotein- cholesterol also approved by the EFSA panel. All differences were assessed by Student's t test with P values .05 are considered as statistically significant. Statistical analysis was performed by using Excel.

Results: Treatment with RYR (10 mg monacolin K) led to a reduction of total cholesterol (20%) and low-density lipoprotein-cholesterol (21%). The combination with resveratrol however, compared to RYR alone significantly reduced triglyceride (-18 %) levels, systolic blood pressure (-2 %) and HOMA index (-17 %).

Discussion: These results indicate that the nutraceutical supplementation of RYR associated with resveratrol not only shows lipid-lowering activity but compared to RYR treatment alone significantly also ameliorates other metabolic parameters. Thus, may represent a valid and safe approach, especially in people with moderate cardiovascular risk, in which a pharmacologic intervention may not be appropriate.

Introduction

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Resveratrol (trans-3,5,4'-tri-hydroxic-stilbene) is a stilbenic structure polyphenol, initially isolated from the root of the white hellebore and later from the root of Polygonum cuspidatum, a plant used in traditional Chinese and Japanese medicine. Resveratrol becomes popular only in 1992, when suggested that it could be the reason behind red wine's cardio-protective effects (the French paradox), from then its popularity increases because in 1997 it was proved as able to prevent colon-rectal cancer in mice (1). Resveratrol based compounds present anti-oxidant, anti-inflammatory, anti-viral, cardio-protective, neuro-protective, anti-cancer, anti-angiogenetic activities (2, 3). It has been demonstrated that in healthy obese human subjects the treatment with trans-resveratrol reduces glucose, triglycerides and levels of inflammation markers with an effect similar to the one induced by caloric restriction (4). The mechanism of action of resveratrol has yet not been completely demonstrated, and for this reason, recent studies have been carried out in order to point out and understand the aspects that still remain unclear. The induction of the caloric restriction which is thought be at the basis of resveratrol's multiple effects, has been associated to the increase of cyclic adenosine monophosphate's levels (cAMP) resulting from the inhibition of type IV phosphodiesterase (PDE4) caused by resvera-

trol (5). However, resveratrol is poorly bioavailable because of reduced absorption linked mainly to its low solubility (6) and possibly also due to an increased metabolism, characterized by conversion into glucuronides compounds and sulfated, generally inactive and with an elevated kidney clearance (1, 7).

Recently, many formulative strategies have been developed and are on the market in order to increase resveratrol's bioavailability. In the present study, a patent new ingredient of natural resveratrol from (Polygonum cuspidatum, 98%) supported on magnesium was used (8). In vivo studies have demonstrated that the absorption of resveratrol contained in Revifast® versus that of Polygonum cuspidatum is about 3 times greater and its concentration in the blood profile is better in terms of amplitude and duration of peak, a behavior demonstrating a sustained chemical formulation of the compound (unpublished data).

Red yeast rice (RYR) is a traditional food spice consumed throughout Asia known for its medicinal values that date back to more than a thousand years, with the first recorded use being in 800 A.D (9). RYR is derived from rice that has been allowed to ferment with the mold *Monascus purpureus* (*M. purpureus*) have been widely used for therapy of patients with cardiovascular (CV) disorders in China for centuries, 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. A meta-analysis, involving placebo-controlled clinical 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 (10).

The main objective of the present study was the evaluation of the synergic association of a nutraceutical combination composed of RYR extract (containing 10 mg of monacolin K in association with 48 mg of resveratrol) on a set of biomarkers associated with the cardiometabolic risk in patients with moderate dyslipidemia and the comparison of its efficacy with RYR extract alone. Studied biomarkers include lipid and glycemic biochemical parameters and cardiac function.

Materials and Methods

Study design and population

The study was performed at the department of Clinical Medicine and Surgery of University of Naples (Federico II) from March 2016 to August 2016 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. The study protocol follows the guidelines of the Ethics Committees and institutional review boards at University of Naples (Federico II). Patients received either RYR (1 pill/day, containing 200 mg of RYR (equivalent to 10 mg of monacolin K) or RYR with resveratrol (1 pill/day containing 200 mg red yeast rice extract of which 10 mg of Monacolin K and 160 mg of Revifast® containing 48 mg of resveratrol) for a period of 6 weeks. The dosage of RYR was selected on the basis of its expected efficacy in reducing low-density lipoprotein- cholesterol also approved by the EFSA panel (11). Sixty patients, 50 men and 10 females were selected and completed the study. The inclusion criteria were patients of both sexes, aged 18 years or older (up to 60), diagnosis of 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/m^2) pharmacologic treatments known to interfere with the study treatment and pregnancy (**Table 1**). Clinical and biochemical evaluations were performed at the beginning (baseline) and at the end of the six-week treatment period. 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). The RYR supplement containing resveratrol (REVIFAST®CARDIO) and the RYR supplement alone (containing 10 mg of monacolin k) were kindly provided in an anonymous packaging by S&R Farmaceutici Bastia Italy.

Table 1. Main basline clinical charateristics of the study population

Characteristics	Value
No. Of participants	60
Age, years	50.4 ± 9,7
Weight	87,5 ± 9,5
BMI	29.8 ±2,3
Smokers	32

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 Excel.

Results

The main baseline clinical data (**Table 2**), indicate that the study subjects showed moderate dyslipidemia. Both treatments were well tolerated by patients and no side effects were reported. As expected, treatment with RYR resulted in an overall reduction of TC (20%; **Table 2**), LDL-C (20%; **Table 2**), the same trend was observed with RYR plus resveratrol (**Table 2**). RYR and its combination with resveratrol effects were similar on most lipid

Table 2. Summary of primary and secondary end points (RYR and RYR + RES)

	RYR (10 mg monacolin/d)		RYR (10 mg monacolin + 48 mg resveratrol/d) REVIFAST®CARDIO		
	Baseline	After 6 weeks	Baseline	After 6 weeks	P value for comparison of Δ RYR versus Δ RYR+ resveratrol
Total cholesterol, mmol/L	6.7± 0,7	5,4 ± 0,4*	6,6 ± 0,7	5,35 ± 0,4*	0,75
LDL-C, mmol/L	3,87 ± 0,45	3,07 ± 0,43*	3,82 ± 0,45	3,08 ± 0,43*	0,82
HDL-C, mmol/L	1,02 ± 0,21	1,01 ± 0,24	1,02 ± 0,18	1,03 ± 0,20	0,97
TGs, mmol/L	2,36 ± 0,19	2,12 ± 0,14*	2,33 ± 0,12	1,92 ± 0,11*	0,04*
Glucose mmol/L	5,12 ± 0.18	5,08 ± 0.12	5,15 ± 0.10	4,91 ± 0.15*	0,04*
Insulin, mU/L	10.1± 1,3	9,8 ± 1,2	10.4± 1,2	9,5 ± 1,1*	0,04*
HOMA	2,3 ± 0,12	2,2 ± 0.15	2,4 ± 0,11	2,0 ± 0,09*	0,04*
Systolic blood pressure mmHg	128,5 ± 2,1	129,5 ± 2,5	128,3 ± 3	125,1 ± 1,8*	0,05*

biochemical parameters, except for TG, fasting glucose levels, insulin, HOMA index, in which a significant reduction was observed by RYR plus resveratrol compared to only RYR formulation. Interestingly the treatment with RYR plus resveratrol slightly lowered systolic blood pressure (**Table 2**), a finding that together with plasma glucose and insulin indicate a positive effect on plasma markers that predict the metabolic risk for the development cardiovascular disease.

Discussions

Cardiovascular disease (CVD) is the leading cause of mortality worldwide and causes 17 million deaths a year (12). Hyperlipidemia, particularly increased total cholesterol in the serum, is one of the leading risk factors. Recently, lipid disorders are strictly associated with the metabolic syndrome, a clinical condition characterized by a series of CV risk factors, that is, dyslipidemia, arterial hypertension, hyperglycemia, and central adiposity, which involves about 25% adults in Europe alone (13).

In the present open-label, randomized, parallel-group controlled clinical trial we demonstrated that a nutraceutical combination that contains RYR and resveratrol was quite effective in reducing TC and LDL-C and display with a superior to that of 10 mg of monacolin K, a standard nutraceutical therapy used in our study as a reference treatment, to reduce triglyceride levels and metabolic parameters such as glucose levels and blood pressure. According to the demonstrated cardioprotective effects of resveratrol (14, 15) the formulation with stilbenes slightly lowered systolic blood pressure a finding that together with the reduction of plasma glucose and insulin levels, indicate a positive effect on plasma markers that predict the metabolic risk for the development cardiovascular disease.

Despite the ongoing debate about the factors that lead to the Metabolic Syndrome and on the appropriateness of the diagnosis, correction of the associated risk factors by lifestyle changes and eventually medications appear to be of potential value in reducing the rates of morbidity and mortality in these patients (16). A nutraceutical approach is of great interest for the control of dyslipidemia, in fact, this field is growing because patients with the conditions hyperlipidemia seem to appreciate a therapeutic intervention as opposed to drug treatments (e.g., statins) of proven efficacy but associated with a high incidence of clinical side effects, involving common muscle adverse effect (17).

This present study demonstrates that the supplementation of RYR containing 10 mg of monacolin K in association with a highly bioavailable form of resveratrol, is a synergic association that further improves the lipid profile compared to that of a standard RYR therapy. The presence of resveratrol, decreases glucose levels, blood pressure and improves insulin sensitivity (HOMA index). In view of the high interest of physicians and of patients for innovative well-tolerated treatments for moderate dyslipidemia, nutraceutical association of RYR and resveratrol is potentially of great interest with a significant clinical value in controlling hyperlipidemia. These results indicate that the nutraceutical supplementation of RYR associated with resveratrol not only shows a significant lipid-lowering activity

compared to RYR treatment alone but is also capable of ameliorating other metabolic parameters. Thus, may represent a valid and safe approach, especially in people with moderate cardiovascular risk, in which a pharmacologic intervention may not be appropriate.

Conflict of interest statement

The authors declare that they have no conflicting and competing interests.

Ethics approval and consent to participate

The study protocol was approved by the appropriate ethics committees and institutional review boards at University of Naples (Federico II) and all patients provided written informed consent before any study procedures were administered.

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