

Red Yeast Rice for Hypercholesterolemia

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ABSTRACT: The extract of red yeast rice (RYR) is the most effective cholesterol-lowering nutraceutical on the market. In particular, its effectiveness is directly related to the amount of monacolin K within the extract (up to 10 mg/day). Consuming monacolin K on a daily basis reduces low-density lipoprotein (LDL) cholesterol plasma levels between 15% and 25% within 6 to 8 weeks. Certainly, the decrease in LDL-cholesterol is accompanied by a similar reduction in total cholesterol, non-high-density lipoprotein cholesterol, plasma apolipoprotein B, matrix metalloproteinases 2 and 9, and high-sensitivity C-reactive protein. Furthermore, the RYR lipid-lowering effect is associated with significant improvements in pulse wave velocity and endothelial function, which are validated and reliable biomarker tools able to detect vascular aging. Although it has a mechanism of action similar to statins, a daily consumption of between 3 and 10 mg monacolin K has only minimal associated risks, and mild myalgias are seen only in the frailest patients (those who also cannot tolerate minimal dosages of statin). The monacolin K found in RYR is a safe and effective supplement for managing mild to moderate hypercholesterolemia in people with no additional cardiovascular risk factors.

INTRODUCTION

Among the modifiable cardiovascular (CV) risk factors, high levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are the most important for the development of coronary heart disease (CHD).¹ The recent American Heart Association 2016 update on Heart Disease and Stroke Statistics once again verified that only 75.7% of US children and 46.6% of US adults present targeted TC levels (< 170 mg/dL for untreated children and < 200 mg/dL for untreated adults), a trend that is comparable to other Western countries.^{2,3}

Current treatment involves lifestyle changes such as diet and exercise and may include lipid-lowering therapy, depending on the severity of dyslipidemia and CV risk.⁴ Specific lifestyle interventions for hypercholesterolemia include a diet low in saturated fat (< 7% of total energy), such as the Mediterranean diet and DASH (Dietary Approaches to Stop Hypertension). These and other diets high in fruits, vegetables, whole grains, nuts, low-fat dairy products, poultry, and fish, with limited portions of lean red meat and sugary foods and beverages, are the most recommended.⁵ Other lifestyle changes include moderate- to high-intensity physical activity (\geq 150 min/week), weight loss of 5% to 10% for overweight or obese patients, and smoking cessation, including avoidance of passive tobacco smoke.⁶ If maintained over the long-term, these lifestyle modifications can reduce LDL-C and non-high-density lipoprotein cholesterol (HDL-C) levels by 5% to 15% and may even significantly reduce the risk of CVD.⁷ Patients unable to reach their target cholesterol goals through

lifestyle interventions should consider using lipid-lowering nutraceuticals. These can be taken alone or in conjunction with pharmacological therapy, which is indicated for those with out-of-target lipid values or who are intolerant to statins.⁸

It is in this context that we review the available clinical evidence on the efficacy and safety of red yeast rice (RYR) extract, a widely used and effective nutraceutical with a lipid-lowering effect.⁹

RED YEAST RICE: MECHANISM OF ACTION

The nutraceutical RYR is created by fermenting yeast (eg, *Monascus purpureus*, *M. pilosus*, *M. floridanus*, *M. ruber* and, more recently, *Pleurotus ostreatus*) in red rice (*Oryza sativa*); the typical red coloration is due to the presence of pigments produced by secondary fermentation.

Red yeast rice contains 25% to 73% sugars (starch in particular), 14% to 31% proteins, 2% to 7% water, 1% to 5% fatty acids, sterols, isoflavones, pigments such as rubropunctamine and monascorubramine, and polyketides.¹⁰ The fermentation of yeast and rice produces a complex of substances called monacolins that have recognized lipid-lowering qualities. The concentration of monacolins in the most commonly used RYR nutraceuticals usually reaches up to 1.9%.¹¹ Several types of monacolins have been identified based on the strain of yeast used and the fermentation conditions. One of these subtypes is monacolin K, which was first isolated by Professor Akira Endo and found to be structurally identical to lovastatin.¹² Its primary mechanism of action is to inhibit

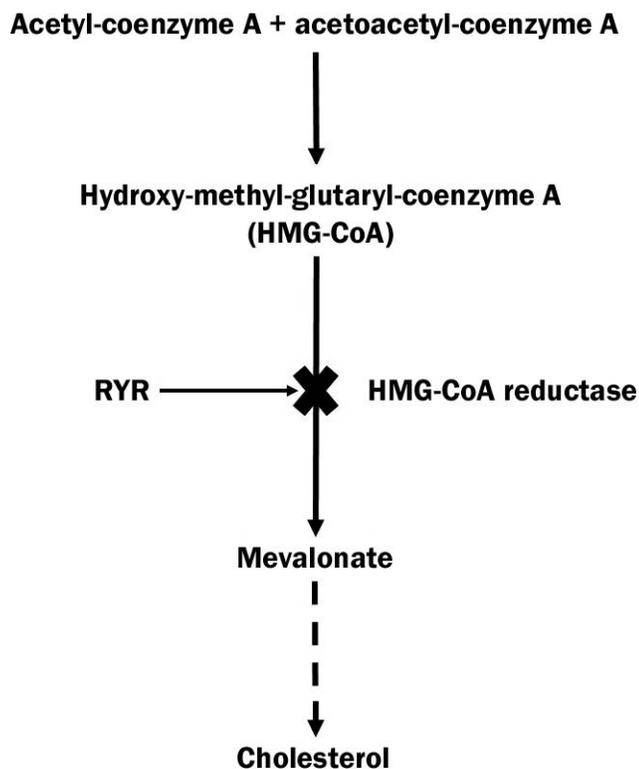


Figure 1.
Main cholesterol-lowering mechanism of action of red yeast rice.

3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-controlling enzyme of the cholesterol synthesis pathway (Figure 1).

Although monacolin K and lovastatin have the same structure, their pharmacokinetic profiles and bioavailability are different. Lovastatin is administered as a single active ingredient with 31% bioavailability in humans, whereas monacolin K is only one of several RYR components that can change the pharmacokinetic profile of lovastatin. The chemical structure of monacolin K also highlights the possible differences in pharmacokinetics and efficacy compared to lovastatin since there are strong variations in the lactone-to-acid ratio. In particular, the better-absorbed acid form ranges from 5% to 100% of total monacolin K—depending on the product—and greatly influences the molecule's bioavailability. The lactone ring opening can occur under alkaline conditions or can be enzymatically hydrolyzed in the small intestine and liver by the cytochrome P450 (CYP450) 3A family.¹³

EFFICACY OF RED YEAST RICE

Several meta-analyses of randomized controlled clinical trials (RCTs) have verified the lipid-lowering effects of RYR. The

most recent, by Gerard et al., included 20 studies with RYR doses varying between 1,200 mg and 4,800 mg/day and containing from 4.8 mg to 24 mg of monacolin K. The meta-analysis demonstrated that RYR reduced LDL-C by an average of 1.02 mmol/L (39.4 mg/dL) after 2 to 24 months of treatment compared to placebo. This effect on LDL lowering was not different from moderate-intensity statins (0.03 mmol/L) such as pravastatin 40 mg and lovastatin 20 mg. The authors also found a small increase in HDL-C (0.07 mmol/L) and a decrease in triglycerides (TG) of 0.26 mmol/L compared to placebo.¹⁴

Red yeast rice has also been shown to improve endothelial function in humans. In a clinical trial by Zhao and colleagues, 50 patients with CHD were randomized to 1,200 mg/day of RYR (containing 11.4 mg monacolin K) or placebo for 6 weeks and were monitored for lipid levels, high sensitivity C-reactive protein (hsCRP), and flow-mediated dilation (FMD) after consuming high-fat meals (50 g). At 6 weeks follow-up, those receiving RYR showed reductions in hsCRP and in the total area under the TG curve (TG-AUC) ($P < .001$ for both) as well as improved post- and pre-prandial FMD ($P < .001$), whereas the placebo group showed no significant changes in serum lipids and FMD.¹⁵ However, significant improvements in endothelial reactivity (measured as pulse volume displacement) and arterial stiffness have been documented by adding 30 mg coenzyme Q10 (CoQ10) or a mix of other antioxidants such as 100 mg green tea dry extract, 20 mg CoQ10, and 20 mg resveratrol to RYR extract.^{16,17}

Red yeast rice is a rare example of a nutraceutical that has been evaluated in some long-term studies for its effect on CV outcomes. In a trial from China involving 1,445 patients aged 65 to 75 years, all with a history of myocardial infarction, those receiving RYR supplementation over a 4-year period had a reduced risk of CHD (31%), all-cause mortality (31.9%), stroke (44.1%), the need for coronary artery bypass graft or a percutaneous coronary intervention (48.6%), and malignancies (51.4%) compared to placebo. Death from coronary heart disease was 6.4% in those receiving RYR and 9% in those receiving placebo, indicating that RYR significantly decreased the risk of CHD death by 29.2%; however, no long-term studies have specifically evaluated the effect of RYR on CVD mortality as a primary end point. The same study also estimated that 18, 33, and 23 elderly patients ≥ 65 years old or 23, 82, and 51 adults would need to be treated with RYR supplementation over those 4 years to prevent one coronary event, one coronary death, and one all-cause death, respectively.¹⁸

RED YEAST RICE COMBINED WITH OTHER NUTRACEUTICALS

As recently suggested by the International Lipid Expert Panel, consuming combinations of nutraceuticals with different

lipid-lowering actions, especially in conjunction with a healthy lifestyle, could be a valid alternative for preventing CHD in patients with moderate hypercholesterolemia and, in some cases, with statin intolerance.^{19,20} In particular, the interaction between RYR and natural products with different mechanisms of action may have a synergistic effect. For example, RYR inhibiting the HMG-CoA reductase enzyme might be advantageously coupled with other nutraceuticals to increase lipid excretion in the bowel (plant sterols, soluble fibers, probiotics, glucomannan), enhance the hepatic uptake of cholesterol (soybean proteins, berberine), or induce LDL-C excretion (chlorogenic acid, soy proteins, berberine).²¹

Red Yeast Rice and Policosanols

Several studies have evaluated the efficacy and safety of RYR in combination with policosanols, a mixture of aliphatic alcohols derived from purified sugar cane.²² Cicero et al. administered RYR extract (340 mg containing 5 mg of monacolin K) combined with octacosanols (10 mg) to 111 patients with normal/borderline triglyceridemia, moderate hypercholesterolemia, and low risk for CVD (< 20% by Framingham Risk Score). After 2 months of treatment, LDL-C was reduced by an average of 20% without any serious safety concerns, a result similar to that seen in patients treated with pravastatin 20 mg/day.²³

In a different placebo-controlled clinical study, 240 patients with an overall coronary risk < 20% and primary-moderate hypercholesterolemia were treated with RYR extract (200 mg, corresponding to 3 mg of monacolin K) combined with linear aliphatic alcohols (10 mg). At 4 months of follow-up, patients had experienced a 29% reduction in LDL-C and 26% reduction in non-HDL-C.²⁴

Red yeast rice (200 mg, corresponding to 3 mg of monacolin K) combined with policosanols (10 mg) was also evaluated in 1,665 adult and 743 elderly patients in a large, single-blind, randomized, multicenter study that compared the metabolic effect of nutraceuticals plus diet versus diet alone. At 16-week follow-up, patients had experienced a 21% reduction in LDL-C and 13% improvement in HDL-C with no significant change in TG levels.²⁵

Beneficial results were also obtained in 40 children affected by heterozygous familial hypercholesterolemia or familial combined hyperlipidemia. In a randomized, double-blind, placebo-controlled, cross-over trial, patients received either placebo or a dietary supplement of RYR extract (200 mg, corresponding to 3 mg of monacolins) and policosanols (10 mg). After 8 weeks, the treatment was determined to be effective, safe, and well tolerated, with those receiving the RYR combination showing

an 18.5% reduction in total cholesterol, a 25.1% reduction in LDL-C, and a 25.3% reduction in apolipoprotein B.²⁶

Red Yeast Rice, Policosanols, and Berberine

The lipid-lowering properties of RYR (3 mg monacolin K) combined with policosanols (10 mg) and berberine (500 mg) is the most-studied association and the one for which meta-analyses of RCTs are available. Data from a recent meta-analysis of 14 RCTs involving 3,159 subjects indicated that the RYR-policosanols-berberine association can improve LDL-C by 23.6 mg/dL, HDL-C by 2.71 mg/dL, TG by 14.2 mg/dL, and glucose by 2.52 mg/dL—with improvements in lipid and glucose profiles maintained in the long-term.²⁷ This combination was also found to be safe and well tolerated in 80% of adult and elderly patients who were previously intolerant to statin treatment.²⁸

De Castro-Orós et al. investigated the genetic variants of LDL receptor (*LDLR*) and proprotein convertase subtilisin-kexin type 9 (*PCSK9*) and their role in the variations of responses to this RYR-policosanols-berberine supplement and determined that they may be linked to three polymorphisms in the 3' UTR region of *LDLR* and two at the 5' UTR region of *PCSK9*. These results may explain the variable responses among patients with moderate hypercholesterolemia and may be useful in identifying subjects who could potentially benefit the most from this supplementation.²⁹ Other studies of this nutraceutical combination found that it improved endothelial function and pulse wave velocity in dyslipidemic patients³⁰ and was as effective as moderate-dose statins in lowering LDL-C in patients with primary hypercholesterolemia and a history of statin intolerance or refusal of statin treatment.³¹

Red Yeast Rice and Plant Sterols

In a study by Feuerstein and Bjerke, 18 patients with hypercholesterolemia received a nutraceutical product of RYR 1,200 mg (titration in monacolin K not reported) and phytosterols 1,250 mg daily and showed a 33% reduction of LDL-C after 6 weeks of treatment.³² This effect was confirmed in a double-blind, placebo-controlled RCT evaluating a similar RYR-phytosterol combination in 90 hypercholesterolemic subjects, showing 27% and 19% reductions in LDL-C and apolipoprotein B, respectively.³³

Red Yeast Rice and Artichoke

Some clinical trials have evaluated the combination of RYR (166.67 mg, 0.4% monacolin K), artichoke leaf extracts (200 mg, 5%-6% chlorogenic acid) and sugarcane-derived policosanols (3.70 mg, 90% policosanols; 60% octacosanol) taken 3 times daily and its effect on lipid and inflammatory

parameters. In a randomized, double-blind, controlled study involving 39 mildly hypercholesterolemic patients, there was a 21.4% reduction in LDL-C and a 12.2% reduction in TG after 16 weeks.³⁴ In a similar study of 100 patients, the authors reported a 14.3% reduction in LDL-C and improvements in total cholesterol, apoB100, and apoB100/apoA-I ratio without any effect on safety.³⁵ Although there were no safety concerns when the authors conducted another study that doubled the dose, the higher dosage did not result in additional benefit.³⁶

The association of RYR (200 mg, containing monacolin K 10 mg), artichoke extract (500 mg), and banaba extract (50 mg) was recently evaluated for primary prevention of CVD in a trial involving 30 adults with suboptimal LDL-C levels. Patients were treated for 6 weeks with the tested nutraceutical compound or placebo and assigned to the second sequence of the study after 2 weeks of wash out. The treatment led to improvements in LDL-C (-18.2%), non-HDL-C (-15%), glutamic oxaloacetic transaminase (-10%), glutamate-pyruvate transaminase (-30.9%), and hs-CRP (-18.2%) compared to placebo, while no changes were observed in the other investigated parameters.³⁷

RED YEAST RICE, POLICOSANOL, AND SILYMARIN

A double-blind, placebo-controlled trial involving 134 low-risk dyslipidemic patients studied the effects of RYR (334 mg, 10 mg monacolin), policosanol (30 mg), and silymarin (150 mg) on lipid profile and endothelial and inflammatory parameters. After 3 months of treatment, LDL-C in the treated group decreased compared with baseline ($P = .041$) and placebo ($P = .037$) while triglycerides decreased compared with baseline ($P = .039$) but not with placebo ($P = .061$). All tested inflammatory parameters (ie, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, soluble E-selectin, MMP-2 and -9, hs-CRP, IL-6 and TNF-alpha) decreased in the treated group.³⁸

The same nutraceutical compound was tested by another research group in an 8-week randomized clinical trial of 80 hypercholesterolemic patients. Compared to placebo, those receiving the active treatment experienced significant improvements in LDL-C (-23.3%), hs-CRP (-2.4%), and endothelial function (pulse volume displacement vs baseline: +17%) but no significant differences in TG, HDL-C, and safety parameters.³⁹

RED YEAST RICE AND OMEGA-3 POLYUNSATURATED FATTY ACIDS

Cicero et al. tested the efficacy of RYR (5 mg monacolin K) and omega-3 polyunsaturated fatty acids (183 mg EPA, 122 mg DHA) for primary prevention of CVD in 107 untreated patients with polygenic hypercholesterolemia and metabolic syndrome. Patients experienced significant decreases in LDL-C (-22%

$\pm 3\%$), TG (-9% $\pm 5\%$), and non-HDL-C (-21% $\pm 3\%$) and a significant increase in HDL-C (+1.5% $\pm 0.5\%$) after 8 weeks of treatment, with no changes in safety parameters. Furthermore, 75% of patients achieved an LDL-C target < 160 mg/dL and 25% < 130 mg/dL. The study highlighted a greater decrease in serum TG levels only in patients with baseline TG > 150 mg/dL, who reached 11% reduction, compared to participants with baseline TG < 150 mg/dL.⁴⁰

SAFETY OF RED YEAST RICE

Inducers or inhibitors of CYP450 may alter plasma concentrations of monacolin K. For this reason, the simultaneous use of nutraceuticals with certain foods or drugs that are CYP450 inhibitors (eg, grapefruit juice, cyclosporine, HIV protease inhibitors, fibrates, niacin, coumarin, nefazodone, macrolides, antifungals) may increase the myotoxicity risk and, although rarely, cause rhabdomyolysis.⁴¹⁻⁴³ Even if chronic use of monacolins could cause mild to moderately severe side effects, they are usually safe and well tolerated. The one exception is citrinin, which is a mycotoxin metabolite derived from *Monascus* fermentation.⁴⁴ In several animal studies, chronic use of citrinin is nephrotoxic and gradually leads to hyperplasia of the renal tubular epithelium, renal adenomas, and sometimes to renal tumors (ie, a dose of 50 mg/kg causes tumors in 100% of the tested animals). Furthermore, citrinin causes reproductive toxicity, malformations, and certain embryo toxicity (even in vitro).^{45,46} The European Food Safety Agency (EFSA) has determined that the maximum dose of citrinin that can be ingested in humans without experiencing nephrotoxicity is 20 $\mu\text{g}/\text{kg}$ per day.⁴⁷ However, neither genotoxic nor carcinogenic effects can be excluded with certainty. Certain RYR supplements labeled "600 mg/capsule" have been detected with citrinin levels that exceed 114 $\mu\text{g}/\text{capsule}$, so that the recommended dosage of four capsules per day would significantly exceed the EFSA recommended level.¹¹

Recent concerns have been voiced regarding the safety of RYR after publication of case reports that claimed toxicity.⁴⁸ However, according to a recent meta-analysis of 53 RCTs with a total of 8,535 patients (4,437 in the RYR treatment arm and 4,303 in the control arm), use of monacolin K is not associated with an increased risk of muscular adverse events (OR 0.94, 95% CI, 0.53-1.65).⁴⁹ Furthermore, the study demonstrated a reduced risk of nonmuscular adverse events (OR 0.59, 95% CI, 0.50-0.69) and serious adverse events (OR 0.54, 95% CI, 0.46-0.64) compared to the control group. The high tolerability profile of RYR was confirmed by the subgroup analyses. In addition, increasing daily doses of monacolin K was associated with a reduced risk of nonmusculoskeletal adverse events (slope: -0.10; 95% CI, -0.17 to -0.03; two-tailed $P < .01$).⁴⁹ Thus, RYR seems to be an overall tolerable and safe lipid-lowering dietary

PARAMETER	MODIFICATION	NOTES
Total, LDL, and non-HDL cholesterol (HDL-C)	Mild-to-moderate reduction	Confirmed in different ethnicities
Apolipoprotein B	Mild-to-moderate reduction	Confirmed in different trials
Triglycerides	Mild reduction	Confirmed in different trials
HDL-C	Mild increase	Confirmed in different trials
hsCRP, MMP-2, MMP-9	Mild decrease	Reported in some trials
Flow-mediated dilation	Mild increase	Reported in some trials
Pulse wave velocity	Mild decrease	Reported only when red yeast rice is combined with other nutraceuticals
Cardiovascular disease prevention	Moderate reduction	Limited to one large study examining secondary prevention of coronary artery disease in elderly Chinese patients

Table 1.

Positive effects of red yeast rice in humans. LDL: low-density lipoprotein; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; MMP-2: matrix metalloproteinase-2; MMP-3: matrix metalloproteinase-3

supplement, even in patients previously intolerant to statin treatment, especially when they are adequately monitored and contain low monacolin K content (3 mg/day).²⁰

DISCUSSION AND SUMMARY

Several meta-analyses and clinical trials have shown the correlation between decreased LDL-C levels and reduction of the relative risk for CVD.⁵⁰ A meta-analysis performed by the Cholesterol Treatment Trialists' (CTT) Collaboration group that included data from 14 RCTs and 90,056 individuals showed that a greater decrease in LDL-C serum concentrations correlated with a greater reduction in vascular and coronary events.⁵¹ Another meta-analysis by the CTT Collaboration involving > 170,000 patients showed that for every 1 mmol/L (~40 mg/dL) reduction in LDL-C, the risk of coronary artery disease, revascularization, and ischemic stroke decreased by just over one-fifth, suggesting that a 3.2 mmol/L (125 mg/dL) reduction in LDL-C could result in a 40% to 50% decrease in risk without affecting deaths due to cancer, stroke, or other nonvascular events.⁵² A reduction of 1 mmol/L is achievable through lipid-lowering nutraceuticals.

The Heart Protection Study Collaborative Group determined that every 1% reduction in LDL-C levels correlates with a > 1% reduction in the relative risk of CV events.⁵³ This reduction could

be achieved by therapeutic lifestyle interventions and daily use of RYR. The positive effect of RYR on laboratory parameters other than LDL-C and on instrumental biomarkers of vascular aging (Table 1) supports its use in patients with moderately elevated LDL-C, especially in primary prevention.⁵⁴

In light of the evidential data, the EFSA provided a scientific opinion substantiating the health claims related to RYR administration and plasma LDL-C levels, specifying that the relationship is possible when ingesting a dose of RYR that contains between 3 and 10 mg of monacolin K.⁵⁵ However, some European national regulatory agencies have suggested using a lower dose of monacolin K due to safety concerns. In particular, specific attention should be given when prescribing full-dosed RYR for statin-intolerant patients.

Conflict of Interest Disclosure:

Dr. Banach conducts research on behalf of Sanofi and Valeant and is a consultant for Abbott/Mylan, Abbott Vascular, Actavis Generics, Akcea Therapeutics, Amgen, Biofarm, KRKA, MSD Pharma, Sanofi-Aventis, Valeant, Daiichi Sankyo, Esperion Therapeutics, Eli Lilly, and Resverlogix Corp.; Dr. Cicero is a consultant for Amgen, Menarini Group, Mylan, and Sanofi; and Dr. Fogacci is a consultant for Mylan.

Keywords:

red yeast rice, monacolin k, nutraceutical, lipid-lowering supplement

KEY POINTS

- Red yeast rice (RYR) extract is the most effective nutraceutical for lowering cholesterol.
- RYR efficacy is proportional to its content of monacolin K.
- The combination of RYR and other natural products with different mechanisms of action has a supposed synergistic effect that can be functional in the treatment of hypercholesterolemia.
- Recent studies confirm the high tolerability profile of RYR.

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