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REVIEW

Red yeast rice with monacolin K for the improvement of hyperlipidemia: A narrative review

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Abstract

Low-density lipoprotein cholesterol (LDL-C) is the most causal risk factor for atherosclerotic cardiovascular disease (ASCVD). Red yeast rice (RYR) is a nutraceutical widely used as a lipid-lowering dietary supplement. The main cholesterol-lower agents in RYR are monacolins, particularly monacolin K, a weak reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, whose daily consumption (up to 10 mg/day) reduces LDL-C plasma levels up to 34% within 6-8 weeks when compared to placebo. The reduction in LDL-C is often accompanied by lower levels of plasma apolipoprotein B, total cholesterol, matrix metalloproteinases 2 and 9, high-sensitivity C-reactive protein, non-high-density lipoprotein cholesterol, and blood pressure. RYR has also demonstrated favorable reductions of up to 45% compared to placebo in the risk of ASCVD events in secondary prevention studies. The mechanism of action is similar to statins. When consumed appropriately, RYR is associated with only minimal side effects. Mild myalgia may be seen in patients who cannot tolerate low-dose statins. In individuals with no additional ASCVD risk factors, RYR is a safe and effective supplement in treating mild to moderate hyperlipidemia.

Key Words: Hyperlipidemia; Red yeast rice; Monacolin K; Low-density lipoprotein; Atherosclerosis; Lovastatin; Coronary artery disease; Statin; Cholesterol

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Core Tip: Red yeast rice (RYR) has cholesterol-lowering properties due to its active ingredient, monacolin K (MK), which mainly inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase. It is an excellent option for patients with mild to moderate dyslipidemia and low atherosclerotic cardiovascular disease risk factors who otherwise would not qualify for statin therapy. RYR can also serve as a valuable alternative in patients with statin intolerance or patients who otherwise are against medical treatment. Although effective, it is noteworthy to mention that the quantity of MK in commercial RYR products varies by brand. This article narratively reviews some existing data on RYR in the treatment of mild to moderate dyslipidemia.

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INTRODUCTION

Elevated low-density lipoprotein cholesterol (LDL-C) is an alterable risk factor for atherosclerotic cardiovascular disease (ASCVD)[1,2]. Current clinical standards recommend lifestyle modifications, including diet and exercise, and may include lipid-lowering therapy based on ASCVD scoring[2,3]. In several cases, there are patients with mild to moderate cholesterol imbalance and less than average ASCVD risk who would not qualify for lipid-lowering therapy and otherwise would not be able to achieve normal lipid values *via* diet and exercise alone. Nutraceuticals such as red yeast rice (RYR) are an excellent option for management in these patients and individuals with mild to moderate dyslipidemia and high ASCVD risk who decline pharmacotherapy[4,5].

RYR is a Chinese folk medicine created by the process of fermenting white rice with yeast, mainly *Monascus purpureus* [6]. The fermentation process produces numerous chemicals, including the ones responsible for its typical red color[6,7]. This process creates monacolins, including monacolin K (MK), a subtype of monacolin similar in structure to lovastatin (Figure 1) with lipid lowering properties, which serves as the active ingredient in RYR[6-8]. Under acidic states, MK deploys one of two configurations: Acidic or lactone[8,9]. The acidic version plays a part in cholesterol reduction[9,10]. For decades, RYR has been used in Asia as a medicine and a coloring agent for food[9-11]. More recently, it has been extensively used as a cholesterol-lowering dietary supplement. The quality of RYR products can differ and are regulated variously. In Europe, commodities with MK are treated as food supplements, while in the United States, they are regulated as drugs[12].

This article comprehensively reviews the use of RYR in the management of hypercholesterolemia. We also reviewed the biological activity and mechanism of action regarding MK in the reduction process and clinical data supporting its use in mild to moderate dyslipidemia. Its anti-inflammatory and antibacterial properties are briefly mentioned.

HISTORY OF RYR

RYR is a food substance that has been used since the Tang dynasty in 800 AD as a naturally occurring remedy for stomach pain[13]. It has also been used to manufacture alcoholic refreshments and several fermented foods in Korea and China[13,14]. Following the 18th century, RYR has been used to produce *tofuyo* (Okinawan-style fermented tofu) in Japan [15]. More recently, MK (lovastatin), which possesses lipid plunging effects, was discovered in some strains of *Monascus* fungi[16]. At present, it is ingested as an ordinary food supplement in a large number of Chinese meals. In North America, it is used as a supplement to reduce cholesterol and enhance cardiac well-being[16,17].

Monascus purpureus yeast is fermented over rice to yield RYR that exhibits a deep red color[18]. This process produces a product that contains several mevinic acids or monacolins, with lovastatin being one of many[18,19]. MK is the main active ingredient in RYR, which is the principal agent responsible for reducing blood cholesterol levels[18-20].

CHEMICAL STRUCTURE OF MK

MK, found in RYR, is structurally identical to lovastatin[21]. It is a white, transparent, needle-shaped crystal under normal laboratory conditions with hydrophobic properties, making it dissolvable in organic substances like acetone and benzene[21,22]. MK possesses the molecular formula $C_{24}H_{36}O_5$ with a weight of 404.55. At low pH states, it adopts either the acidic (active) or lactone (inactive) form[8,22,23]. The lactone form is structurally identical to lovastatin, while the hydroxyl acid is responsible for the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoAR), the enzyme catalyzing the rate-limited step in cholesterol formation[22-24]. The proportion of the acid form varies between 5% and 100%, depending on the pH[25]. The lactone version prevails at low pHs, whereas at neutral and basic pHs, the hydroxy acid predominates[25,26].

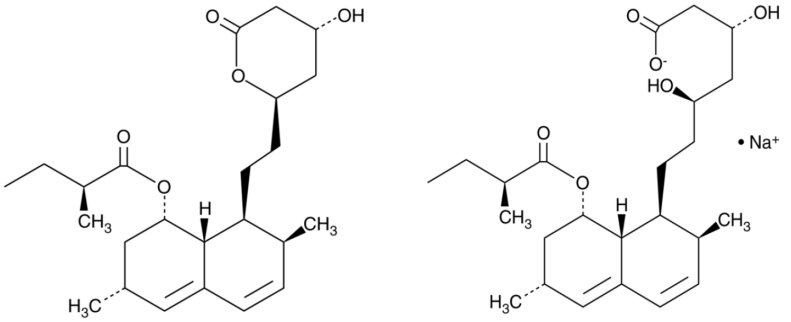


Figure 1 The inactive lactone prodrug of monacolin K (lovastatin) is on the left, and its lipid-lowering active metabolite, monacolin K hydroxy acid, is on the right.

Lovastatin, structurally similar to MK, is a prodrug hydrolyzed to the acidic form, which is the active metabolite that blocks HMG-CoAR and cholesterol synthesis[27]. The acidic version is the only form that can form bonds with amino acid residues in the binding pocket of HMG-CoAR, stabilizing the interaction between the two molecules[27-29]. As such, the acidic form is naturally present in RYR, resulting in differences in clinical profiles and bioavailability between lovastatin and RYR[30,31].

LIPID REDUCTION

Mechanism of action of MK in lipid reduction

The mechanism through which MK facilitates cholesterol reduction is complicated, performing *via* a host of various avenues within the human body. It lowers lipid levels by decreasing internal lipid creation, decreasing digestion of exogenous lipids, and facilitating their dispatch and evacuation[13,32]. In the cholesterol synthesis passageway (Figure 2), acetyl-CoA synthesizes HMG-CoA, which then synthesizes mevalonate[33,34]. Cholesterol is then ultimately made *via* a sequence of biological reactions. HMG-CoA conversion to mevalonate occurs *via* HMG-CoAR, serving as the rate-limiting step in the biosynthetic pathway[33,34]. MK, the active ingredient in RYR, possesses a similar chemical structure to HMG-CoAR, owing to a high degree of competitive inhibition of the enzyme, resulting in the prevention of cholesterol synthesis and a decrease in blood lipid contents[35]. MK in RYR also works to decrease blood lipid levels through the LDL receptor [33-36]. LDL is an essential substance in controlling blood cholesterol. This key complex is responsible for circulating cholesterol to the peripheral tissues[37]. LDL is mostly dissipated and remodeled by the LDL receptors. MK inherently increases LDL receptor output, thereby decreasing LDL levels and lowering cholesterol within the blood[37,38]. Compared with purified lovastatin, RYR extract has a higher bioavailability, which makes it more effective in reducing cholesterol levels[39,40].

Hypolipidemic effects of RYR

Hypercholesterolemia, especially elevated LDL-C, is a major adjustable risk factor for ASCVD[41]. Guidelines recommend lifestyle modifications and, when indicated, pharmacotherapy to reduce LDL-C and minimize ASCVD risk[42, 43]. In patients requiring pharmacologic therapy, statins are commonly used for therapeutic intervention[44]. However, in certain persons, these medications induce grave side effects such as myalgia and rhabdomyolysis[45,46]. These adverse effects can often worsen when combined with other lipid-lowering therapies, such as fibrates[45-47]. Ezetimibe is frequently used as a supplement to statins, although it can also be used as a monotherapy for patients who possess intolerance[48]. In some instances, ezetimibe can induce transaminitis[48,49]. Studies have shown that RYR, when used as a food addendum for patients with dyslipidemia, drastically provides symptom relief[50-52].

SAFETY AND EFFICACY

Several studies have confirmed the efficacy and safety of RYR in patients with hyperlipidemia[53-55]. Liu *et al*[56] performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the effectiveness and safety of RYR preparations on lipid modification in primary hyperlipidemia. The study consisted of 93 trials, using a total of 9625 participants, in which three RYR formulations were tested. The integrated outcomes showed a drastic reduction of total cholesterol (TC) weighted mean difference (MD) -0.91 mmol/L, 95%CI: -1.12 to -0.71, LDL-C (-0.73 mmol/L, -1.02 to -0.043), and triglycerides (TG) (-0.41 mmol/L, -0.6 to -0.22) by RYR treatment compared with placebo. The study also showed an increase in high-density lipoprotein cholesterol (HDL-C) values (0.15 mmol/L, 0.09 to 0.22) *vs* placebo. Overall, the lipid-

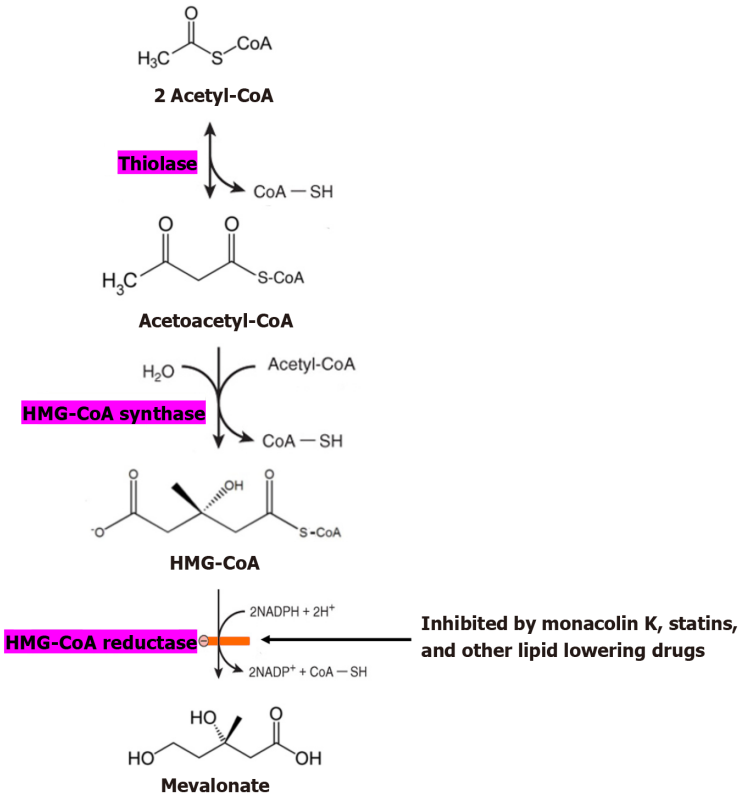


Figure 2 Cholesterol synthesis pathway showing the mechanism of action through which monacolin K, the active ingredient in red yeast rice reduces blood lipid levels. HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A.

changing effects of RYR unfolded to be similar to simvastatin, pravastatin, atorvastatin, lovastatin, and fluvastatin. Contrasted with agents that are not statins, RYR formulations appeared superior to fish oils and nicotinate but equal to or less effective than gemfibrozil and fenofibrate. RYR preparations were associated with nonserious side effects such as gastrointestinal discomfort and dizziness.

Gerards *et al*[57] also conducted a meta-analysis of 20 RCTs to authenticate the safety and efficacy of RYR preparations in lowering LDL-C. These doses of RYR varied between 1200 mg and 4800 mg/day, containing a range from 4.8 to 24 mg of MK. The results showed that RYR decreased LDL-C by a mean of 1.02 mmol/L (39.4 mg/dL) after 2 to 24 months juxtaposed to placebo. These results signified that RYR extract could significantly reduce the LDL-C, which is comparable in effectiveness with statins. The study, therefore, concluded that RYR may be a safe and acceptable option for hyperlipidemia in patients with intolerance to statins to reduce the risk of ASCVD.

There have also been studies that confirmed the tolerability of RYR in patients with intolerance to statins[58-60]. Stefanutti *et al*[61] conducted a clinical study on 55 patients with heterozygous familial hypercholesterolemia who ceased statin therapy due to myalgia. They received a low-cholesterol diet that constituted 300 mg of RYR rice, equivalent to 10 mg of MK per day. Results showed a significant reduction in LDL-C after 6 months (16% for females and 17% for males, $P < 0.005$). These levels further declined to 27% and 24% in women and men at 12 months, respectively. There were no encounters of elevated C-reactive protein or aminotransferase.

Several other studies have been conducted that show that when RYR is used as a food addendum for patients with dyslipidemia, it dramatically reduces their symptoms[62,63]. Researchers have also collected clinical data from several other trials in patients who have used RYR as monotherapy for hypercholesterolemia[64-66]. These results showed that RYR can decrease cholesterol levels and often serve as a suitable alternative for patients who are intolerant to statins.

COMBINATATION OF RYR WITH OTHER NUTRACEUTICALS

The combination of nutraceuticals with different mechanisms of action for patients with mild to moderate hypercholesterolemia who otherwise do not qualify for statin therapy based on ASCVD risk or intolerance is a valid alternative in preventing coronary artery disease (CAD)[67]. Certain interactions between RYR and natural commodities with different mechanisms of action may have harmonious effects[67,68]. For example, the combination of RYR, which inhibits HMG-CoAR, and berberine, which extends the half-life of LDL receptor messenger ribonucleic acid (mRNA), has been shown to reduce LDL-C comparable to those with prescription statin therapy[69]. Other nutraceuticals with lipid-lowering properties are listed in Table 1.

Table 1 Other nutraceuticals and their main effects on low density lipoprotein cholesterol

Nutraceutical	Active ingredient(s)	Mechanism of action	Side effect(s)	Dosing
Bergamot (Citrus bergamia)	Flavonoids	Inhibits HMG-CoAR and ACAT	GI discomfort and muscle cramps	500-1500 mg/day
Garlic extract	Allicin (diallyl thiosulfinate)	Inhibits HMG-CoAR, acetyl-CoA synthetase, and squalene-monooxygenase	GI upset, body odor, and increase risk of bleeding	0.3-20 g/day
Artichoke leaf extract	Flavonoids, caffeic acid, volatile sesquiterpene, and mono- and dicaffeoylquinic acid	Flavonoids (luteolin) inhibits HMG-CoAR, SREBP, ACAT, and increase GI excretion of bile acids	Skin reactions, GI upset, and potential asthma exacerbation	500-2800 mg/day
Green tea	Catechins	Inhibits inducible NO synthase and HMG-CoAR. Activates AMPK	GI discomfort, hypertension, and skin rashes. Rare adverse effects include hepatotoxicity, hypokalemia, and TTP	100-500 mg/day
Oryza sativa	Gamma-Oryzanol	Inhibition of GI cholesterol absorption and increase fecal excretion of bile acids	Well tolerated	100-300 mg/day
Olive extract	Phenols	Reduce lipid peroxidation, increases bile excretion, inhibits HMG-CoAR and ACAT activity	Well tolerated	136.2 mg of oleuropein and 6.4 mg of hydroxytyrosol per day
Lupin protein	Lupin	Inhibits HMG-CoA and PCSK9 activity. Upregulated SREBP-2	GI discomfort	≤ 35 g/day
β-Glucan	β-Glucan	Decrease absorption from GI tract	Well tolerated	3-5 g/day
Plantago seed	Psyllium	Increases hepatic LDL receptor expression	GI discomfort, allergic reactions, bowel and esophageal obstruction	2-20 g/day
Amorphophallus konjac	Glucomannan	Inhibits HMG-CoAR	GI upset, esophageal, and bowel obstruction	1-15 g/day
Guar (*Cyamopsis tetragonoloba* or *Cyamopsis psoraloides*)	Guar Gum	Prevent absorption of cholesterol in the GI tract and increase bile acid excretion	GI upset, esophageal, and bowel obstruction	30-100 g/day
Nigella Sativa	Thymoquinone, flavonoids, and PUFA	Increase biliary excretion, reduce cholesterol synthesis, inhibit lipid oxidation, and upregulate LDL receptors	GI discomfort and transaminitis	200 to 3000 mg for capsules, powders, and extracts. 1-2 mL for oil suspensions
Silymarin	Flavonolignans	Increase lipolysis and β-oxidation *via* the upregulation. Increase cholesterol efflux *via* the increased expression of ABCA1	GI discomfort, headache, ureteric stones, and hemolytic anemia	140-700 mg/day
Anthocyanins	Flavonoids	Downregulate the messenger RNA expression of SREBP-1c	Well tolerated	100-450 mg/day
Spirulina	C-phycocyanin	Activates heme oxygenase-1	GI discomfort, rashes, bleeding, cholestasis, and elevated transaminases	1-10 g/day
Alpha lipoic acid	Alpha lipoic acid	Module fat synthesis, mitochondrial β-oxidation of fat, clearance of TG-rich lipoproteins in the liver, and adipose TG accumulation	GI discomfort, skin rashes, and rarely, insulin autoimmune syndrome	300-1800 mg/day
Chitin	Chitosan	Interferes with GI absorption by binding to negatively charged fatty acids and bile acids and disrupting the emulsification of neutrally charged cholesterol	GI discomfort. Avoid use in patients with allergies to shellfish or crustaceans	0.3-3 g/day
Pantothenic acid (B5)	Pantethine	Inhibits HMG-CoA reductase and acetyl-CoA carboxylase	GI upset	600-1200 mg/day

ABCA1: ATP-binding cassette transporter A1; ACAT: Acyl-coenzyme A cholesterol acyltransferase; AMPK: AMP-activated protein kinase; GI: Gastrointestinal; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; NO: Nitric oxide; PCSK9: Proprotein convertase subtilisin/kexin type 9; PUFA: Polyunsaturated fatty acid; SREBP: Sterol regulatory element-binding protein; TTP: Thrombotic thrombocytopenic purpura.

RYR and Nattokinase

Natto, a fermented soybean product, has been used as a food supplement in Japan for many decades[70]. Nattokinase (NK), a potent fibrinolytic and antithrombotic compound, has been shown to have anti-atherosclerotic and cholesterol-lowering properties[70,71]. It is created by the bacterium Bacillus subtilis during the fermentation of soybeans to yield Natto[70-72]. Several RCTs have shown favorable outcomes of hypercholesterolemia in patients who combine RYR and NK[73-75].

An RCT was conducted by Yang *et al*[73] to evaluate the lipid-lowering effect of oral NK *vs* NK and the extract of RYR on lipids in patients with dyslipidemia. A total of 47 patients with hyperlipidemia were designated to one of three groups: NK mono formula (50 mg per capsule), the combined formula of NK with RYR (300 mg per capsule), and placebo. Compared to the mono group, which revealed no effects on blood lipids until 6 months, the conjoined formula improved all measured lipids at the end of month one. The combined formula also resulted in abatement in TG by 15%, TC by 25%, LDL-C by 41%, TC/HDL-C by 29.5%, and increases in HDL-C by 7.5%. After controlling for baseline levels, only the combined set revealed a noticeable difference ($P < 0.0001$) in LDL-C, TC, and TC/HDL-C ratio when compared with the placebo group.

Another RCT conducted by Liu *et al*[74] probed the influence of NK and RYR supplementations on cardiometabolic parameters in patients with stable CAD. One hundred seventy-eight patients with CAD were randomized into four groups: RYR, NK + RYR, RYR, and placebo. In comparison across groups, NK + RYR reduced TG (-0.39 mmol), TC (-0.66 mmol/L), and increased HDL-C (0.195 mmol/L) compared to all other groups ($P < 0.01$). Both NK + RYR and NK sets had noteworthy improved lactate dehydrogenase than the others (-29.1 U/L and -26.4 U/L). The NK + RYR group also showed more potent reductions in thromboxane B2 and elevations in antithrombin III compared to placebo ($P < 0.01$). This study revealed that combined NK and RYR are safe and more effective than their counterparts in reducing blood lipid levels.

RYR and policosanols

Policosanol possesses a mixture of concentrated primary aliphatic alcohols withdrawn from sugar cane wax, widely respected as a lipid reduction agent, with some studies reporting its usefulness in treating hypertension[76]. Several studies have evaluated the safety and efficacy of combined RYR with policosanols. In an RCT by Stefanutti *et al*[61] 240 patients with an overall coronary risk of < 20% and moderate dyslipidemia were treated with RYR extract (200 mg = 3 mg on MK) combined with aliphatic alcohols (10 mg). Patients had a 26% reduction in HDL-C and a 29% reduction in LDL-C at their 4-month follow-up.

Cicero *et al*[77] administered octacasanols (10 mg) and RYR extract (340 mg containing 5 mg of MK) to 111 patients with moderate hypercholesterolemia and low risk for cardiovascular disease, defined by a Framingham Risk Score of < 20%. LDL-C was reduced by an average of 20% at the 2-month mark, a result that is comparable to patients taking pravastatin 20 mg per day.

Another randomized, multicenter investigation compared the metabolic effect of nutraceuticals plus diet *vs* diet alone on hypercholesterolemia[78]. RYR (200 mg = 3 mg of MK) combined with policosanol (10 mg) was evaluated in 743 elderly and 1665 adults. A 21% reduction in LDL-C and a 13% increase in HDL-C with no change in TG levels were seen at the 16-week follow-up.

RYR, policosanols, and berberine

Berberine is a Chinese herbal supplement used to treat heart failure and diabetes in China[79]. It has been shown to increase the hepatic expression of LDL receptors by extending the half-life of LDL-C mRNA, which serves as the primary mechanism by which it lowers cholesterol[80,81]. This effect is similar to the increased transcription of mRNA promoted by statins[82]. Berberine is well tolerated, apart from occasional GI upset in some patients[83]. When combined with RYR, it can achieve reductions in LDL-C comparable with prescription statins but without the associated adverse effects such as myopathy or hepatic damage[83,84].

The lipid-lowering characteristics regarding the combination of RYR (3 mg of MK), policosanols (10 mg), and berberine (500 mg) is one of the most studied associations for which several meta-analyses of RCTs are available. Millán *et al*[85] conducted a meta-analysis regarding the effect of the above combinations on lipid parameters. Data from 11 RCTs constituting 1970 nutraceutical combinations and 1954 control patients were included in the study. The results showed a 9.9% reduction in TC, a 13.7% decrease in LDL-C, a 7.0% reduction in TG, and a 3.7% increase in HDL-C.

Pirro *et al*[86] also conducted a meta-analysis of 14 RCTs involving 3159 patients to evaluate the cholesterol-lowering efficacy of RYR (3 mg of MK) compounded with policosanols (10 mg), and berberine (500 mg). Data showed that the RYR-policosanol-berberine combination enhanced LDL-C by 23.6 mg/dL, TG by 14.2 mg/dL, HDL-C by 2.71 mg/dL, and glucose by 2.52 mg/dL. These effects were maintained in the long term, and this mixture was found to be safe and well-received by the majority of adult and elderly patients who reported previous statin intolerance.

RYR and phytosterols

A double-blind, placebo-controlled RCT evaluated the effectiveness of the RYR-phytosterol combination in 90 patients with hypercholesterolemia[87]. Results showed a 19% and 27% reduction in apolipoprotein B and LDL-C, respectively.

LITERATURE DATA REGARDING THE EFFECTS OF RYR ON METABOLIC PARAMETERS

RYR vs placebo and statin metal-analyses

Li *et al*[88] conducted a meta-analysis regarding the safety and efficacy of RYR in treating hyperlipidemia using 15 RCTs as determined by a Jadad scale of ≥ 4 points. A total of 1012 individuals participated in the study. Results showed that contrasted to statins, RYR was more successful in decreasing TG (MD: -19.90; 95%CI: -32.22 to -7.58; P = 0.002), less effective in lowering TC (MD: 12.24; 95%CI: 2.19 to 22.29; P = 0.02) and comparable in lowering LDL-C and elevating HDL-C. Compared with nutraceutical, RYR drastically lowered LDL-C (MD: -14.40; 95%CI: -22.71 to -6.09; P = 0.0007) and TC (MD: -17.80; 95%CI: -27.12 to -8.48; P = 0.0002), and elevated HDL-C (MD: 7.60; 95%CI: 4.33 to 10.87; P < 0.00001). RYR additionally effectively combined nutraceutical to further lower LDL-C (MD: -27.91; 95%CI: -36.58 to -19.24; P < 0.00001), TC (MD: -31.10; 95%CI: -38.83 to -23.36; P < 0.00001), and TG (MD: -26.32; 95%CI: -34.05 to -18.59; P < 0.00001). RYR also dramatically decreased apoB (MD: -27.98; 95%CI: -35.51 to -20.45; P < 0.00001) and was associated with no heightened risk of adverse events.

Another meta-analysis of 20 RCTs by Gerards *et al*[57] involving more than 6000 patients revealed that RYR (1200-4800 mg/day) was better than a placebo at decreasing TC (MD: -1.00 mmol/L; 95%CI: -1.23 to -0.77, P < 0.00001) and LDL (MD: -1.02 mmol/L; 95%CI: -1.20 to -0.83, P < 0.00001). The effect of RYR was homogenous to that of low-intensity statins on TC (MD: -0.05 mmol/L; 95%CI: -0.28 to 0.18, P = 0.67) and LDL (MD: 0.03 mmol/L; 95%CI: -0.36 to 0.41, P = 0.89).

RYR and metabolic syndrome

Metabolic syndrome (MetS) is denoted by the coexistence of insulin resistance, dyslipidemia, hypertension, and obesity [89,90]. A meta-analysis was conducted by Yuan *et al*[91] to decipher whether RYR preparations enhance clinical endpoints and decrease risk factors for MetS. The primary outcome points were mortality and major adverse cardiac events (MACEs), and the alternative outcome estimates were blood glucose, blood lipids, and blood pressure. Of the 30 articles included in the analysis, RYR preparations showed drastic improvement in MetS compared to controls. RYR preparations lowered mortality and MACEs (RR = 0.62, 95%CI: 0.49-0.78; RR = 0.54, 95%CI: 0.43-0.66). Regarding glucose metabolism, fasting plasma glucose (MD: -0.46 mmol/L, 95%CI: -0.71 to -0.22), hemoglobin A1c (MD: -0.49, 95%CI: -0.71 to -0.26), and the homeostasis model assessment of insulin resistance (MD: -0.93, 95%CI: -1.64 to -0.21) were reduced. Mean arterial blood pressure (MD: -3.79 mmHg, 95%CI: -5.01 to -2.57) was decreased. With respect to blood lipids, TC (MD: -0.74 mmol/L, 95%CI: -1.02 to -0.46), TG (MD: -0.45 mmol/L, 95%CI: -0.70 to -0.21), and LDL-C (MD: -0.42 mmol/L, 95%CI: -0.78 to -0.06) were reduced, while HDL (MD: 0.14 mmol/L, 95%CI: 0.09-0.20) increased. The incidence of adverse events did not increase with RYR preparations (RR = 1.00, 95%CI: 0.69-1.43).

RYR and cardiovascular outcomes and atherosclerosis

Sungthong *et al*[92] conducted a meta-analysis to assess the efficacy of RYR extract on cardiovascular outcomes in patients with myocardial infarction (MI) and borderline hypercholesterolemia. Seven investigations with 10699 MI patients with borderline hypercholesterolemia were included, with follow-up periods that ranged from 4 weeks to 4.5 years. RYR extract (1200 mg per day) decreased nonfatal MI (RR = 0.42, 95%CI: 0.34-0.52), sudden death (RR = 0.71, 95%CI: 0.53-0.94), and revascularization (RR = 0.58, 95%CI: 0.48-0.71). RYR extract also reduced LDL [weighted MD (WMD) = -20.70 mg/dL, 95%CI: -24.51 to -16.90], TG (WMD = -24.69 mg/dL, 95%CI/L -34.36 to -15.03), and TC (WMD = -26.61 mg/dL, 95%CI: -31.65 to -21.58), and increased HDL levels (WMD = 2.71 mg/dL, 95%CI: 1.24-4.17).

Another meta-analysis was conducted by Wang *et al*[93] to study the effects of RYR in carotid atherosclerosis. Carotid plaque score (SCORE), carotid plaque area (AREA), and intima-media thickness were set as the primary endpoints, while safety indicators and lipid profile were set as the secondary outcomes. The analysis performed with 20 RCTs including 2217 patients showed that compared to the control group, intima-media thickness [standardized MD (SMD) = -0.588, 95%CI: -0.792 to -0.384, P < 0.001], AREA (SMD = -0.855, 95%CI: -1.259 to -0.451, P < 0.001), LDL-C (SMD = -0.938, 95%CI: -1.375 to -0.502, P < 0.001), SCORE (SMD = -0.708, 95%CI: -1.135 to -0.282, P = 0.001), TG (SMD = -0.766, 95%CI: -0.980 to -0.551, P < 0.001), and TC (SMD = -0.858, 95%CI: -1.254 to -0.462, P < 0.001) were significantly lowered and HDL-C (SMD = 0.389, 95%CI: 0.044-0.733, P = 0.027) was significantly enhanced following RYR therapy. Based on these results, the study concluded that RYR supplementation showed significant efficacy in the treatment of carotid atherosclerosis in the Chinese population.

ANTI-INFLAMMATORY AND ANTIBACTERIAL PROPERTIES

Song *et al*[94] discovered that fluconazole, in combination with lovastatin, has complementary effects on the repression of planktonic *Candida albicans* (*C. albicans*) cells *in vitro* and can induce gene expression in the prenylation and ergosterol passageways. Zhou *et al*[95] in 2018 substantially authenticated that combining itraconazole and lovastatin is an effective strategy against planktonic *C. albicans* cells and biofilms, even in itraconazole-resistant strains.

Strains of *C. albicans* with dysfunctional *ERG3* and *ERG11* genes are sensitive to lovastatin monotherapy but resistant to itraconazole[96,97]. This investigation revealed that the drug combination is effective in the treatment of resistant fungal pathogens and has an evident antibacterial effect against *C. albicans* when combined with other antibacterial agents.

POTENTIAL ADVERSE EFFECTS OF RYR

RYR is generally safe for consumption, with most patients experiencing little to no symptoms[12,63]. However, in some cases, consuming RYR can lead to myalgias similar in nature to the side effects of statin-based therapies, which vary from mild muscle discomfort to severe pain or myopathy[98,99]. Additionally, MK in RYR can cause hepatic dysfunction[100]. In prospective controlled trials, RYR extract combinations have not been associated with clinically apparent liver injury. However, there have been several case reports of liver injury in patients who took RYR extracts[101-103]. Both myopathies and liver injury are thought to be related to the presence of lovastatin, which releases an immunogenic or toxic metabolite[102-104]. Lastly, RYR has the potential to be nephrotoxic due to the presence of mycotoxin citrinin[105,106]. There have been several reported cases of acute kidney injury accompanied by Fanconi syndrome in patients taking RYR extract[107-109]. The exact mechanism through which this occurs is still not fully understood. Larger clinical trials are needed to assess the long-term side effects of RYR.

GUIDANCE AND LIMITATIONS

Studies have shown that RYR significantly reduces TC, LDL-C, and TG and provides a new, novel, and supplemental approach to lowering cholesterol in patients with low ASCVD risk who otherwise would not qualify for statin therapy as well as those with statin intolerance or strong patient preference[110,111]. Although effective, it should not be customarily used in place of standard treatments (ezetimibe, statins, and PCKS9 inhibitors) for which higher quality long-term data exist[112-114]. However, in the specific situations listed above, RYR may be considered as an alternative in managing mild to moderate dyslipidemia. If the treating physician decides to use RYR as the lipid lower agent for their patients, most studies have shown that 600 mg, 2 to 4 times daily, for a total of 1200 to 2400 mg for 4 to 12 weeks has proven clinical benefit.

Despite the established causative connections between LDL reduction and decreased cardiovascular mortality, there are few data regarding the long-term use of RYR for lipid reduction. Furthermore, the quantity of MK in commercial RYR preparations varies by brand and is commonly unreported. A 2017 review analyzed 28 brands of RYR products from mainstream retailers in the United States, and none of the products included MK on the label[115]. MK was not detected in two brands, and the quantity significantly varied among the other 26 products. Given this significant variability based on the manufacturer, patients may be insufficiently treated. As such, careful research by providers is needed to choose the appropriate RYR preparation to facilitate cholesterol reduction. Physicians should consider the recommendations provided in this article for the appropriate patients based on the clinical context. However, oneness still lies with the medical professional in making the right clinical decision that is in the best interest of the patient and correlates well with evidence-based medicine.

CONCLUSION

RYR is a suitable option for decreasing LDL-C levels in patients with mild-to-moderate hypercholesterolemia who are unable to implement lifestyle modifications, intolerant to statins, and ineligible for pharmacologic treatment. Given the large amount of commercially available RYR nutraceutical products with its limited regulation, physicians should do their appropriate research to choose the best available RYR preparation that is high quality with a suitably low dose of MK, produced under good manufacturing practices. Choosing the best preparations of RYR may limit adverse effects and provide consistent MK dosing, which produces better clinical outcomes. Additional research, including larger clinical trials, is needed to further assess the safety and efficacy of RYR in the management of dyslipidemia.

FOOTNOTES

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