Curr Atheroscler Rep (2015) 17: 22
DOI 10.1007/s11883-015-0495-8

NONSTATIN DRUGS (EM DEGOMA, SECTION EDITOR)

Red Yeast Rice for the Treatment of Dyslipidemia

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Published online: 3 March 2015

Abstract Red yeast rice (RYR) is a Chinese herbal supplement produced by fermenting white rice with the yeast, *Monascus purpureus*. The Chinese have used RYR to flavor, color, and preserve foods and as a traditional medicine for many years. In the USA, RYR has been used as an alternative to statin therapy in treating patients with mild to moderate hypercholesterolemia. RYR contains a variety of monacolins, which inhibit hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. Consumption of RYR has increased recently especially among patients who might be intolerant to standardized therapy due to statin-associated myalgia (SAM). Several clinical trials have shown RYR to be safe, effective, and well tolerated; however, the studies are small and of short duration. The US Food and Drug Administration has prohibited the sale of all RYR products containing monacolin K, which is chemically identical to lovastatin, because it is considered an unapproved drug. However, many RYR supplements continue to remain on the market and lack standardization and quality control.

Keywords Red yeast rice · Monacolin K · Lovastatin · Hypercholesterolemia · Dyslipidemia · Statin-associated myalgia (SAM) · HMG CoA reductase inhibitor · Xuezhikang · Mevacor

This article is part of the Topical Collection on *Nonstatin Drugs*

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Introduction and Background

Red yeast rice (RYR), also known as Hong Qu, is a Chinese herbal supplement first described in the Tang Dynasty in 800 AD [1]. It is made by fermenting white rice with the yeast, *Monascus purpureus*, which turns the rice a red color [2]. The Chinese use RYR as a food preservative, a flavor enhancer, and a food-coloring agent for fish sauce, rice wine, red soybean curd, pickled vegetables, and salted meats. It has also been used in Chinese folk medicine for treating indigestion and diarrhea [2, 3]. In the USA, RYR has been used as an alternative to statin therapy especially among patients opposed to taking statins or who might be intolerant to standardized therapy due to statin-associated myalgia (SAM) [4]. Available as an over-the-counter supplement, several studies have shown RYR to be safe and effective in treating patients with mild to moderate hypercholesterolemia [1]. Consumption of RYR has risen dramatically by almost 80 % in the USA from 2005 to 2008 [1, 4].

Proposed Mechanism of Action

Red yeast rice contains varying amounts of monacolins, a family of naturally occurring substances that inhibit hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis. One such monacolin, monacolin K, is chemically identical to lovastatin (Fig. 1) [1, 3]. Approximately 90 % of the total monacolin content of RYR consists of monacolin K and its hydroxy acid form, monacolin KA [3, 5, 6]. Other active ingredients with the potential to lower cholesterol in commercially available RYR products include plant sterols (beta-sitosterol, campesterol, stigmasterol), isoflavones, and monounsaturated fatty acids [3].

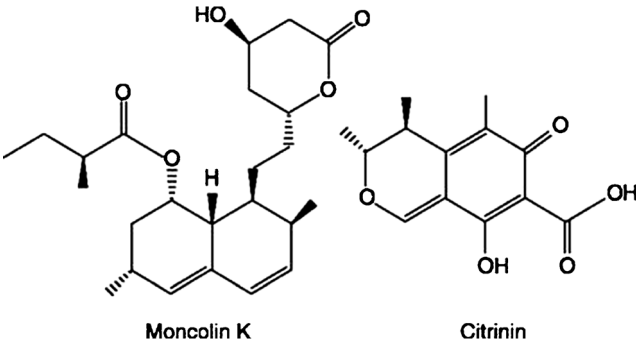

Fig. 1 Chemical structures of monacolin K (lovastatin) and citrinin [1]

In various populations, RYR has been shown to reduce low-density lipoprotein cholesterol (LDL-C) by 22 to 30 % [1]. A greater reduction was observed in one trial when a more potent RYR product with a higher monacolin K content was combined with fish oil and lifestyle changes [7]. Clinical trials have found that a relatively small dose of RYR (equivalent to a daily lovastatin dose of 5 to 7 mg) is as effective as 20 to 40 mg of pure lovastatin in lowering cholesterol [1, 8, 9]. Little is known about the pharmacodynamics of the other monacolins contained in RYR, but it has been suggested that they may also have lipid-lowering effects or potentiate the effects of monacolin K [10]. A recent study demonstrated that the oral bioavailability and dissolution rate of lovastatin is enhanced when given as RYR, which may improve its efficacy [11].

Clinical Trial Evidence

Lipid-lowering Effects

Several clinical trials have proven RYR's efficacy in treating mild to moderate hypercholesterolemia (Table 1) [1]. The total amount of RYR per day in the various trials ranged from 1200 to 4800 mg, generally divided into two doses [5]. The first prospective, double-blind, placebo-controlled study evaluating RYR in an American population was conducted by Heber et al. in 1999 [8]. Eighty-three healthy adults with untreated hyperlipidemia were randomly assigned to receive 2.4 g per day of RYR (Cholestin, Pharmanex, Inc, Simi Valley, CA) or placebo for 12 weeks. Both groups were counseled on an American Heart Association cardioprotective diet, which contained less than 10 % of calories from saturated fat and less than 300 mg from cholesterol per day. At week 12, LDL-C levels were significantly different ($P<0.001$) between the two groups. Compared to baseline, LDL-C levels decreased by 39±19 mg/dL (22 %) in the RYR-treated group and by 5±22 mg/dL (5 %) in the placebo group. There were no reported adverse events in either group [8]. Other studies have shown similar results in different populations [12, 13]. However, all these studies have several limitations, including small sample size, short duration, and single-site design.

Becker et al. compared the efficacy of an "alternative treatment" which included RYR (Res-Q LDL-X, N3 Oceanic, Palm, PA), fish oil, and therapeutic lifestyle changes with simvastatin 40 mg per day in 74 primary prevention patients with known or newly diagnosed hypercholesterolemia [7]. Each 600 mg RYR capsule contained 2.53 mg of monacolin K (lovastatin). Depending on baseline LDL-C, patients were given 1200 mg RYR (10 mg lovastatin) or 1800 mg (15 mg lovastatin) twice daily for a period of 12 weeks. All patients in the alternative treatment group (ATG) received six fish oil capsules.

At the conclusion of the study, both groups had a similar reduction in LDL-C which was statistically significant ($P<0.001$ for both), and no significant differences were found between the two groups. LDL-C levels were reduced by 42± 15 % in the ATG and 40±20 % in the simvastatin group. Participants in the ATG, however, lost more weight during the study (−4.7±2.4 kg vs −0.3±2.2 kg) and had a significant reduction in triglycerides compared with the simvastatin group. The authors concluded that both the weight loss and addition of fish oils likely contributed to the lower triglyceride levels in the ATG [7].

A recently published multicenter trial [14••] was done testing the efficacy of a partially purified extract of RYR, Xuezhikang (XZK), in lowering non-high-density lipoprotein cholesterol (non-HDL-C) and LDL-C in patients with dyslipidemia. Patients were randomized to a placebo or one of two different doses of XZK, 1200 mg containing 12 mg of lovastatin or double the dose for 4 to 12 weeks. The trial was conducted at 15 sites between the USA and China with a total of 116 participants. Treatment with XZK was well tolerated and resulted in significant reductions in both non-HDL-C (24 %) and LDL-C (27 %) compared with placebo ($P<0.001$ for both). Doubling the dose at week eight resulted in an additional 4.6 % reduction in LDL-C. Approximately 50 % of the patients receiving XZK achieved a 30 % reduction in LDL-C from baseline [14••].

The majority of reported adverse events were gastrointestinal in both groups. Four percent of participants experienced muscle spasms or myalgia with XZK; however, no one had myopathy, defined in the study protocol as muscle pain with creatine phosphokinase (CPK) elevations ≥10 times the upper limit of normal (ULN). None of the patients in the placebo group reported muscle symptoms. The findings from this trial were similar in both patient populations and consistent with results from previous trials. Other trials have demonstrated XZK's efficacy in larger populations [15, 16].

Li et al. recently published a large meta-analysis, which examined the effectiveness and safety of RYR as an alternative approach for treating dyslipidemia. Thirteen randomized, placebo-controlled trials were included dating from 1999 to 2013 with treatment duration of 4 weeks to 6 months. All but

Table 1 Summary of clinical trial results demonstrating RYR efficacy in treating dyslipidemia

References	Sample size (I/C)	Total dose of RYR mg/day	Total dose lovastatin mg/day[a]	Duration	Results (*P* values)	Comments
[8]	42/41	2400 mg	7.2 mg	12 weeks	TC ↓16 % LDL-C ↓22 % (*P*<0.001)	No other ingredients in RYR preparation
[12]	37/38	1200 mg	13.9 mg	8 weeks	TC ↓22 % LDL-C ↓28 % (*P*<0.001)	Chinese population
[7]	37 ATG 37 Simvastatin	2400–3600 mg Dose dependent on initial LDL-C level	18–27 mg	12 weeks	TC ↓32 % LDL-C ↓42 % (*P*<0.001)	No difference in LDL↓ vs simvastatin 40 mg/day Significant reduction in TG (−29 vs −9 %) ATG—RYR and fish oil
[19]	31/31	3600 mg	9.8 mg	24 weeks	TC ↓21 % week 12 TC ↓15 % week 24 LDL-C ↓27 % week 12 (*P*<0.001) LDL-C ↓21 % week 24 (*P*=0.011)	No difference in incidence of myalgia; 93 % of patients with history of SAM tolerated RYR
[15]	2429/2441	1200 mg Xuezhikang	10–12.8 mg	4.5 years	TC ↓13 % LDL ↓20 % (*P*<0.001)	CCSPS 45 % relative ↓ in major coronary events (*P*<0.001)
[18]	21 RYR 22 Pravastatin	4800 mg	14.2 mg	12 weeks	TC ↓23 % LDL-C ↓ 30 % (NS)	No difference in LDL↓ vs pravastatin 40 mg/day; No difference in discontinuation rates due to myalgia
[13]	31/21	2 capsules	10 mg	8 weeks	TC ↓15 % LDL-C ↓22 % (*P*<0.001)	Belgian physicians and spouses
[14••]	38 Placebo 36 XZK 1.2 g 42 XZK 2.4 g	1200 mg	12 mg	12 weeks	non-HDL-C ↓24 % LDL-C ↓27 % (*P*<0.001)	Multicenter trial 53 % White, 37 % Asian Doubling dose resulted in additional LDL-C ↓4.6 %

RYR red yeast rice, *I* intervention group, *C* control group, *CCSPS* China coronary secondary prevention study, *CV* cardiovascular, *SAM* statin-associated myalgia, *ATG* alternative treatment group, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *non-HDL-C* non-high-density lipoprotein cholesterol, *TG* triglyceride, *XZK* Xuezhikang, *NS* not significant

[a] Total lovastatin dose includes the sum of monacolin K and its hydroxy acid form (monacolin KA)

two trials were conducted at a single site, and no serious side effects were reported. Overall, RYR significantly lowered total and LDL-C levels [−34 (95 % CI −28 to −40) mg/dL; $P<0.001$] compared with placebo, but its effect did not appear to be related to the dose, duration of therapy, or geographic location [17].

Tolerability in Patients with a History of Statin Intolerance

Three randomized and one observational trial looked at the tolerability of RYR in patients who discontinued or refused treatment with statins. Halbert et al. compared the tolerability of RYR (Sylvan Bioproducts, Kittanning, PA) with pravastatin in patients with a history of SAM [18]. Patients were eligible to participate if they discontinued use of at least one statin other than pravastatin due to SAM, although many had been rechallenged with other statins. The two primary outcome measures were the incidence of treatment cessation due to recurrent muscle pain and a validated daily pain severity score. Forty-three dyslipidemic patients were randomized to 2400 mg RYR or 20 mg pravastatin twice daily for 12 weeks. Both treatment groups reported low rates of recurrent myalgia, which were not significantly different (5 % in the RYR group and 9 % in the pravastatin group) and achieved similar LDL-C reduction (30 % in the RYR group and 27 % in the pravastatin group). In addition, the mean pain severity score did not significantly differ between the two groups. This study showed that RYR was as well tolerated as pravastatin in a population with a previous history of statin intolerance [18].

Becker et al. evaluated the efficacy and tolerability of the same RYR product (Sylvan Bioproducts, Kittanning, PA) in

lowering LDL-C in 62 patients from a community cardiology practice with dyslipidemia and a history of SAM to at least one statin [19]. All patients were asked to complete a self-administered validated questionnaire (Brief Pain Inventory Short Form) at baseline and at weeks 12 and 24, which assessed pain severity and its effect on the functions of daily living. CPK and liver enzymes were measured in all patients to assess safety. Patients were randomized to receive 1800 mg of RYR or placebo twice daily for 24 weeks and were enrolled in a weekly 3.5-h therapeutic lifestyle change program for 12 weeks. LDL-C levels were measured at baseline, at week 12 after the lifestyle program, and at week 24. The mean reduction in LDL-C from baseline was 27 % at week 12 and 21 % at week 24 for the RYR group and 6 and 9 % at weeks 12 and 24, respectively, for the placebo group. The secondary outcome measures including CPK, liver transaminase levels, and pain severity scores did not significantly differ between groups at week 12 or 24. Persistent intolerable myalgias developed in 7 % of the patients in the RYR group and 3 % in the placebo group, but their CPK levels were within normal limits [19].

The RYR product used in this study contained 1.02 mg monacolin K per 600 mg capsule, equivalent to a daily lovastatin dose of 6 mg. This is far less than a standard therapeutic dose, and the authors hypothesized it was likely below the threshold necessary to cause SAM [19]. RYR significantly decreased mean LDL-C levels at week 12 ($P<0.001$) and week 24 ($P=0.011$) compared with placebo and did not increase the incidence of myalgias. Thirty percent of the participants achieved an LDL-C less than 100 mg/dL [1]. This same group of investigators looked at the lipid-lowering effects of adding 1800 mg phytosterols in tablet form to RYR and found no additional benefit compared to placebo [20•]. These results are surprising because several studies looking at the use of plant stanols and sterols in combination with a statin medication have shown an additive effect of 10 % on average [21, 5].

A small, retrospective, observational study was performed involving 25 patients from a lipid clinic with a history of intolerance to lipid-lowering medications who were treated with RYR for more than 4 weeks. Patients were included if they experienced myalgia (68 %), gastrointestinal side effects (16 %), or elevated liver transaminase levels (8 %) with previous lipid-lowering therapy. Of the 17 patients with myalgias on statins, 53 % had intolerance to daily ezetimibe. Patients randomly selected a 1200 mg RYR supplement taken at bedtime, and CPK and liver transaminase levels were measured in addition to lipids [22].

Similar to that found in other studies, over-the-counter RYR significantly lowered LDL-C by 21 % ($P<0.001$) in this clinical population during 74±39 days of treatment. It was well tolerated by 92 % of the study participants, including 89 % of patients with a history of myalgia [22]. One patient developed myalgia, and another reported abdominal bloating. The highest posttreatment CPK level was 130 mg/dL, and alanine aminotransferase levels were initially elevated at two times the ULN in two patients, which persisted at follow-up [22].

Secondary Prevention Trials

The China Coronary Secondary Prevention Study (CCSPS) was the only randomized, double-blinded, placebo-controlled, multicentered study to demonstrate that RYR reduces cardiovascular (CV) risk [15]. This trial recruited 4870 Chinese patients with a history of myocardial infarction and moderate hypercholesterolemia. Patients were randomized to receive twice-daily treatment with 600 mg Xuezhikang (XZK) or placebo. Each 300 mg capsule of XZK contained 2.5 to 3.2 mg of monacolin K equivalent to a total daily lovastatin dose of 10 to 12.8 mg. The primary endpoint was a major coronary event that included nonfatal myocardial infarction and death from coronary heart disease (CHD). After 4.5 years, XZK was associated with a highly significant reduction in frequency of coronary events (10.4 % in the placebo vs 5.7 % in the XZK group) and a relative risk reduction of 45 % [10, 15]. Treatment with XZK also significantly decreased total mortality by 33 %, cardiovascular deaths by 30 %, and the need for coronary revascularization by 33 %. Total cholesterol and LDL-C levels decreased by 13 and 20 %, respectively, compared to baseline ($P<0.001$). Adverse effects were similar in both groups, and the XZK appeared to be well tolerated. A sub-study of elderly hypertensive patients in the same CCSPS cohort found that RYR was effective in lowering rates of coronary events and death from CHD compared with placebo [16].

Long-term treatment with XZK significantly reduced the recurrence of coronary events and total mortality in Chinese patients with average LDL-C levels. The results of the CCSPS showed a greater reduction in coronary events than those reported in statin-based outcome trials in Western populations and therefore should be interpreted with caution [23–25]. Additional trials are warranted to confirm these results in other populations

Table 2 Pros and cons of using RYR for lipid-lowering [1]

Pros	Cons
Potential alternative therapy, given under the supervision of an experienced health-care provider, for patients with intolerable statin-associated myalgia or patients who refuse statins in favor of a more "natural" approach	No government regulation and standardization
	Wide variability of active ingredients among available products
	Potential of toxic byproducts
	Lack of long-term safety data
May be effective in lowering LDL cholesterol 22–30 %	May be more expensive than generic statins
May reduce CV risk in patients with established coronary heart disease (although available evidence is very limited)	Lack of primary prevention data

with CHD [26]. Review of ClinicalTrials.gov revealed no ongoing outcomes trials.

Legal and Regulatory Status

In 1998, the US Food and Drug Administration (FDA) ruled that Cholestin, the RYR product used in Heber et al.'s study, was "an unapproved drug under the terms of the Federal, Food, Drug, and Cosmetic Act" because Cholestin contained lovastatin, the active ingredient in the prescription drug, Mevacor [1]. Since 2001, the FDA has required manufacturers to remove the monacolin K content from all RYR products, and it continues to be widely available to the public as an over-the-counter supplement. Some recently tested RYR products have been found to contain monacolin K in substantial amounts, and other products may contain little or none of this active ingredient [5]. To avoid violating FDA policy, many commercial RYR products do not disclose the monacolin content on the package label [1]. Therefore, consumers have no way of knowing how much active ingredient is actually present, leaving them unaware as to whether a particular RYR product is effective [27].

Clinical Implications

Public interest in the use of complementary and alternative medications, and skepticism regarding the benefits of available pharmacotherapy, may explain the increased use of RYR in the USA [1]. Compared to statin therapy, RYR is perceived as a "natural" product providing fewer side effects and fewer drug-drug interactions [4]. RYR may be an alternative for patients with a history of statin-related adverse effects. The incidence of SAM may be as high as 15 % [1]. Although an association with statin use is not always clear, muscle pain can undermine medication compliance [13]. Currently, the FDA does not regulate the manufacture of RYR products and as a result there is a lack of quality control and a wide variability of active ingredients [1, 5]. Gordon et al. [28] evaluated the RYR content in ten commercial preparations and found a 100-fold difference in the monacolin K content (0.10 to 10.09 mg) per capsule, although each capsule was labeled as "600 mg per capsule." Four of the preparations tested contained citrinin, a potential mycotoxin. Citrinin has been shown to cause kidney failure in animal models with a median lethal dose of 35 mg per kg [4, 5, 28]. Similar effects have not been proven in humans, and more studies are needed to clarify if levels detected are toxic [5, 28].

Summary

A growing number of studies have evaluated the effectiveness of RYR in lowering plasma lipids. RYR may have cholesterol-lowering ability because it contains monacolins with HMG CoA reductase activity and possibly other active compounds. Clinical trials have demonstrated significant total, non-HDL-C, and LDL-C lowering with RYR products as monotherapy and as part of a comprehensive preventive strategy. One randomized, placebo-controlled clinical trial demonstrated a reduction in cardiovascular events, but results must be interpreted with caution [15]. Well-powered, multicenter clinical trials, inclusive of Western populations, are needed to examine the efficacy and safety of RYR in the primary and secondary prevention of CHD.

Marketing RYR supplements, which contain more than trace amounts of monacolins, is prohibited in the USA. Monacolin K is identical to lovastatin, and therefore may present an increased risk of muscular and other side effects especially in patients with a history of SAM. Myopathy, hepatoxicity, and rhabdomyolysis have all been reported in patients taking RYR, as one would expect from any statin therapy [29]. For this reason, RYR should be taken under the guidance of a physician who will closely monitor its efficacy, safety, and tolerability [4]. Physicians should weigh the evidence before recommending RYR as an appropriate nonstatin therapy for their patients (Table 2). Until the FDA regulates all over-the-counter supplements, including RYR, physicians and patients should be wary regarding their use [4].

Compliance with Ethics Guidelines

Conflict of Interest Frances Burke declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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