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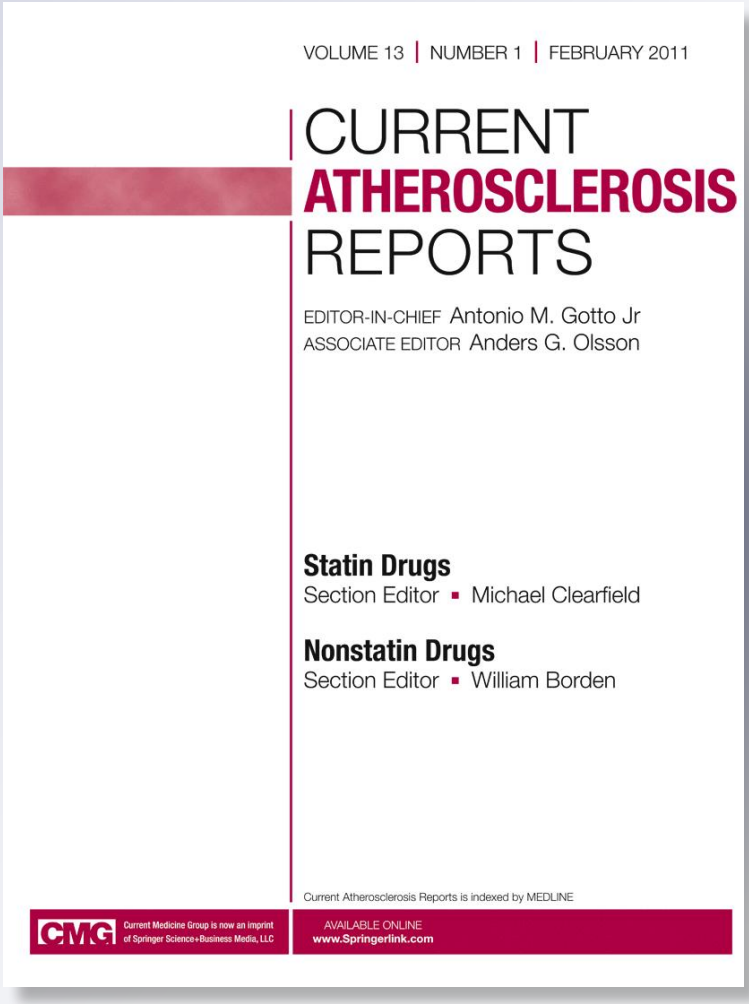

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The Role of Red Yeast Rice for the Physician

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Abstract Red yeast rice is an ancient Chinese dietary staple and medication used by millions of patients as an alternative therapy for hypercholesterolemia. In recent years, the use of red yeast rice has grown exponentially due to increased public interest in complementary and alternative medications and the publication of several randomized, controlled trials demonstrating its efficacy and safety in different populations. The most promising role for red yeast rice is as an alternative lipid-lowering therapy for patients who refuse to take statins because of philosophical reasons or patients who are unable to tolerate statin therapy due to statin-associated myalgias. However, there is limited government oversight of red yeast rice products, wide variability of active ingredients in available formulations, and the potential of toxic byproducts. Therefore, until red yeast rice products are regulated and standardized, physicians and patients should be cautious in recommending this promising alternative therapy for hyperlipidemia.

Keywords Red yeast rice · Supplements, complementary and alternative therapy · Alternative medications · Herbal medications · Hyperlipidemia · Hypercholesterolemia · Lipid-lowering · Statin-associated myalgias · Statin refusal · Statin intolerance

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Introduction

Millions of people take statins and other prescription lipid-lowering medications for the primary and secondary prevention of cardiovascular disease. However, many patients seek complementary and alternative therapies to lower lipid levels. One of the best studied alternative medications is red yeast rice, also known as red Koji or Hong Qu, a widely available herbal supplement made by culturing a yeast, *Monascus purpureus* on rice. It has been used in China for centuries to make rice wine, as a flavor enhancer and food colorant, and to "promote digestion and circulation" [1]. The first documented use of red yeast rice was during the Tang Dynasty in 800 AD, and Dutch scientists noted its use by local populations in Java in 1884 [2]. *Monascus purpureus,* named for its purple color, was isolated from red yeast rice in 1895 [3].

Over the past decade, there has been increased scientific interest in red yeast rice, resulting in several important research publications that have evaluated its efficacy and safety in treating hypercholesterolemia [4••, 5••, 6, 7•, 8]. These studies have demonstrated that red yeast rice may be especially useful for treating patients who refuse to take statins because of philosophical reasons or patients who are unable to tolerate statin therapy due to statin-associated myalgias (SAM) [4••, 5••, 9]. Because of these studies and increased usage of herbal medications by the American public, consumption of red yeast rice has increased dramatically over the past several years. In 2008, American consumers spent $20 million on this dietary supplement, an 80% increase compared with 2005 [10]. In this article, we review the chemistry of red yeast rice, studies evaluating its efficacy in different populations, safety issues and controversies, and future directions.

Production and Mechanism of Action

Red yeast rice is made by fermenting *Monascus purpureus* on rice, which is then dried, pulverized, and encapsulated. This process, when performed under sterile and controlled conditions, produces 14 monacolins, compounds that inhibit hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting step in hepatic cholesterol synthesis [11]. One of the monacolins produced is monacolin K (lovastatin or mevinolin) (Fig. 1), first synthesized by Endo [12] from Aspergillus in 1979 and later purified and marketed by Merck & Co. (Whitehouse Station, NJ) as Mevacor, the first HMG-CoA reductase inhibitor. There is no standardization of red yeast rice products, and each 600-mg capsule of red yeast rice may have between 0.1 and 10 mg of monacolin K, depending on the product tested [13].

Several clinical trials have documented red yeast rice's efficacy in lowering total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) [4••, 5••, 14]. Participants in these studies took the equivalent of only 5 to 6 mg/d of lovastatin, with resultant LDL-C reductions of 25% to 40%, equivalent to reductions seen with 20 to 40 mg/d of lovastatin in other trials [4••, 5••, 14]. Red yeast rice's potency is likely explained by the presence of monacolins other than monacolin K that may act synergistically to inhibit HMG-CoA reductase. Red yeast rice also contains fiber, sterols, isoflavones and isoflavone glycosides, and monounsaturated fatty acids, all of which may also contribute to its lipid-lowering effects [14].

Therapeutic Role of Red Yeast Rice

Lipid-lowering Efficacy

The first randomized controlled trial evaluating red yeast rice was published by Heber et al. [14] in 1999. Hyperlipidemic patients took 2.4 g/d (four 600-mg capsules) of a particular formulation of red yeast rice (Cholestin; Pharmanex, Simi, CA) or placebo and followed an American Heart Association Step I diet (<30% calories from fat, <10% calories from saturated fat, and <300 mg/d of cholesterol). After 12 weeks, the red yeast rice group achieved LDL-C lowering of −37.9 mg/dL (−22%) compared with −4.7 mg/dL (−1%) in patients who took placebo ($P<0.001$). In addition, mean TG levels were significantly lower in the red yeast rice group (124±44 mg/dL) compared with placebo (146± 47 mg/dL) ($P=0.05$). There were no serious adverse events in either group.

A second study randomized 79 patients with a mean LDL-C of 204 mg/dL to 600 mg of red yeast rice (Y & B Pharmaceuticals, Taipei, Taiwan) twice daily versus placebo and followed them for 8 weeks. At week 8, the red yeast rice group had significant decreases in TC (21.5%), LDL-C (−27.7%), and TG (−15.8%). Safety outcomes were comparable [15].

A recent study randomized 42 Norwegian patients to 2.4 g of red yeast rice (HypoCol; Wearnes Biotech and Medicals, Singapore) or placebo and followed them for 16 weeks. Patients were also instructed to follow a National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) Step One diet starting 4 weeks before the study. Total cholesterol (−15.5%) and LDL-C levels (−23%) decreased significantly in the red yeast rice compared with placebo after 16 weeks ($P<0.001$), with no serious adverse events. Diet and weight changes were equivalent in the two groups [6].

A meta-analysis by Liu et al. [16], published in 2004, examined the effectiveness and safety of several different proprietary red yeast rice formulations on lipid levels in patients with primary hyperlipidemia. Ninety-three randomized trials were included, with all but one (Heber et al.'s [14] trial) published in the Chinese literature. Overall, red yeast rice was noted to significantly lower TC, LDL-C, and TG, and raise HDL-C compared with placebo. Treatment duration ranged from 4 to 24 weeks (mean, 8 weeks). However, the authors noted that many of the included trials had low methodologic quality, with little mention of randomization process, sample size calculations, and the strong possibility of publication bias.

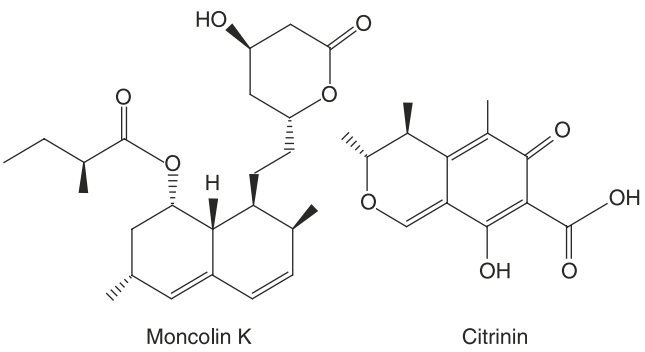

Fig. 1 Chemical structures of monacolin K (lovastatin) and citrinin

Secondary Prevention of Cardiovascular Disease

The only trial that has evaluated red yeast rice for the secondary prevention of cardiac disease was the Chinese Coronary Secondary Prevention Study (CCSPS), a multicenter, randomized, double-blind study that evaluated the efficacy of a proprietary Chinese red yeast rice product (Xuezhikang; WPU, Beijing, China) on the incidence of cardiovascular events in 4,870 Chinese patients with average LDL-C levels (mean LDL-C, 129 mg/dL) and a

history of myocardial infarction [8]. Patients were randomized in a 1:1 manner to red yeast rice or placebo. The primary endpoint was nonfatal myocardial infarction or death from coronary heart disease.

After 4.5 years, the primary endpoints were reached by 10.4% in the placebo group and 5.7% in the red yeast rice-treated group ($P<0.001$). Treatment with red yeast rice also significantly decreased total mortality by 33% ($P=0.0003$), cardiovascular deaths by 30% ($P=0.005$) and the need for coronary revascularization by 33% ($P=0.004$). Red yeast rice also produced significant reductions in total cholesterol (−10.9%; $P<0.001$), LDL-C (−17.6%; $P < 0.001$), and TG (−14.6%; $P < 0.001$), and an increase in HDL-C (4.2%; $P<0.001$) compared with placebo. No treatment-related serious adverse events or deaths were reported during the study period, and the red yeast rice was well tolerated by patients. Total adverse experiences and discontinuation of therapy were similar in both the red yeast rice and placebo groups.

A substudy of the CCSPS evaluated the incidence of cardiovascular events in 1,530 elderly (age ≥65 years) hypertensive patients with a history of prior myocardial infarction and showed that red yeast rice was effective in lowering rates of coronary events (−38.2% risk reduction; $P=0.0009$), and death from coronary heart disease (CHD) (−29.2%; $P=0.05$) when compared with placebo [17••]. Another sub-study examined the effect of red yeast rice on coronary events and mortality in 591 patients with type 2 diabetes and a history of myocardial infarction. It noted significant reductions in coronary events in the red yeast rice group (50.8% reduction; $P<0.001$), CHD deaths (44.1% reduction; $P<0.05$), and all-cause mortality (44.1% reduction; $P<0.01$) when compared to placebo [18].

Role in Patients Who Refuse to Take Statins

To date, we have published the only study that evaluated the use of red yeast rice in a hyperlipidemic population desiring an alternative approach to lipid lowering [5••]. The trial enrolled 74 patients with hyperlipidemia (mean LDL-C, 156 mg/dL) and randomized them to 40 mg/d of simvastatin and traditional diet and exercise counseling, or an alternative regimen consisting of 1.8 g of red yeast rice twice daily (LDL-X; N3 Oceanic, Palm, PA), 3 capsules of over-the-counter fish oil twice daily (ResQ 1250; N3 Oceanic, Palm, PA), and a 12-week, intensive lifestyle-modification program. After 12 weeks, LDL-C reductions were 42.4% in the alternative group and 39.6% in the simvastatin group. The alternative group demonstrated significant decreases in TG (−29% vs −9.3%; $P=0.003$) and weight (−5.5% vs −0.4%; $P<0.001$) compared with the simvastatin group. In the simvastatin group, three patients experienced myalgias and one had elevated liver enzymes. One patient in the alternative therapy group had an elevated creatine phosphokinase (CPK) that occurred after vigorous exercise and resolved after the study was completed.

Role in Patients with Statin-associated Myalgias

Red yeast rice may also have a role in the treatment of hyperlipidemic patients who develop SAMs. Although statins are generally well tolerated, SAMs are an important clinical issue, typically described as pain, cramps, stiffness, or weakness in the proximal limbs and trunk [19]. Symptoms may be generalized in 25% of patients, and tendon-associated pain may occur [20]. With SAM, there is no elevation in creatine phosphokinase levels, as there is with myositis or rhabdomyolysis (the rarest and most severe of statin myopathies). The incidence of SAMs may be as high as 15% [21, 22] and may affect approximately 1.3 million people in the United States [23]. It can occur anytime after initiation of statin use, with a range of 1 week to 48 months [24]. There is no consensus on optimal therapy for patients with SAM, but there are many approaches for treating hyperlipidemia in this population (Table 1).

Red yeast rice has been evaluated for patients with SAMs in three recent trials. The first, published in June, 2009, examined 62 statin-intolerant patients with an average LDL-C of 164 mg/dL [4••]. All participated in a 12-week lifestyle-modification program. Half were randomized to red yeast rice, 1,800 mg twice daily, (Sylvan Bioproducts, Kittaning, PA) and half to placebo. Serum lipids were drawn at baseline, 12 weeks, and 24 weeks. Mean percentage change in LDL-C in the red yeast rice group was −27.3% at week 12 and −21.3% at week 24. In the placebo group, mean percentage change was −5.7% at week 12 and −8.7% at week 24. Mean LDL-C differed significantly between the red yeast rice and placebo groups at week 12 ($P<0.001$) and week 24 ($P=0.011$). There were no significant differences between groups in TG or HDL-C levels. Adverse events were similar, with two of 29 patients in the red yeast rice group and one in 30 patients in the placebo groups discontinuing treatment due to persistent myalgias.

The second study enrolled 43 patients with SAMs and randomized them to red yeast rice, 2.4 g twice daily (Sylvan Bioproducts, Kittaning, PA) or pravastatin, 20 mg/d for 12 weeks. All participated in a 12-week lifestyle-modification program. LDL-C levels decreased 30% in the red yeast rice group and 27% in the pravastatin group, and there were no significant differences in other serum lipid levels between groups. One of 21 patients in the red yeast rice group and two of 22 patients in the pravastatin group stopped taking the supplement due to myalgias ($P=0.99$). There was no difference in muscle strength, as measured by a hand-held dynamometer, between groups.

The third study was a retrospective analysis of 1,400 charts of patients with a history of statin intolerance [9].

Table 1 Approach to patients with a history of statin-associated myalgias [4••, 19, 48]

1. Initiate or intensify therapeutic lifestyle changes (NCEP-ATP III guidelines) [49]
2. Add co-enzyme Q10 (ubiquinone) 200 mg/d to statin therapy [50]
3. Check Vitamin D levels and replete if 25-OH Vitamin D level <30 ng/mL [51]
4. Decrease statin dose
5. Discontinue statin and re-challenge at a later date
6. Reduce dose of statin and add fiber [52], niacin, phytosterols, or ezetimibe [53]
7. Use a different statin or statin-like supplement or change frequency of dosing
   a. Fluvastatin XL 80 mg/d [54]
   b. Rosuvastatin at a low dose (5 or 10 mg/d) [55]
   c. Rosuvastatin once weekly [56], twice weekly [57], or every other day [58]
   d. Atorvastatin 10–40 mg 3 times weekly [59]
   e. Red yeast rice 1,800–2,400 mg twice daily [4••, 7•, 9]
8. Pulse statin therapy [48]
9. Switch class of lipid-lowering agent
   a. Omega-3 fatty acids, 2–4 g/d of EPA + DHA, especially if triglycerides >150 mg/dL
   b. Niacin or niacin ER (Niaspan[a]), 500–2,000 mg/d
   c. Phytosterols, 2 g/d in divided doses with food
   d. Ezetimibe alone [53] or combine with colesevelam [60]
10. LDL-C apheresis in qualified patients [48]

NCEP-ATP III National Cholesterol Education Program Adult Treatment Panel III; *LDL-C* low-density lipoprotein cholesterol

[a] Abbott Laboratories, Abbott, IL

The authors found 17 patients with a history of SAMs who were treated with red yeast rice for at least 4 weeks. In those patients, total cholesterol decreased 13% ($P<0.001$) and LDL-C decreased 19% ($P<0.001$) during an unspecified duration of treatment. Most patients (89%) tolerated the treatment with no adverse effects.

Safety and Monitoring

Most studies noted similar rates of adverse events between red yeast rice and placebo [4••, 5••, 8], and one study found that the incidence of SAMs was similar between red yeast rice and pravastatin, with a possible trend toward fewer myalgias with red yeast rice [7•]. However, red yeast rice has been reported to have serious side effects, including myopathy [25–29], rhabdomyolysis (in a renal transplant patient) [30], hepatoxicity [30], and anaphylaxis [31]. Other adverse effects that have reported include loose stools, dizziness, headache, and rash [4•, 14]. Of note, red yeast rice should not be taken by pregnant women and patients who are allergic to yeast products.

A major safety issue with red yeast rice is its status as an unregulated, over-the-counter supplement. Although prescription and over-the-counter medications are subject to strict regulation and proof of efficacy and safety by the US Food and Drug Administration (FDA), dietary supplements are produced with very little government oversight and, generally, with little or no safety or efficacy data. We recently published a study that found that 12 widely-available red yeast rice products had marked variability of monacolin content and, presumably, very different lipid-lowering efficacy and potential for adverse events [13]. Similar results were published by Heber et al. [32] in 2001, who found striking variation of monacolin levels in nine commercial red yeast rice formulations. Because of limited oversight, the monacolin content of different red yeast rice products may even differ dramatically from batch to batch, or bottle to bottle. In addition, most red yeast rice products are imported from China, where there have been increased reports and concerns about tainted supplements and counterfeit medications [33]. Up to 80% of red yeast rice products may contain citrinin (Fig. 1), a mycotoxin produced by several *Monascus, penicillium* and Aspergillus species [32] that can cause kidney failure in animals [34] and may be found in human foods. Its effects on human health are unknown [35]. Thus, because of these issues that surround the production and oversight of red yeast rice, there are no reliable methods for physicians and patients to know the true contents of commercial red yeast rice products.

Finally, because red yeast rice does contain lovastatin and other monacolins with HMG-CoA reductase activity, it should be taken only under a physician's direction, and lipid levels, liver enzymes, and muscle symptoms should be followed frequently. It should also be used cautiously in patients with hepatic or renal impairment and patients taking potent CYP3A4 inhibitors.

Controversies

One of the most import controversies surrounding the use of red yeast rice is the question of whether it is a supplement or a drug. In May, 1998, the FDA ruled that

Cholestin, the red yeast rice product used in Heber et al.'s [14] trial, was not a dietary supplement but rather "an unapproved drug under the term of the Federal Food, Drug, and Cosmetic Act" [36]. Although Pharmanex, the producer of Cholestin, argued that their product was simply a traditional Chinese health food, the FDA based its decision on the fact Cholestin contained lovastatin, an active ingredient in the prescription drug Mevacor. Furthermore, the FDA cryptically stated that Cholestin was not a dietary supplement because lovastatin was not "marketed as a dietary supplement or food" before the FDA approved Mevacor as a drug [37].

The 10th US Circuit Court of Appeals upheld the ruling on July 24, 2000 [38, 39]. The United States District Court of the District of Utah affirmed the decision on March 30, 2001, and Pharmanex removed red yeast rice from Cholestin. Since that ruling, the FDA has asked several other herbal manufacturers to eliminate red yeast rice from their products, including Heart and Cholesterol (Mason Vitamins, Miami Lakes, FL) in 2001, Cholestrix (Sunburst Biorganics, Baldwin, NY), and Red yeast rice and Red yeast rice/Policosonal Complex (Swanson Health Care Products, Fargo, ND) in 2007, and Red yeast rice (Nature's Way Products, Springville, UT) in 2008.

Despite these actions by the FDA, red yeast rice remains widely available to the public as an over-the-counter product in pharmacies, supermarkets, health food stores, vitamin stores, and on the Internet, although companies are generally careful to not include information about levels of lovastatin (or other monacolins) on product labels. Many available red yeast rice products do not actually contain lovastatin and are thus legal, but presumably do not effectively reduce serum lipids. Products that do contain lovastatin are effective but illegal, per the Cholestin ruling. The controversy about whether red yeast rice is a supplement or a drug continues to this day, confusing both physicians and patients. Although Cholestin remains on the market in several countries, it does not contain any lovastatin.

This regulatory debate leads to another major controversy: should doctors recommend red yeast rice to their patients? Red yeast rice's quasi-legal and unregulated status has led several influential thinkers to caution against its use [20, 40–42]. Their arguments are based on several key points: 1) there are no primary prevention data for red yeast rice; 2) red yeast rice is not approved for lipid lowering and its ingredients are not standardized; 3) red yeast rice may contain toxic byproducts; 4) patients who take red yeast rice without a doctor's knowledge are potentially putting themselves in harm's way; and 5) red yeast rice is more expensive than generic statins. Most authors simply conclude that patients should take statins because of their proven efficacy, standardization, safety, and cost.

Although this argument is cogent, it should be balanced against the recent evidence that certain red yeast rice products, tested in a laboratory to quantify monacolin levels and to confirm the lack of toxins, have been proven to lower lipid levels in patients who desire a "natural" approach to lipid-lowering [5••] and patients with SAMs [4••, 7•]. We currently have no effective therapies for these patients and should therefore consider red yeast rice and other unconventional treatments that have been subjected to rigorous scientific testing to attempt to serve the needs of all of our patients. We believe that physicians should consider recommending a trial of red yeast rice to these particular patients, with close monitoring for efficacy and adverse effects.

A third controversy concerns the lack of a consensus definition for SAMs [43], leading to a debate about which patients should be characterized as having statin intolerance. Most patients with SAMs have myalgias, not myopathy (elevated creatine phosphokinase), and the diagnosis is usually made solely by history, with no objective data, such as a laboratory or radiologic test, to confirm it. Although many patients have true SAMs, with onset of pain or weakness when they take a statin and cessation of pain when the agent is withdrawn, there may be previously undiagnosed musculoskeletal or even psychological components to other patients' myalgias. Patients may fear the development of muscle pain because of anecdotes from friends or family, or from information they have read on the Internet [44]. Also, the preference of some patients for "natural products" could explain the better tolerability of red yeast rice [9].

As Philips [41] noted: "definitions of muscle toxicity are inadequate, as are the methods to measure it." In our studies, we have attempted to provide objective evidence of SAMs by using the Brief Pain Inventory—Short Form to evaluate the incidence and severity of myalgias [4••, 7•] and a hand-held dynamometer to evaluate muscle strength [7•].

Future Directions

Randomized trials have proven red yeast rice's efficacy in mild-to-moderate hyperlipidemia, with LDL-C lowering of about 22% to 30% in various populations [4••, 6, 7•, 14]. However, red yeast rice may not be sufficiently potent to treat patients with moderate or severe hyperlipidemia, or patients with diabetes mellitus (goal LDL-C <100 mg/dL) or coronary disease (goal LDL-C <70 mg/dL). In one of our studies, only 30% of patients were able to achieve an LDL-C of <100 mg/dL after taking red yeast rice for 24 weeks [4••]. Thus, future research will need to focus on combining red yeast rice with other "natural" therapies that have been

previously combined with statins to improve serum lipid levels, such as niacin [45], fish oil [46], and phytosterols [47]. This approach could potentially expand the use of red yeast rice for almost all patients who desire an alternative to prescription drugs. We are presently conducting the Phytosterols and Red Yeast Rice Instead of Statins (PARIS) trial, a double-blinded, controlled, year-long trial that began in November, 2009 and enrolled 168 hyperlipidemic patients who refused statin therapy or had a history of SAMs. Participants are taking red yeast rice and either phytosterols or placebo. Outcomes are LDL-C lowering, effects on other lipoproteins and high-sensitivity C-reactive protein, and safety and tolerability. Treatment allocation will be unblinded in November, 2010.

Other future trials evaluating red yeast rice need to enroll larger patient cohorts and follow them for a longer time period (≥1 year) to provide further efficacy and safety data. Future studies are also needed to assess cardiovascular outcomes for primary prevention of cardiovascular disease and provide additional efficacy data for secondary populations.

Finally, the lack of consistency of red yeast rice products between different manufacturers and the potential presence of citrinin in 30% to 80% of products [13, 32] is a major obstacle in recommending red yeast rice to patients. There remains an ongoing need for the FDA to assume the oversight and quality control of red yeast rice if it is to have an increased and widely accepted role in the treatment of hyperlipidemia.

Conclusions

Red yeast rice has been used in China for centuries for its medicinal properties and is an increasingly popular alternative lipid-lowering therapy. Studies over the past few years have demonstrated the efficacy and safety of different formulations of red yeast rice for secondary prevention of cardiovascular disease and as an alternative therapy for hyperlipidemia, especially in patients with statin-associated myalgias. However, there are complex regulatory and legal issues surrounding red yeast rice, with wide variability of monacolin levels in available formulations and the potential of toxic byproducts. In our practice, we advocate a trial of red yeast rice in patients who refuse statins or prefer a "natural" approach to pharmacotherapy, or in patients with a history of statin-associated myalgias, and provide close monitoring and follow-up. Until there is improved regulation and standardization of red yeast rice, its use will remain controversial, and physicians should remain cautious in recommending this promising alternative therapy for hyperlipidemia.

Disclosure Ram Y. Gordon reports no potential conflict of interest relevant to this article. David J. Becker reports no potential conflict of interest relevant to this article.

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- •• Of major importance

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