

Safety and Efficacy of Red Yeast Rice (*Monascus purpureus*) as an Alternative Therapy for Hyperlipidemia

Matthew Klimek, PharmD, Shan Wang, PharmD, and Adeleye Ogunkanmi, PharmD

Key words: red yeast rice, *Monascus purpureus*, hyperlipidemia, myopathy, dietary supplement, lovastatin

ABSTRACT

Red yeast rice is a Chinese fermented rice product (*Monascus purpureus*) that some have claimed improves blood circulation by decreasing cholesterol and triglyceride levels in humans. The supplement contains naturally occurring monacolin K, the active ingredient found in Merck's prescription agent lovastatin (Mevacor). Lovastatin is associated with various adverse effects such as myopathy and abnormal liver function test results, which can lead to serious problems if patients are not monitored and treated. The inclusion of lovastatin in red yeast rice and the lack of dietary supplement regulation by the FDA raise safety concerns for health care professionals as well as for patients. Studies have shown that red yeast rice products can be beneficial in lowering serum cholesterol levels, but they are not without risk. Furthermore, product uniformity, purity, labeling, and safety cannot be guaranteed.

BACKGROUND

Despite the increase in FDA-approved prescription medications, alternative therapies have become more prevalent in the U.S. About 42% of Americans use alternative medicine, and the demand for these therapies continues to grow.^{1,2} In 1997, patients paid approximately 629 million visits to alternative medicine practitioners, a rate that was 47% higher than in 1990. At approximately \$27 billion, total out-of-pocket expenditures for alternative therapies exceeded total out-of-pocket expenditures for all hospitalizations in the U.S.¹

Red yeast rice, a Chinese dietary supplement, has gained popularity because of its properties as a natural statin. This fermented rice product is used as a medicinal food to improve blood circulation by decreasing cholesterol and triglyceride levels.^{3,4} The supplement contains varying amounts of natural monacolins as a result of the different strains of *Monascus purpureus* used in fermentation.⁵ Monacolins lower cholesterol by inhibiting HMG-CoA (5-hydroxy-3-methylglutaryl-coenzyme A) reductase, the rate-limiting step for cholesterol synthesis in the liver. The primary monacolin in red yeast rice

is monacolin K, which has the same chemical structure as lovastatin. Although levels of lovastatin vary in the product, 2.4 g of red yeast rice daily may contain about 4.8 mg of lovastatin, or 0.2% of the total dose. Red yeast rice supplements may also contain isoflavonoids, monounsaturated fats, and sterols that help to reduce cholesterol levels even further.³

The natural inclusion of low-dose lovastatin raises concerns for patient safety. In 2007, the FDA warned consumers to avoid red yeast rice supplements promoted on the Internet (Red Yeast Rice, Red Yeast Rice/Policosonal Complex, and Cholestrix) to lower cholesterol because of the possibility of myopathy, leading to kidney impairment.⁶ The widespread use of evidence-based medicine has caused health care professionals to become skeptical about dietary supplement use. The lack of studies and regulations to ensure the safety of these products has the result of steering health care professionals away from herbal products and toward prescription medications that have been demonstrated to be safe and efficacious. Health care practitioners should become aware of herbal products that patients might be using in place of commonly prescribed medications. This article reviews the safety and effectiveness of red yeast rice as a "natural" alternative treatment to statins for hypercholesterolemia.

LITERATURE FINDINGS

Before performing a MEDLINE search, we identified the most appropriate search terms using the MeSH (medical subject headings) database provided by the National Library of Medicine (www.pubmed.gov). Instead of using this database to perform the search, we conducted a "text word" search (from 1966 to November 2008) using PubMed to include articles indexed for MEDLINE as well as those not yet indexed (those that do not yet have MeSH terms assigned).

When a relevant article was located, we reviewed the MeSH terms assigned to that article to identify other relevant search terms. To be as complete as possible, we did not use any limitations.

PubMed includes millions of citations from MEDLINE and other life science journals for biomedical articles. We reviewed the bibliographies of all relevant articles to identify any other pertinent articles that the previous searches might have missed. Our article includes some of the more provocative data about red yeast rice but might not include all available relevant literature.

Disclosure. The authors have no financial or commercial relationships to report in regard to this article.

Matthew Klimek and Adeleye Ogunkanmi are postdoctoral fellows at Rutgers University Ernest Mario School of Pharmacy in Piscataway, New Jersey. Shan Wang is a clinical pharmacist at Winthrop University Hospital in Mineola, New York.

Accepted for publication March 9, 2009

Red Yeast Rice for Hyperlipidemia

EFFICACY

Lu et al.⁷

Lu et al. conducted a randomized, double-blind, placebo-controlled clinical trial of 4,870 Chinese subjects over 4.5 years to evaluate the efficacy of XuezhiKang (XZK), an extract of cholestin and derived from fermented red yeast rice. The study medication consisted of 300-mg capsules of XZK. Each capsule contained 2.5 to 3.2 mg of lovastatin and a small amount of hydroxyl acid, ergosterol, and other components. To be included in the study, patients must have had a myocardial infarction (MI) within 60 months of enrollment.

Patients underwent a four-week initial period of a controlled diet beginning with the cessation of all lipid-lowering agents. At the end of four weeks, baseline lipid levels were measured. Baseline characteristics were similar for all treatment groups except for sex (3,986 men and 884 women).

Mean low-density lipoprotein-cholesterol (LDL-C) levels were 129 mg/dL in both groups at baseline. Patients treated with XZK showed a significant decrease in frequency of major coronary events such as nonfatal MI and death from coronary or cardiac causes when compared with those receiving placebo (-10.4% and -5.7%, respectively; $P < 0.001$). They also experienced a 33% decrease in the need for coronary revascularization compared with the placebo recipients ($P = 0.004$).

Within eight weeks after randomization, total cholesterol (-10.9%) and LDL-C (-17.6%) levels decreased significantly and were maintained over the duration of the study in the XZK-treated group ($P < 0.001$). The authors concluded that XZK demonstrated efficacy in decreasing cholesterol, recurrent coronary events, and mortality rates.

Lin et al.⁸

Lin and coworkers assessed the lipid-lowering effect and safety of *M. purpureus* in a randomized, double-blind, placebo-controlled study of 79 patients 23 to 65 years of age with hyperlipidemia. Subjects received *M. purpureus* 600 mg twice daily or placebo for eight weeks. The mean baseline LDL-C level was 203.9 mg/dL. At week eight, *M. purpureus* therapy significantly reduced concentrations of LDL-C by 27.7%, total cholesterol by 21.5%, triglycerides by 15.8%, and apolipoprotein B (apo-B) by 26%. High-density lipoprotein-C (HDL-C) and apolipoprotein A-I (apo A-I) levels were increased nonsignificantly by 0.9% and 3.4%, respectively.

Gheith et al.⁹

Gheith and colleagues compared the efficacy and safety of *M. purpureus* Went rice (red yeast rice) with fluvastatin (Lescol, Novartis) in the management of nephrotic dyslipidemia. The investigators conducted an open-label study of 72 patients with dyslipidemia secondary to idiopathic persistent nephrotic syndrome. Patients were randomly divided into three groups: 20 patients received *M. purpureus* Went rice 600 mg twice a day for one month, then 600 mg once daily; 30 patients were treated with fluvastatin 20 mg daily; and 22 controls group received no therapy.

The fluvastatin group had average total cholesterol readings of 436, 333, 313, and 302 mg/dL at baseline, three months, six months, and one year, respectively. Similar reductions were observed in the Went rice group, with cholesterol averages of 457

mg/dL at baseline, 408 mg/dL at three months, 283 mg/dL at six months, and 303 mg/dL at one year. A significant reduction in proteinuria was noted in the fluvastatin group (8.3 g/day at baseline vs. 2.4 g/day at one year) and in the Went rice group (8.6 g/day at baseline vs. 3.2 g/day at one year) but not in the control arm.

Compared with baseline evaluations, there was no clinical evidence of myopathy or neuropathy in patients who received statins or Went rice. The authors concluded that *M. purpureus* Went rice was a safe and effective strategy for treating nephrotic dyslipidemia.

Summary

In each of these studies, *M. purpureus* provided beneficial effects in hyperlipidemic patients⁷⁻⁹ and might have also positively affected cardiac outcomes.⁷ Studies like these give confidence to patients seeking alternative cholesterol-lowering therapies in place of more conventional statin therapies.

SAFETY

All three controlled trials (Lu, Lin, Gheith) showed that *M. purpureus* was well tolerated with few safety concerns.⁷⁻⁹ In the trial conducted by Lin et al.,⁸ none of the subjects receiving *M. purpureus* experienced alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine phosphokinase (CPK) measurements that were more than three times the upper limit of normal (ULN) at the fourth or eighth week. Gheith et al.⁹ also found no evidence of significant adverse effects in neuromuscular function associated with *M. purpureus*.

Despite these findings, published case reports show potential safety problems with the use of red yeast rice. The following case reports of myopathy and rhabdomyolysis illustrate these potential dangers.

Myopathy

Vercelli et al.¹⁰

A 76-year-old man with type-2 diabetes received statins for four years; 20 mg of simvastatin (Zocor, Merck) daily for two years, followed by 20 mg of atorvastatin (Lipitor, Pfizer) daily for two years. After four years of therapy, atorvastatin was discontinued upon patient complaints of generalized muscle weakness and serum creatinine kinase (CK) levels of 3,000 U/L. Six months later, generalized muscle weakness improved slightly, but CK levels climbed to 3,700 U/L.

An open quadriceps muscle biopsy revealed muscular atrophy. The patient then admitted that three months after discontinuing atorvastatin, he had begun using a product derived from red yeast rice as an alternative therapy to lower cholesterol. Red yeast rice was discontinued at this point. Muscle weakness improved and CK levels fell to 1,000 U/L three months after he stopped taking red yeast rice. The authors concluded that patients with statin-induced muscle damage should not use red yeast rice as a way to lower cholesterol.

Smith et al.⁴

Smith and colleagues described a case of symptomatic myopathy associated with the use of Chinese red yeast rice.⁴ A 50-year-old man visited his primary care physician, reporting joint pain and muscle weakness for two months. At pres-

Red Yeast Rice for Hyperlipidemia

entation, he had diffuse body aching, upper-extremity weakness, and lower-back stiffness along with a CK level of 358 U/L. He had no history of muscle diseases or problems. According to the patient, the only new medications in his regimen were ginseng, Chinese red yeast rice, and rofecoxib (Vioxx, Merck). The patient had started taking ginseng and Chinese red yeast rice four weeks before his symptoms developed and then started to take rofecoxib after the onset of symptoms. He was instructed to discontinue both of these products. At the three-week follow-up visit, his muscle weakness and joint pain resolved completely and the CK level fell to 179 U/L. Eight months later, the patient resumed taking Chinese red yeast rice, and his CK level increased again to 212 U/L.

Mueller¹¹

A case of symptomatic myopathy was attributed to red yeast rice in a 61-year-old woman with hyperlipidemia.¹¹ She was started on simvastatin 20 mg daily along with estradiol from a transdermal patch at a dose of 0.05 mg/week, aspirin 81 mg daily, and a multivitamin. The patient was otherwise in good health; vital signs and laboratory parameters were within normal limits. After four months of therapy, simvastatin was increased to 40 mg daily. At this point, the CK level was 189 U/L. Within one month, diffuse myalgia and an elevated CK level of 451 U/L were reported.

After simvastatin was discontinued, symptoms resolved and CK levels returned to 170 U/L. Soon afterward, the patient began using red yeast rice 600 mg twice daily as an alternative treatment. Three months later, diffuse myalgia returned and CK levels increased to 475 U/L. Red yeast rice was then discontinued; symptoms resolved, and CK levels decreased to 122 U/L. Like simvastatin, red yeast rice caused diffuse myalgia and elevated CK levels. After these products were discontinued, symptoms resolved soon thereafter.

Summary

Although the effects of red yeast rice are mild, the product can cause muscle pain and weakness similar to that associated with conventional statins. These events can become serious if the patient's intake is not monitored appropriately. Awareness of the previous two cases can help health care professionals understand the potential for myopathy when red yeast rice is used as a natural alternative to statins.

Rhabdomyolysis

Prasad et al.¹²

Prasad and coworkers reported on a 28-year-old stable renal transplant recipient who developed rhabdomyolysis after therapy with red yeast rice.¹² The patient experienced an asymptomatic elevation of CK to 1,050 IU/L; a second assessment showed a CK level of 2,600 IU/L. After questioning, the patient stated she had taken red yeast rice for the previous two months to lower cholesterol naturally. After she stopped taking the supplement, her CK levels fell to 600 IU/L within two weeks and she remained clinically asymptomatic.

The patient was also taking cyclosporine to prevent transplant rejection. Cyclosporine, a known cytochrome P450 3A4 inhibitor, most likely elevated red yeast rice serum concentrations by inhibiting its metabolism. It is important to note the

probable drug-herbal interaction between cyclosporine and red yeast rice. Cyclosporine is a commonly prescribed prescription medication, and taking concomitant red yeast rice can result in serious rhabdomyolysis.

Consistency and Content of Red Yeast Rice

Besides the adverse effects caused by *M. purpureus*, the composition of red yeast rice can cause patient harm if quality control is inadequate. Heber et al. conducted an analysis of nine proprietary Chinese red yeast rice dietary supplements: Cholesterex, Cholestene, Cholactive, Cholester-Reg, Beyond Cholesterol, Hongqu, Cholesterol Power, red yeast rice, and Cholestin.¹³ The authors of this study aimed (1) to determine whether the cholesterol-lowering effect of red yeast rice was consistent among all red yeast rice products and (2) to detect impurities in the product. They measured monacolin concentrations in each supplement along with citrinin, a nephrotoxic by-product of fermentation (Table 1). Citrinin, a dangerous nephrotoxin, was measured by radioimmunoassay and served as an indicator of potential danger as a result of its contents other than the active ingredients.

Results showed a wide range of monacolin K (0.15–3.37 mg) and monacolin L (less than 0.006–0.02 mg) content per capsule. Only one of the tested products included all 10 monacolin compounds that a quality red yeast rice product should contain. Citrinin was found at measurable concentrations in seven of nine preparations (0.47–64.7 mcg/capsule). The quality and contents varied between each product, indicating that not all red yeast rice products are equal. The authors concluded that standardized manufacturing practices and adequate labeling are needed to ensure the equivalence of active ingredients for efficacy and a low concentration of unwanted fermentation by-products to ensure safety.¹³

DISCUSSION

The efficacy of dietary supplements is usually questionable because of the lack of controlled clinical trials supporting their use. Two randomized, double-blind, placebo-controlled trials^{7,8} and an open-label trial⁹ demonstrated that red yeast rice might be effective in lowering LDL-C levels.

Lu et al. further demonstrated that red yeast rice might be able to reduce cardiac events and provide positive effects on cardiovascular outcomes in a fashion similar to that of prescription statin therapy.⁷ Although larger-scale trials are necessary to confirm these findings, red yeast rice seems promising in the treatment of hyperlipidemia. Such efficacy data influence patients to try natural remedies before using more common prescription drug therapies. The vast amount of data demonstrating the benefits of statin therapy in cardiovascular disease supports its continued use, but practitioners should be aware of alternative therapies being used by their patients.

Unlike prescription drugs, dietary supplements have not traditionally undergone extensive testing by the FDA. Without adequate testing, dietary supplements are not guaranteed to contain the quantity or quality of ingredients stated on the product label. As shown by Heber et al., red yeast rice is no exception.¹³ Each of the nine products tested had different monacolin levels. Supplements with a lower monacolin content would be less effective in lowering cholesterol.

Red Yeast Rice for Hyperlipidemia

Table 1 Contents of Monacolin and Citrinin in Chinese Red Yeast Rice Products

Red Yeast Rice Supplements	Monacolin K (mg per Capsule)	Monacolin L (mg per Capsule)	Citrinin (mcg per Capsule)
Cholestere ^a	1.35	<0.006	4.87
Cholestene ^b	2.87	<0.006	2.22
Cholactive ^c	1.80	<0.006	6.06
Cholester-Reg ^d	3.37	<0.006	3.23
Beyond Cholesterol ^e	0.15	0.02	No data available*
Hongqu ^f	2.86	<0.005	11.82
Cholesterol Power ^g	2.51	<0.007	0.47
Red Yeast Rice ^h	1.56	<0.006	64.7
Cholestin ⁱ	2.46	0.015	No data available*

* Limits of detectability = 0.04 mcg per capsule.

(a) Oralabs, Englewood, Colo.; (b) HPF, LLC, Hatboro, Pa.; (c) Herbscience, Windmill Health Products, West Caldwell, N.J.; (d) Nature's Sunshine, Provo, Utah; (e) TwinLab, Hauppauge, N.Y.; (f) Nature's Sunshine, Provo, Utah; (g) Nature's Herbs, Hauppauge, N.Y.; (h) Solaray, Park City, Utah; (i) Pharmanex, Brisbane, Calif.

Adapted with permission from Heber S, Audra L, Qing-Yi L, et al. *J Altern Complement Med* 2001;7(2):133-139. Copyright, Mary Ann Liebert Publishers, Inc.¹³

Seven of the tested samples contained citrinin, a mycotoxin produced by a variety of fungi in the production of foods intended for human consumption such as grain, cheese, and red pigments. Citrinin is a nephrotoxin in all animal species tested, but its acute toxicity varies.¹⁴ Citrinin is genotoxic at high concentrations in cultured human lymphocytes; therefore, its concentration in supplements should be minimal.¹⁵

Inconsistencies such as these led the FDA to require current good manufacturing practices (CGMPs) for dietary supplements.¹⁶ Final CGMPs were expected to become effective in June 2008 for large companies and are to be implemented in June 2009 for companies with fewer than 500 employees and in June 2010 for companies with fewer than 20 employees. Under this ruling, all domestic and foreign supplements must be processed in a consistent manner and to meet quality standards. To demonstrate quality and consistency, tests will be performed on all supplements to ensure their identity, purity, strength, and composition.

Statin drugs such as Merck's Mevacor (lovastatin) are associated with various side effects such as headache, dizziness, rash, upset stomach, and hepatic dysfunction. The most common adverse effect is muscle weakness, which can be a sign of more serious myopathy or, in rare cases, rhabdomyolysis.¹⁷ Double-blind, controlled clinical trials have demonstrated that red yeast rice is effective and well tolerated in a wide range of patients;^{7,8} however, case reports have linked it to muscular myopathy and rhabdomyolysis. In three cases described here,^{4,10,11} red yeast rice caused or exacerbated myopathy marked by elevated serum CK levels. Rhabdomyolysis, the most severe adverse effect associated with statins, occurred in a renal transplant patient who used red yeast rice while concomitantly taking cyclosporine.¹² Although the more reliable controlled trials showed no need for safety concerns, case reports warn of the possibility of adverse effects with wider use. These reports should not be ignored for patients who are taking red yeast rice as an alternative to common prescription statins.

Lovastatin as a prescription drug is contraindicated in pregnancy and is a Category X agent. This labeling is a main reason for the FDA's rejection of the application submitted by Merck to sell lovastatin over the counter.¹⁸ Red yeast rice, when used by pregnant women, places the fetus at unnecessary risk of central nervous system defects during the first trimester. Although red yeast rice contains a lower dose of lovastatin compared with the FDA-approved product, the risk posed may be similar.

CONCLUSION

Despite the growing interest in dietary supplements, red yeast rice (*M. purpureus*) is not recommended for patients with hypercholesterolemia. A lack of uniformity among products, the possibility of contamination, and the risk of severe adverse reactions pose a threat to individuals using this product. Overall, red yeast rice has not been shown to be a safe alternative to statins for patients with hyperlipidemia despite its demonstrated efficacy in controlled clinical trials. Physicians should be aware of its popularity as a "natural" way to lower serum cholesterol, and they should discuss the risks and benefits of this supplement with their patients.

REFERENCES

- Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. *JAMA* 1998;280(18):156-175.
- Kessler RC, Davis RB, Foster DF, et al. Long-term trends in the use of complementary and alternative medical therapies in the United States. *Ann Intern Med* 2001;135:262-268.
- Patrick L, Uzick M. Cardiovascular disease: C-reactive protein and the inflammatory disease paradigm: HMG-CoA reductase inhibitors, alpha-tocopherol, red yeast rice, and olive oil polyphenols: A review of literature. *Altern Med Rev* 2001;6(3):248-270.
- Smith DJ, Olive KE. Chinese red rice-induced myopathy. *South Med J* 2003;96(12):1265-1267.
- Liu J, Zhang J, Shi Y, et al. Chinese red yeast rice (*Monascus purpureus*) for primary hyperlipidemia: A meta-analysis of randomized controlled trials. *Chinese Med* 2006;1(4):1-13.

continued on page 327

Red Yeast Rice for Hyperlipidemia

continued from page 316

6. FDA warns consumers to avoid red yeast rice products promoted on Internet as treatments for high cholesterol. August 9, 2007. Available at: www.fda.gov/bbs/topics/NEWS/2007/NEW01678.html. Accessed March 3, 2008.
7. Lu Z, Kou W, Du B, et al. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol* 2008; 101(12):1689–1693.
8. Lin CC, Li TC, Lai MM. Efficacy and safety of *Monascus purpureus* Went rice in subjects with hyperlipidemia. *Eur J Endocrinol* 2005;153(5):679–686.
9. Gheith O, Sheashaa H, Abdelsalam M, et al. Efficacy and safety of *Monascus purpureus* Went rice in subjects with secondary hyperlipidemia. *Clin Exp Nephrol* 2008;12(3):189–194.
10. Vercelli L, Mongini T, Olivero N, et al. Chinese red rice depletes muscle coenzyme Q₁₀ and maintains muscle damage after discontinuation of statin treatment. *J Am Geriatr Soc* 2006;54(4):718–720.
11. Mueller PS. Symptomatic myopathy due to red yeast rice. *Ann Intern Med* 2006;145(6):474–475.
12. Prasad GV, Wong T, Meliton G, et al. Rhabdomyolysis due to red yeast rice (*Monascus purpureus*) in a renal transplant recipient. *Transplantation* 2002;74(8):1200–1201.
13. Heber S, Audra L, Qing-Yi L, et al. An analysis of nine propriety Chinese red yeast rice dietary supplements: Implications of variability in chemical profile and contents. *J Altern Complement Med* 2001;7(2):133–139.
14. Bennett JW, Klich M. Mycotoxins. *Clin Microbiol Rev* 2003;16(3): 497–516.
15. Donmez-Altuntas H, Dumlupinar G, Imamoglu Z, et al. Effects of the mycotoxin citrinin on micronucleus formation in a cytokinesis-block genotoxicity assay in cultured human lymphocytes. *J Applied Toxicol* 2007;27(4):337–341.
16. FDA. Dietary supplement current good manufacturing practices (CGMPs) and interim final rule (IFR) facts, 2007. Available at: www.cfsan.fda.gov/~dms/dscgmps6.html. Accessed August 27, 2007.
17. Mevacor (lovastatin), package insert. Updated September 2008. Merck & Co. Available at: www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf. Accessed September 2008.
18. Dyer O. FDA rejects sale of over the counter statins. *BMJ* 2005; 330(7484):164. ■