Abstract
With the growing popularity of red yeast rice (RYR) as a lipid-lowering agent, it is important to ensure that this dietary supplement is safe and effective. The objective of this review was to provide current evidence-based guidance on the use of RYR. PubMed was searched for RYR studies published 2009–2011. The review confirmed that RYR is safe and efficacious for dyslipidemia and has other potential cardioprotective applications.

Introduction
Xuezhikang, extract of red yeast rice (RYR), is a traditional Chinese medicine with multiple cardioprotective effects. RYR is a fermented product of rice on which red yeast (Monascus purpureus) has been grown. For centuries, Xuezhikang has been used as a medicinal food in China to promote "blood circulation." It is used to make rice wine and to give Peking duck its red color. RYR contains numerous statins, including lovastatin, and has been shown in clinical trials to improve lipid profiles. In 1999, articles began to be published about a RYR supplement tested in an American population at University of California, Los Angeles School of Medicine. A 2001 review appearing in Alternative Medicine Review brought more attention to RYR in the natural medicine community, and this author reviewed the use of RYR in a chapter of Integrative Cardiology, published in 2007. The focus of the present review is on several studies published in the past 2 years on RYR's safety and effectiveness for dyslipidemia and its potential cardioprotective applications for other cardiovascular conditions as well.

Background of RYR
Statin drugs are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that have been demonstrated to reduce lipid levels and risk for stroke and coronary events and mortality. They have also been shown to suppress the production of cholesterol and inflammatory cells in plaque, enhance endothelial function, reduce serum fibrinogen, and possibly reduce thrombosis. These benefits are not without the risk of some serious adverse effects: hepatotoxicity, myositis, and rhabdomyolysis. Hypothyroidism and hepatic and renal impairment increase the risk of myopathy.

Analysis of RYR has revealed 14 monacolins, which are HMG-CoA reductase inhibitors, in addition to sterols, isoflavones, glycerides, and monounsaturated fatty acids. A common misconception is based on the belief that, since lovastatin is one of the constituents in RYR, it is simply equivalent to taking lovastatin. However, the effect of RYR on cholesterol concentration cannot be explained by its constituent monacolin K alone (lovastatin), but rather is the combined benefit of monacolins and other substances in RYR.

The potent effect of statins on cholesterol biosynthesis is not specific and results in parallel inhibition of several other end products, such as nonsterol isoprenoid end products, including coenzyme Q10 (CoQ10) and dolichol. The CoQ10-lowering effect of statins and its compensation by administration of CoQ10 were described 20 years ago and since then have been confirmed in numerous studies of animals and humans. CoQ10 is involved in the stabilization of cell membranes and is a potent scavenger of reactive oxygen species, preventing oxidative injury to DNA, lipids, proteins, and other molecules. This action retards or prevents the development of many cardiovascular and possibly neoplastic and neurodegenerative disease states. In some patients, statin-associated myopathy is due to an inability of myocytes to efficiently use respiratory pathways to produce ATP. Therefore, reduced levels of CoQ10 in these individuals who lack alternate pathways for ATP synthesis results in myopathy. The high concentration of CoQ10 in cardiac muscle is also adversely affected in some patients taking statins and may predispose an individual to congestive heart failure and cardiomyopathy.

Despite numerous clinical trials documenting a relatively good safety profile, side effects resulting from treatment with statins occur not infrequently. Some of the adverse reactions—myalgia; myopathies; rhabdomyolysis; gastrointestinal symptoms, including hepatic injury; and the initiation or accelerated
progression of cataracts and neoplasia—could be a direct or indirect consequence of the CoQ10-deficiency state associated with statin treatment. CoQ10 supplementation should be considered during extended therapy with statins to support cellular bioenergetic demands.¹¹

**Dosage and practical considerations**

The therapeutic dosage of RYR is 1,200–4,800 mg daily. As with statin therapy, the lower dosage is sufficient for many patients, and higher dosages can be reserved for those whose lipid profiles do not adequately respond at the lower dose. Monacolins in RYR are light-sensitive and thermal-sensitive; therefore RYR should be stored in a cool place and protected from light.¹² Administration of CoQ10, 50 mg daily, is reasonable to use with RYR to prevent the theoretical CoQ10 deficiency that could occur. Niacin has been reported to increase the efficacy of statins,¹³ and there is no reason to suspect that the same would not be true in combination with RYR. A dosage of 100 mg niacin daily has been used in the author’s practice for this purpose. A small study found that in 10 of 12 patients with statin-induced myopathy unresponsive to CoQ10 supplementation, creatine monohydrate, 5 grams twice daily, was effective in providing tolerance to statins.¹⁴ Creatine supplementation should be limited to those with normal renal function.

It remains unlikely, though unclear whether the lipid-lowering effect of RYR is due solely to the monacolin K content, or if other monacolins, sterols, and isoflavones contribute. The monacolin K content in RYR, although variable, does not come close to approaching the therapeutic dosages of lovastatin (20–40 mg daily). The lovastatin content of RYR, depending on the strain and manufacturer, is generally around 0.2 percent of total product.³ At a daily dosage of 1,200 mg of RYR, the lovastatin dosage would be 2.4 mg.

**Adverse reactions to RYR**

With the wide use of RYR over the past 20 years, safety concerns appear much less prevalent than for statin drugs. One case report exists of acute hepatitis associated with a RYR-containing product.¹⁵ A 63-year-old woman presented with severe hypertransaminasemia that had developed progressively over a few weeks. For 6 months she had been taking Equisterol, an over-the-counter lipid-lowering product containing guggulsterol and RYR extract. The product had been prescribed for hypercholesterolemia because the patient had developed hepatotoxicity while on lovastatin. Liver biopsy revealed severe lobular necroinflammatory changes with an eosinophilic infiltrate. The episode was regarded as an adverse drug reaction after exclusion of other possible causes of acute liver disease and the prompt normalization of liver function tests after Equisterol had been discontinued.

Patients for whom dietary modification, exercise, and stress management have been unsuccessful, or who are statin-intolerant or philosophically opposed to statins, may benefit from RYR.

Another case report mentions an adverse drug-nutrient interaction between cyclosporine and a RYR-containing preparation.¹⁶

Citrinin is a nephrotoxin found in some sources of RYR. Gordon et al sent 12 commercial RYR products out for analysis and found that citrinin was present in one-third of the products tested.⁸ It is important to use only RYR that is certified citrinin-free.

**Review of recent studies of RYR (2009–2011)**

A review published in the July-August 2011 Canadian Journal of Cardiology included 136 meta-analyses and randomized controlled trials of lipid-lowering diets and dietary supplements and concluded that RYR, along with green tea and red wine, could be “considered for improvement of the lipid profile.”¹⁷ The authors state that omega-3 fatty acid supplementation “can be recommended fully.” These findings seem to reflect the “level of evidence” more than the level of efficacy, as RYR is much more potent in correcting dyslipidemia than green tea, red wine, and omega-3 fatty acids. Becker and Gordon et al published results in the *Annals of...*
Becker and Gordon, in collaboration with another group, published a study in the American Journal of Cardiology in January 2010 on the tolerability of RYR 2,400 mg twice daily versus pravastatin 20 mg twice daily for 12 weeks in statin-intolerant patients who were simultaneously enrolled in a therapeutic lifestyle change program. The LDL cholesterol decreased 30% in the RYR group and 27% in the pravastatin group.

Gordon et al published another article in the Archives of Internal Medicine in October 2010 on the variability of monacolin levels in commercial RYR products. They note that RYR contains 14 active monocolins that inhibit cholesterol synthesis. They had ConsumerLab send 12 commercial RYR products out for analysis and found that total monocolins varied from 0.31 to 11.15 mg/capsule and monacolin K (lovastatin) varied from 0.10 to 10.09 mg/capsule. Citrinin was present in one-third of the products tested.

Another review article published in February 2011 by Becker and Gordon concluded that RYR was a promising therapy for patients who object to statins on a philosophical basis or who have had statin-induced myopathy. They warn, however, that RYR products carry the risk of toxic levels of citrinin, and that until they are standardized, they should be used with caution.

A group of researchers reported in the American Journal of Cardiology in March 2010 that a review of 25 patients with myalgias, gastrointestinal intolerance, and/or elevated alanine aminotransferase levels with previous use of other lipid-lowering agents who then took RYR had a decrease in LDL cholesterol of 21% and tolerated the treatment well. Abd and Jacobson from Emory University School of Medicine reviewed statin-induced myopathy, and their findings were published in May 2011. Noting that observational studies estimate 10–15% of statin users develop myopathy, they reviewed the clinical features, risk factors, and mechanisms and proposed an evidence-based algorithm for statin-intolerant patients that was both patient-related and drug-related, including the option of RYR.

In addition to lipid-lowering, RYR has been investigated for other cardioprotective effects. Several Western population studies have showed that statins may help reduce blood pressure; however, a recent trial or RYR found that it did not show any such benefit. The Chinese Coronary Secondary Prevention Study looked at 2,704 hypertensive patients with previous myocardial infarction who were randomized to RYR or placebo for an average of 4.5 years. In their analysis, there was no significant antihypertensive effect of RYR on blood pressure in this high-risk group.

No medical interventions for abdominal aortic aneurysm (AAA) have been discovered, and regular monitoring has been the only option prior to surgical correction. In July 2011, a study was published in the Journal of Nutritional Biochemistry showing that RYR suppressed angiotensin II–induced AAA in mice and may have preventive potential for patients with AAA.

Li et al showed that RYR in rats inhibited tissue factor and hypercoagulable state through suppressing nicotinamide adenine dinucleotide phosphate (NADP) oxidase and extracellular signal-regulated kinase activation. They also showed that RYR was more potent than lovastatin in inhibiting NADP oxidase activation, and that RYR significantly reduced blood coagulation activation in high cholesterol diet–induced atherosclerotic rats.

Conclusion
In conclusion, the evidence for the safety and efficacy of RYR in dyslipidemia continues to be confirmed. Patients for whom dietary modification, exercise, and stress management have been unsuccessful, or who are statin-intolerant or philosophically opposed to statins, may benefit from RYR. Although there is no evidence that RYR lowers blood pressure, animal studies suggest it may be beneficial for patients with abdominal aortic aneurysm and hypercoagulable states.

References
10. Ibid.

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