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Review of red yeast rice content and current Food and Drug Administration oversight

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BACKGROUND: Red yeast rice (RYR) is a commonly used dietary supplement for the management of dyslipidemia. In 2007, the Food and Drug Administration (FDA) issued a consumer warning to avoid RYR products because they may contain unauthorized drug (lovastatin) and also implemented Current Good Manufacturing Practices (CGMP) requiring that proper controls be in place by dietary supplement companies to ensure products are manufactured and processed in a consistent manner and produce high-quality products that are not adulterated with impurities or contaminants and are accurately labeled.

OBJECTIVE: To assess the FDA oversight of companies manufacturing RYR products and review the labeled content of available RYR products.

METHODS: The FDA was audited through the Freedom of Information Act, we requested answers to a series of questions concerning their oversight of companies manufacturing RYR products. The labeled content of each RYR product listed in the Natural Medicines Comprehensive Database (NMCD) was tabulated and summarized. Statin-related product warnings and if product certification and verification by an independent laboratory had been performed were documented.

RESULTS: The FDA had no information on the number of RYR manufacturers and their compliance with CGMP regulations. A total of 101 products containing RYR were reviewed. No product could be confirmed as passing any independent laboratory verification testing. Nearly one-half (42.6%) of the RYR product labels contained statin-related warnings (ie, potential for muscle pain or weakness, etc).

CONCLUSION: Currently, the FDA is not regulating manufacturers of RYR products and as a result, many of these products may contain monacolin K and toxins such as citrinin.

The use of red yeast rice (RYR) has become very common as an alternative to statin therapies. Available as a dietary supplement, this therapy has been reported to be tolerated in patients who develop statin-associated myalgia.[1,2] The use of this product has grown by nearly 80% from 2005 to 2008 in the United States, with sales of $20 million reported in 2008.[3] The increase in use may be attributed to a number of factors, including the population's perception of RYR as being a "natural" therapy compared to a statin, a perceived better side-effect profile with regards to myalgia, and lack of drug-drug interactions.

RYR is produced by the red yeast (*Monascus purpureus*) that is grown on white polished rice. It has been widely

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used in the Chinese culture as a food preservative, food colorant, and to make rice wine. The fermentation of Chinese RYR produces a family of monacolins. Monacolin K, one of the produced monacolins from RYR, is the same substance that is synthetically isolated from *Aspergillus terreus* and Food and Drug Administration (FDA) approved as lovastatin (Mevacor; Merck, Whitehouse Station, NJ), an inhibitor of hydroxymethylglutaryl-coenzyme A reductase and cholesterol synthesis.[4] In addition to monacolin K, there are other monacolins and related products, including monacolins J, L, and X and dihydromonacolin L, monacolin M, and dihydromevinolin, known as secondary metabolites and have been isolated from *Monascus* species grown in liquid culture. Polyketides, polyketide pigments, and saturated fatty acids have also been reported to have been isolated from RYR. The process of fermentation of RYR can largely impact the byproducts. One byproduct worth mentioning, citrin, is a mycotoxin produced by numerous Penicillium and Aspergillus species. Citrinin has been shown to be nephrotoxic in animals with a reported median lethal dose (LD_{50}) of 35 mg/kg.[5] Also citrinin in food colorants has been shown to be mutagenic at concentrations between 0.2 and 1.7 μg/g.[6]

Many studies have been published in which investigators reported the effect of different RYR preparations on the lipid profile. A meta-analysis of previous controlled trials summarized the beneficial effects of lipid modifications and safety of RYR preparations for patients with primary hyperlipidemia. Trials were included with RYR as a dietary supplement in forms of cholestin 2.4 g/day, Xuezhikang 1.2 g/day, and Zhibituo 3.15 g/day (corresponding to 5 mg, 10 mg and 9 mg of lovastatin, respectively) which were compared with placebo, no treatment, statins, or other lipid-lowering agents with a median duration of 8 weeks. This review reported, when compared with placebo, that RYR produced a significant reduction of serum total cholesterol, triglyceride levels, and low-density lipoprotein cholesterol and a significant increase in high-density lipoprotein cholesterol. In addition, the lipid modification was reported to be similar when compared with statins (at simvastatin 10−20 mg/day, pravastatin 10 mg/day, lovastatin 20 mg/day, atorvastatin 10 mg/day, and fluvastatin 20 mg/day). The majority of the clinical trials mentioned in this review did have flaws in terms of insufficient reporting of methods, patient allocation sequence, allocation concealment, and double blinding. In addition, all studies except one were published in China with unusually high reports of positive results.[7]

A prospective controlled trial studied the efficacy of lipid lowering and reduction of cardiovascular events in 4870 Chinese patients with previous documented myocardial infarction using RYR as Xuezhikang 300 mg/day (2.5-3.2 mg/capsule of lovastatin, a small quantity of lovastatin hydroxy acid, ergosterol, and other components) for an average of 4.5 years. The study showed significant reduction in major coronary events (nonfatal myocardial infarction and death from coronary heart disease) with reported absolute and relative decreases of 4.7% and 45%, respectively. Also, cardiovascular and total mortality was shown to be significantly reduced (30% and 33%, respectively). No safety data was reported in this study.[8] The authors in this study commented that "future use of this product will depend on the separation, identification, characterization, and development of a carefully formulated preparation of RYR. Additional studies of its properties and therapeutic potential are necessary."

The regulations that are applied to the dietary and herbal supplements are very limited compared to prescription and even over-the-counter medications. On the basis of the definition of dietary supplement, food supplement, or nutritional supplement that is intended to supplement the diet and provide nutrients,[9] these supplements are regulated by the FDA as a category of food and not as drugs. These supplements do not require assessment of the risks and benefits before they enter into the market. On June 25, 2007, the FDA published dietary supplement Current Good Manufacturing Practices (CGMP), which require that proper controls be in place by dietary supplement companies to ensure products are manufactured and processed in a consistent manner. The CGMP also requires companies produce high-quality products that are not adulterated with impurities or contaminants and that they are accurately labeled.[10]

On August 9, 2007, the FDA issued a consumer warning to avoid RYR products promoted as treatment for high cholesterol because they may contain unauthorized drugs. However, the assumption is that the FDA has the appropriate resources to enforce these regulations. Certainly, the popularity of taking RYR as an alternative to a statin, because of public perception regarding the use of "natural" products to possibly lower the cost of therapy[11] or avoid statin-associated myalgia,[1] draws the attention to the safety and efficacy of this dietary supplement. Standardization of the production of RYR is of great importance because, as mentioned previously, the preparation method can highly affect the formation of unwanted byproducts, particularly the nephrotoxic citrinin and the amount of active compounds of monacolins. In a recent study published in 2010, 3 years after the FDA warning to avoid RYR products, the authors tested 12 commercially available 600 mg RYR products, all containing monacolins ranging from 0.31 to 11.15 mg per capsule. The study reported four of the 12 products had elevated levels of citrinin ranging 24 to 189 parts per million.[12] An earlier study analyzed nine commercially available RYR products and reported total monacolin content varied from 0% to 0.58% w/w and citrinin was found in seven of nine preparations.[13]

Adverse events from dietary supplements are not frequently reported to the FDA, as is suggested by the low rate of 1% of all adverse events.[14] One study surveyed 2743 participants and whereas 73% of them were users of dietary supplements, only 4% among those reported at least one adverse event during the past twelve months. The adverse