Red yeast rice preparations: are they suitable substitutions for statins?

Carlos A. Dujovne, MD, Fellow NLA, Certified Clinical Lipidologist

PII: S0002-9343(17)30591-0
DOI: 10.1016/j.amjmed.2017.05.013
Reference: AJM 14116

To appear in: The American Journal of Medicine

Received Date: 26 April 2017
Revised Date: 6 May 2017
Accepted Date: 8 May 2017

Please cite this article as: Dujovne CA, Red yeast rice preparations: are they suitable substitutions for statins?, The American Journal of Medicine (2017), doi: 10.1016/j.amjmed.2017.05.013.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Red yeast rice preparations: are they suitable substitutions for statins?
Running Head: Red rice for statin intolerance

Carlos A. Dujovne, MD, Fellow NLA, Certified Clinical Lipidologist
Fr. Professorships of Medicine and Clinical Pharmacology, University of Kansas, and Medicine (Cardiology), Oregon Health and Sciences University

1920 SW River Drive, Portland, Oregon 97201 * (913) 238-1715
cadujovneconsulting@me.com
http://www.dujovneclinpharmacoltotoxicol.org

Keywords: Nutraceuticals, Red yeast rice, Lovastatin, Dyslipidemia, Statin Side Effects.

Word count (abstract): 250
Word count (text): 1404

As the sole author, I had access to the data and a single role in writing the manuscript.
Abstract

Red yeast rice, a commercially available food supplement known to reduce serum cholesterol, has been repeatedly advocated as alternative therapy for hypercholesterolemic patients that refuse statins, cannot tolerate statin therapy’s side effects, or request a “naturopathic” medicine.

Red yeast rice contains a fungus (*Monascus purpureus*), which was utilized in the original production of lovastatin (Mevacor™), the first marketed pharmaceutical statin, and is chemically identical to such product. Their identical properties account for the similarity in therapeutic and side effects of red yeast rice and lovastatin.

The red yeast rice ingredient that blocks cholesterol production is monacolin K. Since red yeast rice preparations have large variability in monacolin K content, predicting or understanding dose-related efficacy and side-effect risks of red yeast rice is practically impossible. The lipid-regulating potency of red yeast rice in commercial preparations was found extensively different according to the number and/or concentration of monacolin K they possess. Furthermore, more than one type of monacolins were found in different preparations (or batches) of red yeast rice. Other ingredients found in red yeast rice are also known to be potentially toxic.

The FDA issued warnings to consumers in 2007 and in 2013 against taking red yeast rice products due to the lack of assurance regarding its efficacy, safety, and lack of standardized preparation methods.

This article discusses my clinical trial results with red yeast rice, reviews the literature on its therapeutic and side effects, and discusses why red yeast rice is not an acceptable substitution to statins.
Background

Red yeast rice is known to reduce serum LDL and total cholesterol levels. It has been repeatedly advocated as alternative therapy for statins (1,2,3).

Monascus purpureus was utilized in the original production of lovastatin, the first marketed pharmaceutical statin (4,5). The lipid-regulating component of red yeast rice, monacolin K, is chemically identical to lovastatin. The identical properties account for the similarity in therapeutic and side effects of red yeast rice and lovastatin.

Objective

This presentation reviews red yeast rice’s properties, my clinical experiences and others’ clinical experiences which support the pitfalls of using this preparation in clinical practice.

Methods

A thorough literature search was conducted using online databases in addition to print publications. Controlled clinical trials of red yeast rice, conducted worldwide, in all languages, were used to contribute to the content of this paper. This paper is intended to review the efficacy and side effects noted within the red yeast rice clinical trials.

Reviews of Efficacy, Safety & Side-effects of Red Yeast Rice

Monacolins block the production of cholesterol. Since red yeast rice preparations rarely declare their monacolin K content, understanding dose-related efficacy and side-effect risks in red yeast rice is practically impossible.
Statins may cause muscle injury with symptoms of increasing severity e.g. weakness, soreness and cramps, which can lead to kidney damage and renal failure. This is why statins are “by prescription only” in the United States - with recommendations to schedule safety tests on a regular basis.

Red yeast rice has been reported to occasionally have the same serious side effects as statins including myopathy, rhabdomyolysis, and hepatotoxicity. To complicate matters further, different batches of red yeast rice crops may contain citrinin and additional toxic chemicals if they are grown with insecticides and/or pesticides.

Up to 80% of red yeast rice products were found to contain high levels of the nephrotoxic mycotoxin citrinin. Gordon, et al, tested for citrinin levels in 12 commercial red yeast rice preparations; they found a 0-119 ppm range in citrinin content (6). In patients receiving red yeast rice, the potential nephrotoxicity by citrinin can lead to renal failure (7).

It would be ideal to perform controlled clinical trials with several commercial red yeast rice products. However, those trials would be futile and un-interpretable until the FDA conducts inspection and issues rules on standardization of red yeast rice’s preparation products.

The lipid-regulating potency of red yeast rice in commercial preparations could be extensively different according to the number and/or concentration of lovastatin-like monacolin K they possess. More than one monacolins have been found in different preparations (or batches) of red yeast rice. Farmers of red rice and producers of red yeast rice are likely to be unable to ensure any particular efficacy or safety of their particular crop or brand. Some suppliers were suspected of "spiking" red yeast rice preparations with lovastatin - the currently synthetic drug. One analysis reported several red yeast rice products as being almost entirely monacolin K -
which was speculated could only occur if the drug lovastatin had been added - rather than the expected variability of monacolin concentration.

Gordon, et al, evaluated monacolin levels in 12 commercial red yeast rice preparations. They found up to an 11-fold difference in the concentration of monacolin K among red yeast rice preparations (6).

**Pharmaceutical Regulatory Issues**

Red yeast rice is a yeast extracted from red rice; the extraction methods are not standardized. The FDA had no information about the number of red yeast rice manufacturers or their compliance with their current good manufacturing practice (CGMP) regulations. The FDA issued warnings to consumers in 2007 and in 2013 not to take red yeast rice products (8).

As stated by Childress, et al, and Becker, et al, a total of 101 and 12 products respectively containing red yeast rice were reviewed (2,9). They noted: a) no product could be confirmed as passing independent laboratory verification testing, b) 42.6% of red yeast rice product labels contained statin-related warnings (i.e, muscle pain, weakness, etc) (9), c) many products avoid FDA restrictions by declaring no monacolin content, d) labels and websites said no more than "fermented according to traditional Asian methods" or "similar to that used in culinary applications", e) labeling often says nothing about efficacy on cholesterol levels, and f) if they do not claim to contain lovastatin or to lower cholesterol, they are not subject to FDA regulations.

There was no information regarding absence, presence and/or concentration of monacolin K. They confirmed that the monacolin content of red yeast rice dietary supplements varies over a wide range, with some containing negligible amounts and types of monacolins and others containing several monacolins at various concentrations.
The use of red yeast rice in patients with statin intolerance has been advocated based on trials finding no replication of myositis after red yeast rice administration to such patients (9). This conclusion disregards the frequent occurrence of no replication of myositis in 11-70% of patients after challenge with the same statin which caused the myositis; these data were also derived from controlled clinical trials. (10)

Despite multiple reports of relatively satisfactory efficacy and safety of red yeast rice preparations (9,11), over-the-counter preparations are not as standardized and pure as the preparation of lovastatin made by reputable pharmaceutical companies. Therefore, it will be possible that some, if not all, red yeast rice preparations will have issues of unpredictable therapeutic efficacy and/or side effects. Since differences in composition of red yeast rice were found among such products made in the USA, (6) the differences might be equal or larger in products from outside the USA.

*My experience with lovastatin used under placebo-controlled clinical trials*

Before red yeast rice preparations existed in the market, my lipid research clinic at the University of Kansas was one of the sites for the largest multicenter placebo controlled phase IV study (12) with Lovastatin (Mevacor, TM). Because of the above precedent, we were commissioned by a Chinese producer of red yeast rice to perform a clinical trial use of red yeast rice in patients with hypercholesterolemia. This sponsor intended to obtain FDA approval to sell red yeast rice supplement as an OTC naturopathic medicine. The study was an informed-consent, double-blind placebo-controlled in 80 patients, half of them on a 600 mg red yeast rice capsule and half of them on identical-looking placebo capsules. The trial was approved by the University of Kansas IRB (data not published due to its non-proprietary nature).
Results

The efficacy and side effects results were similar to those of my previous study (12) with the lovastatin 20-40 mg doses’ preparation from Merck (Mevacor). However, the FDA had justifiable concerns regarding the reproducibility of results with unregulated red yeast rice preparations in general, as they existed or could become part of the OTC market. For this reason, approval was denied.

Discussion and Conclusions

There are many publications attesting to the LDL-lowering properties of red yeast rice preparations. Epidemiological data of areas in China where red rice consumption is prevalent indicate lower incidence of atherosclerotic cardiovascular disease (3,11,13,14,15,16). These observations seem to justify using red yeast rice as a substitution for statins.

Most, if not all, clinical trials have shown great inter-individual variability of efficacy and safety responses to red yeast rice and to statins (including lovastatin). When that same variability occurs under standardized pharmaceutical preparations of statins, we know it originates from variabilities in inter-individual responses. Contrarily, when it occurs among red yeast rice recipient patients, it would be impossible to know if the variable extent of serum lipid responses to red yeast rice are due to the usual inter-patient variability or the variability in monacolin K content within the various red yeast rice preparations.

For the reasons discussed in this article, I do not recommend the use of red yeast rice as alternative therapy, regardless of patients’ needs (statin-induced myopathy or desire to take a “natural” remedy), nor do I justify the use of red yeast rice in addition to statins. I certainly do
not recommend red yeast rice sales and/or consumption until the FDA is ready to inspect the content and purity of all red yeast rice preparations marketed and provide strict CGMP quality controls, regulations, and standards of extractions and ingredients. Furthermore, randomized controlled trials will have to prove predictable safety and efficacy for each particular red yeast rice preparation.

Financial disclosure. The author has no conflicts of interest or financial disclosures to make related to the subject of this article.
References


• Statins are the most-commonly prescribed category of drugs world-wide.
• Many side effects (myalgias, etc) require statin discontinuation.
• Red yeast rice (RYR) is often considered as a substitute.
• The fact that RYR contains natural lovastatin is ignored.
• This review reveals multiple caveats and potential risks for patients and healthcare practitioners using RYR products.
• Dictums are presented from the USA’s current drug regulatory agency (FDA) on the use of RYR.