Rolling the Dice on Red Yeast Rice

Laura Gerik, MS

HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER, HOUSTON, TEXAS

"Excerpta" columns are editorials to supplement reviews in each journal issue with author interviews and a look at the practical aspects of the science reviewed in the Journal. Any opinions stated are the author's own. Quotations reflect the ideas of the persons interviewed and do not represent their respective institutions.

Published online October 12, 2019; Updated June 10, 2021

Among the myriad dietary supplements marketed to improve cardiovascular health, red yeast rice (RYR) stands out as a rare bright spot—one of the only popular supplements whose purported benefit holds up in randomized control trials. As Cicero and colleagues report in their review of RYR in the *Methodist DeBakey Cardiovascular Journal*, there is substantial evidence to suggest that RYR supplements, which include a statin-equivalent compound called monacolin K, can help lower cholesterol and are well tolerated in most patients.[1] For patients who don't want to take prescription statins, RYR sounds like a promising alternative. However, there's a caveat. The positive results come from clinical trials with specified doses of monacolin K. But thanks to a deregulated supplement industry, the quantity of monacolin K in commercial RYR products varies wildly, from none at all to well over the recommended dose—and there's no way for consumers and physicians to know what they're going to get.

IT'S ALL ABOUT THE MONACOLINS

Red yeast rice is made by fermenting fungi from the genus Monascus on red rice. It has been used in traditional Chinese medicine for centuries to lower cholesterol, improve blood circulation, and improve digestion.[2] The cardiovascular benefits come from compounds called monacolins that are created during fermentation. The Holy Grail monacolin for lowering cholesterol is monacolin K, which is chemically identical to lovastatin, the statin in prescription drugs Mervacor and Altoprev. Although monacolin K and lovastatin have some differences in bioavailability, and RYR supplements may contain added plant compounds that act synergistically with monacolin K,[1] they are close enough to make RYR's legal status complicated in the United States.

Thanks to its unique chemistry, RYR exists in a particularly murky area of U.S. Food and Drug Administration (FDA) regulations, blurring the line between supplement and drug. Under the Dietary Supplement Health Education Act (DSHEA) of 1994, dietary supplements are regulated as food rather than drugs, and RYR usually falls into the supplement category. In practical terms, the DSHEA's loose requirements for supplements means that they're hardly regulated at all. Unlike drugs, which require rigorous clinical trials to prove efficacy and safety before entering the market, supplements can be sold without any such evidence. Instead, the burden is on the FDA to prove that a product that is already available to consumers is unsafe before it can be removed from the market.[3] However, the agency's oversight abilities are limited. Supplement manufacturers are not required to register products or ingredients with the FDA, submit to FDA quality control testing, or meet formula or quality standards. A 2013 review of RYR content and FDA oversight highlighted the problem: Researchers requested information from the FDA concerning RYR quality control, inspections, and monacolin K and citrinin (a hepatotoxic byproduct sometimes formed during RYR fermentation) content for RYR supplements marketed in the US. The FDA couldn't provide any of that information because, as the agency pointed out, manufacturers were not obligated to report it.[4]

With most other supplements, consumers see how much of the active ingredient is in each dose. Labels reporting the amount of CoQ_{10} or vitamin D in a serving are fairly straightforward, but a RYR label reporting RYR quantity reveals nothing about the amount of monacolin K. In fact, a 2017 study testing 26 RYR supplements sold in the US revealed a 60-fold range in monacolin K content per 1,200 mg RYR, and a 120-fold range in monacolin K content per manufacturer's recommended daily servings. Two supplements didn't have any of the active ingredient needed to affect cholesterol, whereas two others had slightly over the 10 mg dose usually recommended to see a cholesterol-lowering benefit. None of the products listed monacolin K quantity on their labels.[5] Similarly, researchers testing five RYR supplements sold online in Europe found monacolin K levels ranging from 1.5 to 25.[2] mg per daily dose.[6] In both studies, label warnings about side effects or against taking RYR with other statins were rare.

This uncertainty makes prescribing or purchasing RYR difficult, says Albert Raizner, MD, cardiologist at Houston Methodist Hospital. He occasionally recommends red yeast rice to patients who need modest reductions in LDL cholesterol but do not want to take—or cannot tolerate—statin drugs.

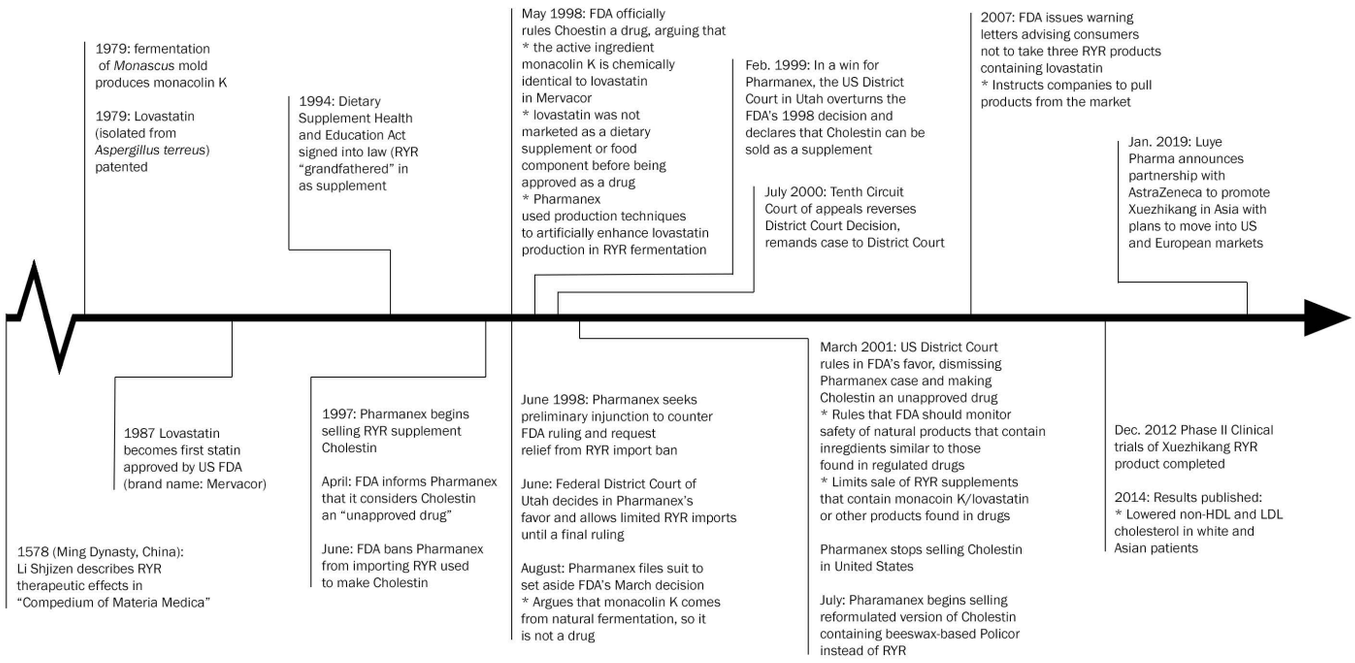

Figure 1.
Molecular Microscope Diagnostic System report. The yellow arrow shows the biopsy. AMBR: antibody-mediated rejection; NR: normal; TCMR: T-cell-mediated rejection; PC: principal component

"Sometimes I'm flabbergasted by the improvement in cholesterol levels that some patients have by taking red yeast rice," he said. "But the other side of the coin is that I've seen patients that did not have success. I don't view it as a substitute for a prescribed statin, but I do see it as an alternative if somebody has tried several statins and doesn't tolerate them. The problem always comes down to: What dose do you prescribe? What specific product to you prescribe? It's unclear. I think the inconsistency is why red yeast rice has not become a first- or even second-line recommendation for physicians."

RED YEAST RICE GOES TO COURT

Making things more complicated, the FDA considers any RYR product with more than trace levels of monacolin K an unapproved new drug,[7] subject to FDA drug regulations and testing. Considering that the recommended daily dose of monacolin K needed to lower cholesterol is 10 mg, this rule makes it technically illegal to sell a RYR supplement that contains enough of the active ingredient to be useful. Of course, since the FDA has limited oversight over supplement manufacturers, the standard is difficult to enforce and, as illustrated in the aforementioned studies, choosing a RYR supplement remains a gamble.

On occasion, the FDA has taken action against RYR supplements that contained substantial levels of monacolin K. Notably, in the late 1990s, the FDA won a four-year legal with Pharmanex, Inc., to reclassify their RYR product Cholestin from supplement to unapproved drug and remove it from the US market (Figure 1). The FDA argued that Pharmanex used manufacturing practices that increased the concentration of monacolin K above that which is found in traditionally fermented RYR products. Indeed, 2.4 g of Cholestin contained approximately 10 mg of monacolin K, meaning it contained doses of lovastatin comparable to lovastatin in the prescription drug Mervacor, which was already on the market at that time.[9] Under an exclusion clause in the definition of supplements under the DSHEA, a product that contains an ingredient already approved as a drug cannot be classified as a supplement, making Cholestin legally an unapproved drug. Ultimately, the FDA prevailed, and Cholestin disappeared from US store shelves.[8]

NEW ROADS TO THE US MARKET

Two decades later, it appears that the RYR market might be in store for another shakeup, with a major pharmaceutical company betting on a RYR product, and seemingly inching toward drug status. In January 2019, UK-based pharmaceutical giant AstraZeneca and China-based Luye Pharma announced a strategic partnership giving AstraZeneca exclusive rights to promote Xuezhikang—a RYR "natural drug"—in China. (Xuezhikang is the RYR formulation used in some of the well-known Chinese studies showing the cholesterol-lowering effects of RYR.) In press releases, the

companies declared their long-term goal to introduce Xuezhikang to international markets, including the United States and Europe.[10] Like Cholestin, Xuezhikang is manufactured to produce enhanced quantities of monacolin K, so presumably it would have to be approved as a drug by the FDA. Indeed, Xuezhikang completed a phase II clinical trial, in compliance with FDA regulations (biospace PR, clinical trial). The trial showed that Xuezhikang treatment significantly lowered non-HDL and LDL cholesterol in white and Asian patients.[11]

Although this announcement raises the possibility that someday a FDA-approved and regulated RYR drug could be available in the United States, for now, consumers are left in the dark. Compounding the problem, RYR supplements are often significantly more costly than generic statins, so picking a product that actually contains monacolin K can be an expensive game of trial and error. Until something changes in supplement law or RYR legal status, promising results in RYR studies have limited utility when choosing a product that actually contains the active ingredient remains a medical and financial gamble.

Corresponding Author:
lgerik@houstonmethodist.org

Conflict of Interest Disclosure:
Laura Gerik is Assistant Managing Editor of the *Methodist DeBakey Cardiovascular Journal.*

Keywords:
red yeast rice, monacolin K, Dietary Supplement Health & Education Act, DSHEA

REFERENCES

1. Cicero AFG, Fogacci F, Banach M. Red Yeast Rice for Hypercholesterolemia. Methodist DeBakey Cardivasc J; 15(3):132-9.
2. Red yeast rice. Penn State Hershey Health Information Library website. http://pennstatehershey.adam.com/content.aspx?productid=107&pid=33&gid=000323 Accessed September 17, 2019.
3. Binns CS, Lee MK, Lee AH. Problems and Prospects: Public Health Regulation of Dietary Supplements. Annu Rev Public Health. 2018 Apr 1;39:403-20.
4. Childress L, Gay A, Zargar A, Ito MK. Review of red yeast rice content and current Food and Drug Administration oversight. J Clin Lipidol. 2013 Mar-Apr;7(2):117-22.
5. Cohen PA, Avula B, Khan IA. Variability in strength of red yeast rice supplements purchased from mainstream retailers. Eur J Prev Cardiol. 2017 Sep;24(13):1431-4.
6. Lachenmeier D, Monakhova Yulia, Kuballa T, et al. Regulatory evaluation of red yeast rice (Monascus spp.) food supplements sold via the Internet. Deutsche Lebensmittel-Rundschau: Zeitschrift für Lebensmittelkunde und Lebensmittelrecht. 2012;108:357-60.
7. Thompson D. 'Red Yeast Rice' Statin Alternative Not Harmless. WebMD website. https://www.webmd.com/cholesterol-management/news/20170124/red-yeast-rice-statin-alternative-not-harmless-either-study-says. January 24, 2017. Accessed September 10, 2019.
8. Wheeler CD, Woodlee JW, Young AL. Lessons from Red Yeast Rice: Factors to Consider Regarding FDA's Position on CBD Supplements. Kleinfeld Kaplan & Becker LLP website. http://www.kkblaw.com/lessons-from-red-yeast-rice-factors-to-consider-regarding-fdas-position-on-cbd-supplements/. Accessed September 18, 2019.
9. Havel RJ. Dietary supplement or drug? The case of cholestin [Editorial]. Am J Clin Nutr. 1999 Feb;69(2):175-6.
10. Luye Pharma Reaches Strategic Partnership with AstraZeneca, Strengthens Commitment to Cardiovascular Therapeutic Field [press release]. Shanghai, China: Luye January 16, 2019. https://www.biospace.com/article/releases/luye-pharma-reaches-strategic-partnership-with-astrazeneca-strengthens-commitment-to-cardiovascular-therapeutic-field/. Accessed September 19, 2019.
11. Moriarty PM, Roth EM, Karns A, et al. Effects of Xuezhikang in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study. J Clin Lipidol. 2014 Nov;8(6):568-75.