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Are Red Yeast Rice Supplements Safe and Effective Alternatives to Statin Therapy?

As many might already know, we have repeatedly advised caution when recommending the use of red yeast rice (RYR) products for the modulation of lipids (LDL cholesterol, etc.) or other cardiovascular outcomes. However, in the past several years a number of "physician-channel" dietary supplement companies have marketed products with RYR as a primary (or sole) ingredient, implying that they are efficacious for lipid or cardiovascular outcomes. This has prompted us to put out this brief explanation for why we are still very cautious about RYR products, and why we do not recommend them for clinical use. Most of these issues have arisen from the unique regulatory status of RYR products in the United States and other countries, which directly affect both the quality and efficacy of RYR products sold in the US. For this discussion, we will leave aside our opinions on whether FDA's decisions related to RYR are lawful (based on our interpretation of DSHEA) or helpful to consumers confused by the availability of RYR products still on the market.

The Basics of our Position

- The regulatory environment in the United States prevents the truthful labeling of the main active ingredient in RYR products, guaranteeing that the clinician does not know the efficacy of the product(s) they are using or recommending.
- Companies selling red yeast rice must willfully market a product which they know is of little clinical value (in order to achieve legal dietary supplement status) or one that is likely to be effective (but is most certainly an unapproved drug).
- Recommending RYR is therefore fraught with legal, regulatory, quality and potential safety issues.
- Since low-dose HMG-CoA reductase inhibition (i.e., statin therapy) rarely addresses the root cause of cardiovascular risk, other more appropriate (and legal) strategies are often neglected when attempting to rely upon RYR therapy.

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What is red yeast rice, and how does it relate to statins in the first place?

Red yeast rice (RYR) describes several different products derived from rice that have been fermented with the mold *Monascus purpureus* (i.e., red yeast). Traditional preparations of this and other similar fermented rice products have been used for centuries within Traditional Chinese Medicine. In the past few decades, the discovery of lipid-altering compounds within RYR preparations (primarily the compound known as monacolin K) has given rise to products in both the pharmaceutical and natural-product arenas. Lovastatin, the first statin drug to be FDA-approved for lowering cholesterol (1987), is chemically identical to the RYR compound monacolin K.[1] The source of commercially available lovastatin is not RYR however; instead, it is derived from the fermentation of bran, rice or other substrates using the mold *Aspergillus terreus*.[2,3,4] Lovastatin and other "statins" have been discovered from the natural fermentation process of several other fungal species as well. Most other approved statin compounds are synthetically-modified derivatives or analogs of these fermented compounds.[5]

What is the regulatory status of RYR products in the United States?

We often describe the regulatory status of RYR products in the United States as an unfortunate "gray area" formed by the Dietary Supplement Health Education Act (DSHEA) and FDA's enforcement after the passage of DSHEA in late 1994. This particular issue began in 1997, when a shipment of RYR that was being imported into the United States for a product known as Cholestin, was deemed to contain an "unapproved new drug" (i.e., lovastatin).[6] After a number of court cases that initially challenged FDA's 1997/1998 position, and later upheld their ruling, FDA was able to prevent the sale of Cholestin in the United States. FDA subsequently declared that any RYR product that advertised, marketed or labeled the level of monacolin K would be considered an unapproved drug, and furthermore, products containing levels of monacolin K above "natural, food-grade" levels (even if undeclared) would also to be deemed unapproved drugs.

This is where the gray-area comes in. FDA has not technically banned the sale of all products that are called "Red Yeast Rice," but these products must contain low levels of monacolin K from "traditional" preparations; and cannot disclose the amount of monacolin K or market specific claims about their level of monacolin K. Since 1998, companies that sold RYR products with claims of standardization to this active ingredient, or pursued structure/function claims related to RYR and monacolin K received letters from FDA about their "unapproved" and "illegal" status.[7,8] These and other warning letters continued for over 10 years, including those where FDA had tested products for monacolin K (lovastatin) or examined vendor certificates of analysis for their monacolin K levels. More recently, FDA has made public warnings to consumers about these products.[9,10,11] As recently as June of 2014, "voluntary" product recalls of RYR products containing undeclared lovastatin have been issued.[12]

There is great debate about what level of monacolin K (lovastatin) constitutes "natural" levels based on historical fermentation of rice by *Monascus purpureus*.[13] Unfortunately, since commercial sources of lovastatin (derived from *Aspergillus* fermentation) are virtually indistinguishable from that found naturally in RYR (making it easy to adulterate RYR ingredients with *Aspergillus*-derived lovastatin), detectable levels above 0.4% are usually deemed adulterated and hence unapproved drugs (though FDA has not formally declared a level of monacolin K that they deem as proof of adulteration).

Currently, many companies sell RYR products that make no claim as to the amount of monacolin K on the label, assuming this will allow them to avoid the issue altogether. This has resulted in a "don't ask, don't tell" marketing of these products leading to a wide range of diverse RYR products on the market. Some of these products contain no detectible levels of monacolin K (a legal dietary supplement if labeled and marketed correctly), while others contain levels of monacolin K that would be deemed "therapeutic" (an unapproved drug based on previous FDA warning letters). Both issues will be explored further in the next two questions.

Is monacolin K (lovastatin) necessary for the lipid-altering effects of RYR products?

As with most issues surrounding RYR, this too is controversial. The discovery of monacolin K as a hypocholesterolemic by-product of *Monascus spp*. fermentation was first published in 1979.[14] While other monacolins and related compounds were later discovered as by-products of *Monascus* fermentation, several of which were also able to modify lipids in animal studies, the most abundant and potent of these compounds was determined to be monacolin K (lovastatin).[15,16,17] Research in humans using RYR preparations for lipid modulation were performed using ingredients derived from optimized fermentation for monacolin K content (i.e., Cholestin). Also, when the European Food Safety Authority (EFSA) evaluated the scientific substantiation concerning health claims related to RYR and monacolin K, their scientific opinion was that the lipid-altering (i.e., LDL cholesterol-reducing)

benefit of RYR was dependent on providing a daily dose of 10 mg of monacolin K.[18] A recent clinical trial using a product combining 3.0 mg of monacolin K (in 200 mg of RYR) with 200 mcg of folic acid did, however, did show a statistical reduction in LDL-C compared to placebo, suggesting that levels below 10 mg may prove to be beneficial in some patients.[19] While some have speculated other monacolin compounds found in RYR may create a synergistic enhancement of the effects of monacolin K, these hypotheses have never been fully tested.[20]

In nearly all studies to date, whether the product is a commercial capsule/tablet sold as RYR or based on the traditionally fermented food, the active lipid-lowering benefit has been attributed to the presence and amounts of monacolin K.[21] We are not aware of any human clinical trial using a RYR product showing lipid-lowering outcomes using products where monacolin K is absent or substantially low. Other (non-lipid-altering) effects of RYR may indeed be unrelated to monacolin K levels, though more research is needed to substantiate these effects in humans.[22]

Are there known quality control issues with RYR products sold in the United States?

Here, then, is the crux of the problem for those distributing (or recommending) RYR products to patients in the attempts to use a "natural" statin to help reach target lipid goals and reduce their risk of cardiovascular events. Simply put, the available products have major quality control issues. A clinician does not know whether the product they are relying upon has any measurable level of monacolin K at all, or whether it might provide 10 mg (or more) per serving. Since manufacturers cannot disclose this information, and even testing for and having knowledge of this information can be a liability, many manufacturers simply extend the "don't ask, don't tell" to "don't ask the vendor, don't test the product, don't tell the consumer."

The potential discrepancy in monacolin K levels found in both commercially available RYR raw materials and finished products has been documented several times over the past 10 years.[23,24,25] Indeed, it has been confirmed that some commercially available products contain no detectable levels of monacolin K, while others contain over 10 mg of monacolin K per serving. Our own analysis of raw materials available in 2016, as well as RYR products sold by "physician-channel" distributors in 2016, confirms these data. When examined, four different finished products of RYR distributed by four different physician-channel dietary supplement suppliers would deliver 0.0, 0.46, 1.49 or 2.9 mg of monacolin K per serving based on our laboratory analysis. Since none of these products make a label claim related to monacolin K content, we have no idea if these levels meet their intended monacolin K specification (or even if they have such a specification). We did not perform tests on multiple lots of these products to determine if these levels were consistent between lots of the same product. Our data suggest that physician-channel products labeled as RYR are equally diverse in the amount of likely monacolin K per serving as previous published reports of RYR products available in the retail setting, making it impossible for clinician or patient to know the potential efficacy (or legal status) of the product they recommend or use.

In reviewing RYR raw materials for purchase by several vendors, we found an interesting dichotomy. Some ingredients were sold with a specification of not more than (NMT) a certain concentration of monacolin K and others were sold with a specification as having not less than (NLT) a certain concentration of monacolin K. In other words, some ingredients appear to be designed to sell to companies that want a product that is legal (guaranteed to be low in lovastatin), but most certainly ineffective for lipid modulation; while others ingredients appear to be designed to sell to companies that want certain (higher) levels of active ingredient. In our analysis, these raw materials generally tested near their listed specification, though one raw material with no monacolin specification listed had no detectable level of monacolin K.[26]

With the exception of this last raw material, it would appear that manufacturers purchasing most RYR ingredients would be able to calculate an expected monacolin K level in their product using the specifications listed on the vendor information, even if they choose not to test their products for monacolin K. However, disclosing this amount on their label or product information is likely to raise suspicion by the consumer (if it is too low) or by FDA (if it is too high).

Does RYR have some of the same precautions (side effects) as other statins?

We often hear clinicians tell us that patients can tolerate RYR products when they cannot tolerate statins and, therefore, RYR is often viewed as a safe (and effective) alternative to statin therapy. We believe that, in many cases, since very little lovastatin/monacolin K is being delivered in these products, that statin-like side effects are likely to be limited; though the clinical efficacy is also likely limited as well. It is difficult to question or evaluate anecdotal reports, but it is our belief that few clinicians recommending RYR are measuring lipid alterations in the absence of all other recommendations (diet, omega-3 fatty acids, exercise, etc.), to specifically attribute whatever lipid changes they document to the RYR intervention alone. Nonetheless, if there are adequate levels of lovastatin in the product being used, independent of its legal status, it should be viewed (clinically) as a low-dose lovastatin therapy, with all

the related precautions. In general, this dose of lovastatin (e.g., 10 mg via prescription) is also fairly well-tolerated by most individuals.

RYR use has been reported to have some of the negative effects associated with statin use, though these are fairly rare due to the relatively low amount of lovastatin generally contained in these products. For instance, RYR can deplete CoQ-10 levels in a dose-dependent fashion in animals given doses several-fold higher than is typically recommended on the label.[27] However, one case study did report continued CoQ-10 depletion after a subject switched from atorvastatin use to RYR use (monacolin K levels not given), which resolved after discontinuing the RYR.[28] In general, controlled clinical trials using RYR products report few complaints of myopathies; however, several cases of myopathies have been reported after RYR use, and rhabdomyolysis was reported in a liver transplant patient after consuming RYR.[29,30,31,32]

Finally, there are reports of RYR products containing the mycotoxin citrinin.[21,23] This mycotoxin is a natural secondary metabolite of the fermentation of *Monascus* and other yeast and fungi.[33] Whether the levels of citrinin in RYR products were ever high enough to result in clinically-relevant toxicity is difficult to assess; however, the concern related to the presence of this mycotoxin in RYR products has led to alterations in both the fermentation and purification processes to greatly reduce citrinin levels in RYR products used today.[34,35,36] Ironically, while most companies market their products without specifying levels of monacolin K, many market their products as being free of citrinin. While we cannot say for certain that mycotoxin contamination of RYR products is no longer possible, it appears that this issue is likely to be rarely encountered in the products sold today.

Conclusions, Recommendations and Additional Comments

- Because RYR products are regulated in such a way that manufacturers cannot disclose (or set specifications) for the monacolin K levels contained in the product, this guarantees the consumer (or the clinician recommending it) does not know the activity of the product they are using or recommending.
- Companies selling RYR products must forego inquiring about or testing their product for the best characterized active component (lovastatin/monacolin K), which if absent would make the product of little clinical value (but maintain its dietary supplement status) and, if present at therapeutic levels, would likely make it an unapproved drug (and increase the likelihood of side effects).
- Based on these parameters (and published reports of tested RYR products), it is not even possible to assume the level of active ingredient of any marketed RYR product, nor that these levels would be similar from lot to lot of the same product.
- **For these reasons alone, we must conclude that it would be irresponsible to recommend any RYR product sold in the United States for any specific health outcome, as this would mean recommending a product that is either ineffective (but legal), or effective (but deemed an illegal unapproved drug); though without testing each bottle, one would not know which is being consumed. As frustrating as the regulatory process often is, ignoring these clear boundaries to recommend products with dubious quality and unknown activity levels is hardly a responsible solution.**

So, where do we go from here? We believe there is a way forward that can help clear up these issues, especially if RYR (as traditionally used) is deemed a helpful agent to reduce the risk for chronic disease.

- The first, we submit, is for clinicians to discontinue the use and/or recommendation of RYR products until the regulatory and quality control issues are sorted out. This will clear the deck for renewed research of legal RYR products or legitimate appeals to FDA for a regulatory status of RYR that is void of an ethical gray area.
- While it seems reasonable to petition FDA for the allowance of a specific upper limit of monacolin K that may be permitted in each dose of RYR (perhaps 5 mg), the legal precedent this will set is likely to prevent such a ruling. We should also remember that FDA has rejected several attempts to allow low-dose statins to be made available as over-the-counter medications.[37,38]
- Research into RYR products that contain other naturally occurring monacolins should be encouraged. However, since many of these other naturally occurring compounds are known to be HMG-CoA reductase inhibitors (i.e., statins), and these new ingredients will need to undergo FDA approval through the New Dietary Ingredient Notification process (unless they match a product sold in the United States prior to 1994), they still would have significant barrier to entry as dietary supplement ingredients.
- Related to our first point, there are many ways to reduce risk for chronic cardiovascular events. The reliance upon low-dose statin therapy (via RYR supplementation) does not, in our opinion, address the root cause of CVD risk in most

individuals. In fact, there are many lifestyle, diet and non-pharmacological agents to choose from that are safe, efficacious and legal. Clinicians should become familiar with other options and recommend them to their patients.

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