

# Mini-review: medication safety of red yeast rice products

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André Farkouh<sup>1</sup>  
Christoph Baumgärtel<sup>2</sup>

<sup>1</sup>Division of Clinical Pharmacy and Diagnostics, Department of Pharmaceutical Chemistry, University of Vienna, Vienna, A-1090, Austria; <sup>2</sup>AGES Austrian Medicines and Medical Devices Agency and Austrian Federal Office for Safety in Health Care, A-1200 Vienna, Austria

**Abstract:** High lipid levels in the blood together with high blood pressure and diabetes are among the highest risks for coronary heart disease. In particular, elevated cholesterol levels promote the progression of atherosclerosis. Red yeast rice, also called red fermented rice or red mold rice, is used as a dietary supplement to lower cholesterol levels. It contains varying amounts of natural monacolin K, which is a structural homolog to lovastatin, and shows hypocholesterolemic properties comparable to synthetic statins. Despite being portrayed as a natural alternative, the potential of red yeast rice for side effects and interactions is comparable to statin drugs. Consumers need to be made aware of the varying monacolin K content in red yeast rice products and the insufficient long-term safety data regarding the potential risks of red yeast rice.

**Keywords:** red yeast rice, monacolin K, p-glycoprotein, pharmacokinetics

## Introduction

Hypolipidemic medicinal products belonging to the statin class of drugs inhibit the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the key enzyme in cholesterol biosynthesis that converts HMG-CoA into mevalonate. Due to the reduced cholesterol synthesis, LDL-cholesterol is increasingly broken down and HDL-cholesterol is increasingly formed. In addition, other pleiotropic effects of statins, such as anti-inflammatory, antioxidant or direct vascular effects, are described in the literature.<sup>1</sup>

The substances available on the market differ considerably in efficacy as well as adverse effects and interactions. Muscle symptoms associated with statins range from mild muscle pain to myopathy, and, in extremely rare cases, even to dangerous rhabdomyolysis that can lead to renal impairment.<sup>2</sup> Furthermore, statins can cause new-onset diabetes mellitus that contributes to the risk for hemorrhagic stroke.<sup>2</sup> Elevated levels of liver enzymes have also been reported, yet, events of serious liver injuries are rare.<sup>2</sup> In this context it should be noted that in view of the millions of prescriptions of statins they are generally considered to be a very safe class of drugs.

Although dietary interventions and an active lifestyle are generally recommended to decrease cardiovascular risk, these preventive measures may not directly affect the LDL levels.<sup>3</sup>

For patients with hypercholesterolemia that are not qualified for treatment with statin drugs based on their cardiovascular risk, nutraceuticals like red yeast rice products, which are available without prescription in Europe, are seen by some as a possible further preventive measure that can induce a clinical meaningful decrease of up to 25% in LDL levels.<sup>3</sup>

Correspondence: André Farkouh  
Division of Clinical Pharmacy and Diagnostics, Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria  
Tel +43 664 302 9922  
Email [andre.farkouh@univie.ac.at](mailto:andre.farkouh@univie.ac.at)

In addition, red yeast rice is currently being discussed as an alternative treatment option for statin intolerant patients, as statin intolerance refers to statin associated muscle symptoms that lead to discontinuation rather than complete intolerance.<sup>4</sup> Further, combined nutraceuticals may be a new approach to treat statin intolerant patients, making use of potentially additive mechanism of action.<sup>5</sup>

The regulatory status of nutraceuticals and particularly red yeast rice is still under debate.<sup>6</sup> In contrast to food supplements that exhibit nutritional value, nutraceuticals show specific pharmacological activities.<sup>6</sup> Therefore, efficacy and safety need to be assessed and dose limits need to be regulated.<sup>6</sup> The risks associated with the use of red yeast rice, the alleged natural alternative to statins, are discussed in this review.

## Data sources, searches, and extraction

Relevant articles published between April 2001 and January 2019 were searched using PubMed (incl. PubMed Central and Medline) and an Austrian data source (Austria Codex). Combinations of key terms, which included “red yeast rice”, “pharmacokinetics”, “monacolin K”, “p-glycoprotein”, “side effects”, “pharmacodynamics” and “lovastatin” were used. Additionally, reference lists of the included articles and key systemic reviews were checked manually.

## Pharmacological effects and interactions of red yeast rice

Red yeast rice is offered as a dietary supplement, alone or in combination with a balanced diet, to patients with dyslipidemia.<sup>7,8</sup> It is not a separate rice variety, but produced by the fermentation of ordinary rice (*Oryza sativa*) with a certain mold fungus of the *Monascus* genus. During the fermentation, red dyes and various other potentially pharmacologically and toxicologically active ingredients are produced,<sup>9</sup> including monacolin K which is identical to the statin drug lovastatin.<sup>10</sup>

While often portrayed otherwise in the media, taking red yeast rice products actually has similar effects to taking lovastatin, even though the potency is significantly lower, and the potential for side effects and interactions similar to those of statin drugs is to be assumed.<sup>11–13</sup> The prodrug lovastatin, after gastrointestinal absorption and hydrolysis into the active hydroxy acid form, is metabolized mainly in the liver by CYP-3A4. Hence, numerous interactions can occur.<sup>1,14</sup>

Strong CYP-3A4 inhibitors, in particular, can increase the risk of myopathy by increasing the drug plasma concentration and consequently the inhibition of the HMG-CoA

reductase during lovastatin or red yeast rice therapy.<sup>15</sup> These inhibitors include, for example, cyclosporin, itraconazole, clarithromycin, verapamil, aprepitant, amiodarone as well as HIV protease inhibitors such as ritonavir and other cholesterol lowering agents such as fibrates.<sup>15,16</sup>

Grapefruit juice, if consumed in large amounts, may also significantly increase the inhibitory activity of lovastatin on HMG-CoA reductase.<sup>15</sup> Furthermore, there is clear evidence that lovastatin inhibits the membrane transport protein P-glycoprotein, which plays an important role in the detoxification of drugs.<sup>1,17,18</sup>

This efflux transporter, which is predominantly found in excretory tissues, actively transports not only endogenous substances, such as steroids and cytokines, but also potentially toxic xenobiotics out of cells. Thus, the inhibitory effect of monacolin K (lovastatin) on this transporter can also significantly influence the bioavailability and the distribution of drugs.<sup>17,18</sup>

## Variability of monacolin content of red yeast rice products

It is evident from the literature that the ratio of monacolin K and its hydroxyl acid form monacolin KA varies widely in various red yeast rice products.<sup>19</sup> This results in variable bioavailability, because monacolin KA, the active form, is much more readily absorbed.<sup>19</sup>

Concentrations of HMG-CoA reductase inhibitors in red yeast rice products can be increased by optimization of the fermentation conditions and selection of the rice variety.<sup>20,21</sup> In cultures with Thai rice (*Oryza sativa* L.) cv. RD6, up to 34 mg monacolin K as well as 22 mg compactin (desmethyl-monacolin K, mevastatin) per gram of powder can be found among other monacolines.<sup>22</sup>

It is also worth mentioning that the biological activity of the other monacolins occurring in red rice, such as the previously mentioned compactin, have not been considered so far. Compactin is likely to be only half as effective with respect to HMG-CoA reductase inhibition as monacolin K.<sup>20,21</sup> Therefore, the bioavailability of the individual monacolins is difficult to determine in the presence of monacolin K. It may be useful to specify a total monacolin content in the form of “monacolin equivalents”.

The literature points out a lack of standardization of monacolin content and also the detection of the mycotoxin citrinin.<sup>23</sup> Citrinin is described as nephrotoxic and teratogenic and resulted in the development of renal tumors in rats.<sup>24</sup>

Finally, it should also be noted that taking red yeast rice products and statins at the same time can easily lead to

overdosing and side effects. On a side note, lovastatin should also be used with caution in patients who consume significant amounts of alcohol and/or have a history of liver disease.<sup>15</sup>

## Safety profile of red yeast rice

The safety of red yeast rice alone or in combined nutraceuticals has been investigated in clinical trials, where low (3 mg/day) as well as high dose (10 mg/day) regimes of monacolin K were well tolerated by patients with dyslipidemia, with few or no adverse events.<sup>25–28</sup> In combination with a low-dose statin therapy, a nutraceutical combination containing red yeast rice has been shown to be tolerated equally to a low-dose statin therapy alone in high-risk patients that were high-dose statin intolerant.<sup>29</sup> However, since the majority of the clinical trials had a short treatment duration of about four to twelve weeks, assessment of long-term side effects is limited.

Adverse effects associated with red yeast rice that are repeatedly reported, include symptomatic myopathy,<sup>30–32</sup> gastrointestinal symptoms,<sup>31,33</sup> and elevated levels of hepatic enzymes indicative for liver injury.<sup>31–33</sup> Recently, exacerbation of myasthenia gravis and development of erectile dysfunction have also been attributed to red yeast rice intake in two individual cases.<sup>34,35</sup>

Overall, the majority of adverse effects reported for red yeast rice are also commonly associated with statin drugs.<sup>31,33</sup>

The safety profile of red yeast rice is mainly based on case reports and assessment is complicated by self-medication and varying product composition. Continuous monitoring and further long-term trials are indispensable.

## Misleading reporting

Misrepresentations of red yeast rice products in the media may give patients the impression that an adequate intake of red yeast rice products can provide sufficient treatment for dyslipidemia.<sup>36,37</sup> However, this is grossly negligent, especially in the secondary prophylaxis of cardiovascular events which requires sufficient efficacy levels of a potent statin for therapeutic success.<sup>36–38</sup>

It should also be noted that consumers often assume dietary supplements to be less dangerous. In the case of red yeast rice this can be very deceptive and even harmful. Statins, and thus also red yeast rice products, are generally contraindicated during pregnancy and lactation due to their teratogenicity observed in animal experiments.<sup>15</sup>

Another major factor of uncertainty is the self-medication outside of medical monitoring and the fact

that there is no systematic recording of adverse effects, as required by law for authorized drugs.<sup>36–39</sup>

## Conclusion

The claim that red yeast rice “naturally” lowers or maintains cholesterol levels without comparable side-effects to synthetic statins is untenable. Furthermore, monacolin K cannot be considered a common nutrient as it is rare in common foods. In corresponding studies on fungi, such as mushrooms or oyster mushrooms, only trace amounts could be detected.<sup>40</sup> It is recommended that red yeast rice products are only made available with appropriate warnings as they have the same clinically relevant risk potential as statins.

## Disclosure

The authors report no conflicts of interest in this work.

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