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A questionable way to lower cholesterol: food supplements containing red yeast rice to be taken only on medical advice

BfR opinion No 003/2020 issued 15 January 2020

Red “yeast” rice (also known as red rice) has its traditional origin in China. Red yeast rice is made by fermenting boiled white rice with a type of mould of the *Monascus* genus. This produces substances that dye the rice bright red. In East Asia in particular, red yeast rice is therefore used as a food colouring. The fermentation process also leads to the production of compounds that can have pharmacological effects (like medicines) and that may also be harmful to health.

Important in this context are monacolins: these are chemical compounds that occur naturally in certain types of mould. Monacolins can also be found in red yeast rice and can inhibit an enzyme in the liver that the body requires in order to make cholesterol. **Monacolin K** is especially important, since red yeast rice contains considerable amounts of this compound. In terms of its structure and activity, monacolin K is identical to the drug substance **lovastatin**. This substance is used in medicinal products requiring authorisation, to lower cholesterol levels.

Possible side effects of lovastatin include headaches, nausea, diarrhoea, weakness, skin rashes and muscle cramps. In rare cases, it can also disrupt kidney and liver function or damage skeletal muscle (known as ‘rhabdomyolysis’). Medicinal products with the active ingredient lovastatin require a prescription. In all cases, the doctor will weigh risks against benefits to decide whether it makes sense for a patient to receive a medication with lovastatin.

In Asia, red yeast rice has long been consumed on account of its ability to lower cholesterol levels, and also to treat digestive problems as well as cardiac and vascular disorders. Food supplements containing various quantities of red yeast rice are also marketed within the EU. The monacolin K contained in these products can also cause the same side effects as listed above. People do not usually consult their doctor before taking these food supplements, however.

In some circumstances, the toxic substance citrinin can also be formed by the fermentation process. This substance can trigger genetic mutations, and can also cause harm to the kidneys and to the unborn child. The maximum permitted level of citrinin in rice-based food supplements has been lowered by the EU Commission from 2,000 micrograms per kilogram ($\mu\text{g}/\text{kg}$) to 100 $\mu\text{g}/\text{kg}$, and this figure will apply from 1 April 2020 on.

The EU Commission recently commissioned a safety assessment of monacolin K in food supplements from the European Food Safety Authority (EFSA). The EFSA report was unable to identify a dietary intake of monacolins that does not give rise to concerns about harmful effects to health. The German Federal Institute for Risk Assessment (BfR) concurs with this finding.

In March 2019, a meta-analysis was published that addressed the tolerability and safety of red yeast rice products containing monacolin K sold as food supplements (Fogacci et al.). One conclusion drawn by the authors was that there is no increased risk of the occurrence of muscular complaints. The BfR has reviewed this paper and is of the opinion that it exhibits a

number of key limitations: its overall findings cannot therefore be viewed as conclusive. Accordingly, this meta-analysis offers no appropriate basis on which to rebut the significant health concerns about red yeast rice food supplement products containing monacolin K.

In Germany, no official approval is required for the marketing of food supplements as these are not subject to the pharmaceutical law but to the food law. However, before they are placed on the market for the first time, they must be registered with the German Federal Office of Consumer Protection and Food Safety (BVL). Due to serious questions about their safety, the BfR does not recommend the consumption of food supplements based on red yeast rice. Anyone who still wishes to use such a food supplement should only do so under medical supervision or after consulting with their doctor. In particular, consumers should be aware that levels of monacolin K in supplements may vary widely from one product to another.

		BfR risk profile: food supplements made from red yeast rice (opinion no. 003/2020)			
A Affected persons	General population 				
B Probability of an impairment to health from the consumption of food supplements made from red yeast rice	Practically impossible	Unlikely	Possible	Probable	Certain
C Severity of an impairment to health from the consumption of food supplements made from red yeast rice	No impairment	Mild impairment [reversible/irreversible]	Moderate impairment [reversible]	Severe impairment [reversible]	
D Validity of available data	High: The most important data are available and are internally consistent		Medium: Some important data are missing or inconsistent	Low: A large volume of important data is missing or inconsistent	
E Controllability by the consumer	Control not necessary	Controllable with precautionary measures [1]	Controllable by avoidance	Not controllable	

Fields with a dark blue background indicate the properties of the risk assessed in this opinion (for more details, see the text of opinion no. 003/2020 from the BfR dated 15 January 2020).

Line E – controllability by the consumer

[1] Details given in the row “Controllability by the consumer” are merely descriptive and not to be understood as a recommendation by the BfR. The BfR has given recommendations for action in its opinion. The BfR recommends seeking medical advice before consuming any food supplements made from red yeast rice.

1 Subject of the assessment

In 2010, the BfR assessed the health implications of a red yeast rice product in tablet form that provided a daily dose of 3 mg of monacolin K, among other ingredients. The BfR concluded that this product should not be placed on the market in Germany on health protection grounds and because of serious health risks.

In answering a request made by the official food control authorities in Germany in 2014, the BfR also completed two health assessments of a red yeast rice product marketed as a food supplement in capsule form, which provided a daily dose of 10 mg of monacolin K. The BfR identified serious health risks associated with this product. In light of the known contraindications, interactions and adverse events applicable to lovastatin (lactone form of monacolin K) when used as a medicinal substance, and its necessary controls for use, the BfR expressed doubt that consumer safety was sufficiently addressed by the typical details provided for food supplements as required by normal food labelling law in the case of the red yeast rice product assessed, with its daily dose of 10 mg of monacolin K.

In March 2019, the authors Fogacci, Banach et al. published a meta-analysis examining the tolerability and safety of red yeast rice products sold as food supplements containing monacolin K.

Fogacci F, Banach M, Mikhailidis DP, Bruckert E, Toth PP, Watts GF, Reiner Ž, Mancini J, Rizzo M, Mitchenko O, Pella D, Fras Z, Sahebkar A, Vrablik M, Cicero AFG; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group; International Lipid Expert Panel (ILEP) (2019). Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*, 143:1-16.

In light of this meta-analysis, the BfR was asked for a renewed statement from a risk assessment perspective.

2 Results

The substance monacolin K in red yeast rice products offered as food supplements has repeatedly been evaluated in detail by the BfR.

The BfR identified serious health risks for monacolin K in red yeast rice products offered as food supplements, both for the daily dose of 10 mg monacolin K as well as for a daily dose of 3 mg monacolin K. These risks relate in particular to the contraindications, interactions and adverse events known for lovastatin as a medicinal substance, as well as the controls necessary when taking this substance. This evidence-based assessment therefore continues to apply.

While the published meta-analysis (Fogacci, Banach et al., 2019) may be considered a contribution to scientific research on red yeast rice products, key limitations identified in the work and in the studies included by the meta-analysis mean that its findings cannot be viewed as reliable. Accordingly, it offers no appropriate basis on which to rebut the significant health concerns about red yeast rice food supplement products containing monacolin K.

The EU Commission recently commissioned a safety assessment of the use of monacolin K in food supplements from the European Food Safety Authority (EFSA). EFSA was unable to identify any safe daily level for the consumption of monacolin K in food supplements. The EFSA Panel further concluded that the intake of monacolin K from red yeast rice via food supplements could lead to the ingestion of a therapeutic dose of lovastatin. On the basis of the information available about red yeast rice and its adverse events in humans, EFSA concluded that the consumption of a daily dose of 10 mg monacolin K from red yeast rice products as food supplements would be associated with serious concerns about human health. Other cases were also taken into account where a daily dose of 3 mg of monacolin K from red yeast rice products resulted in severe side effects (EFSA, 2018).

3 Rationale

3.1 Publication by Fogacci, Banach et al., on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group, the International Lipid Expert Panel (ILEP), 2019

A meta-analysis was published by Fogacci et al. in 2019. The focus of this work was to consider the side effects that occurred or were reported following the consumption of red yeast rice products by previously published clinical trials, as well as other data on safety and tolerability in comparison to the respective controls in these studies. A primary endpoint of the analysis was the occurrence of musculoskeletal disorders (MuD). A secondary endpoint concerned non-musculoskeletal adverse events (Non-MuD) as well as serious adverse events (SAEs). The red yeast rice products used also typically included other—potentially active—ingredients.

The data in the meta-analysis are based on a pool of 53 controlled clinical trials involving a total of 112 treatment groups. A total of 8,535 patients were enrolled with hypercholesterolemia. Of these, 4,437 patients received a red yeast rice product, while 4,303 patients were placed in control groups. Control groups generally received a placebo. In some studies, however, active medicinal substances such as atorvastatin 10 mg [literature no. 66], pravastatin 40 mg [literature no. 57], fluvastatin 20 mg [literature no. 61], simvastatin 20 mg [literature no. 31], a “low-dose statin” (not further specified) [literature no. 29] or other substances like berberine 500 mg [literature no. 63] were given to control groups. The meta-analysis looked at red yeast rice products with daily doses of monacolin K of ≤ 3 mg, 3.1 to 5 mg and >5 mg. In the vast majority of cases, the investigational medicinal product administered as the red yeast rice product in the studies contained other substances also considered to be active ingredients, such as coenzyme Q10, phytosterols, artichoke extract, folic acid, berberine, hydroxytyrosol, policosanol, astaxanthin, silymarin, nattokinase, green tea extract, quercetin, resveratrol, guggul extract, grape seed extract, black pepper extract, garlic extract, pine bark extract, niacin, vitamin E, procyanidins or bitter melon.

The studies included in the meta-analysis were published between 1999 and 2019. Most studies were carried out in Italy (n=24). Other countries included China (n=11), USA (n=6), France (n=3), Taiwan (n=3), Belgium (n=2), Egypt (n=1), India (n=1), Norway (n=1), Spain (n=1) and Germany (n=1). (The sum total of 54 studies matches the details given in the meta-analysis.) The duration of the studies included in the meta-analysis varied between 4 weeks and 4.5 years, although the duration of almost all studies ranged between 4 and 12 weeks.

In terms of the primary endpoint of the meta-analysis (occurrence of musculoskeletal disorders), Fogacci et al. stated that disorders of this kind were not reported on by 37 studies. In the remaining studies, the data showed that monacolin K consumed from red yeast rice products was not linked to an increased risk of musculoskeletal disorders (odds ratio = 0.94; 95 percent confidence interval between 0.53 and 1.65).

Concerning the secondary endpoint (occurrence of non-musculoskeletal adverse events), Fogacci et al. stated that these kinds of adverse events were not reported on by 34 studies. In the remaining trials, the consumption of monacolin K from red yeast rice products compared to the control group resulted in a statistically less likely risk of the occurrence of non-musculoskeletal disorders (odds ratio = 0.59; 95 percent confidence interval between 0.50 and 0.69). In terms of the occurrence of serious adverse events (another secondary endpoint

of the meta-analysis), it was stated that these kinds of adverse events were not reported on by 48 of the 53 studies. In terms of the remaining studies, Fogacci et al. stated that the treatment group consuming red yeast rice products had a statistically less likely risk of serious adverse events (odds ratio = 0.54; 95 percent confidence interval between 0.46 and 0.64) compared to the control group.

In the course of review by the BfR of the meta-analysis, and after subjecting the original 53 publications to targeted scrutiny, serious limitations were found to apply.

With a study duration of 4.5 years (the stated average value according to the original publication of just five pages [literature no. 62]), the longest study by a wide margin enrolled noticeably more patients than the other studies cited in the meta-analysis (n=4,870, sum of 2,429 patients in the treatment group and 2,441 patients in the placebo group). This, it may be noted, creates a considerable misalignment between this study and the other studies, each with far fewer participants and a much shorter study duration, which raises the question of a potential systematic error (bias) in drawing conclusions. The study was performed in China, and all 4,870 patients enrolled had a previously diagnosed myocardial infarction in their medical history [literature no. 62]. This is a serious condition that, from a medical perspective, is also not a particularly typical indication for red yeast rice products taken as a food supplement.

While evaluating the studies included in the meta-analysis as originally published, it is also noticeable that—as is typical for clinical trials—a wide range of exclusion criteria applied for the recruitment and acceptance of patients in the respective trial. In the vast majority of cases—in nearly all of the studies, in fact—a series of illnesses and health impairments were listed as exclusion criteria:

Literature numbers [23], [24], [25], [8], [26], [27], [28], [29], [30], [31], [32], [11], [33], [34], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [52], [53], [54], [55], [10], [57], [58], [59], [60], [61], [62], [63], [64], [65], [67], [68], [69] and [71].

In each of these publications, several of the following disorders or health impairments (most of these being liver or kidney disorders in conjunction with other indicators) were considered to be exclusion criteria for participation in the study. Those affected were not treated with the red yeast rice product to be tested (or the respective control):

Liver disorders, hepatitis in medical history, kidney disorders, peripheral oedema, taking certain medicinal products, changes in dose while taking certain medicinal products, taking certain kinds of food supplements, glucose metabolism disorders, thyroid disorders with and without effects on lipid metabolism, endocrine disorders, gastrointestinal illnesses (including colitis and pancreatitis), current or previous history of ischaemic heart diseases, coronary heart disease, cardiac insufficiency, cardiac arrhythmias, heart failure in medical history, change in body weight of more than 3 kg during the last 3 months, cancers, neurological and/or psychiatric illnesses, current or previous history of alcohol abuse, consumption of alcohol above a certain defined daily amount, current or previous history of drug abuse, being overweight (at or above a defined body mass index (BMI)), specific lipid metabolism disorders, musculoskeletal disorders as well as muscular disorders/myopathies whether current or in medical history and/or elevated values for creatine kinase (CK) in serum, type 2 diabetes, disorders affecting the vascular system of the brain, arteriosclerosis, pregnancy, breastfeeding, disorders of the peripheral vascular system, surgical operations or hospital stays during the last 3 months, secondary arterial hypertension, uncontrolled arterial hy-

pertonia, Behçet's disease, vasculitis, immune system disorders, psoriasis, active smoker (current medical history), eating disorders (such as anorexia or bulimia) whether current or in medical history, current or recent calorie-reduced diet, earlier or existing treatment for lipid metabolism disorders, statin-associated myositis or rhabdomyolysis in medical history, symptoms of chronic pain, connective tissue disorders, and acute infections.

Following the exclusion of patients with liver and kidney disorders in particular or with other illnesses as stated above, and including adequate monitoring by primary care practitioners, it is to be generally expected that, compared with the practice of consuming red yeast rice products as a food supplement, a differing incidence of adverse events would be seen instead (see also section 3.6, "Current literature on the frequency of adverse events from statins"). This considerably weakens the reliability of the meta-analysis in question.

After perusing the original publications included in the meta-analysis, it is noticeable that a number of studies do not clarify whether (or how) the systematic recording of data on safety and tolerability was in fact completed. This applies in the case of literature numbers [23], [25], [8], [26], [32], [33], [34], [38], [43], [44], [46], [47], [51], [53], [60], [61], [63], [64], [65], [67], [9] and [68] (see also section 3.4, "Controlled clinical trials often with inadequate reporting on safety and adverse events"), which weakens reliability in terms of the significance of adverse events.

In the course of current scrutiny of individual studies, the content of some of the studies could not or only in part be followed: for two publications of Chinese origin, no contextual information could be procured whatsoever [literature no. 66 and no. 70], while a further publication is available only as an Italian-language study [literature no. 35].

Ultimately, the conclusions as drawn by the authors of the meta-analysis in question, namely that "...R.Y.R. [Red Yeast Rice] supplementation is safe and is not associated with increased incidence of muscular adverse effects...this nutraceutical compound can be used in order to promote health in general population with mildly increased cardiovascular disease risk and in statin-intolerant patients" (Fogacci et al., 2019), cannot be adequately substantiated. As a result of the stated limitations, the meta-analysis in question is not sufficiently reliable and therefore offers no appropriate basis on which to rebut the significant health concerns about red yeast rice food supplement products containing monacolin K.

3.2 Publication by Banach, Patti et al., on behalf of the International Lipid Expert Panel (ILEP), 2018

As with the meta-analysis described in detail in section 3.1 (publication by Fogacci, Banach et al, 2019), some of the authors of the publication by Banach, Patti et al., 2018, were also members of the International Lipid Expert Panel (ILEP). One of the goals of this second paper was to investigate the suitability of red yeast rice products for lowering cholesterol levels in patients with an existing statin intolerance. The conclusions drawn by the authors seem to be contradictory. While the potential use of an explicitly stated formulation (3 mg monacolin K in the form of 200 mg of red yeast rice, 10 mg policosanol, 500 mg berberine, 200 µg folic acid, 2 mg co-enzyme Q10, 0.5 mg astaxanthin) is described in positive terms, the authors also admit that the presence of the ingredient monacolin K can give rise to the typical adverse events associated with statins, and that additional studies with more patients and longer periods of use would be needed in order to make more accurate statements about safety for long-term use of monacolin K.

Smollich, 2018, provided a detailed response to the use of monacolin K from red yeast rice in statin-intolerant patients as presented in the publication by Banach, Patti et al., 2018. Smollich concluded that some of the findings presented by Banach, Patti et al., 2018, were “not scientifically comprehensible,” and that the consumption of red yeast rice products by patients with lipid metabolism disorders would be associated with incalculable health risks and is not to be recommended (Smollich, 2018). A publication by Dujovne (2017) also has described adverse events from red yeast rice products and also presents clear arguments against the use of red yeast rice products as a substitute for statins on the grounds of patient safety (Dujovne, 2017). As late as 2017, a position paper from ILEP still advised exercising caution with red yeast rice products for statin-intolerant patients (Cicero et al., 2017).

3.3 Assessment of monacolin K by EFSA, 2018

In 2018, EFSA’s ANS Panel (EFSA Panel on Food Additives and Nutrient Sources Added to Food) prepared a safety assessment for monacolin in red yeast rice as part of an assessment conducted as an Article 8 procedure according to Reg. (EU) No 1925/2006 (EFSA, 2018). When rice is fermented with the mould *Monascus purpureus*, multiple monacolin metabolites are produced. The most abundant of these in quantitative terms is the substance monacolin K, which was therefore the primary focus of this assessment. In China, red yeast rice has traditional uses—as a food colouring, for example. The reason for commissioning EFSA with this assessment were the discussions and safety concerns expressed by bodies in a number of EU member states after EFSA had given a positive judgment on a health claim for red yeast rice, and stated that the daily intake of 10 mg monacolin K was an effective dose (EFSA, 2011).

The assessment confirmed that the monacolin K contained within red yeast rice products fluctuated in dependence on the pH value, and was present as a lactone or in the acid form. As a lactone, monacolin K is chemically identical to the substance lovastatin, a statin used as the active ingredient in cholesterol-lowering medicinal products subject to EU authorisation. Monacolin K in the lactone form and lovastatin are rapidly hydrolysed in the body into the corresponding acid form (= active form). This is the active form of the molecule, which inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase and thus the body’s own cholesterol biosynthesis.

According to the summary of product characteristics (SPC) presented by the ANS Panel for lovastatin when used as a medicinal product, the recommended doses for the treatment of hypercholesterolemia are initially 20 mg per day and no more than 80 mg per day; mild to moderate hypercholesterolemia is treated initially with 10 mg per day. Contraindications for lovastatin include liver disorders, including elevated serum values for various liver function parameters, cholestasis, myopathy, simultaneous treatment with certain other medications, pregnancy and breastfeeding, and alcohol abuse. Other warnings and cautionary advice concern the risk of myopathies involving pain, muscular weakness and elevated levels of creatine kinase (CK) in serum, with and without disruption to kidney function, and even including rhabdomyolysis (muscular destruction) in severe cases.

Before starting treatment or increasing the dose, patients should be informed about the potential risks of myopathies. If patients develop a complaint, medical advice must be sought immediately. For certain patients, measuring creatine kinase (CK) in serum is recommended before treatment starts. Use of lovastatin must be stopped if creatine kinase in serum is significantly elevated or if persistent muscle problems occur. In the available repository of data

about the occurrence of adverse events during treatment with lovastatin as a medicinal product, the most common types of adverse events reported related to muscle symptoms and the musculoskeletal system (myopathies), also including rhabdomyolysis, and to the nervous system and the gastrointestinal tract, as well as to kidney and liver function.

Interested parties had reported daily recommended doses to the EFSA of monacolin K from red yeast rice ranging from 9 to 20 mg. Labelling data for 40 new products (January 2012 to February 2018) from European countries as sourced from the Mintel Global New Products Database (Mintel GNPD), a database for new products placed on the global market, listed daily doses from 2 to 48 mg monacolin K, although the recommended daily dose was 10 mg for most products. Only 8 of these 40 products contained monacolin K as the only active ingredient: most food supplements included other ingredients—mostly of plant origin—as well as monacolin K.

In assessing the safety of monacolin K from red yeast rice and a maximally safe daily dose in particular, the EFSA Panel considered data from the scientific literature dating up to May 2018, inclusively. Reports of adverse events from food supplements with monacolin K were considered as collected in databases maintained by the WHO (Vigibase database maintained by the WHO Collaborating Centre for International Drug Monitoring), and in France (French Phytovigilance System, cited by ANSES, 2014, and Philibert et al., 2016) and Italy (Italian Surveillance System of Natural Health Products, cited by Mazzanti et al., 2017); some reports were also used from databases maintained by the US FDA.

The adverse events most frequently reported concerned the musculoskeletal system (myalgia) and connective tissue or muscular damage (myopathies), both with and without elevated creatine kinase levels in serum. Four cases of rhabdomyolysis were also reported: some involved doses as low as 3 mg monacolin K daily over a period of 25 to 90 days, while other cases involved consumption over several months. Other cases involved disorders of the hepatobiliary system (acute liver inflammation, elevated values for liver parameters in serum such as ALT, AST, gamma GT; dose: 3 mg monacolin K daily for a period of 15 to 76 days), the gastrointestinal tract (diarrhoea, nausea, stomach pain) and the skin (hives, pruritus). Some cases of adverse events were classified as serious (e.g. 6 out of 10 cases of acute hepatitis).

The EFSA Panel was unable to derive concrete details from this set of data about the occurrence of adverse events while using monacolin K. Accordingly, the Panel concluded that there were insufficient data available for deriving a clear correlation between the dose and the occurrence of adverse events. A safe maximum dose for monacolin K could not be determined. Even a dose of 3 mg daily had the effect of lowering cholesterol. At this dose, however, the case reports and a recent review already reported adverse events, in the form of liver inflammation and muscle damage—damage even as severe as rhabdomyolysis.

The Panel therefore concluded its assessment by stating that the intake of monacolin K from red yeast rice products can achieve treatment doses comparable to lovastatin used in a medicinal product. The adverse events reported for lovastatin and monacolin K do not essentially differ.

For food supplements with monacolin K from red yeast rice, a number of uncertainties were pointed out. These concerned the formulation and actual quantities of monacolins present, the previously inadequate evaluation of partner substances used together with monacolins in combined formulations, a lack of clarity about the ratio of the lactone and acid forms for the monacolin K used in each case, the inadequate state of available data on the safety of mon-

acolin K for certain consumer groups (such as pregnant or breastfeeding women), and expected effects resulting from potential interactions with other (active) substances.

In the EFSA's opinion, significant safety concerns are present in the case of monacolin K made from red yeast rice taken as a food supplement at a daily dose of 10 mg. The Panel highlighted the fact that serious adverse events have been reported for monacolins made from red yeast rice when taken at a dose of just 3 mg per day. The Panel concluded that exposure to monacolin K from red yeast rice products can have severe effects on the musculoskeletal system, including rhabdomyolysis, as well as causing disruptions in liver function. On the basis of the available information and multiple uncertainties as mentioned in their assessment, the Panel was not able to identify a quantity of intake of monacolins from red yeast rice as a food supplement that would not give rise to any concerns in terms of adverse effects on health for the general population and for specific vulnerable subgroups within the population (EFSA, 2018).

3.4 Controlled clinical trials frequently exhibiting inadequate reporting in terms of safety and adverse events

A meta-analysis performed by Gerards et al., 2015, investigated 20 controlled trials in humans (total of 6,663 patients, most from China) with monacolin K in doses between 4.8 and 24 mg compared to a placebo or an active treatment programme (including statins). The side effects reported included gastrointestinal disorders (diarrhoea, malaise), musculoskeletal complaints (muscle pain, arthralgia, weakness), changes in various lab test results and dizziness, as well as disruptions to kidney and liver function. On the one hand, the meta-analysis authors did not find any statistically significant differences in the occurrence of adverse events between the treatment groups. However, the authors did note that an evaluation of safety and tolerability had not been presented in all studies, while some studies were ambiguous about quantitative data presentation in this context or omitted it entirely. In their own words: "Quality of safety assessment was low in the majority of studies."

According to the authors, the incidence of reported adverse events was especially low in the studies in which the evaluation of safety and tolerability was not performed adequately. Gerards et al., 2015, state that in controlled clinical trials, adverse events associated with statins occur less often than in general clinical practice, and state that the reason for this is that certain kinds of risk factors for patients in trials are less common due to the use of exclusion criteria. The authors also assume that the true incidence of adverse events with monacolin K are likely to be underestimated as a result of inadequate evaluation of safety in the majority of the clinical trials included. They write: "Our results do not suggest that RYR [Red Yeast Rice] results in different adverse reactions than the usual statin-associated adverse reactions." The authors also find fault with the fact that the quantity of monacolin K is not always stated for red yeast rice preparations, and that there is no standardisation in the production of supplements available on the market; as a result, the declaration is often inadequate (Gerards et al., 2015). The assessment by the EFSA Panel also found that the studies included in the meta-analysis by Gerards et al., 2015, provided an inadequate level of reporting on safety and tolerability, as well as a poor general evaluation of these two topics (EFSA; 2018).

In their review (21 clinical trials with 4,558 patients on the effects of red yeast rice products on blood pressure and cholesterol levels), Xiong et al., 2017, also criticise the frequently inadequate reporting about safety and tolerability, and warn against drawing positive conclusions prematurely: „Furthermore, most clinical studies have not demonstrated severe AEs

[Adverse Events] such as statin-associated myalgias, or increases in ALT, AST, BUN, Cr, and CK occurring with RYR [Red Yeast Rice] use to date, which was likely one of the main reasons for its popularity. There may be a common misconception among some patients and physicians that “natural” means safe (...). In this review, a lack of knowledge about detailed reporting of AEs was observed. Only nine trials reported AEs, with no significant difference in either symptoms and signs or biochemical indicators, whereas AEs were not mentioned in the remaining studies. Although the reported AEs appeared to be safe and were well tolerated in hypertensive patients, definite conclusions about the safety of RYR cannot be drawn due to the limited, inadequate recording and reporting” (Xiong et al., 2017).

In a publication by Xue et al., 2017, looking at a clinical comparative study involving 60 patients (two groups, receiving a daily dose of 1,200 mg of red yeast rice or 20 mg of simvastatin over a period of four weeks), the authors noted that no significant changes in certain lab test parameters had been reported for either treatment group, nor had adverse events been reported for any patient. This result cannot be taken to mean that the applicable contraindications, precautionary measures and potential adverse events are to be doubted for the medicinal substance simvastatin. One criticism voiced by the authors is that further studies are needed on the long-term safety and efficacy of red yeast rice (Xue et al., 2017). In their review based on ten clinical trials, in which red yeast rice products were administered in comparison with simvastatin (10 mg or 20 mg daily), Ong and Aziz, 2016, note that the adverse events observed were comparable in both groups. These events included stomach complaints, nausea, abdominal problems, changes in certain lab test parameters involving liver function, anorexia and other non-specific gastrointestinal symptoms. The authors highlight the lack of clarity about the red yeast rice products used in the studies as well as significant shortcomings in reporting in the studies (Ong and Aziz, 2016).

In a mini-review, Farkouh and Baumgärtel, 2019, note that the risk profile and observed adverse events following consumption of red yeast rice products generally results from case reports, and that a systematic classification of the same is made more difficult by self-medication and the significant variations in product formulations. The authors conclude that continuous monitoring and further longitudinal studies are essential (Farkouh and Baumgärtel, 2019).

One frequent criticism is that reporting on safety and tolerability in clinical intervention studies is not properly attended to. These are designed to prove the superior efficacy of certain substances. Andres et al., 2018, address this point in a comparable case concerning food supplements: „Only a few studies provided detailed information on the occurrence of adverse events or on relevant safety lab parameters (a situation which frequently can be found with substances used as ingredients of dietary supplements). In this context, it is noted that the fact that no adverse events were mentioned for many of the published human intervention studies cannot be taken as proof that no adverse events occurred” (Andres et al., 2018).

3.5 Recent scientific literature on the safety and tolerability of red yeast rice products

Cohen et al., 2017, analysed 28 formulations with red yeast rice in terms of their monacolin K content. The substance was undetectable in two products, while the remaining 26 products contained monacolin K at levels ranging from 0.09 to 5.48 mg per 1,200 mg of red yeast rice: this would yield daily doses of 0.09 to 10.94 mg of monacolin K if the product was consumed in the amounts as recommended. The authors refer to the known (and partially dose-

dependent) adverse events for statins and point out that, given the quantities of monacolin K detected in red yeast rice products and the often inadequate product declarations that fail to provide patients with warnings, a combined dose of prescription-only statins with these products should be considered especially problematic from the perspective of patient safety (Cohen et al., 2017). Patel, 2016, also views the lack of standardisation in supplements based on red yeast rice as a risk: „The fluctuation in monacolin levels can either render RYR [Red yeast rice] to be ineffective or cause deleterious consequences. ... Standardization must be rigorously ensured as in many cases, the content labelling are erroneous. It is difficult to set a cut-off as safe limit of monacolin K, as their content in RYR vary based on the mold strain and fold purification” (Patel, 2016).

Stroes et al., 2015, state that the safety of monacolin K from red yeast rice is not adequately substantiated for long-term use and that standardisation in production methods is lacking: bioavailability therefore varies considerably, depending on the individual formulation. Nor can toxic effects from undesirable co-formulants be entirely excluded. In the authors' opinion, the occurrence of the kinds of adverse effects known from the use of statins must also be expected from monacolin K use (Stroes et al., 2015). Peng et al., 2017, also criticise the lack of standardisation in the manufacture of formulations and conclude that red yeast rice products cannot be recommended for use in clinical practice. If patients inform their doctor that they are taking red yeast rice products, the authors argue that clinical examination and laboratory tests will be necessary because of potential adverse events and disruption to organ function—especially in relation to the liver and kidneys (Peng et al., 2017). Li et al., 2014, and Xue et al., 2017, also note that studies on the long-term safety and efficacy of red yeast rice are not available (Li et al., 2014; Xue et al., 2017).

In an overview of 'nutraceuticals' in the context of dyslipidaemia, which also mentions red yeast rice products, Patti et al., 2017, also state that the consumption of these kinds of formulations cannot yet be recommended without more extensive data on the risk-benefit ratio, as well as further studies addressing the questions of tolerability and safety for long-term use (Patti et al., 2017). In a similar way, the position paper authored by Poli et al., 2018, also calls for the monitoring of red yeast rice product use by medical practitioners. The authors note in particular the need to monitor potential interactions between red yeast rice products containing monacolin K and certain kinds of medicines (Poli et al., 2018). In a subsequent publication, Poli and Visioli, 2019, underline the urgency of their recommendation for medical supervision during the consumption of red yeast rice products, referring once more to the potential for relevant interactions between certain kinds of medicines and for adverse events, which may occur at daily doses as low as 3 mg of monacolin K (Poli and Visioli, 2019). Other authors call for the systematic collection of more extensive clinical data on safety and efficacy before the placing on the market of formulations (some of which also referred to as 'nutraceuticals') such as red yeast rice products (Santini et al., 2018).

In a paper reviewing the effects and side effects of products made from red yeast rice, Stephan, 2016, concludes that there is no reason to accept the claim that red yeast rice lowers or maintains cholesterol levels 'naturally' without also having side effects that are comparable with those experienced while taking synthetic statins. In the context of using red yeast rice products to lower blood cholesterol levels, the author refers to a multitude of risks: these include the lack of standardisation in terms of monacolin content, the risk of adverse events from monacolin K and the lack of medical supervision (Stephan, 2016).

Steffen, 2017, offers another paper summarising the effects and side effects of products made from red yeast rice: after characterising their risks, the author concludes by advising against the use of these products as food supplements (Steffen, 2017).

In their clinical trial investigating a red yeast rice product with 3 mg of monacolin K and other ingredients such as 200 µg folic acid versus placebo in 142 study participants over twelve weeks, Heinz et al., 2016, stress that the comparison of published intervention studies involving red yeast rice products can involve some fundamental difficulties. The authors note the frequent lack of data about the exact dose of monacolin K. For a specified quantity of red yeast rice, very different proportions of monacolin K may be present, as well as varying proportions of other monacolins (Heinz et al., 2016). Gold et al., 2018, also point to significant differences between red yeast rice prepared using traditional techniques and such products that are manufactured as a supplement based on red yeast rice, both in terms of the formulation as well as the presence of monacolin K and other substances (Gold et al., 2018). For one supplement, which provided 2,500 mg of red yeast rice extract with a daily dose of 4 capsules, the analysis revealed an active ingredient content equivalent to a daily dose of 2 mg lovastatin per capsule. The data analysis was performed in response to adverse events suffered by a 53-year-old patient after four months of use, including myalgia, weakness, regurgitation, loss of appetite and discomfort in the upper abdomen. These were categorised as typical statin-related side effects. The authors criticise the fact that, as long as these kinds of products are offered as food supplements rather than actual medicinal products, an appropriate set of usage information and warnings does not need to be declared. Nor is any active monitoring of adverse events being provided (Venhuis et al., 2016).

After reviewing databases maintained by the FDA on reported adverse events, Raschi et al., 2018, recommend medical supervision during the consumption of red yeast rice products so as to guard against the potential incidence of muscular and hepatic adverse events. The authors also criticise the lack of regulatory harmonisation for the status of such formulations (Raschi et al., 2018). Other authors also criticise the frequently unclear and non-standardised formulations of red yeast rice products, as well as the lack of adequate information about existing risks, and call for medical supervision during use (Burke, 2015; De Backer, 2017; Nguyen et al., 2017; Farkouh and Baumgärtel, 2019).

Other current case reports of adverse events in relation to the use of red yeast rice products are also available. In one case, a 39-year-old man developed erectile dysfunction after three weeks of consuming 3.5 to 4.4 g of a red yeast rice formulation on a daily basis. After stopping use, improvement was seen after one week and complete recovery was achieved after five weeks (Liu and Chen, 2018). Another case involved an acute worsening of an existing condition of myasthenia gravis in a 69-year-old patient following one week of consuming a red yeast rice product every day at a dose of 450 mg of red yeast rice (Dobremez et al., 2018).

In the USA, Loubser et al., 2019, reported on a 64-year-old patient who suffered acute hepatitis after taking a red yeast rice supplement for a period of six weeks. A differential diagnosis and liver biopsy led to the diagnosis of a causal correlation with supplement use (drug-induced liver injury, DILI), with the patient consuming a daily dose of 1,200 mg red yeast rice as recommended on the product. The authors note that red yeast rice products may contain highly variable amounts of monacolin K, and recommend greater efforts be made to inform consumers about the risks of liver damage and the importance of medical supervision during use. The authors also state that supplements of this kind are not necessarily any safer than prescription-only medicinal products (Loubser et al., 2019).

3.6 Recent literature on the frequency of adverse events with statins

Among the most frequent adverse events reported for statins, including lovastatin, is damage to skeletal muscle, which may range from minor complaints such as muscle cramps and myalgia (frequency between 1 and 10 percent) to myopathies and elevated creatine kinase (CK) levels in serum (frequency between 0.1 and 1 percent). These kinds of symptoms can be associated with a significant reduction in quality of life, and may give rise to complications as serious as rhabdomyolysis (frequency approximately 1:100,000 to 1:10,000). Rhabdomyolysis is accompanied by highly elevated CK activity and myoglobinuria, and can lead to acute renal failure (Stroes et al., 2015; Laufs et al., 2015; Joint Expert Commission of the BfL and BfArM, 2016; Collins et al., 2016; Meyer, 2019; Cholesterol Treatment Trialists' Collaboration, 2019; Newman et al., 2019). According to estimates from the American Heart Association, elevated transaminases in serum are to be expected for 1 percent of patients taking a course of statins. Serious cases of liver toxicity are to be expected for 0.001 percent of these patients, although the authors also note that reliable predictions about the potential occurrence of serious liver disorders for individual patients are not achievable (Newman et al., 2019).

In this context, Laufs et al., 2015, highlight a clear discrepancy between the incidence of statin-associated muscular symptoms in clinical practice and in registries, compared to the incidence of the same in randomised trials. While 10 to 30 percent of patients in clinical practice and observational studies report statin-associated muscular symptoms, the frequency of muscular complaints in randomised trials with control groups is lower and may, in some cases, differ only marginally between the statin group and the placebo group. In explaining this discrepancy, the authors point to the fact that some trials exclude patients with muscular complaints or statin intolerance. In some studies, minor muscular complaints were not recorded systematically or evaluations of safety and tolerability were not adequate (see also Gerards et al., 2015).

On the other hand, the actual occurrence of statin-associated muscular symptoms can be overestimated in observational studies without a control group. Clinical clarification of symptoms is based on a detailed medical history, the typical form of presentation, the chronological association of complaints with statin medication and potential re-exposure following a pause in medication under critical control (Laufs et al., 2015). Newman et al., 2019, also address the discrepancy between controlled trials and observational studies without a control group, in which the statin-associated muscular symptoms are mentioned comparatively more often. One explanation for this observation given by the authors is that the patients tend to link muscular complaints to statin medication uncritically and their expectations may already be prejudiced—as a kind of 'nocebo effect' (Newman et al., 2019).

3.7 Assessments/classifications made by panels/authorities and in other countries

In 2012, the Permanent Senate Commission on Food Safety at the German Research Foundation (DFG) issued a critical opinion on red yeast rice products sold as food supplements (SKLM, 2012, Toxicological assessment of red yeast rice: updated, final version dated 18 December 2012). In its assessment, the Senate Commission concluded that "red yeast rice is not currently a safe food/food supplement."

Other critical opinions on red yeast rice products as food supplements are available from France (ANSES Opinion Request No 2012-SA-0228, Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the risks associated with the presence

of 'red yeast rice' in food supplements, 14. Februar 2014) and from Belgium (Belgian Superior Health Council, Avis du Conseil Supérieur de la Santé No 9312: Compléments alimentaires à base de 'levure de riz rouge', 3. Februar 2016).

In France, consumers were informed about the risks of red yeast rice products as food supplements in 2017, and reference was made to the need to take such products only under medical supervision (ANSES - French Agency for Food, Environmental and Occupational Health & Safety. Red yeast rice-based food supplements - Before taking these supplements, advice of a healthcare professional should be sought. Updated on 01/12/2017).

In an opinion published in 2016, the Joint Expert Commission of the BVL and BfArM recommends classification of red yeast rice food supplement products as either a medicinal product or a food, depending on product presentation and the claims made for their use. Moreover, products providing a dose of 5 mg monacolin K per day have a considerable pharmacological/metabolic effect and can be classified as a medicinal product regardless of their presentation. Products with a daily dose of less than 5 mg should be investigated for potential risks in the context of approving their placement on the market as a food and should be classified as an unsafe food as appropriate (art. 14, Regulation (EU) No 178/2002). In other foods, such as dietetic foods, use of the ingredient red yeast rice or monacolin K is not permitted, since this is classified as a novel food ingredient and a corresponding authorisation in terms of Regulation (EU) No 258/97 is not available (opinion of Joint Expert Commission of the BVL and BfArM: classification of red yeast rice products, 02/2016). In 2002, the BfArM had already expressed concerns about red yeast rice products with monacolin K as food supplements (BfArM, 2002), and confirmed the assessment made by the Joint Expert Commission in a press release of its own (BfArM again issues warning about red rice food supplements: products with a daily dose equal to or exceeding 5 mg monacolin K should be classified as medicinal products. Press release number 3/16, year of issue 2016, dated 24 February 2016).

In 2014, the Swiss surveillance authority Swissmedic published an opinion that prohibited the marketing of red yeast rice products in Switzerland either as a medicinal product or food ("Marketing of preparations containing *Monascus purpureus* (red yeast rice) is not permitted in Switzerland", Swissmedic Journal 2/2014, pp. 80–85, Swiss Agency for Therapeutic Products, Bern).

The US Food and Drug Administration (FDA) has classified red yeast rice products that contain more than trace amounts of monacolin K as non-approved novel drug products and prohibited these kinds of products from being marketed as food supplements (National Center for Complementary and Integrative Health, US Department of Health & Human Services, National Institutes of Health). Red Yeast Rice. D475—Created June 2012—Updated July 2013).

The Austrian Agency for Health and Food Safety (AGES) recommends "only consuming food supplements containing monacolins after consulting with your doctor/pharmacist until a decision is made for the European Union as a whole" ("Red yeast rice products – what is red yeast rice?" Last modified: 08 April 2019, <https://www.ages.at/en/topics/food/food-supplements/rotschimmelreis-produkte/>).

3.8 Citrinin

Under certain conditions, the fermentation of rice with mould strains of the *Monascus* genus can form the toxic metabolite citrinin. Citrinin is a potential mutagen, and a toxin affecting the kidneys and the unborn embryo or foetus (Flajs/Peraica, 2009; Patel, 2016; Cicero et al., 2017; Santini et al., 2018).

The maximum permissible level of citrinin in food supplements based on rice fermented with the mould *Monascus purpureus* has been set at 2,000 µg/kg. A draft regulation from the EU Commission to amend Regulation (EU) No 1881/2006 has since been issued, which was approved by the Committee of Permanent Representatives on 29 March 2019. This draft envisages reducing the current maximum permissible level for citrinin in food supplements with red fermented rice from 2,000 µg/kg to 100 µg/kg. This reduced maximum permissible level will apply from 1 April 2020 on.

Further information on food supplements is available from the BfR website

A-Z index of food supplements:

https://www.bfr.bund.de/en/a-z_index/food_supplements-129789.html



BfR "Opinions app"

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