

Pharmacologically effective red yeast rice preparations marketed as dietary supplements illustrated by a case report

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This paper reports a typical statin-related adverse reaction from a red yeast rice (RYR) supplement and the analytical findings from the supplement. It also examines the regulatory framework governing botanical supplements in Europe. Two key events that shaped the current regulatory framework are reviewed. First, the Hecht-Pharma judgement by the European Court of Justice (ECJ) that inverted the precautionary principle in the Medicines Act to a reactionary principle. Following the Hecht-Pharma judgement, pharmacologically active dietary supplements can be sold until sufficient signals of harm show that they are an unregistered medicine, placing a huge burden on regulatory authorities. Secondly, the European Food Safety Authority (EFSA) in 2011 approved the first health claim for pharmacologically active RYR dietary supplements. If the current regulatory status for pharmacologically active RYR dietary supplements does not permit adequate warning and active monitoring of adverse drug reactions, then the current regulatory framework may not be adequate to ensure consumer safety. Copyright © 2016 John Wiley & Sons, Ltd.

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Introduction

The European Union (EU) definition of a medicine includes any substance or combination of substances which may be administered to humans with a view to restoring, correcting, or modifying physiological functions in human beings.^[1] This definition allowed the enforcement of foods with active ingredients (e.g. dietary supplements) under the Medicines Act, if deemed necessary. However, the definition was contested by the company Hecht-Pharma before the European Court of Justice (ECJ) arguing that pharmacologically active substances were naturally present in many common foods without causing pharmacological effects.^[2] The subject of the court case was the regulatory status of a Hecht-Pharma product with lovastatin, a cholesterol-lowering drug from red yeast rice (RYR). As a medicine, it would require rigorous clinical trials and registration whilst as a dietary supplement it would not. In 2009, the ECJ ruled that dietary supplements with pharmacologically active ingredients were not medicines unless national authorities could demonstrate that they caused 'considerable pharmacological effects'.^[3] What pharmacological effects are 'considerable' has to be ascertained for each individual product. For the RYR product, the ECJ ruled that it was not a medicine because: (1) there was no clinical data on the RYR dietary supplement available, and (2) in the opinion of the ECJ the daily consumption of 1.33 to 4 mg of lovastatin would not cause a considerable pharmacological effect. This judgement eliminated the precautionary principle from the EU Medicines Act and cleared the way for the marketing of untested drug substances and formulations (e.g. concentrated extracts) as dietary supplements. Because the costly burden of evidence was placed with the national authorities, this greatly troubled

tackling, for example, the many untested sildenafil analogues and pressor amines commonly reported in dietary supplements.^[3,4]

RYR is produced by a mold (*monascus purpureus*) grown on rice grains and contains several structurally related substances called monacolins.^[5–7] The most abundant is monacolin K, which is pharmacologically known as lovastatin. Lovastatin is a 3-hydroxy-3-methyl-glutaryl-coenzyme-A (HMG-CoA) reductase inhibitor and the active ingredient in the cholesterol-lowering drug Mevacor® (Merck).^[8] Mevacor® was introduced in the USA in 1987 as a treatment for high cholesterol.^[8] The Mevacor patient information leaflet states that the recommended therapeutic dose range for lovastatin is 10–80 mg/day.^[9] The recommended starting dose for treating dyslipidemia is 20 mg/day but clinical studies report pharmacologically effective doses as low as 2.5–5 mg/day.^[10–12] As a licensed medicine, lovastatin was three times denied an over-the-counter status application in the USA.^[13–15] Nevertheless, lovastatin became widely available in Europe as an ingredient in RYR dietary supplements. The pharmacotherapeutic efficacy of RYR in the treatment of dyslipidemia has been demonstrated in many clinical studies.^[16–18] Case reports show that RYR preparations have the potential to cause serious adverse effects.^[19,20] Other reports express concern over

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variability in monacolin content and inaccurate labeling.^[21–23] In 2011, the European Food Safety Authority (EFSA) concluded that a causal relationship had been established between the consumption of lovastatin from RYR and ‘maintaining normal LDL cholesterol levels’. To obtain the claimed effect, ≥ 10 mg lovastatin/day should be consumed.^[24]

In the absence of a premarket safety assessment for each product, identifying pharmacologically effective dietary supplements in the market strongly relies on reports of adverse drug reactions. However, adverse drug reactions caused by dietary supplements are poorly recognized as such by users and healthcare professionals.^[25] The paradox is that foods must be safe and thus cannot carry a warning for pharmacological or adverse effects. This paper describes a recent example of an RYR dietary supplement causing a typical statin-related adverse drug reaction. The patients’ remaining dietary supplement capsules were analyzed for pharmacologically active substances and to assess whether it might have caused an adverse drug reaction. These findings are used to discuss the regulatory status of RYR dietary supplements.

A typical case report

A 53-year-old female (70 kg, 1.70 m) experienced myalgia, regurgitation of food, appetite absence, fatigue, and upper abdominal pain following the use of an RYR supplement with a latency of four months after the start. The patient had bought the product through an online web shop. Because the product lacked an information leaflet, the patient was not aware that the supplement could cause adverse drug reactions and it took her several months to relate her complaints to the use of the supplement. The patient recovered after the RYR supplement was withdrawn. No use of concomitant/interacting medication or food (e.g. grapefruit juice) was reported.

The patient reported these adverse effects to the Netherlands Pharmacovigilance Centre Lareb and was requested to submit the remaining product for laboratory evaluation. The RIVM received a plastic jar with 30 of the original 90 capsules still present. The label of the dietary supplement stated that the product was an RYR extract to ‘help maintain a responsible cholesterol level’ but no active

ingredient. The recommended daily intake was 4 capsules daily for the first 3 months, continued with 2 capsules daily. According to the label, 4 capsules contained an extract of 2500 mg RYR to be used ‘as a treatment or as a maintenance dose’. Two of the patient’s remaining capsules were analyzed for pharmacologically active substances, using ultra-performance liquid chromatography–quadrupole time of flight–tandem mass spectrometry (UPLC–QTOF–MS/MS) and standard methods. Briefly, chromatographic separation was performed using a Waters Acquity™ ultra-performance liquid chromatography (UPLC) system fitted with an HSS C18 column (150 mm x 2.1 mm i.d., 1.8 μ m). Detection of the analytes was carried out using a Waters Synapt™ G2 QTOF mass spectrometer with a Z-spray electrospray ionization (ESI) source operating in the positive ion mode. The presence of an analyte was confirmed by retention time, MS and MS/MS using a lovastatin reference standard. Quantification was performed using the K^+ ion of lovastatin, using calibration samples in three concentrations in duplicate, from two independently weighted reference standards.

The analyzed capsules contained 2.0 ± 0.2 mg of lovastatin per capsule. Chromatograms showed the three principal components consistent with lovastatin, dehydro-lovastatin, and lovastatin-acid (Figure 1). The levels of dehydro-lovastatin and lovastatin-acid were not quantified.

Causality

The recommended therapeutic dose range for lovastatin is 10–80 mg/day but clinical studies report pharmacologically effective doses as low as 2.5–5 mg/day.^[10–12] The recommended daily dose of the RYR supplement (4 capsules/day) contained sufficient lovastatin to cause a considerable pharmacological effect. This product could therefore be considered an unregistered medicine. Among the expected adverse drug reactions are gastrointestinal complaints such as acid regurgitation, dry mouth, vomiting, anorexia, pancreatitis, and hepatitis. Like other inhibitors of HMG-CoA reductase, lovastatin occasionally causes myopathy manifested as muscle pain, tenderness, or weakness with very high creatine kinase levels indicating possible myopathy. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to

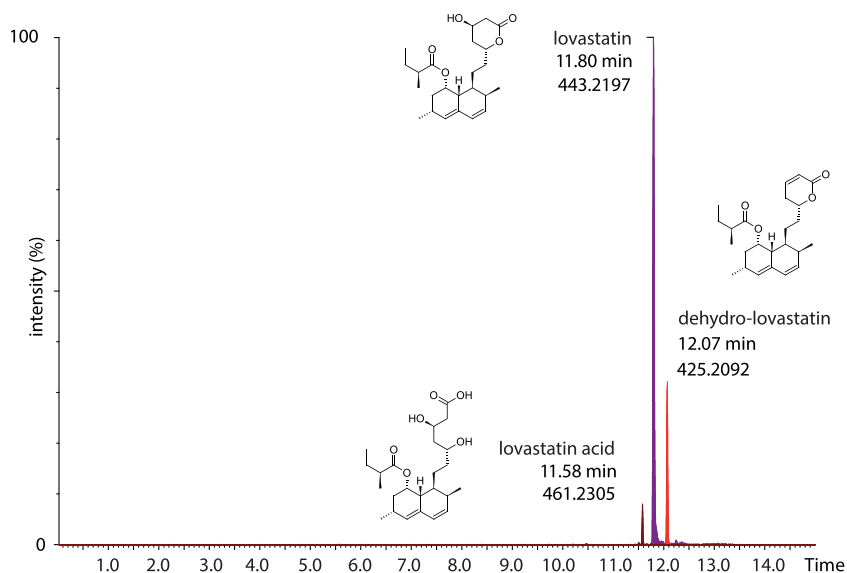


Figure 1. Extracted ion chromatograms of the K^+ adducts of the three principle monacolins in the analyzed product.

myoglobinuria, and rare fatalities have occurred.^[9] It is also well documented that myotoxicity of statins is dose dependent.^[26] Potent inhibitors of CYP3A4 (e.g. itraconazole, ketoconazole, voriconazole, clarithromycin, HIV protease inhibitors, nefazodone, erythromycin) and grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin.^[9]

Using the WHO-UMC assessment tool in this case, a score of 'Probable/Likely' was obtained for the relationship between the patient's complaints and use of the suspect lovastatin containing dietary supplement. The WHO-UMC causality model is meant as a practical tool for assessing case reports.^[27] It is a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

Regulatory aspects

The Hecht-Pharma judgement can be criticized because it hinges on comparisons with clinical studies that were not designed to investigate the onset of desirable or undesirable pharmacological effects. Furthermore, it is questionable to judge the regulatory status by considering a single active substance rather the marketed combination of substances (i.e., the formulation), which is mandatory in the assessment of medicines. As for medicines, the formulation of a dietary supplement may modify the pharmacological profile of the active ingredient. For an RYR dietary supplement the composition and formulation is of particular importance because literature suggests that other monacolins in RYR may also act as HMG-CoA-reductase inhibitors.^[6,17] In 2011, our laboratory confirmed that an extract of an RYR product containing 3 mg lovastatin was 2.2x more potent than 3 mg pharmaceutical grade lovastatin alone when assessed an *in vitro* HMG-CoA-reductase inhibition assay.^[28] The likely explanation for this effect is that the other monacolins present in the product contribute to the inhibitory effect. In 2013, a clinical study demonstrated pharmacotherapeutic effects for a dietary supplement formulation which provided 2 mg lovastatin/day.^[29] For the specific combination of substances in that formulation EFSA approved a health claim that it reduces blood LDL-cholesterol concentrations.^[30]

The EFSA approves health claims for RYR dietary supplements that (intend to) give pharmacotherapeutic effects. They identify consumers rather than patients as the intended user group. However, this suggests that the user should do a blood test for cholesterol before taking an RYR dietary supplement. In reality, patients and consumers in Europe may freely purchase these RYR dietary supplements. It is left to national authorities to regulate such products as medicines but they are confronted with the burden of evidence for each single product. As authorities cannot embark on clinically evaluating dietary supplements, they much rely on signals of harm. One might argue that the ECJ has replaced the precautionary principle in the EU Medicines Act with a reactionary principle without considering the necessity of active monitoring of adverse drug reactions. The challenge is coming to terms with certain dietary supplements being less safe than others in an effect-oriented market.

Conclusion

The presented case shows that an RYR dietary supplement containing <10 mg lovastatin may cause typical statin-related adverse drug reactions. Although the expected adverse effects

are mostly uncomfortable, they can also be very dangerous (e.g. rhabdomyolysis). Based on the lovastatin content alone, the investigated product could be considered an unregistered medicine. Yet, the same would apply to other RYR products that carry EFSA-approved health claims. In addition, additive pharmacological effects may be expected for other monacolins present. At present, pharmacologically active dietary supplements may enter and remain on the market because there is no pre-market screening. Without active post-market surveillance for adverse drug reactions valuable signals of product safety are lost. If the current regulatory status for pharmacologically effective RYR dietary supplements does not permit adequate warnings and active monitoring of adverse drug reactions, then their regulatory status may not be appropriate.

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