Supplements with monacolin K from red yeast rice

No. 2023/02Le, The Hague, February 7, 2023

Background document to the advisory report:
Dutch dietary guidelines for people with atherosclerotic cardiovascular disease
No. 2023/02e, The Hague, February 7, 2023

Health Council of the Netherlands

Contents

1 Introduction

This background document belongs to the advisory report Dutch dietary guidelines for people with atherosclerotic cardiovascular disease (ASCVD).[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship of supplementation with monacolin K from red yeast rice with health outcomes in people with ASCVD. It also describes the scientific evidence on this topic and the conclusions that have been drawn by the council's Committee on Nutrition.

1.1 Supplements with monacolin K from red rice yeast

This background document describes the scientific evidence regarding supplementation with supplements containing monacolin K from red yeast rice. Red yeast rice is made by fermenting rice with the fungus Monascus, and was originally used as ingredient in traditional foods in east Asia. Depending on the Monascus strains used and the fermentation conditions, the products may contain monacolins, which are secondary metabolites produced during fermentation.[2] Monacolin K is the main monacolin in Monascus purpureus-fermented rice (75-90% of total monacolin content).[3,4] An alternative name for Monacolin K is lovastatin. Lovastatin is a registered cholesterol lowering drug in many countries, but not in the Netherlands.

1.2 Recommendation on supplements with red yeast rice in the Netherlands

There currently is no Health Council recommendation regarding the use of supplements with monacolin K from red yeast rice. Regarding the use of nutrient supplements, the *Dutch dietary guidelines 2015* state that nutrient supplements are not needed, except for specific groups for which supplementation applies.[5] For instance, vitamin D supplements are recommended for various groups of people, such as 0 to 4-year-olds, women aged 50 and over, and everyone aged 70 and over.[6]

In 2011, the European Food and Safety Authority (EFSA) approved a health claim on monacolin K from red yeast rice[7], which was authorized by the European Union (EU). The claimed effect is that consumption of 10 mg/d monacolin K from red yeast rice contributes to the maintenance of normal blood LDL cholesterol concentrations. In 2018, EFSA published a report on the safety of monacolins from red yeast rice, and reported there were safety concerns with dosages of 3 mg/day or higher.[8] In June 2022, the European Committee therefore reduced the maximum allowed daily dosage of Monacolin K from red yeast rice from 10 mg/d to less than 3 mg/day.[9]

2 Methodology

Supplements with monacolin K from red yeast rice are targeted at people who wish to reduce their LDL cholesterol levels. Since people with ASCVD (the target group of the current advisory report, further explained below) often have elevated LDL cholesterol levels and lipid management is one of the pillars of cardiovascular risk management,[10,11] the Committee aimed to evaluate the health effects of these supplements on health outcomes in people with ASCVD. The studies on the health effects of these supplements were performed in people with elevated cholesterol levels, and not specifically in people with established ASCVD. Since this topic was not previously evaluated for the *Dutch dietary guidelines 2015*, the Committee additionally evaluated the evidence on this topic in people without ASCVD but with elevated LDL cholesterol levels.

2.1 Questions

The Committee aimed to answer the following question: What is the effect of supplementation with less than 3 mg/d monacolin K from red yeast rice on health outcomes in people with elevated LDL cholesterol levels?

2.2 Target group

The target group of the current advisory report is people with ASCVD. The Committee defines this group as people with clinically established coronary heart disease (CHD, consisting of acute coronary syndromes [myocardial infarction and unstable angina], stable angina and revascularisation procedures such as percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]), peripheral arterial disease (PAD) or cerebrovascular disease (consisting of stroke and transient ischemic attack). In the target population, atherosclerosis in the coronary arteries, aorta, iliac and femoral arteries, and cerebral arteries is the main underlying pathological process. Groups with a high risk (but no manifestation) of ASCVD, such as people with hypertension or elevated LDL cholesterol levels, fall outside this definition. Also, the target group of this advice does not include people with heart failure (except when those people also suffer from ASCVD). A detailed description of the target group of this advisory report is provided in the background document *Methodology for the evaluation of the evidence*.[12]

As explained above, the Committee additionally evaluated studies performed in people without established ASCVD, but with elevated LDL cholesterol levels.

2.3 Nutritional topics

The Committee searched for studies into the effects of supplements with monacolin K from red yeast rice. Given that dosages of 3 mg/d or higher monacolin K from red yeast

rice are not allowed on the market anymore, the Committee specifically searched for studies that addressed dosages of less than 3 mg/d.

2.4 Health outcomes

The Committee selected the following health outcomes for this advisory report (further explained in the background document Methodology for the evaluation of the evidence[12]):

- short-term surrogate outcomes:
  - body weight
  - systolic blood pressure
  - low-density lipoprotein (LDL) cholesterol
  - estimated glomerular filtration rate (eGFR)
  - glycated haemoglobin (HbA1c) and fasting blood glucose
- long-term health outcomes:
  - all-cause mortality
  - morbidity and/or mortality from total CVD, CHD, stroke (cerebrovascular disease), heart failure, atrial fibrillation, type 2 diabetes, chronic obstructive pulmonary diseases (COPD), total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression
  - subtypes of CHD, such as myocardial infarction, angina pectoris and revascularisation procedures (i.e., coronary artery bypass surgery and percutaneous coronary intervention)

2.5 Selection and evaluation of the literature and drawing conclusions

2.5.1 Search and selection of studies

The Committee searched for RCTs on the supplementation of less than 3 mg/d monacolin K from red yeast rice in EFSA's report on efficacy. EFSA used one systematic review (SRs) with meta-analysis (MA)[2], of which one RCT was selected as being appropriate for EFSA's evaluation.[3] One additional report of an individual RCT was selected for EFSA's evaluation.[13] Both RCTs investigated effects of approximately 10 mg monacolin K from red yeast rice on LDL cholesterol. Due to the high doses addressed in these RCTs, the Committee did not select these RCTs for her evaluation. Next, the Committee searched for SRs with MAs on RCTs published after the search dates of the MAs evaluated by EFSA (2005). To identify such publications, the Committee searched PubMed and Scopus in June 2022. Based on this search, 5 MAs were selected[14-18], in which two RCTs were identified that investigated a dosage of monacolin K from red yeast rice of less than 3 mg/d.[19,20] These RCTs were included in the Committee's evaluation. The Committee additionally searched for individual RCTs published after the search date of the most complete MA (November 2015). This

yielded one additional RCT suitable for the Committee's evaluation.[21] Thus, in total 3 RCTs were included in the Committee's evaluation. The search strategy and specification of the study selection are presented in Annex A.

2.5.2 Drawing conclusions

A detailed description of the approach used for drawing conclusions is provided in the background document *Methodology for the evaluation of the evidence*.[12] In short, the Committee drew conclusions on (the certainty of) the evidence regarding the effect of supplementation with risk of health outcomes in people with elevated LDL cholesterol, based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, it took the quality of the studies, in particular the risk of bias, and the heterogeneity between studies into account. The risk of bias of RCTs was assessed by the Committee using the revised Cochrane Collaboration's tool RoB 2.[22] The Committee used the decision tree (presented in the background document *Methodology for the evaluation of the evidence*[12]) as a tool to support consistency in drawing conclusions.

3 Effects of monacolin K from red yeast rice

In this chapter, the Committee describes the scientific evidence from RCTs on the effects of supplementation with less than 3 mg/d monacolin K from red yeast rice with health outcomes.

Conclusion:
There is too little research from intervention studies to draw conclusions regarding the effects of supplementation of 2.0 to 2.4 mg per day monacolin K from red yeast rice on LDL cholesterol, blood pressure, and body weight in people with elevated LDL cholesterol levels.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion: There are three RCTs that reported on the effects of supplements with monacolin K from red yeast rice or (in one study) fermented garlic with dosages less than 3 mg/d. This excludes a conclusion with strong evidence, for which at least 5 studies are required. All RCTs showed favourable effects on LDL cholesterol of such supplementation. However, there were serious concerns regarding the quality of the largest RCT, since it was judged as high risk of bias, among others due to exclusion of non-compliant people from the data-analyses. The remaining two RCTs were rather small (73 participants together), of which for one there were some concerns regarding the study quality due to lack of blinding. Taken together, the Committee judged these studies provided too little evidence to base conclusions on. One RCT also reported on the effects on blood pressure and body weight. However, one RCT per outcome provides too little evidence to base conclusions on. Therefore, the Committee concluded there was too little evidence to draw a conclusion on these outcomes as well.

Explanation:
There were three RCTs found, which are briefly described below.
The study by Wang et al. (1997)[19] was performed in 502 Chinees participants with hyperlipidaemia. The participants discontinued the use of medication for hyperlipidaemia for more than 4 weeks and received dietary advice for 2 to 4 weeks. For the analyses, data of 446 participants were used. The data of the remaining 56 participants (~10%) were not used due to non-compliance and incomplete data collection. A preparation of red rice yeast was given twice a day for 8 weeks to people in the intervention group (n=324). This contributed 2.4 mg monacolin K per day. The control group (n=122) received a traditional Chinese medicine with putative hypolipidemic properties, named Jiaogulan. The study was single blinded. LDL cholesterol levels were calculated using the Friedewald formula. After 8 weeks of

intervention, there were statistically significantly greater reductions in LDL cholesterol in the intervention (30.9%) compared to the control group (8.3%). For the analyses on LDL cholesterol, data of 321 participants were used. The authors explained that, for the remaining participants, the Friedewald formula does not give useful information on LDL cholesterol since their triglyceride values were too high (>400 mg/dL).
Two of the authors were appointed at Pharmanex inc., a company that sells (among other things) nutritional supplements. The role of the authors in this work was not reported. There were no notable funding sources for this study.
The overall risk of bias was judged as high by the Committee. The judgement was mainly due to the exclusion of ~10% of the participants due of noncompliance or missing outcome data and the uneven distribution of missing outcome data between intervention and control group.

The study by Minamizuka et al. (2021)[21] was performed in 18 Japanese participants with elevated LDL cholesterol levels who received diet therapy only (thus, were not on statins). Originally, 19 participants were enrolled and randomised. However, one of the participants in the intervention group did not visit the hospital after randomisation and was excluded from the study and analyses. The study was open-labelled. People in the intervention (n=10) and control (n=8) group both received diet therapy according to the American Heart Step One diet. Participants in the intervention group consumed processed foods containing 200 mg/d red yeast rice for 8 weeks. This provided 2 mg of monacolin K per day. There was no placebo given to the control group. LDL cholesterol levels were calculated using the Friedewald formula. After 8 weeks of intervention, greater reductions in LDL cholesterol (-0.20 (-0.64, 1.19) mmol/L in the control group versus -0.96 (-1.05, -0.34) mmol/L in the intervention group), and systolic and diastolic blood pressure were observed in the intervention than the control group. There were no differences in body weight changes between the groups.
The red yeast rice was provided by Asahi Group Holdings (Japan), a global corporation of companies that produce (among others) alcoholic beverages, soft drinks and food. One of the authors was affiliated at Asahi Group Holdings. The funding source had no role in the design of the study and neither in the execution, analyses, interpretation of the data and the decision to submit the work.
The Committee notes that it has some concerns based on their risk of bias assessment. In particular, these concerns raised from the observations that neither participants nor outcome assessors were blinded and that the control group received no placebo. Overestimation of the effect due to performance bias can therefore not be excluded.

The study by Higashikawa et al. (2012)[20] assessed the effects of capsules with fermented garlic containing 2 mg/day monacolin K in 55 Japanese people with mild hyperlipidaemia. People with regular use of medication and people who consumed

functional foods that may affect body weight or serum lipids were excluded. The study had a double-blind, randomised, placebo-controlled, parallel-group design. Participants received intervention capsules or placebo capsules for 12 weeks. The study followed an intention-to-treat analysis. One participant dropped out after 4 weeks because of the need to start treatment for hypertension. Missing data was filled using multiple imputation. After 12 weeks, serum LDL cholesterol concentrations reduced more in the intervention (-20.6 ± 24.9 mg/dL) than in the control group (+0.5 ± 22.6 mg/dL). There were no differences in abdominal circumference after 12 weeks.

The study was funded by Pharmaceutical Co., Ltd., Japan, a company that produces health care products. This company also provided the study capsules. Moreover, one of the authors is an employee of Wakunaga Pharmaceutical. This author had no role in the collection, analysis, or interpretation of the data.

The Committee notes it is unsure whether the effects of monacolin K from fermented garlic are entirely comparable to those of monacolin K from red yeast rice. The Committee furthermore remarks that it has some minor concerns based on its risk of bias assessment since the authors did not provide information on the amount and distribution of missing outcome data and on whether the data were analysed according to a pre-specified data-analysis plan.

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Annexes

Annex A Search strategy and study selection

A.1 Search SRs/MAs

PubMed

("red yeast rice" [Supplementary Concept] OR "red yeast rice"[TIAB] OR "monascusic lactone A" [Supplementary Concept] OR "monascusic lactone A" [TIAB] OR "monascusic acid A" [Supplementary Concept] OR "monascusic acid A" [TIAB] OR "monascustin" [Supplementary Concept] OR "monascustin" [TIAB] OR “Monacolin K” [TIAB] OR “Monascus purpureus” [TIAB] OR “lovastatin” [TIAB] OR “mevinolin” [TIAB] OR “Monascus purpureus-fermented rice” [TIAB] OR “RYR” [TIAB] OR “red mold rice” [TIAB] OR “M. purpureus” [TIAB])

AND

(“Systematic review”[publication type] OR “Meta-analysis”[publication type] OR “Review Literature as Topic”[MeSH] OR “review”[TIAB] OR "meta-analysis"[TIAB] OR “meta analysis”[TIAB] OR “metaanalysis”[TIAB] OR “quantitative review”[TIAB] OR “quantitative overview”[TIAB] OR “Systematic Reviews as Topic”[MeSH] OR “systematic review”[TIAB] OR “systematic overview”[TIAB] OR “methodologic review”[TIAB] OR “methodologic overview”[TIAB] OR “individual participant data”[TIAB] OR “individual patient data”[TIAB] OR “IPD”[TIAB] OR “individual-level data”[TIAB] OR “pooled analysis”[TIAB] OR “Pooled analyses”[TIAB] OR “multi-center study”[TIAB] OR “multi-cohort study”[TIAB])

From: December 2004

Scopus

TITLE-ABS("red yeast rice") OR TITLE-ABS("monascusic lactone A") OR TITLE-ABS("monascusic acid A") OR TITLE-ABS("monascustin") OR TITLE-ABS(“Monacolin K”) OR TITLE-ABS(“Monascus purpureus”) OR TITLE-ABS(“lovastatin”) OR TITLE-ABS(“mevinolin”) OR TITLE-ABS(“Monascus purpureus-fermented rice”) OR TITLE-ABS(“RYR”) OR TITLE-ABS(“red mold rice”) OR TITLE-ABS(“M. purpureus”)

AND

TITLE-ABS("Systematic Review") OR TITLE-ABS(Review) OR TITLE-ABS(Meta-Analysis) OR TITLE-ABS("Meta Analysis") OR TITLE-ABS(metaanalysis) OR TITLE-ABS("quantitative review") OR TITLE-ABS("quantitative overview") OR TITLE-ABS("methodologic review") OR TITLE-ABS("methodologic overview") OR TITLE-ABS("individual participant data") OR TITLE-ABS("individual patient data") OR TITLE-

ABS(IPD) OR TITLE-ABS("individual-level data") OR TITLE-ABS("pooled analysis") OR TITLE-ABS("Pooled analyses") OR TITLE-ABS("multi-center study") OR TITLE-ABS("multi-cohort study")

From: December 2004

A.2 Search RCTs

PubMed

("red yeast rice" [Supplementary Concept] OR "red yeast rice"[TIAB] OR "monascusic lactone A" [Supplementary Concept] OR "monascusic lactone A" [TIAB] OR "monascusic acid A" [Supplementary Concept] OR "monascusic acid A" [TIAB] OR "monascustin" [Supplementary Concept] OR "monascustin" [TIAB] OR “Monacolin K” [TIAB] OR “Monascus purpureus” [TIAB] OR “lovastatin” [TIAB] OR “mevinolin” [TIAB] OR “Monascus purpureus-fermented rice” [TIAB] OR “RYR” [TIAB] OR “red mold rice” [TIAB] OR “M. purpureus” [TIAB])

AND

("Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [publication type] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Historically Controlled Study"[Mesh] OR “randomized” [TIAB] OR “randomized” [TIAB] OR “RCT” [TIAB] OR “controlled*” [TIAB] OR “placebo” [TIAB] OR “clinical trial” [TIAB] OR “trial” [TIAB] OR “intervention” [TIAB])

NOT

("Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Review"[Publication Type] OR "meta analysis"[Publication Type] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Network Meta-Analysis"[MeSH Terms] OR cohort studies[MeSH] OR cohort stud*[TIAB] OR longitudinal studies[MeSH] OR longitudinal stud*[TiAB] OR prospective studies[MeSH] OR prospective stud*[TIAB] OR “Observational study”[publication type])

From: December 2004

Scopus

TITLE-ABS("red yeast rice") OR TITLE-ABS("monascusic lactone A") OR TITLE-ABS("monascusic acid A") OR TITLE-ABS("monascustin") OR TITLE-ABS(“Monacolin K”) OR TITLE-ABS(“Monascus purpureus”) OR TITLE-ABS(“lovastatin”) OR TITLE-

ABS(“mevinolin”) OR TITLE-ABS(“Monascus purpureus-fermented rice”) OR TITLE-ABS(“RYR”) OR TITLE-ABS(“red mold rice”) OR TITLE-ABS(“M. purpureus”)

AND

TITLE-ABS-KEY ("Clinical Trial") OR TITLE-ABS-KEY ("Cross-Over Studies”) OR TITLE-ABS-KEY("Double-Blind Method") OR TITLE-ABS-KEY("Single-Blind Method") OR TITLE-ABS-KEY("Controlled Before-After Studies") OR TITLE-ABS-KEY("Historically Controlled Study") OR TITLE-ABS-KEY(“randomized”) OR TITLE-ABS-KEY(“randomized”) OR TITLE-ABS-KEY(“RCT”) OR TITLE-ABS-KEY(“controlled*”) OR TITLE-ABS-KEY(“placebo”) OR TITLE-ABS-KEY(“clinical trial”) OR TITLE-ABS-KEY(“trial”) OR TITLE-ABS-KEY(“intervention”)

AND NOT

TITLE-ABS-KEY ("Systematic Review") OR TITLE-ABS-KEY (Review) OR TITLE-ABS-KEY ("Meta-Analysis") OR TITLE-ABS-KEY ("Meta Analysis”) OR TITLE-ABS-KEY ("Network Meta-Analysis”) OR TITLE-ABS-KEY(“cohort stud*”) OR TITLE-ABS-KEY(“longitudinal stud*”) OR TITLE-ABS-KEY(“prospective stud*”) OR TITLE-ABS-KEY(“Observational study”)

From: December 2004

A.3 Selection of SRs and MAs, and from these records the selection of RCTs

Step 1. Identification SRs and MAs
752 records retrieved
- PubMed: 364
- Scopus: 388

300 duplicates excluded

Step 2. Screening SRs and MAs
492 records screened,
439 records excluded after first selection

Step 3. Eligibility SRs with MAs
53 full-texts assessed,
46 records excluded after second selection due to:
- Different study design: 9
- No exposure of interest: 3
- No outcome of interest: 2

- No systematic approach: 31
- Already covered in EFSA report: 1
- Language: 2

Step 4. Selection of SRs with MAs
5 records of SRs with MAs selected, together including a total of 35 individual RCTs

Step 5. Eligibility RCTs
35 records screened,
33 records excluded due to:
- Exposure contained ≥ 3 mg/d monacolin K: 20
- Exposure consisted of a multi-supplement instead of monacolin K alone: 13

Step 6. Inclusion RCTs
2 records of RCTs included

A.4 Selection of RCTs

Step 1. Identification
750 records retrieved:
- PubMed: 344
- Scopus: 406

258 duplicates excluded

Step 2. Screening
492 records screened,
485 records excluded after first selection

Step 3. Eligibility
7 full-texts assessed,
6 records excluded after second selection due to:
- No exposure of interest: 3
- Exposure contained ≥ 3 mg/d monacolin K: 3

Step 4. Inclusion
1 record included

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
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