



REVIEW

Monacolin K supplementation in patients with hypercholesterolemia: A systematic review of clinical trials



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KEYWORDS

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Supplementation

Abstract Monacolin K is the major active component in red yeast rice (RYR) which is structurally identical to lovastatin and has the most powerful effect, in terms of reducing blood cholesterol levels. This review aimed to examine the effect and safety of different doses of monacolin K on blood cholesterol levels. PubMed and Cochrane were searched for articles published between 2012 and 2023 for clinical-trials and randomized-controlled-trials. Eligible studies included participants > 18-years-old, of any gender and ethnicity. The intervention/exposure of interest was monacolin K. Hypercholesterolemia was considered the outcome of interest defined as the elevated total or low-density-lipoprotein (LDL) cholesterol levels. 12 randomized-controlled-trials were eligible for inclusion in the analysis including 769 participants > 18-years-old. 11 out of 12 studies were assessed with high methodological quality and one study with low methodological quality. Monacolin K supplementation varied between 2 mg and 10 mg per day and the maximum period of supplementation was 12 weeks. All studies indicated a beneficial effect of monacolin supplementation on LDL and total cholesterol levels ($p < 0.05$) regardless the dose and period of supplementation. Also, 3 of the included studies reported adverse side effects after treatment with monacolin K. Low doses of monacolin K equal to 3 mg/day exert potential cholesterol-lowering effects although the number of relative studies is limited. Regarding the safety of monacolin K supplementation, findings seem to be more controversial and therefore, it is suggested for all patients treated with monacolin K to be routinely monitored regardless the dose of supplementation.

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PALABRAS CLAVE

Monacolina K;
Arroz de levadura
roja;
Hipercolesterolemia;
Suplementación

La suplementación con monacolina K en pacientes con hipercolesterolemia: una revisión sistemática de ensayos clínicos

Resumen La monacolina K es el principal componente activo en el arroz de levadura roja (RYR) que es estructuralmente idéntico a la lovastatina y tiene el efecto más poderoso, en términos de reducción de los niveles de colesterol en la sangre. Esta revisión procuró examinar el efecto y la seguridad de diferentes dosis de monacolina K sobre los niveles de colesterol en sangre. Se realizaron búsquedas en PubMed y Cochrane de artículos publicados entre 2012 y 2023 para obtener ensayos clínicos y ensayos controlados aleatorios. Los estudios elegibles incluyeron participantes > de 18 años de edad, de cualquier sexo y etnia. La intervención/exposición de interés fue monacolina K. La hipercolesterolemia se consideró el resultado de interés definido como los niveles elevados de colesterol total o lipoproteína de baja densidad (LDL). Doce ensayos controlados aleatorios fueron elegibles para su inclusión en el análisis con 769 participantes > 18 años de edad. Once de 12 estudios se evaluaron con alta calidad metodológica y un estudio con baja calidad metodológica. La suplementación con monacolina K varió entre 2 mg y 10 mg por día y el período máximo de suplementación fue de 12 semanas. Todos los estudios indicaron un efecto beneficioso de la suplementación con monacolina sobre los niveles de LDL y colesterol total ($p < 0,05$) independientemente de la dosis y el período de suplementación. Además, 3 de los estudios incluidos informaron efectos secundarios adversos después del tratamiento con monacolina K. Las dosis bajas de monacolina K iguales a 3 mg/día ejercen efectos potenciales reductores del colesterol, aunque el número de estudios relativos es limitado. Con respecto a la seguridad de la suplementación con monacolina K, los hallazgos parecen ser más controvertidos y, por lo tanto, se sugiere que todos los pacientes tratados con monacolina K sean monitoreados rutinariamente independientemente de la dosis de suplementación.

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Introduction

Recent decades have shown tremendous progress in the prevention of cardiovascular diseases as a result of several pharmaceuticals and dietary improvements. Modifications in diet have focused not only on the macronutrient components but also on some micronutrients with drug-like properties.^{1,2} In particular, there are some natural food components with potential properties related to health and disease including lipid and blood pressure-lowering effects.^{3,4} Therefore, based on scientific findings, many patients are more reluctant to use natural dietary products instead of conventional medicines causing several side-effects. Recently, health professionals are asking for more high-quality evidence-based recommendations relating to the efficacy of these natural products.^{4,5}

RYR¹ (RYR) is a new natural therapeutic agent, grown on white rice. It is a nutrient produced by the fermentation of rice with the fungus *Monascus Purpureus* and contains monacolins, pigments, organic acids and amino acids having anti-hyperlipidemic effects.⁶ RYR is recognized as a functional food, known for its cholesterol-lowering.^{1,6-9} It is a common dietary component of the Asian diet and it is widely used in the Chinese Medicine.¹⁰

Monacolin K is the major active component in RYR which is structurally identical to lovastatin and has the most pow-

erful effect, in terms of reducing blood cholesterol levels.^{1,7} Under laboratory conditions, monacolin K is a transparent, white crystal with low solubility in water, but highly soluble in organic solvents such as methanol, ethanol, acetone, chloroform and benzene. Under low pH conditions, it adopts one of two forms, acidic or lactone. The acidic form plays a role in reducing blood lipid.¹¹ Particularly, monacolin K acts as an inhibitor of HMG-CoA reductase preventing its conversion to mevalonic acid and thus reducing cholesterol biosynthesis in the liver.^{10,12}

Researchers from around the world have conducted in-depth research on monacolin K to investigate its effects in cholesterol levels. A previous meta-analysis of 47 RCTs² with studies published since 1997, aimed to examine the therapeutic effect of Chinese patented drugs containing RYR in people with hyperlipidemia and found that RYR supplements were more effective than simvastatin in regard to LDL³ and total cholesterol levels.¹³ A more recent meta-analysis of 30 RCTs aiming to examine the effect of RYR preparations in patients with Metabolic Syndrome found that RYR was associated with significant reductions in mortality, total cholesterol, triglycerides, fasting plasma glucose, and blood pressure without causing any adverse side effects compared to placebo.¹⁴ Moreover, another review of 22 CTs⁴

¹ Red yeast rice.

² Randomized controlled trials.

³ Low density lipoprotein.

⁴ Clinical trials.

published in 2012 focused in evaluating the effect of RYR in dyslipidemia and showed that RYR supplementation had similar effects to statin, even in combination with other dietary supplements.¹⁵

RYR has been shown to be well-tolerated by patients at doses of monacolin K up to 10 mg/day although previous studies reported mild side effects including myalgia.¹⁶ In 2011, EFSA,⁵ based on scientific evidence approved a health claim regarding the intake of RYR containing 10 mg of monacolin K, as a dietary supplement for controlling blood cholesterol levels.¹⁷ Nevertheless, EFSA, in 2018, re-examined the safety of monacolin K and found that monacolin K, in lactone form, is identical to lovastatin and that the side effects of taking 10 mg of monacolin K are similar to those caused by lovastatin supplementation, which are well.^{16,18} Thus, EFSA reviewed the recommended daily intake of monacolin K from 10 mg to 3 mg per day.¹⁸ Indeed, existing data regarding the efficacy and safety of 3 mg supplementation of monacolin K in blood cholesterol levels is limited and requires further investigation. Therefore, the current systematic review aimed to examine the effect and safety of different doses of monacolin K on blood cholesterol levels.

Materials and methods

Search strategy and eligibility criteria

A systematic literature search was conducted through international databases, including PubMed and Cochrane Library using MeSH⁶ terms. The references cited in the selected articles were also searched manually. The literature search was conducted independently by two researchers from inception to September 2023. The search was limited to papers published in English; there was a date restriction on the studies included (2012–2023) in order to examine the most recent data. Moreover, the reference lists of the selected articles were searched to identify other eligible studies. Any discrepancies between reviewers were resolved in consultation with a third author. The search strategy used is presented in Table 1.

To identify included studies, we used specific inclusion criteria. Participants were ≥ 18 -year-old adults of any gender and ethnicity. The intervention/exposure of interest was monacolin K. Hypercholesterolemia was considered the outcome of interest defined as the elevated total or LDL cholesterol levels. For the comparison, we used participants with hypercholesterolemia taking placebo. Only clinical trials and randomized controlled trials were eligible for inclusion. Published conference abstracts, dissertations, narrative reviews, and case reports were excluded.

Study selection and data extraction

The titles and abstracts from the electronic searches were examined independently by two reviewers and the full-text articles from the selected studies that were likely to

meet the inclusion criteria were retrieved. Following the first stage, the same authors contacted a second evaluator in order to make the final decision. Any discrepancies between reviewers were resolved in consultation with a third author. From each study, we extracted the following variables: author, year, and country; study design, follow up time; population; main measures; intervention and main findings.

Quality assessment

The assessment of the methodological quality of the included studies was performed by two independent reviewers. The Jadad score was used for assessing RCTs based on the randomization, the blinding and the participants' dropout. The final score ranges from 0 to 5 points and is considered of "high quality" for Jadad score ≥ 3 and of "low" quality for Jadad score ≤ 2 .¹⁹

Results

From the initial search, 99 articles were identified out of which 30 duplicate records were removed. Out of 69 articles that were screened based on their title and abstract, 46 articles were excluded as they did not meet the required inclusion criteria. From the remaining 23 articles, 11 articles were excluded after reading the whole text and the remaining 12 articles were included for qualitative analysis. The flow chart of selection studies regarding the systematic review is presented in Fig. 1. Regarding the methodological quality assessment, results showed that almost all studies ($n=11$) were assessed with high methodological quality (score ≥ 3) and only one study was assessed with low methodological quality receiving a score equal to 2. Results of the methodological quality assessment are presented in Tables 2 and 3.

The current analysis included 769 participants > 18 years of age in order to examine the potential effect that monacolin K has on hypercholesterolemia. All studies employed a randomized controlled design and were published between 2012 and 2021. Monacolin K dosage used in the studies ranged between 2 mg and 10 mg per day. In particular, 5 out of 12 studies examined the effect of lower doses of monacolin K ranged between 2 mg and 3.75 mg whereas 6 studies examined the effect higher doses of monacolin K ranged between 8 mg and 10 mg. Only one study compared the effectiveness of both doses of monacolin K in patients with hypercholesterolemia (10 vs 3 mg/day). The main characteristics and findings of the included studies are presented in Table 4.

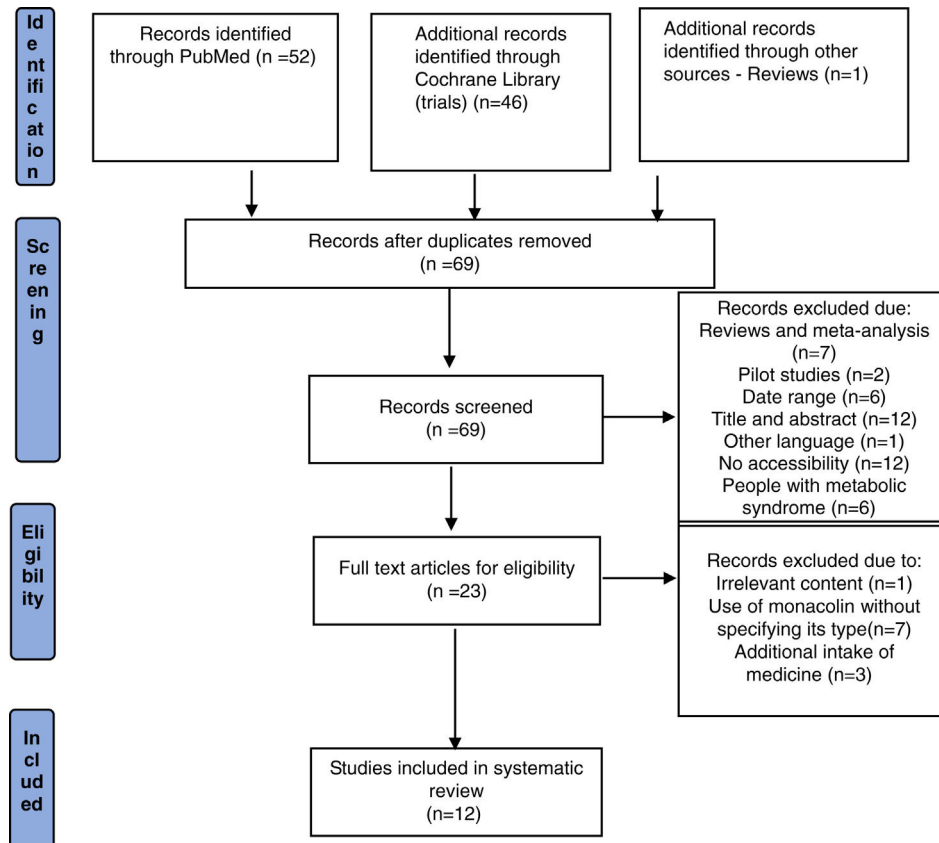
Five of the included studies examined the effect of low doses of monacolin K (2–3.75 mg/day) compared to either another supplemented group and a control group or just to a control group under placebo treatment. In the first cross-over clinical trial by Trimarco et al. (2015),²⁰ the 1st group was administered with the dietary supplement "Armolipid Plus" containing 3 mg of monacolin K, polycosanols, berberine, astaxanthin, folic acid and CoQ10 and the 2nd group was administered with the supplement "LopiGLIK" containing 3.3 mg of monacolin K, berberine and Morus alba leaf extract for 10 weeks. The results showed a statisti-

⁵ European food safety authority.

⁶ Medical subject headings.

Table 1 Strategic search and keywords used to find studies investigating the relationship between monacolin and hypercholesterolemia from PubMed and Cochrane Library (trials).

	Key-words	Number of studies found in databases	
		PubMed	Cochrane library (trials)
Exposure factor: Monacolin	1. Monacolin	367	91
Outcome: Hypercholesterolemia	2. Hypercholesterolemia	49.850	8.334
	3. Dyslipidemia	117.788	6.640
	4. Cholesterol	328.412	42.280
	5. Total cholesterol	103.161	22.848
	6. LDL cholesterol	83.547	20.100
	7. #2 OR #3 OR #4 OR #5 OR #6	398.924	48.337
Study design: Experimental studies	8. Randomized clinical trial	771.210	70.345
	9. Clinical trial	1.378.172	792.127
	10. #8 OR #9	1.378.172	792.127
	11. #1 AND #7 AND #10	52	46

**Figure 1** Flow chart of the selected studies.

cally significant reduction in LDL and total cholesterol in the 2nd group compared to the 1st ($p < 0.05$). Moreover, the randomized double-blind clinical study by Heinz et al. (2016),²¹ used a RYR supplement containing 3 mg monacolin K, folate and CoQ10 for 12 weeks and indicated a significant decrease in LDL, total cholesterol, LDL to HDL⁷

ratio compared to the control group ($p < 0.05$). The study by Iskandar et al. (2020)²² used a dietary supplement containing 3.75 mg of monacolin K, gugulipidium extract and chromium picolinate for 12 weeks. The study showed a significant reduction in LDL and total cholesterol compared to the control group ($p < 0.05$). However, individuals in the intervention group experienced some adverse effects such as indigestion, flatulence and bloating. Also, the most recent study by Minamizuka et al. (2021)⁶ used RYR supplement

⁷ High density lipoprotein.

Table 2 Assessment of methodological quality of studies based on the JADAD score (Jadad et al., 1996).

Study	Publication		Double blindness		Withdrawals/abandonments	Jadad score
	Indicated	Appropriate	Indicated	Appropriate		
Trimarco et al., 2015	Yes	Yes	Yes	Yes	No	4
Heinz et al., 2016	Yes	Yes	Yes	Yes	Yes	5
D'Addato et al., 2017	Yes	Yes	Yes	Yes	Yes	5
Giuseppe et al., 2017	Yes	Yes	Yes	Yes	Yes	5
Magno et al., 2018	Yes	Yes	No	No	Yes	3
Mazza et al., 2018	Yes	Yes	No	No	No	2
Domenech et al., 2019	Yes	Yes	Yes	Yes	No	4
Ruscica et al., 2019	Yes	Yes	Yes	Yes	Yes	5
Wang et al., 2019	Yes	Yes	Yes	Yes	Yes	5
Iskandar I. et al., 2020	Yes	Yes	Yes	Yes	Yes	5
Minamizuka et al., 2021	Yes	Yes	No	No	Yes	3
Cicero et al., 2021	Yes	Yes	Yes	Yes	No	4

Table 3 Distribution of clinical studies on the risk of bias (Jadad et al., 1996).

Low risk of bias(Score 4–5)	Medium risk of bias(Score 3)	High risk of biasScore (0–2)
Trimarco et al., 2015	Magno et al., 2018	Mazza et al., 2018
Heinz et al., 2016	Minamizuka et al., 2021	
D'Addato et al., 2017		
Giuseppe et al., 2017		
Domenech et al., 2019		
Ruscica et al., 2019		
Wang et al., 2019		
Iskandar et al., 2020		
Cicero et al., 2021		

containing 2 mg of monacolin K for 12 weeks and showed a significant reduction in LDL, total and non-HDL cholesterol compared to the control group ($p < 0.05$). Also, no severe treatment-related adverse effects were observed. Furthermore, the randomized double-blind clinical study by Cicero et al. (2021)²³ used a supplement containing 2.5–2.9 mg monacolin K along with linear aliphatic alcohols, niacin and *Olea europaea* for 8 weeks and indicated a significant decrease in LDL, total cholesterol, non-HDL cholesterol and a significant increase in HDL cholesterol compared to the control group ($p < 0.05$).

On the other hand, 6 studies examined the efficacy of supplementation with higher doses of monacolin K compared either to another supplemented group or to a control group. In particular, the randomized double-blind clinical trial by Giuseppe et al. (2017)²⁴ used a dietary supplement containing 10 mg of monacolin K and KA (a type of monacolin), berberine and silymarin for 4 months and showed significant improvements in LDL and total cholesterol compared to the control group ($p < 0.05$). The other study by Mazza et al. (2018)²⁵ compared the dietary supplement "Colenorm Plus" containing 10 mg of monacolin K, octocosanol, resveratrol, chromium pinolate and piperine with a standardized Mediterranean diet for one month and showed significant reduction in LDL, total cholesterol in the monacolin K group compared to the control group ($p < 0.05$). Moreover, the study by Domenech et al. (2019)²⁶ used the

dietary supplement "Aquilea Coolesterol" containing 10 mg of monacolin K, phytosterols, hydroxytyrosol and vitamin E for 3 months and showed significant reduction in LDL cholesterol and total cholesterol compared to the control group ($p < 0.05$). In addition, the study by Ruscica et al. (2019)²⁷ used the dietary supplement "Lactoflorene Coolesterol" containing 10 mg of Monacolin K, niacin, CoQ10 and probiotic *Bifidobacterium longum* BB536 for 12 weeks and showed significant reduction in LDL, total cholesterol and non-HDL-cholesterol compared to the control group ($p < 0.05$). Furthermore, the cross-over clinical trial by Magno et al. (2018)²⁸ used two dietary supplements for 8 weeks each with 4 weeks of abstinence between them. The 1st group used the supplement "Argicolina" containing 10 mg of monacolin K, L-arginine, CoQ10 and ascorbic acid and the 2nd group was supplemented with the supplement "Normolip 5" containing 10 mg of monacolin K and CoQ10. Results showed significant reductions in LDL and total cholesterol in both groups ($p < 0.05$). However, the reduction in LDL and total cholesterol levels in the 1st group was significantly higher compared to the 2nd group. The study by Wang et al. (2019)¹² randomized participants in 3 different groups for 3 months. The first group was supplemented with a RYR containing 8 mg of monacolin K, group 2 was supplemented with the same RYR enriched with gamma-aminobutyric acid, and group 3 was given a placebo. Results showed a significant reduction in LDL and total cholesterol levels in group

Table 4 Characteristics and main findings of the included studies.

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Trimarco et al., 2015	Italy	Cross-over, double-blind RCT	N = 23 Men and women 18–70 years' old Diagnosis of hypercholesterolemia not requiring statin use or people who are statin intolerant	10 weeks (4 weeks for each treatment in the 2nd period)	1st period (2 weeks) Placebo + dietary advice Period 2 (8 weeks) Randomization and cross-over of participants Group 1: Armolipid Plus Polycosanol: 10 mg Monacolin K: 3 mg Berberine: 500 mg Astaxanthin: 0.5 mg Folic acid: 200 mg Coenzyme Q10: 2 mg Group 2: LopiGLIK Monacolin K: 3.3 mg Berberine: 531.25 mg Morus alba leaf extract (white berries): 200 mg	Anthropometric characteristics: Waist circumference BMI Blood pressure Biochemical parameters Lipid profile: TC, LDL-C, TG, HDL-C Fasting glucose Insulin HbA1c	Group 2 vs. Group 1: Statistically significant decrease ($p \leq 0.05$): LDL-C (–48.9 mg/dl) *56.6% of participants: < 130 mg/dl TC (–48.2 mg/dl)

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Heinz et al., 2016	Germany	Double-blinded RCT	Initially: $N = 235$ Final: $N = 142$ Men and women 18–70 years' old LDL-C: ≥ 160 – ≤ 220 mg/dl (LDL-C $\geq 4.14 \leq 5.69$ mmol/L)	12 weeks	Group 1: <u>Administration of red yeast rice supplement:</u> Red yeast rice: 200 mg & Monacolin K: 3 mg (main target for LDL-C reduction) Folic acid: 200 mg (secondary target for homocysteine reduction) Coenzyme Q10: 2 mg Astaxanthin: 0.5 mg Group 2: <u>Placebo treatment</u> *Randomization was based on gender and plasma LDL-C concentration.	Anthropometric characteristics: Body weight Height BMI Waist and hip circumference Blood pressure Heart rate Completion of questionnaire: Current health status Current health condition Current medication - Physical activity Biochemical parameters (12-h fasting): TC LDL-C HDL-C TG Homocysteine HbA1c Fasting glucose Fasting insulin Creatinine Creatine kinase Uric acid Aspartate aminotransferase Alanine aminotransferase Gamma-glutamyl transferase CRP *Measurements were performed at each test (at the start of the intervention, 6 and 12 weeks after)	6 weeks after intervention: <u>Statistically significant reduction ($p < 0.05$):</u> LDL-C ($-14.9\% = 159.7$ mg/dl) *53% of participants: < 160 mg/dl TC (-11.2%) LDL-C/HDL-C (-14.1%) <u>12 weeks post intervention:</u> Parameters that had changed at week 6 remained stable TG (-5.0%) * No significant changes were seen in the placebo group. ** All other parameters remained unchanged and no intolerances or significant adverse events were observed.

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
D'Addato et al., 2017	Italy	Double-blinded RCT	Initially: $N = 275$ Final: $N = 130$ Men and women 18–75 years old Clinical diagnosis of mild-to-moderate hypercholesterolemia LDL-C: 115–180 mg/dl TC: 200–260 mg/dl TG: < 250 mg/dl	8 weeks	1st period (4 weeks) Tips for starting an isocaloric and low-fat diet 2nd Period (4 weeks) Randomization of participants + diet continuation: Group 1: BL (body lipid) ($N = 44$) Monacolin K: 10 mg Berberine: 500 mg Coenzyme Q10: 2 mg Hydroxytyrosol: 5 mg Group 2: AM (Armolidip Plus) ($N = 42$) Monacolin K: 3 mg Group 3: Placebo ($N = 44$)	Medical history: Blood pressure Heart rate Anthropometric characteristics: Body weight BMI Waist circumference Energy and macronutrient intake: Fat-saturated fatty acids-cholesterol Protein Carbohydrate Biochemical parameters: Lipid profile: TC, LDL-C, HDL-C, TG AST, ALT CPK, urea	Group 1 vs. 3: Statistically significant decrease ($p \leq 0.05$): LDL-C (-43.8 ± 12.6 mg/dl) TC (-47.7 ± 15.1 mg/dl) Group 2 vs. 1: Statistically significant reduction ($p \leq 0.05$): LDL-C (-31.1 ± 12.8 mg/dl) TC (-32.3 ± 15.3 mg/dl) Group 1 vs. 2: Statistically significant reduction ($p \leq 0.05$): LDL-C (-12.5 ± 18.8 mg/dl) TC (-15.4 ± 15.4 mg/dl) *Adverse effects: Group 1: insomnia Group 2: ear pain and rash Group 3: lumbago
Giuseppe et al., 2017	Italy	Double-blinded RCT	Initially: $N = 143$ Final: $N = 139$ Caucasian men and women >18 years old BMI: 25.0–29.9 kg/m ² Low cardiovascular risk Non-smokers Blood pressure: SBP: < 140 mmHg DBP: < 90 mmHg Diagnosis of hypercholesterolemia: TC: 200–240 mg/dl TG: < 400 mg/dl	4 months	1st period (1 month) Diet: 600 kcal deficit 50% carbohydrates 30% fat (300 mg cholesterol) 20% proteins 35 g dietary fiber Physical activity: 3–4 times/week 20–30 min static bike ride 2nd period (3 months) randomization + diet continuation + PD Group 1: Berberol K administration ($n = 71$) Monacolin K and KA: 10 mg Berberine: 500 mg Silymarin: 105 mg Group 2: Placebo administration ($n = 68$)	Anthropometric characteristics: Height Weight BMI Waist, abdominal and hip circumference Blood pressure Biochemical parameters Lipid profile: TC, LDL-C, TG, HDL Fasting glucose Fasting insulin AST, ALT CPK CRP TNF- α IL-6 HOMA	1st Group vs. 2nd Group: Statistically significant reduction ($p < 0.05$): LDL-C ($-27.8\% = 106.5 \pm 11.4$ mg/dl) TC ($-20.5\% = 171.6 \pm 20.6$ mg/dl)

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Magno et al., 2018	Italy	Crossover RCT	Initially: N= 30 Final: N= 19 Caucasian Men and Women 18–75 years old LDL-C: ≥ 130 - ≤ 180 mg/dl	20 weeks 8 weeks for each treatment 4 weeks abstinence	1 st Treatment (N= 10): "Argicolina": Monacolin K: 10 mg L-arginine Coenzyme Q10 Ascorbic acid 2nd Treatment (N= 9): "Normolip 5": Monacolin K: 10 mg Coenzyme Q10	Anthropometric characteristics: Height Body weight BMI Biochemical parameters: Fasting glucose TC LDL-C HDL-C TG Aspartate aminotransferase alanine gamma-aminotransferase Aminotransferase Glutamyl transpeptidase Blood pressure Heart rate * Measured at the beginning and end of each treatment	At the end of each treatment: 1st treatment: Statistically significant reductions ($p \leq 0.05$): LDL-C (-40.1 mg/dl ± 12.8 mg/dl) TC (-42.7 mg/dl $\pm 178.3 \pm 16.3$ mg/dl) 2nd treatment: Statistically significant improvements ($p < 0.05$): LDL-C (-36.4 mg/dl $\pm 116.7 \pm 15.4$ mg/dl) TC (-34.6 mg/dl $\pm 187.0 \pm 17.1$ mg/dl) HDL-C ($+2.6$ mg/dl $\pm 59.2 \pm 17.1$ mg/dl) * During abstinence: LDL-C levels increased to similar levels as before the intervention.

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Mazza et al., 2018	Italy	RCT	N = 60 Men and women >18 years old Blood pressure: SBP: 140–159 mmHg And/or DBP: 90–99 mmHg Diagnosis of hypercholesterolemia: TC: ≥ 200 mg/dl LDL-C: 130–190 mg/dl	1 month	Group 1: <u>Administration of Diet + Supplement (Colenorm Plus) (n = 30)</u> Standardized Mediterranean diet regimen that weekly included: Cereals: 95.0% Vegetables, pasta and olive oil: 95.0% Yoghurt: 85.0% Fruits: 95.0% Fish and meat: 70.0% Red wine: 90.0% Eggs: 70.0% Cheese: 95.0% Monacolin K: 10 mg Octacosanol: 12 mg Resveratrol: 20 mg Chromium picolinate: 50 μ g piperine: 2.99 mg 2nd group: <u>Dietary administration (n = 30)</u> Standardized Mediterranean diet regimen that weekly included: Cereals: 76.7% Vegetables, pasta and olive oil: 96.7% Yoghurt: 73.3% Fruits: 90.0% Fish and meat: 74.0% Red wine: 76.7% Eggs: 86.7% Cheese: 93.3%	Anthropometric characteristics: BMI Heart rate Blood pressure Heart rate Smoking Biochemical parameters Lipid profile: TC, LDL-C, TG, HDL Glucose AST, ALT Creatinine	1st Group vs. 2nd Group: Statistically significant reduction ($p < 0.05$): LDL-C (–23.88%) TC (–18.32%)

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Domenech et al., 2019	Spain	Double-blinded RCT	N = 40 Men and women 35–75 years' old Low to moderate cardiovascular risk Diagnosis of hypercholesterolemia: TC: 200–250 mg/dl LDL-C: >115 mg/dl Absence of hypolipidemic medication	3 months	Group 1: <u>Aquilea Colesterol administration (n = 20)</u> Monacolin K: 10 mg Phytosterols: 1.5 g - Hydroxytyrosol: 5 mg Vitamin E: 12 mg Group 2: <u>Placebo administration (n = 20)</u>	Anthropometric characteristics: Weight BMI Waist circumference Blood pressure Cardiovascular risk (REGICOR) MedDiet score Biochemical parameters: Lipid profile: TC, LDL-C, TG, HDL, non-HDL, apo-A1, apo-B Glucose Creatinine AST, ALT, γ GT LDH: Galactate dehydrogenase CK: creatine kinase Aldolase CRP IL-6	1st Group vs. 2nd Group: Statistically significant reduction ($p < 0.05$): LDL-C (–19.7%) TC (–14.1%)
Ruscica et al., 2019	Italy	Double-blinded RCT	Initially: N = 33 Final: N = 32 Men and women 18–70 years old LDL-C: 130–200 mg/dl Non-smokers Primary prevention for cardiovascular disease	12 weeks	Group 1: <u>Lactoflorene Colesterolo (N = 16)</u> Probiotic Bifidobacterium longum BB536 Monacolin K: 10 mg Niacin: 16 mg Coenzyme Q10: 20 mg 2nd group: <u>Placebo (N = 16)</u> *Pre-intervention instructions were given to start a eutermic and low-fat diet, which continued throughout the intervention	Anthropometric characteristics: Height Body weight Waist circumference Blood pressure Heart rate Abdominal and visceral fat Biochemical parameters Lipid profile: TC, LDL-C, HDL-C, non-HDL-C, TG, Apo-B, apo-A1, Lp(a), PCSK9 Fasting glucose HOMA-IR Serum uric acid Hepatic transaminases γ -Glutamyl transpeptidase CPK FGF 19 CRP Lathosterol Dietary sterols	1st Group vs. 2nd Group: Statistically significant reduction ($p < 0.05$): LDL-C (–45 mg/dl) TC (–45 mg/dl) Non-HDL-C (–45 mg/dl)

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Wang et al., 2019	China	Double-blinded RCT	Initially: $N = 69$ Final: $N = 50$ Men and women ≥ 18 years' old LDL-C: >100 mg/dl TC: >200 mg/dl	3 months	Group 1 ($N = 16$): <u>R/YR enriched with Monacolin K:</u> R/YR: 400 mg Monacolin K: 8 mg Group 2 ($N = 17$): <u>R/YR enriched with gamma-aminobutyric acid (GABA):</u> R/YR: 335 mg GABA: 0.14 mg Group 3 ($N = 17$): Placebo	Anthropometric characteristics: BMI Biochemical parameters: Glucose Insulin Lipid profile: TC, LDL-C, HDL-C, TG Blood pressure Renal function: BUN, creatinine, GFR Liver enzymes: SGOT, SGPT, total bilirubin, alkaline phosphatase, r-GT Electrolytes: sodium, potassium, phosphorus, calcium CRP	Group 1 vs 2 and 3: <u>Statistically significant decrease ($p \leq 0.05$):</u> LDL-C (-31 mg/dl) TC (-44.5 mg/dl) * One person from Group 1 and 2 had an increase in liver enzymes.
Iskandar et al., 2020	Indonesia	Double-blinded RCT	Initially: $N = 80$ Final: $N = 76$ Men and women 18–65 years' old LDL-C: 100–159 mg/dl TC: 200–239 mg/dl Normal range of blood tests and laboratory tests (ALT, AST, blood urine, nitrogen, creatinine, eGFR, urinalysis and electrocardiogram)	12 weeks	1st period (4 weeks) Placebo administration Period 2 (8 weeks) Randomization of participants Group 1: <u>NutraforChol ($N = 40$)</u> Monacolin K: 3.75 mg Gugulipidium extract: 110 mg Chromium picolinate: 50 μ g Group 2: <u>Placebo ($N = 36$)</u> *In both groups, participants followed a low-fat and low-cholesterol diet and physical activity.	Anthropometric characteristics: Height Body weight BMI Blood pressure Heart rate Biochemical parameters Lipid profile: TC, LDL-C ALT, AST Blood urea nitrogen Creatinine eGFR	1st Group vs. 2nd Group: Statistically significant reduction ($p < 0.05$): LDL-C (-19.9%) TC (-15.9%) *Adverse effects: Group 1: indigestion, flatulence, bloating

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Minamizuka et al., 2021	Japan	RCT	Initially: N = 32 Final: N = 18 Men and women 20–80 years old LDL-C: 139.98–179.8 mg/dl (3.62–4.65 mmol/L) No history of cardiovascular disease	12 weeks	1st period (4 weeks) Dietary intake: Fat: < 30% Saturated fatty acids: < 10% Polyunsaturated fatty acids: ≤10% Cholesterol: < 300 mg/d Carbohydrates: 50–60% Protein: 10–20% Monacolin K: 0 mg Period 2 (8 weeks) Randomization of participants: Group 1: <u>Red rice yeast</u> Red rice yeast: 200 mg/day 2 mg Monacolin K + continuation of diet Group 2: <u>Placebo</u> -Continuation of Diet	Anthropometric characteristics: Body weight BMI Waist circumference Biochemical parameters: HbA1c TC LDL-C HDL-C TG Non-HDL apo-B Ankle-arm index Brachial-ankle pulse wave velocity	1st period: Non statistically significant differences between the 2 groups ($p < 0.05$) Period 2: 1st group vs 2nd group: Statistically significant decrease ($p < 0.05$): LDL-C (–37.12 mg/dl) TC (–35.57 ± 22.04 mg/dl) Non-HDL-C (–37.89 [–44.85, –31.71] mg/dl) *RYR caused no adverse effects on muscle, liver and kidney.

Table 4 (Continued)

Study	Country	Study design	Population	Follow-up	Intervention	Measures	Results
Cicero et al., 2021	Italy	Double-blinded RCT	N = 40 Men and women 25–65 years' old Primary cardiovascular risk LDL-C: 150–190 mg/dl	3 months	1st period (1 month) <u>Healthy diet</u> <u>and physical activity</u> Period 2 (2 months) Randomization of participants: Group 1: <u>DIF1STAT (1 capsule/day)</u> Monacolin K: 2.5–2.9 mg/capsule linear aliphatic alcohols titrated at 60% in octacosanols and niacin Olea europaea total extract of pomace and leaves (titrated at 15% in oleuropein) Camellia sinensis extract Vitamins E, B6, B9, B12 Group 2: <u>Placebo</u>	Anthropometric characteristics: Body weight Height BMI Waist circumference Blood pressure Completion of questionnaire: Personal history Dietary and smoking habits Physical activity Pharmacological Treatment Biochemical parameters: TC LDL-C HDL-C TG SUA (serum uric acid) Creatinine ALT, AST, γ -GT CPK GFR	1st Group vs. 2nd Group: Statistically significant reduction ($p < 0.05$): TC (–12.25% vs. –1.8%, $p < 0.01$) LDL-C (–28.7% vs. –1.1%, $p < 0.01$) HDL-C (+4.99% vs. +0.9%, $p < 0.05$) Non-HDL-C (–16.02% vs. –1.5%, $p < 0.01$) SUA (–12.96%, $p < 0.05$) Endothelial reactivity (+6.73% vs. –1.4%, $p < 0.01$)

Abbreviations: RCT; randomized clinical trial, RYR; red yeast rice, BMI; body mass index, TC; total cholesterol, LDL-C; low density lipoprotein cholesterol, HDL-C; high density lipoprotein cholesterol, TG; triglycerides, apo-A1; apolipoprotein-A, apo-B; apolipoprotein-B, SBP; systolic blood pressure, DBP; diastolic blood pressure, HbA1c; hemoglobin A1c, HOMA(-IR); Homeostatic Model Assessment for Insulin Resistance, CRP; C-reactive protein, AST; aspartate aminotransferase, ALT; alaline aminotransferase, γ GT; gamma-glutamyl transferase, CPK; creatine phosphokinase, TNF- α ; tumor necrosis factor alpha, IL-6; interleukin-6, FGF-19; fibroblast growth factor 19, BUN; blood urea nitrogen, SGOT; serum glutamic-oxaloacetic transaminase, SGPT; serum glutamic pyruvic transaminase, GFR; glomerular filtration rate, SUA; serum uric acid, MedDiet score; Mediterranean diet score.

1 compared to the other groups ($p < 0.05$). In addition, 2 participants reported elevated liver enzymes.

One study compared the effectiveness of two different doses of monacolin K on cholesterol levels. D'Addato et al. (2017)²⁹ randomized participants in 3 groups for 8 weeks. Group 1 was given the dietary supplement "Body Lipid" containing 10 mg of monacolin K, berberine, CoQ10 and hydroxytyrosol, group 2 was given the dietary supplement "Armoliplus" containing only 3 mg of monacolin K and group 3 was given placebo. The results showed that LDL and total cholesterol levels were significantly reduced in group 1 compared to the other groups ($p < 0.05$). In addition, a significant decrease in LDL and total cholesterol levels was shown in group 2 compared to group 3 ($p < 0.05$). Adverse effects were observed in all 3 groups such as insomnia, ear pain, rashes and back pain.

Discussion

The main purpose of this review was to examine the efficacy and safety of monacolin K supplementation in adult patients with hypercholesterolemia. All the included studies demonstrated a beneficial effect of monacolin K regardless the dose and duration of supplementation. Half of the included studies ($N=6$) used higher doses of monacolin K (8–10 mg) and five studies examined the effect of lower doses of monacolin K (2–3.75 mg) on hypercholesterolemia. The maximum duration of supplementation was 12 weeks for all studies. Regarding the safety of supplementation, 3 studies using both high and low doses of monacolin K reported side effects such as insomnia, indigestion, flatulence, bloating and increase in liver enzymes. Notably, the study by D'Addato et al. (2017)²⁹ which used both high (10 mg/day) and low doses (3 mg/day) of monacolin K reported side effects in all groups. Therefore, it seems that patients treated with monacolin K should be monitored regardless the dose and duration of supplementation.

Our findings seem to be in line with previous reviews that examined the potential effect of monacolin K in people suffering from hypercholesterolemia. Particularly, the previous systematic review and meta-analysis by Gerards et al. (2015),⁸ included 20 randomized controlled trials in order to examine the effect monacolin K in patients with hypercholesterolemia. The dosage of monacolin K used ranged between 2.4 mg and 24 mg for a period of 6 weeks to 168 weeks. The meta-analysis indicated that monacolin K treatment had a significant effect on reducing LDL cholesterol levels. However, in contrast to the present review, the Gerards et al. (2015)⁸ study included several clinical trials assessed with low methodological quality. Another meta-analysis with similar findings is the one conducted by Li et al. (2014)³⁰ which aimed to investigate the safety and efficacy of RYR and monacolin K in people with dyslipidemia. The analysis included 13 randomized controlled trials with 804 participants that were supplemented with monacolin K in dosages ranged between 2 mg and 11.4 mg for a period of 4 weeks and 24 weeks. The results demonstrated that RYR and monacolin K had a significant effect on reducing

LDL, total cholesterol and TG⁸ levels. Notably, no serious adverse effects were reported. Moreover, our findings are also in line with those of a previous review by Yang et al. (2012)¹⁵ that aimed to examine the effect of RYR in various diseases including hypercholesterolemia. The review included 11 clinical trials using monacolin K in doses varied from 1.02 mg to 5.1 mg for a period between 8 weeks and 4.5 years. The results indicated that monacolin K significantly contributed to the reduction of LDL and total cholesterol. In addition, the authors supported that the supplementation of RYR has the same efficacy as statin, regardless of its combination with other dietary supplements. Nevertheless, based on our findings, it seems that any dose of monacolin K ranged between 3 and 10 mg is effective in reducing cholesterol levels in people suffering from hypercholesterolemia. Overall, we could assume that RYR is an effective lipid-lowering dietary supplement regardless monacolin K content. However, since EFSA suggested using a lower dose of monacolin K (3 mg/day) due to safety concerns an attention should be given when prescribing high doses RYR for statin-intolerant patients.

Regarding the safety, it seems that any dose may cause side effects and therefore all treated patients should be routinely monitored. Previous research support that the safety of RYR, generally is not related to the monacolin content, per se, but to variability in monacolin content and especially the presence of contaminants (particularly citrinin, a nephrotoxic product of rice fermentation). Therefore, it is very important to focus on the quality of production of RYR supplements together with monacolin K dose control.³¹ Recent concerns have been reported regarding the safety of RYR after publication of studies claiming toxicity.¹⁸ However, according to a recent meta-analysis of 53 RCTs with a total of 8,535 patients the supplementation of monacolin K is not associated with an increased risk of muscular adverse events.¹⁶ Also, the study demonstrated a reduced risk of nonmuscular adverse events and serious adverse events compared to the control group. Notably, our findings regarding the safety of monacolin K are more conflicting. Three studies using both low and high doses of monacolin K reported side effects indicating the need of monitoring patients treated with monacolin K regardless the dose of supplementation. Indeed, in the study by D'Addato et al. (2017)²⁹ all groups showed side effects after the treatment indicating that factors other than monacolin K dose may cause side effects and should be further investigated.

Strengths and limitations

The key strength of the current review is the sole inclusion of RCTs, a study design, which is less likely to be biased and affected by confounding variables. The majority of the included studies were assessed as high quality (11/12) thus ascertaining reliability of the current review. Additionally, another strength is the fact that the current review included recent studies published during the last 10 years. Yet, our review has also some limitations. One limitation is the small number of studies included in the current analysis, while

⁸ Triglycerides.

most of the studies have been conducted in the same country (Italy). Furthermore, all studies used monacolin K together with other dietary supplements that differed among the studies and therefore it was difficult to identify the effect of monacolin K as a single supplement. Moreover, another limitation is the different definition of hypercholesterolemia used in the included studies.

Conclusions

In conclusion, this review has highlighted the potential effect of monacolin K together with other dietary components in people with hypercholesterolemia. It seems that even in lower doses equal to 3 mg/day, monacolin K exerts potential cholesterol-lowering effects although the number of relative studies is very low. Regarding the safety of monacolin K supplementation, findings seem to be more controversial and therefore, it is suggested for all patients treated with monacolin K to be routinely monitored regardless the dose of supplementation. Interestingly, the quality of the RYR supplement seems to play a role on the efficacy of treatment and should be taken into consideration. Overall, the current review seems to support EFSA recommendation for lowering the recommended intake of monacolin K from 10 to 3 mg per day although more RCTs are required to confirm the efficacy and safety of the lower dose of monacolin K supplementation.

Ethical considerations

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Conflict of interest

None.

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References

- Xiong Z, Cao X, Wen Q, Chen Z, Cheng Z, Huang X, et al. An overview of the bioactivity of monacolin K/lovastatin. *Food Chem Toxicol.* 2019;131:110585, <http://dx.doi.org/10.1016/J.FCT.2019.110585>.
- Ferrari R, Luscher TF. Reincarnated medicines: using out-dated drugs for novel indications. *Eur Heart J.* 2016;37:2571–6.
- Banach M, Pawel B, Krzysztof C, Dobrowolski P, Dudek D, Dyrbus K, et al. PoLA/CFPiP/PCS/PSLD/PSD/PSH guidelines on diagnosis and therapy of lipid disorders in Poland 2021. *Arch Med Sci.* 2021;17:1447–547, <http://dx.doi.org/10.5114/aoms/141941>.
- Mazidi M, Mikhailidis DP, Sattar N, Toth PP, Judd S, Blaha MJ, et al. Association of types of dietary fats and all-cause and cause-specific mortality: a prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants. *Clin Nutr.* 2020;39:3677–86.
- Chopra AS, Lordan R, Horbanczuk OK, Atanasov AG, Chopra I, Horbanczuk JO, et al. The current use and evolving landscape of nutraceuticals. *Pharmacol Res.* 2022;175:106001.
- Minamizuka T, Koshizaka M, Shoji M, Yamaga M, Hayashi A, Ide K, et al. Low dose red yeast rice with monacolin K lowers LDL cholesterol and blood pressure in Japanese with mild dyslipidemia: a multicenter, randomized trial. *Asia Pac J Clin Nutr.* 2021;30:424–35, [http://dx.doi.org/10.6133/apjcn.202109_30\(3\).0009](http://dx.doi.org/10.6133/apjcn.202109_30(3).0009).
- Banach M, Bruckert E, Descamp OS, Ellegard L, Azhova M, Foger B, et al. The role of red yeast rice (RYR) supplementation in plasma cholesterol control: a review and expert opinion. *Atheroscler Suppl.* 2019;39:e1–8.
- Gerards MC, Terlou RJ, Yu H, Koks CHW, Gerdes VEA. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain – a systematic review and meta-analysis. *Atherosclerosis.* 2015;240:415–23, <http://dx.doi.org/10.1016/j.atherosclerosis.2015.04.004>.
- Anagnostis P, Paschou SA, Goulis DG, Athyros VG, Karagiannis A. Dietary management of dyslipidaemias. Is there any evidence for cardiovascular benefit? *Maturitas.* 2018;108:45–52, <http://dx.doi.org/10.1016/J.MATURITAS.2017.11011>.
- Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, et al. Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Arch Med Sci.* 2017;13:965–1005.
- Halpin RA, Ulm EH, Till AE, Kari PH, Vyas KP, Hunninghake DB, et al. Biotransformation of lovastatin V. Species differences in in vivo metabolite profiles of mouse, rat, dog, and human. *Drug Metab Dispos.* 1993;21:1003–11.
- Wang TJ, Lien ASY, Chen JL, Lin CH, Yang YS, Yang SH. A randomized clinical efficacy trial of red yeast rice (*Monascus pilosus*) against hyperlipidemia. *Am J Chin Med.* 2019;47:323–35, <http://dx.doi.org/10.1142/S0192415X19500150>.
- Xu G, Lin M, Dai X, Hu J. Comparing the effectiveness of Chinese patent medicines containing red yeast rice on hyperlipidaemia: a network meta-analysis of randomized controlled trials. *Endocrinol Diabetes Metab.* 2022;5. Article: e00314.
- Yuan R, Yuan Y, Wang L, Xin Q, Wang Y, Shi W, et al. Yeast rice preparations reduce mortality, major cardiovascular adverse events, and risk factors for metabolic syndrome: a systematic review and meta-analysis. *Front Pharm.* 2022;13:744928.
- Yang CW, Mousa SA. The effect of red yeast rice (*Monascus purpureus*) in dyslipidemia and other disorders. *Complement Therap Med.* 2012;20:466–74, <http://dx.doi.org/10.1016/J.CTIM.201207004>.
- Fogacci F, Banach M, Mikhailidis DP, Bruckert E, Toth PP, Watts GF, et al. Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res.* 2019;143:1–16.
- Agostoni C, Bresson JL, Fairweather-Tait S, Flynn A, Golly I, Korhonen H, et al. Scientific Opinion on the substantiation of health claims related to monacolin K from red yeast rice and maintenance of normal blood LDL cholesterol concentrations (ID 1648, 1700) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J.* 2011;9:2304, <http://dx.doi.org/10.2903/J.EFSA.2011.2304>.
- Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, Filipic M, et al. Scientific opinion on the safety of monacolins in red yeast rice. *EFSA J.* 2018;16:e05368, <http://dx.doi.org/10.2903/J.EFSA.2018.5368>.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1–12, [http://dx.doi.org/10.1016/0197-2456\(95\)00134-4](http://dx.doi.org/10.1016/0197-2456(95)00134-4).

20. Trimarco V, Izzo R, Stabile E, Rozza F, Santoro M, Manzi MV, et al. Effects of a new combination of nutraceuticals with *Morus alba* on lipid profile, insulin sensitivity and endothelial function in dyslipidemic subjects. A cross-over, randomized, double-blind trial. *High Blood Pressure Cardiovasc Prevent*. 2015;22:149–54, <http://dx.doi.org/10.1007/s40292-015-0087-2>.
21. Heinz T, Schuchardt JP, Möller K, Hadji P, Hahn A. Low daily dose of 3mg monacolin K from RYR reduces the concentration of LDL-C in a randomized, placebo-controlled intervention. *Nutr Res (New York, N.Y.)*. 2016;36:1162–70, <http://dx.doi.org/10.1016/J.NUTRES.201607005>.
22. Iskandar I, Harahap Y, Wijayanti TR, Sandra M, Prasaja B, Cahyaningsih P. Efficacy and tolerability of a nutraceutical combination of red yeast rice, guggulipid, and chromium picolinate evaluated in a randomized, placebo-controlled, double-blind study. *Complement Ther Med*. 2020;48, <http://dx.doi.org/10.1016/J.CTIM.2019.102282>.
23. Cicero AF, Bove M, Cincione RI, Fogacci F, Veronesi M. Effect of combined lipid-lowering and antioxidant nutraceutical on plasma lipids, endothelial function, and estimated cardiovascular disease risk in moderately hypercholesterolemic patients: a double-blind, placebo-controlled randomized clinical trial. *Arch Med Sci Atheroscler Dis*. 2021. Available from: <https://doi.org/10.5114/amsad.2021.107843> [cited 5.9.23].
24. Derosa G, D'Angelo A, Romano D, Maffioli P. Effects of a combination of berberis aristata, silybum marianum and monacolin on lipid profile in subjects at low cardiovascular risk; a double-blind, randomized, placebo-controlled trial. *Int J Mol Sci*. 2017;18:343.
25. Mazza A, Schiavon L, Rigatelli G, Torin G, Montanaro F, Lenti S. The short-term supplementation of monacolin K improves the lipid and metabolic patterns of hypertensive and hypercholesterolemic subjects at low cardiovascular risk. *Food Funct*. 2018;9:3845–52, <http://dx.doi.org/10.1039/c8fo00415c>.
26. Domenech M, Casas R, Ruiz-León AM, Sobrino J, Ros E, Estruch R. Effects of a novel nutraceutical combination (Aquilea Colesterol®) on the lipid profile and inflammatory biomarkers: a randomized control trial. *Nutrients*. 2019;11:949.
27. Ruscica M, Pavanello C, Gandini S, Macchi C, Botta M, Dall'Orto D, et al. Nutraceutical approach for the management of cardiovascular risk – a combination containing the probiotic *Bifidobacterium longum* BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study. *Nutr J*. 2019;18:13, <http://dx.doi.org/10.1186/s12937-019-0438-2>. Erratum in: *Nutr J*. 2019 Sep 9. 18(1). 54. PMID: 30795775; PMCID: PMC6387491.
28. Magno S, Ceccarini G, Pelosini C, Jaccheri R, Vitti J, Fierabracci P, et al. LDL-cholesterol lowering effect of a new dietary supplement: an open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. *Lipids Health Dis*. 2018;17:124, <http://dx.doi.org/10.1186/s12944-018-0775-8>.
29. D'Addato S, Scandiani L, Mombelli G, Focanti F, Pelacchi F, Salvatori E, et al. Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q10 on lipid levels: a randomized, double-blind, placebo controlled study. *Drug Des Dev Therapy*. 2017;11:1585.
30. Li Y, Jiang L, Jia Z, Xin W, Shiwei Y, Yang Q, et al. A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia. *PLoS ONE*. 2014;9:98611, <http://dx.doi.org/10.1371/JOURNAL.PONE.0098611>.
31. De Backer GG. Food supplements with red yeast rice: more regulations are needed. *Eur J Prevent Cardiol*. 2017;24:1429–30, <http://dx.doi.org/10.1177/2047487317716500>.