



Review Article

Impact of Red Yeast Rice on LDL Cholesterol: A Meta-Analysis of Clinical Studies

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ABSTRACT

Elevated levels of low-density lipoprotein (LDL) cholesterol are associated with an increased risk of cardiovascular and thrombotic events. This meta-analysis systematically reviewed the dietary supplement red yeast rice and its impact on lowering LDL cholesterol levels. We utilized a systematic review approach and methodology to collect and compile relevant data, followed by a comprehensive analysis evaluating the effectiveness of red yeast rice supplementation on LDL cholesterol reduction. Our review suggests a significant reduction in LDL cholesterol levels following red yeast rice supplementation, with a Cohen's d effect size of -1.24. This finding underscores the potential for red yeast rice as a natural supplement for the management of high LDL cholesterol levels and for reducing the risk of cardiovascular events. The findings of this study provide valuable insights for healthcare providers and individuals looking for naturopathic alternatives for the management of blood cholesterol levels. Further research is needed to identify optimal dosages, long-term efficacy, and safety profiles related to the manufacturing process of red yeast rice to establish evidence-based dietary recommendations for use in clinical practice.

Keywords:

Keywords: Red Yeast Rice, Monacolin K, Hyperlipidemia, LDL, Dietary Supplement, Meta-Analysis.

Article History:

Received: August 10, 2024

Accepted: August 19, 2024

Published: August 20, 2024

Editor: Dr. Md. Khairul Islam, MBBS, FCPS (Medicine)

Citation: Sood S, Hossain MF. Impact of Red Yeast Rice on LDL Cholesterol: A Meta-Analysis of Clinical Studies. *Am J Nat Med Facts*. 2024;1(3):1-5.



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Introduction

A study conducted in 2021 by the CDC concluded that the number one leading cause of mortality in the United States was heart disease.[1] There are a variety of risk factors that contribute to the development of heart disease with smoking status, serum cholesterol level, and high blood pressure representing the major individual risk factors.[2] A high blood cholesterol level is defined by the NCEP as an LDL level greater than 240 mg/dL and is positively associated with an increased risk of all-

cause mortality among women and men.[2] Patients who reduced their serum cholesterol levels to a recommended target LDL of <1.4 mmol/L (54.14 mg/dL) experienced significantly lower risks of all-cause mortality when compared to those with an LDL of \geq 3.4 mmol/L (131.48 mg/dL).[3] A variety of pharmacological agents work to lower LDL levels, but statins have become the cornerstone treatment for dyslipidemia primarily due to their marked lowering of LDL levels.[4] While statins are considered safe and efficacious for most patients, some may experience statin intolerance or

treatment-limiting adverse events.[5] Red yeast rice is a commercially available food supplement that has been advocated as an alternative therapy for hyperchloremic patients who refuse statins, are statin intolerant, or prefer a naturopathic approach to their care.[6] It comes in a variety of strengths, with one study looking at 19 brands of supplement products, and finding that the monacolin content ranged from as little as 0.32 mg to as high as 10 mg depending on batch variability.[7] Furthermore, brands might include a variety of bioactive and probiotic compounds to their product that may confer additional health benefits, including but not limited to garlic extract, olive oil, policosanols, berberine, and omega 3 polyunsaturated fatty acids to name a few.[7,8]

Red yeast rice is a fermented food product originating from eastern Asia that can be traced as far back as the Ming Dynasty.[7] It has been used traditionally for the variety of biological activity conferred by polyketides produced in the fermentation process including antimicrobial, anticancer, and antioxidant effects.[7] The nutraceutical is created by fermenting various varieties of yeast, mainly *Monascus purpureus*, in red rice (*Oryza sativa*).[8,9] This fermentation process produces a family of polyketides called monacolins, all of which can inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-controlling enzyme of the cholesterol biosynthesis pathway.[10] The fermentation process may also give rise to citrinin, a mycotoxin metabolite derived from *Monascus* fermentation associated with nephrotoxicity in animal studies.[8] Citrinin is also known to cause reproductive toxicity, malformations, and certain fetal toxicities but it should be noted that red yeast rice supplementation was found to have a reduced risk of nonmuscular adverse events and serious adverse events compared to control by one meta-analysis concerned with studying the nutraceuticals' safety profile.[8,18] Our meta-analysis aims to study the LDL-lowering effect of red yeast rice.

Method

A systematic review was performed using the electronic database PubMed. The keywords “Red Yeast Rice, Monacolin K” were used yielding 178 articles that were filtered down by randomized controlled trials (RCT) and clinical trials (CT) and further evaluated for appropriateness. The search produced 25 results from which we had free full-text access to 17 articles. For inclusion, the study had to have a clearly identifiable amount of red yeast rice or monacolin K supplementation throughout the trial. Studies that utilized mixed bioactive nutraceuticals in addition to red yeast rice were excluded from our review due to potential confounding.

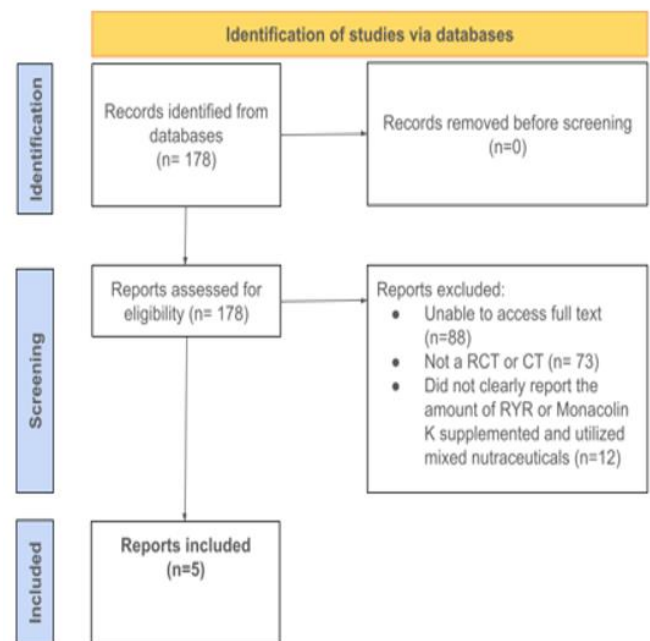


Figure 1: Flow Chart and Study Selection showing the number of articles identified after the initial keyword search and the number of articles included after the final screening.

Results and Discussion

We identified 5 articles for review which varied in duration from 4 weeks to as long as 16 weeks. All included studies conveyed positive outcomes in lowering LDL cholesterol levels, despite strong variability in the amount of dosed red yeast rice or monacolin K.

Table 1: Study Designs and Outcomes. [11,12,13,14,15]

Author (Year)	Dose	Duration (Weeks)	Participants	% weight	Outcomes (+/-)
Takuya et al. (2021)[11]	200 mg/day or RYR containing 2 mg of MK	8	10	5.4%	+
Luke J et al. (2023)[12]	2400 mg of RYR containing an unspecified amount of MK	4	23	12.5%	+
Martin Prøven et al. (2010)[13]	7.2 mg of MK	16	22	12%	+
Chen et al. (2022)[14]	12 mg of MK	8.5	37	20.1%	+
Ravi R et al. (2016)[15]	1200 mg of RYR containing an unspecified amount of MK	12	92	50%	+

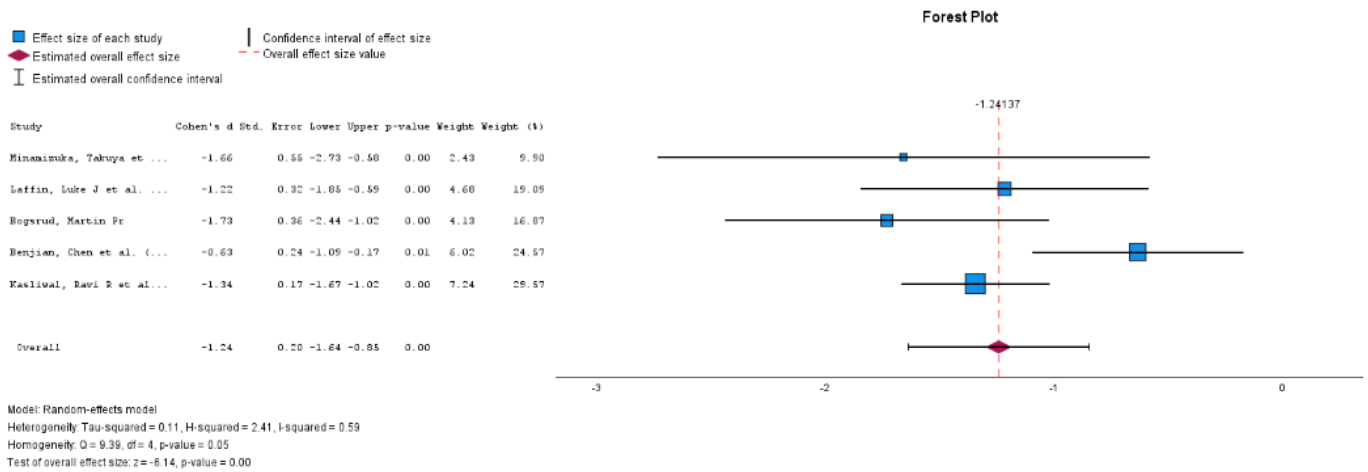


Figure 1: Forest Plot and meta-analysis (Random-effects model)

The effect size (Cohen's d) obtained from the meta-analysis is -1.24. A negative value indicates that red yeast rice has a significant effect in lowering LDL cholesterol levels compared to a control group. The confidence interval ranges from -1.64 to -0.85 with an error of 0.2. This means that with 95% confidence, the true effect of red yeast rice on LDL cholesterol reduction falls between -1.64 and -0.85. The p-value obtained from the analysis is 0.00, indicating that the effect of red yeast rice on lowering LDL cholesterol is statistically significant. The heterogeneity statistics show a Q value of 9.39 with degrees of freedom (DF) equal to 4. The I-squared value is 0.59%, suggesting low to moderate heterogeneity among the studies included in the meta-analysis. The test of the overall effect size shows a Z-value of -6.14 with $p < 0.05$, indicating that the overall effect of red yeast rice on lowering LDL cholesterol is significant.

The meta-analysis demonstrates that red yeast rice has a significant and beneficial impact on reducing LDL cholesterol levels. The effect size is substantial (Cohen's d is -1.24), and the results are statistically significant with low to moderate heterogeneity among the studies included. Therefore, based on this analysis, red yeast rice can be considered effective in lowering LDL cholesterol, often referred to as "bad" cholesterol. Our research aligns with other studies that have also shown significant effects of red yeast rice on reducing low-density lipoprotein in addition to reducing total cholesterol, triacylglycerides, and increasing HDL levels. The 2023 systematic review and meta-analysis of randomized controlled trials highlighted a substantial decrease in LDL-C levels (WMD: -28.94 mg/dl, 95% CI: -32.90, -24.99, $P < 0.001$). [16] Similarly, a study from 2017, involving 13 studies with a total of 1,246 participants and an

additional 7,467 participants across two meta-analyses, also pointed to significant reductions in LDL cholesterol.[17] Furthermore, the 2019 systematic review and meta-analysis, which included data from 53 RCTs and 8535 subjects, reinforced the tolerability and safety of red yeast rice as a lipid-lowering dietary supplement in moderately hypercholesterolemic individuals.[18]

Limitations of this Study

One limitation of this study is the timeframe of articles published from 2000 to 2024, potentially excluding relevant studies conducted before this period. Furthermore, the meta-analysis only included five clinical trials and a total of 184 participants, which may limit the generalizability of the findings due to a relatively small sample size.

Conclusion

The results of this meta-analysis align with previous studies suggesting the beneficial effects of red yeast rice on lipid profiles, specifically in reducing LDL cholesterol levels. The significant effect size observed underscores the potential clinical relevance of red yeast rice supplementation as a cholesterol-lowering agent. However, it is essential to consider individual variations in response to red yeast rice supplementation and potential interactions with other medications. In conclusion, the meta-analysis indicates that red yeast rice supplementation is associated with a significant reduction in LDL cholesterol levels. The effect size of -1.24 suggests a strong impact of red yeast rice in managing cholesterol levels. The findings support the use of red yeast rice as a potential natural intervention for individuals seeking to lower LDL cholesterol and improve cardiovascular health. Further research and clinical trials are warranted to validate these results and explore the long-term effects of red yeast rice supplementation.

Conflict of interest

The authors declare no conflict of interest.

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