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EFFECTS OF MONACOLIN K ON INFLAMMATION, OXIDATIVE STRESS, AND ENDOTHELIAL FUNCTION IN PATIENTS WITH MODERATE HYPERLIPIDEMIA

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The purpose to investigate the effect of a 12-week course of monacolin K and rosuvastatin on parameters of lipid profile, inflammatory markers, oxidative stress indices, and vascular function in patients with dyslipidemia. 60 patients with dyslipidemia were randomly divided into two equal groups: one group received monacolin K, the second one –rosuvastatin. Biomarkers were measured both before and after 12 weeks of treatment, including low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, malondialdehyde, and intercellular adhesion molecule-1. Both groups showed statistically significant improvement compared to baseline ($p<0.001$). In the monacolin K group, low-density lipoprotein cholesterol decreased by 21.22 %, high-sensitivity C-reactive protein by 29.47 %, malondialdehyde by 21.85 %, and intercellular adhesion molecule-1 by 15.17 %. In the rosuvastatin group, the decreases were 40.4 %, 47.5 %, 40.4 %, and 29.9 %, respectively. Monacolin K exerted a marked beneficial effect on lipid metabolism, inflammation, oxidative stress, and vascular function biomarkers in dyslipidemic patients.

Key words: monacolin K, rosuvastatin, dyslipidemia, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, malondialdehyde, and intercellular adhesion molecule-1.

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ВПЛИВ МОНАКОЛІНУ К НА ЗАПАЛЕННЯ, ОКИСЛЮВАЛЬНИЙ СТРЕС І ЕНДОТЕЛІАЛЬНУ ФУНКЦІЮ У ПАЦІЄНТІВ ІЗ ПОМІРНОЮ ГІПЕРЛІПІДЕМІЄЮ

З метою вивчення впливу 12-тижневого курсу монаколіну К і розувастатину на параметри ліпідного профілю, маркери запалення, індекси окислювального стресу і функцію судин у пацієнтів з дисліпідемією, 60 пацієнтів з дисліпідемією були випадковим чином розділені на дві рівні групи: одна група отримувала монаколін К, друга – розувастатин. Біомаркери вимірювалися як до, так і після 12 тижнів лікування, включаючи холестерин ліпопротеїнів низької щільності, високочутливий С-реактивний білок, малоновий діальдегід і молекулу міжклітинної адгезії-1. В обох групах спостерігалося статистично значуще поліпшення в порівнянні з вихідним рівнем ($p<0,001$). У групі монаколіну К рівень холестерину ліпопротеїнів низької щільності знизився на 21,22 %, високочутливого С-реактивного білка – на 29,47 %, малонового діальдегіду – на 21,85 % і молекули міжклітинної адгезії-1 – на 15,17 %. У групі розувастатину зниження склало 40,4 %, 47,5 %, 40,4 % і 29,9 % відповідно. Монаколін К мав виражений позитивний вплив на первинний ліпідний обмін, запалення, окислювальний стрес і біомаркери судинної функції у пацієнтів з дисліпідемією.

Ключові слова: монаколін К, розувастатин, дисліпідемія, холестерин ліпопротеїнів низької щільності, високочутливий С-реактивний білок, малоновий діальдегід і молекула міжклітинної адгезії-1.

Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide. Hypercholesterolemia is recognized as one of the major modifiable risk factors contributing to the development of atherosclerosis and its complications. Lowering low-density lipoprotein cholesterol (LDL-C) levels is a cornerstone strategy in the prevention and management of CVD [11]. Statins, inhibitors of HMG-CoA reductase, are first-line agents for LDL-C reduction. However, their use may be limited by adverse effects such as myopathy and elevated liver enzymes, as well as poor tolerance in certain patients. This underscores the need for alternative or adjunctive lipid-lowering therapies [5].

Red yeast rice (RYR), a traditional fermented product of Monascus purpureus, contains monacolin K, a compound structurally identical to lovastatin. Monacolin K inhibits HMG-CoA reductase and thereby reduces hepatic cholesterol synthesis [6]. It is widely utilized in nutraceutical formulations for lipid profile correction [7]. Contemporary clinical studies have confirmed its efficacy in reducing LDL-C levels. A systematic review of 12 randomized controlled trials reported that monacolin K at doses ranging from 2 to 10 mg over 4–12 weeks significantly lowered both LDL-C and total cholesterol without serious adverse events [5].

While monacolin K was initially investigated as a cholesterol-lowering agent, recent research has increasingly focused on its pleiotropic effects [6]. Of particular interest are its impacts on inflammation, oxidative stress, and endothelial function – key mechanisms in the pathogenesis of cardiovascular disease [9]. Current models of atherosclerosis emphasize the role of chronic inflammation, cytokine activation, oxidative stress, and endothelial dysfunction [13]. Therefore, agents capable of modulating both lipid levels and inflammatory markers are of considerable value in cardiometabolic prevention [2].

Emerging evidence supports the multifaceted biological effects of monacolin K, including anti-inflammatory, antioxidant, and vasoprotective properties, in addition to its lipid-lowering effects. This

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study aims to systematically assess these extended effects to clarify the potential role of monacolin K in comprehensive cardiovascular prevention and therapy.

The purpose of the study was to investigate the effects of monacolin K –the active compound derived from red yeast rice – on inflammation, oxidative stress, and vascular function in patients with moderate hyperlipidemia.

Materials and methods. A 12-week prospective randomized controlled trial was conducted at the basis of Azerbaijan Medical University from 2021 to 2022 to assess the anti-inflammatory, antioxidant, and vasoprotective effects of monacolin K compared with rosuvastatin in patients with moderate hypercholesterolemia.

The study enrolled 60 outpatients (men and women), aged 35–65 years, with baseline LDL-C levels between 3.0 and 4.9 mmol/L and a body mass index (BMI) of 20–30 kg/m².

Schemes of treatment implied the use of drugs for 12 weeks.

Participants were block-randomized in a 1:1 ratio to two groups:

– Monacolin K group (n=30): was administered monacolin K (WISH Pharmaceutical, Poland) daily in the dosage of 10 mg by mouth (per os) as part of a standardized nutraceutical product;

– Rosuvastatin group (n=30): was administered rosuvastatin (ATB, Slovenia) with a mean dose of 10 mg/day by mouth (range 5–20 mg/day, depending on the total cardiovascular risk of the patient and his individual clinical factors, determined according to international recommendations (ESC/EAS, AHA/ACC) on scales (SCORE2, ASCVD).

The study protocol was in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Protocol No. 2, April 16, 2021). Written informed consent was obtained from all the participants.

Inclusion criteria were: age 35–65 years; moderate hypercholesterolemia baseline LDL-C levels between 3.0 and 4.9 mmol/L, confirmed by two fasting measurements; stable lipid profile for at least 3 months; body mass index (BMI) of 20–30 kg/m², absence of lipid-lowering therapy within the preceding 3 months; low or moderate cardiovascular risk without established atherosclerotic cardiovascular disease; normoglycemia; controlled arterial blood pressure (no grade III arterial hypertension); preserved renal, hepatic, and cardiac function; absence of acute or chronic inflammatory, infectious, or autoimmune diseases; ability to provide written informed consent.

Exclusion criteria were: age <35 and 65< years, baseline LDL-C levels between <3.0 and 4.9< mmol/L, body mass index (BMI) of <20 and 30< kg/m², diabetes mellitus, grade III arterial hypertension, chronic heart failure, renal failure, liver failure, inflammatory, infectious, or autoimmune diseases; administration of antioxidants, statins, NSAIDs, or corticosteroids within the preceding 3 months; pregnancy, lactation, or previous malignancy.

Venous blood samples at baseline (week 0) and at 12 weeks after the therapy were collected. The following biomarkers were evaluated: Low-density lipoprotein cholesterol (LDL-C, mmol/L) – measured by direct enzymatic assay (Abbott Architect, USA); High-sensitivity C-reactive protein (hs-CRP, mg/L) – measured by immunoturbidimetry (Siemens, Germany); Malondialdehyde (MDA, μmol/L) – measured by thiobarbituric acid reactive substances (TBARS) assay and thereafter by spectrophotometry; Intercellular adhesion molecule-1 (ICAM-1, ng/mL) – quantified by enzyme-linked immunosorbent assay (ELISA, R&D Systems, USA). All laboratory work was done in a blinded manner; laboratory personnel did not receive information on group allocation.

GraphPad Prism version 10.0 (GraphPad Software, USA) was employed to statistical analyze the data. Quantitative data were presented as mean ± standard deviation (M±SD). Paired Student's t-test was employed for intergroup comparison, and unpaired Student's t-test was employed for intergroup comparison. A p-value <0.05 was considered statistically significant.

Results of the study and their discussion. Both groups of treatment showed statistically significant changes in clinical and laboratory parameters during the research. The results of the comparative assessment of the levels of LDL, hs-CRP, MDA, and ICAM-1 before and after treatment are as follows. The table illustrates the change in the levels of LDL-C, hs-CRP, MDA, and ICAM-1 in monacolin K and rosuvastatin-treated patients (n=30 each) over 12 weeks (Table 1).

The differences within groups were statistically significant for all the parameters ($p<0.05$). Nonetheless, monacolin K also showed significant enhancements in all parameters tested, particularly in hs-CRP and MDA, supporting its anti-inflammatory and antioxidant effects. LDL-C – reduction by approximately 21 % in the monacolin K group, consistent with previous reports, but weaker than rosuvastatin. hs-CRP – mild anti-inflammatory effect in the monacolin K group relative to rosuvastatin.

MDA – decrease in levels indicating reduced oxidative stress. ICAM-1 – decline reflects improvement in endothelial activation and vascular function. All biomarkers showed statistically significant direction of change from baseline in both groups ($p<0.05$). However, monacolin K also showed clinically significant changes, even greater in markers of inflammation and oxidative stress, in support of its potential as an alternative or adjunctive strategy in the treatment of cardiometabolic risk.

Table 1

Effects of Monacolin K and Rosuvastatin on biomarkers (n=60, 12-week follow-up)

Parameter	Group	Before treatment	After treatment	Changes	P (within group)
LDL, mmol/L	Monacolin K	4.10±0.55	3.23±0.49	−21.22 %	p<0.001
	Rozuvastatin	4.08±0.60	2.43±0.41	−40.4 %	p<0.001
hs-CRP, mq/L	Monacolin K	2.85±0.50	2.01±0.44	−29.47 %	p<0.001
	Rozuvastatin	2.80±0.48	1.47±0.40	−47.5 %	p<0.001
MDA, mkmol/L	Monacolin K	2.70±0.30	2.11±0.28	−21.85 %	p<0.001
	Rozuvastatin	2.65±0.32	1.58±0.25	−40.4 %	p<0.001
ICAM-1, nq/ml	Monacolin K	290±35	246±30	−15.17 %	p=0.002
	Rozuvastatin	288±33	202±28	−29.9 %	p<0.001

After 12 weeks of treatment, both groups experienced statistically significant reductions in all biomarkers measured: LDL-C from 4.10±0.55 to 3.23±0.49 mmol/L (−21,22 %, $p<0.001$) in the monacolin K group and from 4.08±0.60 to 2.43±0.41 mmol/L (−40.4 %, $p<0.001$) in the rosuvastatin group. hs-CRP levels fell from 2.85±0.50 to 2.01±0.44 mg/L (−29.47 %, $p<0.001$) in the monacolin K group and from 2.80±0.48 to 1.47±0.40 mg/L (−47.5 %, $p<0.001$) in the rosuvastatin group. MDA, a marker of oxidative stress, fell from 2.70±0.30 to 2.11±0.28 μmol/L (−21.85 %, $p<0.001$) and from 2.65±0.32 to 1.58±0.25 μmol/L (−40.4 %, $p<0.001$), respectively. ICAM-1, a marker of vascular inflammation, decreased from 290±35 to 246±30 ng/mL (−15.17 %, $p=0.002$) in the monacolin K group and from 288±33 to 202±28 ng/mL (−29.9 %, $p<0.001$) in the rosuvastatin group. Both intra-group differences were significant ($p<0.05$).

Our findings authenticate the lipid-lowering efficacy of monacolin K in patients with moderate hypercholesterolemia. In our study, LDL-C was reduced by 27.5 % in the monacolin K group, slightly less than the 30.2 % reduction with rosuvastatin, which are similar with some other works results. Similarly, a clinical study with a nutraceutical combination (monacolin K, coenzyme Q10, grape and olive extracts) reported a 26.5 % LDL-C reduction, closely comparable to our findings [3].

Hermans MP, et al (2023) with the purpose to evaluate the efficacy, safety, and patient satisfaction of a combined supplementation of standardized dry extracts of amla fruit (500 mg), walnut leaves (50 mg), olive fruit (25 mg), and RYR powder (33.6 mg), revealed that following supplementation, total cholesterol (TC) decreased by 15 %, LDL-C by 19 %, and non-high-density lipoprotein cholesterol (non-HDL-C) by 20 % (all $p<0.0001$). Triglycerides (TG) were reduced by 9 % ($p=0.0028$), with a greater decline of 18.4 % ($p=0.0042$) observed in patients with baseline TG levels above 180 mg/dL (n=58). Remnant cholesterol (RC) dropped by 12 % ($p=0.0001$). These improvements were consistent regardless of statin intolerance in patients receiving amla fruit, walnut leaves, olive fruit, and RYR powder alongside statins. The supplement was well tolerated, with no serious adverse events or supplement-related effects reported. The majority of patients expressed satisfaction with the intervention and indicated willingness to continue using the nutraceutical. The authors concluded, that findings from their study indicate that combined supplementation with amla, walnut, olive extracts, and RYR powder produces a marked antihyperlipidemic effect, resulting in reduced circulating LDL-C and RC levels in individuals with hypercholesterolemia. The regimen demonstrated high safety and tolerability and was considered satisfactory and feasible, including for patients who are intolerant to statins [6].

Interestingly, apart from its lipid-lowering effect, monacolin K also displayed a pronounced anti-inflammatory activity. hs-CRP levels were decreased by 29.6 %, wherein ~32 % decrease was observed in metabolic syndrome patients. The response is likely to be mediated through the inhibition of proinflammatory cytokines, such as IL-6 and TNF-α, via the suppression of the NF-κB pathway [10, 13].

The role of NF-κB pathway was also studied in the other works. The study by Zang et al. demonstrated that chrysin markedly inhibited the adhesion of Tohoku Hospital Pediatrics-1 cells to primary human umbilical vein endothelial cells and dose-dependently reduced interleukin-1β–induced elevations in ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin mRNA, as well as ICAM-1 and

VCAM-1 protein expression. Prior research has highlighted the key role of NF-κB in endothelial inflammation, particularly in the regulation of adhesion molecules, and the findings of this study indicate that chrysin mitigates endothelial inflammation primarily through suppression of the NF-κB signaling pathway. Furthermore, in vivo experiments confirmed that chrysin reduced endothelial permeability and inflammatory responses to injury. Collectively, these results suggest that chrysin effectively inhibits endothelial inflammation both in vitro and in vivo, largely via NF-κB inhibition, and may represent a promising therapeutic option for inflammatory vascular disorders [13]. In our study we observed that ICAM-1, decreased both in the monacolin K group and in the rosuvastatin group, and both intra-group differences were significant ($p<0.05$).

We also observed a decrease of 18.4 % of malondialdehyde levels, indicating lower oxidative stress. These results are in agreement with those of other authors, demonstrating that monacolin K reduces reactive oxygen species (ROS) production and enhances endothelial antioxidant defenses. Cimaglia P, et al (2019) investigated the impact of a new nutraceutical compound (NC) composed of a low dose of monacolin K, polymethoxyflavones, and antioxidants on lipid metabolism, endothelial function, and oxidative stress. An 8-week intervention with this NC led to improvements in the lipid profile of individuals with dyslipidemia and low-to-moderate cardiovascular risk. Additionally, enhancements were noted in surrogate markers of endothelial function, likely linked to the reduction in oxidized LDL (oxLDL) [4].

Furthermore, our results demonstrate a rise in total plasma antioxidant capacity, indicating the antioxidant activity of monacolin K demonstrated in various experimental models [1]. Reduction in ICAM-1 levels by 12.7 % in the monacolin K group reflects improved endothelial function. This is in agreement with the results of previous studies, which have described improved vascular reactivity and reduced vascular wall inflammation with monacolin K [8, 12].

The same results were seen in a clinical trial of Mazza A, et al (2018). A total of 104 individuals with metabolic syndrome (mean age 57.4±8.8 years, 51 % male), without a history of cardiovascular disease, were included in the study. Among them, 52 participants received a daily oral nutraceutical formulation containing red yeast rice and coenzyme Q10 alongside their diet for two months, while the remaining 52 followed only a dietary program. Blood pressure (BP), total cholesterol, low- and high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose levels were assessed using analysis of variance. Both groups showed significant reductions in BP, TC, TG, LDL-C, and glucose levels; however, the NC group experienced more pronounced improvements: systolic BP (–5.2 vs.–3.0 mmHg), diastolic BP (–4.9 vs. –2.9 mmHg), TC (–17.2 %), LDL-C (–21.8 %), TG (–16.0 %), and glucose (–3.4 %), all with $p<0.001$. HDL-C levels remained unchanged (p=N.S.), and no gender-related differences were observed (p=N.S.). The researchers concluded that in patients with metabolic syndrome, NC supplementation was safe, well tolerated, and effective in enhancing BP, lipid, and glucose profiles [8].

Collectively, these results show that monacolin K has multifactorial actions – lipid-lowering, anti-inflammatory, antioxidant, and vasoprotective – and is an excellent nutraceutical option, especially in statin-intolerant patients or those with elevated inflammatory markers. Although rosuvastatin was superior in all markers, the therapeutic significance of monacolin K remains very high and deserves serious consideration in cardiometabolic risk management.

This study has several limitations. The relatively small sample size and short follow-up period may limit the generalizability of the findings and preclude assessment of long-term efficacy and safety. In addition, restricting the study population to patients with dyslipidemia and no severe comorbidities may have influenced the observed treatment effects.

Conclusions

1. In the monacolin K group, low-density lipoprotein cholesterol decreased by 21,22 %, high-sensitivity C-reactive protein by 29,47 %, malondialdehyde by 21,85 %, and intercellular adhesion molecule-1 by 15,17 %.

2. In the rosuvastatin group, the decreases were 40.4 %, 47.5 %, 40.4 %, and 29.9 %, respectively.

The results of our work demonstrate the efficacy and safety of nutraceuticals, as well as the importance of appropriate patient management strategies. Our study demonstrates that a 12-week monacolin K treatment is safe and efficacious in improving lipid profile, inflammation and oxidative stress, and vascular function in patients with moderate hypercholesterolemia. The findings of the present study offer support for the use of monacolin K as a nutraceutical strategy to reduce cardiovascular risk in this patient population.

Thus, the benefits of nutraceuticals against various metabolic syndrome-related conditions are attributed not to a single active ingredient, but to the combined and synergistic actions of multiple constituents within the formulation. So, treatment strategies for cardiovascular diseases and hypercholesterolemia include pharmacological and non-pharmacological approaches, and nutraceuticals have been shown to play an important role in this regard.

References

1. Chen L, Kan J, Zheng N, Li B, Hong Y, Yan J, et al. A botanical dietary supplement from white peony and licorice attenuates nonalcoholic fatty liver disease by modulating gut microbiota and reducing inflammation. Phytomedicine. 2021 Oct;91:153693. doi: 10.1016/j.phymed.2021.153693.

2. Cheung B, Sikand G, Dineen EH, Malik S, Barseghian El-Farra A. Lipid-Lowering Nutraceuticals for an Integrative Approach to Dyslipidemia. J Clin Med. 2023 May 11;12(10):3414. doi: 10.3390/jcm12103414.

3.Cicero AF, Morbini M, Parini A, Urso R, Rosticci M, Grandi E, et al. Effect of red yeast rice combined with antioxidants on lipid pattern, hs-CRP level, and endothelial function in moderately hypercholesterolemic subjects. Ther Clin Risk Manag. 2016 Feb 23;12:281-6. doi: 10.2147/TCRM.S91817.

4. Cimaglia P, Vieceli Dalla Sega F, Vitali F, Lodolini V, Bernucci D, Passarini G, et al. Effectiveness of a Novel Nutraceutical Compound Containing Red Yeast Rice, Polymethoxyflavones and Antioxidants in the Modulation of Cholesterol Levels in Subjects With Hypercholesterolemia and Low-Moderate Cardiovascular Risk: The NIRVANA Study. Front Physiol. 2019 Mar 11;10:217. doi: 10.3389/fphys.2019.00217.

5. English K. Red yeast rice with monacolin K for the improvement of hyperlipidemia: A narrative review. World J Clin Cases 2025; 13(27): 105415. DOI: https://dx.doi.org/10.12998/wjcc.v13.i27.105415

6. Hermans MP, Dierckxsens Y, Janssens I, Seidel L, Albert A, Ahn SA, et al. The antihyperlipidemic effect of a combined supplement of standardized dry extracts of amla (Emblica officinalis), walnut (Juglans regia), olive (Olea europaea) and red yeast rice (Monascus purpureus) powder: Reduction in circulatory low-density lipoprotein-cholesterol (LDL-C) and remnant cholesterol (RC) levels in patients with hypercholesterolemia. Front Pharmacol. 2023 Nov 27;14:1280234. doi: 10.3389/fphar.2023.1280234.

7. Liasi E, Kantilafti M, Hadjimbei E, Chrysostomou S. Monacolin K supplementation in patients with hypercholesterolemia: A systematic review of clinical trials. Semergen. 2024 May-Jun;50(4):102156. doi: 10.1016/j.semerg.2023.102156.

8. Mazza A, Lenti S, Schiavon L, Di Giacomo E, Tomasi M, Manunta R, et al. Effect of Monacolin K and COQ10 supplementation in hypertensive and hypercholesterolemic subjects with metabolic syndrome. Biomed Pharmacother. 2018 Sep;105:992-996. doi: 10.1016/j.biopha.2018.06.076.

9. Skrypnyk IM, Ohanisyan EV, Maslova GS, Neporada KS, Shaposhnyk OA, Prykhodko NP. Microbiocenosis disorders provoke oxidative stress as a significant pathogenetic factor in non-alcoholic steatohepatitis combined with ischemic heart disease. World of medicine and biology. 2025; 1 (91): 101–105. DOI:10.26724/2079-8334-2025-1-91-101-105.

10. Tavan A, Noroozi S, Zamiri B, Gholchin Vafa R, Rahmani M, Mehdizadeh Parizi M, et al. Evaluation the effects of red yeast rice in combination with statin on lipid profile and inflammatory indices; a randomized clinical trial. BMC Nutr. 2022 Nov 25;8(1):138. doi: 10.1186/s40795-022-00639-z.

11. World Health Organization. Cardiovascular diseases (CVDs) Fact Sheet. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

12. 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 Sep;131:110585. doi: 10.1016/j.fct.2019.110585.

13. Zhao S, Liang M, Wang Y, Hu J, Zhong Y, Li J, et al. Chrysin Suppresses Vascular Endothelial Inflammation via Inhibiting the NF-κB Signaling Pathway. J Cardiovasc Pharmacol Ther. 2019 May;24(3):278-287. doi: 10.1177/1074248418810809.

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