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Effect of a Red Yeast Rice Complex (RYRC) Supplement on Diet-İnduced Dyslipidemia in Hamsters

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Abstract

Hypercholesterolemia is a significant risk factor for cardiovascular disease. Microbial metabolites such as red yeast rice and nattokinase, as well as flavonoids and polyphenols from plants like bergamot and grapes, have shown potential in lipid regulation. This study aimed to evaluate the lipid-regulating effects of a red yeast rice complex (RYRC) supplement containing microbial metabolites and plant extracts.

In this study, hyperlipidemia was induced in Syrian hamsters using a high-cholesterol diet (HCD), followed by intervention with RYRC at doses of 0, 123.3, 246.7, and 616.7 mg/kg (n=9 per group) for six weeks. Lipid and cholesterol levels in the blood, liver, and feces were analyzed post-intervention.

The results demonstrated that, compared to the HCD control group, RYRC supplementation significantly reduced serum TG, TC, LDL-C, and LDL-C/HDL-C ratio while increasing the HDL-C/TC ratio. Additionally, hepatic TG and TC levels were significantly reduced, and fecal TG and TC excretion were significantly increased.

These findings suggest that RYRC regulates blood lipids by reducing cholesterol accumulation in the blood and liver and enhancing cholesterol excretion via feces. RYRC shows promise as a functional food supplement for lipid regulation.

INTRODUCTION

Cardiovascular disease (CVD) represents a prevalent chronic non-communicable disease (NCD) and remains a leading cause of mortality globally. Projections indicate that annual CVD-related deaths will rise from 19 million in 2019 to 22.2 million by 2030 (Banach et al., 2023). While interventions targeting modifiable risk factors like hypertension and elevated low-density lipoprotein (LDL) cholesterol have proven effective, the burden of atherosclerotic cardiovascular disease (ASCVD) persists. Lowering LDL cholesterol consistently reduces cardiovascular risk, with benefits proportional to LDL reduction, regardless of baseline factors (Brandts & Ray, 2023). Current treatments, including statins, antihypertensive drugs, and antiplatelet therapies, often have side effects, highlighting the need for alternative and innovative therapies (Rashki, Ghasemzadeh Rahbardar, & Boskabady, 2025).

The pharmacological approach to hyperlipidemia management has increasingly been supplemented by dietary interventions, food supplements, and nutraceuticals, which show promising outcomes (Elmowafy et al., 2022). Certain microbial fermentation products are known for their lipid-regulating properties and cardiovascular health benefits. Natto, a traditional Japanese fermented soy product, ferments soybeans with *Bacillus subtilis var. natto* (Granito et al., 2024). Fermentation extensively degrades soybean components and generates bioactive compounds such as nattokinase, riboflavin, and polyglutamic acid (D. Li et al., 2022). In a study involving 76 participants, oral nattokinase supplementation significantly reduced total cholesterol (TC), LDL cholesterol, and plaque size, demonstrating its lipid-lowering efficacy (Dwivedi et al., 2024). Another fermentation product, red yeast rice (also known as Hong Qu, Hon-Chi, Anka, or red Koji), is derived from steamed rice fermented with the fungus *Monascus purpureus* (Yuan et al., 2022). Its primary active compound, monacolin K, is chemically identical to lovastatin and functions as a natural inhibitor of HMG-CoA reductase, the key enzyme in cholesterol biosynthesis (Banach et al., 2022).

Polyphenols are known to enhance endothelial function, prevent platelet aggregation, reduce inflammation, and improve plasma lipid profiles, contributing to cardiovascular

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health (Iqbal et al., 2023). Resveratrol, a non-flavonoid polyphenol abundant in grapes and red wine, has been identified as a potential agent for preventing and managing inflammatory conditions, including ischemic stroke, heart failure, atrial fibrillation, and metabolic syndrome (Teimouri, Homayouni-Tabrizi, Rajabian, Amiri, & Hosseini, 2022). Flavonoids, acting as free radical scavengers, exhibit antioxidant, hepatoprotective, and anti-inflammatory properties, while also modulating gene expression and molecular pathways involved in chronic diseases (Fogacci, Di Micoli, Veronesi, & Cicero, 2023). Bergamot, which rich in flavonoids, show significant antioxidant and anti-inflammatory effects. Oral administration of bergamot juice has demonstrated substantial lipid-lowering effects, reducing TC, LDL cholesterol, and triglycerides (TG) by up to 40% and increasing high-density lipoprotein (HDL) cholesterol, along with notable blood glucose reductions (Ferrarese et al., 2023).

Cardiovascular disease remains a significant challenge for human health. Although numerous pharmaceuticals are available for the treatment and management of cardiovascular diseases, most are associated with side effects (Paci et al., 2022). In contrast, microbial fermentation products and natural plant extracts generally exhibit fewer adverse effects, with studies suggesting that these functional supplements can aid in regulating lipid metabolism. Thus, this study employed a high-cholesterol diet (HCD)-induced hyperlipidemia model to investigate the effects of red yeast rice complex (RYRC) supplement on lipid and cholesterol accumulation in both the blood and liver.

MATERIALS AND METHODS

Experimental Supplement

The RYRC complex supplement was provided by HealthTake Co., Ltd. (500 mg per tablet). The formula contained red yeast rice, *Bacillus subtilis natto* ferment, plant extract (bergamot, grape seed, and sesame), and vitamin E.

Animal and Study Design

Male Syrian hamsters, aged 8 weeks, were sourced from the National Laboratory Animal Center in Taipei, Taiwan, and housed at the Animal Facility of National Taiwan Sport University. A total of 45 hamsters were kept under controlled conditions, including a temperature of 22 ± 2°C and a 12-hour light-dark cycle (6 AM to 6 PM). All animals had unrestricted access to the experimental diet and sterilized water during the study, which was approved by the IACUC of National Taiwan Sport University (Approval No. 11116).

After a one-week acclimatization period, the hamsters were randomly assigned to five groups (9 animals per group): (1) ND group, (2) HCD control group, (3) HCD + RYRC-1X group, (4) HCD + RYRC-2X group, and (5) HCD + RYRC-5X group. The ND group was fed standard Rodent Laboratory Chow 5001, while the HCD groups received a modified diet containing 0.2% cholesterol (94.8% Chow 5001, 5% lard, and 0.2% cholesterol). The RYRC treatment groups were administered daily oral doses of RYRC at 1X, 2X, and 5X (123.3, 246.7, or 616.7 mg/kg, respectively). After 6 weeks, blood samples were collected following a 12-hour fasting period for biochemical analysis. Subsequently, the animals were euthanized by carbon dioxide asphyxiation, and their livers were harvested, rinsed, and stored at -80°C for lipid analysis. Fecal samples were also collected three days before euthanasia for lipid analysis.

Blood Lipid Level Analysis

The blood samples were centrifuged at 3000×g for 15 minutes. The supernatant serum samples were collected, and serum levels of TG, TC, HDL cholesterol, and LDL cholesterol were analyzed using an automated clinical chemistry analyzer (Hitachi 7060, Hitachi, Tokyo, Japan).

Hepatic Lipid Level Analysis

Liver tissue samples (100 mg) were homogenized in 1 mL of a solvent mixture (chloroform: isopropanol: NP40 = 7:11:0.1). The homogenates were centrifuged at 15,000 × g for 10 minutes, and 400 µL of the supernatant was collected and dried under vacuum at 50°C for 30 minutes. After the drying process, the samples were rehydrated with Cholesterol assay buffer and thoroughly mixed using ultrasonic waves and vortexing. The hepatic TG content was measured using the GPO-PAP method kit (TR1697, RANDOX), while TC levels were determined using the CHOD-PAP method kit (CH3810, RANDOX).

Fecal Lipid Level Analysis

Fecal samples (100 mg) were dried in an oven to a constant weight, then extracted with 1 mL of extraction solvent (chloroform: methanol = 2:1, v/v), and the mixture was filtered through filter paper. The filtrate was evaporated under vacuum and then reconstituted in DMSO. The sample was thoroughly mixed using ultrasonication and vortexing. Fecal TG levels were quantified using the GPO-PAP method kit (TR1697, RANDOX), while TC content was measured using the CHOD-PAP method kit (CH3810, RANDOX).

Statistical Analysis

The data are expressed as the mean ± standard deviation (SD). Statistical comparisons among groups were made using one-way analysis of variance (ANOVA), followed by Duncan's post hoc test. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were done using SAS software (SAS Institute, Cary, NC, USA).

RESULTS

Effect of RYRC on the Body Weight in the Hamsters Receiving an HCD

The average weekly body weights for each group are presented in Table 1. No significant differences in body weight were observed between the five groups at weeks 0 and 1 (p

> 0.05). However, from weeks 3 to 6, the body weights of the four groups on the HCD were significantly higher than that of the ND group ($p < 0.05$). By week 6, the body weights of the HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups had increased by 1.11, 1.08, 1.08, and 1.07 times, respectively, compared to the ND group ($p < 0.001$).

Table 1. Effect of the RYRC supplement on the body weight in the hamsters receiving the HCD

Body weight (g)	ND	HCD			
		Control	RYRC-1X	RYRC-2X	RYRC-5X
Week 0	113.47 ± 3.65[a]	113.10 ± 6.20[a]	113.00 ± 6.72[a]	113.19 ± 3.55[a]	113.09 ± 5.89[a]
Week 1	115.47 ± 3.74[a]	116.33 ± 6.40[a]	115.92 ± 6.85[a]	115.91 ± 3.87[a]	115.53 ± 5.84[a]
Week 2	117.58 ± 3.88[a]	120.67 ± 6.76[a]	120.27 ± 6.64[a]	120.09 ± 3.91[a]	119.64 ± 5.89[a]
Week 3	119.90 ± 3.99[a]	125.47 ± 6.77[a]	124.57 ± 6.41[a]	124.12 ± 3.83[a]	123.77 ± 6.01[a]
Week 4	122.15 ± 3.86[a]	135.68 ± 6.68[a]	133.05 ± 6.20[a]	132.72 ± 3.74[a]	131.88 ± 5.96[a]
Week 5	124.47 ± 3.85[a]	139.98 ± 6.57[a]	136.88 ± 6.20[a]	136.34 ± 3.78[a]	135.79 ± 5.91[a]
Week 6	124.59 ± 4.06[a]	137.46 ± 6.52[a]	134.43 ± 6.26[a]	134.18 ± 3.81[a]	133.74 ± 5.95[a]

The reported values are the mean ± SD (n = 9). Different superscript letters (a and b) indicate significant differences between groups ($p < 0.05$).

Effect of RYRC on the Feed Intake and Water Intake in the Hamsters Receiving an HCD

The feed intake of each group is shown in Table 2. At week 6, the average daily intake was 9.53 ± 0.77, 9.38 ± 0.74, 9.36 ± 0.75, 9.37 ± 0.74, and 9.38 ± 0.75 (g/day) for the ND, HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups, respectively. The average daily intake of the HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups was significantly increased by 1.05-fold, 1.05-fold, 1.04-fold, and 1.05-fold, respectively, compared to the ND group ($p < 0.0001$). The water intake of each group is shown in Table 4. During the six experimental weeks, the water intake of the five groups showed no significant difference ($p > 0.05$).

Table 2. Effect of the RYRC supplement on the feed intake and water intake in the hamsters receiving the HCD

Characteristics	ND	HCD			
		Control	RYRC-1X	RYRC-2X	RYRC-5X
Feed intake (g/hamster/day)					
Week 1	8.98 ± 0.30[a]	8.86 ± 0.82[a]	8.81 ± 0.38[a]	8.82 ± 0.18[a]	8.83 ± 0.33[a]
Week 2	9.04 ± 0.13[a]	8.88 ± 0.26[a]	8.83 ± 0.26[a]	8.84 ± 0.28[a]	8.88 ± 0.34[a]
Week 3	9.04 ± 0.17[a]	8.93 ± 0.17[a]	8.89 ± 0.18[a]	8.93 ± 0.11[a]	8.93 ± 0.27[a]
Week 4	9.43 ± 0.29[a]	9.25 ± 0.12[a]	9.28 ± 0.22[a]	9.32 ± 0.16[a]	9.31 ± 0.25[a]
Week 5	9.62 ± 0.14[a]	9.48 ± 0.16[a]	9.49 ± 0.22[a]	9.50 ± 0.12[a]	9.50 ± 0.19[a]
Week 6	11.06 ± 0.33[a]	10.87 ± 0.36[a]	10.82 ± 0.22[a]	10.83 ± 0.42[a]	10.84 ± 0.32[a]
Water intake (g/hamster/day)	11.48 ± 0.33[a]	11.53 ± 0.29[a]	11.52 ± 0.30[a]	11.52 ± 0.34[a]	11.45 ± 0.37[a]

The reported values are the mean ± SD (n = 9). There is no significant difference between groups ($p < 0.05$).

Effect of RYRC on the Blood Lipid Levels in the Hamsters Receiving an HCD

The blood lipid levels of each group after 6 weeks of RYRC supplement treatment are shown in Table 5. The serum TG levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 2.71-fold, 2.16-fold, 1.93-fold, and 1.81-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the serum TG concentrations in the 1X, 2X, and 5X groups decreased significantly by 20.30%, 28.95%, and 33.46% respectively compared to the HCD group control ($p < 0.0001$).

The serum TC levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 2.67-fold, 2.40-fold, 2.31-fold, and 2.19-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the serum TC concentrations in the 1X, 2X, and 5X groups decreased significantly by 9.91%, 13.62%, and 17.86% respectively compared to the HCD group control ($p < 0.0001$).

The serum HDL cholesterol levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 1.55-fold, 1.52-fold, 1.53-fold, and 1.50-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the serum HDL cholesterol

concentrations in the 1X, 2X, and 5X groups showed no significant difference compared to the HCD group control ($p > 0.05$).

The serum LDL cholesterol levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 4.00-fold, 3.42-fold, 3.32-fold, and 3.08-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the serum LDL cholesterol concentrations in the 1X, 2X, and 5X groups decreased significantly by 14.47%, 17.11%, and 23.03% respectively compared to the HCD group control ($p < 0.0001$).

The serum LDL cholesterol/HDL cholesterol ratios of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 2.56-fold, 2.25-fold, 2.14-fold, and 2.02-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the serum LDL cholesterol/HDL cholesterol ratios in the 1X, 2X, and 5X groups decreased significantly by 12.20%, 16.46%, and 21.34% respectively compared to the HCD group control ($p < 0.0001$).

The serum LDL cholesterol/TC ratios of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant decreases compared to the ND group by 40.82%, 36.73%, 32.65%, and 30.61% respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the serum LDL cholesterol/TC ratios in the 1X, 2X, and 5X groups decreased significantly by 1.07-fold, 1.14-fold, and 1.17-fold respectively compared to the HCD group control ($p < 0.0001$).

Table 3. Effect of the RYRC supplement on the blood lipids in the hamsters receiving the HCD

Blood lipids (mg/dL)	ND	HCD			
		Control	RYRC-1X	RYRC-2X	RYRC-5X
TG	83 ± 4^{a}	286 ± 16^{d}	243 ± 14^{c}	230 ± 9^{b}	244 ± 14^{b}
TC	98 ± 5^{a}	351 ± 12^{e}	321 ± 14^{d}	286 ± 11^{c}	268 ± 15^{b}
HDL cholesterol	55 ± 4^{a}	119 ± 7^{b}	119 ± 6^{b}	120 ± 6^{b}	118 ± 8^{b}
LDL cholesterol	27 ± 3^{a}	153 ± 6^{d}	126 ± 4^{c}	116 ± 11^{b}	111 ± 8^{b}
LDL cholesterol/HDL cholesterol ratio	0.50 ± 0.04^{a}	1.29 ± 0.04^{d}	1.06 ± 0.02^{c}	0.97 ± 0.04^{b}	0.95 ± 0.08^{b}
HDL cholesterol/TC ratio	0.56 ± 0.02^{e}	0.34 ± 0.01^{a}	0.38 ± 0.01^{b}	0.42 ± 0.01^{c}	0.44 ± 0.01^{d}

The reported values are the mean ± SD (n = 9). Different superscript letters (a, b, c, and d) indicate significant differences between groups ($p < 0.05$). TG, triglyceride. TC, total cholesterol. HDL cholesterol, high density lipoprotein-cholesterol. LDL cholesterol, low-density lipoprotein-cholesterol.

Table 4. Effect of the RYRC supplement on the hepatic lipids in the hamsters receiving the HCD

Hepatic lipids (mg/g wet liver)	ND	HCD			
		Control	RYRC-1X	RYRC-2X	RYRC-5X
TG	6.83 ± 0.57^{a}	20.77 ± 0.93^{e}	17.09 ± 1.27^{d}	15.08 ± 0.43^{c}	13.33 ± 1.68^{b}
TC	4.34 ± 0.46^{a}	19.03 ± 1.77^{e}	15.64 ± 0.86^{d}	14.01 ± 1.46^{c}	12.28 ± 0.99^{b}

The reported values are the mean ± SD (n = 9). Different superscript letters (a, b, c, d, and e) indicate significant differences between groups ($p < 0.05$). TG, triglyceride. TC, total cholesterol.

Table 5. Effect of the RYRC supplement on the fecal lipids in the hamsters receiving the HCD.

Fecal lipids (mg/g dried feces)	ND	HCD			
		Control	RYRC-1X	RYRC-2X	RYRC-5X
TG	0.77 ± 0.21^{a}	2.66 ± 0.28^{b}	4.19 ± 0.74^{c}	5.03 ± 0.66^{d}	5.90 ± 0.34^{e}
TC	0.57 ± 0.03^{a}	3.99 ± 0.64^{b}	4.61 ± 0.49^{c}	5.37 ± 0.53^{d}	5.89 ± 0.38^{e}

The reported values are the mean ± SD (n = 9). Different superscript letters (a, b, c, d, and e) indicate significant differences between groups ($p < 0.05$). TG, triglyceride. TC, total cholesterol.

Effect of RYRC on the Hepatic Lipids Level in the Hamsters Receiving an HCD

The hepatic lipid levels of each group after 6 weeks of RYRC treatment are shown in Table 6. The hepatic TG levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 3.49-fold, 3.21-fold, 2.97-fold, and 2.72-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the hepatic TG concentrations in the 1X, 2X, and 5X groups decreased significantly by 7.98%, 14.88%, and 21.93% respectively compared to the HCD group control ($p < 0.0001$).

The hepatic TC levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 3.46-fold, 3.14-fold, 2.74-fold,

and 2.46-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the hepatic TC concentrations in the 1X, 2X, and 5X groups decreased significantly by 9.41%, 20.95%, and 29.05% respectively compared to the HCD group control ($p < 0.0001$).

Effect of RYRC on the Fecal Lipids Level in the Hamsters Receiving an HCD

The fecal lipid levels of each group after 6 weeks of RYRC treatment are shown in Table 7. The fecal TG levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 1.57-fold, 2.49-fold, 2.81-fold, and 3.07-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the fecal TG concentrations in the 1X, 2X, and 5X groups increased significantly by 1.59-fold, 1.79-fold, and 1.95-fold respectively compared to the HCD group control ($p < 0.0001$).

The hepatic TC levels of HCD, HCD + RYRC-1X, HCD + RYRC-2X, and HCD + RYRC-5X groups exhibited significant increases compared to the ND group by 4.17-fold, 5.07-fold, 5.90-fold, and 6.72-fold respectively ($p < 0.0001$). After 6 weeks of RYRC treatment, the hepatic TC concentrations in the 1X, 2X, and 5X groups increased significantly by 1.22-fold ($p = 0.002$), 1.42-fold, and 1.61-fold respectively compared to the HCD group control ($p < 0.0001$).

DISCUSSION

Dyslipidemia is one of the major contributors to cardiovascular diseases (Rashki et al., 2025). Functional components derived from microbial fermentations and plant extracts are known to have potential in regulating blood lipid levels. This study utilized an HCD-induced hyperlipidemic hamster model to investigate the effects of RYRC supplementation on lipid metabolism in vivo. The results indicated that a 6-week supplementation with RYRC reduced blood TG, TC, LDL cholesterol LDL-C, and the LDL-C/HDL-C ratio, while increasing the HDL-C/TC ratio. Moreover, RYRC supplementation reduced hepatic storage of TG and TC and enhanced the fecal excretion of these lipids, suggesting that RYRC holds promise as a lipid-regulating agent.

Dietary cholesterol is a well-known contributor to hyperlipidemia. Inducing hyperlipidemia in Syrian hamsters using as HCD is a widely used model for hyperlipidemia research. Previous studies have shown that mice fed an ND (2.7 kcal/g), a high-fat diet (HFD)(5.21 kcal/g), or a HCD (4.53 kcal/g) for 12 weeks exhibit distinct physiological responses. Specifically, HFD led to significant weight gain, whereas HCD did not; however, only the HCD group showed significant increases in blood TC, LDL cholesterol as well as hepatic TG and TC levels (H. Liang et al., 2021). In hamsters, consuming a HFD containing 0.1% and 0.2% cholesterol for 6 weeks increased blood TC levels by 131% and 152%, blood LDL cholesterol levels by 145% and 171%, and hepatic TC levels by 180% and 277%, respectively (Chang, Lan, Chung, & Chien, 2021). Another study revealed that feeding hamsters a HCD containing 0.5% and 1% cholesterol for 8 weeks elevated blood cholesterol levels by 234% and 313%, respectively, but significantly reduced body weight, suggesting that excessively high dietary cholesterol concentrations might have adverse effects (C. H. Huang, Hsu, & Chiang, 2024). In the present study, hamsters fed an HCD for 6 weeks exhibited no significant changes in body weight, food intake, or water consumption (Table 1-2), while lipid content in the blood, liver, and feces increased significantly (Table 3-5). These findings indicate that this experimental model does not affect the normal growth of hamsters and is suitable for evaluating the efficacy of lipid-regulating functional supplements.

Blood lipid levels are critical determinants of CVD risk, with elevated LDL cholesterol and reduced HDL cholesterol as key factors. Lowering LDL cholesterol has been shown to slow atherosclerosis progression and enhance vascular function (Lee, Kang, & Park, 2025). The results of this study demonstrate that RYRC supplementation effectively reduces serum TG, TC, and LDL cholesterol levels while improving the LDL cholesterol /HDL cholesterol and HDL cholesterol / TC ratios (Table 3). Previous studies support these findings. For example, a 4.5-year study of 4,870 patients with heart failure who consumed 600 mg/day of red yeast rice extract reported significant reductions in serum TC (10.9%), TG (15.2%), and LDL cholesterol (17.4%)(Banach et al., 2019). Similarly, a 12-month intervention with nattokinase (10,800 FU/day) in 1,062 hyperlipidemic patients resulted in decreases in TG (15.7%), TC (15.9%), and LDL cholesterol (18.1%). Moreover, in hyperlipidemic individuals (TC: 5.4–7.0 mmol/L), supplementation with 500 mg/day of bergamot extract for 4 weeks significantly reduced serum TC, LDL cholesterol, LDL cholesterol /HDL cholesterol ratio, and TC/HDL cholesterol ratio (Rondanelli et al., 2021). In another study, hyperlipidemic hamsters fed an HCD and supplemented with resveratrol for 6 weeks showed reduced serum TC, TG, and LDL cholesterol levels, alongside an improved HDL cholesterol /LDL cholesterol ratio (Su et al., 2022). These findings align with the present study, suggesting that the functional components in RYRC supplementation might help mitigate dyslipidemia.

Approximately 50% of cholesterol in the human body is synthesized in the liver. HMG-CoA reductase, a polytopic protein anchored in the ER membrane, catalyzes the rate-limiting step in cholesterol synthesis (H. Li, Yu, Ou, Ouyang, & Tang, 2021). Red yeast rice is known to reduce cholesterol synthesis by inhibiting HMG-CoA reductase activity (Banach et al., 2022). Studies have shown that in mice with HFD-induced alcoholic liver disease, 16 weeks of red yeast rice supplementation significantly reduced hepatic TG and TC accumulation and downregulated *SREBP-1* mRNA expression (Zou, Yan, & Wan, 2022). Similarly, treatment of HepG2 cells with 50 and 100 μg/mL bergamot polyphenols significantly reduced TC levels, decreased HMG-CoA reductase expression, and promoted AMPK phosphorylation, contributing to improved cholesterol metabolism (Y. Huang, Tocmo, Nauman, Haughan, & Johnson, 2021). Furthermore, hamsters supplemented with sesamin (0.2% and 0.5% of diet) for 6 weeks exhibited reduced serum and hepatic TC levels,

downregulated *HMG-CoA* reductase and *LXRα* expression, and increased *CYP7A1* expression, which inhibited cholesterol synthesis and promoted bile acid-mediated cholesterol excretion via feces (Y. T. Liang et al., 2015). In the present study, RYRC supplementation reduced hepatic cholesterol accumulation and increased fecal cholesterol content (Table 4-5). These findings suggest that RYRC might lower cholesterol levels by inhibiting HMG-CoA reductase activity and promoting bile acid-mediated cholesterol excretion.

It is challenging to isolate the individual effects of supplements and their combinations in human studies. Furthermore, determining the most beneficial combinations or identifying a single most effective combination remains unclear without extensive testing (Nogiec & Kasif, 2013). In a study involving 47 hyperlipidemic patients, supplementation with nattokinase for six months significantly reduced blood TG levels and the TC/HDL-C ratio compared to baseline but showed no significant difference compared to the placebo group. However, the group supplemented with both nattokinase and red yeast rice demonstrated significant reductions in TG, TC, LDL-C, and the TC/HDL-C ratio compared to both baseline and the placebo group, indicating that the combination provided superior lipid-regulating effects compared to nattokinase alone (Yang, Chou, Chen, Hwang, & Yang, 2009). Additionally, single-ingredient supplements often require higher dosages, increasing the risk of side effects. For example, red yeast rice is typically dosed at 1,200–4,800 mg as a standalone supplement but only 100–800 mg in combination formulations (Fogacci et al., 2019). These findings suggest that combination formulations might offer greater health benefits than single-ingredient supplements. The RYRC supplement, which reduces blood and liver lipid accumulation while promoting cholesterol excretion via feces, shows promise as a multifunctional health-promoting compound.

CONCLUSION

Hamsters with HCD-induced hyperlipidemia supplemented with RYRC for 6 weeks exhibited reduced cholesterol accumulation in the blood and liver, increased fecal cholesterol excretion, and demonstrated a dose-dependent effect. RYRC shows potential as a lipid-regulating agent and is suitable for development as a dietary supplement. The effective low dose of RYRC (123.3 mg/kg in hamsters) corresponds to a daily intake of 1,000 mg for a 60 kg human.

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