Original Article

Low dose red yeast rice with monacolin K lowers LDL cholesterol and blood pressure in Japanese with mild dyslipidemia: A multicenter, randomized trial

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Background and Objectives: Red yeast rice contains monacolin K, an inhibitor of cholesterol synthesis, and gamma-aminobutyric acid, a neurotransmitter. The daily dose of red yeast rice and monacolin K in previous studies was relatively high; therefore, there were safety concerns. We aimed to examine the effects of low daily dose red yeast rice on arteriosclerosis in patients with mild dyslipidemia. **Methods and Study Design:** Eighteen patients without known cardiovascular disease and unsatisfactory low-density lipoprotein cholesterol (3.96±0.19 mmol/L) controlled only by diet therapy were randomly allocated to receive low dose red yeast rice (200 mg/day) containing 2 mg monacolin K or diet therapy alone for 8 weeks. The primary outcome was the absolute change in low-density lipoprotein cholesterol. Secondary outcomes included total cholesterol, apolipoprotein B, and blood pressure. **Results:** Low-density lipoprotein cholesterol decreased significantly in the red yeast rice group than in the diet therapy group (median [interquartile range]: control −0.20 [−0.62, 1.19] mmol/L vs. red yeast rice −0.96 [−1.05, −0.34] mmol/L, p=0.030). The red yeast rice group also exhibited significant decreases in total cholesterol, apolipoprotein B, and blood pressure. No severe treatment-related adverse effects on muscles, liver, or renal function were observed. **Conclusions:** We found that patients in the red yeast rice group exhibited significant reductions in low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B, and blood pressure without any recognised adverse effect. This suggests that low daily dose red yeast rice could reduce cardiovascular risk in patients with dyslipidemia.

Key Words: cardiovascular risk, gamma-aminobutyric acid, hypertension, low-density lipoprotein cholesterol, *Monascus purpureus*

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INTRODUCTION

Cardiovascular disease is a major cause of death worldwide.[1] A high LDL cholesterol is a well-established risk factor for cardiovascular disease. Therefore, a reduction in blood LDL cholesterol can reduce the risk of cardiovascular disease.[2,3] Although hydroxymethylglutaryl-CoA (HMG-CoA) reductases (statins) are the first choice for patients with dyslipidemia, some patients hesitate to use statins due to nocebo effects[4] and negative coverage by the media.[5] Some patients without a history of cardiovascular diseases prefer to avoid medication therapy and continue diet and exercise therapy. However, these therapies have only moderate reducing effects on LDL cholesterol, and better options that can be incorporated into daily life are needed. Supplements are widespread, with a market penetration of approximately 50% in the United States[6-8] and 10–40% in Japan.[9,10] Supplements could be accepted by those who perceive the use of medicines negatively. However, there is insufficient evidence to support the health benefit claims of many food supplements.[11]

Red yeast rice, made by fermenting rice with the fungus Monascus purpureus, is a popular traditional food supplement in East Asian countries. This food component has been used to make tofu, wine, and vinegar. Notably, red yeast rice contains monacolins, pigments, and organic acids, and amino acids. Monacolins, including monacolin K, a low dose of lovastatin, a type of statin,[12,13] and gamma-aminobutyric acid (GABA), a neurotransmitter, has anti-hyperlipidemic effects. Moreover, red yeast rice also includes stigmasterol, which also has an anti-hyperlipidemic impact. Supplementation with this dietary component has reduced LDL cholesterol and blood pressure in various countries worldwide.[14-16]

However, few randomized controlled studies of the effects of red yeast rice in patients with dyslipidemia have been conducted in Japan. The daily dose of red yeast rice and monacolin K in previous studies performed in other countries was relatively high; therefore, there were safety concerns.[17-20] Moreover, some reports also noted that its effect as anti-hypertension is controversial.[21] Therefore, this study aimed to examine the ability of low daily red yeast rice dose to improve the quality of life and clinical outcomes as a supplement to diet therapy in Japanese patients with dyslipidemia.

METHODS

This was a multicenter, prospective, open-label, controlled study conducted in five facilities in Japan. This study protocol was approved by the Institutional Review Board (IRB) of Chiba University Hospital (ID number: G23073), which assessed all the participating study sites and served as a centralized IRB (ID numbers: N26010, N26011, N26012, N26013). Participants in this study were enrolled from May 2012 to October 2016, and all of them provided signed written informed consent. The study was conducted in full compliance with the articles of the Declaration of Helsinki and was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-ID: UMIN 000007694; Website at https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000009074). Based on previous reports,[14,22] a sample size calculation showed that 16 patients were needed to establish an LDL cholesterol reduction of 0.65 mmol/L in the red yeast rice group than in the control group (power: 0.80, significance level: 0.05).

Patients were screened for eligibility at the first visit. The following eligibility criteria were applied to the potential subjects: LDL cholesterol between 3.62 mmol/L and 4.65 mmol/L, no history of cardiovascular diseases, age between 20 and 80 years, compliance with diet therapy, and an understanding of the study and provision of written informed consent. Additionally, patients who met the following criteria were excluded: familial hypercholesterolemia; LDL cholesterol <3.62 mmol/L after diet therapy; triglyceride (TG) ≥4.52 mmol/L; administration of a statin within 4 weeks or of a probucol within 8 weeks to avoid carry-over effects; type 1 diabetes; current glycated hemoglobin (HbA1c) >63.9 mmol/mol; severe liver, kidney, or heart disease; allergy to food, including rice; excessive alcohol intake; pregnancy or lactation, or the possibility or scheduling of pregnancy; and other determination of inappropriateness for participation by a physician. Subsequently, diet therapies were conducted in line with the American Heart Association Step One diet, which allows ≤30%, 50-60%, and 10-20% of total daily calories as fat, carbohydrates, and protein, respectively (Table 1), during the run-in period for 4 weeks.

After the run-in period, the eligible patients were randomized using an allocation table. The patients were randomly assigned to either the red yeast rice group or the control group based on the following two allocation factors: man or woman and LDL cholesterol ≥4.14 or <4.14 mmol/L. Following allocation, the patients either began the intake of red yeast rice or continued the existing diet therapy. The changes in the run-in period between the two groups showed no significant difference (Table 2).

Table 1. Nutrient composition of diet during the run-in and study periods

Nutrient	Percentage of total daily calories†
Total fat	<30
Saturated fatty acids	<10
Polyunsaturated fatty acids	≤10
Cholesterol	<300 (daily intake, mg)
Carbohydrates	50-60
Protein	10-20
Monacolin K‡	0

†Except cholesterol, data are expressed as percentage of total daily calories. Cholesterol are expressed as daily intake.
‡Basically, all patients were not recommended to take monacolin K from background diet. The patients in red yeast rice group take monacolin K only from red yeast rice supplement.

Table 2. Absolute changes during the run-in period

Parameter†	Control group n=8	Red yeast rice group n=10	p-value‡
ΔBody weight (kg)	0.0 (-0.3, 0.2)	0.1 (-0.1, 0.7)	0.555
ΔBMI (kg/m^2)	0.0 (-0.1, 0.1)	0.0 (0.0, 0.3)	0.623
ΔWaist circumference (cm)	0.1 (-5.1, 2.0)	1.1 (-1.9, 2.0)	0.592
ΔTC (mmol/L)	-0.02±0.14	0.07±0.13	0.646
ΔTG (mmol/L)	-0.19±0.23	0.08±0.20	0.391
ΔLDL-C (mmol/L)	-0.02±0.14	0.07±0.13	0.646
ΔHDL-C (mmol/L)	-0.10±0.05	0.02±0.05	0.726
ΔNon-HDL-C (mmol/L)	-0.13 (-0.27, -0.05)	-0.04 (-0.21, 0.05)	0.197
ΔHbA1c (mmol/mol)	0.55±2.26	0.30±1.00	0.881
ΔSBP (mmHg)	-4.2±4.6	2.4±3.5	0.274
ΔDBP (mmHg)	-1.2±4.2	-2.5±3.2	0.805
ΔbaPWV (cm/s)	-89.5 (-169, 80)	4.75 (-56.3, 402)	0.377
ΔABI	-0.1±0.1	0.0±0.0	0.255

Δ: absolute change; TC: total cholesterol; TG: triglyceride; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; HbA1c: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; baPWV: brachial-ankle pulse wave velocity; ABI: ankle brachial pressure index.

†Absolute changes were calculated by subtracting the values at the start from the values at the end of the run-in period. Data are shown as mean±standard deviation or median values and interquartile range.

‡p-values indicate differences between the control and red yeast rice groups.

Patients in both groups continuously received diet therapy according to the American Heart Association Step One diet described above. Daily cholesterol intake was limited to <300 mg. Patients in the red yeast rice group orally consumed processed foods containing 200 mg/day red yeast rice (Asahi Group Holdings, Ltd., Tokyo, Japan), which contained 2 mg monacolin K, once a day with water after dinner, for 8 weeks in addition to diet therapy.

The primary outcome was the absolute change in the LDL cholesterol from the baseline to 4 and 8 weeks after the start of the intervention. This absolute change was described as ΔLDL cholesterol and was calculated by subtracting baseline values from the values at 4 or 8 weeks. LDL cholesterol was calculated using the Friedewald equation: LDL cholesterol = total cholesterol (TC) − [(TG/5) × (HDL cholesterol)]. From the results of previous studies,[14,22] the LDL cholesterol in the red yeast rice group was expected to decrease by 0.78 mmol/L, and the LDL cholesterol in the control group was expected to decrease by 0.13 mmol/L. Therefore, a difference of 0.65 mmol/L was set as a significant difference between the two groups. The following secondary outcomes were also investigated: absolute changes in sitting blood pressure measured using automated blood pressure devices in the clinic after five minutes rest, body weight, waist circumference, TC, HDL cholesterol, fasting TG, non-HDL cholesterol, apolipoprotein B (ApoB), HbA1c, ankle brachial pressure index (ABI), and brachial-ankle pulse wave velocity (baPWV). The ABI and baPWV were measured using an automated oscillometric device (form PWV/ABI, BP-203RPE; Nippon Colin, Aichi, Japan). Blood examination was carried out on patients after more than 12 hours of fasting.

Statistical analyses were performed using JMP Pro 13 (SAS, Cary, NC, USA). Some variables were normally distributed, while others were not. Therefore, the Student's t-test or the Wilcoxon signed-rank test was used for statistical comparisons of the diet therapy and red yeast rice groups, as appropriate. Pearson's correlation analysis was used to analyze correlations between different variables. Differences were considered statistically significant at $p<0.05$.

RESULTS

Thirteen patients were excluded from the study during the run-in period because they failed to meet the inclusion criteria due to LDL cholesterol amelioration by diet therapy or other reasons. Finally, 19 patients were enrolled and randomly assigned to the study groups (Figure 1). Subsequently, one patient did not visit the hospital after randomization and was withdrawn from the study. Because there were no significant changes between the two groups during the run-in period, the cholesterol- and blood pressure-lowering effects were determined to have not been caused by the diet therapy. The baseline characteristics of the patients are shown in Table 3. As indicated, there were no significant differences between the control group and the red yeast rice group at baseline. Therefore, it was not adjusted with age, sex, and body mass index.

Diet therapy was performed in both groups. There was no difference in compliance in both groups. Absolute changes in the clinical parameters after 4 and 8 weeks from the baseline were measured in both groups and are presented in Table 4. In particular, the reductions in LDL cholesterol (mean change±standard deviation: control 0.34±0.41 mmol/L vs red yeast rice −0.57±0.58 mmol/L, p=0.002 at 4 weeks; median [interquartile range]: −0.20 [−0.64, 1.19] mmol/L vs −0.96 [−1.05, −0.34] mmol/L, p=0.030 at 8 weeks), TC (0.31±0.15 mmol/L vs. −1.10±0.42 mmol/L, $p<0.001$ at 4 weeks; 0.00±0.75 mmol/L vs −0.92±0.57 mmol/L, p=0.014 at 8 weeks), non-HDL cholesterol (0.19±0.13 mmol/L vs −0.65±0.12 mmol/L, $p<$ 0.01 at 4 weeks, −0.28 [−0.66, 0.56] mmol/L vs −0.98 [−1.16, −0.82] mmol/L, p=0.023 at 8 weeks), and ApoB (0.05 [−0.01, 0.11] g/L vs −0.11 [−0.26, −0.01] g/L, p=0.015 at 4 weeks; 0.03±0.16 g/L vs −0.18±0.11 g/L, p=0.011 at 8 weeks) were significantly greater in the red yeast rice group than in the control group at both time points. Similarly, the reductions in systolic blood pressure (4.9±10.8 mmHg vs −6.8±11.2 mmHg, p=0.040) and dias-

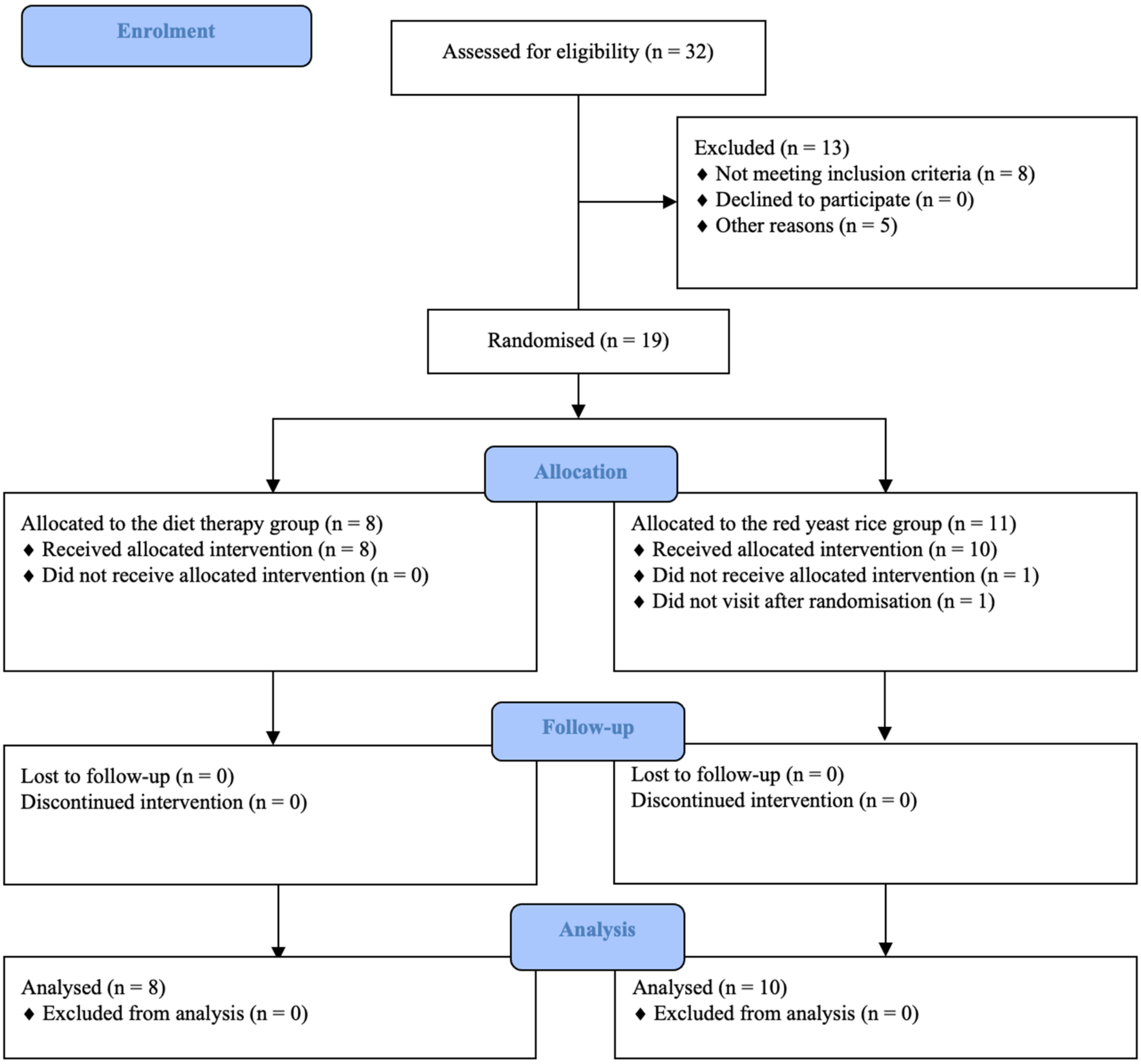

Figure 1. CONSORT diagram for this study.

Table 3. Baseline characteristics

Characteristic†	Control group n=8	Red yeast rice group n=10	*p*-value‡
Age (years)	56.0±16.2	59.6±14.8	0.629
Man (%)	3 (37.5)	4 (40.0)	0.958
Body weight (kg)	62.0 (56.9, 73.1)	63.0 (59.0, 66.8)	0.894
BMI (kg/m^2)	24.4 (22.7, 27.8)	25.1 (21.9, 28.1)	0.965
Waist circumference (cm)	87.5 (80.0, 96.5)	86.3 (84.4, 102)	0.884
TC (mmol/L)	6.12±0.19	6.29±0.30	0.421
TG (mmol/L)	1.50±0.78	1.84±0.90	0.401
LDL-C (mmol/L)	3.93±0.19	3.99±0.19	0.477
HDL-C (mmol/L)	1.51± 0.51	1.46±0.33	0.778
Non-HDL-C (mmol/L)	4.61±0.15	4.83±0.13	0.277
HbA1c (mmol/mol)	43.5±7.8	44.7±8.3	0.562
SBP (mmHg)	122±18.4	130±16.0	0.339
DBP (mmHg)	70.5±8.9	71.5±7.5	0.799
baPWV (cm/s)	1335±284	1510±295	0.251
ABI	1.1±0.1	1.2±0.1	0.076
Type-2 diabetes, n (%)	3 (37.5)	7 (70)	0.198
Anti-hypertensive treatment, n (%)	1 (12.5)	2 (20)	0.731

TC: total cholesterol; TG: triglyceride; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; HbA1c: glycated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; baPWV: brachial-ankle pulse wave velocity; ABI: ankle brachial pressure index.
†Data are shown as mean ± standard deviation, median values and interquartile range, numbers, and percentages.
‡*p*-values indicate differences between the control and red yeast rice groups.

Table 4. Baseline characteristics

Parameters†	At week	Control group n=8	Red yeast rice group n=10	*p*-value‡
ΔBody weight (kg)	4	0.1±1.3	0.3±1.9	0.793
	8	-0.1±2.3	-0.0±1.6	0.981
ΔWaist circumference (cm)	4	-1.0±2.2	-0.8±4.3	0.933
	8	-2.5±2.3	-1.1±3.0	0.314
ΔTC (mmol/L)	4	0.31±0.15	-1.10±0.42	<0.001
	8	0.00±0.75	-0.92±0.57	0.014
ΔTG (mmol/L)	4	-0.33±0.54	-0.18±0.79	0.665
	8	-0.05 (-0.38, 0.19)	0.24 (-0.56, 0.40)	0.505
ΔLDL-C (mmol/L)	4	0.34±0.41	-0.57±0.58	0.002
	8	-0.20 (-0.64, 1.19)	-0.96 (-1.05, -0.34)	0.030
ΔHDL-C (mmol/L)	4	0.12±0.09	-0.05±0.05	0.038
	8	0.03±0.14	-0.13±0.21	0.082
ΔNon-HDL-C (mmol/L)	4	0.19±0.13	-0.65±0.12	<0.001
	8	-0.28 (-0.66, 0.56)	-0.98 (-1.16, -0.82)	0.023
ΔApoB (g/L)	4	0.05 (-0.01, 0.11)	-0.11 (-0.26, -0.01)	0.015
	8	0.03±0.16	-0.18±0.11	0.011
ΔHbA1c (mmol/mol)	4	0.11±1.31	0.82±2.14	0.715
	8	-0.33±2.68	2.88±6.11	0.111
ΔSBP (mmHg)	4	-1.5±11.8	-9.1±10.4	0.167
	8	4.9±10.8	-6.8±11.2	0.040
ΔDBP (mmHg)	4	4.5±10.9	-3.3±5.1	0.061
	8	7.9±10.4	-2.4±5.8	0.018
ΔbaPWV (cm/s)	8	18.5 (-22.3, 40.5)	-85.8 (-296, 39.1)	0.128
ΔABI	8	0.0±0.1	0.0±0.1	0.123

Δ: absolute change; TC: total cholesterol; TG: triglyceride; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; ApoB: apolipoprotein B; SBP: systolic blood pressure; DBP: diastolic blood pressure; baPWV: brachial-ankle pulse wave velocity; ABI: ankle brachial pressure index.
†Data are shown as mean ± standard deviation or median values and interquartile range.
‡*p*-values indicate differences between the control and red yeast rice groups.

tolic blood pressure (7.9±10.4 mmHg vs −2.4±5.8 mmHg, *p*=0.018) were significantly greater in the red yeast rice group than in the control group after 8 weeks. Although the difference between the groups was not significant, the red yeast group exhibited greater reductions in baPWV (18.5 [−22.3, 40.5] cm/s vs −85.8 [−296, 39.1] cm/s, *p*=0.128) after 8 weeks.

We also investigated whether the blood pressure-lowering effect by red yeast rice was associated with its LDL cholesterol-lowering effect. Figure 2 presents the results of a Pearson's correlation analysis. The ΔbaPWV was shown to correlate with the Δsystolic blood pressure (r = 0.65, *p*=0.006; Figure 2A) but not with the ΔLDL cholesterol (Figure 2B). No correlations were observed between the ΔLDL cholesterol and Δsystolic blood pressure (Figure 2C).

No severe treatment-related adverse events were observed. Laboratory analyses revealed that the red yeast rice had no adverse effects on muscles, liver, or renal function (Table 5).

DISCUSSION

This study investigated the effects of supplementation with low daily dose red yeast rice on absolute changes of LDL cholesterol in Japanese patients with mild dyslipidemia without previous cardiovascular diseases. The strength of our study is the use of a supplement for diet therapy instead of drug therapy. Modification of lifestyle is important because excessive intake of cholesterol and saturated fatty acids leads to increased serum LDL cholesterol.[23] The main advantage of supplements is its acceptance by those who view the use of medicine negatively due to nocebo effects and concerns regarding the chemical nature of

Table 5. Adverse events

Adverse event†	Control group	Red yeast rice group	*p*-value‡
Skin rash	0/8	0/10	N/A
Muscle pain	0/8	0/10	N/A
ΔCK (IU/L)	-16.3±29.8	-1.9±42.6	0.432
ΔAST (IU/L)	-0.9±2.4	-0.9±3.6	0.987
ΔALT (IU/L)	-1.9±4.1	-2.1±5.2	0.922
ΔCre (μmol/L)	0.0±8.8	0.0±8.8	0.353
Termination	0/8	0/10	N/A

Δ: absolute change; N/A: not available; CK: creatine phosphokinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Cre: creatinine.
†Data are shown as mean ± standard deviation or numbers.
‡*p*-values indicate differences between the control and red yeast rice groups.

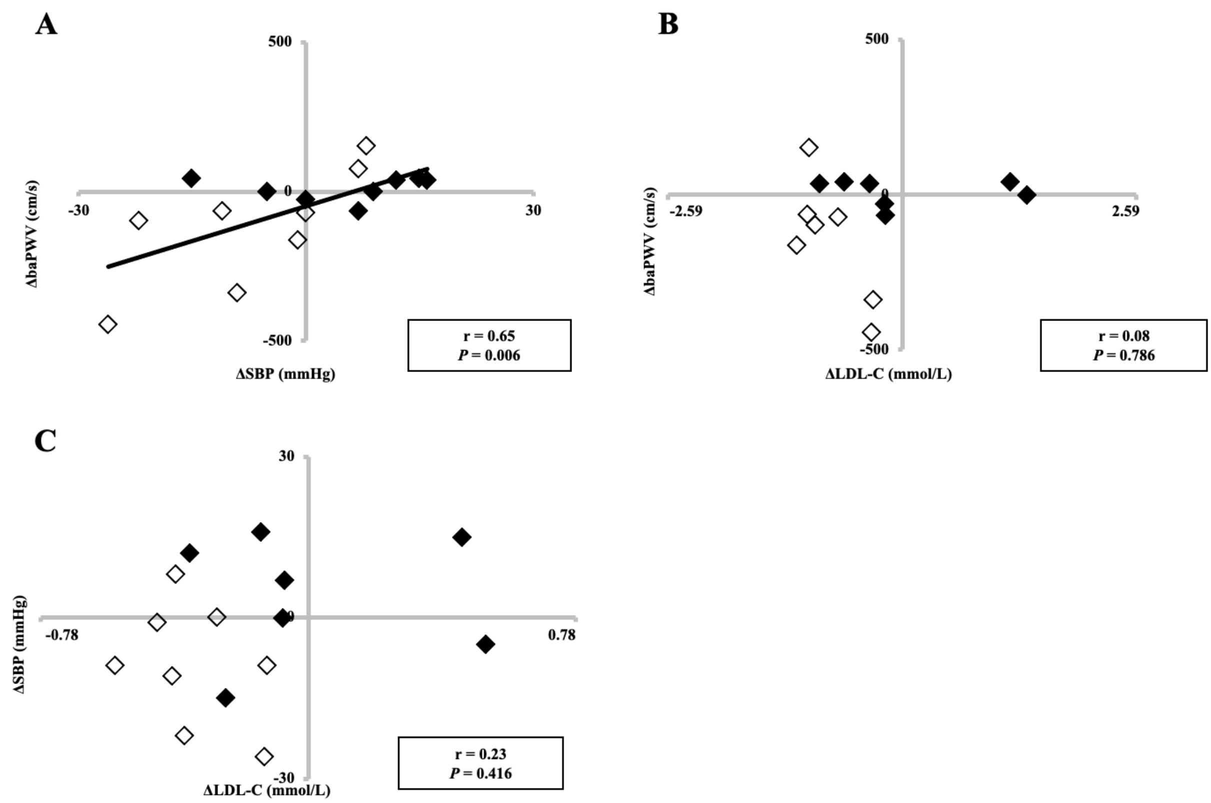

Figure 2. Correlations between the change in baPWV and the change in SBP or LDL-C. Closed and open diamonds represent the control group and the red yeast rice group, respectively. baPWV, brachial-ankle pulse wave velocity; Δ: change; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.

drugs imparted by negative media coverage. However, the lack of evidence regarding their health effects is one of the main problems associated with supplements. The real add-on value of this randomized controlled study is the evidence showing that lower daily dose red yeast rice containing 2 mg monacolin K can simultaneously reduce LDL cholesterol, blood pressure, and several secondary outcomes in Japanese patients with dyslipidemia. The reduction of ApoB, which reflects the total number of circulating atherogenic particles,[24] was greater in the red yeast rice group. Although the reduction in baPWV was not significant, there was an amelioration tendency in the red yeast rice group.

In a previous meta-analysis, subjects treated with red yeast rice exhibited a greater reduction in LDL cholesterol (1.02 mmol/L) than those treated with a placebo.[14] Another meta-analysis reported a 5.62 mmHg greater reduction in systolic blood pressure among patients treated with red yeast rice than those who received conventional therapy.[16] Consistent with these findings, we observed reductions in both LDL cholesterol and blood pressure in the red yeast rice group.

While a meta-analysis of 20 randomized control studies with 6653 participants (follow-up between 2 months and 3.5 years) and a monacolin K dose varying from 4.8 to 24 mg per day showed that red yeast rice supplementation lowered LDL cholesterol than the placebo (−1.02 mmol/L).[14] However, since monacolin K is structurally identical to lovastatin, there are safety concerns related to some side effects commonly associated with the treatment with statins.[17,18] Table 6 summarized similar randomized control trials that evaluated the lipid-lowering effects of red yeast rice. Even in studies with a low monacolin K, a lowering effect on LDL cholesterol and TC was observed. The correlation coefficient of the content of red yeast rice, monacolin K, and ΔLDL cholesterol, ΔTC, ΔApoB, Δsystolic blood pressure, and Δdiastolic pressure of these studies have been evaluated (Table 7). The correlation coefficients were found low. Red yeast rice and monacolin K are not dose-dependent. Therefore, for the patients with mild dyslipidemia, low dose monacolin K administration is preferable. In our study, the patients were treated with a lower dose of monacolin K, 2 mg per day, than in previous studies. However, the LDL cholesterol lowering effect was not so different from the previous high-dose monacolin K treatment. Our study shows that the low daily dose monacolin K treatment is effective and safe.

As described above, red yeast rice contains a low dose of lovastatin and monacolin K, which is likely responsible for the observed reductions in TC, non-HDL-cholesterol, and LDL cholesterol by inhibiting HMG-CoA reductase.[57,58] However, red yeast rice contains complex nutrients; therefore, other nutrients may have a lipid-lowering effect.

In a study with Japanese adults regarding the management of elevated cholesterol in primary cardiovascular disease prevention, patients treated with pravastatin exhibited an approximately 18% reduction in LDL cholesterol and a 33% reduction in the incidence of cardiovascular disease.[59] In our study, red yeast rice supplementation was associated with a 24% reduction in the LDL cholesterol, suggesting that this supplement can reduce the risk of cardiovascular disease.

Blood pressure reduction effects are an additional bene-

Table 6. Randomized control trials that evaluated the effects of red yeast rice

Study[References]	Year	Country	Main eligibility criteria	Number of patient	Number of intervention	Number of control
Minamizuka	2021	Japan	LDL-C 3.62-4.65 mmol/L, TG <4.52 mmol/L	18	10	8
Guerrero-Bonmatty[25]	2021	Spain	TC ≥5.17 mmol/L	39	21	18
Cicero[26]	2020	Italy	LDL-C 2.97-4.91 mmol/L, TG <4.52 mmol/L	85	43	42
Iskandar[27]	2020	Indonesia	TC 5.69-6.18 mmol/L, LDL-C 2.59-4.11 mmol/L	76	40	36
Nafrialdi[28]	2019	Indonesia	LDL-C 3.36-4.65 mmol/L	49	25	24
Domenech[29]	2019	Spain	TC >5.69 mmol/L, LDL-C >2.97 mmol/L	40	20	20
Mazza[30]	2019	Italy	TG >3.88 mmol/L, HDL-C <1.03 mmol/L (man), <1.29 mmol/L (woman) with MetS, in primary prevention for CVDs	104	52	52
Pirro[31]	2018	Italy	LDL-C >2.97 mmol/L with HIV-1 infection	30	15	15
Mazza[32]	2018	Italy	TC ≥5.17 mmol/L and LDL-C 3.36-4.91 mmol/L	60	30	30
Derosa[33]	2018	Italy	TC 5.17-6.21 mmol/L, TG <4.52 mmol/L	80	40	40
Spigoni[34]	2017	Italy	non-HDL-C ≥4.14 mmol/L	39	30	9
Cicero[35]	2017	Italy	LDL-C 3.36-4.91 mmol/L and TG 1.69-4.52 mmol/L with MetS, in primary prevention for CVDs	30	30	30
Cicero[36]	2017	Italy	LDL-C 2.97-4.14 mmol/L	50	25	25
D'Addato[37]	2017	Italy	LDL-C 2.97-4.65 mmol/L, TC 5.17-6.72 mmol/L, TG <2.82 mmol/L	130	44 / 42	44
Heinz[38]	2016	Germany	LDL-C 4.14-5.69 mmol/L	142	70	72
Verhoeven[39]	2015	Belgium	TG >1.69 mmol/L, HDL-C <1.03 mmol/L (man), <1.29 mmol/L (woman) with MetS	50	26	24
Moriarty[40]	2014	USA and China	TC ≥6.21 mmol/L, LDL-C 4.14-5.69 mmol/L and TG <4.52 mmol/L	116	78	38
Ogier[41]	2013	France	TC >5.69 mmol/L	39	19	20
Barrat[42]	2013	France	LDL-C 3.28-5.79 mmol/L, TG ≤2.48 mmol/L and HDL-C ≥1.03 mmol/L	100	50	50
Barrat[43]	2012	France	LDL-C 3.28-5.79 mmol/L, TG ≤2.48 mmol/L and HDL-C ≥1.03 mmol/L	45	30	15
Karl[44]	2012	USA	man 20-80 years of age and postmenopausal woman 55-80 years of age	45	23	22
Lee[45]	2012	Taiwan	TG >1.69 mmol/L, HDL-C <1.03 mmol/L (man), <1.29 mmol/L (woman) with MetS	96	52	44
Higashikawa[46]	2012	Japan	TG 1.35-2.26 mmol/L	55	28	27
Affuso[47]	2010	Italy	TC >5.69 mmol/L and LDL-C >3.36 mmol/L	50	25	25
CCSPS[48]	2010	China	TC 4.40-6.47 mmol/L and TG ≤4.52 mmol/L with previous MI and HT	2704	1363	1341
Becker[49]	2009	USA	LDL-C 2.59-5.43 mmol/L, TG <4.52 mmol/L, dyslipidemia and history of discontinuation of statin therapy due to myalgias	62	31	31
CCSPS[50]	2008	China	TC 4.40-6.47 mmol/L and TG ≤4.52 mmol/L with previous MI	4870	2429	2441
Hu[51]	2006	China	MI and/or AP	50	25	25
Lin[52]	2005	Taiwan	TC ≥6.21 mmol/L, LDL-C ≥4.14 mmol/L and TG ≤4.52 mmol/L	79	39	40
Zhao[53]	2004	China	MI and/or AP	50	25	25
Zhao[54]	2003	China	MI and/or CHD	50	25	25
Keithley[55]	2002	USA	TC >5.17 mmol/L, LDL-C >3.36 mmol/L and TG >1.52 mmol/L with HIV-1 infection	12	6	6
Heber[56]	1999	USA	LDL-C >4.14 mmol/L and TG <1.29 mmol/L	83	42	41

LDL-C: LDL cholesterol; TG: triglyceride; TC: total cholesterol; HDL-C: HDL cholesterol; MetS: metabolic syndrome; MI: myocardial infarction; HT: hypertension; AP: angina pectoris; Δ: absolute change; ApoB: apolipoprotein B; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 6. Randomized control trials that evaluated the effects of red yeast rice (cont.)

Study[References]	ΔSBP (mmHg)	ΔDBP (mmHg)	Other ingredients
Minamizuka	-6.8	-2.4	–
Guerrero-Bonmatty[25]	Not mentioned	Not mentioned	Lactoplantibacillus plantarum strains (CECT7527, CECT7528, and CECT7529)
Cicero[26]	Not mentioned	Not mentioned	Phytosterols 800 mg, niacin 27 mg, policosanols 10 mg
Iskandar[27]	Not mentioned	Not mentioned	Guggulipid extract 11 0mg, chromium picolinate 50 µg
Nafrialdi[28]	Not mentioned	Not mentioned	Guggulipid extract 110 mg, chromium picolinate 50 µg
Domenech[29]	Not mentioned	Not mentioned	Phytosterols 1.5 g, hydroxytyrosol 5 mg, vitamin E 12 mg
Mazza[30]	-5.2	-4.9	Coenzyme Q10 30 mg
Pirro[31]	-1.9	-1.2	Policosanol 10 mg, berberine 500 mg, astaxanthin 0.5 mg, folic acid 0.2 mg, coenzyme Q10 2 mg
Mazza[32]	Not mentioned	Not mentioned	Octacosanol 12 mg, resveratrol 20 mg, chromium picolinate 50 µg, piperine 2.99 mg
Derosa[33]	Not mentioned	Not mentioned	Sterol esters 720 mg, stanols 425 mg, curcumin 45 mg, olive polyphenols 25 mg
Spigoni[34]	Not mentioned	Not mentioned	Berberine 200mg, chitosan 10mg, coenzyme Q10 10mg
Cicero[35]	-1.7	-0.9	Artichoke extract 500 mg, banaba extract 75 mg, coenzyme Q10 50 mg, vitamin B-3 9 mg, B-6 1.4 mg, B-12 0.83 µg, folic acid 110 µg
Cicero[36]	-12.6	-7.3	Phytosterols 400mg, L-tyrosol 2.5mg
D'Addato[37]	Not mentioned	Not mentioned	Berberine 500 mg, coenzyme Q10 2 mg, hydroxytyrosol 5 mg / berberine 500 mg, policosanol 10 mg, folic acid 0.2 mg, coenzyme Q10 2.0 mg, astaxanthin 0.5 mg
Heinz[38]	Not mentioned	Not mentioned	Coenzyme Q10 20 mg, astaxanthin 0.5 mg, folic acid 200 µg
Verhoeven[39]	-10.4	-7.6	Hydroxytyrosol 9.32 mg
Moriarty[40]	Not mentioned	Not mentioned	–
Ogier[41]	Not mentioned	Not mentioned	Sugar cane extract 11.1mg, artichoke leaf dry extract 600 mg, garlic dry extract 30 mg, pine bark extract 60 mg, vitamins E 38.6 mg, B-2 4.8 mg, B-3 8.8 mg, dicalcium phosphate 597 mg, microcrystalline cellulose 262 mg, calcium citrate 262 mg, tricalcium phosphate 102 mg, magnesium stearate 66 mg
Barrat[42]	Not mentioned	Not mentioned	Policosanol, artichoke leaf extract
Barrat[43]	Not mentioned	Not mentioned	Policosanol, artichoke leaf extract
Karl[44]	Not mentioned	Not mentioned	Niacin 25 mg, phytosterol esters 1300 mg, L-carnitine 300 mg, vitamin C 1000 mg, coenzyme Q10 50 mg
Lee[45]	-4	-5.3	Fresh bitter gourd 40 g, chlorella 1.5 g, soybean 1.1 g, licorice 2.2 g
Higashikawa[46]	Not mentioned	Not mentioned	Garlic
Affuso[47]	Not mentioned	Not mentioned	Berberine 500 mg, policosanol 10 mg
CCSPS[48]	-5.5	-4.3	–
Becker[49]	Not mentioned	Not mentioned	–
CCSPS[50]	Not mentioned	Not mentioned	–
Hu[51]	Not mentioned	Not mentioned	–
Lin[52]	Not mentioned	Not mentioned	–
Zhao[53]	Not mentioned	Not mentioned	–
Zhao[54]	Not mentioned	Not mentioned	–
Keithley[55]	Not mentioned	Not mentioned	Not mentioned
Heber[56]	Not mentioned	Not mentioned	–

LDL-C: LDL cholesterol; TG: triglyceride; TC: total cholesterol; HDL-C: HDL cholesterol; MetS: metabolic syndrome; MI: myocardial infarction; HT: hypertension; AP: angina pectoris; Δ: absolute change; ApoB: apolipoprotein B; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 7. Correlation of red yeast rice, monacolin K and lipids, blood pressure

	ΔTC (mmol/L)	ΔLDL-C (mmol/L)	ΔApoB (g/L)	ΔSBP (mmHg)	ΔDBP (mmHg)
Content of red yeast rice (mg/day)	-0.21	-0.30	-0.61	-0.39	-0.57
Content of monacolin K (mg/day)	-0.45	-0.46	-0.62	-0.03	-0.26

ApoB: apolipoprotein B; Δ: absolute change; TC: total cholesterol; LDL-C: LDL cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure.
The correlation coefficient of the content of red yeast rice, monacolin K, and absolute change of LDL cholesterol, TC, ApoB, systolic blood pressure, and diastolic pressure of randomized clinical trials are indicated.

fit of red yeast rice consumption. Lovastatin and monacolin K have a blood pressure-lowering effect. Moreover, red yeast rice contains GABA,[60] a neurotransmitter in the sympathetic nervous system that controls cardiovascular function. GABA has been reported to decrease blood pressure in animals and humans.[61,62] Its presence may explain the observed reduction in blood pressure in this study. Monacolin K and GABA contained in red yeast rice could contribute to ameliorate atherosclerosis.

Our results indicate that red yeast rice has a pleiotropic effect on the cardiovascular system. Therefore, red yeast rice can comprehensively treat patients with multiple cardiovascular risk factors, even as a supplement. We expected that baPWV would also reduce due to red yeast rice consumption. Our finding that baPWV tended to decrease after treatment was also consistent with previous studies.[63,64] Previous studies also reported that statins could reduce PWV.[65] The presence of monacolin K and GABA in red yeast rice may explain the observed reduction in baPWV in this study.

There is a famous Japanese menu called Tofuyo, in which red yeast rice has been traditionally used in Okinawa Prefecture, Japan. Tofuyo, a food made by fermenting bean curd with red yeast rice and sake, was introduced to Okinawa from China in the 1800s and reportedly contained much monacolin K. Although the exact monacolin K content was not reported. According to a Tofuyo recipe, the ingredients for 5 people contain 2 teaspoons (10 g) of red yeast rice. In Okinawa, red yeast rice has also been traditionally used as red yeast rice vinegar and a colorant for celebration foods, such as cooked red rice, red boiled eggs, red fishcake, red cuttlefish meat, and so on since the 1800s.[66] The life expectancy in Okinawa was longer than in other areas in Japan.

Despite these encouraging findings, we emphasize that statin drugs remain the best option for reducing LDL cholesterol in high-risk cardiovascular patients. In Japan, drug therapy for hyper-LDL cholesterolemia should be considered early if the improvement of lifestyle habits cannot be expected at a high risk of primary prevention.[67] This study was targeted at patients under the medium risk of primary prevention and between periods of improvement of lifestyle habits and drug therapy. Red yeast rice supplementation can be recommended for patients with only moderately high LDL cholesterol. If such patients cannot achieve appropriate results with diet and exercise therapy alone, they should not hesitate to take statins. However, red yeast rice may be a solution for patients who refuse to use statins because of nocebo effects and negative media coverage.

This study had a few noteworthy limitations. First, the study design was not double-blinded, and the lack of a placebo may have affected the patients' behavior. Second, the number of patients was small. According to the exclusion criteria, five patients with cancer were excluded. The sample size might have limited the opportunity to detect adverse side effects, the most usual concern with red yeast rice. It may also have been insufficient to evaluate the change of baPWV, a secondary endpoint. Furthermore, large and long-term studies are needed. However, this study showed the simultaneous reduction of LDL cholesterol and blood pressure in the low daily dose red yeast rice group. This was the first randomized controlled study to evaluate the effects of low daily dose red yeast rice for lipid profile and blood pressure control in Japanese patients with mild dyslipidemia.

In conclusion, this study showed the usefulness of low daily dose red yeast rice as a supplement to the diet therapy administered to Japanese patients with mild dyslipidemia in a clinical setting. Our findings that patients in the red yeast rice group exhibited significantly greater reductions in LDL cholesterol and blood pressure relative to the controls suggest that red yeast rice could reduce cardiovascular risks in this population. Low daily dose red yeast rice is suitable for patients who are reluctant to take statins because of nocebo effects, concerns regarding the chemical nature of drugs, or negative media coverage.

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AUTHOR DISCLOSURES

The authors declare no potential conflict of interest associated with this research. Red yeast rice was provided by Asahi Group Holdings, Ltd. The funding source had no role in the design of this study and its execution, analyses, interpretation of the data, and the decision to submit results.

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