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Original Article

No Additional Cholesterol-Lowering Effect Observed in the Combined Treatment of Red Yeast Rice and *Lactobacillus Casei* in Hyperlipidemic Patients: A Double-Blind Randomized Controlled Clinical Trial*

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ABSTRACT **Objective**: To observe the effect of combining red yeast rice and *Lactobacillus casei* (*L. casei*) in lowering cholesterol in patients with primary hyperlipidemia, the later has also been shown to remove cholesterol in *in vitro* studies. **Methods**: A double-blind clinical trial was conducted to evaluate the cholesterol-lowering effect of the combination of red yeast rice and *L. casei*. Sixty patients with primary hyperlipidemia were recruited and randomized equally to either the treatment group (red yeast rice + *L. casei*) or the control group (red yeast rice + placebo). One red yeast rice capsule and two *L. casei* capsules were taken twice a day. The treatment lasted for 8 weeks, with an extended follow-up period of 4 weeks. The primary endpoint was a difference of serum low-density lipoprotein cholesterol (LDL-C) level at week 8. **Results**: At week 8, the LDL-C serum level in both groups was lower than that at baseline, with a decrease of 33.85±26.66 mg/dL in the treatment group and 38.11±30.90 mg/dL in the control group; however, there was no statistical difference between the two groups ($P>0.05$). The total cholesterol was also lower than the baseline in both groups, yet without a statistical difference between the two groups. The only statistically significant difference between the two groups was the average diastolic pressure at week 12, which dropped by 2.67 mm Hg in the treatment group and increased by 4.43 mm Hg in the placebo group ($P<0.05$). The antihypertensive activity may be associated with *L. casei*. Red yeast rice can significantly reduce LDL-C, total cholesterol and triglyceride. **Conclusion**: The combination of red yeast rice and *L. casei* did not have an additional effect on lipid profiles.

KEYWORDS red yeast rice, *Lactobacillus casei*, low-density lipoprotein cholesterol, randomized controlled trial

Hyperlipidemia is a major risk factor for atherosclerosis and cardiovascular disease (CVD).[1] The risk of CVD can be reduced by lowering serum cholesterol levels and low-density lipoprotein cholesterol (LDL-C).[2] Cholesterol absorbed from the intestine is a mixture of exogenous and endogenous cholesterol, with the former deriving from dietary cholesterol, representing only about one-third of the total intestinal cholesterol pool, while the endogenous sources including bile and to some extent intestinal mucosal cholesterol, account for the remaining two-thirds.[3]

3-Hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA) reductase inhibitor, or statin, is the preferred drug to reduce LDL-C and cardiovascular events in patients at variable risk levels.[4] However, statins might have serious adverse effects such as myopathy, rhabdomyolysis

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and hepatitis. Ezetimibe, on the other hand, inhibits dietary cholesterol absorption from the intestinal wall by inhibiting the niemann-pick C1-like 1 (NPC1L1) cholesterol transporter,[5] thus inducing up-regulation of LDL receptors on the cell surface, and resulting in a decrease in LDL-C levels. The Study of Heart and Renal Protection demonstrated a reduction in major atherosclerotic events with a statin/ezetimibe combination therapy;[6] this dual therapy resulted in a significantly greater LDL-C reduction and the subsequent achievement of treatment goals.[7]

There are also alternative therapies that have become more prevalent throughout the world.[8,9] Red yeast rice is one such example. As a Chinese dietary supplement, it has gained popularity due to its properties as a natural statin. This fermented rice product is used as a medicinal food to improve blood circulation by decreasing cholesterol and triglyceride (TG) levels.[10] While the supplement contains natural monacolins in varying amounts as a result of the different strains of red yeast rice used in fermentation,[11] the primary monacolin in red yeast rice is monacolin K, which has the same chemical structure as lovastatin. A secondary metabolite produced from red yeast rice is γ-aminobutyric acid (GABA), a hypotensive agent.[12]

Other agents that can have positive effects on hypercholesterolemia include many probiotic strains, such as *Lactobacillus acidophilus* (*L. acidophilus*), *Lactobacillus plantarum*, *Lactobacillus casei* (*L. casei)*, *Lactobacillus bulgaricus*, *Lactobacillus fermentum*, and others (*Bacillus coagulans*, *Bifidobacterium longum*).[13] Histopathological data have confirmed the partial protection of the gastrointestinal tract in rats dosed with *L. acido* philus and *L. casei*, as well as the improvement of liver functioning, anticholesterolemic effects, and the reduction of enterobacteria in the gut.[14] *L. casei* can remove cholesterol while growing in a culture medium in the laboratory.[15] One *in vitro* study indicated that *L. casei* strains removed cholesterol by destabilizing cholesterol micelles and coprecipitating cholesterol with deconjugated bile salts at pH <6.0.[16] In an animal study, it was found that *L. paracasei* NTU 101 (*L. casei* strain) expressed LDL-C content with a reduction of 32.9 % compared to that of the control group.[17] However, the hypolipidemia effect of *L. casei* in humans is not clear. In an *in vitro* study, *L. casei* showed higher cholesterol assimilation activity than *L. acidophilus* 43121, and *B. longum* showed the highest bile acid deconjugation and dehydroxylation activity in a comparison of 181 species.[18] It has also been observed that the growth of *L. acidophilus* and *L. casei* in a culture medium can deconjugate bile acid by producing bile acid hydrolase.[19] In terms of improving liver function, fighting against cholesterolemia, and protecting infected bowels, *L. casei* is superior to *L. acidophilus*. For these reasons, we selected *L. casei* rather than *L. acidophilus* in our study. Since statins inhibit the production of cholesterol in the liver, and ezetimibe inhibits dietary cholesterol absorption from the intestinal wall, the combination of these two drugs is likely to achieve a synergistic effect in the reduction of LDL-C. We performed a clinical trial using these natural products to evaluate the combination of *L. casei* (a bacillus strain that lowers cholesterol through action in the gastrointestinal tract) and red yeast rice (which lowers cholesterol by inhibiting cholesterol synthesis in the liver), and determine whether the combination of red yeast rice with *L. casei* is similar to statins combined with ezetimibe, in which would have intensified positive effects.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria were adults aged over 18 years, with LDL-C greater than 160 mg/dL or TG greater than 200 mg/dL. Exclusion criteria included the following: pregnant or lactating women who were required to undergo a 30-day washout period prior to screening for HMG-CoA reductase inhibitors, bile acid binding resins, nicotinic acids or niacins, fibrate derivatives, or cholesterol absorption inhibitors; those who changed their chemical glucose-lowering drugs, e.g., to α-glucosidase inhibitor, sulfonylurea, biguanide, meglitinide, or peroxisome proliferator-activated receptor agonists within 30 days prior to screening; those who had taken other health foods within 30 days prior to screening; those whose biochemistries were abnormal, or whose serum creatinine was ⩾3.0 mg/dL and alanine aminotransferase (ALT) 5 times the normal value.

Patients

The study was approved by the Institutional Review Board of Chung Shan Medical University. A total of 60 patients with primary hyperlipidemia from Chung Shan Medical University were recruited for this study. Written informed consent was obtained from all subjects.

Experimental Design

Assuming that the effect of the treatment group ($\mu 1$) was a decrease of LDL-C, which was 20, and the control group ($\mu 0$) was 10, a two-sided test was used, with type Ⅰ error (α) 0.05 and statistical power ($1-\beta$) 0.8. It was estimated that this study required 41 subjects in each group to achieve 95% power. The expected dropout rate was 25% in this research. The targeted sample size for the study was 60 patients. Therefore, the study had >95% power to detect a treatment effect with this sample size.

Sixty patients were randomized to either the treatment group (30 subjects) or the control group (30 subjects). Block randomization was done by envelops with a computer-generated allocation sheet of 1:4. A statistician assigned the allocation sheet to the participants. Blind research coordinators enrolled the participants sequentially based on the allocation sheet. The trial subjects and investigators were both blinded throughout the trial period.

Therapy and Follow-up

One red yeast rice capsule was taken twice a day (Chuang Song Zong Pharmaceutical Co., Ltd. within 30 min after breakfast and dinner, respectively). Two *L. casei* capsules were taken twice a day (within 30 min after breakfast and dinner, respectively). The red yeast rice, *L. casei* and placebo used in this study were manufactured according to good manufacturing practices (certified pharmaceutical companies). The indications of red yeast rice are hypercholesterolemia and hypertriglyceridemia; each capsule contained monacolin K (lovastatin) 5.7 mg, GABA 6.8 mg, citrinin non-detected (<1.0 μg/mL). Each capsule of the investigational *L. casei* contained at least 1×10^8 colony-forming units. The placebo used in the control group was starch. The treatment lasted 8 weeks and the extended follow-up period lasted 4 weeks. Subjects were asked to return to the clinic for follow-up at week 0, 4, 8, and 12, where both routine physical examinations (blood pressure, height, weight) and assessments of kidney and liver functions (creatinine, ALT), LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), TG, and glucose were performed. At the same time, side effects, adverse events (AEs), and serious adverse events (SAEs) were also assessed.

Primary and Secondary Endpoints

The primary endpoint was the mean percent change of LDL-C from baseline to week 8. The secondary endpoints were the mean percent changes from baseline in TC, TG and safety issues. Blood samples for measurement of lipids (LDL-C, HDL-C, TC, TG) were collected at weeks 0, 4, 8, and 12 and sent to a central laboratory for analysis. Serum levels of TC, TG, HDL-C and LDL-C were determined by enzymatic methods using commercial kits (OLYMPUS AU2700 analyzer, Japan).

Statistical Analysis

The study analysis was done by per-protocol analysis. This method was preferred to prevent overestimated efficacy and to reduce non-compliance bias.

Baseline characteristics of the two groups (red yeast rice + *Lactobacillus* versus red yeast rice + placebo) were presented by mean and standard deviation (SD) for continuous variables, and frequency for categorical variables. In addition, the endpoints including weight, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C, HDL-C, TC, TG, ALT, creatinine, and glucose were presented by differences from the different visits after treatment compared to baseline (week 4–week 0; week 8–week 0; week 12–week 0).

All data were analyzed with SAS 9.2 (SAS Institute, Cary, NC, USA) and statistical tests were two-sided. Comparisons were made using student's *t*-test for continuous variables and the χ^2 test for discrete variables between the two groups. Paired *t*-test was used to compare differences between weeks 4, 8 and 12 and baseline in both groups. A repeated measures analysis of variance was conducted to compare the time trend curves for each variable. $P<0.05$ was considered to be statistically significant.

RESULTS

Flow Chart

Figure 1 shows the subject enrollment flow chart. During the study, 60 subjects were screened, and 60 subjects were enrolled into the study and randomly assigned to either the treatment group (30 cases) or the placebo group (30 cases). After 12 weeks, 27 subjects in the treatment group and 28 in the placebo group had completed the study. Three subjects in the treatment group withdrew from the study (2 had AEs with gastrointestinal-upset and 1 withdrew their consent),

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and 2 subjects in the placebo group withdrew from the study due to withdrawal of consent (1 subject), and failure of follow-up (1 subject). Given that the missing values were filled in by means of the last observation carried forward (LOCF) method, the actual analysis population in this study consisted of 55 subjects.

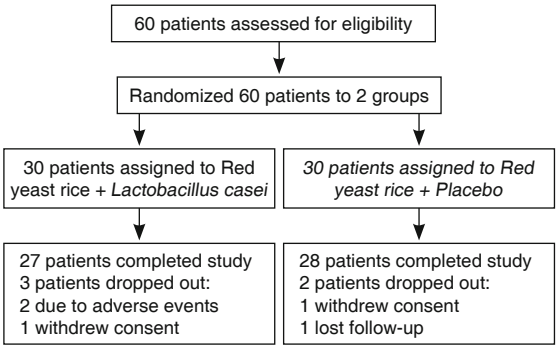

Figure 1. Enrollment Flow Chart of Subjects with Hypelipidemia

Patients Baseline Demographic Characteristics and Laboratory Tests

Table 1 shows the demographic characteristics, physical measurements, and biochemistry data of all subjects at week 0. The baseline demographics characteristics between the groups were not statistically significant (P>0.05).

Table 1. Baseline Demographics Characteristics ($\bar{x} \pm s$)

Items	Red yeast rice + *Lactobacillus casei* (30 cases)	Red yeast rice + Placebo (30 cases)	*P* value
Age (Year)	49.13 ± 9.83	46.03 ± 12.51	0.290
Male [Case (%)]	23 (76.7)	20 (66.7)	0.568
Weight (kg)	75.07 ± 10.75	74.36 ± 15.54	0.840
Height (cm)	164.50 ± 7.15	164.30 ± 9.57	0.956
BMI (kg/m^2)	27.75 ± 3.56	27.38 ± 4.22	0.720
SBP (mm Hg)	141.50 ± 24.52	134.20 ± 18.61	0.207
DBP (mm Hg)	85.00 ± 15.48	79.31 ± 12.53	0.127
LDL-C (mg/dL)	150.10 ± 31.16	146.80 ± 29.35	0.680
HDL-C (mg/dL)	42.70 ± 7.55	43.31 ± 10.66	0.800
TC (mg/dL)	241.70 ± 36.93	231.10 ± 28.91	0.229
TG (mg/dL)	199.30 ± 66.87	221.10 ± 83.35	0.316
ALT (IU/L)	39.87 ± 28.14	38.97 ± 29.50	0.905
Creatinine (mg/dL)	1.09 ± 0.28	1.01 ± 0.20	0.217
Glucose (mg/dL)	104.70 ± 11.95	103.40 ± 13.90	0.704

Comparison of LDL-C, TG and HDL-C Levels between Groups

Figures 2 and 3 compare the differences between the two groups before enrollment in the study (at week 0) and at weeks 4, 8 and 12 after enrollment, and show the average differences with the values at week 4, 8, and 12 minus those at week 0. A positive result indicates that the value has increased since week 0 and a negative result indicates that it has decreased since week 0.

The results showed that red yeast rice significantly decreased LDL-C at week 4 and 8, while the addition of

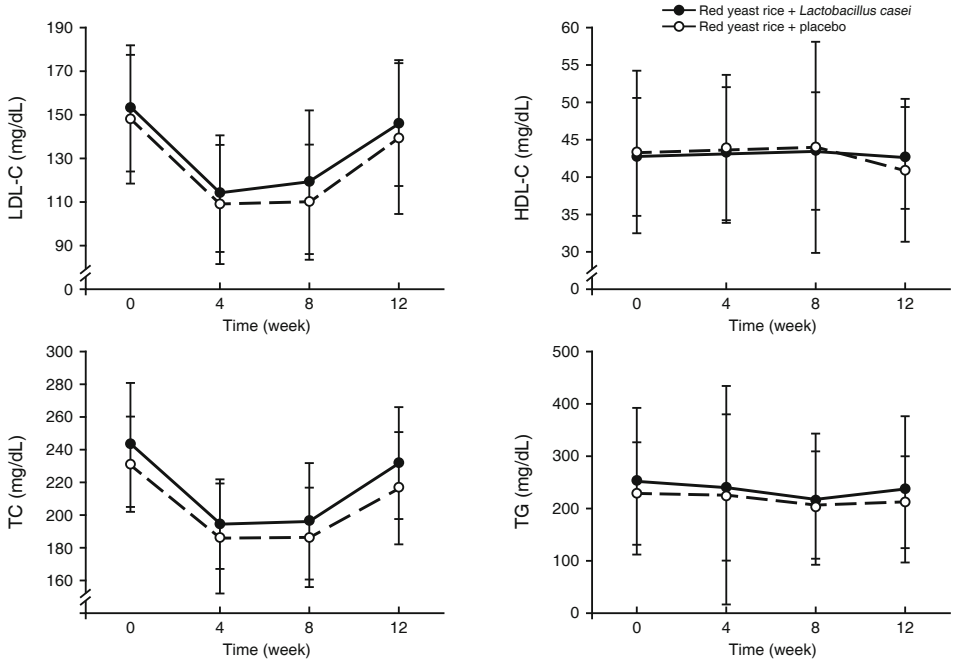

Figure 2. Results of Primary and Secondary Endpoints at Baseline, Week 4, 8 and 12

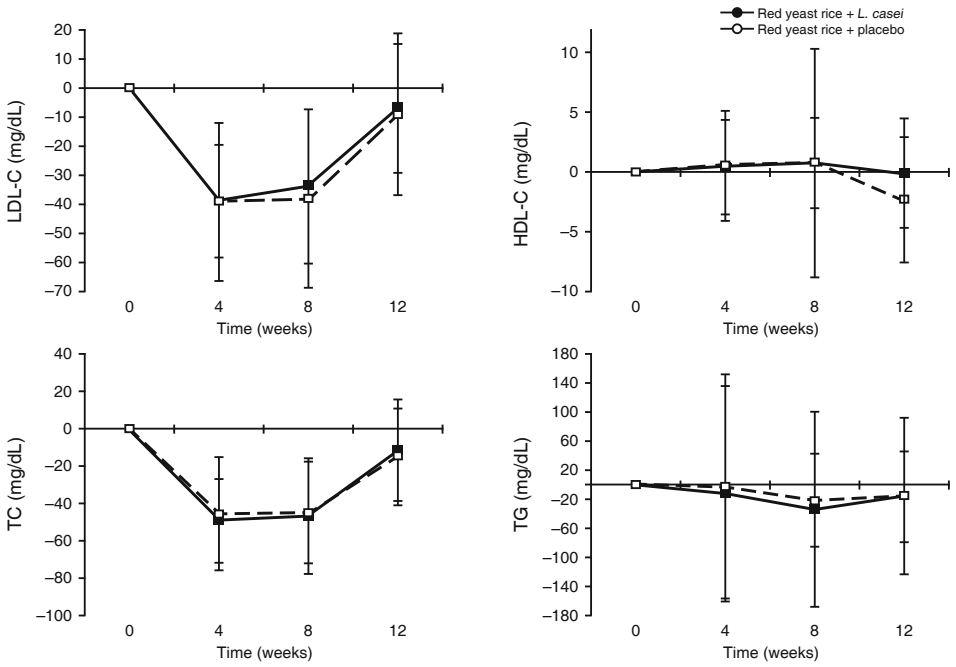

Figure 3. Difference of Primary and Secondary Endpoints between Baseline and Week 4, 8 and 12

Lactobacillus casei in the combination therapy did not have an additional effect. The difference between the in decreasing LDL-C was not significant. The change of TC in red yeast rice + *Lactobacillus casei* group was similar to LDL-C. Although we found that red yeast rice could decrease TG, and that the addition of *L. casei* led to a trend in the decrease of TG, the standard variation was so large that we found the difference between the two groups was not significant for the decrease of TG. It was found that red yeast rice can not increase HDL-C, even in combination with *Lactobacillus casei*.

Comparison of Blood Pressure between Groups

The change of SBP in the red yeast rice + *Lactobacillus casei* group was –1.96 ± 17.68, –5.70 ± 19.51, and –5.04 ± 15.82 mm Hg at week 4, 8 and 12, respectively. The change of SBP in the red yeast rice + placebo group was 1.86 ± 22.39, –0.68 ± 18.32, and –1.79 ± 14.17 mm Hg at week 4, 8 and 12, respectively. Whereas we found that red yeast rice cannot decrease SBP and SDP, adding *Lactobacillus casei* revealed a significant difference between the two groups (P<0.05) at week 12, which dropped by 2.67 mmHg in the red yeast rice + *L. casei* group and increased by 4.43 mmHg in the red yeast rice + *Lactobacillus casei* group.

Safety

The change of ALT and renal creatinine levels in the two groups was not significant. It was found that the liver function and renal function were not influenced by red yeast rice.

Table 2 listing the incidence of adverse events, shows that there were no statistically significant differences between treatment with red yeast rice +

Table 2. AEs by Individual and Event (Cases)

Adverse event	Red yeast rice + *L. casei* (27 cases)	Red yeast rice + Placebo (28 cases)	*P* value
Upper respiratory tract intection	1	1	1.000
Headache	0	1	1.000
Leg edema	1	1	1.000
Flank soreness	0	1	1.000
Fever	0	2	0.492
Left breast throbbing pain	0	1	1.000
GI-upset	2	3	1.000
Chest tightness	0	1	1.000
Insomnia	0	1	1.000
Palpitations	0	1	1.000
Soreness	0	1	1.000
Organic mental disorder	0	1	1.000
Pneumonia	0	1	1.000
Abdominal distention	1	0	1.000
Dyspepsia	1	0	1.000
Oral ulcer	1	0	1.000

Lactobacillus casei and with red yeast rice + placebo.

DISCUSSION

In this study, we observed that red yeast rice significantly decreases LDL-C and TC, while adding on *Lactobacillus casei* in the combination therapy did not have any additional effect. The efficacy was in fact similar to that found in the previous studie.[20] However, it had little effect on TG and HDL-C. One reason for not achieving this effect may be that we did not add prebiotics to probiotics to achieve a better cholesterol-lowering/removing effect. Another reason may be due to insufficient dosage or destruction of *L. casei* by gastric acid and bile salts.

Response surface methodology (RSM) has demonstrated that *L. casei* ASCC 292 reduced the highest amounts of cholesterol *in vitro* in the presence of fructo-oligosaccharides (FOS) and maltodextrin.[21] The greatest reduction of cholesterol was observed with the combination of 1.71% (w/v) *L. casei* ASCC 292, 4.95% (w/v) FOS and 6.64% (w/v) maltodextrin. This optimized formulation was further explored in rats[22] fed with the synbiotic product (*L. casei* at 109 CFU/g), which showed significantly lower (P<0.05) TC and TG (16.7% and 27.1% lower, respectively) compared to those of the control. These findings illustrated the different stimulative effects of different prebiotics on probiotics, leading to different hypocholesterolemic outcomes. Adding prebiotics (e.g., FOS or maltodextrin) to *L. casei* may help achieve a better synergistic cholesterol-lowering effect. From the above information, we can speculate that the reason why there was no additive effect may be that we did not add prebiotics to our formulations to exhibit a better hypocholesterolemic effect.

L. casei N19 and E5 and *L. acidophilus* L1 and ATCC 43121 were compared for their ability to deconjugate bile salts and remove cholesterol from MRS broth during growth at pH 6.0 and during growth without pH control. Samples grown without pH control dropped to pH 4.2 to 4.5 during the 20 h incubation, depending on the culture. The amount of cholesterol removed from the broth was similar for both strains of *L. acidophilus* grown with and without pH control. However, the strains of *L. casei* differed significantly in the amount of cholesterol removed during growth with or without pH control. Both cultures of *L. casei* that were grown at pH 6.0 removed very little cholesterol from the broth, but cells grown without pH control removed up to 60 mg/mL of cholesterol. All cultures of both species deconjugated 60%–90% of the bile salts. *L. casei* most likely removes cholesterol from broth by means of the destabilization of cholesterol micelles and the coprecipitation of the cholesterol with the deconjugated bile salts at a pH less than 6.0.[16] To prevent destruction by gastric acid and intestinal bile salts, some probiotic preparations may be enteric coated or microencapsulated. For colonization to occur, probiotics must contain living, viable organisms and must be ingested on a regular basis in order to maintain effective concentrations.[23] Alternating *L. casei* formulations to avoid the destruction by gastric acid and bile salts may exhibit a better hypocholesterolemic effect, but this needs further study to verify.

Studies examining the efficacy of probiotics in reducing cholesterol often do not sufficiently address the mechanisms by which probiotics modulate hypocholesterolemic effects, as well as the optimum dose, frequency, and duration of treatment for different probiotic strains. Thus, more studies are required, not only to determine the effective dosage of synbiotic that will exhibit hypocholesterolemic effects, but also to evaluate the effects of symbiosis between probiotics and prebiotics on cholesterol-lowering/removing properties. The prescribed dosage should also be justified by well-designed *in vivo* studies specifically investigating cholesterol profiles.[24]

In our study, each capsule contains 6.8 mg GABA, a secondary metabolite produced from red yeast rice that can lower blood pressure. As both the treatment group and the placebo group contained red yeast rice, the antihypertensive activity may have been associated with *L. casei*. Antihypertensive compounds have been purified from an extract of autologous *L. casei* cell lysat, with the most effective compounds being polysaccharide-glycopeptide complexes, found in the cell wall.[25] In a placebo-controlled trial with 28 human hypertensive subjects, powdered cell extract were administered orally and effects on SBP, SDP and heart rate were recorded. Small, but significant decreases in all three were noted.[26] It was found in this study that SBP and SDP pressures of subjects in the treatment group decreased at weeks 4 and 8; furthermore, the difference between the treatment group and the placebo group at week 12 in terms of

subjects' average diastolic pressure was statistically significant (P<0.05). For the antihypertensive activity of *L. casei*, additional studies need to corroborate this effect.

Statins are generally well tolerated, although some patients experience adverse effects, such as elevated hepatic enzyme levels, gastrointestinal symptoms, and statin-associated myalgias (SAMs), which include muscle pain and weakness. Myositis [elevated creatinine phosphokinase (CPK) level] and rhabdomyolysis are more serious but rare complications of the therapy.[27] As red yeast rice acts like statin drugs, there may be concerns that it might lead to myopathy;[28] however, no indication of a risk of myopathy associated with red yeast rice was observed in this study. Furthermore, red yeast rice demonstrated LDL-C-lowering and TC-lowering effects, which make it an alternative therapeutic option to be used in place of blood lipid-lowering statin drugs.[29]

During the past 10 years, some researchers have discovered and demonstrated that some strains of Monascus can produce citrinin, a nephrotoxin that was previously found mainly in the Aspergillus and the Penicillium genera,[30] in which might contaminate red fermented rice (RFR).[31] Citrinin has often been found in solid and submerged cultured products of Monascus, and detected at levels from 0.2 to 122 mg/kg.[32] This triggered a controversy about the safety of RFR. Although recent research has confirmed that RFR poses no threat to health at all, researchers generally consider that some action should be taken to control the citrinin concentration in RFR. In Japan, the maximum allowed level of citrinin in RFR is 200 ng/g. In China and the European Economic Community, a similar authorized citrinin level in RFR is still under debate.[33] Therefore, to avoid citrinin contamination of RFR, or to keep the citrinin concentration low, screening some strains of Monascus that have non-producing/low-producing citrinin is very important. In our study, the amount of citrinin could not be detected, and the liver function (ALT) and the renal function (creatinine) were not influenced by red yeast rice.

In conclusion, the combination of red yeast rice and *L. casei* did not have an additional effect on lipid profiles comparing to their individual effects.

Conflicts of Interest

All authors have declared no conflicts of interest.

Author Contributions

Lee CY contributes to the conception or design of the work, Min-Chien Yu MC and Wei JCC contributes to data collection, Lee MY, Lin CC and Perng WT contributions to data analysis and interpretation, Shih HC contributions to critical revision of this article, Lee YC, Lai YY, Chang L and Kuan YH contributes to draft the article.

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