

## CLINICAL STUDY

## Efficacy and safety of *Monascus purpureus* Went rice in subjects with hyperlipidemia

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### Abstract

**Objective:** The purpose of this study was to assess the lipid-lowering effect of *Monascus purpureus* Went rice on serum lipids in patients with hyperlipidemia, and to assess its safety by reporting adverse events and clinical laboratory measurements.

**Design and methods:** This was a randomized, double-blind, placebo-controlled study. In all, 79 patients (aged 23–65 years) with a mean baseline low-density lipoprotein cholesterol (LDL-C) level of 5.28 mmol/l (203.9 mg/dl) received a twice daily dose of placebo or *Monascus purpureus* Went rice (600 mg) for 8 weeks.

**Results:** At week 8, *Monascus purpureus* Went rice therapy reduced LDL-C by 27.7%, total cholesterol by 21.5%, triglycerides by 15.8% and apolipoprotein B by 26.0%. High-density lipoprotein cholesterol and apolipoprotein A-I levels were increased by 0.9 and 3.4% respectively (not significant). No patient in the *Monascus purpureus* Went rice treatment group had an alanine aminotransferase (ALT), aspartate aminotransferase (AST) or creatine phosphokinase (CPK) measurement that was  $\geq 3$  times the upper limit of normal at week 4 and week 8.

**Conclusion:** *Monascus purpureus* Went rice significantly reduced LDL-C, total cholesterol, triglycerides and apolipoprotein B levels, and was well tolerated in patients with hyperlipidemia. However, this study only provides data from an 8-week trial and long-term safety and efficacy data are needed.

European Journal of Endocrinology 153 679–686

### Introduction

*Monascus purpureus* rice (紅麴 in Chinese), popularly called red yeast rice, is described as the fermented product of rice on which red yeast (*Monascus purpureus*) has been grown. This product has been used for centuries in China to make rice wine and to flavor foods. Traditional red yeast rice continues to be a dietary staple in many Asian countries, including China and Japan, with consumption ranging from 14 to 55 g/person per day (1). Recent studies have shown that *Monascus purpureus* rice contained 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), large quantities of unsaturated fatty acids ( $> 125$  mg/g *Monascus purpureus* rice preparation), beta-sitosterol, campesterol and stigmasterol (2–4). These components are effective in reducing serum lipid (5). The lipid-lowering effects of *Monascus purpureus* rice have been shown in several animal models of hyperlipidemia to inhibit and prevent increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides (6). In this study, the efficacy and safety of *Monascus purpureus* Went rice were evaluated by measuring percentage changes of lipid profiles, observing any adverse effects and

completing laboratory tests at regular intervals in subjects with hyperlipidemia.

### Subjects and methods

#### Participants

The study's clinical phase began in December 2001 and was completed in January 2003. Subjects with hyperlipidemia in this study were recruited from the outpatient clinic at the China Medical University Hospital, Taichung, Taiwan or by advertising. Study participants were men and women aged 18–65 years with a body mass index of  $< 30$  kg/m<sup>2</sup>. Participants had to have a total cholesterol level  $\geq 6.22$  mmol/l (240 mg/dl), an LDL-C level  $\geq 4.14$  mmol/l (160 mg/dl) and a triglycerides level  $\leq 4.52$  mmol/l (400 mg/dL) at two qualifying visits 4 weeks apart. Women who were pregnant or breastfeeding were excluded from the study, as were patients who met any of the following conditions: hypothyroidism, nephrotic syndrome or renal dysfunction (serum creatinine  $> 132.6$   $\mu$ mol/l (1.5 mg/dl)); diabetes mellitus; chronic gout; active liver disease or hepatic dysfunction (aspartate aminotransferase

(AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal (ULN)); creatine phosphokinase (CPK) > 3 times the ULN; uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg); cerebrovascular disease, cardiovascular surgery, myocardial infarction, coronary angioplasty, coronary artery bypass graft, severe or unstable angina, or major operations within 6 months prior to the study period; current or recent history of alcohol abuse; significant abnormalities that the investigator believed could compromise the patient's safety in participating in the study; participation in another clinical trial within the 30-day period before consideration for entry into this study; known hypersensitivity to lipid-modifying agents; and use of any drugs known to affect lipid levels, immunosuppressive agents, drugs associated with rhabdomyolysis in combination with statins (e.g. cyclosporine and erythromycin), or mibefradil dihydrochloride. Patients taking a lipid-lowering drug could be considered for screening after a 4-week washout period, with the exception of probucol – which had to have been discontinued for at least 6 months. The study complied with the Declaration of Helsinki. The institutional ethics review boards approved the protocol, and all participants gave their informed consent.

### Randomization and sample size determination

A permuted-block randomization was employed to generate the random assignment of subjects by order of entry into two different treatment groups. Each group of subjects received either *Monascus purpureus* Went rice or placebo. In this study, a sample size of 79 patients was used for characterizing and comparing

the efficacy as well as the safety of *Monascus purpureus* Went rice and placebo.

The sample size for this study was based on the primary efficacy outcome, the change from baseline to 8 weeks in mean LDL-C was compared between the two groups. The standard deviation (s.d.) of the mean LDL-C level was 1 mmol/l (the s.d. of the mean for the treatment group and that of the placebo group were similar). We set the two-sided alpha (type I error) at 0.05 and the beta (type II error) at 0.10 (power of 90%). According to these assumptions, a sample size of approximately 17 subjects in each group was needed to detect a difference of 1 mmol/l in mean LDL-C.

### Protocol

After a minimum of 4 weeks on an American Heart Association Step I diet, 79 patients were instructed to continue the diet and were randomly assigned to 8 weeks of treatment with rice powder placebo or *Monascus purpureus* Went rice (Fig. 1). All patients received dietary instruction from a registered dietitian at every research visit and were contacted by telephone every week during the study. The study was double-blind. We reviewed participants every 4 weeks and blood samples were obtained after 12-h overnight fasts. The laboratory staff responsible for analyses were blinded to treatment and received samples labeled with name codes and dates. The study protocol was approved by the Institutional Review Board of China Medical University Hospital and by the Department of Health, Taiwan.

### *Monascus purpureus* Went rice therapy

For the treatment group, *Monascus purpureus* Went rice was pulverized and 600 mg of this milled preparation

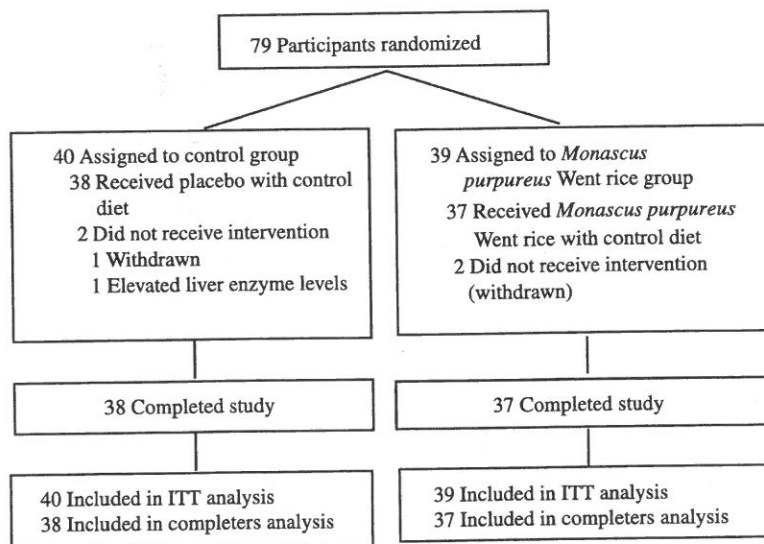


Figure 1 Flow of patients through the trial.

**Table 1** Composition of *Monascus purpureus* Went rice.

	Concentration
Protein	17.00%
Starch	68.00%
Fat	4.00%
Of which:	
Linoleic acid	48.13%
Oleic acid	28.78%
Palmitic acid	18.61%
Stearic acid	4.49%
← Ergosterol	0.30%
Fiber	2.00%
Water	< 5.00%
HMG-CoA reductase inhibitors (statins)	1.16%
Lovastatin	0.95%
Other statins	0.21%
r-Aminobutyric acid (GABA)	2.55%
Alkaloids	
Water-soluble	0.30%
Lipid-soluble	0.05%
Glycosides	0.06%
Flavonoids	0.05%
Natural pigments	0.01%
Ethanol extracts	≥ 12.00%
Water extracts	≥ 10.00%
Citrinin	< 1.5 p.p.m. <sup>a</sup>
Pb	< 20.0 p.p.m.
Cd	< 0.6 p.p.m.
Hg	< 0.5 p.p.m.
As	< 5.0 p.p.m.
Cu	< 70.0 p.p.m.

Data are based on unpublished analyses on file with Y & B Pharmaceuticals Co., Ltd, Taipei, Taiwan. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A. Percentage concentrations are percentage by weight.

<sup>a</sup> Mostly not detectable by HPLC.

encapsulated in each capsule under Good Manufacturing Practices conditions (Y & B Pharmaceuticals Co., Ltd, Taipei, Taiwan). The composition of *Monascus purpureus* Went rice is shown in Table 1. The placebo was made of grounded rice with food color mimicking the color and appearance of the active drug. Both *Monascus purpureus* Went rice and placebo capsules were dispensed by the hospital pharmacy in identical containers marked with the participant's name codes. Participants were asked to take one capsule (600 mg *Monascus purpureus* Went rice or placebo) twice daily, 30 min after breakfast and dinner, for the 56 days of the study, and to return the containers for capsule counts on each clinic visit.

## Analyses

All samples from a given individual were labeled by code. Total cholesterol and triglycerides were determined by the enzymatic method using commercial kits (Beckman & Coulter, Fullerton, CA, USA). High-density lipoprotein cholesterol (HDL-C) and LDL-C were measured by the direct method (7) using commercial kits (Beckman & Coulter, LX 20 Pro, Japan). All the

analyses were performed by Beckman & Coulter, Tokyo autoanalyzer. The intra-assay coefficients of variation (CV%) were 3.1, 2.3, 3.5 and 3.6% for LDL-C, total cholesterol, triglycerides and HDL-C respectively. Serum apolipoprotein A-I and apolipoprotein B were measured by nephelometry (8) (intra-assay coefficient of variation, 2.2 and 1.9 respectively).

## Evaluation of efficacy

The primary analysis of efficacy endpoints was based on the intent-to-treat population and completing participants. Baseline was defined as the measurements taken at randomization. The primary measure of efficacy was the percentage change in LDL-C level from baseline to week 8. Secondary measures of efficacy were percentage changes (from baseline to week 8) in total cholesterol, HDL-C, triglycerides, apolipoprotein A-I and apolipoprotein B.

## Safety analyses

Safety was evaluated in all randomized patients who had taken at least one dose of study medication and provided any follow-up information. All adverse effects that occurred during the clinical trial were recorded. Their relation to the study drug (definitely, probably, possibly, unlikely, definitely not) and their intensity (mild, moderate, severe) were assessed by the investigator. Because statins are present in *Monascus purpureus* Went rice, ALT, AST and CPK were measured. In addition, physical examinations and clinical laboratory determinations were performed at screening, randomization, week 4 and study termination.

## Statistical methods

Descriptive statistics such as a number of observations, means, standard deviations and percentages were used to summarize the baseline variables. All available tests were two sided and were evaluated at the 0.05 level of significance. For subjects' demographic information, the comparability between two groups was examined using an unpaired *t*-test for continuous variables, and Fisher's exact test and Mantel-Haenszel test for categorical variables. Blood lipids, safety parameters, vital signs and laboratory examinations were analyzed based on change from baseline; they were analyzed by unpaired *t*-test for between-group variation, and by paired *t*-test for within-group variation. Fisher's exact test was used to compare the number of subjects with adverse effects between groups.

## Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Table 2** Patient characteristics at baseline by treatment group.

	Placebo (n = 40)	<i>Monascus purpureus</i> Went rice (n = 39)	P value
Age (years)	46.5±9.5	46.3±10.1	0.922 <sup>a</sup>
Sex, male	22 (55%)	23 (59%)	0.821 <sup>b</sup>
BMI (kg/m <sup>2</sup> )	23.4±2.7	24.3±3.3	0.161 <sup>a</sup>
Smoking history			0.681 <sup>c</sup>
Never smoked	34 (85%)	32 (82%)	
Current smoker	4 (10%)	6 (15%)	
Alcohol history			0.193 <sup>c</sup>
Never	33 (83%)	36 (92%)	
Abusive	0 (0%)	0 (0%)	

Data are means±s.d. or number with percentage in brackets. BMI, body mass index.

<sup>a</sup> Unpaired *t* test.

<sup>b</sup> Fisher's exact test.

<sup>c</sup> Mantel-Haenszel test.

## Results

### Patient characteristics at baseline

The characteristics of subjects who entered the study are summarized in Table 2. The demographics and baseline characteristics of subjects in the two groups were similar. The percentage of males and females was about equal in both groups. The age of subjects in both groups was about 46 years with a range of 23–65 years. Over 80% of subjects in both groups had never smoked. A high percentage of subjects in both groups had never had alcohol. Both groups had comparable body mass indices (BMI).

At baseline, there were no significant differences between groups for the efficacy parameters (LDL-C, total cholesterol, HDL-C, triglycerides, apolipoprotein A-I and apolipoprotein B). All these data affirmed that the distribution of subjects between the two groups was well balanced (Table 3).

### Exposure

Of the 79 patients randomized to treatment, 39 received *Monascus purpureus* Went rice and 40 placebo. Four participants who were randomized did not start the study (*Monascus purpureus* Went rice, 2 patients (5.1%); placebo, 2 patients (5.0%)). Compliance with study therapy (defined as ≥80% of pills taken) was 81.6% for placebo and 89.2% for *Monascus purpureus* Went rice.

### Lipid and lipoprotein response

Efficacy evaluation was carried out on completing participants, in which 75 subjects were included. LDL-C levels, the primary efficacy endpoint, were comparable between the two groups at baseline (Table 3). The *Monascus purpureus* Went rice reduced LDL-C levels

by 27.7% but placebo caused only a 1.5% decrease at week 8. At baseline, the two groups showed comparable total cholesterol, triglycerides and apolipoprotein B levels ( $P > 0.05$ ). The 8-week treatment with *Monascus purpureus* Went rice significantly reduced total cholesterol levels by 21.5%, triglycerides by 15.8% and apolipoprotein B by 26%. Worthy of special mention is that *Monascus purpureus* Went rice resulted in reductions in LDL-C level by 30.6%, total cholesterol level by 23.7%, triglycerides level by 13.4% and apolipoprotein B level by 28.9% that were observed as early as 4 weeks after its administration (Table 3). In contrast, the placebo treatment resulted in almost no reduction of total cholesterol (−0.4%) and triglycerides (+1%) at week 4 and week 8. A 3.9% reduction of apolipoprotein B levels was observed after the placebo treatment at week 8. The capacity of *Monascus purpureus* Went rice to change HDL-C and apolipoprotein A-I levels was limited. The difference in the percentage change of HDL-C and apolipoprotein A-I was comparable between the two groups ( $P > 0.05$ ).

### Safety analyses

A safety evaluation was performed based on the 'safety population', which included a total of 75 subjects ( $n = 37$  in the *Monascus purpureus* Went rice group and  $n = 38$  in the placebo group) who were randomized and had taken at least one dose of the study medication, with follow-up information after randomization. We recorded any complaints mentioned, however trivial. Therefore, up to 65% of the total safety population ( $n = 49$ ) reported one or more adverse events and 8% of the total safety population ( $n = 6$ ) had one or more drug-related adverse events. Nevertheless, the incidence of 'one or more adverse events', 'drug-related adverse events' and 'serious adverse events' between the two groups were comparable ( $P > 0.05$ ) (Table 4). *Monascus purpureus* Went rice treatment produced a slight increase in ALT (2.3 U/l) and AST (0.8 U/l), but no patient had an ALT or AST measurement ≥3 times the ULN at week 4. At week 8, *Monascus purpureus* Went rice had the same safety profile. Baseline serum CPK was similar in both groups and was not significantly different after 8 weeks of the treatment. In the *Monascus purpureus* Went rice group, mean serum CPK at baseline was 116.4 U/l (s.d. = 66.0) and mean serum CPK at week 8 was 129.6 U/l (s.d. = 42.3). In addition, there was no patient with myopathy (defined as a CPK level ≥10 times the ULN with muscle symptoms) or CPK values ≥3 times the ULN at weeks 4 and 8. In particular, no cases of rhabdomyolysis or anaphylaxis were observed. In addition, *Monascus purpureus* Went rice did not alter other safety parameters including vital signs, results of physical examination, hematology, serum chemistry, urine analysis and electrocardiogram.



**Table 3** Change from baseline in serum lipid variables, by week and treatment group (completer population).

Lipid parameter	Week	Placebo (n = 38)		<i>Monascus purpureus</i> Went rice (n = 37)	
		Level	Percentage change	Level	Percentage change
LDL-C (mmol/l) <sup>a</sup>	0	5.34±1.15		5.20±0.86	
	4	5.27±1.14	-0.5±14.1	3.61±0.83*,‡	-30.6±10.1‡
	8	5.19±1.01	-1.5±16.0	3.76±0.85*,‡	-27.7±12.2‡
TC mmol/l <sup>a</sup>	0	7.41±1.12		7.27±0.83	
	4	7.34±1.15	-0.5±10.9	5.54±0.76*,‡	-23.7±7.2‡
	8	7.37±1.19	-0.4±9.5	5.68±0.79*,‡	-21.5±9.4‡
HDL-C mmol/l <sup>a</sup>	0	1.32±0.28		1.31±0.39	
	4	1.32±0.30	0.5±11.5	1.30±0.35	0.4±8.8
	8	1.33±0.31	1.0±10.2	1.30±0.32	0.9±10.6
TG mmol/l <sup>b</sup>	0	1.38±0.66		1.46±0.72	
	4	1.38±0.71	5.3±32.3	1.26±0.82†§	-13.4±33.5§
	8	1.31±0.63	1.0±34.4	1.22±0.72†§	-15.8±25.1§
Apo A-I (g/l) <sup>c</sup>	0	1.34±0.25		1.34±0.22	
	4	1.32±0.23	0.0±16.3	1.34±0.21	1.0±12.2
	8	1.35±0.20	2.3±12.8	1.37±0.21	3.4±14.0
Apo B (g/l) <sup>c</sup>	0	1.57±0.30		1.54±0.27	
	4	1.51±0.30	-3.2±12.7	1.10±0.25*,‡	-28.9±8.9‡
	8	1.50±0.33	-3.9±12.2	1.14±0.27*,‡	-26.0±14.3‡

Data are means±s.d. TC, total cholesterol; TG, triglycerides; Apo A-I, apolipoprotein A-I; Apo B, apolipoprotein B.

<sup>a</sup>To convert total cholesterol, HDL-C and LDL-C to mg/dL, divide values by 0.0259.

<sup>b</sup>To convert triglycerides to mg/dL, divide values by 0.0113.

<sup>c</sup>To convert Apo A-I and Apo B to mg/dL, divide values by 0.01.

\*Significantly different from baseline,  $P < 0.001$ .

†Significantly different from baseline,  $P < 0.05$ .

‡Significantly different from control group at the same week,  $P < 0.001$ .

§Significantly different from control group at the same week,  $P < 0.05$ .

**Table 4** Number and percentage of patients with adverse events (AEs).

	<i>Monascus purpureus</i> Went rice		P value
	Placebo (n = 38)	Went rice (n = 37)	
All AEs	28 (74%)	21 (57%)	0.168
Drug-related AEs	3 (8%)	3 (8%)	1.000
Serious AEs	0 (0%)	1 (3%) <sup>a</sup>	0.494
Serious drug-related AEs	0	0	
ALT or AST ≥3 times ULN	0	0	
CPK ≥3 times ULN	0	0	
CPK ≥10 times ULN with muscle symptoms	0	0	

<sup>a</sup>Breast cancer: unrelated to the study drug.

During the trial, one serious adverse event (breast carcinoma) occurred in the *Monascus purpureus* Went rice-treated group. The 63-year-old female was diagnosed with breast cancer after a 4-week administration of *Monascus purpureus* Went rice. However, the incident was not related to *Monascus purpureus* Went rice.

### Intention-to-treat analysis

This study was also analyzed on the basis of intention to treat, including the four individuals with baseline values who dropped out or were withdrawn. The differences in blood lipid levels were significantly different

between the treatment groups, as was observed when these participants were not included in the analysis (Table 5). Furthermore, the mean reduction in LDL-C level across treatments was still significant at 26.3% (13.4%) ( $P < 0.001$ ) for the *Monascus purpureus* Went rice-treated group when it was assumed that the four additional participants showed no change in response to the treatment.

### Discussion

Coronary artery disease (CAD) is a leading cause of death in the developed world today. It is well established that increased total cholesterol, LDL-C and triglycerides concentrations, as well as decreased HDL-C concentrations, are strong independent predictors of CAD (9). The statins have repeatedly been shown to reduce mean serum LDL-C concentrations by 28–35% in long-term trials (10–12), with corresponding reductions in cardiovascular death of 23–32% in both primary and secondary prevention trials (11, 12). A previous study showed that red yeast rice resulted in significant reductions in LDL-C (1.00 mmol/l), total cholesterol (1.09 mmol/l) and triglycerides (0.17 mmol/l) levels (2). In this study, *Monascus purpureus* Went rice resulted in significant reductions in LDL-C (1.59 mmol/l (30.6%)), total cholesterol (1.73 mmol/l (23.7%)) and triglycerides (0.21 mmol/l (13.4%)) levels from baseline to week 4. These reductions were maintained at 8 weeks.

**Table 5** Change from baseline in serum lipid variables, by week and treatment group (intent-to-treat population).

Lipid parameter	Week	Placebo (n = 40)		<i>Monascus purpureus</i> Went rice (n = 39)	
		Level	Percentage change	Level	Percentage change
LDL-C (mmol/l) <sup>a</sup>	0	5.35±1.12		5.20±0.84	
	4	5.01±1.61	-0.5±13.7	3.43±1.14*,‡	-29.1±12.0‡
	8	5.22±0.99	-1.4±15.6	3.83±0.89*,‡	-26.3±13.4‡
TC (mmol/l) <sup>a</sup>	0	7.40±10.9		7.28±0.84	
	4	6.97±1.97	-0.5±10.7	5.26±1.44*,‡	-22.5±8.8‡
	8	7.36±1.16	-0.4±9.3	5.78±0.89*,‡	-20.4±10.3‡
HDL-C (mmol/l) <sup>a</sup>	0	1.32±0.28		1.32±0.42	
	4	1.25±0.41	0.5±11.2	1.23±0.45	0.4±8.6
	8	1.33±0.30	1.0±10.0	1.32±0.36	0.9±10.4
TG (mmol/l) <sup>b</sup>	0	1.34±0.67		1.46±0.72	
	4	1.31±0.75	5.0±31.5	1.19±0.84†,§	-12.7±32.8§
	8	1.27±0.63	0.9±33.5	1.22±0.72†,§	-15.0±24.7§
Apo A-I (g/l) <sup>c</sup>	0	1.33±0.25		1.37±0.29	
	4	1.26±0.37	0.0±15.9	1.27±0.36	1.0±11.9
	8	1.34±0.20	2.2±12.4	1.40±0.28	3.2±13.6
Apo B (g/l) <sup>c</sup>	0	1.56±0.30		1.55±0.26	
	4	1.43±0.44	-3.1±12.4	1.05±0.35*,‡	-27.4±10.8‡
	8	1.50±0.32	-3.7±11.9	1.16±0.28*,‡	-24.7±15.1‡

Data are means±s.d. Abbreviations and symbols are as in Table 3.

The results of this study again confirm that *Monascus purpureus* Went rice has positive effects on plasma lipids.

It is noteworthy that *Monascus purpureus* Went rice reduced apolipoprotein B levels by 26.0% in this study. Each of the atherogenic particles – namely, very low density lipoprotein, intermediate-density lipoprotein, LDL and lipoprotein(a) – contain one molecule of apolipoprotein B. Thus, the serum concentration of apolipoprotein B reflects the total number of these particles. A systematic review showed the apolipoprotein B concentration to be a better estimate of the risk of vascular events than the LDL-C level (13). This is supported by the fact that apolipoprotein B has been accepted as an alternative to the cholesterol indices in the new Canadian Lipid Working Group on hypercholesterolemia and other dyslipidemias (14) and in the new Canadian Diabetes Association Guidelines (15).

A specialist commented that *Monascus purpureus* Went rice contains statins and yields similar hypolipidemic effects to statins (16), therefore the other active components may only play a minor role in the action of *Monascus purpureus* Went rice. One study (17) reported mean LDL-C reductions to be 20, 26, 19 and 24% for fluvastatin (80 mg), lovastatin (80 mg), pravastatin (40 mg) and simvastatin (20 mg) respectively; mean apolipoprotein B levels were reduced by 16, 19, 16 and 20% respectively. In this study, 1200 mg of *Monascus purpureus* Went rice contains a total of 13.9 mg statins (contains 11.4 mg lovastatin) but reduced LDL-C by 27.7% and apolipoprotein B by 26.0%. Hence, we infer that the hypolipidemic effect of *Monascus purpureus* Went rice is unlikely to be due solely to statins, but rather to result from other substances in the *Monascus purpureus* Went rice. *Monascus*

*purpureus* Went rice also contains phytosterols, mainly beta-sitosterol with campesterol and stigmasterol. Plant sterols have been shown to decrease total cholesterol and LDL-C concentrations in several population groups (18–21).

In this study, all patients received dietary consultation but there was no record of diets of the participants. We compared BMI in the two treatment groups at baseline, at 4 weeks and at 8 weeks. There were no significant differences in BMI within or between study groups. Therefore, we infer that neither dietary fat intake or exercise had an impact on lipid profile in the study period.

Asymptomatic elevations of transaminases (>3 times the ULN) have been observed with all the statins, are relatively common (0.1–2.0%) and are dose related (22). It is interesting to note that no patient in the *Monascus purpureus* Went rice treatment group had an ALT or AST measurement ≥3 times the ULN at week 4 or week 8. Statin therapy is also known to cause increases in CPK activity, mostly during the initial stages of treatment and upward dose titration. Nevertheless, no trials have examined the effect of red yeast rice on CPK so far. In this study, no cases of CPK measurement ≥3 times the ULN or rhabdomyolysis were reported. Possible *Monascus purpureus* Went rice-related adverse events were one abnormal liver function test (ALT, 57 U/l; ULN 40 U/l), one CPK increase (151 U/l; ULN, 140 U/l), and one lactate dehydrogenase increase (208 U/l; ULN, 192 U/l). All these events were mild in severity and required no treatment. On the other hand, mild leukopenia (n = 1), diarrhea (n = 1) and nausea (n = 1) were found to be possibly drug-related adverse events in the placebo treated group. In general, *Monascus purpureus* Went rice was well tolerated and no

one discontinued the study due to adverse effects caused by the study drug. Extensive animal studies of red yeast rice extracts have been conducted. In an acute toxicity study in mice, there were no toxic effects noted when a single dose of the extract was administered at 533 times the typical human dose (23).

More recently, citrinin has also been isolated from *Monascus ruber* and *Monascus purpureus*, industrial species used to produce red pigments (24). Citrinin acts as a nephrotoxin in all animal species tested, but its acute toxicity varies in different species (25). The 50% lethal dose for ducks is 57 mg/kg; for chickens it is 95 mg/kg; and for rabbits it is 134 mg/kg (26). In addition, wheat, oats, rye, corn, barley and rice have all been reported to contain citrinin (27). Although citrinin is regularly associated with human foods, its significance for human health is unknown. In the present study, citrinin was not detected in *Monascus purpureus* Went rice.

Worthy of mention is the fact that *Monascus purpureus* Went is a specific strain of red yeast and a different strain of *Monascus* could result in different efficacy and safety profiles. Accordingly, red yeast rice material produced in the traditional way has yielded different amounts of active compounds compared with the *Monascus purpureus* Went rice extract. In other words, the home-processed red yeast rice may not exhibit the same hypolipidemic effect as the *Monascus purpureus* Went rice extract (16).

In summary, the significant effect of *Monascus purpureus* Went rice in reducing LDL-C, total cholesterol, triglycerides and apolipoprotein B levels was found as early as week 4 and was consistent until week 8. Moreover, no patient in the *Monascus purpureus* Went rice treatment group had an ALT, AST or CPK measurement  $\geq 3$  times the ULN at week 4 and week 8. However, this study only provides 8 weeks of data and further studies on the long-term safety and efficacy of *Monascus purpureus* Went rice in a larger population are needed.

## Acknowledgements

Y & B Pharmaceuticals Co., Ltd, Taipei, Taiwan supplied the rice extract.

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Received 16 May 2005

Accepted 27 July 2005