

MULTI-CENTER CLINICAL TRIAL OF THE SERUM LIPID LOWERING EFFECTS OF A MONASCUS PURPUREUS (RED YEAST) RICE PREPARATION FROM TRADITIONAL CHINESE MEDICINE

JUNXIAN WANG,¹ ZONGLIANG LU,² JIAMIN CHI,³ WENHUA WANG,⁴ MEIZHE SU,¹ WENRONG KOU,¹ PULIN YU,³ LIJIANG YU,⁵ LI CHEN,⁵ JIA-SHI ZHU,⁶ AND JOSEPH CHANG⁶

1. Dongzhimen Hospital, Beijing University for Traditional Chinese Medicine, Beijing,
2. Cardiovascular Institute and Fuwai Hospital, Chinese Academy of Medical Sciences, Beijing.,
3. Beijing Hospital, Ministry of
4. Public Health of China, Beijing,
5. Clinical Pharmacology Research Center of the Ministry of Public Health at Haerbin Medical
6. WBL Peking University Biotech. Co. Ltd., Beijing, People's Republic of China,
7. Pharmanex Inc., Simi Valley, California

ABSTRACT

The ability of a natural product, *Monascus purpureus* (red yeast) rice preparation, to regulate serum lipids was assessed in multicenter, singlemasked clinical trial. A total of 446 patients with hyperlipidemia were randomly assigned to two groups: a group of 324 patients received a *M purpureus* (red yeast) rice preparation, and a positive control group of 122 patients received another Chinese herbal medicine, Jiaogulan (*Gynostemma pentaphylla*). After 8 weeks, serum total cholesterol decreased significantly by 22.7% and lowdensity lipoprotein cholesterol by 30.9% in the patients treated with a *M purpureus* rice preparation, and patients in the positive control group showed 7.0% and 8.3% reductions, respectively. *M purpureus* treatment also significantly increased high density lipoprotein (HDL) cholesterol by 19.9%, which was a significantly larger increase than the 8.4% increase observed in the positive control group. Notably, *M purpureus* rice preparation significantly lowered serum triglycerides by 34.1% after 8 weeks, which was a significantly greater decrease than the reduction of 12.8% observed in the positive control group. When the overall therapeutic effects of *M purpureus* rice were scored, with one or more lipid risk factors being reduced and HDL cholesterol being increased, according to criteria established by the Ministry of Public Health of China, 93.2% of patients in the treatment group benefited from *M purpureus*. This total efficacy rate was significantly better than the rate of 50.8% in the positive control group. Therefore, use of *M purpureus* rice preparation in conjunction with a proper diet produced a favorable lipid lowering effect in hyperlipidemic patients. The patients experienced a few mild side effects (heartburn, dizziness and flatulence) during the eight week treatment with *M purpureus* rice preparation. We concluded that this traditional Chinese rice preparation used as a dietary supplement is extremely effective and well tolerated in reducing elevated serum cholesterol and triglycerides. Key words: *Monascus purpureus* (red yeast) rice preparation, hyperlipidemia, cholesterol, triglycerides.

INTRODUCTION

Hyperlipidemia is a highly predictive risk factor for atherosclerosis, coronary artery disease, and cerebral vascular diseases.¹⁻³ Regulating hyperlipidemia has proven to be effective in lowering the morbidity and mortality associated with coronary artery disease.³⁻⁵

Among the current lipid lowering agents, hepatic hydroxy methylglutaryl coenzyme A (HMGCoA) reductase inhibitors are effective in reducing total cholesterol (TC) and low density lipoprotein (LDL) cholesterol. Nonetheless, the high cost of these drugs and their limited availability to the majority of the Chinese population, have prompted Chinese medical investigators to search for alternative agents to lower serum lipids. Because traditional Chinese medicine, through centuries of empirical use, has produced an extensive library of active herbs, it seemed reasonable to investigate whether a lipid lowering dietary supplement could be identified from this library. After an intensive investigation, *Monascus purpureus* (red yeast) rice was identified as an effective herb to lower serum cholesterol and triglycerides (TG) in animals, and its hypolipidemic effects were confirmed in pilot clinical studies 6 ~9.

The *M purpureus* preparation is derived from a strain of *M purpureus* Went yeast (Xuezhikang in Chinese) that is prepared by a traditional rice fermentation method. Red Yeast rice has been used for centuries in China to make rice wine and to flavor foods. It was reported in the ancient Chinese pharmacopoeia, *BenCaoGang Mu DanShiBuYi*, which was published during the Ming Dynasty (1368-1644),¹¹ to promote blood circulation. Recent studies showed that *M purpureus* rice contains HMGCoA reductase inhibitors that reduce the synthesis of cholesterol in the liver. This preparation also contains large quantities of unsaturated fatty acids (>125 mg/g M acids. Although the function of these unsaturated fatty acids is not known, they may help reduce serum lipids. 13 Other components include proteins, amino acids, saccharides, beta sitosterol, campesterol, stigmasterol, isoflavone and its glycosides, saponin and sapogenin, and many trace elements.¹² The lipid lowering effects of *M purpureus* rice have been shown in several animal models of hyperlipidemia to inhibit and prevent increases in TC, LDL cholesterol, and TG 6. For example, in rabbits fed a diet of 25% casein to induce endogenous hypercholesterolemia, treatment with *M purpureus* rice for 30 days at daily dosages of 0.4 and 0.8 g/kg significantly lowered serum TC concentrations and the TC/high density lipoprotein (HDL) cholesterol ratio 6. In a second rabbit model in which hyperlipidemia was induced exogenously by an atherogenic diets oral *M purpureus* rice preparation prevented increases in serum TC and TG concentrations and the TC:HDL cholesterol ratio ($P < 0.05$, compared with untreated hyperlipidemic controls). When hyperlipidemia was induced exogenously in quail by feeding them an atherogenic diet that included 1% cholesterol, 14% lard, and 6% soybean oil, *M purpureus* rice preparation administered orally significantly reduced serum TC and TG concentrations. Acute and chronic animal toxicity studies further showed that *M purpureus* rice is well tolerated, even at doses several times higher than the effective therapeutic dose (manuscript in preparation). In the present study, we demonstrated that a standardized *M purpureus* rice preparation reduced both elevated serum cholesterol levels and TG, as compared with another herb, *Jiaogulan* (*Gynostemma pentaphylla*), which is believed to be an antihyperlipidemic agent in China.”

PATIENTS AND METHODS

This randomized, singlemasked trial included a total of 502 patients with a clinical diagnosis of primary hyperlipidemia who were enrolled at four clinical sites in China. Before their blood tests, patients abstained from alcoholic beverages and meals that were high in fats for 1 day. Patients also discontinued any medication for hyperlipidemia for more than 4 weeks and received dietary advice for 2 to 4 weeks. Eligible patients were recruited if their serum TC was ≥ 230 mg/dL (5.95 mmol/L) or higher, LDL cholesterol was ≥ 130 mg/dL (3.41 mmol/L), or TG was 20 to 400 mg/dL (2.26 to 4.52 mmol/L). In addition, it was required that the levels of HDL cholesterol was < 40 mg/dL (1.04 mmol/dl for men or , or ≥ 45 mg/dL (1.16 mmol/L) for women.

Patients were excluded from the trial if they had any of the following during the last 6 months: myocardial infarction, stroke, severe trauma or major surgery, nephrotic syndrome, hypothyroidism, acute or chronic hepatobiliary disorders, diabetes mellitus, gout, allergies, or psychosis.

Patients who agreed to participate in this clinical trial were informed of the possible benefits and risks.

Based on pretreatment TC and TG values, patients were prospectively randomized by a statistician into two unequal arms using a strategy of four group randomization required by the Chinese Ministry of Public Health for clinical studies of traditional Chinese medicine. 15 Groups A, C, and D were the “treatment groups, and group B was the positive control group. The equality of the randomization distributions was verified by computer analysis.

STUDY DESIGN

Patients were treated in a single masked fashion. The treatment group was given a standardized preparation (alcoholic extraction) of *M purpureus* rice 0.6 g twice a day (1.2 g/d) for 8 weeks. Patients in the positive control group were treated with a traditional Chinese medicine with putative hypolipidemic properties, Jiaogulan, “three tablets twice a day (1.2 g/d)”.

2-4 weeks before the trial and continuing throughout the study, all patients were asked to maintain their normal lifestyles, including smoking, exercise, and dietary habits as advised by physicians. All medications were allowed during the trial except those that could affect serum lipids.

HYPOLIPIDEMIC EFFECT

In the enrolled patients, serum lipids (TC, TG, and HDL cholesterol) were measured after fasting for at least 12 hours before enrollment and at the end of weeks 4 and 8 of the trial. Serum lipid measurements and other tests were performed in hospital laboratories; quality was routinely monitored by the Central Biochemistry Laboratory, Institute of Geriatrics of Beijing Hospital, as authorized by the Chinese Ministry of Public Health. LDL cholesterol was calculated according to the Friedewald equation, LDL cholesterol (mg/dL) = TC (HDL cholesterol + .TG/5); data from patients with TG measurements >400 mg/dL were excluded. A ratio of non HDL (TC HDL = cholesterol HDL cholesterol) was also calculated as an estimated risk factor for atherosclerosis.

The overall efficacy of *M purpureus* rice preparation was also assessed by an integrated analysis of the improvement in serum lipid levels. The criteria for the assessment of the overall clinical efficacy of *M purpureus* rice preparation are as follows: (1) clinically controlled: posttreatment serum lipids are within the normal ranges: TC, <200 mg/dL, LDL cholesterol, <130 mg/dL, TG, <160 mg/dL, and HDL cholesterol, >40 mg/dL for men or >45 mg/dL for women; (2) highly effective: at least one of the following changes in serum lipids after treatment: TC reduced > or =20%, TG reduced > or =40%, HDL cholesterol increased > or =10 mg/dL, or the ratio of non HDL:HDL cholesterol reduced > or =20%; (3) effective: at least one of the following changes in serum lipids after treatment: TC reduced > or =10% to <20%, TG reduced > or =20% to <40%, HDL cholesterol increased :4 mg/dL to <10 mg/dL, or the ratio of non HDL cholesterol HDL cholesterol reduced > or =10% to <20%.

SAFETY ASSESSMENT

Patients visited the clinic before the trial and after 4 and 8 weeks of treatment. Patient compliance (determined by counting the remaining pills during clinic visits, general physical health, and symptoms) were assessed at each visit. Physical examination (body weight, heart rate and rhythm, liver and spleen palpation), electrocardiogram, complete blood counts, serum alanine aminotransferase, blood urea nitrogen, creatinine, glucose, and creatine kinase, and urinalysis were performed on all patients before and after 8 weeks of therapy.

STATISTICAL ANALYSIS

Data is analyzed using the SAS statistical software package (SAS Institute, Inc., Cary, North Carolina) expressed as mean t SE. Student’s t test was used to analyze the quantitative data, with the group

test for comparisons of data from the two groups and the paired t test for comparisons of continuous variables before and after treatment. A chisquared test (odds ratio) was used for analyzing the qualitative data and the Breslow Day test for analyzing homogeneity of odds ratios for the two groups. Regression analysis was used to analyze the relationship between changes in body weight and individual serum lipids.

RESULT

A total of 446 (89010) of the 502 enrolled patients completed the study; data from 56 could not be used for analysis for reasons of noncompliance and incomplete data collection. Two patients discontinued treatment because of exacerbation of their preexisting stomachache, and seven patients were determined to be noncompliant because of their inconsistent use of medication. The data for these nine patients was not used for final calculation. Missing serum lipid results for the rest of the 47 patients were found, and the data from those patients were not included from the final analysis. Table I shows baseline characteristics of the study population; the characteristics of the patients in the two groups were similar. The treatment group comprised 324 patients (188 men and 136 women, aged 56.0 +/- 0.50 years) and the positive control group comprised 122 patients (73 men and 49 women, aged 56.4 t 0.83 years). Patients in the two groups had hyperxlipidemia for a similar number of years.

Table 1 Baseline characteristics

	Treatment Group	Positive Control Group	P
# of patients	324	122	
male	188	73	
female	136	49	
male:female	1.38:1	1.49:1	0.73
age (y)	56.0+/- 0.50	56.4 +/- 0.83	0.66
bodyweight (kg)	68.7 +/- 0.67	68.7 +/- 1.09	
height (m)	1.656 +/- 0.004	1.662 +/- 0.007	
disease history (y)	5.14 +/- 0.30	5.09 +/- 0.35	0.92

SERUM TOTAL CHOLESTEROL

Among the 446 patients who completed the study, 345 (251 in the treatment group and 94 in the positive control group) had pretreatment TC > or = 230 mg/dL (Table II). After 4 weeks of therapy with M purpureus rice preparation, TC was significantly decreased by 17.1% on average; (47.5 mg/dL, P < 0.001), whereas a 4.8% reduction (13.2 mg/dL) was obtained in the positive control group (P < 0.001, between group comparison). At 8 weeks, patients who received M purpureas treatment had an average reduction in TC of 22.7% (62.8 mg/dl, P<0.001), whereas a 7.0% reduction (18.9mg/dL) was found in the positive control group (P<0.001, between group comparison)

Table II. Effect of Monascus purpureus rice preparation on serum lipids.

Metabolic Variable	Time	M purpureus	Treatment Group Positive Control Group	P
Total cholesterol (mg/dL)	Pretreatment	274 +/- 1.98 (n=251)	268 +/-2.64 (n=94)	0.117
	After 4 weeks	226 +/-2.14*	255 +/- 3.50*	<0.001
	After 8 weeks	211 +/- 2.12*	250 +/-4.05*	<0.001
Triglycerides (mg/dL)	Pretreatment	73 +/-3.91 (n=157)	273 +/-7.14 (n=65)	0.995
	After 4 weeks	219 +/- 6.67*	248 +/-12.0*	0.035
	After 8 weeks	178 +/- 6.01*	238 +/-10.6	<0.001
LDL cholesterol (mg/dL)	Pretreatment	186 +/-2.34 (n=236)	180 t 3.37 (n=85)	0.169
	After 4 weeks	140 +/-2.49*	168 +/-3.74*	<0.001

	After 8 weeks	127 +/- 2.36*	165 +/-4.56*	<0.001
HDL cholesterol (mg/dL)	Pretreatment	36.2 +/-0.39 (n=129)	35.5 +/-0.56 (n=5)	0.297
	After 4 weeks	40.7 +/-0.66*	37.1 +/- 0.75*	<0.001
	After 8 weeks	43.4 +/-0.73*	38.5 +/-0.97*	<0.001
Ratio of nonHDL:HDL	Pretreatment	4.86 +/-0.09 (n=251)	5.07 +/-0.18 (n=94)	0.319
	After 4 weeks	3.61 + 0.08*	4.69 +/-0.17*	0.001
	After 8 weeks	3.19 ± 0.08*	4.54 +/-0.16*	<0.001

LDL = lowdensity lipoprotein;HDL=highdensity lipoprotein; ratio of nonHDL:HDL cholesterol=(total cholesterolHDL cholesterol)+ HDL cholesterol. P<0.001, by paired t test, as compared with the pretreatments values.

SERUM LOW DENSITY LIPOPROTEIN

The data for 321 patients (236 in the treatment group and 85 in the positive control group) with pretreatment serum LDL cholesterol \geq 130 mg/dL and TG<400 mg/dL are shown in Table I. Patients with TG>400 mg/dL were excluded from the analysis because using the Friedewald equation to calculate LDL cholesterol cannot be used to provide useful information about such patients. After 4 weeks of treatment with M purpureus rice preparation, LDL cholesterol was reduced by 24.6% on average (45.9 mg/dL, P < 0.001), with a mean reduction of 6.3% (12.3 mg/dL) in the positive control group (P < 0.001, between group comparison). After 8 weeks, LDL cholesterol was reduced by 30.9% (58.2 mg/dL, P < 0.001) in the M purpureus treated group; this reduction was significantly greater (P < 0.001) than that (8.3%, 15.3 mg/dL) in the positive control group yes; (Figure I)

SERUM TRICLYCERIDES

A total of 222 patients (157 in the treatment group and 65 in the positive control group) had pretreatment serum TG \geq 200 mg/dL and <400 mg/dL (Table II). Serum TG had decreased by an average of 19.8% (-54.0mg/dL, P < 0.001) after 4 weeks of treatment with M purpureus rice preparation, as compared with a reduction of 9.2% (24.6 mg/dL) in the Positive control group (P = 0.012, between group comparison). At 8 weeks, average reductions of 34.1% (94.1 mg/dL, P < 0.001) and 12.8% (34.7 mg/dL) were found in M purpureus treated patients and control group, respectively (P < 0.001, between group comparison)

SERUM HIGH DENSITY LIPOPROTEIN

Among the patients enrolled in this trial, 186 patients (129 in the treatment group and 57 in the positive control group) had low baseline serum HDL cholesterol levels (male <40 mg/dL, female <45 mg/dL) (Table II). After 4 weeks of treatment with M purpureus rice preparation, HDL cholesterol had increased by 12.8% on average (+4.5 mg/dL, P < 0.001), while an average 4.9% increase (+1.6 mg/dL) was found in the positive control group (P = 0.002, between group comparison). The 8 week treatment with M purpureus rice preparation resulted in a 19.9% increase (+7.2mg/dL) in HDL cholesterol (P < 0.001), which was significantly greater (P < 0.001) than the 8.4% increase (+2.9 mg/dL) in the positive control group (Figure 1).

RATIO OF NONHIGH DENSITY LIPOPROTEIN VS HIGH DENSITY LIPOPROTEIN CHOLESTEROL

The ratio of non HDL cholesterol (TC - HDL cholesterol) to HDL cholesterol was calculated for 345 patients (251 in the treatment group and 94 in the positive control group) who had pretreatment TC \geq 230 mg/dL. Overall, patients in the M purpureus treatment group showed marked improvement in this ratio (Table II) and a significant (P < 0.001) improvement in comparison with the positive control group. The 8 week treatment with M purpureus rice preparation resulted in a 34.5% decrease (1.7) in the ratio (P < 0.001), which was significantly better (P < 0.001) than the 8.3% decrease (0.5) in patients in the positive control group.

INTEGRATED ANALYSIS OF EFFECTS

We further analyzed the general efficacy of *M purpureus* rice preparation using a rating system detailed in Patients and Methods. As shown in Table III, there were 258 patients in the treatment group who achieved the criterion of clinically controlled (n =169) or highly effective (n = 89), which resulted in a total highly effective rate of 79.6%. In the positive control group, 38 patients (31.1%) satisfied the same criteria .The total effective rate was obtained in 93.2% of patients in the treatment group, which was also significantly better (P < 0.001) than the same rating obtained in 50.8% of the positive control patients.

SUBGROUP ANALYSIS

Figure 2A displays a 22% to 26% decrease in TC in the patients with different baseline pretreatment TC (P < 0.001, as compared with the pretreatment baseline). The percentage reduction was similar for the two groups of patients whose pretreatment TC was <240, mg/dL or >or =300 mg/dL. However, a nearly twofold reduction in TC (86mg/dL) was seen in patients with pretreatment TC>or =300 mg/dL, as compared with an average reduction of 47.1 mg/dL in patients with pretreatment TC <240 mg/dL(P < 0.001, comparing the two subgroups). The actual decrease in LDL cholesterol also appeared to be dependent on the level of the pretreatment LDL cholesterol (Figure 2B). However, the percentage reduction of LDL cholesterol did not differ significantly (p = 0.11) between the patients with pretreatment LDL cholesterol of 130 to 160 mg/dL (22.4 t 7.2%) and pretreatment LDL cholesterol >200 mg/dL (34.6 t 2.1%).

The reduction in TG, both actual (mg/dL) and percentage reduction, was more marked when pretreatment TG levels were highly elevated. For example, patients with pretreatment TG >or=300 mg/dL had the largest percentage drop (40.1%, 152 mg/dL; .P < 0.001) from pretreatment baselines compared with the decrease (8.8%, 17 mg/dL) in those with pretreatment TG <200 mg/dL (P < 0.001, comparing the subgroups). Pretreatment HDL cholesterol also determined the percentage increase in this lipid (Figure 2D). In patients with HDL cholesterol >45mg/dL, *M purpureus* rice preparation therapy resulted in a minor 4.0% increase in HDL cholesterol (+1.81 mg/dL, P = 0.041, compared with prextreatment baseline). In contrast, the percent increase in patients with pretreatment HDL cholesterol 35 to 45 mg/dl was +16%(=6.3 mg/dL,P<0.001, as compared with pretreatment baseline); in patients with pretreatment HDL cholesterol <35mg/dL, the increase was 25.1% (+7.9mg/dL, P<0.001, as compared with pretreatment baseline)

Table 111. Integrated analysis of clinical efficacy of *Monascus purpureus* rice preparation

	Efficacy After 8Week Treatment*				Total Highly Effective Rating+	Total Effective Rating++
	Clinically Controlled	Highly Effective	Effective	Not Effective		
Treatment Group						
(n=32)	169 (52.2%)	89 (27.5%)	44 (13.6%)	22 (6.8%)	258 (79.6%)	302 (93.2%)
Positive Control Group						
(n=122)	1 (10.7%)	25 (20.5%)	24 (19.7%)	60 (49.2%)	38 (31.1%)	62 (50.8%)
P	<0.001				<0.003	<0.001
(treatment vs positive control)						

Clinically Controlled=posttreatment serum lipid levels within normal ranges (total cholesterol [TC]<200mg/dL, low density lipoprotein cholesterol [LDL cholesterol] <130 mg/dL, triglycerides (TG) <160 mg/dL, and high density lipoprotein cholesterol (HDL cholesterol) >40 mg/dL for males and >45 mg/dL for females; Highly Effective = at least one of the following post treatment changes in serum lipids: TC reduced > /=20%, TG reduced > /=40%, HDL cholesterol increased > /=10 mg/dL, or ratio of non HDL:HDL cholesterol reduced > / =20%; Effective = at least one of the following post treatment changes in serum lipids: TC reduced > /=10% to <20%, TG reduced > /=20% to <40%, HDL cholesterol increased > /=4 mg/dL to <10 mg/dL, or non HDL cholesterol : HDL cholesterol reduced > /=10% to <20%; and Not Effective = post treatment serum lipids unchanged or below the criteria for a rating of Effective.

+ Total Highly Effective rating obtained by adding the numbers of patients whose outcomes were rated Clinically Controlled or Highly Effective.

++Total Effective rating obtained by adding the numbers of patients whose outcomes were rated Clinically Controlled, Highly Effective, or Effective.

BODY WEIGHT REDUCTION

The hypolipidemic effects of M purpureus rice preparation may be related to body weight changes because of dietary control. At 8 weeks, no significant differences in changes in body weight were found between the patients treated with M purpureus rice preparation (1.40 +/- 0.28 kg) and positive controls (0.91 +/- 0.15 kg). Regression analysis of changes in body weight and serum lipids did not reveal a correlation between these variables in either group.

SAFETY ASSESSMENT

Of the 324 patients who received 8 weeks of treatment with M purpureus rice preparation, 6 patients (1.9%) experienced heartburn, 3 (0.9%) flatulence in the stomach, and 1 (0.3%) dizziness. These symptoms resolved without specific treatment, and the patients completed their trial treatment. Two patients (0.6%) withdrew from the trial due to exacerbation of their pre-existing stomach ache during treatment with M purpureus rice preparation. None of the 54 patients that withdrew from the trial developed any symptoms or medical conditions related to the trial treatment. No patients in either the treatment or positive control groups had increased alanine amino transferase twice the upper limit of normal (normal, <40 IU/L) after the 8 week trial: The abnormal pretreatment electrocardiographic findings improved in 18 patients (5.6%) after M purpureus treatment. Serum creatine kinase (normal, <200 IU/L) increased after 8 weeks in both groups: +31 IU/L (+46%) on average in the M purpureus rice preparation group and +24 IU/L (+39%) in the positive control group. In the treatment group, 1 patient (0.3%) had post treatment serum creatine kinase approximately 2.5 times the upper limit of normal. There were, however, no significant differences in-either pretreatment or post treatment serum creatine kinase between the two groups:

DISCUSSION AND CONCLUSIONS

This single masked clinical study involving patients from four clinical sites demonstrated that M purpureus rice preparation administered daily for 8 weeks was very effective in reducing serum cholesterol, with an average 22.7% reduction in TC and 30.9% in LDL cholesterol. The percentage reduction in TC and LDL cholesterol obtained with M purpureus rice preparation was independent of pretreatment levels, but the absolute reduction was greatest in those patients with baseline TC >300 mg/dL or LDL cholesterol >200 mg/dL. Based on guidelines developed by the Chinese Ministry of Public Health¹⁶ M purpureus rice preparation was effective in 93.2% of the patients, and highly effective in 79.6% of the patients treated.

In addition to lowering TC and LDL cholesterol, this study showed that M purpureus rice preparation was effective in reducing serum TG in patients with hyperlipidemia. This TG lowering effect was more evident when pretreatment TG were >300 mg/dL. There was also a 19.9% increase in HDL cholesterol in patients who received M purpureus rice preparation. This effect was also dependent on the pretreatment baseline, with an inverse relationship between the two variables. Lower pretreatment HDL cholesterol resulted in a greater increase in HDL cholesterol. Notably, the 34.5% decrease in the ratio of non-HDL cholesterol to HDL cholesterol after 8 weeks of treatment with M purpureus rice preparation suggests that there may be a reduced risk of atherosclerosis in patients receiving this therapy. Animal studies have demonstrated that atherosclerosis was significantly reduced in hyperlipidemic rabbits and quail after M purpureus rice treatments.

The mechanism by which M purpureus rice preparation reduces serum TG and raises HDL cholesterol is not completely understood. This natural food product (original form available in the United States as cholestin³ [Pharmanex, Inc.; Simi Valley, California]) does, however; contain many nutritional components, such as unsaturated fatty acids, sterols (betaxsitosterol, campesterol, stigmasterol), proteins, saccharides, isoflavone and its glycosides, saponin and saponogenin, and trace elements such as selenium and zinc, in addition to compounds that inhibit HMGCoA reductase.¹² It should

be emphasized that the small quantity (<14 mg/dL) of total structure-related HMGCoA reductase inhibitors found in this natural dietary product cannot account for all the lipid lowering effects of *M purpureus* rice. Decreased absorption of ingested lipids, reduced very low density lipoprotein cholesterol, and/or facilitated removal of very low density lipoprotein cholesterol are all events that may also contribute to a reduction in cholesterol and TG and an increase in HDL cholesterol. Interestingly, our data indicate that there was no complete correlation between any of the changes in patients serum lipids and decreased body weight in either group. Severe side effects with *M purpureus* rice treatment were rare, and the treatment was well tolerated in this study. Although mild side effects (ie, heartburn, flatulence, and dizziness) were found in a few patients, these symptoms resolved quickly. No changes in alanine aminotransferase were found after the 8 week treatment; mild increases in creatine kinase were found in both groups. Because of regulatory requirements mandated by the Chinese government¹⁶ it was not possible to include a placebo control group to establish whether the rise in creatine kinase was related to treatment. However, it is worth noting that in the EXCEL study,¹⁷ the placebo control group had an increase in creatine kinase similar to that seen in the group treated with mevinolin.

In summary, we suggest that *M purpureus* rice preparation is a highly effective and well tolerated dietary supplement that can be used to regulate elevated serum cholesterol and TG. The reductions in serum TC, LDL cholesterol, and TG, and the increase in HDL cholesterol are achieved quickly and are clinically meaningful. *M purpureus* rice preparation may therefore, enable people whose serum lipids are significantly elevated to maintain serum cholesterol and TG within a normal range.

ACKNOWLEDGMENTS

This study was supported by WBL Peking University Biotech. Co. Ltd.; Beijing, China. The authors thank Dr: David Chang for the statistical analyses he performed for this study:

References:

1. Castelli WP, Wilson PWF, Levy D, Anderson K Serum lipids and risk of coronary artery disease. In: Leaf A, Weber P, eds. *Atherosclerosis Reviews*: New York: Raven Press;1990;21:720.
2. Dart AM. Managing elevated blood lipid concentrations. Who, when and how? *Drugs*. 1990;39:374-387
3. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *NEJM*. 1995;333:1301-1307.
4. Brown MS, Goldstein JL. Heart attacks: Gone with the century? *Science*. 1996;272:629.
5. Schonfeld G, Shepherd J. Introduction. *Am J Cardiol*. 1995;76:1A-2A.
6. Li C, Zhu Y, Wang Y, et al. *Monascus purpureus* fermented (red yeast rice): A natural food product that lowers blood cholesterol. in animal models of hypercholesterolemia. *Nutr Res*. 1997;18:71-82.
7. Shen Z, Yu P, Sun M, et al. Treatment of primary hyperlipidemia with Zhitai (Xuezhikang) capsule: A pilot clinical study. *Natl Med J China*. 1996;76:156-157.
8. Su M, Wang X, Li Y, Gao Z. A clinical trial of Xuezhikang capsule in the treatment of hyperlipidemia. *New Chin Herb Med Clin Pharmacol*. 1995;6:1316.
9. Liu Z, Zhao L, Zhang Y, et al. Clinical observation of treatment of hyperlipidemia with Xuezhikang. *Chin Med News*. 1996;11:1213.
10. Li C, Li Y, Hou Z. Toxicology of Xuezhikang. *Inf Chin Pharmacol Soc*. 1995;12:12.
11. Sung Y-H. *Chinese Technology in the Seventeenth Century*. University Park: The Penn
12. Xie S, Duan Z. Xuezhikang capsule regulates blood lipids with high efficacy: An overview of its preparation, pharmacology, toxicology, and results of clinical trials. *Chin Med News*. 1996;11:1314.
13. Katan MB, Zock PL, Mensink RP. Effects of fats and fatty acids on blood lipids in humans:

Anoverview. Am J Clin Nutr. 1994;60(Suppl 6):10175-1022S.

14. Cour B, Molgaard P, Yi Z. Traditional Chinese medicine in treatment of hyperlipidemia. yes">J Ethnopharmacol. 1995;46:125129.
15. The Guideline or Clinical Trials for New Traditional Chinese Medicine. tad ed. Beijing. Ministry of Public Health of China; 1993.
16. The Guide for Cinical Trials for Therapeutic Agents Regulating Blood Lipids (Provisional). Beijing: Ministry of Public Health of China; 1988.
17. Dujovne CA, Chremos AN, Pool JL, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results: IV. Additional perspectives on the tolerability of lovastatin. Am J Med. 1991;91(1B):25S305.