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Hypolipidemic and anti-atherogenic effects of long-term Cholestin (*Monascus purpureus*-fermented rice, red yeast rice) in cholesterol fed rabbits

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Abstract

Long-term effects of Cholestin (*Monascus purpureus* rice; red yeast rice) on serum lipids and severity of atherosclerosis were examined in rabbits fed for 200 days on a semi-purified diet containing 0.25% cholesterol. Serum total cholesterol was 25 and 40% lower, respectively, in rabbits fed 0.4 or 1.35 g/kg/day of Cholestin (*Monascus purpureus* rice; red yeast rice) compared to controls. This treatment also lowered serum LDL cholesterol. This 200-day treatment significantly reduced serum triglycerides and atherosclerotic index (ratio of non-HDL-cholesterol to HDL-cholesterol). Although similar reductions of total, LDL-cholesterol and triglycerides were observed, a parallel group of rabbits fed lovastatin (0.0024g/kg/day) failed to reduce the index significantly. Apolipoprotein A_1 was increased and apolipoprotein B was reduced in all treatment groups. Severity of atherosclerosis was reduced significantly in all treatment groups. The sudanophilic area of involvement was 80.6% in controls, and reduced significantly; to 30.1% on the low dose of Cholestin (*Monascus purpureus* rice; red yeast rice), and 17.2% on the high dose. Lovastatin reduced severity of lesions by 89% (sudanophilia) and 84% (visual). Visual grading of lesion severity showed reduction by 38% and 68%. © 2003 Elsevier Inc. All rights reserved.

Keywords: Atherosclerosis; Cholestin (*Monascus purpureus* rice; red yeast rice); HMG-CoA reductase inhibitors; Hyperlipidemia; Red yeast rice

1. Introduction

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 in food, as a preservative or to maintain taste and color in fish and meat or for its medicinal properties [1]. Red yeast rice is a dietary staple in many Asian countries with typical consumption ranging from 0.5 to 2 oz/person/day [2]. The medicinal properties of red yeast rice were described by pharmacologists of the Ming Dynasty (1368-1644) as cited by Ma et al. [3].

A pharmacological preparation from *Monascus purpureus* fermented on rice has been in public use in China as well as in many countries including the United States: *Monascus purpureus* rice, Cholestin™ (*Monascus purpureus* rice; red yeast rice), is composed, in part, of 73.4% starch, 5.8% protein, less than 2% fat and a number of compounds called monacolins, which are inhibitors of HMG-CoA reductase. The total monacolin level of the *Monascus purpureus* rice product is 0.4% [3]. Cholestin (*Monascus purpureus* rice; red yeast rice) also contains 2-6% fatty acids, palmitic acid, linoleic acid, oleic acid, stearic acid [4], some of which may help reduce serum lipids [5].

Endo initially isolated the series of compounds known as monacolins from various molds [6-9]. The first of these to be used as a hypocholesterolemic agent in humans was monacolin K has been marketed under the names of mevinolin or lovastatin [10-12]. There are several other monacolin derivatives (now generally referred to as "statins") which are used to treat hypercholesterolemia. Ma et al. [3] have identified thirteen different monacolins in red yeast rice, and Monacolin K represents about half of the total monacolin yield.

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Mevinolin (lovastatin) was shown to inhibit experimental atherosclerosis in rabbits two decades ago [13]. The hypolipidemic and anti-atherogenic effects of lovastatin in rabbits have been confirmed by several authors [14,15], and it has also shown to be anti-atherogenic in hamsters [16]. We have recently shown 2-month therapy with *Monascus purpureus* rice to be hypocholesterolemic in rabbits and quail, as well as in humans [17-19]. However, long-term effects of *Monascus purpureus rice* on serum lipids and atherosclerosis, as well as on oxidative stress are unknown.

This paper describes the long-term (200-day) hypolipidemic and anti-atherogenic effects on reducing oxidative stress in rabbits of *Monascus purpureus* rice (red yeast rice) (Cholestin, *Monascus purpureus* rice; red yeast rice) and offers a direct comparison with lovastatin.

2. Materials and methods

2.1. Test compounds

Cholestin (*Monascus purpureus* rice; red yeast rice) powder (Batch #T970303) was provided by WBL Peking University Biotech Co. Ltd. (Beijing, China). Lovastatin (Batch #970100) was purchased from Qingyuan Lanbao Pharmaceutical Ltd., Guangdong, China.

2.2. Reagents and assay kits

Assay kits for total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c), apolipoprotein A_1 and apolipoprotein B were purchased from Zhongsheng Hightech Bioengineering Co. (Beijing, China). TEP and EDTA were products of Fluka Co. NADPH and NADP were products of Sigma (St. Louis, MO). The assay kit for endothelin radioimmunoassay was purchased from Eastern Asian Immuno Technology Institute (Beijing, China).

2.3. Animals

Sixty male New Zealand White rabbits (1.6-2.2 kg) were used. The rabbits were housed individually and maintained on commercial ration in order to stabilize their blood lipids and metabolic status before instituting the experimental procedure. Fifty rabbits were used for this study.

2.4. Treatment groups and dosages

The rabbits were randomized to five groups of 10 rabbits each. The groups were: a) normal diet control; b) atherogenic diet (AD) control (Table 1); c) AD plus 0.4 gm red yeast rice/kg/day; d) AD plus red yeast rice 1.35 g/kg/day; and e) AD plus lovastatin, 2.36 mg/kg/day. The dosage of red yeast rice used was based on our earlier study [17]. The rabbits were weighed weekly and treatment adjusted accordingly. The rabbits had *ad libitum* access to food and water. The experimental feeding period was 200 days.

Table 1
Composition of semi-purified diet used to induce atherosclerosis in rabbits

Ingredient	% Of total	% Of total calories
Casein	25.00	25.5
Sucrose	39.45	40.2
Coconut oil	14.00	32.0
Soybean oil	1.00	2.2
Cellulose	15.00	
Vitamin mix	1.00	
Mineral mix	4.00	
Choline bitartrate	0.30	
Cholesterol	0.25	
Total	100.00	100.0

Blood was obtained from the ear vein of rabbits which had been fasted for 12 hr previous to bleeding. Serum total, LDL and HDL cholesterol levels, apolipoproteins A and B and triglyceride levels were quantitated using a Biochemical Analyzer (Beijing Zhongsheng Hightech Bioengineering Company, Beijing, China).

After 200 days rabbits were killed and livers and aortas removed. The aortas were stained with Sudan Red and plaque area quantified using an imager analyzer (QT-80). Aortas were also graded visually on a 0-4 scale as described by Duff and McMillan [20].

Plasma endothelin was isolated and liver endothelin levels were determined by radioimmunoassay [21,22]. Malondialdehyde levels in blood and liver were determined using the thiobarbituric assay of Asakawa and Matsushita [23].

2.5. Statistical analysis

All data are expressed as mean ± standard error of the mean (SEM). Student's t test was used in comparing mean values of two groups; analysis of variance was used to analyze variations of means of multiple groups and linear correlations were used for analyzing linear correlation of different parameters.

3. Results

Table 2 details changes of body weight and liver weights of the rabbits after 200 days of red yeast rice treatment. There were no significant differences in weight gain or liver weight. Table 3 presents data relating to lipids and lipoproteins. It is evident that rabbits on the atherogenic diet for 200 days had significantly higher total and LDL- cholesterol and triglyceride levels than did the rabbits on commercial ration. The ratio of non-HDL-cholesterol to HDL-cholesterol (atherosclerotic index) was significantly increased. HDL-cholesterol did not change significantly. Among the groups on the atherogenic diet, serum total cholesterol was

Table 2
Effect of Cholestin (*Monascus purpureus* rice; red yeast rice) on body weight gain and liver weight of rabbits

Necropsy data					
	Normal	Control diet	Cholestin* low dose	Cholestin* low dose	Lovastatin*
n	7	7	6	9	8
Dose (g/kg/d)	—	—	0.4	1.35	0.0024
Wt. gain (kg)	0.96 ± 0.09ab	0.93 ± 0.13c	1.37 ± 0.10ac	1.22 ± 0.08b	1.09 ± 0.10
Liver wt. (g)	77.4 ± 3.58abc	88.4 ± 2.49a	84.3 ± 2.61	90.9 ± 1.67b	89.5 ± 2.72c
Liver (% body wt.)	2.92 ± 0.09	3.08 ± 0.88a	2.54 ± 0.20a	2.86 ± 0.06	2.93 ± 0.11

[a]Normal = commercial ration.
Control = 0.25% cholesterol (C).
* = C + Cholestin (*Monascus purpureus* rice, red yeast rice) or lovastatin.
Diets fed for 200 days.
Values in horizontal row bearing the same letter are significantly different.

reduced by 25% and 43% ($p \leq 0.05$) on the lower and higher doses of Cholestin (*Monascus purpureus* rice; red yeast rice) and 47% ($p \leq 0.05$) when treated with lovastatin. LDL cholesterol was reduced by 7%, 24%, and 44% ($p \leq 0.05$) on the three treatments and HDL-cholesterol was increased by 52%, 55%, and 28%, respectively. Thus, while lovastatin reduced total and LDL-cholesterol compared to the atherogenic diet control group, it did not significantly raise HDL-cholesterol. Compared to the control diet, the ratio of non-HDL cholesterol to HDL cholesterol was reduced significantly by 47 and 48% with the lower and higher doses of Cholestin (*Monascus purpureus* rice; red yeast rice). Triglycerides were reduced in all three treatment groups. Table 4 shows changes in serum apolipoproteins. Apo-A_1 was increased and apo-B reduced in all groups as compared to normal rabbits controls.

The data relative to severity of atherosclerosis are presented in Table 5. We found that even at the lower dose Cholestin (*Monascus purpureus* rice; red yeast rice) reduced severity of atherosclerosis significantly, compared to the diet control. A clear dose-dependent response in protection of atherosclerosis was shown in animals received Cholestin (*Monascus purpureus* rice; red yeast rice). There were no significant differences in severity of atherosclerosis between the higher dose of Cholestin (*Monascus purpureus* rice; red yeast rice) and lovastatin.

To determine if the effects of Cholestin (*Monascus purpureus* rice; red yeast rice) went beyond effects on lipid metabolism, we determined plasma malondialdehyde (MDA), a measure of oxygen free radicals. As Table 6 shows, addition of cholesterol to the diet raised plasma MDA significantly. The increase in plasma MDA was muted by the treatments. In particular, a dose-response relationship can be seen with Cholestin (*Monascus purpureus* rice; red yeast rice) administration. Liver endothelin was not influenced by atherogenic diet or by either treatment (data not shown).

4. Discussion

Atherosclerosis is a disease of multiple etiology. There is, as yet, no simple, non-invasive method for assessing the severity of this disease in situ. Instead there are a number of factors (risk factors) often associated with increased susceptibility to coronary heart disease. One of the major risk factors associated with coronary heart disease is elevated plasma or serum total or LDL cholesterol. Lowering serum cholesterol may lower the risk of heart disease, and enormous effort has been expended to achieve this aim.

Pharmaceutical agents which lower cholesterol by interfering with cholesterol synthesis have been studied for sev-

Table 3
Effects of Cholestin (*Monascus purpureus* rice; red yeast rice) on serum lipids of rabbits fed an atherogenic regimen (0.25% cholesterol) for 200 days

	Normal	Control diet	Cholestin* low dose	Cholestin* high dose	Lovastatin
No.	7	7	6	9	8
Dose (g/kg/d)	—	—	0.4	1.35	0.0024
Cholesterol (C) (mmol/L)					
Total (TC)	1.29 ± 0.21abcd	18.01 ± 0.11aef	13.50 ± 2.24b	10.75 ± 0.80ce	9.54 ± 1.26df
LDL-C	1.04 ± 0.12abcd	9.06 ± 1.43ae	8.47 ± 1.34bf	6.85 ± 0.54cfg	5.11 ± 0.58deg
(TC-HDLC)/HDL-C	3.70 ± 0.76abcd	28.25 ± 3.10aef	14.94 ± 2.69be	14.67 ± 2.69be	16.65 ± 4.88d
Triglycerides (mmol/L)	1.10 ± 0.18ab	3.50 ± 0.36abcde	1.74 ± 0.23bcf	1.41 ± 0.19d	1.09 ± 0.10ef

* See footnote in Table 2.
Values in horizontal row bearing same letters are significantly different.

Table 4
Effects of Cholestin (*Monascus purpureus* rice; red yeast rice) and lovastatin on serum apolipoproteins A1 and B (mmol/L) in rabbits fed an atherogenic regimen (0.25% cholesterol) for 200 days[a,b]

	n	Dosage (g/kg/d)	Apo A1 (mmol/L)	Apo B (mmol/L)
Normal	7	—	0.45 ± 0.05abcd	0.38 ± 0.07abcd
Control diet	7	—	1.69 ± 0.14ac	1.44 ± 0.03a
Cholestin low dose	6	0.4	1.79 ± 0.12b	1.30 ± 0.06bgh
Cholestin high dose	9	1.35	1.75 ± 0.06cf	1.03 ± 0.06ceg
Lovastatin	8	0.0024	2.05 ± 0.07def	0.97 ± 0.06dfh

[a] See legends in Tables 2 and 3.
[b] Values in vertical row bearing same letter are significantly different.

Table 6
Effects of Cholestin (*Monascus purpureus* rice; red yeast rice) on plasma malondealdehyde (MDA) in rabbits red an atherogenic diet (0.25% cholesterol) for 200 days

	n	Dosage (g/kg/d)	Plasma MDA (nmol/L)	Liver MDA (nmol/g wet wt)
Normal	7	—	4.62 ± 0.34abcd	366 ± 30.2abcd
Control diet	7	—	8.62 ± 0.34aefg	694 ± 42.5a
Cholestin	6	0.4	7.16 ± 0.27behi	647 ± 44.0b
Cholestin	8	1.35	6.11 ± 0.27cfh	592 ± 21.0c
Lovastatin	8	0.0024	5.8 ± 0.26dgi	614 ± 26.5d

*Plasma MDA of normal rabbits is significantly lower than in all the cholesterol-fed groups. Values in a vertical row bearing the same letter are significantly different.

eral decades and the most successful agents are compounds which inhibit the enzyme hydroxymethylglutaryl CoA reductase (HMG-CoA reductase), one of the key steps in cholesterol synthesis. These compounds, referred to as statins, have profound positive effects on the outcome of cholesterol lowering trials [24]. It has been suggested that the statin family of drugs exert beneficial health effects beyond their effects on hyperlipidemia [25-27]. In addition to the previous report showing the 90-day, lipid-lowering effects of Cholestin (*Monascus purpureus* rice; red yeast rice) [17], this dietary supplement was as efficacious in lipid lowering as the positive control drug, lovastatin in rabbits after a long-term 200-day treatment.

In the earliest test of lovastatin in experimental atherogenesis we [13] administered 2.5 mg/kg/day of lovastatin to rabbits maintained on a 2% cholesterol diet. After 2 months, serum cholesterol was 54% lower in the test group. Severity of atherosclerosis in the aortic arch was reduced by 43% ($p < 0.05$) and that in the thoracic aorta was reduced by 27%. In the present study we have shown that treatment with lovastatin (2.7 mg/kg) for 200 days reduced total cholesterol by 47% on average. Cholestin (*Monascus purpureus* rice; red yeast rice), which contains 0.4% of various monacolins (half being Mevinolin), lowered serum total cholesterol by 25 and 40%, respectively, in rabbits fed 0.25% cholesterol when the preparation is fed at a dose of 0.4 or 1.35 g/kg/day. At a higher dosage (1.35 g/kg/day) of Cholestin (*Monascus purpureus* rice; red yeast rice), serum total and LDL cholesterol were reduced by 43 and 24%, comparing well with lovastatin (0.0024 g/kg/day) which gave reductions of 47 and 44% in these parameters. Another risk factor for atherosclerosis is reduced of HDL-cholesterol. Our data showed that Cholestin (*Monascus purpureus* rice; red yeast rice) increased serum HDL-c, even in the lower dose group while lovastatin failed to increase HDL-c significantly.

The ratio of non-HDL-cholesterol to HDL-cholesterol, also referred to as atherosclerotic index, is believed to be another important risk factor for atherosclerosis. Our data clearly demonstrate that Cholestin (*Monascus purpureus* rice; red yeast rice) significantly decreases the ratio, even in the lower dose group. We believe that Cholestin (*Monascus purpureus* rice; red yeast rice) is not merely an impure form of statin drug and that chemical components other than monacolins may be responsible for this observation. The real comparison of these compounds is in their effects on severity of cholesterol-induced atherosclerosis. Aortic sudanophilia was reduced by 63 and 79% on the low and high doses of Cholestin (*Monascus purpureus* rice; red yeast rice) and by 89% on lovastatin. In visual grading of the atherosclerotic lesions, the lower and higher doses of Cholestin (*Monascus purpureus* rice; red yeast rice) significantly reduced severity by 38 and 68%, similar to lovastatin.

Our data demonstrate that the atherogenic diet induced an increase in plasma MDA, which may indicate elevated oxidative stress in the body. It is hypothesized that reduction

Table 5
Effects of Cholestin (*Monascus purpureus* rice; red yeast rice) on severity of atherosclerosis in rabbits fed an atherogenic diet (0.25% cholesterol) for 200 days

	n	Dosage (g/kg/d)	Visual grading		Stain
			Aortic arch	Thoracic aorta	Sudanophilic area %
Normal	7	—	0 abcd	0 abcd	0 abcd
Control diet	7	—	3.75 ± 0.30aefg	2.86 ± 0.46ahfg	80.6 ± 6.87aefg
Cholestin low dose	6	0.4	2.75 ± 0.36behi	1.33 ± 0.33beh	30.1 ± 2.80behi
Cholestin high dose	9	1.35	1.56 ± 0.32cfh	0.56 ± 0.15cfh	17.1 ± 2.725cfh
Lovastatin	8	0.0024	0.88 ± 0.35dgi	0.19 ± 0.19dg	8.7 ± 3.14dgi

See legends in Tables 2 and 3.
Values in vertical column bearing same letter are significantly different.

of such oxidative stress may slow down or prevent onset of the atherosclerotic process. After the long-term preventive treatment with Cholestin (*Monascus purpureus* rice; red yeast rice), the significantly elevated MDA was largely muted. Plasma MDA concentration in the higher dose group was similar to that in the normal diet control group. Liver MDA levels were elevated in all test groups. These data suggest that Cholestin (*Monascus purpureus* rice; red yeast rice) may be capable of lowering or slowing down oxidative-stress related atherosclerosis pathological process.

In summary, the data presented in this paper show that administration of this red yeast rice, (Cholestin, *Monascus purpureus* rice; red yeast rice) is a safe and effective way of lowering serum total and LDL cholesterol, ratio of non-HDL/HDL, and severity of experimental atherosclerosis.

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