

Effect of red yeast rice/policosanol on low density lipoprotein cholesterol reduction in hypercholesterolemic outpatients

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- Background** : *Red yeast rice/policosanol supplements have been studied by many countries that showed cholesterol lowering effect, especially LDL-C, however there has not been any study done on this topic in Thailand.*
- Objective** : *To compare the cholesterol lowering effects of red yeast rice/policosanol with placebo in hypercholesterolemic outpatients.*
- Research design** : *Human experimental study (prospective, randomized, double-blind, two-way crossover study).*
- Setting** : *General internal medicine clinic, King Chulalongkorn Memorial Hospital.*
- Method** : *After informed consent and 4 week washout period, fourteen hypercholesterolemic outpatients were randomly assigned with concealed allocation to receive either red yeast rice/policosanol (each capsule contained 100/5 mg) 2 capsules or 2 capsules of placebo daily for 4 weeks. Then there was a 4-week washout period followed by a crossover to the other treatment for another 4 weeks. Cholesterol lowering effects (total cholesterol, LDL-C, triglyceride and HDL-C), liver and muscle enzymes were assessed at the end of each 4-week treatment period.*

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- Results** : *Baseline patients characteristics were similar between the two groups. ($p > 0.05$) Red yeast rice/policosanol significantly reduced total cholesterol and LDL-C from baseline. Total cholesterol significantly reduced from 235.14 ± 37.77 to 213.64 ± 30.98 mg/dL ($p = 0.007$) and LDL-C significantly reduced from 162.09 ± 25.97 to 139.84 ± 22 mg/dL. ($p = 0.001$) Triglyceride and HDL-C did not change significantly. Serial monitoring of serum hepatic transaminase and creatine kinase level revealed no significant increased in the value after 4 weeks. There was also an insignificant changed in blood pressure, fasting blood sugar or serum creatinine throughout the study period.*
- Conclusion** : *Four-week dietary supplement with red yeast rice/policosanol at a fixed dose 200/10 mg per day significantly reduced total cholesterol and LDL-C from baseline. There was no significant difference in triglyceride and HDL-C levels compared with baseline. The dose and duration of the nutritional supplement of red yeast rice/ policosanol used in this study appeared to be safe.*
- Keywords** : *Red yeast rice, policosanol, hypercholesterolemia, low density lipoprotein cholesterol.*

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โพลีโคซานอลต่อการลดระดับแอลดีแอลคอเลสเตอรอลในเลือด ในผู้ป่วยนอกที่มีภาวะ
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- เหตุผลของการทำวิจัย** : เรดยีสต์ไรซ์/โพลีโคซานอล เป็นผลิตภัณฑ์อาหารเสริมที่มีการศึกษาใน
ต่างประเทศจำนวนมากที่แสดงให้เห็นถึงการลดระดับคอเลสเตอรอล
ในเลือดได้ โดยเฉพาะอย่างยิ่งแอลดีแอลคอเลสเตอรอล แต่ยังไม่เคยมี
การศึกษาผลต่อระดับคอเลสเตอรอลในคนไทย
- วัตถุประสงค์** : เพื่อเปรียบเทียบผลการลดระดับคอเลสเตอรอลในเลือดของเรดยีสต์ไรซ์/
โพลีโคซานอลกับยาหลอก ในผู้ป่วยนอกที่มีภาวะคอเลสเตอรอล
ในเลือดสูง
- รูปแบบการวิจัย** : การศึกษาวิจัยเชิงทดลองในมนุษย์ แบบข้ามกลุ่มการรักษา เชิงสุ่มและ
ปกปิดการรักษาทั้งสองข้าง
- สถานที่ทำการศึกษา** : ห้องตรวจโรคผู้ป่วยนอก แผนกอายุรกรรมทั่วไป โรงพยาบาลจุฬาลงกรณ์
- วิธีการศึกษา** : ผู้ป่วยที่เข้าร่วมการศึกษาจำนวน 14 คน หลังจากสมัครเข้าร่วมการศึกษา
และหยุดยาลดไขมันเป็นเวลา 4 สัปดาห์ ถูกแบ่งกลุ่มการรักษาด้วย
การสุ่มแบบปกปิด ให้กินเรดยีสต์ไรซ์/โพลีโคซานอล (แคปซูลละ 100/5
มิลลิกรัม) วันละครั้ง ๆ ละ 2 แคปซูล หรือยาหลอก นาน 4 สัปดาห์
จากนั้นหยุดการรักษา 4 สัปดาห์ แล้วสลับการรักษาในแต่ละกลุ่มอีก
4 สัปดาห์ มีการประเมินผลการเปลี่ยนแปลงระดับคอเลสเตอรอล
ในเลือด ระดับเอนไซม์ตับและกล้ามเนื้อในแต่ละช่วง
- ผลการรักษา** : ผู้ป่วยทั้งสองกลุ่มมีข้อมูลพื้นฐาน ผลการตรวจร่างกาย และระดับ
คอเลสเตอรอลในเลือดพื้นฐานไม่แตกต่างกัน ($p > 0.05$) ผลการศึกษา
พบว่าเมื่อได้กินเรดยีสต์ไรซ์/โพลีโคซานอลนาน 4 สัปดาห์ ระดับ
คอเลสเตอรอลรวมและระดับ LDL-C ลดลงอย่างมีนัยสำคัญทางสถิติ
เมื่อเทียบกับค่าพื้นฐาน โดยระดับคอเลสเตอรอลรวมลดลงจาก 235.14 ± 37.77 เป็น 213.64 ± 30.98 มิลลิกรัมต่อเดซิลิตร ($p = 0.007$) และระดับ
LDL-C ลดลงจาก 162.09 ± 25.97 เป็น 139.84 ± 22 มิลลิกรัม/
เดซิลิตร ($p = 0.001$) ส่วนระดับไตรกลีเซอไรด์และ HDL-C มีค่าไม่
แตกต่างกันอย่างมีนัยสำคัญทางสถิติจากค่าพื้นฐาน ไม่มีผู้เข้าร่วมการศึกษา

- รายใด ที่มีระดับเอนไซม์ตับและกล้ามเนื้อสูงขึ้นเกินสามเท่าของค่าปกติ นอกจากนั้นค่าความดันโลหิต ระดับน้ำตาลในเลือด และการทำงานของไตซึ่งประเมินจากระดับครีเอตินินในเลือดไม่มีการเปลี่ยนแปลง อย่างมีนัยสำคัญทางสถิติ
- สรุปการศึกษา :** การให้กินเรดยีสต์ไรซ์/โพลีโคซานอลในคนไทย เป็นเวลา 4 สัปดาห์ สามารถลด ระดับคอเลสเตอรอลรวมและ LDL-C ได้อย่างมีนัยสำคัญทางสถิติ แต่ไม่มีผลต่อระดับไตรกลีเซอไรด์และ HDL-C ในด้านของ ความปลอดภัยการให้เรดยีสต์ ไรซ์/โพลีโคซานอลในขนาดและระยะเวลา ดังกล่าวไม่มีผลต่อการทำงานของตับและกล้ามเนื้อ
- คำสำคัญ :** เรดยีสต์ไรซ์, โพลีโคซานอล, คอเลสเตอรอลในเลือดสูง, แอลดีแอล คอเลสเตอรอล.

Many clinical studies found evidences indicating that hyperlipidemia particularly total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) were related to atherosclerosis and coronary artery disease. Therefore, the reduction of these lipid levels would be statistically significant in helping prevent or reduce death rate from coronary artery disease.⁽¹⁻⁴⁾ At present, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III has determined the treatment method of hyperlipidemia by using LDL-C as its major target in treatment.⁽⁵⁻⁶⁾

Dietary supplement has become interesting alternatives as they believed to have fewer side effects than medications. Red yeast rice is the red rice derived from fermentation by culturing yeast, *Monascus purpureus* in rice. It has been used in China for centuries to make rice wine and to flavor foods. This fermented rice product is used as a medicinal food to improve blood circulation by decreasing cholesterol levels.⁽⁷⁾ Red yeast rice contains several monacolins, all of which have ability to inhibit the enzyme HMG-CoA (5-hydroxy-3-methylglutaryl coenzyme A) reductase which is an important enzyme in cholesterol synthesis pathway. In addition, red yeast rice also consists of unsaturated fatty acid and phytosterols that helps increase the efficacy for reduction of lipid level.⁽⁸⁾ Several randomized clinical trials using red yeast rice preparations with 3 - 10 mg/day monacolin K have demonstrated a significant cholesterol-lowering effect.⁽⁹⁻¹²⁾

Policosanols are a mixture of long chain alcohols, naturally found in sugar cane wax. The main component is octacosanol.⁽¹³⁾ The effect of policosanols is more controversial. Although several

clinical studies published by a Cuban research team have shown a reduction in LDL-C in subjects consuming policosanols,⁽¹⁴⁾ these results have not been confirmed elsewhere.⁽¹⁵⁻¹⁶⁾

Red yeast rice/policosanols supplements have been studied in many countries and showed cholesterol lowering effect, especially LDL-C, however there was no parallel study done in Thailand. This study is a cross-over study for testing the result of reduction level of cholesterol by red yeast rice/policosanols in comparison with placebo in Thai hypercholesterolemic patients.

Methods

Patients

This study is a randomized double-blind crossover, certified by the Human Research Ethics Committees of Chulalongkorn University (Certification of Research Project No. 189/2013) to collect data from hypercholesterolemic patients who came for treatment at outpatients internal medicine clinic, King Chulalongkorn Memorial Hospital from April to July, 2013. All participants gave their written informed consent before enrollment.

The patients who participated in the study were 20 - 80 years of age with their LDL-C level higher than 130 mg/dL; they had never been treated with hypolipidemic drugs; or had been treated with hypolipidemic drug; but had stopped the drug for at least one month before participating in the study. Women who were pregnant or breastfeeding were excluded as well as those who met any of the following exclusion criteria: acute coronary syndrome and being admitted to the hospital within three months before study, hypothyroidism, nephrotic syndrome, chronic

renal failure (serum creatinine > 1.5 mg/dL), active liver disease or hepatic dysfunction (AST and ALT enzyme > 2 times the upper limit of normal), creatine kinase (CK) > 3 times the upper limit of normal, known hypersensitivity to HMG-CoA reductase inhibitors, triglyceride > 400 mg/dL, patients who were treated with drug that affected lipid level such as progestogen, estrogen and corticosteroid within 6 weeks period before participating into the study, patients who took medicines, supplementary foods or herbs that affect red yeast rice and policosanol such as cyclosporine, erythromycin, gemfibrozil, diltiazem, itraconazole, grapefruit juice and anticoagulant.

Study design

After giving informed consent and taken 4 week washout period, fourteen hypercholesterolemic outpatients were randomly assigned with concealed allocation to receive either 2 capsules daily of red yeast rice/policosanol or 2 capsules daily of placebo for 4 weeks. Then there was a 4-week washout period followed by a crossover to the other treatment for another 4 weeks.

The dietary supplement was formulated as a capsule and administered 2 capsules once-daily. One capsule was composed of 100 red yeast rice extract (equivalent to 1.5 mg of monacolin K), 5 mg policosanol, 1 mg coenzyme Q10, 0.25 mg astaxanthin, and 0.1 mg folic acid. The placebo was rice-powder mimicking the color and the appearance of the active product.

Determination of biochemical parameters

Blood samples were taken after overnight

fasting at baseline, week 4, 8 and 16. All biochemical parameters including TC, HDL-C, TG, FBG, Scr, AST, ALT, and CK were measured by colorimetric methods. LDL-C was calculated by Friedewald equation.⁽¹⁷⁾

Data analysis

The hypothesis of this study is that red yeast rice/policosanol can reduce the level of LDL-C level more than placebo. By determining the power of analysis for 80%, it will be able to test the differences of LDL-C levels between two types of drugs at 15 mg/dL at 95% confidence level with calculated number of patients to 12.

The discrete data were presented as number and percentage; while the continuous data were presented as mean and standard deviation (mean \pm SD). Paired t-test was used to compare the mentioned parameters before and after the treatment. The parameters were significantly different when $p < 0.05$. The data analysis was performed by SPSS[®] software version 17. Analyses were based on the intention-to-treat in type of last observation carried forward.

Results

Characteristics of the subjects

Fourteen hypercholesterolemic patients participated in this study. However, one patient loss to follow up at week 16. As a result, the data from thirteen patients completed the study. The percentage of males and females was about equal. The age range was 32 - 77 years old with 57.6 years old as average. The characteristics of the patients are summarized in Table 1.

Table 1. Baseline characteristics of the subjects

Characteristics *	n = 14
Sex (n) (%)	
Male	7 (50)
Female	7 (50)
Age (year)	57.6 ± 14.2
Weight (kg)	67.2 ± 12.1
Body mass index (kg/m ²)	25.4 ± 5.4
Exercise (time/week)	3.64 ± 2.87
Coexisting disease (n) (%)	13 (92.9)
Laboratory measurement	
Total cholesterol (mg/dL)	239.1 ± 37.0
LDL-C (mg/dL)	164.5 ± 29.7
Triglyceride (mg/dL)	123.4 ± 38.2
HDL-C (mg/dL)	49.9 ± 13.5
AST (U/L)	20.9 ± 4.7
ALT (U/L)	21.4 ± 8.9
Creatine kinase(U/L)	166.1 ± 120.4

* Data are presented as mean ± SD

Reduction Result of Lipid Level

Change of lipid parameters from baseline in the 2 treatment group are reported in Table 2. Compared to placebo, red yeast rice/policosanol significantly decreased TC and LDL-C levels by 8.49% and 13.12% respectively. But placebo produced a slight increase in the levels of TC and LDL-C. There were no significant differences in mean TG and HDL-C from baseline in both groups.

During the study no adverse events were reported from both groups. Hepatic enzyme levels and creatine kinase at baseline and 4 weeks are shown in Table 3. There were no significant differences between red yeast rice/policosanol at baseline at 4 weeks

Discussion

The present study was aimed to compare the effects of red yeast rice/policosanol and placebo on cholesterol levels in hypercholesterolemic outpatients. We observed significant reduction of total cholesterol and LDL-C levels by 8.49% and 13.12% respectively at 4 weeks of red yeast rice/policosanol. In contrast, there were no significant changes in serum cholesterol in the placebo group. Reduction of TC and LDL-C in the present study were similar to other studies.^(18 - 20)

Red yeast rice contains monacolin K (lovastatin), well known as HMG-CoA reductase inhibitor, so it represents a natural statin.⁽⁸⁾ Other components in red yeast rice including phytosterols, monounsaturated fatty acid, isoflavone glycoside

Table 2. Change of lipid parameters from baseline in treatment group

Lipid parameter (mg/dL)	week	Red yeast rice/policosanols (n = 14)		Placebo (n = 14)	
		Level	Percentage change	Level	Percentage change
Total cholesterol	0	235.14 ± 37.77	-8.49 ± 10.65 [¥]	237.14 ± 31.27	4.56 ± 8.79
	4	213.64 ± 30.98 [¥]		247.29 ± 32.99	
LDL-C	0	162.09 ± 25.97	-13.12 ± 12.02 [¥]	163.16 ± 27.53	7.06 ± 12.05
	4	139.84 ± 22.00 [¥]		173.47 ± 27.17	
Triglyceride	0	121.36 ± 38.28	-2.09 ± 20.59 ^{NS}	112.07 ± 35.11	2.63 ± 22.98
	4	116.71 ± 36.30 ^{NS}		121.93 ± 34.70	
HDL-C	0	48.79 ± 12.78	3.95 ± 18.69 ^{NS}	49.57 ± 12.58	0.72 ± 7.87
	4	50.29 ± 13.41 ^{NS}		49.64 ± 12.07	

Data are presented as mean ± SD; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein

¥ = Significantly different from placebo group ($p < 0.05$) by paired t-test

* = Significantly different from placebo group ($p < 0.05$) by t-test for cross over analysis; NS = Non significant

Table 3. Safety parameters of subjects

Laboratory test Unit/liter	Red yeast rice/policosanols (n = 14)		Placebo (n = 14)	
	Baseline	Week 4 ^a	Baseline	Week 4 ^a
AST	21.21 ± 5.87	19.36 ± 3.89 ^{NS}	20.93 ± 4.63	21.07 ± 4.27 ^{NS}
ALT	22.57 ± 10.99	20.79 ± 7.53 ^{NS}	21.86 ± 8.25	23.07 ± 8.58 ^{NS}
CK	162.86 ± 115.67	125.79 ± 44.21 ^{NS}	147.57 ± 114.48	139.43 ± 62.13 ^{NS}

AST = Aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase

a = compared mean ± SD from baseline by paired t-test ; NS = Non significant ($p > 0.05$)

and anti-oxidants are reported to give synergistic effect for the hypolipidemic effect.⁽⁷⁾ Many studies investigated efficacy of red yeast rice in the hypercholesterolemic patients, and consistent 20-33% decrease of LDL-C has been demonstrated.⁽²¹⁻²⁴⁾ Our results, although not radically different, were slightly below those obtained in other studies. This may be explained by the daily amount of monacolin K used. We administered a daily dose of 3 mg while those studies used 5-10 mg/day. Moreover it contains

policosanols. Several clinical trials demonstrated lowering effects of policosanols 5-20 mg/day on lipid profiles in patients with hypercholesterolemia.⁽¹³⁾ However, these results were not confirmed by other authors and the effect of policosanols on lipid profile remains controversial.⁽²⁵⁻²⁷⁾

These outcomes suggest that natural products containing active principles represented by red yeast rice and policosanols could easily be used for improvement of lipid profile and it should be

recommended for patients with mild hyperlipidemia or in those who a hypolipidemic therapy is not well tolerated or contraindicated.

The limitations of our study included the small sample size and short duration, so adverse event which are uncommon and rare couldn't be detected. Long-term and more sample size studies are necessary to definitively determine the safety of red yeast rice and policosanol.

Summary

The reduction of cholesterol level after daily red yeast rice/policosanol dose of 200/10 mg/day for four weeks significantly see in reduced total cholesterol and LDL-C, and no significant differences were observed in TG and HDL-C. In addition, red yeast rice/policosanol in this dosage and duration had no effect on hepatic and muscle enzyme levels, fasting blood glucose, and kidney function. However, this study only provides 4 weeks of data and further studies on the long-term efficacy and safety of red yeast rice/policosanol in a larger Thai population are needed.

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