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Red Yeast Rice: An Easy Way to Lower Cholesterol

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Introduction

Mortality from cardiovascular disease is the leading cause of death in the industrial world (12). As hypercholesterolemia became a known risk factor for atherosclerosis and associated heart diseases, an interest increased in finding methods to manage elevated cholesterol. Research uncovered statins, potent inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting reaction in cholesterol synthesis (2). Due to this result, statins are widely used to treat patients with high serum low-density-lipoprotein (LDL) (15). Studies have shown that HMG-CoA reductase inhibitors reduce cardiovascular-related disease and death (12). However, due to the non-specificity of statins at the mevalonate level of cholesterol synthesis, parallel inhibition of coenzyme Q10 (ubiquinone) and dolichol occurs. As a result of the direct or indirect consequence of the CoQ10 deficiency, side effects resulting from treatment with statins include: myalgia, myopathies, rhabdomyolysis, gastrointestinal symptoms, and the initiation or accelerated progression of cataracts and neoplasia. Though these side effects can be alleviated with CoQ10 supplementation during treatment, the search for a more natural therapy with fewer complications began (2). The search took researchers back to 800 AD and the Tang Dynasty in China.

Red Yeast Rice

The cereal grass, rice is consumed throughout the world, particularly in Asia with China being recognized as one of the world's largest producers. Evidence of rice production in China occurs more than 11,000 years ago and the Chinese have used fermentation microorganisms to convert this agricultural product into foods for centuries. Red yeast rice, also known as red Koji or "Hongqu", is produced when red yeast (*Monascus purpureus*) is fermented on steamed rice. The use of this fermentation product is believed to date back more than a thousand years and was first documented in the Tang Dynasty in 800 AD. "Hongqu" has been recognized by folk medicine in improving food digestion and blood circulation. It was also reported by the great pharmacologist of the Ming Dynasty Li Shizhen to strengthen the spleen and dry the stomach (9). Commonly, it has been used to make rice wine, red soybean cheese, and for its medicinal properties. In addition, due to its tangy flavor, it has also been used to serve as a food additive to increase the color and taste of meat, fish, and soybean products (8). Red yeast rice is still a dietary staple in many Asian countries, including China and Japan as well as the Asian American community in the United States since World War II (8).

Red Yeast Rice and Statins

Though many Asian countries already used red yeast rice for its medicinal properties, chemical evidence for its ability to lower cholesterol was discovered in 1979 (4). Endo determined that a strain of *Monascus* yeast naturally produced an inhibitor of cholesterol synthesis, which he named monacolin K (also known as lovastatin), as well as 9 monacolin-related substances with the ability to inhibit HMG-CoA reductase. Red yeast rice was also found to contain sterols, isoflavones and isoflavone glycosides, and monounsaturated fatty acids (8). Since red yeast rice naturally contains HMG-CoA

reductase inhibitors, statins, the use of red yeast rice in treating hypercholesterolemia was warranted. Currently, in the United States Chinese red yeast rice preparations manufactured by growing a single strand of *Monascus purpureus* on rice under conditions that increase statin content, are sold as a dietary supplement in pill form (10).

Evidence that Red Yeast Rice Reduces Cholesterol

The first human study, done in China, involved 324 hypercholesterolemic patients treated with Xuezhikang (a traditional Chinese medicinal preparation of red yeast rice) at a dose of 1.2 g/d providing 13.5 mg total monacolins for 8 weeks. The resultant serum cholesterol concentrations decreased by 23%, triacylglycerols decreased by 36.5% and high-density lipoprotein (HDL) cholesterol concentrations increased by 19.6% (16). The results of this study may have been skewed due to the different natural preparations in the comparison group rather than a matched placebo capsule (8). In addition, this landmark study cited in several publications indicating the efficacy of red yeast rice as a treatment for hypercholesterolemia may not be applicable to patients in the United States as the content of Xuezhikang may differ from the red yeast rice dietary supplements available in U.S. stores.

In another study, 83 men and women aged 34-78 with hyperlipidemia (total cholesterol, 204-338 mg/dL); LDL cholesterol 128-277 mg/dL; triacylglycerol, 55-246 mg/dL; and HDL cholesterol 30-95 mg/dL were treated with red yeast rice (2.4 g/d) or placebo for 12 weeks. This study was double-blind, randomized, and controlled for diet by instructing all participants to comply with the American Heart Association Step I diet. As a result of treatment with red yeast rice, total cholesterol concentrations decreased significantly between baseline and week 8 in the red yeast rice treated group compared to the placebo-control group (254 +/- 36 mg/dL to 208 +/- 31 mg/dL; $P < 0.001$). LDL concentrations and total triacylglycerol were also reduced with the supplement though the placebo group did not experience any significant difference in total cholesterol, LDL concentration, or total triacylglycerol, between baseline and weeks 8 or 12. Furthermore, neither group experienced a significant difference in HDL concentration throughout the study (8). The results of this well-controlled study established the beneficial effects of red yeast rice on cholesterol and triacylglycerol levels. However, the inconsistency with the results of the effects on HDL concentration between this study and that by Wang et al. increase the assumption that Xuezhikang probably has a different chemical make-up than that available as red yeast rice in the U.S.

Qin et al., (13) in a placebo-controlled, randomized trial treated 70 elderly hyperlipidemic patients with Cholestin, a Chinese red yeast rice preparation, at 1.2 g/d. After an 8 week trial period, Cholestin was found to have reduced serum total cholesterol by 25.9% and LDL cholesterol by 32.8% (both $P < 0.001$) and lowered triacylglycerols by 19.9% ($p = 0.02$). A similar experiment conducted by Rippe et al. (14) also evaluated the effects of an 8 week trial of Cholestin though this trial increased the dosage to 2.4 g/d. After the course of treatment with Cholestin on 187 subjects with mild to moderately elevated levels of cholesterol, total cholesterol was reduced by 16.4%, LDL cholesterol by 21% and triacylglycerols by 24.5%. Unlike the previous U.S. trials conducted, this study reported an increase in HDL concentration by 14.6% when compared with the placebo

group. This inconsistent finding raises suspicion with the results of the studies and begs the question whether or not the studies all used red yeast rice with the same statin content.

A recent randomized, double-blind, placebo-controlled pilot study involving twelve adult participants with dyslipidemia related to HIV completed an 8 week treatment with Cholestin. At the end of the trial, significant declines from baseline were found in the mean fasting total cholesterol, and LDL cholesterol versus placebo (both $P=0.01$). However, HDL and triacylglycerol levels did not change (10). Although the results of this study are encouraging in finding a treatment for dyslipidemia in HIV patients its results are met with caution due to small sample size and short treatment interval.

Statin Content Insufficient to Explain Effect of Red Yeast Rice on Cholesterol

A multitude of studies show that red yeast rice and its preparation, Cholestin have antihypercholesterolemic effects as well as antihypertriglyceridemic effects (3,5). However, given that Cholestin has a 0.4% content by weight of statin, the highest Cholestin dosage administered in these studies (2.4g/d) delivered only approximately 5 mg of lovastatin (monacolin K) per day. In comparison to efficacy evaluations of lovastatin, comparable levels of cholesterol reduction were seen with dosages of lovastatin ranging from 20 to 80 mg/d. This suggests that the results seen with treatment of red yeast rice are likely the combined effects of monacolins, plant sterols, and other substances in the red yeast rice supplement (1). However, the exact mechanisms by which the individual components of Cholestin act to reduce cholesterol are unknown. Nevertheless, as a result of the antihyperlipidemic effects of the Chinese red yeast rice contained in Cholestin, this supplement has the potential to impact the process of atherosclerosis (6) and serve as a potent therapy to reduce the risk of cardiovascular disease.

Side Effects of Red Yeast Rice

Considering that red yeast rice contains statins it is reasonable to believe that this supplement could potentially have the same negative side effects as conventional statin therapy. In the above study of Cholestin treated HIV patients the associated adverse reactions were 18% and included headache, abdominal bloating, and gas. However, no or few adverse effects were reported in the studies by Heber et al. and Qin et al. In addition, many clinical trials involving thousands of participants undergoing Cholestin treatment did not experience any significant changes in tests of kidney and liver function, though a few cases of mild gastrointestinal discomfort were reported. As a result, red yeast rice preparations shows promise as a more natural, less toxic method to manage hypercholesterolemia (10). Evaluation of these findings, further suggest that red yeast rice and its natural monacolins may act to inhibit cholesterol synthesis in a mechanism different than that mediated by statin.

Efficacy of Red Yeast Rice

Due to the inconsistency in the results of some trials regarding HDL concentrations and the fact that dietary supplements are not controlled, a study was conducted to determine the variability in content between different red yeast rice supplements available in the

United States. This study set out to determine whether the red yeast rice supplements available contained the same amount of monacolin K (Lovastatin) as well as the total content of monacolins. Analyses demonstrated variation in the content of Monacolin K between 0.15 and 3.37 mg per capsule. In addition, while one strain of Chinese red yeast rice containing 10 different monacolins was demonstrated to lower cholesterol levels significantly in clinical trials in China and the United States (8), other Chinese red yeast rice supplements were found to vary in their total content of monacolins from 0% to 0.58% and only one of the nine preparations analyzed had the full complement of ten monacolins (7). Thus, the results of trials utilizing a defined red yeast rice preparation containing 10 different monacolins cannot be generalized to other preparations that do not contain the same levels and distributions. As a result, though the above trials demonstrate the cholesterol lowering effect of the red yeast rice used, these results may not be applicable to red yeast rice supplements available in stores. Furthermore, it should be cautioned that given the large discrepancy in statin content the low side effects reported in past studies also can not be applied to all preparations available.

Conclusion

Though the use of red yeast rice has been dated back to 800 AD its medicinal value is just now being accepted in the Western world. Given its potent inhibition of HMG-CoA reductase and thus, cholesterol synthesis, red yeast rice shows promise as an antihypercholesterolemic treatment. In addition, the absence of any deleterious side effects increases its potential for usage in healthy adults and those with dyslipidemia related to HIV who would suffer further under conventional statin treatment. Currently, Chinese red yeast rice preparations cost \$20-\$30 per month, whereas for those without adequate medical coverage cholesterol-lowering drugs can cost \$120-\$300 per month with an average cost of \$187 per month. Thus, while the cost per month in the above studies was 87% less than that for conventional lipid-lowering drugs, with medical insurance the cost difference can be negligible.(11). When cost, efficacy, and safety are combined red yeast rice preparations may be a viable alternative in the prevention and treatment of patients with hypercholesterolemia and at risk for atherosclerosis and related cardiovascular disease.

With the effect of red yeast rice on cholesterol now realized, further investigations are needed to identify the components other than statins that are responsible for its lipid lowering effects. Additionally, given the potential for Cholestin to inhibit cholesterol synthesis in a different mechanism, more studies are necessary to determine the pathways and levels other than that inhibited by statins, which Cholestin affects (11). Given the differences in the outcomes of HDL concentrations the effects of red yeast rice on this positive health indicator should be studied further. Moreover, given that dietary supplements are not regulated by the FDA and many red yeast rice preparations being sold may not be as efficacious or safe as those tested, standardized manufacturing practices should be established if we are to fully realize the potential of Chinese red yeast rice. Until then, we will continue our battle of cholesterol management with the aid of lipid-lowering drugs, exercise, and a program of rigorous diet.

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