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Red Yeast Rice

DESCRIPTION

Red yeast rice refers to the product of fermentation of rice with various strains of the yeast *Monascus purpureus* (Went). Red yeast rice has been used for centuries in China in foods and in medicines. It was introduced in the U.S. during the latter half of the 1990s as a dietary supplement for the promotion of healthy serum lipid levels. However, because it contains the HMG-CoA reductase inhibitor lovastatin, among other things, the U.S. FDA has contended that it is not a dietary supplement, but an unapproved drug. Presently, it is unclear what the final determination of this product will be; dietary supplement or unapproved drug.

The use of red yeast rice was apparently first noted in the Tang dynasty and was introduced to Taiwan by wine makers of Fukien about a century ago. It is used by the Chinese as a coloring agent in the preparation of foods, including fish, fish sauce, fish paste, rice wine (fu chiu), red soybean curd (hung-lu chiu, a cheese-like product used as a spice), pickled vegetables and salted meats. In addition to adding color, it adds flavor to foods. It has also been used in Chinese folk medicine for treating indigestion, diarrhea, and for improving blood circulation, among other things.

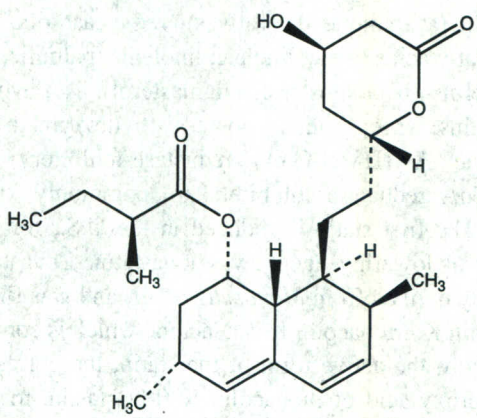
In addition to natural pigments such as monascorubin and monascin (azaphilone derivatives), red yeast rice contains starch, fatty acids (oleic, linoleic, linolenic, palmitic, stearic), phytosterols (beta-sitosterol, stigmasterol), isoflavones and monacolins. Monacolins possess hydroxymethyglutaryl coenzyme A (HMG-CoA) reductase-inhibitory activity. HMG-CoA reductase inhibitors are commonly known as statins. The first statin introduced in the U.S., for use as a cholesterol lowering agent, was lovastatin. Lovastatin was originally derived from *Monascus ruber*, and was first called monacolin K. Monacolin K is a lactone which is converted in the body to the active form of the statin, the corresponding beta-hydroxy acid of monacolin K (lovastastin, mevinolin).

The proprietary red yeast rice product that was first introduced in the U.S. was processed to yield 0.4% HMG-CoA reductase inhibitors in the final product. In addition to monacolin K or lovastatin, which comprises 0.2% of this product, it contains the corresponding beta-hydroxy acid of monacolin K at a concentration of 0.1%, and much smaller amounts of dihydromonacolin, monacolin I, monacolin II (hydroxy acid form), monacolin III, monacolin IV, monacolin V and monacolin VI, to give a total of 9 HMG-CoA reductase inhibitors. Traditional red yeast rice does not contain as high an amount of these substances. The yeast in red yeast rice is inactive.

The legal status surrounding red yeast rice as a dietary supplement has become an ongoing battle. In May, 1998, the FDA determined that the proprietary red yeast rice was an unapproved drug and not a dietary supplement. The FDA argued that although red yeast rice had been used as a food product for many years, neither it nor lovastatin were marketed as dietary supplements prior to the drug approval of the lovastatin drug product in 1987. They further argued that because of that situation, the product would not be covered under the Dietary Supplement Health and Education Act (DSHEA) which was passed in 1994. This meant that the product would be regulated by the FDA.

The manufacturer of the proprietary product argued that the FDA approved the lovastatin drug product and not the drug active (lovastatin) and also, that the product is a food product that had been used for centuries in China and thus, would fall under DSHEA. In February, 1999, the Federal District Court in Utah ruled against the FDA, stating that the proprietary red yeast rice product was not a drug but a dietary supplement. This decision came about as a result of a law suit brought by the manufacturer against the FDA. In the most recent legal turn of events, the 10th U.S. Circuit Court

of Appeals ruled on July 24, 2000 that the proprietary red yeast product *is* subject to regulation by the U.S. FDA. The future of red yeast rice as a dietary supplement is unclear. Lovastatin has the following structural formula:



Lovastatin

Red yeast rice is known by various names, including Chinese red yeast rice, red rice, *Monascus purpureus*-fermented rice, red yeast, anka, ang-kak, ankak, angquac, beni-koji, beni-Jiuqu, aga-Jiuqu, aka-koji, xuezhikang, hung-chu and hongqu.

ACTIONS AND PHARMACOLOGY

ACTIONS

Red yeast rice may have hypocholesterolemic and hypotriglyceridemic activities in some.

MECHANISM OF ACTION

The mechanism of the hypolipidemic activity of red yeast rice is not entirely clear. The possible hypocholesterolemic activity of red yeast rice can be accounted for, in part, by the presence of HMG-CoA reductase inhibitors, especially monacolin I (lovastatin, mevinolin) and its corresponding beta-hydroxy acid, monacolin II. Lovastatin is converted in the body to its corresponding beta-hydroxy acid, which is the form that inhibits HMG-CoA reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in cholesterol biosynthesis. Lovastatin is known to lower plasma total cholesterol, low-density lipoprotein cholesterol (LDL-C), the total cholesterol/HDL-C ratio and the LDL-C/HDL-C ratio. Lovastatin may also produce a modest increase in HDL-cholesterol and modest decreases in VLDL-C and triglyceride levels in some.

LDL is formed from VLDL and is principally catabolized via the high affinity LDL receptor. Lovastatin's mechanism in lowering LDL appears also to involve reduction of VLDL-C levels and upregulation of the LDL receptor, resulting in reduced production of LDL-C, as well as increased catabolism of LDL-C.

The hypolipidemic effects of red yeast rice have been found to be greater than those obtained from equivalent doses of the pharmaceutical form of lovastatin. To be clear about this, the amount of lovastatin delivered by red yeast rice is typically 7.2 milligrams. The amount of lovastatin in the pharmaceutical form of lovastatin ranges from 10 to 40 milligrams. It is unclear why a lovastatin dose of 7.2 milligrams in red yeast rice appears to have more potent lipid-lowering activity than higher doses of pharmaceutical lovastatin. It is speculated that other substances in red yeast rice besides the HMG-CoA reductase inhibitors may have lipid-lowering activity themselves or may work synergistically with the HMG-CoA reductase inhibitors. What these substances are and how they may work synergistically with the HMG-CoA reductase inhibitors is entirely unclear. Beta-sitosterol (see Beta-Sitosterol) is found in red yeast and it is known to have hypocholesterolemic activity. However, the amount of this substance found in red yeast rice is too small to make much of a cholesterol-lowering contribution.

PHARMACOKINETICS

There is little on the pharmacokinetics of red yeast rice in humans. However, the pharmacokinetics of lovastatin, which appears to be the principal bioactive substance in red yeast rice, are known. The efficiency of absorption of lovastatin is approximately 30%. The efficiency of absorption is greater when it is given with food. Following absorption, lovastatin is transported to the liver via the portal circulation where it undergoes extensive first-pass extraction. The liver is the principal site of action of lovastatin. Less than 5% of an oral dose of lovastatin reaches the systemic circulation. Lovastatin is metabolized in the liver to its corresponding beta-hydroxy acid, which is the active HMG-CoA reductase inhibitor. In addition to the beta-hydroxy acid of lovastatin, lovastatin is metabolized to a few other metabolites, including its 6′-hydroxy derivative. Lovastatin is metabolized by the cytochrome P450 3A4 system. Excretion is mainly via the biliary route. Approximately 83% of an oral dose of lovastatin is excreted in the feces (biliary excretion and unabsorbed lovastatin), and approximately 10% is excreted in the urine.

INDICATIONS AND USAGE

Red yeast rice may have favorable effects on lipids, lowering cholesterol and triglycerides in some. However, there is an ongoing legal issue regarding the status of red yeast rice, particularly those preparations that contain statins, as a dietary supplement.

RESEARCH SUMMARY

Recent clinical studies have demonstrated that red yeast rice can significantly lower triglyceride and cholesterol levels in some individuals. In one multi-center, randomized, single-blind trial of the substance in 502 patients with hyperlipidemia, there was a 17% reduction of total cholesterol in the treated group. LDL-cholesterol was reduced an average of 24.6%, and serum triglyceride levels fell an average of 19.8%. HDL-cholesterol rose by 12.8% in the treatment group.

These results were measured after four weeks of treatment. Dosage was 600 milligrams of red yeast rice twice daily for a total of 1,200 milligrams daily. At the end of eight weeks of red yeast rice supplementation, still better results were reported for the treatment group: total cholesterol reduced by 22.7%, LDL-cholesterol reduced by 30.9%, triglycerides reduced by 34.1%, HDL-cholesterol increased by 19.9%.

In another recent study, this one conducted in a double-blind, placebo-controlled fashion, 83 hyperlipidemic subjects who were not being treated with lipid-lowering drugs were randomized to receive red yeast rice, 2.4 grams daily, or placebo. Subjects were instructed to consume a diet deriving 30% of energy from fat (with no more than 10% of this from saturated fat and no more than 300 milligrams of cholesterol daily).

The study continued for 12 weeks. Red yeast rice was found to significantly reduce total cholesterol, LDL-cholesterol and total triacylglycerol concentrations, compared with placebo. HDL-cholesterol was not affected in this study. Research is ongoing. Also ongoing is the legal issue regarding the status of lipid-lowering red yeast rice as a dietary supplement.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Red yeast rice is contraindicated in those who are hypersensitive to any component of a red yeast rice-containing product. Red yeast rice is also contraindicated in pregnant women, nursing mothers, women of childbearing age who are likely to conceive, those with active liver disease and those with unexplained aminotransferase (transaminase) elevations.

PRECAUTIONS

Since the principal bioactive substance in red yeast rice is lovastatin, all of the warnings, precautions and interactions of pharmaceutical lovastatin apply to red yeast rice, as well.

The use of red yeast rice for the management of hyperlipidemia must be medically supervised.

Those with a past history of liver disease and those who routinely use alcoholic beverages should exercise caution in the use of red yeast rice.

Lovastatin and other HMG-CoA reductase inhibitors occasionally cause myopathy. This is manifested as muscle pain or weakness associated with elevated levels of creatine kinase. Rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time. Those using red yeast rice should report promptly to their physicians unexplained muscle pain, tenderness or weakness.

Bleeding and/or increased INR values have been reported in a few patients taking warfarin concomitantly with lovastatin.

Persistent increases (to more than 3 times the upper limit of normal) in serum aminotransferases (transaminases) occurred in 1.9% of adults who received lovastatin for at least one year in some early clinical trials. It is recommended that liver tests be performed before starting red yeast rice, at 6 and 12 weeks after starting its use, and periodically thereafter.

Lovastatin has been reported to lower coenzyme Q (CoQ_{10}) levels.

ADVERSE REACTIONS

In clinical studies of red yeast rice, few adverse reactions were reported. Adverse reactions reported, included flatulence and heartburn. There is one report of anaphylaxis resulting from inhalation of red yeast rice. Adverse reactions from the pharmaceutical form of lovastatin, include elevated liver tests, elevated creatine kinase levels (noncardiac), myopathy and liver dysfunction. Overall, lovastatin is generally well tolerated; adverse reactions usually have been mild and transient.

INTERACTIONS

DRUGS

Azole antifungals (fluconazole, ketoconazole, itraconazole): Concomitant use of red yeast rice and an azole antifungal may increase the risk of myopathy.

Cyclosporine: Concomitant use of red yeast rice and cyclosporine may increase the risk of myopathy.

Fibrates (clofibrate, fenofibrate): Concomitant use of red yeast rice and a fibrate may increase the risk of myopathy.

Gemfibrozil: Concomitant use of red yeast rice and gemfibrozil may increase the risk of myopathy.

Macrolide antibiotics (clarithromycin, erythromycin): Concomitant use of red yeast rice and certain macrolide antibiotics may increase the risk of myopathy.

Nefazodone: Concomitant use of red yeast rice and nefazodone may increase the risk of myopathy.

Protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir): Concomitant use of red yeast rice and a protease inhibitor may increase the risk of myopathy.

Statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin): Concomitant use of red yeast rice with a pharmaceutical statin may increase the risk of adverse reactions.

Warfarin: Concomitant use of red yeast rice and warfarin may result in an increase in the INR as well as bleeding.

NUTRITIONAL SUPPLEMENTS

Nicotinic acid: Concomitant use of red yeast rice and high doses of nicotinic acid may increase the risk of myopathy.

FOODS

Grapefruit juice: Grapefruit juice contains some substances, such as the furanocoumarin bergamottin, which inhibit cytochrome P450 3A4, the enzyme that metabolizes lovastatin, among other substances. Therefore, concomitant use of red yeast rice and grapefruit juice may increase the risk of myopathy.

Meals: When lovastatin was given under fasting conditions, plasma concentrations of lovastatin and its active metabolite were on the average two-thirds those found when lovastatin was administered immediately following a meal.

OVERDOSAGE

There are no reports of overdosage with red yeast rice. A few cases of accidental overdosage have been reported with the pharmaceutical form of lovastatin. The maximum dose taken was 5-6 grams. No patients had any specific symptoms and they completely recovered.

DOSAGE AND ADMINISTRATION

Red yeast rice is currently available in single ingredient and combination products. The red yeast rice dietary supplements are standardized to 0.4% HMG-CoA reductase inhibitors, with 0.3% coming from lovastatin equivalents. A dose of 2,400 milligrams daily delivers 9.6 milligrams of HMG-CoA reductase inhibitors, including 7.2 milligrams of lovastatin equivalents. Red yeast rice typically comes in 600 milligram capsules. The usual dose has been 2,400 milligrams daily. See Precautions.

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Resistant Starch

DESCRIPTION

Resistant starch is defined as the starch and starch degradation products that, on average, resist digestion in the small intestine. And, since resistant starch has similar physiological and metabolic features, like those of soluble and insoluble dietary fibers, resistant starch is now considered one of the three types of dietary fibers, along with soluble fiber and insoluble fiber. (See Pectin, Psyllium and Oat Beta-Glucan).

Starch represents the primary energy source for many animals, including humans. The rate of starch digestion and glucose release and absorption play major roles in human health by helping maintain normal plasma glucose and insulin levels. There are various ways of classifying native starches, including based on the structure as determined by X-ray diffraction, based on the rate of digestion and based on nutritional characteristics. Based on the rate of digestion, starch is classified as rapidly digestible starch (RDS), slowly digestible starch (SDS) and resistant starch (RS). RDS typically leads to rapid increases in plasma glucose and insulin levels. SDS leads to a moderate glycemic and insulinemic response and decreased excursions of plasma glucose when compared with RDS. Chronic consumption of foods with high levels of RDS can cause substantial fluctuations in glucose homeostasis, which is associated with a number of health conditions, including diabetes, obesity