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REVIEW of THE STUDIES on THE RED YEAST RICE (*Monascus purpureus*)

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Abstract

Monascus purpureus is a red mold species which may be cultivated on starch containing substrates. The solid state fermentation of rice by Monascus has a long tradition in East Asian countries which dates back at least to the first century A.D. For centuries fermented rice products such as red yeast rice have been consumed in Asia and Indonesia as dietary staples and food additives. It is formed during the fermentation of rice and it is called as in China 'Ang Khak' or 'Hong Qu' (pronounced approximately 'Hong Zhu' (rhymes with French 'rue'). The Japanese know the product under the name Koji, Ang-Khak, Beni-Koji, Red-Koji, Rotschimmelreis (in Europe) or Red Mould (in the USA).

Red yeast rice is used as food or food additives. Red yeast rice, an Asian dietary staple made by fermenting yeast (*Monascus purpureus*) on rice, is rapidly gaining recognition as a cholesterol-lowering agent in United States. Indonesia, Japan, Taiwan, and Philippine people are been used as Monascus-nata complex. It is used as coloring and flavoring agents and also reduces total cholesterol, hyperlipidemia. Other exciting applications for red yeast rice are suggested by recent discoveries that lovastatin and other statin drugs may be useful for treating or preventing cancer, osteoporosis, stroke, Alzheimer's disease and other dementias, and macular degeneration.

Key Words: *Monascus purpureus*, red mold species, Ang Kak, Koji, starch

Introduction

Historical and traditional use of *Monascus purpureus*

Monascus purpureus is a red mold species which may be cultivated on starch containing substrates. The solid state fermentation of rice by Monascus has a long tradition in East Asian countries which dates back at least to the first century A.D. (Meyer, 1990). For centuries fermented rice products such as red yeast rice have been consumed in Asia

and Indonesia as dietary staples and food additives. In Japan red yeast rice is known as beni-koji and its pigment is widely used as food coloring. Red yeast rice has also been used in China, Taiwan, Okinawa, and the Philippines as a preservative for meat and fish, for adding color and flavor to food, and even for brewing wine and liquor. Interestingly, red yeast rice is also mentioned in an ancient Chinese pharmacopoeia of medicinal foods and herbs, the Ben Cao Gang Mu of Li Shi-zhen, where it is described as a medication useful for improving digestion and revitalizing the blood (Heber et al. 1999). A health promoting effect is ascribed traditionally to the product, thus in a book on Chinese medicine published in Beijing in 1590 by Li, Shin-Chun (1590). The first accounts of this mould appeared more than 2000 years ago in the monograph by Li-Shin-Chun (1590). This book describes the utilization of a pigment as a coloring agent and as a medicine in the treatment of various diseases.

The fermentate is obtained as scarlet to purple red grains which have the original rice grain structure well preserved. It is formed during the fermentation of rice and it is called as in China 'Ang Khak' or 'Hong Qu' (pronounced approximately 'Hong Zhu' (rhymes with French 'rue'). The Japanese know the product under the name Koji, Ang-Khak, Beni-Koji, Red-Koji, Rotschimmelreis (in Europe) or Red Mould (in the USA) (Bakosova et al. 2001).

Up to now, this mould is still used because of its coloring and flavoring properties, in the food industry of many Asian countries for processing of poultry, fish, and meat products. The main application is however, as a food additive, in particular to meat as a preservative and condiment. Its use in the rice wine manufacture is due to its high content of alpha-amylase which promotes the conversion of starch into glucose. The attractive red color of rice wine is caused by Monascus pigments. Monascus became known in Europe through the investigations of Dutch scientist who observed the use of red mold rice by the population in Java. They isolated and classified various Monascus species botanically (Tieghem, 1884; Went, 1895).

The Botanical Data, Active Constituents and The Pigments of *Monascus purpureus*

A special group of natural pigments includes coloring agents produced by micro-organisms. The typical representatives of this group are the pigments of the mould *Monascus spp.* belonging to family *Aspergillaceae*, the genus *Monascus* (Slugen et al. 1997). The mould belongs to the polycetides and has a slight bactericidal effect. The

production of pigments by this mould was studied by Evans and Wang (Evans and Wang, 1987) and Juzlova (Juzlova et al., 1994). The mixtures of pigments are stable from the chemical point of view. As reported, the group includes the orange pigments called Monascorubin and Rubropunctatin, the yellow pigments called Monascin and Ankaflavin, and the red pigments called Monascorubramin and Rubropunctamin (Meyer, 1990; Margalith, 1992). Furthermore, the mould also contains another substance belonging to the polycetides- Mevinolin (Lovastatin, Monacolin and Mevacor). This is commonly used as a medicine in the therapy of hypercholesterolemia (Chen and Johns, 1993). *Monascus spp*. has been well known for red pigment production but less study was investigated for yellow pigment production. A *Monascus purpureus* mutant strain-YLC1 was obtained for yellow pigment production (Chen and Johns, 1993; Evans and Wang, 1987).

Various uses of *Monascus purpureus*

Red yeast rice is one traditional Chinese material that has been shown in animal and pilot human studies to effectively lower serum lipid levels. Red yeast rice, also known as *Monascus purpureus* rice, is derived from the strain of *M. purpureus* Went yeast and is prepared by a traditional rice fermentation method. It has been shown that red yeast rice contains compounds with HMG-CoA reductase inhibitor activity, which is responsible for the inhibition of cholesterol synthesis in the liver. In addition to rice starch, protein, fibre, sterols, and fatty acids, red yeast rice contains numerous active constituents, including Monacolin K, dihydromoncolin, and Monacolin I to VI. Researchers have determined that one of the ingredients in red yeast rice, called monacolin K, inhibits the production of cholesterol by stopping the action of a key enzyme in the liver (e.g., HMG-CoA reductase) that is responsible for manufacturing cholesterol. Among many other things, red yeast rice contains at least nine substances that are similar in structure to the active ingredients in statin drugs. These substances inhibit the activity of the enzyme necessary for the body's production of cholesterol (Heber et al. 1999).

Red yeast rice also contains unsaturated fatty acids that may also help reduce serum lipids (Wang, 1997). Red yeast rice extract may help to reduce total cholesterol levels, lower levels of LDH (bad) cholesterol, increase levels of HDL (good) cholesterol, and lower the level unhealthy fats called triglycerides. It appears to accomplish this by

restricting the liver's production of cholesterol itself. Interestingly, the compound responsible for the effect-mevinolin is chemically identical to the cholesterol-lowering compound lovastatin, sold as the prescription drug Mevacor. Mevinolin is also similar to the active ingredients in such cholesterol medications as Zocor (simvastatin) and Lipiton (atorvastatin). Unsaturated fatty acids in red yeast rice extract are also believed to help, possibly in lowering triglycerides (Heber, 1999; Wang et al. 1997; Qin et al. 1998).

There's still another reason for regarding red yeast rice as a food, and that is the fact that the product contains many other synergistic nutrients with lipid-lowering properties in addition to monacolins. For example, red yeast rice has been reported to contain sterols such as beta-sitosterol and campesterol (Heber et al. 1999), which are known to interfere with cholesterol absorption in the intestines (Moghadasian and Frohlich, 1999). Effects of dietary phytosterols on cholesterol metabolism and atherosclerosis: clinical and experimental evidence. The combination of such dietary sterols with statin drugs has in fact been suggested as a more effective means of lowering cholesterol than statins alone (Plat and Mensink, 2001) so it makes sense to consume a single food which naturally combines both kinds of anti-cholesterol activity. Red yeast rice also contains fiber, trace elements such as magnesium, unsaturated fatty acids such as oleic, linoleic, and linolenic acids (Ma et al. 2000) and B-complex vitamins such as niacin (Palo et al. 1960) all of which have known benefits in decreasing serum lipids such as triglycerides and cholesterol.

Red yeast rice, an Asian dietary staple made by fermenting yeast (*Monascus purpureus*) on rice, is rapidly gaining recognition as a cholesterol-lowering agent in United States. Indonesia, Japan, Taiwan, and Philippine people are been used as Monascus-nata complex (Sheu et al. 2000).

Fermentation conditions for coloration

Carbon source, nitrogen source, and pH have been shown to influence pigment production by *Monascus purpureus* (Su, 1978; Wong et al. 1981; Lin and Demain, 1991; Chen and Johns, 1993).

The microorganisms used for fermenting red yeast rice are various species of a filamentous fungus known as Monascus. The Monascus group includes *M. anka*, *M. ruber*, and a strain of *M. ruber* known as *M. purpureus*, among others. (Ruber and

purpureus are the Latin words for red and purple, respectively.) These fungi can produce an intense red pigment as well as other metabolic byproducts when cultivated on cooked nonglutinous rice (Ma et al. 2000; Su, 1978; Wong et al. 1981).

Monascus sp. 94-25 strain was isolated from red rice with the purpose of red pigments sub-merged production. Morphological characterization on the taxonomically important for the genus media showed that the strain produced cleistothecia with oval ascospores and aleiroconidia. Comparison with a referent strain Monascus purpureus Went 109.07 was made and it was proved that there were no considerable differences between both strains. Monascus sp. 94-25 was a prototroph and had optimal growth temperature 34^{o}C. Investigation of the fermentation and assimilation capacity of both strains was performed. It was found that both of them assimilated well glucose, while highest fermentation ability was observed when grown on galactose. Similarly to the referent strain Monascus sp. 94-25 could grow on starch and protein containing natural substrates. Regarding the morphological and biochemical investigations the newly isolated strain 94-25 could be considered as Monascus purpureus (Rasheva et al. 1998, Qin et al. 1998).

Pharmacological effects of Monascus fermentate

Scientific investigations have confirmed pharmacological effects of Monascus fermentate (Endo and Monacolin, 1980) isolated from *Monascus ruber* a metabolite, Monacolin K which normalized an artificially induced hyperlipoproteinemia in rats. The reduced from of Monacolin K, Mevinolin has meanwhile been introduced as a cholesterol reducing pharmaceutical (by Merck, Sharp and Dohme). Also simple extracts of *Monascus purpureus* fermentate lower the cholesterol, the HDL cholesterol and the triglyceride value in the blood of rats with and induced hyperlipoproteinemia (Fink-Gremmels and Leistner, 1989). The observed effect is weaker than in pharmaceutical preparations and is rather comparable to the effect of certain spices e.g. of garlic (Hansel and Haas, 1984). A Japanese patient (Japan Kokai, 1985) describes the blood pressure lowering by Monascus fermentate itself and by an alcoholic extract thereof.

Monascus extract is marketed in Japan as a dietetic product (under the name Monacolin by Maruzen). The preservative effect of Monascus fermentate has also been confirmed by scientific investigation. Monascidin A, a component isolated from *Monascus*

purpureus cultures inhibits bacteria of the genera *Bacillus*, *Streptococcus* and *Pseudomonas* (Wong and Bau, 1977; Wong and Koehler, 1981; Bau, 1977). Two yellow pigments from *Monascus purpureus* had in low concentration a bacteriostatic function against *Bacillus subtilis* (Wong and Koehler; 1981). Chen (1993) was observed an inhibitory effect in particular against *Staphylococcus aureus.* Further research on the bacteriostatic effect of Monascus fermentate was carried out by Fink-Gremmels et al. 1991 and Leistner and Dresel, 1991. Gram positive bacteria are generally stronger inhibited than gram negative ones. Lactobacillus is not affected. The observation of bacteriostatic effects has lead to the consideration to use Monascus fermentate at least partially as a substitute for nitrite in meat preservation (Fink-Gremmels et al., 1991).

A scientific proof of the flavor enhancing properties of Monascus fermentate is difficult to obtain. However, in a tasting panel tasters called Monascus containing noodles "more salty" then normal noodles although there was actually no difference in the salt content. Monascus extract containing meat products were generally classified as better tasting than comparable products without Monascus (Fink-Gremmels et al., 1991). One may speculate that the relishing effect of Monascus could be caused by flavor enhancing oligopeptides produced by a partial hydrolysis of rice proteins by Monascus enzymes. For the strong color of Monascus fermentate a number of yellow, red, and orange colored pigments are responsible. The pigments are secondary metabolites of the Monascus fermentation; they belong chemically to the group of Azaphilones which are typical fungus metabolites. The chemical structure of most of them is known. Depending on whether the yellow or red pigments predominate or are absent, the colors of *Monascus purpureus* varies from orange yellow to scarlet to purple red. The color can be influenced by the culture conditions, in particular by the pH value and by the phosphorus and nitrogen source in the substrate (Meyer, 1990).

The other medicinal studies about red yeast rice

Along with its evaluation in animal trials (Li et al, 1998), red yeast rice has been clinically investigated as a therapy for reducing cholesterol in two human trials. In one study, both men and women taking 1.2 g (approximately 5 mg total monacolins) of red yeast rice per day for two months had significant decreases in serum cholesterol levels (WANG et al., 1997). In addition, persons taking red yeast rice had a significant

increase in HDL (good) cholesterol and a decrease in LDL (bad) cholesterol. Elevated triglycerides were also found to be lowered (Qin et al. 1997-1998).

Heber et al., (1999), evaluated the lipid-lowering effects of red yeast rice dietary supplement in US adults separate from effects of diet alone. Eighty-three healthy subjects with hyperlipidemia and HDL cholesterol who were not being treated with lipid-lowering drugs participated. Subjects were treated with red yeast rice (2.4 g/d) or placebo and instructed to consume a diet providing 30 % of energy from fat, <10% from saturated fat, and <300 mg cholesterol daily. Main outcome measures were total cholesterol, total triacylglycerol, and HDL and LDL cholesterol measured at weeks 8, 9, 11, and 12. Total cholesterol concentrations decreased significantly between baseline and 8 wk in the red yeast rice treated group compared with the placebo-treated group. LDL cholesterol and total triacylglycerol were also reduced with the supplement. HDL cholesterol did not change significantly. Red yeast rice significantly reduces total cholesterol, LDL cholesterol, and a total triacylglycerol concentrations compared with placebo and provides a new, novel, food-based approach to lowering cholesterol in the general population.

In order to better understand the effectiveness of red yeast rice, Wang et al. (1997), performed a randomized, single-blind trial in 502 patients who were diagnosed with hyperlipidemia. In the red yeast rice using group reduction of hyperlipidemia was significantly greater (Wang et al. 1997).

By the way, protection from cardiovascular disease is only one of many benefits of red yeast rice consumption. A Chinese study demonstrated that red yeast rice extract decreased insulin and blood glucose levels in a group of Type II diabetics (Fang and Li, 2000). Since Type II diabetes is characterized by insulin resistance and impaired glucose tolerance, it appears that red yeast rice can increase insulin sensitivity in diabetics, even in subjects without high lipid levels. Other exciting applications for red yeast rice are suggested by recent discoveries that lovastatin and other statin drugs may be useful for treating or preventing cancer (Dimitroulakos et al. 2001), osteoporosis (Edwards et al. 2000; Garrett et al. 2001) , stroke (Vaughan et al. 2001), Alzheimer's disease and other dementias (Wolozin et al. 2000; Jick et al. 2000; Friedhoff et al. 2001), and macular degeneration (Hall et al. 2001)

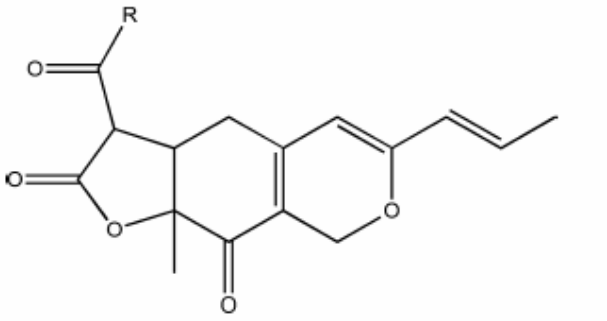
Use of *Monascus purpureus* as food or food additives

Nata is a bacterial cellulose produced by *Acetobacter aceti ssp. xylinum*, was colored by means of fermentation with *Monascus purpureus*. Scanning electron microscopy (SEM) observations showed that the *Monascus* mycelium coulo grow through the cellulose network of nata. The *Monascus*-nata complex has the potential to be new vegetarian foodstuff (Sheu et al. 2000).

The use of Monascus microorganisms is also a rich source of natural color and produces chemical species that give a red color. These include monascin, ankaflavin, rubropunctatin and monascorubrin which have the following molecular skeleton in Figure 1. Colorants are often added to fruit flavored yoghurt to enhance or replace the natural color of the fruit. Pigments produced by the mold, *Monascus purpureus*, offer a possible alternative to certified food dyes or natural pigments now used (Koehler, 2001, Dweck, 2002).

Red yeast rice is commercially available in capsules and should be taken in the amount of 1.2-2.4 grams (5-10 mg monacolins) per day in divided doses for a trial period of up to 12 weeks (Heber et al. 1999; Wang et al. 1997).

Figure1. The molecular skeleton of monascin, ankaflavin, rubropunctatin and monascorubrin



Side effects or interactions

Red yeast rice generally well tolerated with possible temporary mild side effects such as hearth burn, wind, and dizziness (Wang et al. 1997). This product should not to be used by individuals with liver disorders (Burnham et al. 1997).

Side effects with red yeast rice extract have been reported but tend to be mild and resolve quickly upon discontinuation. These include headache, dizziness, hearth burn, gas, and digestive tract discomfort.

The statins in red yeast rice extract pose the risk of rare but serious reactions, including skeletal muscle damage, liver damage, and kidney toxicity. Approximately 1% to 2% of people taking the drug lovastatin have such reactions. Symptoms may include unexplained weakness, muscle pains and tenderness, and other flu like symptoms. It's still unclear whether these types of reactions occur with people taking the standardized red yeast rice extract, however a recent, 12-week clinical trial, for example, liver and kidney function in the participants remained normal (Edwards, 2000; Jick et al. 2000).

Red yeast rice should be used cautiously. It is not recommended for use by pregnant women, by anyone with a liver disorder, or by those taking other cholesterol-lowering medications simultaneously. The use of statin drugs such as lovastatin can sometimes lead to side effects including myopathy (muscle dysfunction) and liver toxicity. Side effects including muscle pain and fatigue may also occur with red yeast rice if consumed at sufficiently high doses. For this reason an incremental dose schedule is suggested, at least at first. Also It is not recommended for use the person who have breast-feeding, liver disease, a serious infection, or a transplanted organ or have recent had major surgery must be use careful. Under age 20, it has to avoid possible complications because of the statin content in red yeast rice extracts. Also persons have to avoid drinking more than two alcoholic drinks a day or large amounts of grapefruit juice while taking red yeast rice extract. According to a report from the National Cancer Institute, supplementing with CoQ10 can prevent the occurrence of myopathy induced by lovastatin (Thibault et al. 1996).

More information on possible side effects should become available as results of studies on red yeast rice extract are completed in the coming years.

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