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Acute administration of red yeast rice (*Monascus purpureus*) depletes tissue coenzyme Q_{10} levels in ICR mice

Hui-Ting Yang[1], Shyh-Hsiang Lin[2], Shih-Yi Huang[2]* and Hsin-Ju Chou[2]

[1]*School of Pharmaceutical Science, Taipei Medical University, Taipei, Taiwan*
[2]*School of Nutrition and Health Sciences, Taipei Medical University, 250 Wu-Hsing Street, Taipei, Taiwan 110*

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In this study, we attempted to evaluate the effect of administration of a high quantity of red yeast rice on coenzyme Q_{10} (CoQ_{10}) synthesis in the tissues of ICR mice. Eighty-eight adult male ICR mice were housed and divided into control and experimental groups for red yeast rice treatment. Animals were gavaged with a low (1 g/kg body weight) or a high dose (5 g/kg body weight, approximately five times the typical recommended human dose) of red yeast rice dissolved in soyabean oil. After gavagement, animals of the control group were immediately killed; mice of the experimental groups (eight for each subgroup) were killed at different time intervals of 0·5, 1, 1·5, 4 and 24 h. The liver, heart and kidney were taken for analysis of monacolin K (liver only) and CoQ_{10} analysis. Liver and heart CoQ_{10} levels declined dramatically in both groups administered red yeast rice, especially in the high-dose group, within 30 min. After 24 h, the levels of hepatic and cardiac CoQ_{10} were still reduced. A similar trend was also observed in the heart, but the inhibitory effect began after 90 min. The higher dose of red yeast rice presented a greater suppressive effect than did the lower dose on tissue CoQ_{10} levels. In conclusion, acute red yeast rice gavage suppressed hepatic and cardiac CoQ_{10} levels in rodents; furthermore, the inhibitory effect was responsive to the doses administered.

Red yeast rice: Coenzyme Q_{10}: Monacolin K: Gavagement

Many large prospective studies have shown that therapy with statins is an effective means to improve the prognoses of CHD patients by lowering plasma cholesterol and triacylglycerol levels (Scandinavian Simvastatin Survival Study Group, 1994; Watts & Burke, 1996). However, the medication has been suspected of decreasing blood levels of coenzyme Q_{10} (CoQ_{10}) and thereby possibly of reducing myocardial function. CoQ_{10}, one of the ubiquinones, is a benzoquinone compound synthesized naturally in the human body. The 'Q' and the '10' in its name refer to the quinone chemical group and the ten isoprenyl chemical subunits, respectively. CoQ_{10} is not only involved in the process known variously as aerobic respiration, aerobic metabolism, oxidative metabolism or cell respiration, but also acts as an endogenous antioxidant (Appelkvist *et al.* 1993; Ghirlanda *et al.* 1993; Laaksonen *et al.* 1994; Davidson *et al.* 1997). Its well-documented functions are in mitochondrial energy coupling and its action as a primary regenerating antioxidant. Thus, the level of CoQ_{10} in organs and tissues has been used as a measure of oxidative stress (Mohe *et al.* 1992; Kontudh *et al.* 1995), especially the level in blood.

Monacolin K, a component of red yeast rice (*Monascus purpureus*) that is a statin, is well known as an inhibitor of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a liver enzyme involved in the production of cholesterol, that can prevent hyperlipidaemia and reduce *de novo* cholesterol biosynthesis. The HMG-CoA reductase inhibitors competitively affect the early critical enzyme of the mevalonate pathway, thus inhibiting the synthesis of cholesterol and other sterol endproducts (Appelkvist *et al.* 1993); one of these products is CoQ_{10}, also known as ubiquinone. Cholesterol and ubiquinone biosyntheses share the core enzyme – HMG-CoA reductase; therefore it is believed that statin-containing health foods, such as red yeast rice which contains various monacolins (monacolin K, etc.), may interrupt the production of ubiquinone while lowering serum lipids and may cause myocardial dysfunction. Studies have shown that lovastatin or pravastatin decreases plasma CoQ_{10} during long-term treatment (Mortenson *et al.* 1997; Palomaki *et al.* 1998). However, although red yeast rice is a popular functional food that has been predominant in the market, some of its side-effects remain unknown. For instance, does red yeast rice affect the biosynthesis of CoQ_{10}? Thus, in the present study we evaluated the effect of acute gavagement of a red yeast rice solution on organ levels of ubiquinone in ICR mice.

Materials and methods

Materials

Monacolin K, pravastatin, ubiquinone-9 and ubiquinone-10 were purchased from Sigma (St. Louis, MO, USA). The silica gel 60 F_{254} TLC plate for CoQ_{10} separation was obtained from Merck (Darmstadt, Germany). All solvents used were HPLC grade and were purchased from TEDIA (Fairfield, OH, USA), as were the high-purity laboratory standards. The red yeast rice, which contained 6·3 % water, 13 % crude protein, 60 % carbohydrates (starch), 19 % crude lipids and 1·5 % monacolins (lovastatin

Abbreviations: CoQ_{10}, coenzyme Q_{10}; HMG-CoA, 5-hydroxy-3-methylglutaryl-coenzyme A.

* **Corresponding author:** Dr S.-Y. Huang, fax +886 2 27373112, email sihuang@tmu.edu.tw

equivalent), was a gift from China Chemical and Pharmaceutics, Taipei, Taiwan.

Animal protocol

Eighty-eight ICR male mice were purchased from the National Animal Breeding Center (Taipei, Taiwan) at 4 weeks of age. All mice were acclimatized to the laboratory for 7 days prior to use. The animals were housed and divided into three treatment groups (control group without red yeast rice; low-dose group, 1 g/kg body weight; high-dose group, 5 g/kg body weight); the red yeast rice was made up as a solution in soyabean oil. Based on the body weight of ICR mice, animals were gavaged with the described doses of red yeast rice. On average, each mouse was gavaged with 0·3 ml of a red yeast rice solution. After treatment, mice in the control group were immediately killed; the other experimental groups were divided and killed after different time intervals (0·5, 1, 1·5, 4 and 24 h). The heart, liver and kidney were taken for determination of monacolin K (liver only) and CoQ_{10} levels. During the experimental period, the body weight of the mice was recorded, and skin colour and appearance of the animals were observed for evaluation of toxic effects.

Observation and examination

Mice were observed for mortality and signs of pharmacotoxicity at approximately 0·5, 1, 1·5, 4 and 24 h after the gavage treatment. Any mortality or pharmacotoxic signs were documented. Individual body weights were determined immediately prior to dosing (at the beginning), at designated time intervals during the course of the study, and again for survivors at the end of the study. Any mice that died during the study were to be weighed as soon as they were found dead. Gross necropsy examinations were performed on all animals that died spontaneously or were euthanized at the end of the study. The mice were euthanized by a CO_2 inhalation overdose. Skin irritation was also evaluated on all animals at the end of the study.

Measurements

CoQ_{10} purification followed published methods (Okamoto *et al.* 1985; Yamashita & Yamamoto, 1997). A portion of the wet liver or heart tissue (approximately 0·5 g) was homogenized in distilled water, extracted three times with equal volumes of an n-hexane–ethanol solution (5:2, v/v), and the n-hexane layers were pooled and concentrated. The residue was dissolved in 2 ml of 98 % ethanol and reacted with 5 % potassium hexacyanoferrate solution for 10 min. Then it was re-extracted three times with the n-hexane–ethanol solution (5:2, v/v), and the upper (hexane) layers were pooled, dried over anhydrous sodium sulphate and transferred to a vial. The extracted fraction was applied to a TLC plate (silica gel 60 F_{254}, art. 5715; Merck) that was developed with a saturated mobile phase (benzene–acetone, 99·5:0·5, v/v) in a 20 cm × 20 cm × 8 cm tank. The separated CoQ_{10} band was identified by comparison with a CoQ_{10} standard under short-wave UV light (254 nm), scraped and dissolved in 2 ml acetone three times. After extraction, the pooled acetone was filtered and dried in an N_2 stream. The dried fraction was dissolved in the proper mobile phase solution for CoQ_{10} analysis by HPLC.

CoQ_{10} was analysed by HPLC on a 10 μm C_{18} reversed-phase column (4·6 mm × 216 mm; Whatman EQC, Maidstone, UK) that was connected to a pre-column (5 μm, 4·6 mm × 20 mm, Inertsil® ODS-2; MetaChem, Torrance, CA, USA). An isocratic mobile phase (methanol–n-hexane, 80:20, v/v) with a 1 ml/min flow rate was used. The HPLC instrument consisted of an L-7100 pump and a model 7125 switching valve with a 20 μl loop injector (Rheodyne, Cotati, CA, USA). This was connected to an L-7420 UV–visible wavelength detector with an LC autocontrol (Hitachi, Tokyo, Japan) set at 275 nm and a computerized integrator. Ubiquinone-9 (coenzyme Q_9) was used as the internal standard.

The analysis of monacolin K was partially modified from the procedures described by Edlund (1988). Wet liver tissue (1 g) was homogenized in normal saline and extracted three times using equal volumes of acetone and hexane. The pooled acetone–hexane solutions were washed with the same volume of deionized water. The upper (hexane) layers were pooled, transferred to a vial and dried over sodium sulphate. The purified fraction was dissolved in the appropriate solution for monacolin K analysis.

Monacolin K was analysed by HPLC on a 10 μm C_{18} reversed-phase column (4·6 mm × 216 mm; Whatman EQC) connected to a guard column (5 μm, 4·6 mm × 20 mm, Inertsil® ODS-2; MetaChem). An isocratic mobile phase of acetonitrile, water, triethylamine and glacial acetic acid (600:400:1:1, v/v) with a 0·8 ml/min flow rate was used. The HPLC instrument consisted of an L-7100 pump and a model 7125 switching valve with a 20 μl loop injector (Rheodyne). This was connected to an L-7420 UV–visible wavelength detector with an LC autocontrol (Hitachi) set at 238 nm and a computerized integrator. Pravastatin was used as the internal standard.

Statistical analysis

Results are expressed as mean and standard error of the mean (SEM). Data on the amounts of monacolin K and CoQ_{10} were analysed separately by one-way ANOVA for the liver and heart. Statistical calculations were conducted using Student's *t* test for paired observations. A 0·05 level of probability was used as the criterion of significance.

Results

Experimental observations

In our study, we gavaged ICR mice with a low (1 g/kg) or high (5 g/kg) dose of red yeast rice, the latter being equivalent to five times the typical recommended human dose (5 mg monacolin K). No drug-related death or toxic response was found in either group (low or high dose). Furthermore, no apparent treatment-related differences were found upon gross pathological examination of the major organs and skin. Within the test period, animals were normal and stable until killed. None died during the experimental period.

Tissue levels of coenzyme Q_{10} and monacolin K

The liver CoQ_{10} level declined dramatically within 30 min of red yeast rice administration (Fig. 1(b)) for both groups. Compared with the other organs, the level of CoQ_{10} in the liver showed a statistically significant decline after 30 min ($P<0·01$), reached its lowest value between 30 and 60 min ($P<0·05$), then rebounded to the basal level after 240 min and remained constant thereafter.

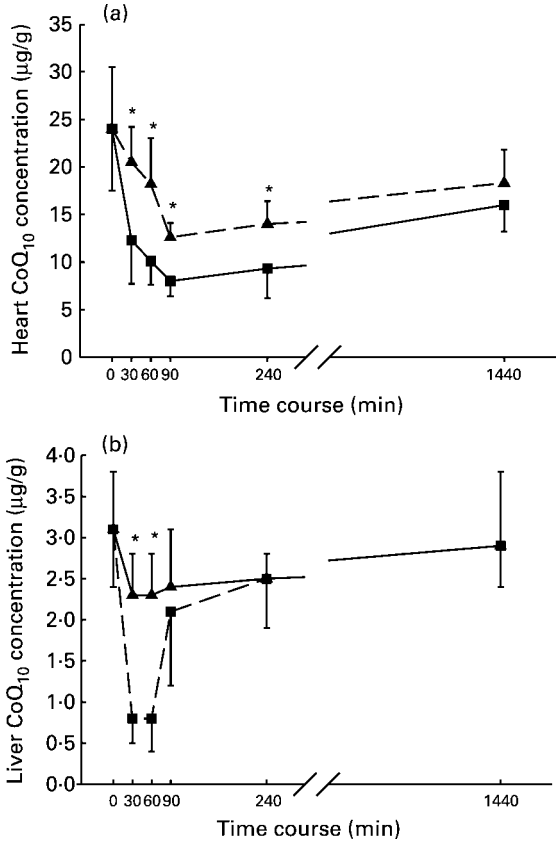

Fig. 1. Changes in coenzyme Q_{10} (CoQ_{10}) levels in the heart (a) and liver (b) of ICR mice after administration of low dose (1 g/kg body weight; ▲) and high dose (5 g/kg body weight; ■) of red yeast rice solution. Values are means with their standard errors represented by vertical bars ($n = 8$ animals at each time interval). Significant difference by Student's t test between the low-dose and high-dose groups at the same time point: $^*P < 0{\cdot}05$.

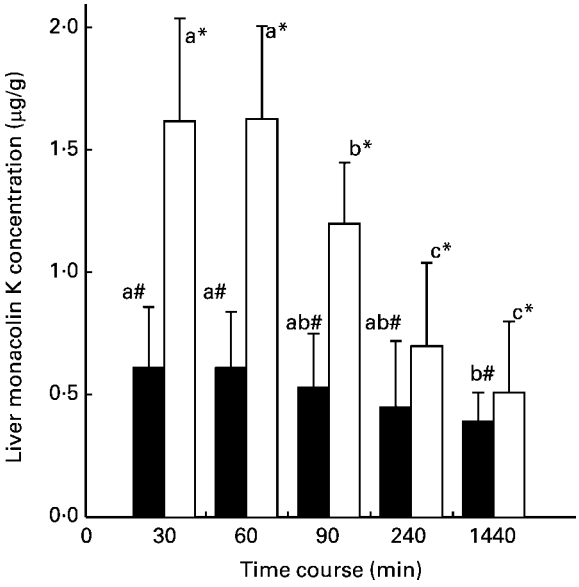

Fig. 2. Hepatic monacolin K concentrations in ICR mice at different times after administration of low dose (1 g/kg body weight; ■) and high dose (5 g/kg body weight; □) of red yeast rice solution. Values are means with their standard errors represented by vertical bars ($n = 8$ animals at each time interval). Values with different superscripts differ significantly by one-way ANOVA with least significant difference at $P < 0{\cdot}05$: letters indicate significant difference between time courses; symbols indicate significant difference between the low-dose and high-dose groups.

However, the CoQ_{10} level in the heart declined after 30 min and showed the lowest value between 90 and 240 min in both groups (Fig. 1(a)). Not surprisingly, the high-dose group showed a significantly greater lowering effect (−47 %) than the low-dose group at the 90 min time point ($P < 0{\cdot}05$). The concentration of cardiac CoQ_{10} remained at a low level and did not recover even 24 h later. Nevertheless, the kidney CoQ_{10} level showed no response to red yeast rice during the entire experimental period (0·7–0·9 μg/g; data not shown).

In the gavage experiment, the liver monacolin K concentration was elevated up to 0·61 and 1·62 mg/g liver (wet weight) for low-dose and high-dose groups within 30 min, respectively (Fig. 2). Monacolin K remained at a high level at 60 min and then decreased continuously for 1 day after administration. After 24 h, the hepatic level of monacolin K still remained at one-third of the original level in the high-dose group. Comparing with the dose efficacy of clearance of monacolin K, the hepatic clearance of monacolin K maintained a lower efficiency (33 % at 24 h). Comparing with the control group (time 0), both doses showed a lower catabolic ability for monacolin K, especially in the low-dose group (0·39 (SEM 0·12) μg/g at 24 h).

Discussion

Many animal studies have been carried out to address safety concerns about red yeast rice (Wang *et al.* 1995; Zhu *et al.* 1995, 1998; Heber *et al.* 1999). The 'Xuezhikang' extract lowered cholesterol levels in the rabbit by 44 and 59 % at doses of 0·4 and 0·8 mg/kg, respectively (Zhu *et al.* 1995). No pharmacological side-effects were mentioned. In a toxicity study in mice Zhou *et al.* (1998) no toxic effects were reported with an extremely high single dose (equal to 533 times the typical human dose) of red yeast rice or even a dose of 5·0 g/kg daily for 90 days. Citrinin has been considered to have hepato-nephrotoxic properties (Lockard *et al.* 1980; Kogika *et al.* 1993). We analysed the citrinin level of the applied red yeast rice and found it was less than 0·167 g/kg, which is much lower than the acute nephrotoxic level (18·4 g/kg; Krejci *et al.* 1996). The pigments (e.g. rubropunctatin, monascorubin, monascin and ankaflavin) found in red yeast rice have been demonstrated to have high LD_{50} values (>20 g/kg) in Sprague–Dawley rats; furthermore, there were no effects on animal weight gain or tissue and organ appearance in a 7-month chronic toxicity test (International Agency for Research on Cancer, 1986.). In our study, we applied five times the human recommended dosage in ICR mice. No histological damage or even skin irritation was observed in any animal. According to such a description, it is believed that, with low citrinin content, no safety concerns exist for the recommended dosage of red yeast rice.

The components of red yeast rice that affect sterol synthesis have been discussed. The red yeast pigments such as rubropunctatin are known and are biosynthesized via the shikimic acid pathway rather than the mevalonic acid pathway. The described pigments were given high priority for demonstrating biological aspects of decreasing oxidative stress potential (Aniya *et al.* 1999); however, the property of lowering cholesterol still remains to be elucidated. Some studies have indicated that citrinin causes hepato-nephrotoxicity in different animals by interfering with the

electron transport system of mitochondria (Lockard *et al.* 1980; Kogika *et al.* 1993; Chagas *et al.* 1995). Citrinin modifies mitochondria homeostasis by decreasing Ca^{2+} accumulation in the matrix and results in imbalance of the Ca^{2+} flow between membranes (Katan *et al.* 2003). In the present study, the citrinin level was low at 0·167 g/kg and could be ignored. In addition to monacolin-related substances, red yeast rice also contains certain sterols such as β-sitosterol, campesterol and sapogenin (Heber *et al.* 1999); however, these components present inhibitory properties of exogenous absorption rather than the endogenous biosynthesis of cholesterol (Crane, 2001; Ostlund, 2002).

Many statin-related studies in animals and man (Ghirlanda *et al.* 1993; Laaksonen *et al.* 1994; Davidson *et al.* 1997) have revealed decreases in systemic CoQ_{10} levels during administration. In our study, the high dose of red yeast rice ingestion depleted CoQ_{10} in the liver and heart but not the kidney. This seems to imply that mitochondria ubiquinone in organs such as heart and liver might be influenced by higher-dose and longer-duration HMG-CoA reductase inhibitor treatments. Thus it is believed that monacolin K, a component of red yeast rice with cholesterol-lowering potential, may indeed inhibit HMG-CoA reductase activity and thereby competitively affect the enzyme's involvement in the early stage of the mevalonate synthetic pathway, thus inhibiting the synthesis of several non-sterol isoprenoid endproducts such as ubiquinone and dolichol (Appelkvist *et al.* 1993; Ghirlanda *et al.* 1993; Laaksonen *et al.* 1994; Davidson *et al.* 1997). In this study, hepatic monacolin K levels were significantly inversely related to the levels of cardiac and hepatic CoQ_{10}. These data suggest that monacolin K may be involved in the early stage of a cholesterol biosynthesis pathway other than that for late-stage enzymes. Monacolin K presents a structure which mimics that of mevalonic acid on HMG-Co A reductase, blocking further synthesis of intermediates.

For more than a decade, the CoQ_{10}-lowering effect of statins and its compensation by administration of CoQ_{10} have been reported with inconsistency in numerous studies on animals and man. Willis *et al.* (1990) reported that male hypercholesterolaemic Holtzman rats fed a lovastatin- and CoQ_{10}-containing chow diet (with or without 400 mg and 15 mg/kg, respectively) for 4 weeks showed decreased CoQ_{10} concentrations in the heart, liver and blood; however, the level of decline could be ameliorated by CoQ_{10} supplementation. We assessed the effect of red yeast rice on CoQ_{10} levels in hyperlipidaemic male hamsters for 4 weeks. Results indicated that red yeast rice decreased the level of hepatic CoQ_{10} and increased CoQ_{10}:cholesterol in statistically significant manners (Shieh *et al.* 2001). In contrast, a randomized, placebo-controlled, cross-over human trial of CoQ_{10} (180 mg daily) supplementation with lovastatin (60 mg daily) therapy revealed that ubiquinones were unable to improve defence against initiation of LDL oxidation which was impaired by statins (Palomaki *et al.* 1998). A cerivastatin-dosed rat experiment showed that the mean coenzyme Q_9 levels in all groups tended to decrease relative to that of controls in type II skeletal muscle (Schaefer *et al.* 2004). The adverse effects of statins, such as reducing the level of ubiquinone and elevating the level of blood endotoxin, may contribute to the progression of chronic heart failure (Ashton *et al.* 2003). We reasonably believe that changes in the energy production in muscle systems may be due to the disability of organs, especially in highly ATP-dependent organelles. Insufficient CoQ_{10} synthesis may contribute to mitochondrial energy release and chronic disease development. However, the mechanism of statins' impact on the ubiquinone system remains to be elucidated.

Although the present study was conducted using acute gavagement of ICR mice, it is noteworthy that the monacolin-containing red yeast rice, a globally popular cholesterol-lowering health food, may have similar effects of lowering CoQ_{10} levels in the liver and heart. Thus, while health food such as red yeast rice has the benefit of lowering cholesterol with long-term consumption, it should be considered that it simultaneously lowers tissue CoQ_{10} levels. In conclusion, acute gavage with red yeast rice caused a decrease in hepatic and cardiac CoQ_{10} levels in ICR mice. Hepatic monacolin K levels were significantly inversely related to the levels of cardiac and hepatic CoQ_{10}.

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