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MINI-REVIEW

Biologically active components and nutraceuticals in the *Monascus*-fermented rice: a review

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Abstract *Monascus*-fermented rice has traditionally been used as a natural food colorant and food preservative of meat and fish for centuries. It has recently become a popular dietary supplement because of many of its bioactive constituents being discovered, including a series of active drug compounds, monacolins, indicated as the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors for reducing serum cholesterol level. The controversy of its safety has been provoked because a mycotoxin, citrinin, is also produced along with the *Monascus* secondary metabolites by certain strains or under certain cultivation conditions. This review introduces the basic production process and addresses on the compounds with bioactive functions. Current advances in avoiding the harmful ingredient citrinin are also discussed.

Keywords Koji · Metabolites · Monascus · Nutraceuticals

Introduction

Monascus-fermented rice (MFR) is a commonly used food colorant and dietary material in Asian countries. In China, Japan, Taiwan, Thailand, and Philippines, MFR is used as a traditional additive for preserving fish and meat. Because of its flavor, aromatic fragrance, and vivid red color, MFR is frequently used as a flavoring agent for a variety of Chinese dishes. Examples of recipes using red yeast rice are roast pork, roast duck, fermented bean curd, preserved dry fish, and vegetable pork stew. MFR is also widely used as starter culture for brewing red rice wine. Several names, including Hung-Chu, Hong Qu, Ang-kak, Ankak rice, Red Yeast rice, Red Mold rice, and Beni-Koji, are used as synonyms for this food product. MFR is described as a mild folk medicine, which has the therapeutic effect to promote the health of cardiovascular system. Its pharmaceutical function has been stated in the ancient Chinese pharmacopeia, *Ben Cao Gang Mu* composed by Shi-Zhen Li (1518–1593 A.D.).

Monascus was classified and named in 1884 by French scientist van Tieghem (1884). In 1895, Went published a careful study on *Monascus purpureus*, a species discovered from the samples collected by Dutch scientists in Java, where it was used largely for coloring rice (Went 1895). The genus *Monascus* is considered to belong to the family Monascaceae, the order Eurotiales, the class Ascomycetes, the phylum Ascomycota, and the kingdom Fungi (Young 1930). Today, there are 58 *Monascus* strains deposited in the American Type Culture Collection. However, based on Hawksworth and Pit's (1983) work on the taxonomy in 1983, most strains belong to only three species: *M. pilosus*, *M. purpureus*, and *M. ruber*. The majority of microorganism for production of MFR is *M. purpureus*, which also has a synonym as *M. anka* Nakazawa et Sato when it was isolated from the rice koji in Taiwan by two Japanese academics in 1930 (Steinkraus 1983; Su et al. 1970).

Production of MFR

The earliest documentation of the production process was described by Ying-Xing Song in his publication "T'ien-kung k'ai-wu" in the seventeenth century, which provides important guidance of koji management for the modern manufacturing (Song 1966). Contemporary method for producing MFR is to steam the rice grains to the status of

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semigelatinization (when the shape of rice kernel is remained and the grains can be pressed into flat with moderate pressure by fingers). After the inoculation by *Monascus* starter, the rice grains are incubated in a temperature-controlled chamber and regularly flipped and damped during the entire fermentation process, until the center of the rice becomes deep red colored.

Temperature and moisture are critical parameters dominating the quality of MFR. To appropriately control both of them, the rice grains as the fermentation substrate are conventionally covered by cotton clothes to maintain the water content and heat and to dissipate them by temporary removal of that coverage. The temperature of fermentation mixture should be maintained at 30–35°C in favor of the best propagation and mycelium growth. The rice grains are flipped daily to ameliorate the heat generated from microbial metabolism. A regular fermentation procedure usually takes 7 days until the center of the rice becomes deep red colored. The final product is traditionally sun dried or oven dehydrated at 45°C for 22 h for storage. The moisture content of the final product should be 10±1%, and each grain should easily crumble between one's fingers (Steinkraus 1983; Su 2001).

Advances in *Monascus* fermentation

The ingredients of MFR are significantly affected by fermentation conditions. Although manufacturers of MFR heavily rely on the experiences and the quality varies lot to lot, the critical parameters in controlled cultivation had just been recognized.

The knowledge of *Monascus* pigment fermentation for substitution of natural colorants in meat products has been summarized by Juzlova et al. (1996). They concluded that the orange pigments of extracts from submerged *Monascus* cultures were responsible for not only antibacterial and antifungal activities but also immunosuppressive, embryotoxic, and teratogenic effects. These samples impaired the concanavalin A-stimulated proliferation of mouse splenocytes and human peripheral blood cells and exhibited toxic and teratogenic effects on chicken embryos. However, the extracts from solid-state-fermented red rice seemed harmless to chicken embryos. The antibacterial pigment was initially discovered and named as monascidin A by Wong and Bau (1977) then identified by Blanc et al. (1995) as the mycotoxin, citrinin (Fig. 3c). The discovery aroused the attention whether cultivation methods could result in dissimilar safety concerns on these products.

Nevertheless, MFR products have been extensively commercialized as dietary supplements to date because a variety of active ingredients were discovered, e.g., monacolins, γ-aminobutyric acid (GABA, Fig. 3d), etc. Many efforts have been put on producing the MFR products with higher active compounds and minimal harmful ingredients (i.e., citrinin). Thus, several critical parameters that dominate the quality of these MFR products are discussed as follows.

Solid-state fermentation

The contemporary method of MFR mass production is still by the traditional solid-state fermentation on cooked whole rice kernel. Successful productions of MFR are often determined by the following factors: the type of substrates (predominantly nonglutinous rice kernel), type of selected *Monascus* strains, temperature and moisture content of the fermentation mixture thorough the process, and control of contamination factors (Su 2001). Until monacolins and GABA were reported in these products, good production quality of MFR was long being regarded as higher pigment accumulation in the fermentation mixture. Juzlova et al. (1996) summarized several articles in a review that addressed solid-state cultivation of *Monascus* sp. in laboratorial scale for pigment production.

Of the rice substrates used in producing MFR, nonglutinous soft rice was superior to glutinous rice in which the former has higher nutritious value (e.g., starch content) to the molds and is easier to absorb water (Steinkraus 1983; Su 2001).

On the control of water content during MFR production, it is reported that the optimal substrate humidity should be adjusted to approximately 40–50% at initial and maintained by temporarily moistening the substrates in favor of fungal growth (Hesseltine 1965; Su and Wang 1977). Recent studies suggested that a lower initial moisture content (25–30%) helps to keep a low glucoamylase activity and, thus, is benefit to the pigment yields (Lotong and Suwanarit 1990; Teng and Feldheim 2000). However, Chen and Hu (2005) concluded that cultivation of a mutant strain *M. pilosus* M12-69 yielded the best monacolin K/citrinin ratio when the water contents is between 55 and 75%.

Sufficient aeration is also a key parameter to pigment production than growth. Pigment formation was dramatically blocked when excess CO_2 accumulated in the incubator (Teng and Feldheim 2000). In the Chinese ancient process, sufficient aeration is achievable by stirring the fermentation mixture on bamboo trays every 2 h to separate grains from agglomerates. The separation is substantially carried out in laboratory scale by shaking the substrates in flasks or dissipating in plastic bags. Recently, a commercial koji maker with a rotary perforated bed of 5-m diameter was adopted for MFR mass production (Chiu et al. 2006). The koji maker provides a perforated bottom plate for up-flow aeration and a plowing mixer for assisting heat removal and preventing koji agglomeration.

To increase the beneficial ingredients and decrease the toxic components, random mutation to *Monascus* has been

performed and have acquired a genetically modified strain with higher monacolin K productivity and lower citrinin content (Chen and Hu 2005; Wang et al. 2004). In the culture of *M. purpureus* NTU 601, the addition of 0.5% ethanol as the carbon source tripled the monacolin K content, elevated the GABA production to sevenfold, and reduced the citrinin content (Wang et al. 2003). Moreover, substrates suitable for production of specific metabolites have also been studied. For example, *Dioscorea batatas* is reported as an enhancer substrate for *Monascus* species to the production of monacolin K (Fig. 1a) and monascin (Fig. 2c; Lee et al. 2006).

Liquid/submerged cultivation

The production of *Monascus* secondary metabolites by liquid/submerged fermentation has been extensively studied. Various culturing parameters including water supplement, temperature, nitrogen source, medium components, and pH value have been investigated (McHan and Johnson 1970; Sato and Naito 1935). Lin was the first to study liquid culture conditions on the pigment production by *Monascus* (Lin 1973; Lin and Suen 1973). The cultural conditions for maximum pigmentation were found to be 5% rice powder (with 3.5% starch content) as the carbon source, 0.5% of sodium nitrate or potassium nitrate as the nitrogen source, initial pH of 6.0, and a temperature of 32°C. Su and Huang (1976) reported that polished rice powder gave higher pigment productions and *Monascus* dry weight than rice starch, which indicates that the minor compositions in rice kernel could benefit fungal growth and pigmentation. Corn powder gave a higher fungal dry weight than rice powder but had poor pigment production. They also suggested that the addition of 1–2% alcohol during incubation has a favorable effect on the pigment production. Carels and Shepherd (1977) investigated the effect of different nitrogen sources on the end culture acidity and the pigment production. During cultivation, the medium pH is around 6.5 when using yeast extract or nitrate as the nitrogen source, and red pigments are formed, whereas when using ammonium or ammonium nitrate, the pH is around 2.5, and the pigments are orange. Chen and Johns (1993) further examined the effect of pH and nitrogen source on individual pigment productions in a pH-controlled fermentor. A lower pH value (pH 4.0) promotes the fungal growth and favors the synthesis of ankaflavin (Fig. 2d); however, the production of other pigments is relatively nonsusceptible to pH value.

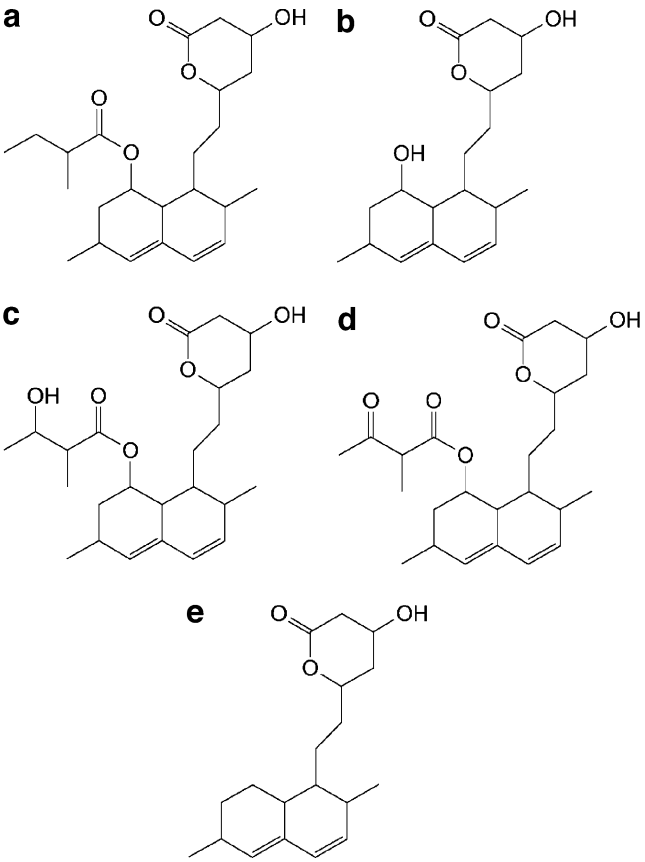

Fig. 1 Chemical structure of monacolins: monacolin K **a**, monacolin J **b**, monacolin M **c**, monacolin X **d**, and monacolin L **e**

Oxygen concentration in the submerged cultivation also affects the biosynthesis of *Monascus* metabolites (Hajjaj et al. 2000). In oxygen-limiting incubation, production of pigments (Fig. 2) and citrinin (Fig. 3c) is growth-related and are both biosynthesized as primary metabolites. Under oxygen-excess condition, however, citrinin is produced as a secondary metabolite, which is mostly produced during the stationary phase. In contrast, the pigments decrease dramatically during the incubation. The formation of the pigments is partially inhibited by metabolites produced in aerobic environments such as L-maltose, succinate, and dicarboxylic acid; however, the formation of citrinin is not affected.

Other components in the cultural medium were also been reported to affect pigment productions. For instance, addition of leucine to the culture medium interfered with the production of red pigment (Lin and Demain 1994). The absence of potassium phosphate in the medium also depresses the red pigment production in the culture of *Monascus pilosus* (Lin et al. 2007).

It is interesting to note that spectrum of light also affects the composition of *Monascus* secondary metabolites (Miyake et al. 2005). Miyake et al. (2005) incubated the *Monascus* in shaking flasks under the dark or exposed to red light (635 nm) or blue light (470 nm). The red light promotes the production of red pigments and citrinin, and the blue light promotes the production of GABA. The spectrum of light also affects mycelium development and spore formation of *Monascus*.

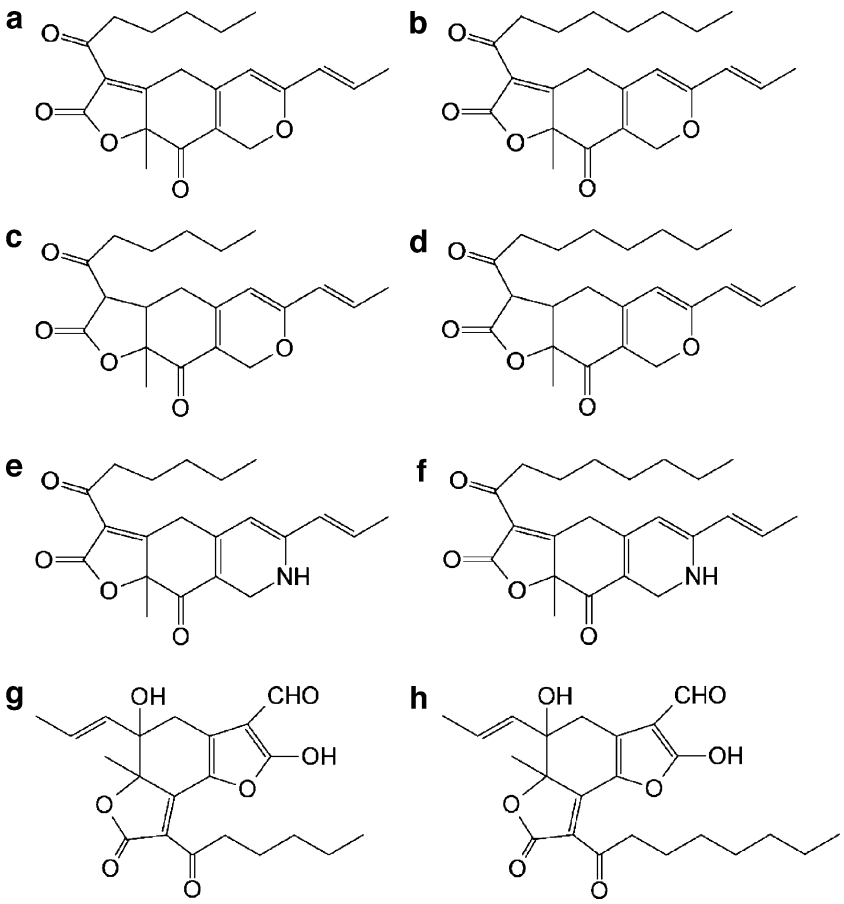

Fig. 2 Chemical structure of pigments from *Monascus*: rubropunctatin **a**, monascorubrin **b**, monascin **c**, ankaflavin **d**, rubropunctamine **e**, monascorubramine **f**, xanthomonasin A **g**, and xanthomonasin B **h**

Systems biology approaches have recently been introduced to elucidate the complex pathways of biosynthesis. For instance, proteome analysis with matrix-assisted laser desorption /ionization–time of flight and tandem mass spectrometry has revealed that the phosphate limitation condition upregulates the expression of aldehyde dehydrogenase and the glycolytic enzymes (Lin et al. 2007). Moreover, the genome of *Monascus* sp. has been sequenced and the database is maintained in Bioresource Collection and Research Center, Taiwan; however, this database is not currently opened for public (http://www.bcrc.firdi.org.tw/genome_project/index.jsp).

MFR has been reported to function in lowering of plasma glucose, cholesterol, and triacylglyceride. In the model of chicken, the addition of MFR powder to their fodder lowers the level of cholesterol, triglyceride, and low-density lipoprotein (LDL) in serum and reduces the cholesterol content in egg yolk. This approach suggests a healthier source of meat or egg products for people who need to control cholesterol intake in their diets (Wang and Pan 2003; Wang et al. 2006). In the model of Wistar rats, oral administration of MFR increases the release of acetylcholine from the nerve terminal, which in turn interacts with muscarinic M3 receptor in pancreatic cells, promotes insulin release, and thus reduces the plasma glucose (Chen and Liu 2006). Oral administration of MFR to streptozotocin-induced diabetic rats decreases their plasma glucose in a dosage-dependent manner from 50 to 350 mg/kg. In normal rats with intravenous glucose injection, oral administration of MFR (350 mg/kg) also attenuates the elevation of plasma glucose (Chang et al. 2006). In a clinical study, 79 patients with hyperlipidemia are randomly and double-blindedly grouped to receive MFR or placebo daily. After 8 weeks, the patients with MFR administration demonstrates reduced levels of LDL cholesterol, total cholesterol, triglycerides, and apolipoprotein B (Lin et al. 2005). In the cell culture model, MFR extracts significantly decreases the enzyme activity and gene expressions, which are related to the adipocyte differentiation. For example, the glycerol-3-phosphate dehydrogenase activity and lipid accumulation are lowered in 3T3-L1 cells. Moreover, the messenger ribonucleic acid levels of CCAAT/enhancer-binding protein and peroxisome proliferator-activated receptor are decreased. The results suggest the inhibitory function of MFR to the susceptibility of adipocyte differentiation (Jeon et al. 2004).

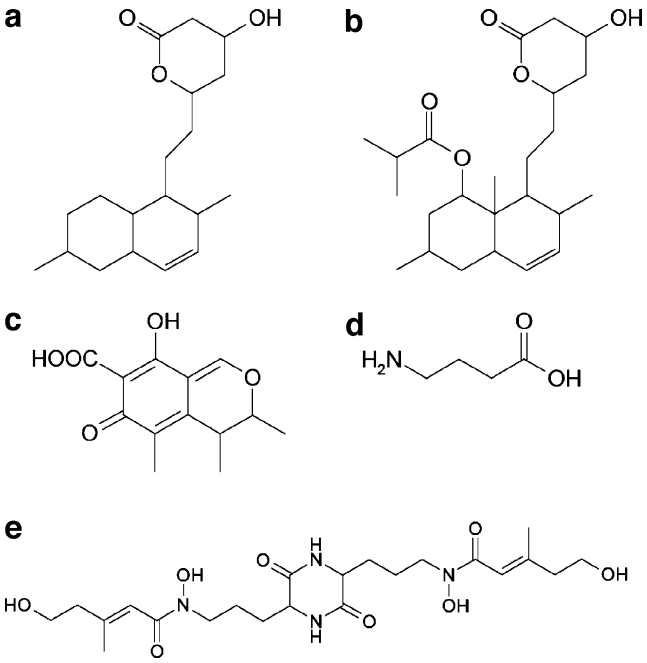

Fig. 3 Chemical structure of other metabolites from *Monascus*: dihydromonacolin-L **a**, dihydromonacolin-MV **b**, citrinin **c**, γ-amino-butyric acid **d**, and dimerumic acid **e**

Bioactive metabolites of MFR

MFR contains various chemical components. Some of them are purified and identified, including monacolins (Fig. 1), pigments (Fig. 2), dihydromonacolins (Fig. 3a, b), citrinin, GABA, and dimerumic acid (Fig. 3e). The metabolites in the MFR are conventionally divided by their practical use and biofunctions. The common division of these compounds is of three categories: bioactive ingredients, toxins, and pigments. However, there is a fine line among these categories. For example, ankaflavin is conventionally categorized as a colorant. Nevertheless, its bioactive functions have recently been discovered. Because the categorization may not be appropriate, each compound will be introduced, respectively, in the following paragraph.

Monacolins

Among the bioactive compounds found in MFR, monacolins are well known for their pharmacological effects to control hyperlipidemia (Endo 1979, 1980). Among the monacolins, monacolin K is considered the most efficacious compound to lower cholesterol in the plasma. It is also named as lovastatin, mevinolin, and mevacor (Akihisa et al. 2005b; Fig. 1).

Hypercholesterolemia and hyperlipidemia are related diseases of civilization. They results from the excessive concentration of LDL/cholesterol complex in the plasma and could induce the atherosclerosis, stroke, and other related diseases. Current therapeutic methodology is to block the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-determining enzyme of the cholesterol synthesis pathway. Compactin (ML-236B) was the first discovered inhibitor to HMG-CoA reductase (Mabuchi et al. 1981; Yamamoto et al. 1980). Afterward, monacolin K (mevinolin) was found as a structurally similar but more effective compound. It was purified from the metabolites of *Monascus ruber* and *Aspergillus terreus* (Alberts et al. 1980; Endo 1979, 1980) and was further commercialized by Merck in the name of Lovastatin. The biosynthesis pathway of monacolin K from its analogs has been elucidated (Kimura et al. 1990; Komagata et al. 1989). Methods for qualitative and quantitative analysis of monacolin analogous compounds are well also established (Li et al. 2004). Structural analogs including Monacolin J, L, and M were also found to reduce the synthesis of cholesterol (Endo et al. 1985a, b, 1986).

Pigments

There are six major pigments. The red colorants named rubropunctamine (Fig. 2e) and monascorubramine (Fig. 2f) are most abundant. The orange colorants are rubropunctatin (Fig. 2a) and monascorubrin (Fig. 2b). The yellowish colorants are monascin (Fig. 2c) and ankaflavin (Fig. 2d). Moreover, a yellowish colorant named Xanthomonasin A (Fig. 2g) in the mutant of *Monascus anka* was identified (Martinkova et al. 1999).

The pigments extracted from *M. anka* inhibited the 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA)-induced carcinogenesis in mice (Yasukawa et al. 1996). Among the pigments, monascorubrin was the most effective one, and its function was assumed through its anti-inflammatory activity (Yasukawa et al. 1994). In the mouse model, oral administration of monascin inhibited the carcinogenesis of skin cancer initiated by peroxynitrite or ultraviolet light and after the promotion of TPA (Akihisa et al. 2005a). Ankaflavin showed selective cytotoxicity to cancer cell lines by an apoptosis-related mechanism and showed relatively low toxicity to normal fibroblasts. The structure analog monascin, however, showed no cytotoxicity to all cell lines tested (Su et al. 2005). The orange pigments, rubropunctatin and monascorubrin, had been found to possess antibiotic activity against bacteria, yeast, and filamentous fungi (Martinkova et al. 1995). Rubropunctatin and monascorubrin could inhibit the growth of *Bacillus subtilis* and *Candida pseudotropicalis*. Yellow pigments, monascin and ankaflavin, showed immunosuppressive activity on mouse T splenocytes (Martinkova et al. 1999).

The stability of *Monascus* pigments had been studied (Fabre et al. 1993). The pigments were prepared by methanol/chloroform (1:1) extraction on freeze-dried cul-

ture broth of *M. ruber* van Tieghem. Results showed that the stabilities of these pigments were seriously affected by light exposure, surrounding temperature, and pH value. To the light exposure for 50 days, the red pigment decayed to 20%. After 100°C treatment for 8 h, red colorants decreased to 30%. The red pigment was found more stable in neutral (pH 7) or alkaline (pH 9.5) than in acidic condition (pH 3) for 5 h. The author further investigated the applicability of these pigments for replacing traditional colorants in meat products (such as nitrite salts or cochineal). The added concentrations of *Monascus* pigment extracts were in the range of 0.25–1.2 g per kilogram of different meat products (sausage or pâté). The *Monascus* colorants incorporated meat products exhibited stable color (95% stability after 3 months at 4°C under vacuum) and enhanced flavor and texture by sensory evaluation. The authors concluded that *Monascus* pigments were superior to nitrite salts and could serve as a suitable substitute for food additives in meat products.

Dihydromonacolins

Dihydromonascolins are structural analogs to monacolins. Dihydromonacolin-MV (Fig. 3b) is derived from the methanolic extract of *M. purpureus*. It contained strong 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and inhibition of lipid peroxidation in a liposome model (Dhale et al. 2007). Dihydromonacolin-L (Fig. 3a) was also isolated from the culture of *M. ruber* and was identified as a potent inhibitor of cholesterol biosynthesis (Endo et al. 1985a).

Citrinin

Citrinin (Fig. 3c) was initially named as monascidin A and was regarded as an antibacterial component in the crude extract of *Monascus*. Monascidin A was then confirmed to be the same compound as citrinin (Blanc et al. 1995).

Citrinin was found to be a hepatotoxic and nephrotoxic ingredient in MFR. It adversely affected the function and ultrastructure of kidney in the canine model (Krejci et al. 1996). Citrinin also has negative effects on liver function and metabolism. A decrease in liver glycogen content and an increase in serum glucose were observed (Chagas et al. 1992). Although the detailed molecular mechanism of the toxicity of citrinin is not well known, it has been demonstrated that citrinin mainly affects on mitochondria in cells. Citrinin permeated into the mitochondria, alters Ca^{2+} homeostasis (Chagas et al. 1995), and interfered the electron transport system (Ribeiro et al. 1997). Citrinin is not a mutagen itself; however, if it is transformed by hepatocytes, it becomes mutagenic to NIH-3T3 cells. The content of citrinin dominated the mutagenicity of *Monascus* fermentation products in a dosage-dependent manner. Only the samples with higher citrinin content showed positive response in the *Salmonella*–hepatocyte assay (Sabater-Vilar et al. 1999). Citrinin has also been reported as a teratogenic agent in chicken embryos (Ciegler et al. 1977).

Although MFR can be purchased in the market without any restrictions, its adverse ingredient citrinin is still a concern. Therefore, efforts have been made to decrease the content of citrinin. Citrinin is synthesized through the polyketide pathway, through which many secondary metabolites are synthesized, especially pigments. However, the synthesis of pigments and citrinin were not necessarily correlated (Wang et al. 2005). Some of the *Monascus* strains produced pigments without citrinin (Pisareva et al. 2005). However, the production of monacolin K without the existence of citrinin is not possible yet. Until now, we can only screen for the most suitable strain and maximize the parameters in production, to reduce the citrinin content to pass the statutory threshold. Currently, the statutory limit in the world is only legislated by the Japanese government. The presence of citrinin should be lower than 0.2 μg/g (200 ppb) of the *Monascus* pigments as used in food additives (The Ministry of Health and Welfare of Japan 2000).

Most molecules decompose in a high-temperature environment, including citrinin, which decomposed and lost its cytotoxicity to HeLa cells after treated with 175°C dry air. Increase in moisture lowered the temperature required to deactivate the cytotoxicity of citrinin. In a moist environment (200 μg citrinin/150 μg H_2O), the deactivation temperature was lowered to 160–175°C (Kitabatake et al. 1991). Citrinin H2, which is less toxic than citrinin, is considered the major product of citrinin decomposition (Hirota et al. 2002). However, Citrinin H1, another identified product of citrinin pyrolysis, also formed and is tenfold more toxic than citrinin (on a weight basis; Bentrivedi et al. 1993).

γ-Aminobutyric acid

Because the crude extract of MFR could alleviate hypertension in rats, a systematic fractionation and isolation of the responsible bioactive compound was conducted. Therefore, GABA and its pharmacological role to alleviate hypertension were discovered (Kohama et al. 1987). GABA has been widely researched on its role of an inhibitory neuronal signal transmitter. It has two receptors: $GABA_A$, which couples to chloride ion channels, and $GABA_B$, which are G protein-coupled receptors. Because GABA receptors exists extensively in the neuronal system and tissues, its pharmacological functions were intensively studied and have been well reviewed before (Blein et al. 2000; Kerr and Ong 1995; Watanabe et al. 2006).

Dimerumic acid

Dimerumic acid (Fig. 3e) showed in vitro antioxidative activity in the DPPH assay and was identified as the major constituent responsible for the antioxidative and hepatoprotective activity in the *Monascus* extract in the liver of injured mice induced by carbon tetrachloride (Aniya et al. 1999, 2000). Dimerumic acid was further found to inhibit the NADPH- and iron(II)-dependent lipid peroxidation of rat liver microsomes at 20 and 200 μM, respectively. The antioxidative property was contributed by the electron donation of the hydroxamic acid group to the oxidants (Taira et al. 2002).

Conclusion

MFR is widely used in Asia as a natural food colorant or Chinese medicine. Among its biofunctional constituents, monacolin K has been used in clinical therapy to lower the blood cholesterol concentration. MFR has been commercialized as a dietary supplement to ameliorate hypertention, hypercholesterolemia, and hyperlipidemia. The production of MFR-related products could be improved by selection of the strains, modification of incubation conditions, and genetic engineering to reduce the content of citrinin as well as to increase the production of monacolin K and GABA. Although MFR is well accepted as a dietary supplement, its complexity of constituents and its citrinin content are still concerns.

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