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MINI-REVIEW

Red mold, diabetes, and oxidative stress: a review

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Abstract Type 2 diabetes is a major health concern and a rapidly growing disease with a modern etiology, which produces significant morbidity and mortality. The optimal management of type 2 diabetes aims to control hyperglycemia, hypertension, and dyslipidemia to reduce overall risks. Diabetes and its complications usually develop as oxidative stress increases. *Monascus*-fermented rice, also called red mold rice or red mold dioscorea are used in China to enhance food color and flavor. Red mold-fermented products are popular health foods that are considered to have antiobesity, antifatigue, antioxidation, and cancer prevention effects. This review article describes the antidiabetic and antioxidative stress effects on humans and animals of red mold-fermented products or their secondary metabolites.

Keywords *Monascus* · Red mold · Secondary metabolite · Diabetes · Oxidative stress

Introduction

Red mold rice (RMR) is a fermented food product that is produced by inoculating *Monascus* into steamed rice, and it is a common food item in China. Red mold-fermented products have been used in Asia for centuries to enhance the flavor of food, as well as serving as a traditional medicine for the treatment of digestive disorders, vascular function, and blood circulation (Lee et al. 2006a; Ma et al. 2000). Red mold-fermented products are now considered to be functional foods, and they have been developed as commercial capsules for cardiovascular disease prevention. *Monascus* species produce several bioactive metabolites, and the secondary metabolites that are produced include pigments (red pigments: monascorubramine and rubropunctanin; orange pigments: monascorubrin and rubropunctanin; yellow pigments: ankaflavin (AK) and monascin (MS)) (Wong and Bau 1977; Wild et al. 2002), antioxidant compounds (e.g., isoflavones, dimerumic acid, phenols, and tannins) (Akihisa et al. 2005; Aniya et al. 2000), polyketide monacolins (antiobesity, anti-inflammatory, antidiabetic, and antioxidative stress-related metabolites, such as azaphilones, furanoisophthalides, and amino acids) (Su et al. 2003; Akihisa et al. 2005; Lee et al. 2006b), and γ-aminobutyric acid (GABA, a neurotransmitter and hypotensive agent) (Su et al. 2003; Juslova et al. 1996; Ma et al. 2000). Oxidative stress is increased during diabetes and caused damage to organisms. Reactive oxygen species (ROS) and the inflammatory response are generated as a result of hyperglycemia, which causes many of the secondary complications of diabetes (West 2000). Previous studies revealed that the level of blood glucose was decreased in experimental rats fed with *Monascus*-fermented products (Chen and Liu 2006); triglyceride (TG) and total cholesterol (TC) levels were decreased (Shi and Pan 2010a). The diabetic rats showed higher ROS and lower antioxidant enzyme (glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT)) activities in pancreas when treated with red mold-fermented products (Shi and Pan 2010b). These results indicated that red mold-fermented products not only regulate hyperglycemia but also provide the prevention effects of hyperglycemia-induced oxidative stress.

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The aforementioned *Monascus*-fermented products and their metabolites may be of great benefit for the amelioration of diabetes symptoms and their development.

Diabetes, oxidative stress, and diabetic complications

Diabetes mellitus is a metabolic disorder that is characterized by an elevated blood glucose concentration and the inadequate secretion or activity of endogenous insulin (Singh et al. 2008). Diabetes leads to hyperglycemia, and it also causes hyperlipidemia, hyperinsulinemia, hypertension, and atherosclerosis (Sowers et al. 2001; Beckman et al. 2002; Sepici et al. 2004). The etiology of this disease is not well defined, but environmental factors, autoimmune disease, and viral infections have been implicated (Like et al. 1979; Kataoka et al. 1983; Shewade et al. 2001; Maritim et al. 2003). Several studies have suggested that a hyperglycemia-induced overproduction of superoxide seems to be activated in all pathways involved in the pathogenesis of diabetes complications (Fig. 1) (Robertson et al. 2003; Ceriello 2006). In vivo evidence supports the major contribution of hyperglycemia to the production of oxidative stress and the acute endothelial dysfunction of patients with diabetes (Ceriello 2006). Free radical-caused oxidative stress and oxidative damage to tissues are common endpoints of age-related or chronic diseases, such as atherosclerosis, diabetes, Alzheimer's disease, and rheumatoid arthritis (Baynes and Thorpe 1999; Tuppo and Forman 2001; Hadjigogos 2003). Abnormally high levels of free radicals and the loss of antioxidant defense mechanisms lead to damage to the cellular organelles and enzymes,

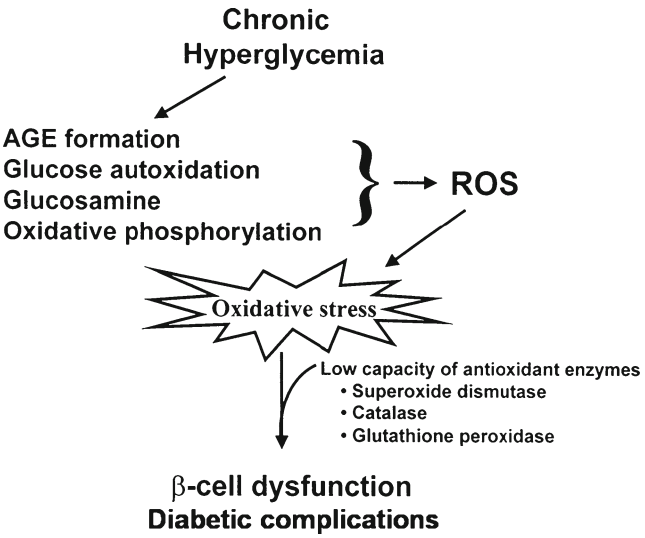

Fig. 1 Hyperglycemia presents excessively high concentrations of glucose for reactive oxidative species formation and oxidative stress (Robertson et al. 2003)

increased lipid peroxidation, DNA damage, and protein derivatives, and the development of insulin resistance (West 2000; Maritim et al. 2003). Vascular function, like impaired endothelium-dependent vasodilatation, has been in diabetic animal models (Mayhan 1989) and has found endothelial dysfunction (Johnstone et al. 1993). Normal or diabetic animals exposed to exogenous hyperglycemia subsequently have exhibited attenuated endothelium-dependent relaxation, an endothelial dysfunction (Kawano et al. 1999). Free radicals generation-induced oxidative stress has produced the hyperglycemia-dependent endothelial dysfunction; it makes diabetes and its complication severe (Diederich et al. 1994).

Microvascular and cardiovascular oxidative stress increases during the development of diabetes complications (Coleman 2001; Maritim et al. 2003). The mechanisms whereby increased oxidative stress leads to the activation of the five major pathways involved in the pathogenesis of complications are as follows: increased formation of advanced glycation end products (AGEs) (Scivittaro et al. 2000), polyol pathway flux (Chung et al. 2003), increased expression of the AGEs receptor and its activating ligands, overactivation of the hexosamine pathway (Horal et al. 2004), and protein kinase C activation (Tuttle et al. 2009; Giacco and Brownlee 2010). Increased intracellular ROS activation occurs in a number of proinflammatory pathways (Bulua et al. 2011), which has been implicated in inflammatory diseases including rheumatoid arthritis, type 1 diabetes (Chen et al. 2008), and multiple sclerosis (Gilgun-Sherki et al. 2004). Overexpression of antioxidant enzymes in transgenic diabetic mice, such as SOD, prevents diabetic nephropathy (Ceriello et al. 2000), retinopathy (Lopes de Jesus et al. 2008), and cardiomyopathy (Singal et al. 2001). Understanding the relationships among oxidative stress, diabetes, and its complications will aid the discovery of novel therapeutic treatments for the prevention of diabetic complications.

Beneficial effects of red mold-fermented products on blood glucose management

Red mold products fermented by *Monascus purpureus* NTU 568 produce secondary metabolites such as monacolin K, MS, AK, and GABA, with potent hypolipidemic and antihypertensive effects that have been characterized in our previous studies (Lee et al. 2006a, b; Wu et al. 2009). We studied the preventive and beneficial effects of *M. purpureus* NTU 568 fermented red mold products on diabetic animals (Shi and Pan 2010a, b; Shi et al. 2011). As discussed below, results from two of these studies might help to explain the main mechanism whereby red mold-fermented products ameliorate the development of diabetes by lowering the levels of blood glucose and lipid profiles in diabetic animals.

Diabetes symptom modification via blood glucose reduction

Red mold-fermented products are known to have a role in the regulation of blood glucose and insulin resistance (Chang et al. 2006; Chen and Liu 2006; Shi and Pan 2010a). Red mold-fermented products can also lower blood cholesterol levels, control cardiovascular complications, and glucose homeostasis (Journoud and Jones 2004; Chang et al. 2006). They are considered useful for the treatment of diabetes. The studies revealed that feeding experimental rats with 150 mg/kg of *Monascus*-fermented products after 12 h of fasting led to the blood glucose level decreasing by 19.4% after 90 min compared with a control group, while the insulin level increased by 60.2% (Chen and Liu 2006). The mediation of acetylcholine (ACh, an inhibitor of choline uptake) release from the nerve terminals to enhance insulin secretion by red mold-fermented products may also be considered (Chen and Liu 2006). Gluconeogenesis augmentation is a major factor affecting plasma glucose increases in diabetic animals (Consoli et al. 1989). Previous studies showed that the phosphoenolpyruvate carboxykinase (PEPCK) mRNA levels in the liver of diabetic rats were inhibited by oral treatment with red mold-fermented products for 14 days (Chang et al. 2006). Red mold-fermented products may act directly or indirectly via endogenous substances to modify hepatic PEPCK gene expression. After 8 weeks of feeding diabetic rats with different types of red mold-fermented products (RMR, red mold adlay and red mold dioscorea (RMD)), it was found that all types of red mold products reduced the blood glucose levels (Shi and Pan 2010a). Moreover, the degraded lipid profiles of TG and TC were improved by red mold-fermented product treatments (Table 1) (Shi and Pan 2010b). Red mold-fermented products can increase the release of ACh from nerve terminals, decrease hepatic gluconeogenesis, and increase insulin secretion, which lowers the blood glucose activity.

Table 1 Serum triglyceride (TG) and cholesterol (TC) levels in diabetic rats were ameliorated by red mold-fermented products treatment

Groups	TG (mg/dL)	TC (mg/dL)
Normal control (NC)	87.9±12.5**	74.7±5.6*
Diabetic control (DC)	437.3±22.5	100.3±9.5
DM + RMR	141.8±34.3**	76.0±7.0*
DM + RMD	122.3±32.5**	75.8±10.1*
DM + RMA	272.6±69.8*	77.7±14.6*

Data are presented as the means ± SE of six rats in each group

DM rat with diabetes mellitus, *RMR* red mold rice, *RMD* red mold dioscorea, *RMA* red mold adlay

*$P<0.05$; **$P<0.001$ (compared with data from normal control and STZ-induced diabetic rats treated with diabetic control)

Inhibiting hyperglycemia-increased oxidative stress and inflammation via antioxidation and anti-inflammatory effects

Red mold-fermented products that contain a variety of antioxidants are mentioned in an ancient Chinese pharmacopoeia of medicinal food and herbs. The antioxidant action of traditional foods has been investigated, and it was shown that *Monascus anka* and *Monascus ruber* have a strong antioxidant action (Aniya et al. 1999). *M. anka* and *M. ruber* scavenged over 60% of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and inhibited lipid peroxidation at a concentration of 1.6% (Aniya et al. 2000). The radical-scavenging, iron-chelating, and DNA-protection activities of liquid fermentation products derived from *Monascus pilosus* were significantly higher when grown in a garlic-containing medium (Kuo et al. 2006). The addition of garlic to the culture medium significantly increased the antioxidant activities of *M. pilosus* fermentation products in terms of DPPH (50% inhibition at a concentration of 4.62%), superoxide (50% inhibition at a concentration lower than 5.0%), and hydrogen peroxide (50% inhibition at a concentration lower than 0.1%) scavenging activity, iron-chelating activity, as well as protecting against lipid peroxidation and DNA damage (Kuo et al. 2006).

Throughout the experimental period (8 weeks), diabetic rats had higher ROS levels (12.1–65.8%) and lower activities of SOD (18.2–35.7%), CAT (26.4–34.9%), and GR (9.0–30.0%) in the pancreas compared with rats treated with red mold-fermented products (Shi and Pan 2010b). Moreover, nitric oxide (leading to oxidative stress) production and endothelin-1 (upregulated in diabetes) levels were improved by red mold-fermented product treatment (Shi and Pan 2010b).

The RMD contained 3,572.7 mg/kg MS and 2,444.3 mg/kg AK higher than RMR (3,099.7 mg/kg MS and 1,048.8 mg/kg AK) (Shi and Pan 2010c). RMD has greater hypolipidemic, antidiabetic, and antioxidant effects than traditional RMR in experimental animals where it reduces oxidative stress and the anti-inflammatory response (Lee et al. 2007b; Shi and Pan 2010a, b). Diabetic rats treated with RMD for 6 weeks had higher activity levels of SOD, GR, glutathione peroxidase (GPx), and CAT in the pancreas compared with diabetic control rats (Table 2) (Shi et al. 2011). The islet inflammatory process in diabetic rats exhibited an increased islet cytokine (interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α) expression (Ehses et al. 2009). The increased production of IL-6 and interferon (IFN)-γ by STZ-induced diabetic rats was identified as autoimmune diabetes (Ishihara and Hirano 2002). RMD inhibited the diabetes-induced elevation in the levels of IL-1β and TNF-α in the pancreas, and it ameliorated pancreatic β-cell damage (Fig. 2) caused by STZ (Shi et al. 2011). It was demonstrated that red mold-fermented products possess several treatment-oriented properties, including the control of hyperglycemia,

Table 2 Antioxidative activity of red mold dioscorea in the pancreas of experimental rats

Groups	GR nmol GSSG/min/mg protein	GPx nmol GSSG/min/mg protein	SOD U/mg protein	CAT nmol H_2O_2/min/mg protein
Normal control (NC)	3.3±0.5*	14.6±1.4*	3.3±0.5*	47.1±1.4*
Diabetic control (DC)	2.6±0.4	5.6±3.6	1.6±0.6	22.7±1.8
DM+RMD	4.2±0.3*	14.4±3.3*	3.5±0.4*	40.0±2.3*

Data are presented as the means ± SE of six rats in each group

DM rat with diabetes mellitus, *RMD* red mold dioscorea, *GR* glutathione reductase, *GPx* glutathione peroxidase, *SOD* superoxide dismutase, *CAT* catalase

*$P<0.05$ (compared with data from normal control and STZ-induced diabetic rats treated with diabetic control

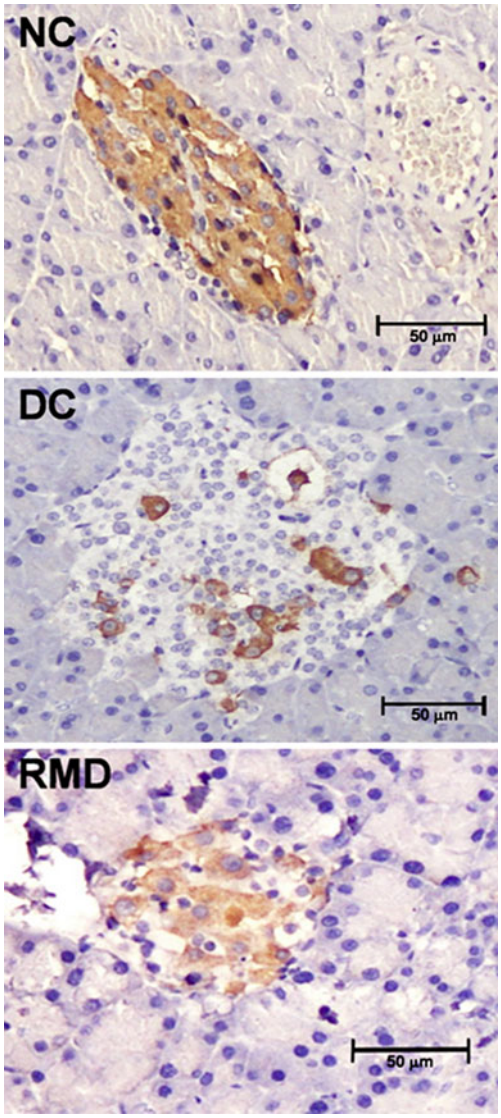

Fig. 2 Immunohistochemical evaluation on pancreas (×400). Immunohistochemical staining was carried out using avidin-biotinylated horseradish peroxidase kit. *NC* normal control group, *DC* diabetic control group, *RMD* diabetic animals with red mold dioscorea treatment (Shi et al. 2011)

antioxidative stress function, as well as anti-inflammatory and cytoprotective effects.

Red mold secondary metabolites with antidiabetic and related beneficial effects γ-aminobutyric acid (GABA)

GABA is an amino acid transmitter that is present in the inhibitory neurons of the central nervous system, which is synthesized from glutamic acid by glutamic acid decarboxylase (Fig. 3) (Gerber and Hare 1980; Pipeleers et al. 1985). GABA has several well-known physiological functions, including antihypertensive and diabetic hyperglycemia prevention activities (Wu et al. 2009; Soltani et al. 2011). Several manufactured functional foods have a high GABA content: GABA-enriched rice germ by soaking in water (Komatsuzaki et al. 2007), GABA-enriched brown rice by high pressure treatment and germination (Kinefuchi et al. 1999), and red mold rice containing the *Monascus* fungus (Rhyu et al. 2000). Some studies have isolated and identified the GABA-rich *Monascus* strains and irradiated them with UV or modified substrates to raise their GABA production (Chuang et al. 2011; Jiang et al. 2011). The importance of GABA for the function of hormonal secretion has been reported (Cavagnini et al. 1977; Sorenson et al. 1991). GABA agonists have been used to modify the blood glucose levels of diabetic rats and increase the plasma insulin concentrations to levels similar to those of non-diabetic animals (Gomez et al. 1999). These experiments demonstrated that GABA and GABA receptor agonist drugs act on the endocrine pancreas in vivo, ultimately increasing the insulin levels and decreasing the blood glucose levels of diabetic rats (Gomez et al. 1999).

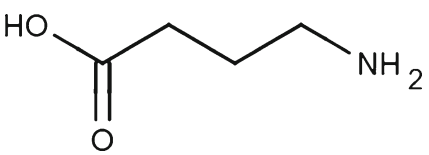

Fig. 3 The chemical structure of γ-aminobutyric acid (GABA)

Type 1 diabetes is an autoimmune disease that is characterized by the infiltration of the pancreatic islets with T lymphocytes and macrophages, where consequent loss of β-cells requires β-cell restoration and immune suppression therapy (Eizirik et al. 2009; Lehuen et al. 2010; Soltani et al, 2011). Research has indicated that GABA exerts antidiabetic effects by acting on the islet β-cells and the immune system. GABA leads to membrane depolarization and the activation of PI3-K/Akt-dependent pathways, which restores β-cell mass and reverses diabetes. GABA has β-cell regenerative and immune inhibitory effects on islet cell function, and it regulates glucose homeostasis (Soltani et al. 2011).

Monascin (MS)

It was reported that MS is the major constituent of the azaphilonoid pigments found in extracts of RMR (Fig. 4) (Hsu et al. 2010). MS is a potential cancer-preventive agent for combating chemical and environmental carcinogenesis. It is also an anti-inflammatory agent that inhibits the 12-*O*-tetradecanoylphorbol 13-acetate-induced inflammatory response in mice (Akihisa et al. 2005). In previous studies, we showed that the RMD may have hypolipidemic and hypoglycemic effects via its secondary metabolite MS (Lee et al. 2010b; Shi and Pan 2010a). Chronic inflammation in muscle tissue is linked with type 2 diabetes, insulin resistance, and diabetic complications. Peroxisome proliferator-activated receptor (PPAR, a member of the nuclear receptor family of transcription factors) ligands have been reported to activate the phosphatidylinositol 3-kinase (PI3K)/Akt pathway (Bulhak et al. 2009). Studies have indicated that MS inhibited the *p*-JNK activity and prevented PPAR-γ phosphorylation via its PPAR-γ activity and the PI3K/Akt pathway (Lee et al. 2011). MS treatment of C2C12 cells may elevate PPAR-γ mRNA expression and prevent PPAR-γ phosphorylation. Moreover, the use of a PPAR-γ antagonist (GW9662) to block PPAR-γ activation in C2C12 cell indicated that MS may be an agonist of PPAR-γ, which improves insulin resistance (Lee et al. 2011).

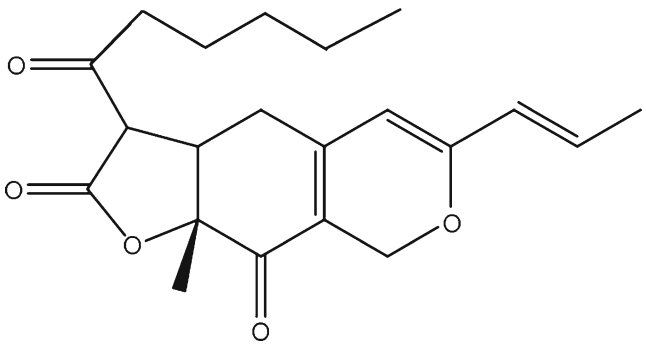

Fig. 4 The chemical structure of monascin (MS)

The mechanisms whereby MS exerts its in vivo action were tested using animal and *Caenorhabditis elegans* models (Shi et al. 2012). The nematode *C. elegans* has been an important animal model for studying the molecular mechanisms of drug effects and disease pathogenesis. In animal experiments, we found that the levels of blood glucose, serum insulin, TG, TC, high-density lipoprotein, and the activities of antioxidant enzymes were ameliorated by MS treatment in STZ-induced diabetic rats (Shi et al. 2012). DAF-16/FOX (Forkhead box) proteins are a family of transcription factors that are involved in metabolism, stress resistance, and antioxidative defense in *C. elegans* and mammals (Henderson and Johnson 2001; Murphy et al. 2002). Studies have indicated that MS induced the hepatic mRNA levels of FOXO1, FOXO3a, catalase, and MnSOD in diabetic rats and enhanced the expression of small heat shock protein, glutathione *S*-transferase, and SOD-3 in *C. elegans* (Fig. 5) (Shi et al. 2012). Mechanistic studies in cells, rats, and *C. elegans* suggest that the protective effects of MS are mediated via the regulation of the FOXO/DAF-16-dependent insulin signaling pathway and the AKT pathway, by inducing the expression of stress response/antioxidant genes, regulating PPAR-γ, and inhibiting JNK activation (Lee et al. 2011; Shi et al. 2012).

Safety

Red mold-fermented products may be contaminated by citrinin, which is regarded as a toxic secondary metabolite of *Aspergillus* and *Penicillium* species to damage the kidneys

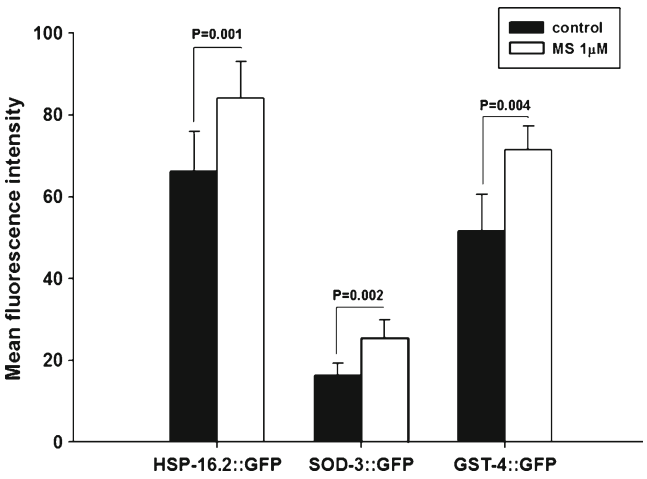

Fig. 5 Effects of monascin (MS) on the expressions of heat shock protein (HSP)-16.2, superoxide dismutase (SOD)-3, and glutathione S-transferase (GST)-4 in *Caenorhabditis elegans*. Transgenic worms were incubated with 1 μM MS or 0.1% DMSO as the solvent control at 22 °C. Total GFP fluorescence for each whole worm was quantified by Image-Pro Plus software. Data shown are the average number of pixels in the transgenic *C. elegans* (n=20) at each indicated treatment. Data are presented as the mean ± SD (Shi et al. 2012)

Table 3 Comparisons between the reduced levels of risk factors for diabetes and its complications caused by red mold-fermented products and its secondary metabolites

Sample	Inhibition					Increase			Reference
	Blood glucose level	Oxidative stress	Inflammation	PEPCK activity	p-JNK activity	Insulin level	Ach activity	FOXO transcription factor activity	
RMFP	+	−	−	−	−	+	+	−	Chen and Liu (2006)
RMFP	+	−	−	+	−	+	−	−	Chang et al. (2006)
RMFP	+	−	−	−	−	+	−	−	Shi and Pan (2010a)
RMFP	−	−	+	−	−	−	−	−	Shi and Pan (2010b)
RMFP	+	+	+	−	−	−	−	−	Shi et al. (2011)
GABA	+	−	−	−	−	−	+	−	Gomez et al. (1999)
GABA	+	+	+	−	−	−	−	−	Soltani et al. (2011)
MS	−	−	−	−	+	−	−	−	Lee et al. (2011)
MS	+	+	−	−	−	+	−	+	Shi et al. (2012)

ACh acetylcholine, *FOXO* Forkhead box family, *GABA* gamma-amino butyric acid, *JNK* c-Jun N-terminal kinases, *PEPCK* phosphoenolpyruvate carboxykinase, *RMFP* red mold-fermented products

and liver. (Hetherington and Raistrick 1931). The lethal dose (LD_{50}) of citrinin has been reported to be about 35–58 mg/kg for oral administration to a mouse, 50 mg/kg to a rat, and 134 mg/kg to a rabbit (Hanika an Carlton 1994). The toxicity evaluations of *Monascus*-fermented products for an experimental period of as long as 4 months have shown no toxicity effects (Li et al. 1998).

Studies on increasing the level of monacolin K and decreasing the level of citrinin have been investigated by several laboratories (Chen and Hu 2005; Wang et al. 2004). The previous study has developed a post-process to remove citrinin yet retain monacolin K in the RMR preparation (Lee et al. 2007a). On the basis of the findings from the 90-day animal test with citrinin (1, 2, 10, 20, and 200 ppm) treatment, the no-observable-adverse-effect level (NOAEL) is 200 ppm citrinin for male Wistar rats (Lee et al. 2010a). Investigations are focused on the conditions of red mold-fermented production to a lower citrinin concentration.

Conclusion

Monascus-fermented rice is mentioned in an ancient Chinese pharmacopoeia of medicinal food. A product fermented with *M. purpureus* NTU 568 has been used to ameliorate hyperlipidemia, hypertension, diabetes, obesity, and Alzheimer's disease. The novel product RMD was found to contain higher amounts of antioxidative and anti-inflammatory substances, GABA, and MS, compared with traditional RMR, and it also had greater potential for ameliorating insulin resistance and diabetes. Table 3 shows that red mold-fermented products and its secondary metabolites utilize a different preventive mechanism for diabetes, and a hypothesis regarding the preventative activity of red mold-fermented products and its secondary metabolites is presented in Fig. 6. Several mechanisms, PI3-K/Akt-dependent pathway and FOXO/DAF-16 transcription factors activation, explaining how *Monascus* species-fermented products ameliorate diabetes and related oxidative stress are

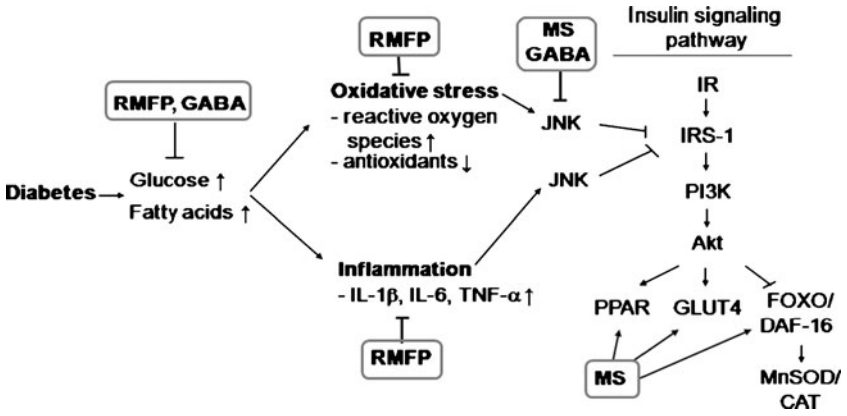

Fig. 6 Hypothesis proposing of the preventative approach of red mold-fermented products and its secondary metabolites with diabetic oxidative stress, inflammatory response, and insulin resistance

available at present, but its underlying functional ingredients and its deep mechanisms remain elusive. Therefore, future studies should be focused on the isolation of functional ingredients and investigations of their mechanisms in different animal models, which will support the development of useful therapies for diabetes and its complications.

References

Akihisa T, Tokuda H, Yasukawa K, Ukiya M, Kiyota A, Sakamoto N, Suzuki T, Tanabe N, Nishino H (2005) Azaphilones, furanoisophthalides, and amino acids from the extracts of *Monascus pilosus*-fermented rice (red-mold rice) and their chemopreventive effects. J Agric Food Chem 53:562–565

Aniya Y, Yokomakura T, Yonamine M, Shimada K, Nagamine T, Shimabukuro M, Gibo H (1999) Screening of antioxidant action of various molds and protection of *Monascus anka* against experimentally induced liver injuries of rats. Gen Pharmacol 32:225–231

Aniya Y, Ohtani II, Higa T, Miyagi C, Gibo H, Shimabukuro M, Nakanishi H, Taira J (2000) Dimerumic acid as an antioxidant of the mold, *Monascus anka*. Free Radic Biol Med 28:999–1004

Baynes JW, Thorpe SR (1999) Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 48:1–9

Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology and management. JAMA 287:2570–2581

Bulhak AA, Jung C, Ostenson CC, Lundberg JO, Sjöquist PO, Pernow J (2009) PPAR-α activation protects the type 2 diabetic myocardium against ischemia-reperfusion injury: involvement of the PI3-kinas/Akt and NO pathway. Am J Physiol Heart Circ Physiol 296:H719–H727

Bulua AC, Simon A, Maddipati R, Pelletier M, Park H, Kim KY, Sack MN, Kastner DL, Siegel RM (2011) Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). J Exp Med 208:519–533

Cavagnini F, Invitti C, Landro AD, Tenconi L, Maraschini C, Girotti G (1977) Effects of a gamma aminobutyric acid (GABA) derivative, baclofen, on growth hormone and prolactin secretion in man. J Clin Endocrino Metabol 45:579–584

Ceriello A (2006) Oxidative stress and diabetes-associated complications. Endocr Pract 12(Suppl 1):60–62

Ceriello A, Morocutti A, Mercuri F, Quagliaro L, Moro M, Damante G, Viberti GC (2000) Defective intracellular antioxidant enzyme production in type 1 diabetic patients with nephropathy. Diabetes 49:2170–2177

Chang JC, Wu MC, Liu IM, Cheng JT (2006) Plasma glucose-lowering action of Hon-Chi in streptozotocin-induced diabetic rats. Horm Metab Res 38:76–81

Chen F, Hu X (2005) Study on red fermented rice with high concentration of monacolin K and low concentration of citrinin. Int J Food Microbiol 103:331–337

Chen CC, Liu IM (2006) Release of acetylcholine by Hon-Chi to raise insulin secretion in Wistar rats. Neurosci Lett 404:117–121

Chen J, Gusdon AM, Thayer TC, Mathews CE (2008) Role of increased ROS dissipation in prevention of T1D. Ann N Y Acad Sci 1150:157–166

Chuang CY, Shi YC, You HP, Lo YH, Pan TM (2011) Antidepressant effect of GABA-rich *Monascus*-fermented product on forced swimming rat model. J Agric Food Chem 59:3027–3034

Chung SS, Ho EC, Lam KS, Chung SK (2003) Contribution of polyol pathway to diabetes-induced oxidative stress. J Am Soc Nephrol 14(Suppl 3):S233–S236

Coleman MD (2001) Monitoring diabetic antioxidant status: a role for in vitro methaemoglobin formation. Environ Toxicol Pharmacol 10:207–213

Consoli A, Nurjhan N, Capani F, Gerich J (1989) Predominant role of gluconeogenesis in increased hepatic glucose production in NIDDM. Diabetes 38:550–557

Diederich D, Skopec J, Diederich A, Dai F (1994) Endothelial dysfunction in mesenteric resistance arteries of diabetic rats: role of free radicals. Am J Physiol 266:H1153–H1161

Ehses JA, Lacraz G, Giroix MH, Schmidlin F, Coulaud J, Kassis N, Irminger JC, Kergoat M, Portha B, Homo-Delarche F, Donath MY (2009) IL-1 antagonism reduces hyperglycemia and tissue inflammation in the type 2 diabetic GK rat. PNAS 106:13998–14003

Eizirik DL, Colli ML, Ortis F (2009) The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. Nat Rev Endocrinol 5:219–226

Gerber JC, Hare TA (1980) GABA in peripheral tissue: presence and action in endocrine pancreatic function. Brain Res Bull 5 (Suppl 2):341–346

Giacco F, Brownlee M (2010) Oxidative stress and diabetic complications. Circ Res 107:1058–1070

Gilgun-Sherki Y, Melamed E, Offen D (2004) The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J Neurol 251:261–268

Gomez R, Asnis N, Tannhauser SL, Barros HMT (1999) GABA agonists differentially modify blood glucose levels of diabetic rats. Jpn J Pharmacol 80:327–331

Hadjigogos K (2003) The role of free radicals in the pathogenesis of rheumatoid arthritis. Panminerva Med 45:7–13

Hanika C, Carlton WW (1994) Toxicology and pathology of citrinin. In: Llewellyn GG, Dashek WV, O'Rear CE (eds) Biodeterioriation research, vol 4. Plenum Press, New York, pp 41–63

Henderson ST, Johnson TE (2001) *daf-16* integrates developmental and environmental inputs to mediate aging in the nematode *Caenorhabditis elegans*. Curr Biol 11:1975–1980

Hetherington AC, Raistrick H (1931) Studies in the biochemistry of micro-organism. XI. On the production and chemical constitution of a new yellow colouring matter, citrinin, produced from glucose by *Penicillium citrinum*. Thom Philos Trans R Soc London Ser B 220:269–297

Horal M, Zhang Z, Stanton R, Virkamäki A, Loeken MR (2004) Activation of the hexosamine pathway causes oxidative stress and abnormal embryo gene expression: involvement in diabetic teratogenesis. Birth Defects Res A Clin Mol Teratol 70:519–527

Hsu YW, Hsu LC, Liang YH, Kuo YH, Pan TM (2010) Monaphilones A–C, three new antiproliferative azaphilone derivatives from *Monascus purpureus* NTU 568. J Agric Food Chem 59:8211–8216

Ishihara K, Hirano T (2002) IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine Growth Factor Rev 13:357–368

Jiang D, Ji H, Ye Y, Hou J (2011) Studies on screening of higher γ-aminobutyric acid-producing *Monascus* and optimization of fermentative parameters. Eur Food Res Technol 232:541–547

Johnstone MT, Creager SJ, Scales KM, Cusco JA, Lee BK, Creager MA (1993) Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. Circulation 88:2510–2516

Journoud M, Jones PJ (2004) Red yeast rice: a new hypolipidemic drug. Life Sci 74:2675–2683

Juslova P, Martinkova L, Kren V (1996) Secondary metabolites of the fungus *Monascus*: a review. J Ind Microbiol 16:163–170

Kataoka S, Satoh J, Fujiya H, Toyota T, Suzuki R, Itoh K, Kumagai K (1983) Immunologic aspects of the nonobese diabetic (NOD) mouse. Abnormalities of cellular immunity. Diabetes 32:247–253

Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, Kugiyama K, Ogawa H, Yasue H (1999) Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. J Am Coll Cardiol 34:146–154

Kinefuchi M, Sekiya M, Yamazaiki A, Yamamoto K (1999) Accumulation of GABA in brown rice by high pressure treatment. Nippon Shokuhin Kagaku Kaishi 46:323–328

Komatsuzaki N, Tsukahara K, Toyoshima H, Suzuki T, Shimizu N, Kimura T (2007) Effect of soaking and gaseous treatment on GABA content in germinated brown rice. J Food Eng 78:556–560

Kuo CF, Wang TS, Yang PL, Jao YC, Lin WY (2006) Antioxidant activity of liquid-state fermentation products of *Monascus pilosus* grown in garlic-containing medium. J Food Sci 71: S456–S460

Lee CL, Tsai TY, Wang JJ, Pan TM (2006a) In vivo hypolipidemic effects and safety of low dosage *Monascus* powder in a hamster model of hyperlipidemia. Appl Microbiol Biotechnol 70:533–540

Lee CL, Wang JJ, Kuo SL, Pan TM (2006b) *Monascus* fermentation of dioscorea for increasing the production of cholesterol-lowering agent-monacolin K and antiinflammation agent-monascin. Appl Microbiol Biotechnol 72:1254–1262

Lee CL, Chen WP, Wang JJ, Pan TM (2007a) A simple and rapid approach for removing citrinin while retaining monacolin K in red mold rice. J Agric Food Chem 55:11101–11108

Lee CL, Hung HK, Wang JJ, Pan TM (2007b) Red mold dioscorea has greater hypolipidemic and antiatherosclerotic effect than traditional red mold rice and unfermented dioscorea in hamsters. J Agric Food Chem 55:7162–7169

Lee CH, Lee CL, Pan TM (2010a) A 90-d toxicity study of *Monascus*-fermented products including high citrinin level. J Sci Food Agric 75:91–97

Lee CL, Kung YH, Wu CL, Hsu YW, Pan TM (2010b) Monascin and ankaflavin act as novel hypolipidemic and high-density lipoprotein cholesterol-raising agents in red mold dioscorea. J Agric Food Chem 58:9013–9019

Lee BH, Hsu WH, Liao TH, Pan TM (2011) The *Monascus* metabolite monascin against TNF-α-induced insulin resistance via suppressing PPAR-γ phosphorylation in C2C12 myotubes. Food Chem Toxicol 49:2609–2617

Lehuen A, Diana J, Zaccone P, Cooke A (2010) Immune cell crosstalk in type 1 diabetes. Nat Rev Immunol 10:501–513

Li C, Zhu Y, Wang Y (1998) *Monascus purpureus* fermented rice (red yeast rice): a natural food product that lowers blood cholesterol in animal models of hypercholesterolemia. Nutr Res 18:71–81

Like AA, Rossini AA, Guberski DL, Appel MC, Williams RM (1979) Spontaneous diabetes mellitus: reversal and prevention in the BB/W rat with antiserum to rat lymphocytes. Science 206:1421–1423

Lopes de Jesus CC, Atallah AN, Valente O, Moça Trevisani VF (2008) Vitamin C and superoxide dismutase (SOD) for diabetic retinopathy. Cochrane Database Syst Rev 23:CD006695

Ma J, Li Y, Ye Q, Li J, Hua Y, Ju D, Zhang D, Cooper R, Chang M (2000) Constituents of red yeast rice, a traditional Chinese food and medicine. J Agric Food Chem 48:5220–5225

Maritim AC, Sanders RA, Watkins JB III (2003) Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol 17:24–38

Mayhan WG (1989) Impairment of endothelium-dependent dilatation of cerebral arterioles during diabetes mellitus. Am J Physiol 256: H621–H625

Murphy GT, McCarroll SA, Bargmann CI, Fraser A, Kamath RS, Ahringer J (2002) Genes that act downstream of DFA-16 to influence lifespan of *Caenorhabditis elegans*. Nature 424:277–284

Pipeleers DG, Schuit FC, Van Schravendijk CF, Van WM (1985) Interplay of nutrients and hormones in the regulation of glucagon release. Endocrinology 117:817–823

Rhyu MR, Kim EY, Kim HY, Ahn BH, Yang CB (2000) Characteristics of the red rice fermented with fungus *Monascus*. Food Sci Biotechnol 9:21–26

Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H (2003) Glucose toxicity in β-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. Diabetes 52:581–587

Scivittaro V, Ganz MB, Weiss MF (2000) AGEs induce oxidative stress and activate protein kinase C-β_{II} in neonatal mesangial cells. AJP-Renal Physiol 278:F676–F683

Sepici A, Gurbuz I, Cevik C, Yesilada E (2004) Hypoglycaemic effects of myrtle oil in normal and alloxan-diabetic rabbits. J Ethnopharmacol 93:311–318

Shewade Y, Tirth S, Bhonde RR (2001) Pancreatic islet-cell viability, functionality and oxidative status remain unaffected at pharmacological concentrations of commonly used antibiotics in vitro. J Biosci 26:349–355

Shi YC, Pan TM (2010a) Anti-diabetic effects of *Monascus purpureus* NTU 568 fermented products on streptozotocin-induced diabetic rats. J Agric Food Chem 58:7634–7640

Shi YC, Pan TM (2010b) Antioxidant and pancreas-protective effect of red mold fermented products on streptozotocin-induced diabetic rats. J Sci Food Agric 90:2519–2525

Shi YC, Pan TM (2010c) Characterization of a multifunctional *Monascus* isolate NTU 568 with high azaphilone pigments production. Food Biotechnol 24:349–363

Shi YC, Liao JW, Pan TM (2011) Antihypertriglyceridemia and anti-inflammatory activities of *Monascus*-fermented diocsorea in streptozotocin-induced diabetic rats. Experi Diab Res 2011:1–11

Shi YC, Liao HC, Pan TM (2012) Monascin from red mold dioscorea as a novel antidiabetic and antioxidative stress agent in rats and *Caenorhabditis elegans*. Free Radic Biol Med 52:109–117

Singal PK, Belló-Klein A, Farahmand F, Sandhawalia V (2001) Oxidative stress and functional deficit in diabetic cardiomyopathy. Adv Exp Med Biol 498:213–220

Singh SK, Rai PK, Jaiswal D, Watal G (2008) Evidence-based critical evaluation of glycemic potential of *Cynodon dactylon*. Evid Based Complement Alternat Med 5:415–420

Soltani N, Qiu H, Aleksic M, Glinka Y, Zhao F, Liu R, Li Y, Zhang N, Chakrabarti R, Ng T, Lin T, Zhang H, Lu WY, Feng ZP, Prud'homme GJ, Wang Q (2011) GABA exerts protective and regenerative effects on islet beta cells and reverses diabetes. PNAS 108:11692–11697

Sorenson RL, Garry DG, Brelje TC (1991) Structural and functional considerations of GABA in islets of Langerhans: beta-cells and nerves. Diabetes 40:1365–1374

Sowers JR, Epstein M, Frohlich ED (2001) Diabetes, hypertension, and cardiovascular disease. Hypertension 37:1053–1059

Su YC, Wang JJ, Lin TT, Pan TM (2003) Production of the secondary metabolites gamma-amino butyric acid and monacolin K by *Monascus*. J Ind Microbiol Biotechnol 30:41–46

Tuppo EE, Forman LJ (2001) Free radical oxidative damage and Alzheimers disease. JAOA 101:S11–S15

Tuttle KR, Anderberg RJ, Cooney SK, Meek RL (2009) Oxidative stress mediates protein kinase C activation and advanced glycation end product formation in a mesangial cell model of diabetes and high protein diet. Am J Nephrol 29:171–180

Wang JJ, Lee CL, Pan TM (2004) Modified mutation method for screening low citrinin-producing strains of *Monascus purpureus* on rice culture. J Agric Food Chem 52:6977–6982

West IC (2000) Radicals and oxidative stress in diabetes. Diabetic Med 17:171–180

Wild D, Toth G, Humpf HU (2002) New *Monascus* metabolite isolated from red yeast rice (angkak, red koji). J Agric Food Chem 50:3999–4002

Wong HC, Bau YS (1977) Pigmentation and antibacterial activity of fast neutron- and x-ray-induced strains of *Monascus purpureus* Went. Plant Physiol 60:578–581

Wu CL, Lee CL, Pan TM (2009) Red mold dioscorea has a greater antihypertensive effect than traditional red mold rice in spontaneously hypertensive rats. J Agric Food Chem 57:5035–5041