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MINI-REVIEW

Benefit of *Monascus*-fermented products for hypertension prevention: a review

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Abstract γ-Aminobutyric acid (GABA) has been reported to play a neurotransmitter in the central nervous system thereby exerting an inhibition in nerve impulse, in turn ameliorating depression; in addition, recent study also reveals the anti-hypertensive effect of GABA in vivo. Edible fungi of the *Monascus* species have been used as traditional Chinese medicine in eastern Asia for several centuries. *Monascus*-fermented products possess a number of functional secondary metabolites, including anti-inflammatory pigments (such as monascin and ankaflavin), monacolins, dimerumic acid, and GABA. Several scientific studies have shown that these secondary metabolites have anti-inflammatory, anti-oxidative, and anti-tumor activities. Moreover, many published reports have shown the efficacy of *Monascus*-fermented products in the prevention or amelioration of some diseases, including hypercholesterolemia, hyperlipidemia, hypertension, diabetes, obesity, Alzheimer's disease, and numerous types of cancer in recent studies. The current article discusses and provides evidence to elucidate the anti-hypertensive benefit of *Monascus*-fermented metabolites, including anti-inflammatory pigments and GABA.

Keywords γ-Aminobutyric acid (GABA) · *Monascus* · Monascin · Ankaflavin · Anti-hypertensive

Introduction

Hypertension is a major chronic disease and is defined as a systolic blood pressure (SBP) above 140 mmHg and/or a diastolic blood pressure (DBP) above 90 mmHg. Hypertension can result in stroke, coronary heart disease (CHD), kidney dysfunction, and disability. Moreover, other factors also lead to hypertension, including heredity, age, body weight, environment, and diet. Treatment of moderate to severe hypertension is a life-long commitment and requires drug therapy in combination with changes in lifestyle, which can include weight reduction, limitation of alcoholic intake, and reduction in salt and fat intake (Perez and Musini 2008). Study has shown that hypertension can be improved with one of several types of medications, including diuretics, β-adrenoreceptor blockers, angiotensin-converting-enzyme (ACE) inhibitors (ACEIs), calcium channel blockers, α-adrenoreceptor blockers, vasodilators, and centrally acting agents (Perez and Musini 2008).

Hypertension is a risk factor for cardiovascular diseases (CVDs). ACE mediates blood plasma, interstitial fluid volume, and arterial vasoconstriction in the rennin–angiotensin system (Imig 2004). ACEIs have beneficial effects in hypertension through inhibiting the production of the vasoconstrictor angiotensin II and degradation of the vasodilator bradykinin (Seppo et al. 2003; Chockalingam 2008). In recent years, there has been considerable interest in the potential for using natural food components in functional foods to treat hypertension.

Hypertension

The renin–angiotensin system is a powerful mechanism for controlling blood pressure. When blood pressure decreases, the kidneys undergo several intrinsic reactions that convert prorenin to rennin. After rennin enters the bloodstream, it hydrolyzes plasma angiotensinogen to release a peptide called angiotensin I. When angiotensin I circulates in the small vessels of the lungs, it is immediately hydrolyzed

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by ACE to release an 8-amino peptide, angiotensin II (Chockalingam 2008), which circulates in the blood before it is inactivated by angiotensinase. Studies have indicated that angiotensin II raises blood pressure by severely constricting the arteries, causing an increase in the peripheral resistance (Chockalingam 2008; Rizzello et al. 2008). It is also able to act on the kidneys to retain both salts and water, leading to an increase in the extracellular fluid volume and thus blood pressure. In addition, this hormone causes the adrenal glands to release aldosterone and in turn increases re-absorption of water and salt in the kidney. ACEIs also decrease the formation of angiotensin II as well as increase bradykinin, further lowering blood pressure (Chockalingam 2008; Rizzello et al. 2008) (Fig. 1).

Some foods and herbs contain natural compounds that show medicinal properties in the control of blood pressure. Indeed, a number of medications used in the treatment of blood pressure originated from foods. The mechanism by which some functional foods and nutraceuticals of a phenolic type lowers blood pressure is through the inhibition and downregulation of ACE and rennin expression (Rizzello et al. 2008).

Association between inflammatory factors and hypertension

Vessel wall inflammation and vascular endothelium activation both increase adhesion of mononuclear cells to the injured endothelial layer, and their subsequent extravasation into the vessel wall is an initial event in atherogenesis and hypertension process (Chockalingam 2008).

Elevated endothelial expression of adhesion molecules as mediators of subintimal immunocyte accumulation in atherosclerosis (Chen et al. 2006; Ross 1999) and increased oxidative stress to result in inflammatory mechanisms for the progression of atherosclerosis (Puddu et al. 2005). Inflammatory cytokine tumor necrosis factor (TNF)-α has been shown to promote the adhesion of leukocytes to endothelial cells through an oxidative stress-related mechanism in recent studies (Koga et al. 2002; Silverman et al. 2002). Moreover, transcriptional regulation involving NF–κB activation has been implicated in endothelial cells in TNF-α induction (Chen et al. 2006). Vascular cell adhesion molecule (VCAM-1) and E-selectin expression are both focally elevated in endothelial cells in vascular regions prone to atherogenesis (Ross 1999; Hofmann et al. 2001), which might reflect a link between elevated TNF-α levels and increased leukocyte infiltration in the development of atherosclerosis (Fig. 2). Recently, statins have been shown to reduce reactive oxygen species (ROS) in endothelial cells through a novel antioxidant mechanism. In this mechanism, the statin-mediated *S*-nitrosylation of thioredoxin enhances antioxidative activity, resulting in a significant reduction in intracellular ROS, and thereby preventing hypertension (Haendeler et al. 2004).

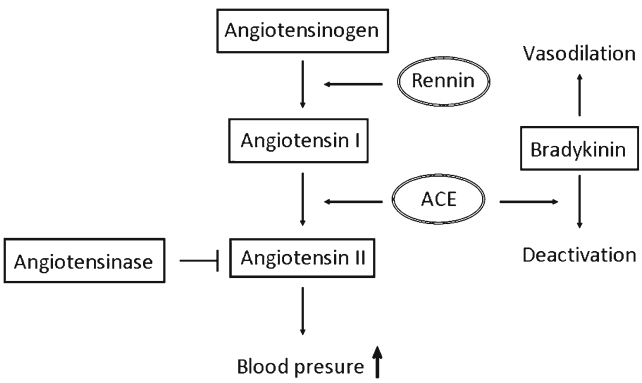

Fig. 1 Mechanism of ACE-regulated blood pressure

Roles of dyslipidemia in hypertension

Atherosclerosis is a chronic disease that involves the accumulation of lipid deposits in the arterial wall; hypercholesterolemia has been reported to promote atherosclerosis, coronary heart disease, hypertension, and stroke (Libby 2002). Although the development of CVD is associated with a number of life-style factors, as well as heredity, the most significant risk factors are related to diet. Pharmacological drug use suppresses elevations of cholesterol and triglyceride (TG), thereby preventing hypertension and CVD (Lloyd-Jones et al. 2010).

Hyperlipidemia is a major risk factor for the development of CVD and hypertension, and considerable evidence suggests that drugs with the ability to lower low-density-lipoprotein cholesterol (LDL-C) also reduce the probability of cardiovascular death, hypertension, and atherosclerosis (Fig. 2). Dairy consumption has been inversely correlated with the prevalence of overweight, hypertension, diabetes, and metabolic syndrome (Zemel 2002; Pereira et al. 2002; Choi et al. 2005).

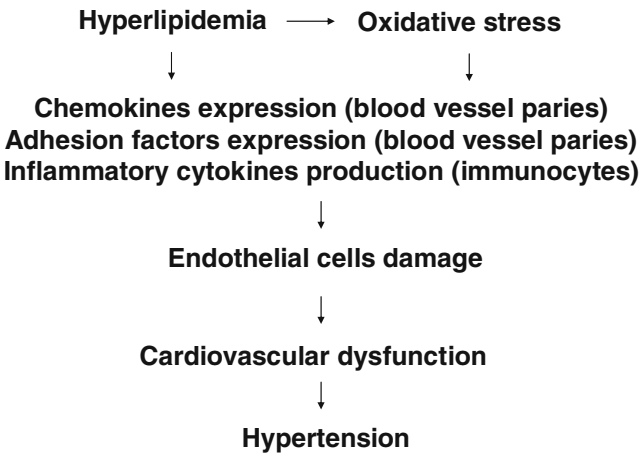

Fig. 2 The potential mechanism for hyperlipidemia inducing hypertension

Numerous experimental investigations in various animal models of hyperlipidemia have suggested that antioxidants have beneficial effects on lipid profiles and reduce atherosclerotic lesions (Miura et al. 2001; Hayek et al. 1997). Albeit the underlying mechanisms for the lipid-lowering effect of antioxidants are not fully elucidated, some of the evidence suggests that antioxidants reduce cholesterol absorption by lowering the solubility of cholesterol in mixed micelles, thereby preventing hypertension (Ikeda et al. 1992).

Therapy for hypertension

α- and β-Adrenoreceptor blockers

Adrenoreceptor blockers attenuate nerve impulses to the heart and blood vessels and reduce the working load of the heart by slowing the heartbeat, which results in a drop in blood pressure (Perez and Musini 2008). Adrenoreceptor blockers reduce the effect of sympathetic nerve impulses to blood vessels and thus resistance to blood flow (Perez and Musini 2008). Vasodilators relax blood vessels and lower blood pressure. For severely and moderately hypertensive patients, the use of these drugs is necessary to bring the blood pressure down to a healthy range.

ACE inhibitors

ACEIs block the formation of angiotensin II, which normally causes blood vessels to narrow, thereby increasing blood pressure (Hara et al. 1987). Some bioactive peptides have ACEI properties and can be used for preventing hypertension as well as for other therapeutic purposes (Hara et al. 1987; Li et al. 2007). Although most of the known ACEI peptides were detected in functional dairy products, some have been recently been identified and characterized from cereal proteins.

γ-Aminobutyric acid

Apart from ACEIs, γ-aminobutyric acid (GABA) has been shown to have the ability to lower blood pressure in spontaneously hypertensive rats (SHRs) and hypertensive humans. GABA is a major inhibitory neurotransmitter in the sympathetic nervous system and plays an important role in cardiovascular function. GABA has been reported to decrease blood pressure in experimental animals and in humans after oral or systemic administration (Li et al. 2007; Kajimoto et al. 2004).

Calcium channel blockers

Calcium channel blockers prevent calcium from entering the muscle cells of the heart and blood vessels, relaxing these cells and lowering the blood pressure (Perez and Musini 2008; Rizzello et al. 2008; He et al. 2002).

Sodium dietary limitation

The consumption of low- and reduced-salt foods and beverages is growing worldwide. Sodium helps to regulate fluid balance and to maintain blood volume and blood pressure. Growing evidence suggests that a higher intake of sodium than potassium is a contributing factor to hypertension (He et al. 2002).

Endothelial nitric oxide synthase activators

Nitric oxide synthase (NOS) contributes to the blood pressure-lowering activity of many commonly used medicines, nutraceuticals, and functional foods. The three major types of NOS are endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase, and inducible nitric oxide synthase. The major function of nitric oxide (NO) is to mediate endothelium-dependent vasodilation (Furchgott and Vanhoutte 1980). NOS catalyzes the oxidation of L-arginine to L-citrulline and forms NO, a freely diffusible gas that exerts a number of physiological functions by acting as an intracellular and intercellular messenger. Endothelium-derived NO diffuses into vascular smooth muscle cells, where it subsequently activates guanylate cyclase which, in turn catalyzes the production of cyclic guanosine monophosphate (cGMP), thereby activating cGMP-dependent protein kinase (PKG) to open the K^+ channel and the resulting membrane hyperpolarization to inhibit Ca^{2+} influx, thereby leading to vasodilation and attenuation of hypertension (Furchgott and Vanhoutte 1980). NO deficiency can lead to clinical hypertension (Furchgott and Vanhoutte 1980; Thomas et al. 2008). Moreover, eNOS knockout mice have been shown to develop mild to moderate hypertension (Huang et al. 1995).

Antioxidants and anti-inflammatory agents

Considerable epidemiological evidence reveals that antioxidant consumption reduces the risk of CVDs and total mortality (Nakachi et al. 2000; Hertog et al. 1993). In general, the mechanisms that have been suggested to explain the ability of these consumed antioxidants to prevent CHD (such as hypertension) primarily entail their powerful radical-scavenging and antioxidative properties (Rice-Evans et al. 1996).

These strong antioxidant properties may also be one explanation for the protective effect of these compounds during the development of atherosclerosis. Oxidative modification of low-density lipoprotein (LDL) is one of the critical steps in the development of atherosclerosis. A class of antioxidants known as flavonoids has been shown to inhibit LDL oxidation, possibly by reducing macrophage superoxide production

(Yoshida et al. 1999), thereby preventing the formation of foam cells in atherosclerotic lesions, which results in an antihypertensive effect (Hayek et al. 1997; Yang and Koo 2000). On the other hand, phenolic compounds can prevent endothelial cell-mediating LDL lipid peroxidation and may accordingly inhibit heme oxygenase, an enzyme that has been linked with the transformation of monocytes into resident macrophages (Soriani et al. 1998; Wang et al. 1998).

Immune cells dominate in early atherosclerotic lesions, and their effector molecules accelerate the progression of the lesions. The resultant activation of inflammation can elicit acute coronary syndromes. Proliferation and migration of vascular smooth muscles cells from the media to the subendothelial space are major events in the development of atherosclerosis, and particularly of restenosis, after balloon angioplasty. Several lines of evidence demonstrate that components in tea interfere with these processes of proliferation and migration. Antioxidants have been suggested to play an important role as well in modulating the expression of adhesion molecules in endothelial cells (Murase et al. 1999).

Functions of *Monascus*-fermented products

Prevention of hypertension through *Monascus*-fermented products

Monascus was classified and named in 1884 by French scientist van Tieghem (van Tieghem 1884). The genus *Monascus* belongs to the family Monascaceae, order Eurotiales, class Ascomycetes, phylum Ascomycota, and kingdom Fungi. To date, 58 *Monascus* strains have been deposited in the American Type Culture Collection. However, based on Hawksworth and Pit (1983), most strains belong to only three species: *Monascus pilosus*, *Monascus purpureus*, and *Monascus ruber*. *Monascus*-fermented products, especially those produced by solid-state rice fermentation, have been used as food colorants and dietary material for more than 1,000 years. In Asian countries, *Monascus*-fermented rice is both common in the diet and used in traditional health remedies. *Monascus*-fermented rice contains various chemical components, some of which have been purified and identified, including monacolin K (Fig. 3a), GABA (Fig. 3b), different pigments, and dimerumic acid (Fig. 3c). Their bioactive functions have recently been discovered.

Monascus pigments are widely studied, and eight types of chemical structures have been identified (Martinkova et al. 1995). These structures can be divided into red pigments (monascorubramine and rubropunctamine), orange pigments (monascorubrin and rubropunctatin), and yellow pigments (yellow II, xanthomonascin A, monascin (Fig. 3d), and ankaflavin (Fig. 3e)). The orange pigments have been found to possess antibiotic activities against bacteria, yeast, and filamentous fungi (Martinkova et al. 1999) and to inhibit the growth of *Bacillus subtilis* and *Candida pseudotropicalis*. Yellow pigments such as monascin and ankaflavin have been shown to have immunosuppressive activities against mouse T splenocytes (Martinkova et al. 1999).

Effects of *Monascus*-fermented products on the inhibition of serum hyperlipidemia and the prevention of atherosclerosis

The oral administration of a powder derived from *Monascus*-fermented products has been reported to decrease total cholesterol (TC), TG, and LDL-C levels in a hyperlipidemia hamster model (Lee et al. 2006a). Our laboratory has further found that *Monascus*-fermented dioscorea shows a more significant hypolipidemic effect than traditional *Monascus*-fermented rice. This effect may be explained by the higher monascin and/or

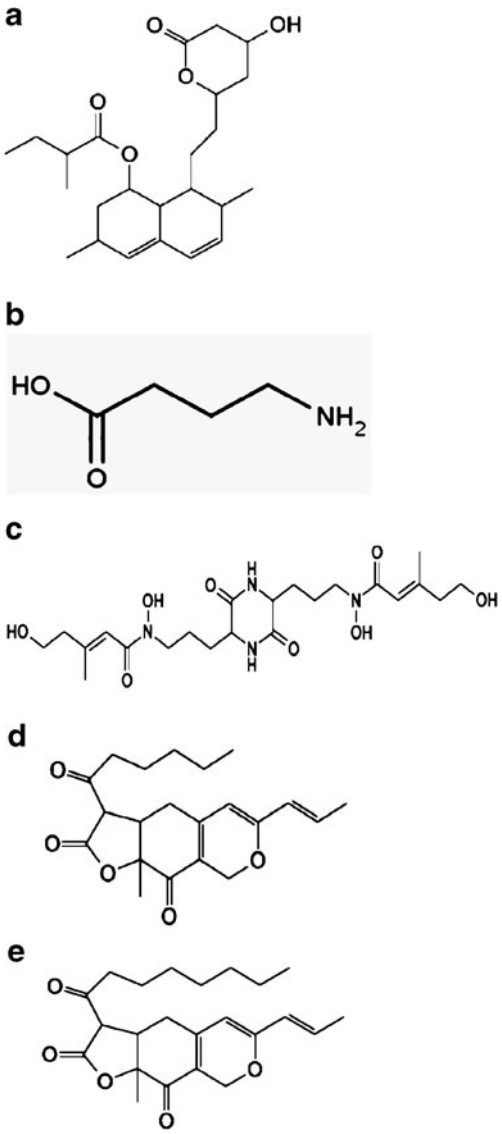

Fig. 3 Structure of *Monascus*-fermented products, including **a** monacolin K, **b** GABA, **c** dimerumic acid, **d** monascin, and **e** ankaflavin

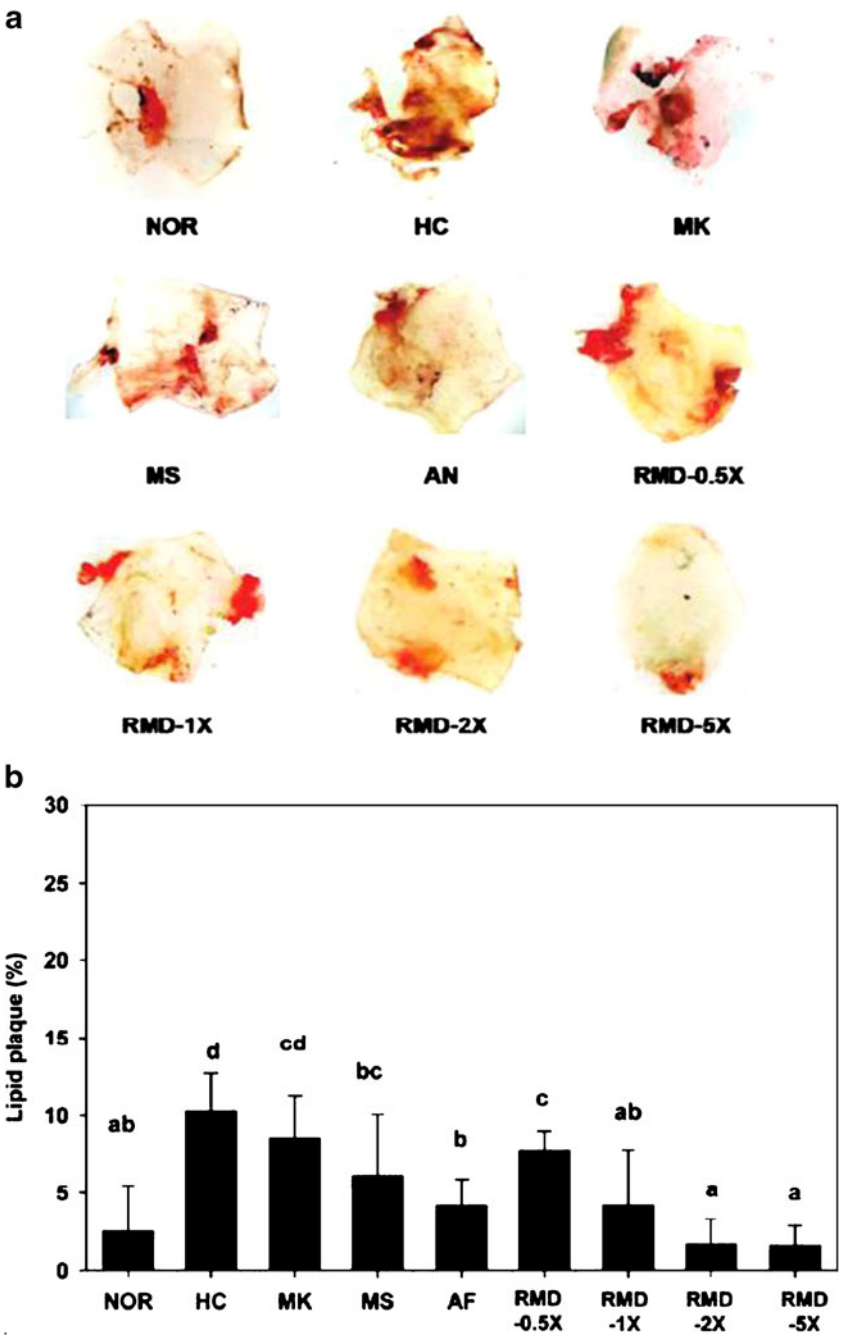

Fig. 4 Effect of *Monascus*-fermented products (monascin, ankaflavin, and monacolin K) on the atherosclerotic plaque in the heart aorta of hyperlipidemic hamsters: **a** atherosclerotic plaque presented as the red dye in the graph; **b** proportion of the area of the atherosclerotic plaque in the aorta. Hamsters were fed a normal diet (NOR group) or a high-cholesterol diet (HC group) without the administration of test materials, respectively. Hyperlipidemic hamsters were administered monacolin K (1.56 mg/kg/day) (MK group), monascin (5.30 mg/kg/day) (MS group), ankaflavin (0.77 mg/kg/day) (AF group), 0.5-fold dose of *Monascus*-fermented dioscorea (RMD; 53.92 mg/kg/day including 0.16 mg of monacolin K, 0.53 mg of monascin, and 0.08 mg of ankaflavin), a onefold dose of RMD (107.83 mg/kg/day including 0.31 mg of monacolin K, 1.06 mg of monascin, and 0.15 mg of ankaflavin), a twofold dose of RMD (215.66 mg/kg/day including 0.62 mg of monacolin K, 2.12 mg of monascin, and 0.31 mg of ankaflavin), or fivefold dose of RMD (539.15 mg/kg/day including 1.56 mg of monacolin K, 5.30 mg of monascin, and 0.77 mg of ankaflavin) (Lee et al. 2010)

ankaflavin levels in the *Monascus*-fermented dioscorea (Lee et al. 2007). In addition, the anti-oxidative activities of *Monascus*-fermented dioscorea provided by various *Monascus* metabolites (e.g., dimerumic acid, tannins, and phenols) show greater anti-atherosclerotic effects than the anti-oxidative activities of *Monascus*-fermented rice and include increased total antioxidant status and catalase levels, and superoxide dismutase activity and the repression of lipid peroxidation and atherosclerotic plaques (Lee et al. 2007). In addition, *Monascus*-fermented products were able to significantly inhibit atherosclerotic plaque formation in the heart aorta of high-cholesterol diet-induced hamsters (Fig. 4) (Lee et al. 2010).

Elevation of high-density lipoprotein cholesterol by *Monascus*-fermented products

Furthermore, animal studies have been conducted to explore the anti-obesity effects of *Monascus*-fermented rice. We found that supplementation with *Monascus*-fermented rice significantly reduced serum TC, serum LDL-C, the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C), and serum insulin. The study revealed for the first time that *Monascus*-fermented rice can prevent body fat accumulation and improve dyslipidemia. The anti-obesity effects of *Monascus*-fermented rice were mainly derived from its lipolytic activity

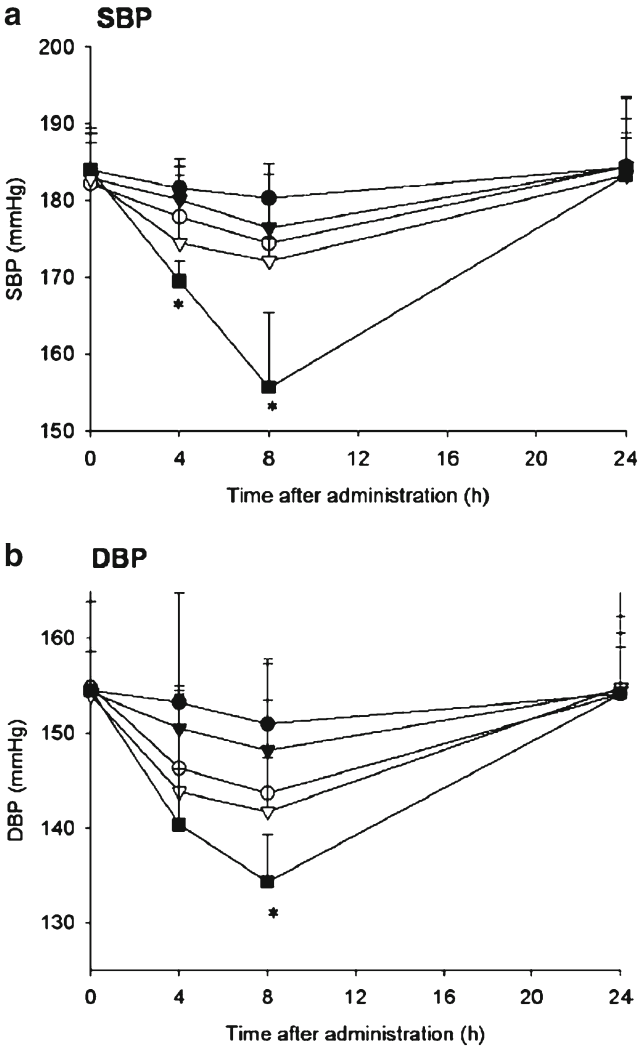

Fig. 5 Effect of single oral administration of *Monascus*-fermented products on **a** SBP and **b** DBP in SHRs. One group of the SHRs were fed a normal diet without the administration of test materials (the control group; *filled circle*). The other SHRs were administrated with a onefold dose of unfermented dioscorea (150 mg/kg/day) (the D-1X group; *inverted filled triangle*), GABA (0.245 mg/kg/day) (the GABA-1X group; *empty circle*), a onefold dose of *Monascus*-fermented rice (150 mg/kg/day including 0.0197 mg of GABA) (the RMR-1X group; *inverted empty triangle*), and a onefold dose of *Monascus*-fermented dioscorea (150 mg/kg/day including 0.0245 mg of GABA) (the RMD-1X group; *filled square*) (Wu et al. 2009)

and mild anti-appetite potency (Lee et al. 2010; Chen et al. 2008). Furthermore, monascin and ankaflavin were shown to elevate serum HDL-C levels in high-cholesterol diet-induced hamsters in a recent study (Lee et al. 2010).

GABA and ACEIs in *Monascus*-fermented products regulate blood pressure in SHR rats

The antihypertensive function of *Monascus*-fermented rice has been previously shown (Brown and Vaughan 1998; Wang et al. 2010). In addition, the regulation of blood pressure by

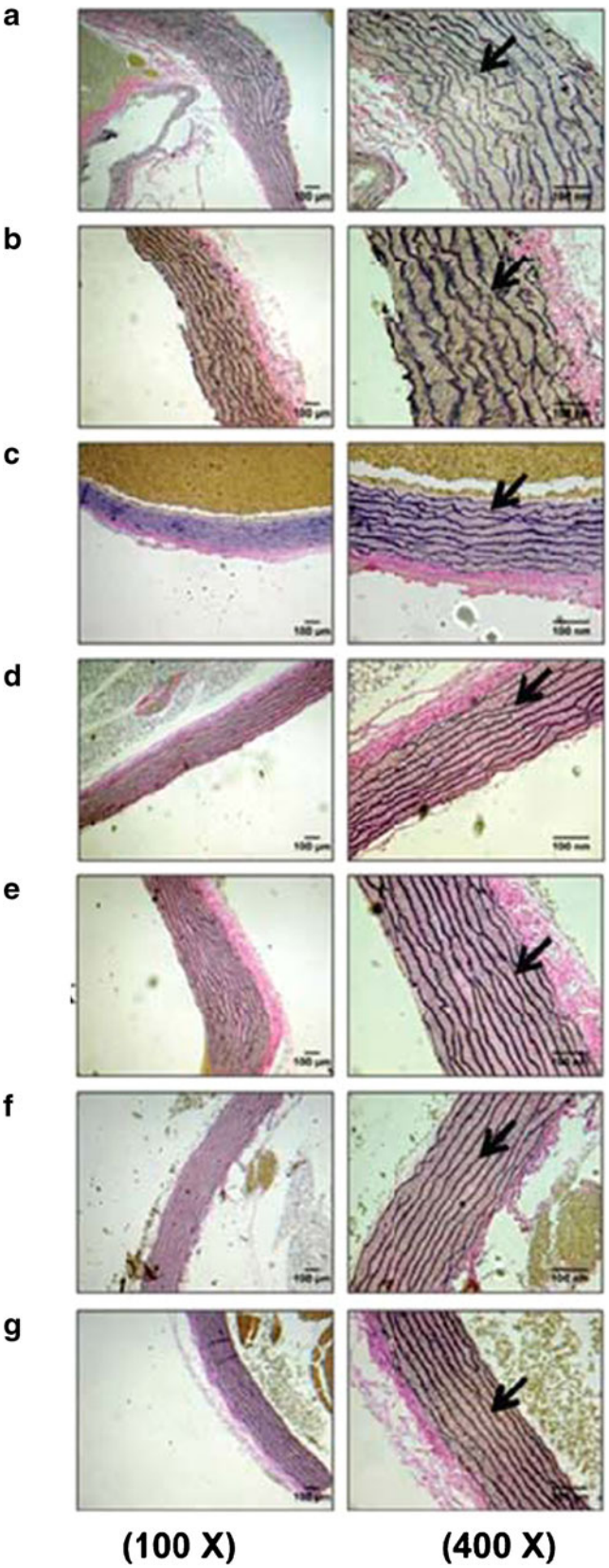

Fig. 6 Microscopic examination (×100 and ×400) of aorta thin section on experimental SHRs: **a** control group, **b** D-1X group, **c** GABA-1X group, **d** RMR-1X group, **e** RMD-0.5X group, **f** RMD-1X group, and **g** RMD-5X group (Wu et al. 2009)

Table 1 The benefit of *Monascus*-fermented products for hypertension attenuation

	Dose	Model	Induction	SBP decrease	Prevention	Reference
M. pilosus IFO 4520-fermented products	5 %	SHR (in vivo)	1 % NaCl	25 mmHg		Tsuji et al. 1992
M. pilosus IFO 4520-fermented products	0.3 %	SHR (in vivo)	Strain	15 mmHg		Tsuji et al. 1993
M. purpureus M 9011-fermented products	Aqueous extract	SD rat (in vivo)	60 % Fructose	17 mmHg		Hsieh and Tai 2003
M. purpureus NTU 568-fermented products	48.8 mg/kg (0.2~0.25 %)	SHR (in vivo)	Normal diet	26 mmHg		Wu et al. 2009
Monascin, ankaflavin, monacolin K	50 μM	HAECs (in vitro)	TNF-α		Inhibitions of VCAM, ICAM, and E-selectin	Lin et al. 2011
Monascin, ankaflavin	20 μM	HUVECs (in vitro)	TNF-α		Elevations of eNOS and NO	Hsu et al. 2012

Monascus-fermented products in high-fructose-induced metabolic syndrome in rats has been reported (Hsieh and Tai 2003). Recent research has focused on the effects of the oral administration of a small amount of *Monascus*-fermented dioscorea, as fermented by *M. purpureus* NTU 568, on the SBP, DBP, heart rate, and the aorta in hypertensive rats (Fig. 5) (Wu et al. 2009). *Monascus*-fermented dioscorea significantly prevented increases in blood pressure and improved vascular elastin remodeling (Fig. 6). The anti-hypertensive effect as well of *Monascus*-fermented dioscorea was better than that of *Monascus*-fermented rice. Moreover, *Monascus*-fermented dioscorea exhibited higher ACEI activity than *Monascus*-fermented rice, thereby preventing hypertension (Wu et al. 2009). In addition, the elastin fibers in the aortas of SHRs fed the *Monascus*-fermented products were significantly straighter than those of the controls (Fig. 6) (Wu et al. 2009).

Other *Monascus* strain-fermented products are also evaluated for attenuating hypertension in various models (Table 1).

Chronic hypertension is associated with structural changes in the resistance vasculature (Mulvany 2000). Histopathological changes, known as "remodeling," represent a complex process that may increase (hypertrophy), decrease (hypotrophy), or rearrange (eutrophy) the vascular wall (Mulvany 2000). Elastin fiber is an important determinant of arterial distensibility (Dobrin 1978). Several models of genetic hypertension have reported abnormalities in the elastin content and structure in large arteries (Boumaza et al. 2001). *Monascus*-fermented products can prevent the rearrangement of the vascular wall; therefore, they may have a hypotensive effect that results from a decrease in the peripheral vascular resistance.

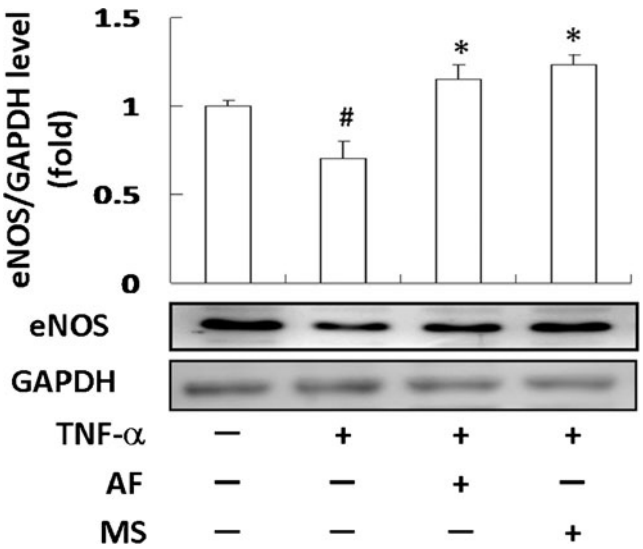

Fig. 7 The preventive effect of ankaflavin and monascin (20 μM) on TNF-α induced a decrease in eNOS expression of HUVECs for 12 h treatment. (#) Significantly different from control group at $p<0.05$; (*) significantly different from TNF-α-treated group at $p<0.05$ (Hsu et al. 2012)

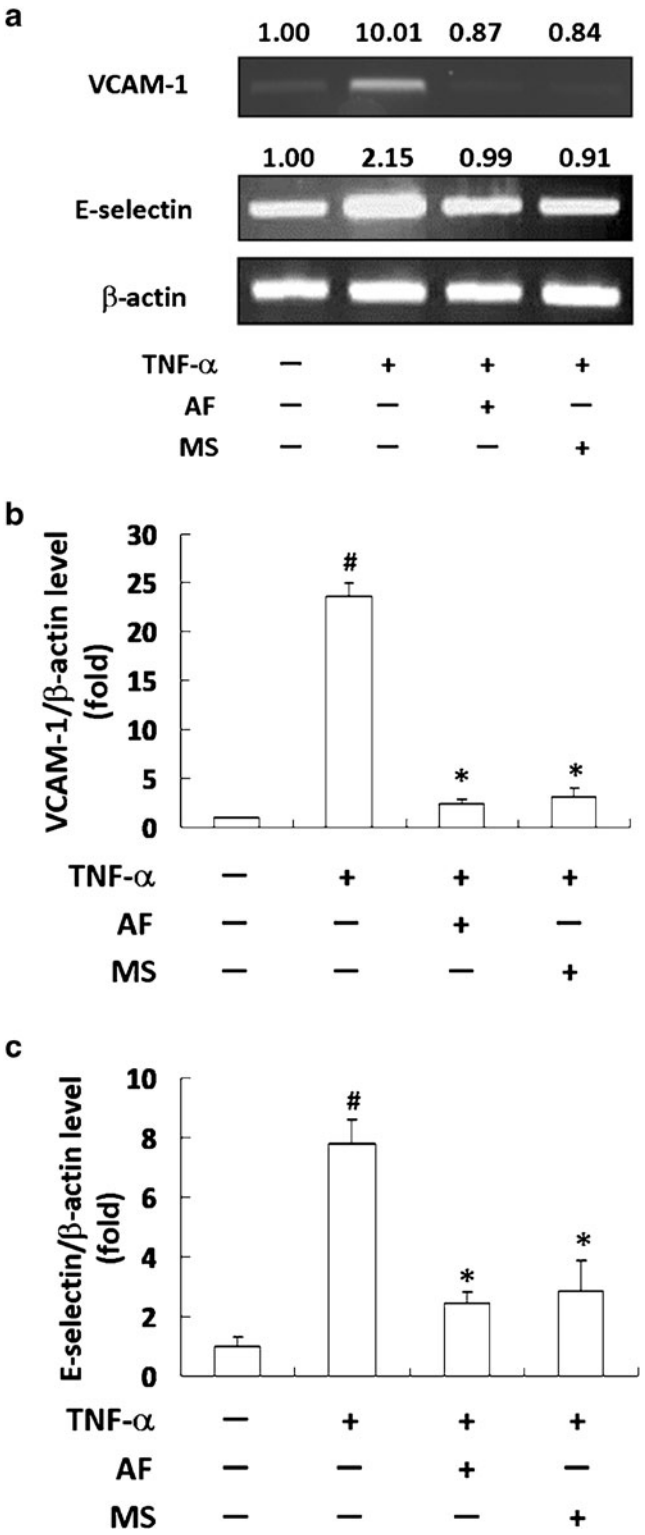

Fig. 8 The inhibitory effects of ankaflavin and monascin (20 μM) on VCAM-1 and E-selectin in HUVECs treatment with 10 ng/mL of TNF-α for 12 h measuring by RT-PCR (**a**). The levels of VCAM-1 (**b**) and E-selectin (**c**) mRNA expression in HUVECs measuring by real-time PCR. (#) Significantly different from control group at $p<0.05$; (*) significantly different from TNF-α- treated group at $p<0.05$ (Hsu et al. 2012)

Kohama et al. (1987) found that GABA and acetylcholine chloride were the major compounds in *Monascus*-fermented products that can lower blood pressure. Acetylcholine acts on a muscarinic receptor of endothelial cells to stimulate the release of a substance that causes relaxation of vascular smooth muscle, resulting in systemic hypotension (Kohama et al. 1987). However, acetylcholine acts only transiently and is easily hydrolyzed by cholinesterase in the body (Kohama et al. 1987). Other studies indicate that beni-food (*Monascus*-fermented food), such as beni-bread, beni-miso, beni-soy sauce, and beni-somen, has a hypotensive effect (Tsuji et al. 1992, 1993). Moreover, a water-soluble extract of *Monascus*-fermented product showed the ability to lower blood pressure (Tsuji et al. 1992, 1993).

Anti-inflammation activities of *Monascus*-fermented products

The arterial and cardiopulmonary baroreceptors are the two most important neural reflex arches associated with the

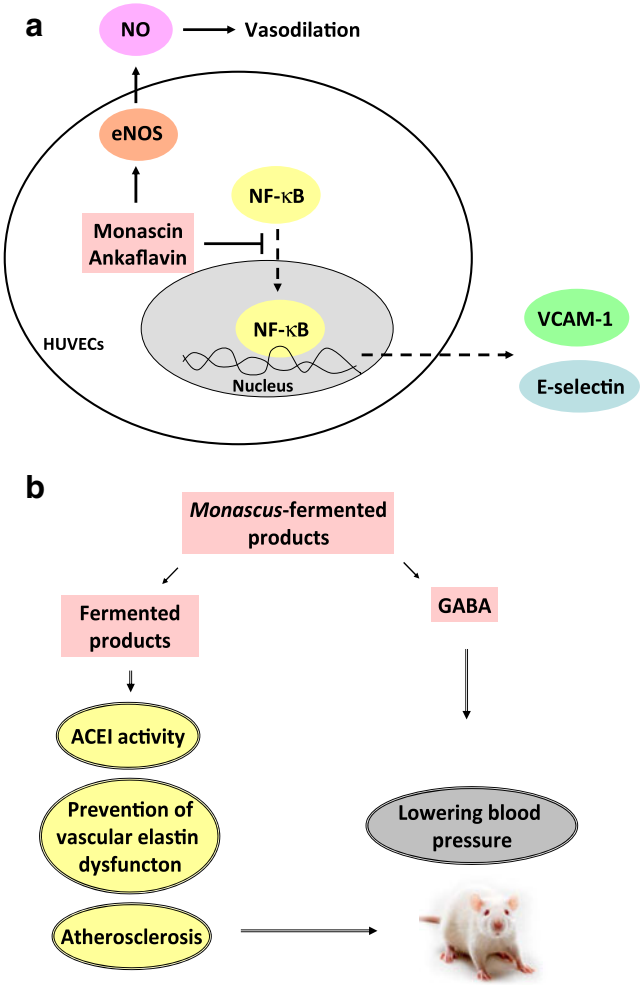

Fig. 9 The potential mechanism of *Monascus*-fermented products for anti-hypertension

regulation of blood pressure. The aortic baroreceptors lower blood pressure both through parasympathetic activation and sympathetic inhibition. When the afferent signals from the baroreceptors enter the vasomotor center in the medulla of the brain, the efferent signals are transferred via sympathetic nerves to the heart, vasculature, and kidneys (Grassi et al. 1998). *Monascus* pigments have been reported to have hypotensive ability (Tsuji et al. 1992, 1993). We found that *Monascus*-fermented dioscorea has a stronger hypotensive effect than *Monascus*-fermented rice because of the higher levels of monascin and ankaflavin (anti-inflammatory agents) in the *Monascus*-fermented dioscorea (Wu et al. 2009).

The expression of intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and E-selectin is focally elevated in endothelial cells in vascular regions prone to atherogenesis (Ross 1999). Dietary supplementation with *Monascus*-fermented products may be a potential means to attenuate TNF-α-stimulated activation of the endothelium and may help reduce the risk of vascular disease associated with inflammation (Lin et al. 2011).

Moreover, monacolin K, ankaflavin, and monascin from *Monascus*-fermented rice were investigated for their effects on the expression of cell adhesion molecules (ICAM-1, VCAM-1, and E-selectin) in TNF-α-treated human aortic endothelial cells (HAECs). The expression of VCAM-1 and E-selectin were significantly elevated by TNF-α stimulation; furthermore, this elevation could be suppressed by various *Monascus*-fermented rice metabolite supplements, suggesting that endothelial VCAM-1 and E-selectin expression, rather than ICAM-1 expression, was more critical to monocyte adhesion in this in vitro model. In addition, supplementing the HAECs with these *Monascus*-fermented rice metabolites significantly suppressed cellular binding between human U937 monocytic cells and TNF-α-stimulated HAECs, suggesting *Monascus*-fermented rice metabolites may decrease TNF-α-induced endothelial adhesiveness to monocytes, thereby attenuating aortic endothelial cell inflammation and preventing hypertension (Lin et al. 2011).

Furthermore, *Monascus*-fermented rice metabolites also attenuated ROS generation in vitro and in TNF-α-treated HAECs (Lin et al. 2011). These health-promoting functions of *Monascus* metabolites could be used to augment the antihypertensive and antiatherogenic effects of *Monascus*-fermented products.

eNOS activation by *Monascus*-fermented products

Study has shown antioxidants promoting eNOS expression in endothelial cells via a p38 MAPK-estrogen receptor alpha-dependent pathway (Anter et al. 2005). We showed that monascin and ankaflavin both activated eNOS expression and increased NO production in human umbilical vein endothelial cells (HUVECs) and prevented a decrease in eNOS expression in TNF-α-induced HUVECs (Hsu et al. 2012) (Fig. 7). In addition, both compounds attenuated TNF-α induction of NF–κB activation and suppressed the expression of adhesion factors, including E-selectin and VCAM-1 (Hsu et al. 2012) (Fig. 8).

In this review, we discussed the potential mechanism for improving hypertension in vitro and in vivo (Fig. 9), including anti-inflammation and NO elevation by *Monascus*-fermented products and downregulation of hypertension by GABA.

ACEI and GABA production by *Monascus* fermentation

We have reported that 0.3 % ethanol supplement can promote GABA production by response surface methodology investigation (Wang et al. 2003). In addition, *Monascus*-fermented dioscorea can produce larger amounts of monascin and ankaflavin than *Monascus*-fermented rice (Lee et al. 2006b).

Conclusions

Hypertension, commonly recognized as a silent killer, is the most common CVD and is a major risk factor for atherosclerosis, metabolic syndrome, renal dysfunction, myocardial infarction, heart attack, and stroke, which are the most important causes of death in industrialized countries. However, *Monascus*-fermented products (including monascin, ankaflavin, and GABA) can inhibit inflammation, suppress atherosclerosis, promote eNOS, and improve dyslipidemia and blood pressure regulation, thereby preventing hypertension.

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