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Full Length Research Paper

Mentha cordifolia extract inhibits the development of hypertension in L-NAME-induced hypertensive rats

Poungrat Pakdeechote[1]*, Upa Kukongviriyapan[1], Warinee Berkban[1], Parichat Prachaney[2], Veerapol Kukongviriyapan[3] and Saowanee Nakmareong[1]

[1]Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
[2]Department of Anatomy, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
[3]Department of Pharmacology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

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This study was to test the inhibitory action of *Mentha cordifolia* (MC) extract on the development of hypertension in N^G-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive rats. Male Sprague-Dawley rats received L-NAME (50 mg/kg/day) in drinking water and were either intragastrically administered with MC extract (200 mg/kg/day) or deionized water for 3 weeks. Significant increases in mean arterial blood pressure (MAP; 162.3 ± 2.7 vs 92.9 ± 5.4 mmHg), heart rate (HR; 414.7 ± 13.1 vs 331.7 ± 16.2 beat/min) and hindlimb vascular resistance (HVR; 39.1 ± 3.8 vs 12.6 ± 0.6 mmHg/min/100 g tissue/ml) in L-NAME-treated group compared to that of control group were observed. The MC extract markedly reduced the MAP about 16.7% in L-NAME group which was associated with reductions in HR and HVR. The MC extract alleviated a decrease in vascular responses to acetylcholine in the hypertensive rats. Increased levels of plasma malondialdehyde (MDA) and superoxide production in vascular tissues in hypertensive rats were restored by MC extract. The MC extract contains high level antioxidant in the form of total phenolic compounds. Our results indicated that the MC extract inhibited progress of hypertension in L-NAME group, and this effect might involve the antioxidant capacity of the extract.

Key words: *Mentha cordifolia* Opiz., L-NAME, hypertension, antioxidants, nitric oxide.

INTRODUCTION

A most common contributory to the pathogenesis hypertension is endothelial dysfunction. The imbalance between vasodilator agents (nitric oxide (NO), endothelium-dependent hyperpolarizing factor (EDHF)) and vasoconstrictor agents (endothelin, thromboxane A2, endoperoxides) released from endothelial cells as well as an increase in free radical production appear to be the most important cause of endothelial dysfunction in hypertension (Kojsova et al., 2006). As Furchgott and Zawadzki showed that nitric oxide released from vascular endothelium mediating vascular smooth muscle cell relaxation plays a key role in the maintenance of vascular tone (Furchgott and Zawadzki, 1980). Subsequently, induction of hypertension by chronic administration of nitric oxide synthase (NOS) inhibitors has been widely accepted as a model of animal hypertension (Ribeiro et al., 1992; Zatz and Baylis, 1998). Many studies supported that L-NAME, a nitric oxide synthase inhibitor, produces a sustained elevation of blood pressure (Bank et al., 1994; Baylis et al., 1992; Gardiner et al., 1999; Gerova et al., 2004) and heart rate (Souza et al., 2001; Vasquez et al., 1994). It is well established that this model of hypertension is likely to be associated with an increase in peripheral vascular resistance (Loeb and Longnecker, 1992). This includes vascular functional, structural changes (Bernatova et al., 1999; Kung et al., 1995; Morton et al., 1993) and cardiac hypertrophy (Kristek and Gerova, 1996). Other possible causes of systemic vasoconstriction in NO-deficient rats were evidently found

*Corresponding author. E-mail: ppoung@kku.ac.th. Tel/Fax: +6643348394.

including, enhancements of sympathetic nerve activation in conscious rats (Augustyniak et al., 2006), alterations of the renin-angiotensin system (Pollock et al., 1993), and an increase in oxidative stress markers (Kojsova et al., 2006; Pechanova et al., 2004). It has been suggested that superoxide production is raised and suppressed NO availability leads to endothelial dysfunction and finally hypertension (Noll et al., 1997; Pechanova et al., 1999). Consequently, there is evidence in animals supporting the notion that supplementation of antioxidant substances may ameliorate hypertension and restore endothelial function (Chen et al., 2001; Zicha et al., 2006).

Mentha cordifolia Opiz. (Family Lamiaceae) is easily grown throughout Thailand and in many Southeast Asian countries. Its common name is kitchen or marsh mint. It is a popular flavoring herb of Thai food and herbal tea. This mint is generally used in traditional medicine to relieve gastrointestinal problem, asthma, muscle spasm and inflammation. Evidence supporting the biological effect of *M. cordifolia* has been reported; such as anti-mutagenicity (Villasenor et al., 2002), analgesic (Villasenor and Sanchez, 2009), anti-nociceptive (Sousa et al., 2009), anti-inflammatory (Moreno et al., 2002) and antioxidant activities (Ka et al., 2005). A vasorelaxing effect of mint leaf extract has been shown in the rat mensenteric bed (Runnie et al., 2004). Many studies showed that the biological activity of this Mentha species is due to the presence of the phenolic compounds especially flavanoids (Bozin et al., 2008; Gursoy and Tepe, 2009; Runnie et al., 2004). The effect of the MC extract on the vascular responsiveness and antioxidative properties has not been elucidated. Therefore, the aim of this study was to explore the protective effect of MC extract on blood pressure and vascular functions.

MATERIALS AND METHODS

Plant and extraction

Fresh plant leaves were collected from a local farm in Khon Kaen city, Thailand, weighed, chopped into small pieces and boiled in distilled water at 95°C for 30 min. The water extract was filtered, evaporated in vacuum evaporator and then lyophilized to get the dry extract. The yield was about 2.4% by weight from the fresh leaves. The powdered MC extract was kept in an airtight container at -20°C and dissolved in distilled water before use. The color of dissolved extract is light green.

Animals

Male Sprague-Dawley rats (220 to 225 g) were obtained from the Animal Care Unit of the Faculty of Medicine, Khon Kaen University (Khon Kaen, Thailand). All animals were maintained in a temperature controlled room at 24°C with a 12 h dark/ light cycle. The animals were given free access to standard chow diet (Chareon Pokapan Co. Ltd., Thailand) and distilled water (DW) or L-NAME (50 mg/kg/day) in DW. All animal procedures were reviewed and approved by the Institutional Animal Ethics Committee of Khon Kaen University (AEKKU 20/2551).

Experimental design

Rats were randomly divided into 4 groups with 6 to 8 in each group. Group I- control group, normal rats received vehicle DW; group II-normal control treated group, were normal rats treated with MC extract (200 mg/kg); group III-hypertension group, comprised rats given L-NAME (50 mg/kg/day) in drinking water and vehicle; group IV hypertension treated group, were rats given L-NAME (50 mg/kg/day) in drinking water and MC extract. Animals received L-NAME and MC extract for 3 weeks. Vehicle and MC extract were orally administrated using a feeding tube. The choice of MC extract dosage used in this study was determined by a preliminary study which showed that MC extract at 200 mg/kg/day prevents the increase in blood pressure of rats treated with L-NAME. To assess the onset and progression of hypertension, systolic blood pressure (SBP) was measured weekly using non-invasive tail-cuff plethysmography (IITC/life science instrument model 229 and model179 amplifier, Woodland Hills, California, USA).

Measurement of hemodynamic status and vascular reactivity

For direct blood pressure measurement, after three weeks of treatment, animals were anesthetized by peritoneal injection of pentobarbital-sodium (50 mg/kg) and placed on a heating pad. Subsequently, a tracheotomy was made to assist respiration. The femoral artery was identified, cleaned of connective tissue and cannulated with a polyethylene tube. SBP, diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and heart rate were continuously monitored by a way of pressure transducers and recorded using the acknowledge data acquisition and analysis software (Biopac Systems Inc., California, USA). The abdominal aorta was carefully separated from the abdominal vein, cleaned of connective tissue and fitted with a flow probe to detect HBF with an electromagnetic Flowmeter (Carolina Medical Electronics, Inc., North Carolina, USA). HVR (mmHg/min/100 g tissue/ml) was calculated as mean arterial blood pressure divided by HBF. Following equilibration, vascular responses to vasoactive agents, acetylcholine (ACh 3, 10 and 30 nmol/kg); an endothelium-dependent vasodilator, sodium nitroprusside (SNP 1, 3 and 10 nmol/kg); an endothelium-independent vasodilator, and phenylephrine (0.01, 0.03 and 0.1 µmol/kg); an α_1 adrenoceptor agonist, were tested to evaluate vascular function via intravenous injection in a stepwise fashion at 5-minute intervals. In separate experiments, after obtaining a stable baseline of hemodynamic measurement, the animals were sacrificed and blood samples were collected via the abdominal aorta for biochemical assays. Carotid arteries (about 2 cm in length) were cut out rapidly from animals to assess superoxide production.

Biochemical assays

Plasma malondialdehyde (MDA), a lipid peroxidation indicator, was examined by measuring the thiobarbituric acid-reactive substance by a spectrometric method as previously described (Luangaram et al., 2007). In brief, plasma samples were reacted with 10% Trichloroacetic acid, 5 mM ethylenediamine tetraacetic acid, 8% sodium dodecylsulfate, 0.5 µg/ml of butylatedhydroxyluene and 0.6% thiobarbituric acid. The mixture was boiled for 30 min. After cooling to room temperature, the absorbance of the supernatant was measured at 532 nm by spectrophotometer. Results were expressed according to a standard curve of 1,1,3,3-tetraethoxypropane (0.3 to 10 µmol/l). The production of superoxide in carotid arteries was determined by the lucigenin-enhanced

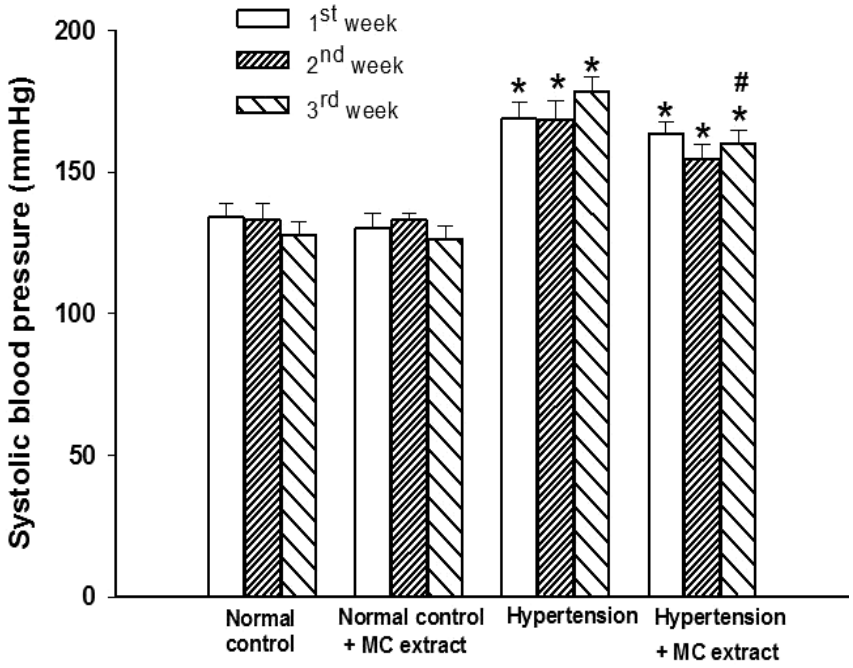

Figure 1. Effect of MC extract on systolic blood pressure in control rats, normal rats with MC extract, L-NAME-treated rats (hypertension), and L-NAME-treated rats (hypertension) with MC extract (n=8-10/group) at 1st, 2nd, and 3rd week. * P< 0.001 vs normal control, # P< 0.05 vs hypertension (ANOVA).

chemiluminescence method as described previously (Luangaram et al., 2007; Sompamit et al., 2009). In brief, the vessel segment was carefully cleaned and incubated in 1 ml oxygenated Krebs–Ringer bicarbonate solution at 37°C for 30 min. The chemiluminescence signal was measured after the addition of lucigenin (30 µM), and counted in a luminometer (Turner Biosystems, 23 CA, USA). The photon counts were integrated every 15 s for 5 min and averaged. The vessels were then dried for 24 h at 45°C and weighed. Superoxide production in vessel tissues was expressed as relative light unit count/mg dry wt/min.

Assay for total phenolic compounds

The determination of total phenolics followed the method previously described with some modifications by Zheng and Wang (2001). The MC extract or vitamin C dilution was mixed with 0.2 N Folin-Ciocalteu reagents and the reaction was neutralized with saturated sodium carbonate 10% w/v. Total phenolic compounds were measured using spectrophotometry and expressed as gram of Gallic acid equivalent (GAE) per 100 g of MC extract.

Chemicals

All chemicals used were of analytical grade quality.

Statistical analysis

Data are presented as mean ± S.E.M. Statistical comparisons between groups were made using one-way analysis of variance (ANOVA) with a post-hoc Duncan' s multiple range test. A value of $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Effect of MC extract on rat body weights

There was no significant difference of rat body weights in control rats, normal rats with MC extract, L-NAME-treated rats, and L-NAME-treated rats with MC extract (309.0 ± 4.1 g, 317.0 ± 8.2 g 281.4 ± 9.0 g, and 303.1 ± 11.2 g, respectively).

Effect of MC extract on hemodynamic changes in L-NAME-induced hypertension

Indirect measurement of blood pressure showed that chronic administration of L-NAME markedly elevated rat SBP (168.7 ± 5.8, 168.5 ± 6.7 and 178.2 ± 4.6 mmHg in the 1st, 2nd and 3rd week, respectively) when compared with the control group (134.1± 5.0, 133.2 ± 5.5 and 127.8 ± 4.7 mmHg in the 1st, 2nd and 3rd week, respectively) (Figure 1). A concomitant administration of MC extract with L-NAME for 3 weeks had a significant effect in inhibiting the development of hypertension as shown by the reduction in SBP in the 3rd week (160.2 ± 4.2 mmHg) as compared to that of L-NAME hypertensive group. Daily treatment of MC extract had no effect on SBP of

Table 1. Effect of MC extract on SBP, DBP, MAP, heart rate, HBF and HVR in all experimental groups.

Parameters	Normal control	Normal control + MC extract	Hypertension + vehicle	Hypertension + MC extract
SBP (mmHg)	129.6 ± 5.1	136 ± 4.3	199.1 ± 3.2*	176.4 ± 4.8*#
DBP (mmHg)	76.1 ± 7.7	74.1 ± 4.8	129.1 ± 3.5*	98.8 ± 6.3*#
MAP (mmHg)	92.9 ± 5.4	102.5 ± 4.7	162.3 ± 2.7*	135.1 ± 5.8*#
HBF (ml/100 g tissue/min)	6.8 ± 0.3	7.4 ± 0.6	3.6 ± 0.2*	5.4 ± 0.3*#
HVR(mmHg/min/100 g tissue/ml)	12.6 ± 0.6	15.3 ± 1.8	39.1 ± 3.8*	28.5 ± 2.2*#
Heart rate (beat/min)	331.7 ± 16.2	368.3 ± 8.8	414.7 ± 13.1*	363.5 ± 9.3#

*P< 0.001 vs normal control, # P< 0.05 vs hypertension (ANOVA) (n = 8-10/group).

normal rats (Figure 1).

Similarly, the results obtained from direct measurement showed that there was a significant increase of SBP, DBP and MAP after three weeks of L-NAME treatment (199.1 ± 3.2, 129.1 ± 3.5 and 162.3 ± 2.7 mmHg, respectively) comparing to those of control group (Table 1). In L-NAME treated rats a decrease of HBF (3.6 ± 0.2 ml/100 g tissue/min) was found when compared to the control group (6.8 ± 0.3 ml/100 g tissue/min). This hemodynamic alteration was related to increased resistance which was determined by the increase in HVR (L-NAME treated rats = 39.1 ± 3.8 mmHg/min/100 g tissue/ml; control group = 12.6 ± 0.6 mmHg/min/100 g tissue/ml) as shown in Table 1.

The effect of MC extract on SBP illustrated by direct measurement showed similar results as those obtained from indirect SBP measurement. Thus, the elevation of SBP, DBP and MAP was significantly attenuated (about 16%) in L-NAME-induced hypertensive rats simultaneously receiving MC extract for three weeks (Table 1). The alterations of HBF and HVR were also markedly prevented in L-NAME-treated rats receiving MC extract. Moreover, a significant increase in heart rate was observed in L-NAME-induced hypertensive rats comparing to those of the control group ($P < 0.05$). The tachycardic effect of L-NAME was clearly prevented by MC extract ($P < 0.05$) (Table 1). Heart rate value was restored about to a normal level in these animals (Table 1).

Effect of MC extract on vascular reactivity in L-NAME-induced hypertension

The decrease in MAP in response to acetylcholine in the L-NAME-induced hypertensive group was significantly attenuated when compared to that of the control group ($P < 0.05$). Interestingly, the vasodilatation response to SNP in all groups was similar (data not shown). In addition, a significant reduction of the increase in MAP in response to phenylephrine was found in hypertensive rats. The treatment of MC extract markedly improved the blunted vascular activity to acetylcholine in L-NAME hypertensive rats (Figure 2a) but did not affect the vascular response to SNP. Nevertheless, the impairment of vascular functions in contractile responses to phenylephrine was not recovered in the hypertensive group treated with MC extract (Figure 2b).

Effect of MC extracts on oxidative stress markers

It was found that there was a significant increase in plasma MDA content and vascular superoxide production in rats receiving L-NAME for three weeks ($P < 0.05$) (Figure 3a and b). The concomitant administration of MC extract improved the oxidative stress status in hypertensive rats but had no effect on the level of plasma MDA vascular superoxide production in normal rats (Figure 3a and b). These results indicated that MC extract exhibited a potential antioxidant capacity in the L-NAME hypertensive rat model.

Total phenolic contents in MC extract

To evaluate the potential antioxidant effect of MC extract used in this study, the total phenolic content in MC extract was evaluated. It was found that MC extract contains a total phenolic compound that was expressed as 13.93 ± 0.09 g of GEA/100 g of MC extract. This amount of total phenols is approximately three times less than that of vitamin C (43.31 ± 0.5 g of GEA/100 g of vitamin C).

DISCUSSION

This study examined the protective effect of MC extract on hemodynamic status, vascular responsiveness and oxidative stress markers in L-NAME-induced hypertension. These hypertensive animals had a sustained high blood pressure and an associated increase in heart rate, HVR and alterations of vascular functions. The main findings of this study are that MC extract partially inhibited the development of hypertension, and restored heart rate and vascular

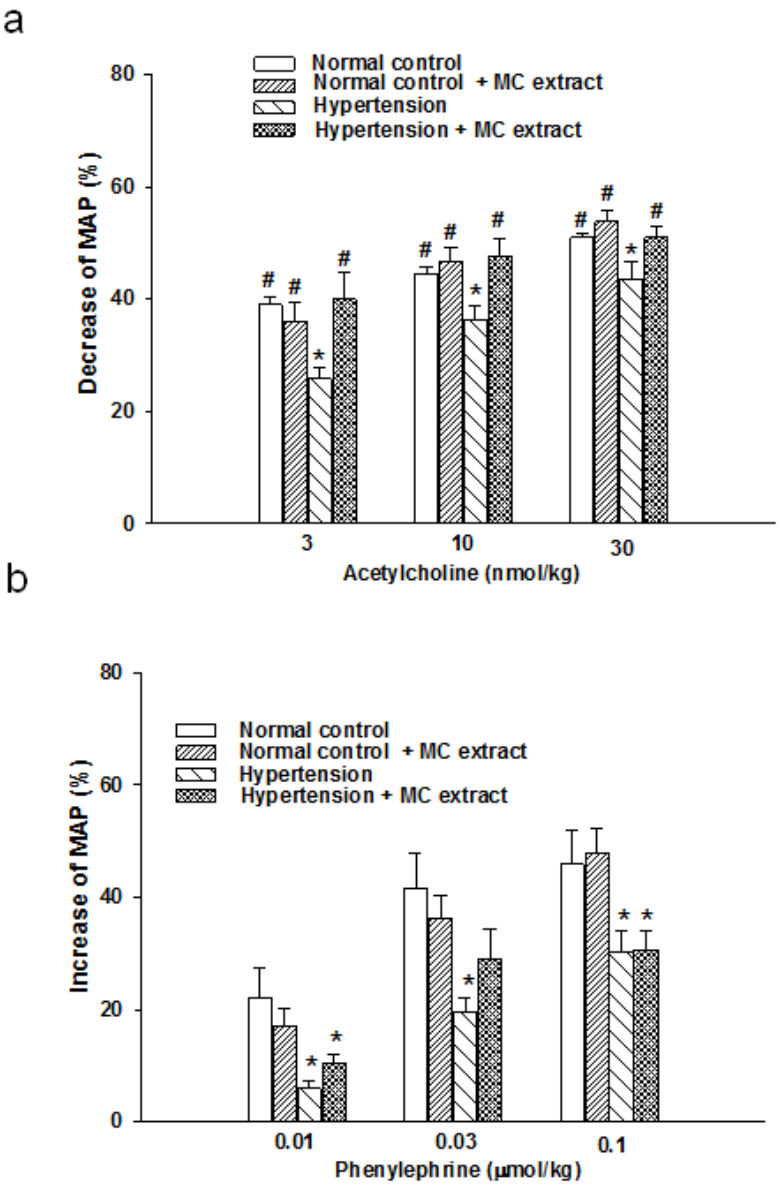

Figure 2. Effects of MC extract on the changes in MAP in response to acetylcholine 3, 10, 30 nmol/kg (a) and phenylephrine 0.01, 0.03, 0.1 µmol/kg (b) in control rats, normal rats with MC extract, L-NAME-treated rats (hypertension), and L-NAME-treated rats (hypertension) with MC extract (n=8-10/group). * P< 0.05 vs control, # P< 0.05 vs hypertension (ANOVA).

reactivity close to normal values. A significant increase in HBF and a reduction of HVR was found in L-NAME treated with MC extract, suggesting an improvement of hemodynamic status after MC extract administration. The results of biochemical assays showed the antioxidant effect of MC extract by reducing plasma MDA level and vascular tissue superoxide production in L-NAME-induced hypertension. This was supported by the finding of the phenolic compounds in the MC extract.

As blood pressure is determined primarily by cardiac output and total peripheral resistance, an increase in one of these factors can cause hypertension. Lack of NO in the circulatory system induces vasoconstriction, an increase in peripheral resistance and eventually leads to hypertension (Gardiner et al., 1990). This study has shown that daily administration of L-NAME for three weeks caused the development of hypertension and that this was associated with an increase in HVR. This finding is consistent with the observation in rats that daily L-NAME treatment for four weeks produced a sustained elevation of blood pressure and regional vascular resistance (Gardiner et al., 1990; Varagic et al., 2000).

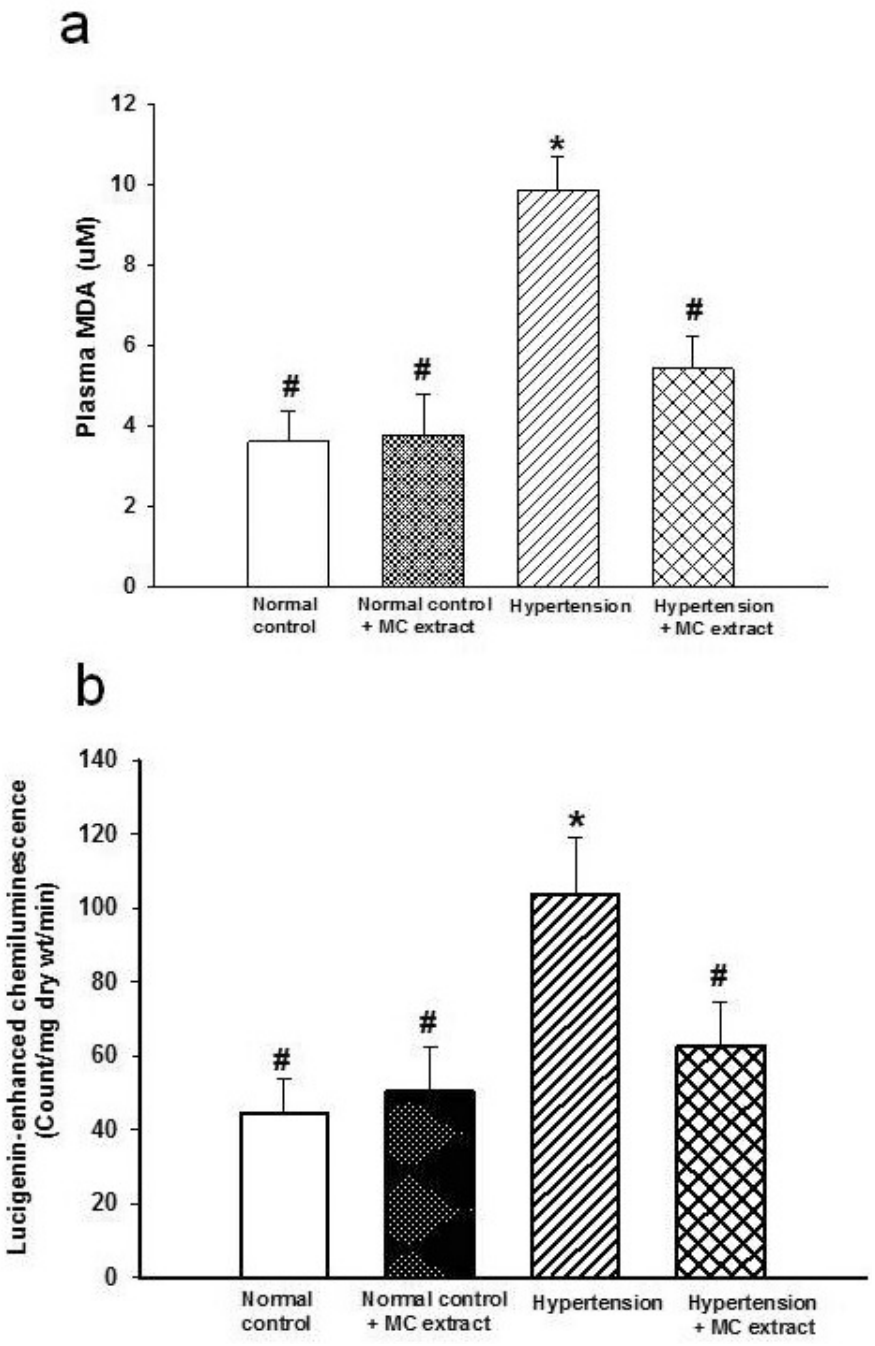

Figure 3. Effect of MC extract on plasma MDA (a) and superoxide production in carotid arteries (b) in control rats, normal rats with MC extract, L-NAME-treated rats (hypertension), and L-NAME-treated rats (hypertension) with MC extract (n=8-10/group) (n=8-10) * P< 0.05 vs control, # P< 0.05 vs hypertension (ANOVA).

An increased heart rate was also found in rats chronically treated with L-NAME. There is accumulating evidence that nitric oxide modulates sympathetic nervous activity by suppressing sympathetic outflow (Gerova et al., 1995; Sander and Victor, 1999) and leading to hypertension. Cunha et al. (1993) demonstrated that treatment of L-NAME in rats for six days induced an increase in blood pressure and heart rate and this was correlated with the overactivity of central sympathetic tone (Cunha et al., 1993). It was demonstrated that, sympathetic drive to the heart in rats treated with L-NAME was abolished by autonomic nerve blockers (Souza et al., 2001).

Therefore, an increase in sympathetic outflow is likely to have an important role in mediating the chronotropic effect in response to chronic administration of L-NAME in rats (Vasquez et al., 1994). Although, the increase in heart rate was observed in this study, this was not sufficient to increase cardiac output in the hypertensive animals. On the other hand several studies reported that hypertensive rats with nitric oxide synthase inhibition showed a lower cardiac output and that this was possibly due to a decrease in stroke volume (Biancardi et al., 2007; Varagic et al., 2000) as well as cardiac hypertrophy (Kristek and Gerova, 1996; Vaskonen et al., 1997).

The present findings show that MC extract significantly inhibited the increase of SBP, DBP and MAP in rats treated with L-NAME. These results suggest that the effect of MC extract against hypertension involved the reduction of total peripheral resistance. We found an improvement in HBF and HVR in L-NAME induced hypertensive rats-treated with MC extract. The vascular relaxation effect of the extract from *Mentha arvensis* has been previously reported in both large conductance and resistance arteries where nitric oxide was a mediating factor (Runnie et al., 2004). In addition, this study demonstrated that there was a decrease in heart rate of nitric oxide deficiency-hypertensive rats simultaneously received MC extract. The mechanism of heart rate alleviation by MC extract in this hypertensive model remains unclear. It could be explained by the antioxidant effect of MC extract leading to an increase in NO bioavailability, and this might subsequently suppress the sympathetic nerve outflow.

It is known that NO is formed and released by vascular endothelial cells in response to acetylcholine to mediate vasodilatation (Furchgott and Zawadzki, 1980). Later, vascular endothelial cell dysfunction was found in L-NAME- induced hypertensive rats and the impairment of vascular responses to endothelium-dependent vasodilator has been shown in both in vitro and in vivo studies (Bryant et al., 1995). In the in vivo study, alterations in the vascular activity of L-NAME hypertensive rats was seen, indicated by a blunted vascular response to acetylcholine, endothelium-dependent vasodilator (Zanchi et al., 1995). A decrease in vasodilatation response to acetylcholine in the aorta of chronic L-NAME-treated rats has been suggested to be due to a reduction of cGMP content (Arnal et al., 1992). Interestingly, the treatment of L-NAME hypertensive rats with MC extract restored this vascular impairment. Since the response to SNP, an endothelium-independent vasodilator, did not alter in this animal model, it has been suggested that the production of cGMP in response to NO donors in vascular tissues did not change in chronic L-NAME induced hypertension (Arnal et al., 1992). These results could imply that there was only an impairment of endothelium dependent vasorelaxation in L-NAME hypertensive rats. An alleviation of oxidative stress after MC extract administration might enhance NO bioavailability in the vessels, and contribute to the improvement of vascular responses to acetylcholine in L-NAME hypertensive rats. The vasoconstriction response to phenylephrine in this model of hypertension was also impaired. The decrease in vascular responses to phenylephrine, α_1-adrenoceptor agonist, in L-NAME hypertensive rats was not recovered by MC extract. These observations were associated with a reduction of contractile response to exogenously administered phenylephrine in isolated aortic rings of L-NAME-hypertensive rats. Henrion and coworkers (1996) suggested that this appear to be a downregulation of the contractile signaling pathways induced by chronic nitric oxide inhibition and associated with a drop in the extracellular Ca^{2+}content of smooth muscle cells (Henrion et al., 1996).

The excessive production of reactive oxygen species was proposed to be a major factor to mediate hypertension (Nakazono et al., 1991). In the L-NAME-induced hypertension model, it was suggested that a large quantity of superoxide production suppressed nitric oxide bioavailability (Pechanova et al., 1999; Torok, 2008). In addition, Duarte et al. (2002) found an increase in plasma and liver MDA levels in L-NAME hypertensive rats, indicating the involvement of oxidative stress in this animal model (Duarte et al., 2002). Our study was carried out to analyze oxidative stress markers in plasma and vascular tissues and evaluate the antioxidant property of MC extract in L-NAME-induced hypertension. The presence of oxidative stress was indicated by an increase in superoxide production in vascular tissues and plasma MDA in L-NAME hypertension. These findings are consistent with the previous studies as mentioned above. A reduction of oxidative stress was found in the hypertensive rats receiving MC extract. We also found that L-NAME-induced hypertension was partially prevented by MC extract, and this preventive effect might be connected with its antioxidant properties. The antioxidant properties of MC extract used in this study were confirmed by the large amount of total phenolic compounds it contained. Moreover, most of phytochemical studies of plant in the mint family, Mentha piperita L., showed the potential antioxidant capacity to exert beneficial biological effects (McKay and Blumberg, 2006). Several lines of evidence have shown that administration of antioxidant substances significantly inhibits the development of L-NAME-induced hypertension. For example, administration of the antioxidant flavonoid, quercetin, prevented the development of L-NAME-induced hypertension which was related to the reduction of oxidative stress status in this animal model. Penchanova and co-workers (2004) found that red wine polyphenols reduced the increase in blood pressure in rats treated with L-NAME, and this was accompanied by a reduction of oxidative stress and an increase of nitric oxide synthase activity (Pechanova et al., 2004).

In conclusion, the present study demonstrates that MC extract inhibited the development of hypertension in nitric oxide deficient rats. This was associated with a reduction in total peripheral resistance and improvement of vascular functions. The underlying mechanisms are likely to be related to the antioxidant properties of MC extract. This finding supports the beneficial effect on the cardiovascular system of a plant in the mint family, which is widely consumed in many countries.

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