

Effect of Ferulic Acid on High-Carbohydrate, High-Fat Diet-Induced Metabolic Syndrome in Rats

Ketmanee Senaphan¹, Orachorn Boonla¹, Aomkhan Timinkul¹, Upa Kukongviriyapan¹, Poungrat Pakdeechote¹, Veerapol Kukongviriyapan², Patchareewan Pannangpetch², Parichat Prachaney³
Department of ¹Physiology, ²Pharmacology and ³Anatomy Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Background and objective: Metabolic syndrome (MS) is the presence of multiple risk factors for diabetes and cardiovascular disease, including obesity, hyperglycemia, hypertension, and dyslipidemia. Ferulic acid (FA) is one of the phenolic compounds that possess strong antioxidant property. The aim of this study was to investigate whether FA could attenuate the metabolic syndrome and oxidative stress induced by a high-carbohydrate, high-fat diet (HCHF) in rats.

Method: Male Sprague Dawley rats (220-250 g) were randomly divided into three groups (n= 5-8/group). Rats in group 1 were fed with standard chow. Rats in groups 2 and 3 were fed with a HCHF diet with 15% fructose in drinking water, for 16 weeks. After receiving HCHF diet for 10 weeks, rats in group 3 were orally administered

with FA (30 mg/kg/day) for the last six weeks of the treatment protocol.

Result: Rats fed with HCHF diet showed the symptoms of MS, including hypertension, dyslipidemia, hyperglycemia and impaired glucose tolerance. FA at test dose significantly reduced blood pressure, fasting blood glucose and plasma triglyceride levels whereas plasma HDL-C level was increased when compared with the untreated MS rats ($p<0.05$). In addition, plasma malondialdehyde and vascular superoxide production were also decreased in MS rats treated with FA ($p<0.05$).

Conclusion: These results suggest that FA treatment attenuated the symptoms of MS with most likely mechanisms being decreases in oxidative stress.

Key words: Ferulic acid, High-fat, high-carbohydrate diet, Metabolic syndrome, Oxidative stress

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Introduction

Metabolic syndrome (MS) is a multifactorial condition leading to atherosclerosis and increased risk of type 2 diabetes and cardiovascular disease¹. This syndrome is characterized by different combinations of three or more of the following features, including abdominal obesity, hyperglycemia, hypertension and dyslipidemia. Patients with MS exhibit activation of biochemical pathways leading to increased delivery of ROS and decreased

antioxidant protection¹. Therefore, the need for prevention and therapy of this syndrome is very important and required urgently. It has been demonstrated that various adverse effects and high rates of secondary failures have been associated with the available antidiabetic drugs². Therefore, natural antioxidants with antihypertensive, antidyslipidemic and antihyperglycemic effects might be useful for alleviation of MS progression. Previous study demonstrated that ferulic acid (4-hydroxy-



3-methoxycinnamic acid, FA), a phenolic compound, possesses strong antioxidant³ and hypoglycemic effect by elevating the glucokinase activity that induces production of glycogen in the liver⁴. Moreover, oral administration of FA have beneficial in improving hypertension and hyperlipidemia in stroke-prone spontaneously hypertensive rats (SHRSP)⁵.

Objectives

The present study aimed to investigate whether FA supplementation could alleviate the symptoms of MS in HCHF diet fed rats.

Methods

1. Animals and experimental procedures

The experimental protocol of this study has been reviewed and approved by the Animal Ethics Committee of Khon Kaen University (AEKKU/19/2555). Male Sprague-Dawley rats (220-250g) were obtained from the National Laboratory Animal Center, Mahidol University. Animals were kept at the Northeast Laboratory Animal Center, Khon Kaen University in a room with controlled temperature ($23 \pm 2^{\circ}\text{C}$), relative humidity (30–60%), ventilation rate (10-15 cycles/h) and lighting cycle (12 h light/12 h dark).

Rats were randomly divided into three groups ($n=5-8$ each). Rats in group 1 were fed with standard chow diet (CP). Rats in group 2 and 3 were fed with high fat (20%) and high carbohydrate (57%) diet (HFHC) with 15% fructose in drinking water, for 16 weeks. After receiving HCHF diet for 10 weeks, rats in group 3 were intragastrically administered with FA (30 mg/kg/day) for the last six weeks of the treatment protocol.

The body weight, food and water intakes were measured daily. Fasting blood glucose and blood pressure was measured every two weeks by using tail cuff plethysmography (IITC model 179 blood pressure analyzer, Life science, USA). At the end of experiment, the animals were anesthetized with pentobarbital sodium (60 mg/kg, i.p.), arterial blood pressure and heart rate were recorded through femoral artery by previously described

method⁶. Blood samples were collected for assessment of blood chemistry and oxidative stress. The carotid arteries were immediately excised for measurement of superoxide ($\text{O}_2^{\cdot-}$) production by using lucigenin-enhanced chemiluminescence technique⁶.

2. Statistical analysis: Data are expressed as means \pm S.E.M. statistical differences were evaluated by one-way analysis of variance (ANOVA) and followed by Student Newman-Keul's test to show specific group difference. All analysis was performed using Sigmasat software version 3.1. Statistical significance was determined at a level of $p < 0.05$.

Results

The HCHF-fed rats showed the symptoms of MS, including hypertension, dyslipidemia, hyperglycemia and impaired glucose tolerance. The baseline values of systolic blood pressure (SBP) at the beginning were similar among all experimental groups. After receiving HFHC diets for two weeks, SBP was significantly increased when compared to those treated with standard chow diet ($p < 0.05$; Figure 1). Treatment with FA (30 mg/kg) for six weeks significantly decreased blood pressure of MS rats. Although the SBP of MS treated rats was still higher than normal controls, a reduction in blood pressure of MS rat treated with FA indicates the antihypertensive property of FA. After 16 weeks of experiment, fasting blood glucose of MS rats treated with FA was significantly decreased ($p < 0.05$; Figure 2), suggesting the hypoglycemic effect of FA. Figure 3 showed the levels of plasma triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) in experimental groups. plasma concentration of TG was higher whereas plasma HDL-C was lower in MS rats compared to control rats. FA at test dose significantly decreased TG and increased HDL-C concentrations of MS rats ($p < 0.05$; Figure 3).

A marked increase in superoxide ($\text{O}_2^{\cdot-}$) production in carotid arteries was observed in MS rats (Figure 4). Interestingly, FA reduced the level of $\text{O}_2^{\cdot-}$ production



($p < 0.05$; Figure 4). Increase of plasma MDA, a lipid peroxidation marker, was found in MS rats and treatment with FA significantly decreased plasma MDA ($p < 0.05$; Figure 5).

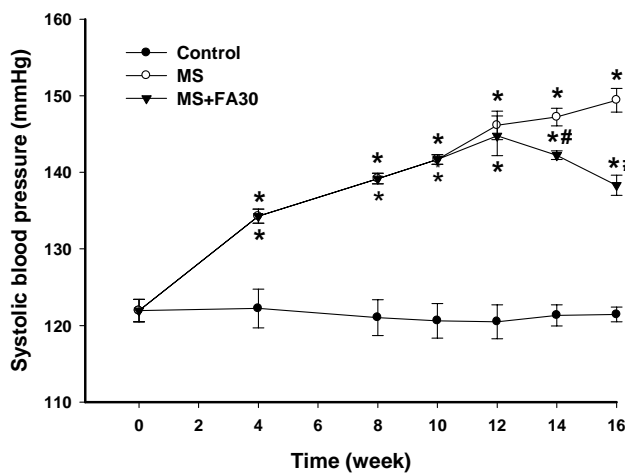


Figure 1 Effect of FA on systolic blood pressure during the experimental period of 16 weeks. Data expressed as mean \pm S.E.M. (N=5-8/group). * $p < 0.05$ vs. control, # $p < 0.05$ vs. MS group.

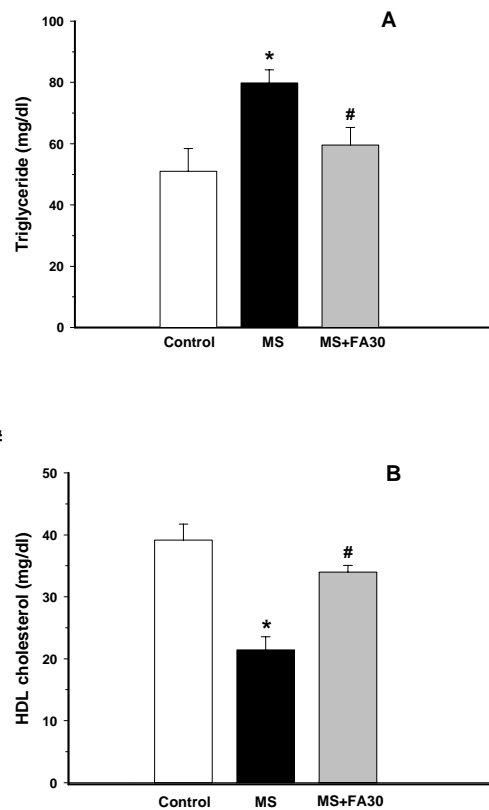


Figure 3 Effect of FA on plasma lipid profiles at 16 weeks in MS rats. Data expressed as mean \pm S.E.M. (N=5-8/group). * $p < 0.05$ vs. control, # $p < 0.05$ vs. MS group.

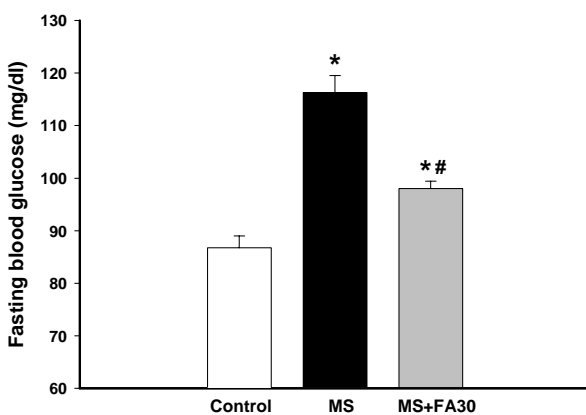


Figure 2 Effect of FA on fasting blood glucose at 16 weeks in MS rats. Data expressed as mean \pm S.E.M. (N=5-8/group). * $p < 0.05$ vs. control, # $p < 0.05$ vs. MS group.

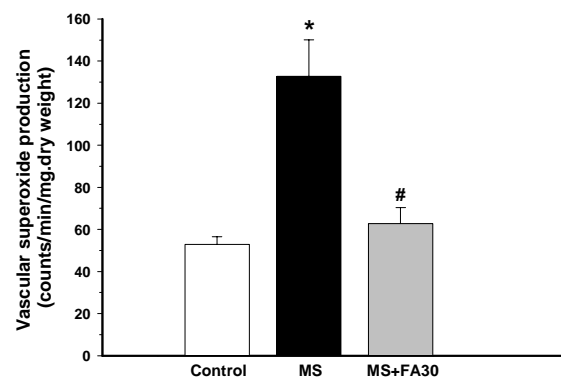


Figure 4 Effect of FA on O_2^- production in carotid arteries of MS rats. * Data expressed as mean \pm S.E.M. (N=5-8/group). $p < 0.05$ vs. control, # $p < 0.05$ vs. MS group.

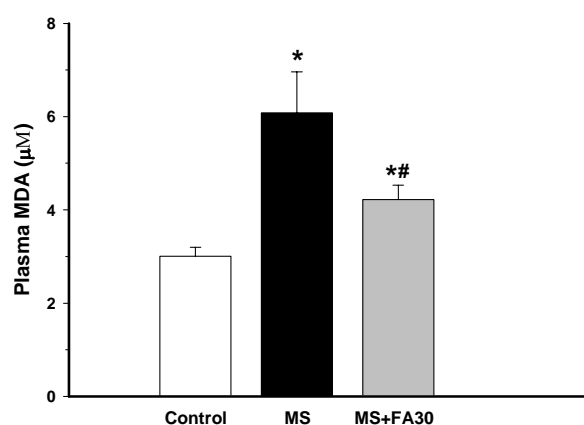


Figure 5 Effect of FA on plasma MDA in MS rats. Data expressed as mean \pm S.E.M. (N=5/group). * $p < 0.05$ vs. control, # $p < 0.05$ vs. MS group.

Conclusion

Results of this study demonstrated that HFHC diet together with high fructose in water induced MS in rats and increased oxidative stress. FA alleviated these effect by reducing blood pressure, FBG, vascular superoxide production and plasma MDA levels. This study indicates that FA may provide a useful dietary supplement to decreases the symptoms of MS by reducing oxidative stress associated with HCHF feeding in rats.

Acknowledgments

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