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Effects of nobiletin on blood pressure, vascular function and oxidative stress in L-NAME-induced hypertensive rats

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Introduction: Chronic inhibition of NO production by N^{ω}-Nitro-L-arginine methyl ester (L-NAME) promotes a potent peripheral vasoconstriction and oxidative stress, and contributes to vascular endothelial dysfunction[1]. Nobiletin is a polymethoxylated flavone found in citrus peels. The beneficial effects of nobiletin have been reported such as anticancer and anti-oxidation[2]. The aim of the present study was to investigate whether nobiletin could alleviate hypertension, vascular dysfunction and oxidative stress in L-NAME induced hypertensive rats.

Method: Male Sprague-Dawley rats weighing 220-250 g were given L-NAME (40 mg/kg/day) in drinking water for five weeks to induce hypertension. Hypertensive rats were intragastrically administered with nobiletin (20 or 40 mg/kg/day) or captopril (5 mg/kg/day) for the last two weeks (n = 6/each group). Systolic blood pressure (SP) and heart rate (HR) were measured using a tail cuff method once a week. Contractile responses to electrical field stimulation (EFS, 5-40 Hz, 1ms, 90V, 30s) and exogenous noradrenaline (NA) were tested in isolated mesenteric vascular beds. Vasorelaxation responses to acetylcholine (ACh) and sodium nitroprusside (SNP) were performed in mesenteric vascular beds. In addition, vascular superoxide production (lucigenin-enhanced chemiluminescence method), plasma malondialdehyde (MDA; TBAR method) and plasma nitric oxide metabolites (NOx; enzymatic conversion method) were evaluated. Data are expressed as mean±SEM and analysis was performed using one way ANOVA.

Results: Rats treated with L-NAME had high SP (Fig.1) and HR (428.8±13.7 vs. 354.7±11.8 beats/min) compared to those of controls (p<0.05). Nobiletin and captopril reduced SP (Fig.1) and HR (N20, N40, captopril; 370.2±2.4, 369.6±8.4, 367.0±10.2 beats/min) in L-NAME treated rats. The enhancement of contractile response to sympathetic nerve stimulation was alleviated in L-NAME hypertension treated with either nobiletin or captopril. Subsequently, both agents also improved the response to ACh in mesenteric vascular beds in L-NAME rats (Fig.2) while the response to NA and SNP did not differ among groups. Moreover, high levels of vascular superoxide production and plasma MDA, and low level of plasma NOx were observed in L-NAME rats. These were restored by either nobiletin or captopril treatment (p<0.05).

Conclusion: Results of this study indicate that antihypertensive effect of nobiletin was associated with suppressing contractile response to sympathetic nerve stimulation, improving endothelium-dependent vasorelaxation, reducing oxidative stress and increasing NO bioavailability in L-NAME-induced hypertensive rats.

References:

1. Maneesai P et al. (2016). *Nutrients* 8:122.
2. 2. Murakami A et al. (2000). *Biofactors* 12: 187-192.

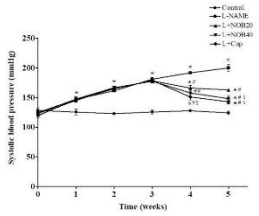

Figure 1 Effects of nobiletin on systolic blood pressure in L-NAME induced hypertension.
*p<0.05 vs. control; #p<0.05 vs. L-NAME; $p<0.05 vs. L-NAME+NOB20

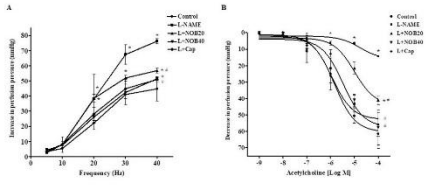

Figure 2 Effect of nobiletin on vascular responses to EFS (A) and ACh (B) in mesenteric vascular beds.
*p<0.05 vs. control; #p<0.05 vs. L-NAME