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Eupatilin attenuates atherosclerosis and improves adipokine profiles in LDL receptor-deficient mice

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Objectives

Eupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone), a pharmacologically active ingredient isolated from *Artemisia princes* Pamp. cv. Sajabal has been reported to have antioxidative and anti-inflammatory activities and to inhibit the activation of NF-kB. In the current study, we investigated anti-atherosclerotic and metabolic risk lowering effects of eupatilin in $LDLr^{-/-}$ mice.

Materials and Methods

○ Material

The aerial parts of *A. princeps* Pamp. cv. Sajabal were provided from Ganghwa County Agricultural Technology Service Center, Incheon, Korea, which were harvested at Gangwha County in 2004 and stored for 3 years in the air. The aerial parts (4 kg) were ground and extracted two times with 80% methanol (15 L) for 24 h at room temperature. The combined methanolic extracts were concentrated in vacuo, and the resulting aqueous suspension was successively partitioned with EtOAc and n-BuOH. The EtOAc-extracted residue was chromatographed on silica gel columns and ODS column to obtain compound **1**. The isolated compound **1** was identified as eupatilin on the basis of the physicochemical properties and spectroscopic analysis (Bang *et al.*, 2005).

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○ Animal Experiments

Homozygous LDL receptor deficient ($LDLR^{-/-}$, C57BL/6J background) mice were purchased from the Jackson Laboratory (Bar Harbor, ME) and cared at the Korean Research Institute of Bioscience and Biotechnology (KRIBB). Ten-week-old male $LDLR^{-/-}$mice (N = 30) were randomly divided into three groups. One negative control group (ND) was fed with a chow diet containing normal diet composition and other control group (HFHC) was fed with a Western diet containing 21% fat and 0.15% cholesterol. Eupatilin group (Eupatilin) were fed a Western diet supplemented with 0.02% eupatilin (wt/wt diet). After 12 weeks, the mice were sacrificed by cervical dislocation. We investigated anti-atherosclerotic and metabolic risk lowering effects of the eupatilin.

Results and Discussion

Eupatilin markedly reduced atherogenic-lesion formation as well as plasma lipid peroxidation (20.6 ± 1.5 MDA nmol/ml versus 23.0 ± 1.3 MDA nmol/ml, $p<0.005$) showing its ability as an antioxidant. Gene expression analysis demonstrated that eupatilin restrained the inflammatory state not only in aorta by decreasing levels of chemoattractants (ICAM-1, VCAM-1, and MCP-1) and cytokines (IL-1β and IL-2) but also in white adipose tissues by improving adipokine profiles, and resistin. Adipose tissue is a major source of inflammatory adipokines, which have very close relationship with metabolic syndrome. It is important to demonstrates that eupatilin reduced fasting blood glucose level in this study. In conclusion, eupatilin prevented atherogenic-lesion formation and plasma lipid peroxidation using their property as an antioxidant in $LDLr^{-/-}$ mice fed with a Western diet. Furthermore, the treatment of eupatilin restrained the inflammatory state not only in aorta by decreasing levels of atherogenic markers but also in white adipose tissues by improving adipokine profiles. The antioxidant properties of eupatilin prevent the development of early stage of atherosclerosis and lower metabolic risk by modulation of adipokine expression.