

[P-78]

Inhibition of Cytokine Induced I- κ B Kinase Activation as a Mechanism Contributing to the Anti-Atherogenic Activity of Tilianin in Hyperlipidemic Mice

Kung-woo Nam¹, Jiyun Kim², Jung-Joo Hong², Jae-Hoon Choi², Woonchon Mar¹, Myung-Haing Cho³, Young-Myeong Kim⁴, Sei-Ryang Oh², Ki-Hoan Nam², Goo Tag Oh²
¹Natural Products Research Institute, Seoul National University, Seoul 110-460 and
²Laboratory of Development and Differentiation, Korea Research Institute of Bioscience and Biotechnology, Yuseong, Taejeon 305-600 and ³ College of Veterinary Medicine, Seoul National University, Seoul 151-742 and ⁴Vascular System Research Center, Kangwon National University, Chunchon 200-701

BACKGROUND: In previous study, we demonstrated tilianin inhibits tumor necrotic factor- α (TNF- α) induced vascular cell adhesion molecule-1 (VCAM-1) expression in human umbilical vein endothelial cells (HUVEC). In this study, we demonstrate inhibition of the production of atherogenic cytokines and the anti-atherogenic effects of tilianin in Ldlr-/- mice.

METHODS AND RESULTS: Twenty-six male low-density lipoprotein receptor deficient mice (Ldlr -/- mice) were divided into three groups. One group of mice received high fat diet (1.25% cholesterol, 15% fat and 0.5% sodium cholate) and two groups of mice received high fat diet plus 1mg/kg lovastatin and 250mg/kg tilianin, respectively. After 10 weeks, mice were sacrificed and plasma lipid level (total cholesterol, HDL cholesterol triglyceride) and atherosclerosis lesion size were determined. Mice fed high fat diet with tilianin had slightly lower levels of total cholesterol than those fed the unsupplemented high fat diet. The atherosclerosis lesion was significantly reduced by 41.9% compared with control group (p<0.01). Tilianin treatment reduced the plasma levels of TNF- α and IL-1 β that can upregulate the expression of cellular adhesion molecules through the activation of nuclear factor κ -B (NF- κ B). Macrophage is one of the major producer of the TNF- α and IL-1 β . To investigate further the possible mechanisms of anti-atherogenic activity of tilianin, the peritoneal macrophage of the Ldlr-/- mice was used. The expression levels of mRNA and productions of TNF- α and IL-1 β were decreased in

the tilianin treated peritoneal macrophages. Tilianin also inhibit the activation of NF- κ B that regulates TNF- α and IL-1 β gene expression, but not the activation of AP-1. The inhibition of NF- κ B activation was due to its blockade of the upstream signals mediated I- κ B kinase (IKK) activation, and subsequent phosphorylation and degradation of I κ B in RAW 264.7 cells.

CONCLUSIONS: Tilianin ameliorates atherosclerosis by inhibition of TNF- α and IL-1 β gene expression that are regulated by NF- κ B. The possible molecular mechanism against atherosclerosis of tilianin is an inhibition of IKK activation, and subsequent phosphorylation and degradation of I κ B.

Keyword : Tilianin, Atherosclerosis, IKK, cytokine