[S3-4] [10/10/2003(Fri) 13:30-14:00/ Grand Ballroom 104]

Anti-atherogenic Effect of Tilianin from *Agastache rugosa*

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Investigation of immunomodulating activities of the *Agastache rugosa* (Bae-cho-hyang) extract and its components was preformed through screening *in vitro* assays and evaluating anti-inflammatory activity and anti-atherosclerotic activity of the extract and tilianin *in vivo*. The extract showed strong anti-inflammatory activity in carrageenan-induced acute edema mouse model and anti-atherogenic activity in LDLR (low density lipoprotein receptor) deficient mouse model. These activities were thought to be resulted from modulation activity of several pathways of inflammation process. Among the main constituents of *A. rugosa*, polyunsaturated fatty acids (PUFA), phytosterols, oleanolic acid and rosmarinic acid showed anticomplement activity, and PUFA, acacetin and tilianin showed potent inhibition activity of ICAM-1 expression.

The effect of tilianin upon inducible nitric oxide synthesis in the plasma of low-density lipoprotein receptor knock-out (*Ldlr-/-*) mice fed high cholesterol diet (HCD) and in primary peritoneal macrophage of *Ldlr-/-* mice was investigated. High cholesterol diet induced NO production in the plasma of *Ldlr-/-* mice. Tilianin reduced the level of NO in plasma from *Ldlr-/-* mice induced by the high cholesterol diet. Tilianin also inhibit the production of nitrite from the primary culture of peritoneal macrophage induced by lipopolysaccharide. The inhibition of NO production was caused by the suppression of iNOS gene expression in peritoneal macrophages isolated from *Ldlr-/-* mice. Moreover, tilianin inhibited the transcriptional activation of iNOS promoter that has NF-κB binding element. Thus, these results provide the first evidence that tilianin inhibit iNOS expression and production of nitric oxide, and may act as a potential anti-inflammatory agent.

Ldlr-/- mice fed a high cholesterol diet showed also increased plasma levels of total cholesterol, triglycerides, and the pro-inflammatory cytokines TNF-α and IL-1β, when compared with *Ldlr-/-* mice fed a normal diet. Mice fed the HCD supplemented with tilianin (0.05% wt/wt HCD diet) showed significantly reduced cytokine levels, without significant

changes in serum cholesterol levels. Primary cultured peritoneal macrophages from *Ldlr-/-* mice showed increased expression of TNF-α and IL-1β mRNA in response to treatment with lipopolysaccharide; these increases were suppressed by co-treatment with tilianin. Moreover, tilianin inhibited NF-κB activation but not AP-1 activation, as determined by electrophoretic mobility shift and NF-κB promoter assays. IκB kinase activation and the subsequent phosphorylation and degradation of IκBα protein of upstream of NF-κB was inhibited by tilianin. These results suggest that tilianin ameliorates atherosclerosis by inhibiting the production of the NF-κB-dependent pro-inflammatory cytokines, TNF-α and IL-1β, via the inhibition of IκB kinase activity.