PC-7

# Suppressive effects on the expression of cyclooxygenase-2 and inducible nitric oxide synthase by a natural sesquiterpenoid in lipopolysaccharide-stimulated mouse macrophage cells

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Prostaglandins (PGs) and nitric oxide (NO) produced by inducible cyclooygenase (COX-2) and nitric oxide synthase (iNOS), respectively, have been implicated as important mediators in the process of inflammation and carcinogenesis. On this line, the potential COX-2 or iNOS inhibitors have been considered as anti-inflammatory and cancer chemopreventive agents. In our continuing efforts of searching for novel cancer chemopreventive agents from natural products, we isolated natural sesquiterpenoids as potential COX-2 and iNOS inhibitors in cultured lipopolysaccharide (LPS)-activated mouse macrophage RAW 264.7 cells. Alantolactone, a natural eudesmane-type sesquiterpenoid, exhibited a potent inhibition of COX-2 (IC50 = 0.4 $\mu$g/ml) and iNOS activity (IC50 = 0.08 $\mu$g/ml) in the assay system determined by PGE2 and NO accumulation, respectively. The inhibitory potential of alantolactone on the PGE2 and NO production was well coincided with the suppression of COX-2 and iNOS protein and mRNA expression in LPS-induced macrophages. Furthermore, alantolactone inhibited NF-kB but not AP-1 binding activity on nuclear extracts evoked by LPS-stimulated macrophage cells, suggesting the possible involvement of NF-kB in the regulation of COX-2 and iNOS expression. In further study with COX-2-expressing human colon HT-29 cells, alantolactone inhibited the cell proliferation, down-regulated COX-2, and inhibited the ERK phosphorylation in the early time. These results suggest that a natural sesquiterpenoid alantolactone might be a potential lead candidate for further developing COX-2 or iNOS inhibitor possessing cancer chemopreventive or anti-inflammatory activity