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Potent inhibition of Lipopolysaccharide-Inducible Nitric Oxide Synthase Expression by Dibenzylbutyrolactone Lignans through Inhibition of I-κB Phosphorylation and of p65 Nuclear Translocation in Macrophages

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Arctigenin and demethyltraxillagenin, dibenzylbutyrolactone lignans, are phenylpropanoid plant metabolites with antioxidative and anti-inflammatory activities. The effects of arctigenin and demethyltraxillagenin on the nuclear factor-κB (NF-κB)-mediated inducible nitric oxide synthase (iNOS) gene expression were studied in Raw264.7 cells. Activation of NF-κB was determined by gel mobility shift assay, immunocytochemistry and immunoblot analysis of I-κB degradation. Expression of the iNOS gene was assessed by Northern and Western blot analyses. Nitrite production was monitored by chemiluminescent detection using nitric oxide analyser. Arctigenin (1 μM) inhibited lipopolysaccharide (LPS)-induced nuclear NF-κB activation and nuclear translocation of p65, which was accompanied by inhibition of I-κB phosphorylation, whereas demethyltraxillagenin was less effective. LPS-inducible increase in the iNOS mRNA level was 80-90% inhibited by 0.01-1 μM of arctigenin, whereas similar extents of inhibition were noted by 50-100 μM demethyltraxillagenin. Immunoblot analysis revealed that arctigenin potently inhibited the expression of iNOS by LPS in a concentration-dependent manner (IC50=0.01 μM). The IC50 value of demethyltraxillagenin was ~50 μM. The production of nitrite and nitrate by LPS in culture medium was also comparably suppressed by the lignans. These results demonstrated that arctigenin potently inhibited LPS-inducible iNOS expression in murine macrophages through suppression of I-κB phosphorylation and nuclear translocation of p65. Potent inhibition of LPS-inducible nitric oxide production in macrophages may constitute the anti-inflammatory effects of dibenzylbutyrolactone lignans.