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Sesquiterpenoids from the rhizomes of *Curcuma phaeocaulis* and their inhibitory effects on LPS-induced TLR activation

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The activation of TLR4 leads to the induction of nuclear factor kappa B (NF-κB) signal cascades that initiate the production of pro-inflammatory molecules, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, IL-8 and IL-12. This pathway is biologically important for regulating host homeostasis; however, the inability to regulate excessive TLR4 activation causes abnormal inflammatory responses. In our ongoing studies of TLR4 inhibitors from traditional medicinal resources, we have determined that a 95% EtOH extract of *Curcuma phaeocaulis* rhizomes has a half maximal inhibitory concentration (IC_{50}) value of 8.8 μg per mL. This extract was progressively fractionated with EtOAc, n-BuOH, and H_2O, and the EtOAc-soluble fraction was subjected to various chromatographic experiments, which allowed us to isolate new guaiane-type (2 and 6) and furanogermacrane-type (11) sesquiterpenoids as well as twelve known compounds: Procurcumenol (1), procurcumadiol (3), zedoarondiol (4), phaeocaulisine E (5), wenyujinin L (7), phacadinane B (8), curcumenolactone A (9), curcumenolactone B (10), zedoarofuran (12), curcolonol (13), 4α-hydroxy-8,12-epoxyeudesma-7,11-diene-1,6-dione (14) and neolitacumone A (15). The THP-1-Blue cell line was used to evaluate the inhibitory effects of our isolated compounds 1-15 on TLR4 activation. LPS-induced TLR4 activation was inhibited by 4, 8 and 9 [with an IC_{50} value of 22.5±1.0 μM (4), 54.8±1.2 μM (8) and 91.0±6.3 μM (9)] relative to the positive control luteolin (IC50 value: 2.6±0.8 μM), whereas the remaining compounds showed little to no inhibition. Interestingly, phaeocaulisine E, a 10-epimer of zedoarondiol that exhibits a β-orientation at OH-10, produced no inhibitory effects (IC_{50}>100 μM), suggesting that in guaiane-type sesquiterpenoids, the configuration at OH-10 may affect the inhibition of TLR4 activity. These findings suggest that sesquiterpenoids from *C. phaeocaulis* may be promising as inhibitors for TLR4-mediated inflammatory disease. Additional research is needed to evaluate relatively effective new candidate compounds that could target LPS-stimulated TLR4 activity.

Biography

Mun-Chual Rho has completed his PhD from Tohoku University and Post-doctoral studies from Kitasato Institute. He is the Director of Natural Product Research Center, Korea Research Institute of Bioscience and Biotechnology. He has published more than 100 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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