

Dioscorin isolated from *Dioscorea alata* activates TLR4-signaling pathways and induces cytokine expression in macrophages.

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Abstract

The Toll-like receptor 4 (TLR4)-signaling pathway is crucial for activating both innate and adaptive immunity. TLR4 is a promising molecular target for immune-modulating drugs, and TLR4 agonists are of therapeutic potential for treating immune diseases and cancers. Several medicinal herb-derived components have recently been reported to act via TLR4-dependent pathways, suggesting that medicinal plants are potential resources for identifying TLR4 activators. We have applied a screening procedure to systematically identify herbal constituents that activate TLR4. To exclude possible LPS contamination in these plant-derived components, a LPS inhibitor, polymyxin B, was added during screening. One of the plant components we identified from the screening was dioscorin, the glycoprotein isolated from *Dioscorea alata*. It induced TLR4-downstream cytokine expression in bone marrow cells isolated from TLR4-functional C3H/HeN mice but not from TLR4-defective C3H/HeJ mice. Dioscorin also stimulated multiple signaling molecules (NF-kappaB, ERK, JNK, and p38) and induced the expression of cytokines (TNF-alpha, IL-1beta, and IL-6) in murine RAW 264.7 macrophages. Furthermore, the ERK, p38, JNK, and NF-kappaB-mediated pathways are all involved in dioscorin-mediated TNF-alpha production. In summary, our results demonstrate that dioscorin is a novel TLR4 activator and induces macrophage activation via typical TLR4-signaling pathways.