Anti-Inflammatory Bioactivities of Honokiol through Inhibition of Protein Kinase C, Mitogen-Activated Protein Kinase, and the NF-κB Pathway To Reduce LPS-Induced TNFα and NO Expression

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Much recent research has demonstrated that honokiol, a phenolic compound originally isolated from Magnolia officinalis, has potent anticancer activities; however, the detailed molecular mechanism of its anti-inflammatory activity has not yet been fully addressed. In this study we demonstrated that honokiol inhibited lipopolysaccharide (LPS)-induced tumor necrosis factor-α secretion in macrophages, without affecting the activity of the tumor necrosis factor-α converting enzyme. At the same time, honokiol not only inhibited nitric oxide expression in LPS-stimulated murine macrophages but also inhibited the LPS-induced phosphorylation of ERK1/2, JNK1/2, and p38. By means of confocal microscopy analysis we demonstrated that phosphorylation and membrane translocation of protein kinase C-α, as well as NF-κB activation, were inhibited by honokiol in LPS-stimulated macrophages. Furthermore, it was found that honokiol neither antagonizes the binding of LPS to cells nor alters the cell surface expression of toll-like receptor 4 and CD14. Our current results have exhaustively described the anti-inflammatory properties of honokiol, which could lead to the possibility of its future pharmaceutical application in the realm of immunomodulation.

KEYWORDS: Honokiol; LPS; cytokines; signaling

INTRODUCTION

The innate immunological response of mammalian cells is typically triggered by pathogen-associated molecular patterns that are shared by groups of different microbial pathogens, which are recognized by toll-like receptors (TLRs) expressed on the cell surface of monocytes and macrophages (1). Lipopolysaccharide (LPS) activates monocytes and macrophages by binding to TLR4, and stimulates the production of tumor necrosis factor-α (TNFα) and nitric oxide (NO) (2). TNFα- and NO-mediated signaling play various physiological processes, including immune defense and smooth muscle relaxation (3); however, overexpression of TNFα and NO are responsible for the origin and progression of rheumatoid arthritis and other inflammatory diseases (4). Development of a potential therapeutic approach to modulate inflammatory disease has become of increasingly greater concern and importance.

Several signal transduction cascades are involved in the regulation of inflammatory mediator expression in LPS-stimulated macrophages, such as protein kinases and transcription factors (5). Protein kinase C (PKC) is one of the signaling molecules in an LPS mediated inflammatory response (6). PKC is phosphorylated and translocated from cytosol when it is activated by physiological stresses; it then triggers a downstream signal transduction cascade via modulation of the mitogen-activated protein kinase (MAPK) pathways, such as extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase 1/2 (JNK1/2), and p38 MAP kinase (7). In addition to protein kinase, nuclear transcription factor kappa-B (NF-κB) also plays a pivotal role in the regulation of inflammatory-related gene expression (8).

Honokiol, a natural product with a small molecular weight—originally isolated from the Chinese medicinal herb Magnolia officinalis— inhibits the growth of various cancer cell lines in vitro (9) and in vivo (10). In addition to its anticancer activity, honokiol reduces Propionibacterium acnes-induced TNFα, as well as the expression of interleukin-8 and cyclooxygenase-2, by the reduction of NF-κB activation in human monocyte THP-1 cells (11). Honokiol also inhibits phorbol-12-myristate-13-acetate- or N-formylmethionyl-leucyl-phenylalanine-induced inflammatory responses by reducing reactive oxygen species release in neutrophils (12). Honokiol-containing materials have been shown...