

The effects of a synthetic curcuminoid analogue, 2,6-bis-(4-hydroxyl-3-methoxybenzylidene)cyclohexanone on proinflammatory signaling pathways and CLP-induced lethal sepsis in mice.

ABSTRACT

We previously showed that 2,6-bis-(4-hydroxyl-3-methoxybenzylidene)cyclohexanone (BHMC), suppressed the synthesis of various proinflammatory mediators. In this study we explain the mechanism of action of BHMC in lipopolysaccharide (LPS)-induced U937 monocytes and further show that BHMC prevents lethality of CLP-induced sepsis. BHMC showed dose-dependent inhibitory effects on p38, JNK and ERK 1/2 activity as determined by inhibition of phosphorylation of downstream transcription factors ATF-2, c-Jun and Elk-1 respectively. Inhibition of these transcription factors subsequently caused total abolishment of AP-1–DNA binding. BHMC inhibited p65 NF- κ B nuclear translocation and DNA binding of p65 NF- κ B only at the highest concentration used (12.5 μ M) but failed to alter phosphorylation of JNK, ERK1/2 and STAT-1. Since the inhibition of p38 activity was more pronounced we evaluated the possibility that BHMC may bind to p38. Molecular docking experiments confirmed that BHMC fits well in the highly conserved hydrophobic pocket of p38 MAP kinase. We also show that BHMC was able to improve survival from lethal sepsis in a murine caecal-ligation and puncture (CLP) model.

Keyword: BHMC; Curcumin; MAPK; NF- κ B; Monocyte; Sepsis.