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Heme oxygenase-1 induction through p38 MAPK/Nrf2 activation by ethanol extract of *Artemisia capillaries* inhibits LPS-activated iNOS, COX-2, and HMGB1 in RAW 264.7 cells

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Abstract

Heme oxygenase-1 (HO-1) negatively regulates inflammatory cytokines in lipopolysaccharide (LPS)-activated RAW 264.7 cells. The purpose of the study was to know whether anti-inflammatory effect of the extract of *Artemisia capillaries* (EAC) is responsible for HO-1 protein expression in RAW264.7 cells. EAC increased HO-1 expression in a time and concentration-dependent manner and inhibited the expression of iNOS (NO) and COX-2 (PGE_2), and release of high mobility group box 1 (HMGB1) in LPS-activated RAW 264.7 cells, respectively. EAC also inhibited NF-kB activity in LPS-activated cells. Finally, the induction of HO-1 as well as inhibition of iNOS and COX-2 by EAC was inhibited by SB203580 but not by SP600125, PD98059, nor LY294002. These results suggest that p38 MAPK/Nrf2-dependent HO-1 induction by EAC is at least rationalized for traditional use of this herb to treat in inflammatory disorders.

Keywords: Heme oxygenase, *Artemisia capillaries,* inflammation, p38MAPK, RAW 264.7 cells

Introduction

Heme oxygenase 1 (HO-1) degrades heme molecule into ferrous iron, carbon monoxide (CO) and biliverdin which is ultimately converted to bilirubin (BR) by biliverdin reductase (Otterbein et al., 1999; Ryter et al., 2006). It has been shown that HO-1 and its by-products play a role in a wide range of actions that could be important during the solution phase of inflammation, with macrophages acting as the pivotal target (Otterbein et al., 1999; Ryter et al., 2006). Administration of HO-1 inducible agents inhibits the expression of the inflammatory genes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in macrophages and subsequently decreases NO and PGE_2 production (Tsoyi et al., 2008). High mobility group box 1 (HMGB1), a nonhistone DNA-binding molecule, has been

