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Anti-Inflammatory Evaluation and Mechanisms of Eugenol and Isoeugenol Derivatives in Lipopolysaccharide-Stimulated Macrophages

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During the past decade, various eugenol and isoeugenol derivatives such as eugenolol, isoeugenolol, isoeugenodilol, and glyceryl-isoeugenol have been synthesized and investigated in our laboratory. Our previous studies have demonstrated that the agents possess vasodilatory, antioxidant, tracheal relaxant β–adrenoceptor blocking properties, or α–adrenoceptor blockade. Several studies have demonstrated isoeugenol and eugenol exert anti-inflammatory actions. However, the anti-inflammatory action of these derivatives is still not determined. In this study, we demonstrated that eugenol derivative, eugenolol, exhibited stronger inhibition effects on cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) as well as NO production than those of eugenol in lipopolysaccharide (LPS)-induced RAW264.7 macrophages. We also found that eugenolol is a more potent inhibitor on Akt and IκB phosphorylation, and decreased the p65 translocating to the nucleus and DNA binding activity of nuclear factor-kappa B (NF-κB) more powerfully than eugenol. Aside from this, we also studied the hypoxia-induced factor-1 alpha (HIF-1α) transcription factor, which transcripts inflammatory mediator genes, and found that eugenolol inhibited the LPS-induced HIF-1α expression at the level which eugenol had no effect on. Besides, we investigated the anti-inflammatory effects of isoeugenol derivatives as well, and revealed that glyceryl-isoeugenol is the strongest COX-2 and iNOS inhibitor of these three derivatives. It's possibly because that glyceryl-isoeugenol is the most significant suppressor on Akt and IαB phosphorylation among the others. Glyceryl-isoeugenol also inhibited the activation of mitogen-activated protein kinases (MAPKs) including p38, JNK, and ERK1/2 which have been shown to be involved in the LPS-induced induction of iNOS and COX-2 expression in RAW264.7 cells.