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Ascofuranone inhibits lipopolysaccharide-induced inflammatory response via NF-kappaB and AP-1, p-ERK, TNF-α, IL-6 and IL-1β in RAW 264.7 macrophages

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The natural fungal compound ascofuranone (5-chloro-3-[(2E, 6E)-7-[(2S)-5, 5-dimethyl-4-oxo-tetrahydrofuran-2-yl]-3-methyl-octa-2, 6-dienyl]-2, 4-dihydroxy-6-methyl-benzaldehyde, MW 420.93) (AF) is isolated from Ascochyta viciae and has been known to promote cell cycle arrest and inhibit invasion of tumor cells. A structurally similar compound ascochlorin (ASC; MW 404.93) has shown to have anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophages. AF is structurally different than ASC in that AF has a unique dimethyl-oxo-tetrahydrofuran structure, whereas ASC has a unique trimethyl oxocyclohexyl structure. The activity of AF is studied herein to observe the relationship between the anti-inflammatory activities and the different structures of AF and ASC. AF inhibited the production of NO and iNOS and the COX-2 mRNA and protein levels in RAW 264.7 cells in a dose-dependent manner. In addition, AF suppressed mRNA expression levels of inflammatory cytokines such as TNF-α, IL-6, and IL-1β when assessed by RT-PCR. When AF (30-50 μg/ml) is treated, the nuclear translocation of NF-κB, AP-1 (p-c-Jun) from the cytosolic space is clearly downregulated. When phosphorylated, IκB maintains the activity of NF-κB and this activity was decreased by AF treatment. AF also suppressed the binding of NF-κB (p65). Inhibition and degradation of IkBa phosphorylation inhibits nuclear translocation of p65. Immunofluorescence confocal microscopy analysis also revealed that translocation of NF-κB and AP-1 (p-c-Jun) was downregulated when AF was treated. AF specifically decreased the expression level of p-ERK, but had no effects on the expression level of p-p38 or p-JNK. Given these results, we suggest that AF has anti-inflammatory effects through targeting p-ERK. These results indicate that AF can be used as a negative regulator of LPS-stimulated nuclear translocation of NF-κB and AP-1 (p-c-Jun) in RAW 264.7 macrophages by specifically targeting p-ERK. Therefore, AF and ASC exert their effects in different ways possibly due to their structural differences that allow AF and ASC to specifically recognize and inhibit their target MAPKs. Our results further suggest that AF could be a useful natural bioactive compound for treating inflammation-mediated pathological diseases

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