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The (2′S,7′S)-O-(2-methylbutanoyl)-columbianetin as a novel allergic rhinitis-control agent

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ABSTRACT

Aims: The (2′S,7′S)-O-(2-methylbutanoyl)-columbianetin (OMC) is a novel secondary metabolite extracted from *Corydalis heterocarpa*, which has long been used as a folk medicine for various inflammatory diseases in Korea. We examined the effect of OMC on allergic rhinitis (AR).
Main methods: We assessed the therapeutic effects and regulatory mechanisms of OMC on the phorbol 12-myristate 13-acetate plus A23187-stimulated mast cell line, HMC-1 cells and ovalbumin (OVA)-induced AR models.
Key findings: OMC significantly decreased the releases of histamine and tryptase from stimulated HMC-1 cells. The degranulation process, characterized by morphological extension of the filopodia on the surface and membrane ruffling, was strongly induced in the stimulated-HMC-1 cell, however OMC suppressed the morphological changes in stimulated-HMC-1 cells. OMC reduced the production and mRNA expression of inflammatory cytokines. These inhibitory actions by OMC were dependent on the regulation of mitogen-activated protein kinases, nuclear factor-κB, and caspapase-1 signaling pathways. In the AR animal model, the increased rub scores and AR biomarkers (histamine and IgE) in ovalbumin (OVA)-sensitized mice were significantly reduced by the administration of OMC. Furthermore, eosinophils and mast cell infiltrations in nasal mucosa tissue were also blocked through the regulation of macrophage-inflammatory protein and intercellular adhesion molecule-1 levels.
Significance: OMC showed the possibility to regulate AR in activated mast cells and OVA-induced AR models. Hence, we suggest that OMC is a powerful and feasible new agent to suppress AR.
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Introduction

Allergic rhinitis (AR), referred to as hay fever, is the most common cause of all atopic diseases afflicting roughly 500 million people worldwide and defined clinically as an inflammatory disorder of the nasal mucous membrane (Barnes, 1999; Bousquet et al., 2008; Gravitz, 2011). AR is a type 1 immune response mediated by T helper 2 (T_H2)-cells and innate immune cells such as eosinophils, mast cells, basophils, and macrophages (Palm et al., 2012). The AR reaction includes a hypersensitivity phase, which induces IgE synthesis and humoral responses, and a clinical phase divided into early, late and chronic phases, which are induced by re-exposure of allergen (Barnes, 1999; Ramírez-Jiménez et al., 2012). In the hypersensitivity phase, dendritic cells (DCs), the antigen presenting cells, in the mucosal surface present the processed allergen peptides to cognate naive T cells using major histocompatibility complex (MHC) class II molecules. Then, naive T cells acquire a T_H2 cell phenotype, which induces B cells to undergo the class-switch recombination to produce IgE antibodies through secreted interleukin (IL)-4 and IL-13 (Min, 2010; Galli and Tsai, 2012). The IgEs bind to FcεRI receptors on mast cells and the subsequent exposure to the allergen induces the cross-linking of IgE on mast cells.

Mast cells play a key part in the early response in the clinical phase because the cross-linking of IgE triggers mast cell de-granulation and the synthesis of a variety of mediators including biogenic amines, serglycin proteoglycans, serine proteases, cytokines, and growth factors. Histamine is an important biogenic amine that leads to clinical symptoms of congestion, rhinorrhea, and bronchoconstriction by increasing vascular permeability and constricting smooth muscle (Perlman,

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1999; Pawankar et al., 2011). Furthermore inflammatory mediators such as IL-3, IL-5, IL-9, IL-6, tumor necrosis factor (TNF)-α, macrophage inflammatory protein-2 (MIP-2), and intercellular adhesion molecule-1 (ICAM-1) induce the recruitment of inflammatory cells leading to the late allergic response manifested by nasal congestion, nasobronchial hyper-reactivity, and chronic wheeze (Mandhane et al., 2011; Xu et al., 1995; Perlman, 1999). Importantly, intracellular signaling pathways such as mitogen-activated kinases (MAPKs), nuclear factor-κB (NF-κB), and caspapase-1 regulate the production of these pro-inflammatory cytokines (Oh et al., 2012).

(2′S,7′S)-O-(2-methylbutanoyl)-columbianetin (OMC, Fig. 1) is a novel secondary metabolite extracted from *Corydalis heterocarpa*, which has long been used as a folk medicine for various inflammatory diseases in Korea. Libanoridin and columbianetin extracted from *C. heterocarpa* were very effective on allergic inflammatory reaction (Jeong et al., 2009; Kim et al., 2010a). Kim et al. identified OMC for the first time in 2010 and reported its anti-proliferative effects against U-937 human leukemia cells (Kim et al., 2010b). However the effect of OMC on AR has not been determined. In this study, we focused on the possibility of OMC for the regulation of AR and considered a possible mechanism in the phorbol 12-myristate 13-acetate plus A23187 (PMACI)-stimulated mast cells and ovalbumin (OVA)-induced AR models.

Materials and methods

Reagents

We purchased OVA, phorbol 12-myristate 13-acetate (PMA), calcium ionophore (A23187), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), phosphate-buffered saline (PBS), bovine serum albumin (BSA), bicinchoninic acid (BCA), and avidin–peroxidase from Sigma Chemical Co. (St Louis, MO, USA); Isocove's Modified Dulbecco's Medium (IMDM), penicillin, streptomycin, and fetal bovine serum (FBS) from Gibco BRL (Grand Island, NY, USA). Anti-mouse IgE/IL-1β [mature form detection antibody (Ab)]/TNF-α/thymic stromal lymphopoietin (TSLP)/interferon (IFN)-γ/MIP-2/ICAM-1 Ab, biotinylated anti-mouse IgE/IL-1β/TNF-α/TSLP/IFN-γ/MIP-2/ICAM-1 Ab, recombinant mouse IgE/IL-1β/TNF-α/TSLP/IFN-γ/MIP-2/ICAM-1, anti-human IL-1β/TNF-α/IL-6/IL-8 Ab, biotinylated anti-human IL-1β/TNF-α/IL-6/IL-8 Ab, and recombinant human IL-1β/TNF-α/IL-6/IL-8 Ab were purchased from BD Biosciences Pharmingen (San Diego, CA, USA). Ab for extracellular signal-regulated protein kinase (ERK), phosphorylated-ERK (pERK), c-jun amino N-terminal kinase (JNK), pJNK, p38, pp38, IκB-α, plκB-α, NF-κB, histone, procaspase-1, caspase-1, actin, and α-tubulin were obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA). The mouse OVA-specific IgE kit was purchased from DS Pharma Biomedical Co. Ltd. (Osaka, Japan). The caspase-1 assay kit was supplied by R&D Systems, Inc. (Minneapolis, MN, USA). The tryptase assay kit was supplied by Millipore Co. (Billerica, MA, USA).

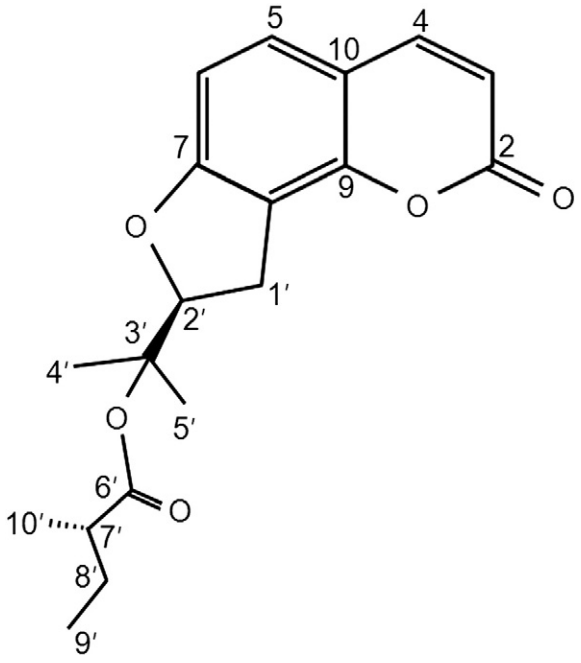

Fig. 1. Chemical structure of OMC.

Cells culture and stimulation

Human leukemic cell line, HMC-1 cells were grown in an IMDM medium supplemented with 100 U/ml penicillin, 100 μg/ml streptomycin, 10 μM monothioglycerol, and 10% heat-inactivated FBS at 37 °C, in 5% CO_2 and 95% humidity. Cells were treated with OMC for 30 min prior to stimulation with PMACI (20 nM of PMA plus 1 μM of A23187) and incubated at 37 °C. The time points by PMACI stimulation were selected according to a previous report (Oh et al., 2012).

Preparation of OMC

The specimens of OMC were collected along the shores of Cheju Island and Busan, South Sea, Korea. The voucher specimens of the plant were identified by an algal taxonomist, Jong-Su Yoo, in the Research Institute of Marine Science and Technology, Korea Maritime University, Busan, Republic of Korea, and deposited in the Herbarium of the Division of Ocean Science, Korea Maritime University, Busan, Republic of Korea, under the curatorship of Jong-Su Yoo (voucher no. 02JP-13). The dried samples (30 g) were extracted twice with 300 ml of methanol for 24 h at room temperature (Lin et al., 1997). The methanol extract (600 ml) was concentrated under reduced pressure. The yield of extraction was about 6.7% (w/w). The extract was stored in a freezer at −80 °C until tests were performed.

MTT assay

Cell viability was assessed by an MTT assay. HMC-1 cells suspension was cultured in 24-well plates for 24 h after treatment by each concentration of OMC. 20 μl of MTT solution (5 mg/ml) was added and the cells were incubated at 37 °C for 4 h. The insoluble formazan product was dissolved in DMSO after washing the supernatant. Then, the optical densities of 96-well culture plates were measured using an ELISA reader at 540 nm.

Histamine assay

HMC-1 cells were preincubated for 30 min at 37 °C before the addition of PMACI for stabilization. The cells were preincubated with OMC for 1 h and then incubated for 6 h with PMACI. The cells were separated from the released histamine by centrifugation at 400 rpm for 5 min at 4 °C. The levels of histamine in the supernatant were measured by the OPA spectrofluorometric procedure (Jeong et al., 2006). The fluorescent intensity was measured at 460 nm (excitation at 355 nm) using a spectrofluorometer.

Tryptase assay

HMC-1 cells were preincubated with OMC for 1 h and then incubated for 6 h with PMACI. Tryptase from culture supernatants was assayed by using a mast cell degranulation assay kit (Millipore Co., Billerica, MA, USA).

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