

β -eudesmol inhibits thymic stromal lymphopoietin through blockade of caspase-1/NF- κ B signal cascade in allergic rhinitis murine model

Phil-Dong Moon^{a,b,1}, Na-Ra Han^{a,1}, Jin Soo Lee^a, Hee-Yun Kim^a, Sungwei Hong^c, Hyeong-Jin Kim^c, Min-Sun Yoo^c, Hyung-Min Kim^{a,**}, Hyun-Ja Jeong^{d,*}

^a Department of Pharmacology, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea

^b Center for Converging Humanities, Kyung Hee University, Seoul, 02447, Republic of Korea

^c Department of Science in Korean Medicine, Graduate School, Kyung Hee University, Seoul, 02447, Republic of Korea

^d Department of Food Science & Technology and Research Institute for Basic Science, Hoseo University, Chungnam, 31499, Republic of Korea

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ABSTRACT

Allergic rhinitis (AR) is a global health problem because of its steadily increasing incidence and prevalence that currently affects about 30% of people worldwide. β -eudesmol has various beneficial effects, including anti-cancer and anti-allergic activities. However, the effects of β -eudesmol on AR have not yet been clarified; thus, we investigated the effects of β -eudesmol in an ovalbumin-induced AR animal model using enzyme-linked immunosorbent assay, histamine assay, Western blotting, and hematoxylin and eosin staining methods. β -eudesmol reduced the nasal rubs score and levels of histamine and immunoglobulin E in serum of AR mouse. In addition, the levels of thymic stromal lymphopoietin, interleukin-1 β , tumor necrosis factor- α , and macrophage inflammatory protein-2 were down-regulated and infiltration of eosinophils and the level of intercellular adhesion molecule-1 were inhibited by β -eudesmol administration. β -eudesmol administration also reduced active caspase-1 and nuclear factor- κ B DNA binding activity in nasal mucosa tissues of AR mice. Taken together, these results indicate that β -eudesmol would be effective for the treatment of allergic and inflammatory diseases, such as AR.

1. Introduction

Allergic rhinitis (AR) is a global health problem because of its steadily increasing incidence and prevalence that currently impacts about 30% of people worldwide. AR is a disorder that has a major impact on patient quality of life resulting from an impaired social life, school performance and work productivity [1]. AR is characterized by nasal rubbing, rhinorrhea, sneezing, and nasal congestion [2,3], and its histological characteristics include enhanced inflammatory cytokines production, infiltration with eosinophils, and IgE production [4,5].

Thymic stromal lymphopoietin (TSLP) plays an important role in the pathogenesis of allergic disorders, such as AR and atopic dermatitis. A high expression of TSLP was shown in nasal epithelial cells of patients with AR compared with the nonallergic control group [6]. Approaches that block upstream cytokines, such as TSLP, have the potential to improve patient outcome in asthma [7] and blockage of TSLP signalling prevented house dust mite-induced airway epithelial barrier disruption

and airway inflammation in mice [8].

Caspase-1 is a member of the caspase family [9] that, unlike most caspases that play an important role in programmed cell death, activates nuclear factor (NF)- κ B [10–12]. Moreover, the activation of NF- κ B by caspase-1 resulted in TSLP gene expression in airway epithelial cells [13].

β -eudesmol is an active component of *Atractylodes lancea* (Thunb.) DC [14], that has been reported to have an anti-cancer effect [14–16]. Kimura and Sumiyoshi suggested that β -eudesmol stimulates gastric emptying or small intestinal motility [17], and a recent study reported that β -eudesmol suppresses allergic reactions, such as ear swelling and cutaneous anaphylaxis [18]. However, the effects of β -eudesmol in AR have yet to be investigated; therefore, we examined the effect of β -eudesmol in an AR animal model.

* Corresponding author.

** Corresponding author.

E-mail addresses: hmkim@khu.ac.kr (H.-M. Kim), hjjeong@hoseo.edu (H.-J. Jeong).

¹ Phil-Dong Moon and Na-Ra Han contributed equally to this study.

2. Materials and methods

2.1. Materials

We purchased β -eudesmol from Wako Pure Chemical (Osaka, Japan). Dexamethasone (Dex), ovalbumin (OVA), bovine serum albumin, bichinchonic acid, and avidin-peroxidase were acquired from Sigma Chemical Co. (St Louis, MO, USA), while recombinant mouse standards (TSLP, interleukin (IL)-1 β , intercellular adhesion molecule (ICAM)-1, macrophage inflammatory protein (MIP)-2) and TSLP, IL-1 β , ICAM-1, and MIP-2 antibodies were obtained from R&D Systems (Minneapolis, MN, USA). Additionally, caspase-1 and GAPDH antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA), while recombinant mouse standards (tumor necrosis factor (TNF)- α and immunoglobulin (IgE), TNF- α and IgE antibodies, and TMB substrate were from Pharmingen (San Diego, CA, USA).

2.2. OVA-induced AR

Female BALB/c mice (6 weeks old, Dae-Han Experimental Animal Center, Eumsung, Republic of Korea) were maintained under a pathogen-free condition. All experiments were conducted in accordance with internationally accepted principles for laboratory animal use and care, as found in the United States guidelines (NIH publication no. 85–23, revised in 1985). The experimental procedure for the animal model of allergic rhinitis is summarized in Fig. 1. Mice were sensitized i.p. with 100 μ g of OVA emulsified and 20 mg of aluminum hydroxide (Sigma-Aldrich) in 100 μ l of phosphate buffered saline (PBS) on days 1, 5, and 14 [19,20]. Then, local immunization was performed once a day from day 15 to day 24 by instilling the OVA (1.5 mg in 2 μ l of PBS). As an OVA-unsensitized mice group, mice were treated i.p. with PBS on days 1, 5, and 14 and instilled PBS into nasal cavity once a day from day 15 to day 24. Mice were administered orally with distilled water (DW) or β -eudesmol (0.2, 2, and 20 μ M) or Dex (5 mg/kg) using a stomach sonde once a day for 10 days 1 h before intranasal OVA challenge. Mice were anesthetized at day 24 and blood samples and nasal tissue specimens were collected. Nasal symptoms were only evaluated by counting the number of nasal rubs that occurred in the 10 min after OVA intranasal provocation from day 21 to day 23 (three times).

2.3. Preparation of nasal mucosa tissue proteins

Nasal mucosa tissue was chopped with scissors and homogenized in homogenization buffer (20 mM HEPES, 1.5 mM MgCl₂, 0.2 mM EDTA, 0.1 M NaCl, 0.2 mM DTT, 0.5 mM Na₃VO₄, 1% protease inhibitor cocktail), then centrifuged at 15,000 $\times$ g for 30 min at 4 °C. The supernatants were subsequently used for enzyme-linked immunosorbent assay (ELISA), Western blotting, and NF- κ B DNA binding assay.

2.4. ELISA

The levels of TSLP, IL-1 β , ICAM-1, MIP-2, and TNF- α in the supernatants of homogenized nasal tissues, as well as the level of IgE in serum of mouse were evaluated by ELISA [21–23]. Briefly, TSLP, IL-1 β , ICAM-1, MIP-2, TNF- α , and IgE antibodies were coated by incubation of each antibody in PBS on 96-well microplate surface overnight at room temperature. The samples and standard solutions were then loaded and incubated for 2 h. After washing the plate, biotinylated TSLP, IL-1 β ,

ICAM-1, MIP-2, TNF- α , and IgE antibodies were loaded and again incubated for 2 h. Following additional washing of the plate, avidin-peroxidase was loaded and the plates were incubated for 30 min. The plate was again washed and the TMB substrate was loaded. Finally, the plate was measured at 405 nm using a colorimetric microplate reader.

2.5. Western blotting

The supernatants of homogenized nasal tissues were prepared in a sample buffer [62.5 mM Tris-HCl, pH 6.8, 2% sodium dodecyl sulphate (SDS), 20% glycerol, and 10% 2-mercaptoethanol], as previously described [24–27]. The lysed samples were heated at 95 °C for 5 min and briefly cooled on ice. Following centrifugation at 15,000 $\times$ g for 5 min, the proteins in the lysates were separated by 10% SDS-polyacrylamide gel electrophoresis and transferred to nitrocellulose paper. The membrane was then blocked with 5% skim milk in PBS-tween-20 for 1 h at room temperature, after which it was incubated with primary and secondary antibodies. Finally, the protein bands were visualized by an enhanced chemiluminescence solution purchased from Amersham Co. (Newark, NJ, USA) following the manufacturer's instructions.

2.6. Histamine assay

Histamine levels in serum of AR mouse were determined using o-phthalaldehyde spectrofluorometric analysis [28,29]. The fluorescent intensity was determined at 440 nm (excitation at 360 nm) in a spectrofluorometer.

2.7. Histological examination

Nasal mucosa tissue samples were immediately fixed with 4% formaldehyde and embedded in paraffin, as previously described [30,31]. The sections of the sample were cut to a thickness of 4 μ m, dewaxed, cleared in xylene, and hydrated. The sections were subsequently stained with hematoxylin (Sigma Chemical Co.) and eosin (Sigma Chemical Co.) to visualize eosinophils, after which the sections were dehydrated, placed in xylene, and mounted with mounting solution and glass coverslips. The numbers of eosinophils on both sides of the septal mucosa were then counted and sections were coded and randomly analyzed by three blinded observers.

2.8. NF- κ B DNA binding assay

NF- κ B DNA binding activity was measured using nasal mucosa tissue samples, as previously described [32]. In brief, a 96-well ELISA plate was coated by incubation of avidin peroxidase in PBS on a microplate surface overnight at room temperature. The coated plate was then washed with PBS-tween-20 and blocked with 3% skim milk, after which it was incubated with a 5'-biotinylated 21-single-strand DNA oligonucleotide sequence (1 μ g/ml) that contained the previously described NF- κ B-binding motif for 1 h at room temperature (5'-AGT TGA GGG GAC TTT CCC AGG-3'). Next, anti-NF- κ B antibody was added to PBS containing 3% bovine serum albumin for 1 h at a concentration of 1: 500 and the corresponding alkaline phosphatase (AP)-coupled secondary antibody was added. The AP activity was subsequently detected by the addition of p-nitrophenyl phosphate solution (Sigma Chemical Co.). After a 10 min incubation period, the reaction was stopped by the addition of 0.5 M H₂SO₄. Color intensities were measured at 405 nm using a colorimetric microplate reader.

2.9. Acute toxicity assay

An acute toxicity assay was conducted based on previous reports [33,34]. Briefly, female BALB/c mice (6 weeks old, Dae-Han Experimental Animal Center, Eumsung, Republic of Korea) were orally administered DW or β -eudesmol (20 μ M) using a stomach sonde once a

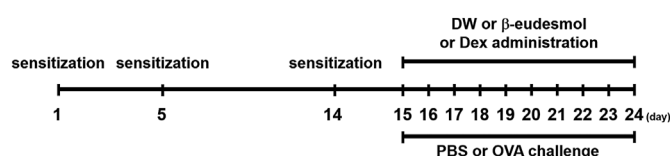


Fig. 1. Schematic protocols of an AR animal model.

day for 14 days. At 24 h after the last administration, mice were weighed, blood was collected, and various organs (liver, spleen, kidneys, lung, and heart) were weighed. The collected blood was then centrifuged immediately to prepare serum and preserved for biochemical analysis. The following biochemical parameters were measured: lactate dehydrogenase (LDH), serum glutamate oxalate transaminase (SGOT), and creatinine. All biochemical parameters were measured using an automatic analyzer DRI-CHEM NX500i (FUJIFILM, Japan).

2.10. Statistical analysis

Results were analyzed using the SPSS software (version 23.0, SPSS Inc, Chicago, IL, USA) and expressed as the mean $\pm$ standard error of the mean (S.E.M.). Statistical analysis consisted of an independent *t*-test and ANOVA followed by Tukey's post hoc test. The results were considered significant at a value of $P < 0.05$.

3. Results

3.1. Inhibitory effects of β -eudesmol on OVA-induced AR mice

To investigate the inhibitory effects of β -eudesmol in the AR mouse model, we sensitized mice on days 1, 5, and 14 by intraperitoneal injection of OVA. Various concentrations of β -eudesmol (0.2, 2, and 20 μ M) were administered orally 1 h before intranasal OVA challenge once a day from days 15–24. We measured the nose rubs for 10 min in the OVA-induced AR mice and found that they had increased significantly ($P < 0.05$, Fig. 2A). However, increased rub scores were significantly inhibited in the β -eudesmol treated mice ($P < 0.05$, Fig. 2A). Moreover, significantly increased histamine levels were observed in AR mice compared with PBS-treated mice (OVA-unsensitized mice) ($P < 0.05$, Fig. 2B); however, this increased histamine level was reduced by treatment with β -eudesmol ($P < 0.05$, Fig. 2B). Next, we assessed the level of IgE in the sera of AR mice. The results revealed increased IgE levels in OVA-induced AR mice compared to PBS-treated mice (OVA-unsensitized mice); however, this increase was down-regulated by administration of β -eudesmol ($P < 0.05$, Fig. 2C).

3.2. Inhibitory effects of β -eudesmol on TSLP levels and inflammatory cytokine levels of nasal mucosa tissues

TSLP is an upstream cytokine in the pathogenesis of asthma [7]; thus, it could be very important in AR as well. To evaluate the inhibitory effects of β -eudesmol on TSLP, we assessed the level of TSLP in

the nasal mucosa of AR mice. The results revealed increased TSLP in nasal mucosa tissue of AR mice compared to PBS-treated mice (OVA-unsensitized mice) ($P < 0.05$, Fig. 3A). However, the level of TSLP decreased in response to administration of β -eudesmol ($P < 0.05$, Fig. 3A).

We examined whether β -eudesmol could inhibit pro-inflammatory cytokines, such as IL-1 β , TNF- α , and MIP-2, in nasal mucosa tissues. The results revealed that OVA significantly up-regulated the levels of IL-1 β , TNF- α , and MIP-2 compared with PBS (OVA-unsensitized mice; $P < 0.05$, Fig. 3B–D). However, oral administration of β -eudesmol significantly inhibited all of the investigated cytokines at high concentration (20 μ M, $P < 0.05$, Fig. 3B–D). The inhibitory effects of 20 μ M of β -eudesmol were greater than 0.2 and 2 μ M; thus, we evaluated the effects of 20 μ M of β -eudesmol in subsequent experiments (eosinophils infiltration, caspase-1 activation, and NF- κ B DNA binding activity).

3.3. Inhibitory effects of β -eudesmol on eosinophils infiltration into nasal mucosa tissue

Eosinophils infiltration of nasal mucosa tissue in AR mice was significantly elevated [35]. Thus, we examined the inhibitory effects of β -eudesmol on the infiltration of eosinophils into nasal mucosa tissue. As shown in Fig. 4A and B, the numbers of eosinophils in the nasal mucosa tissues were significantly higher in OVA-sensitized mice than in the OVA-unsensitized mice. However, this increased eosinophils infiltration was significantly suppressed by β -eudesmol administration ($P < 0.05$, Fig. 4A and B).

Because ICAM-1 is involved in eosinophils infiltration [36], we examined the inhibitory effects of β -eudesmol on the level of ICAM-1 in nasal mucosa tissue in AR mice. The results revealed that increases in ICAM-1 levels induced by OVA by significantly inhibited by β -eudesmol ($P < 0.05$, Fig. 4C).

3.4. Inhibitory effects of β -eudesmol on activations of caspase-1 and NF- κ B in nasal mucosa tissue

Caspase-1 is associated with inflammation and production of inflammatory cytokines, such as TSLP, is mediated by caspase-1 [12,37]. The active caspase-1 consists of 20 and 10 kDa polypeptides derived from the processing of a cytosolic 45 kDa precursor protein (pro-caspase-1) [38]. Thus, we investigated the inhibitory effects of β -eudesmol on the expression of active caspase-1 and pro-caspase-1 in nasal mucosa tissues. Protein levels of active caspase-1 were up-regulated by OVA challenge; however, β -eudesmol inhibited OVA-induced caspase-1

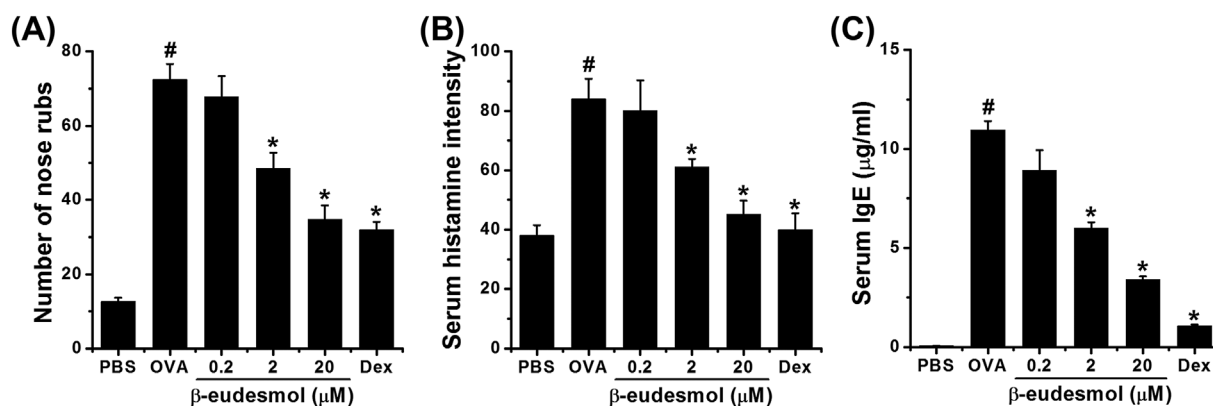


Fig. 2. Effects of β -eudesmol on clinical symptoms and serum levels of histamine and IgE in the AR animal model. (A) The number of nose rubs that occurred 10 min after OVA intranasal provocation. (B) The level of serum histamine was measured as described in the methods. (C) The serum IgE levels were measured by ELISA. Dex (5 mg/kg) was used as a reference drug. PBS, OVA-unsensitized mice; OVA, OVA-sensitized and then OVA-challenged mice. Data are presented as the mean $\pm$ S.E.M. of three independent experiments with $n = 4$ mice per group. # $P < 0.05$; significantly different from OVA-unsensitized mice. * $P < 0.05$; significantly different from OVA-sensitized mice.

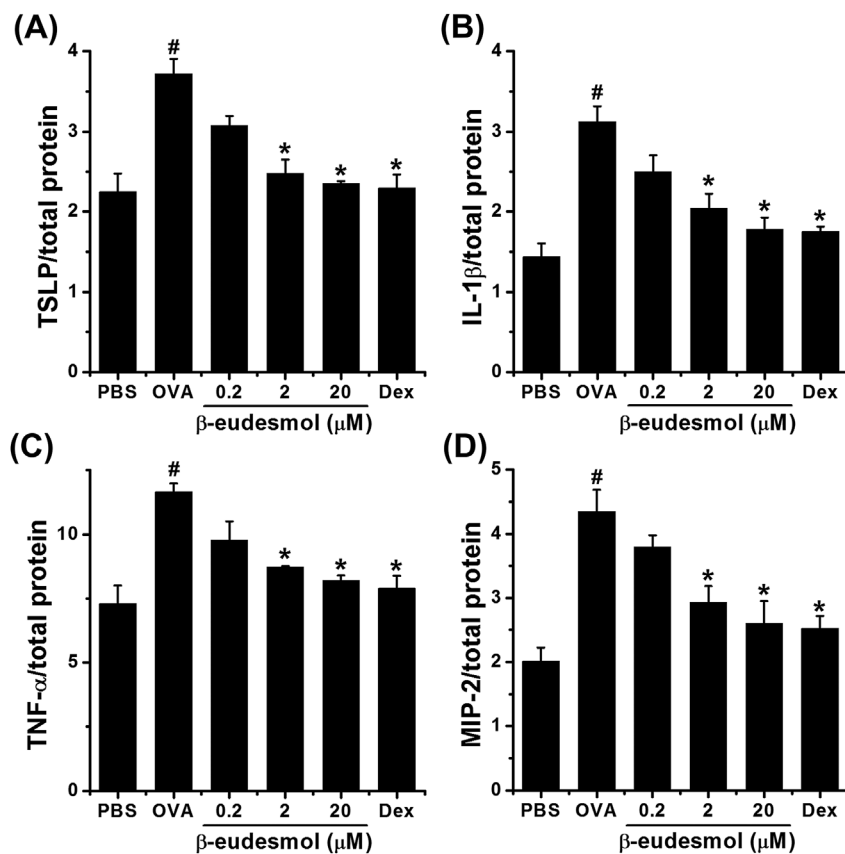


Fig. 3. Effects of β -eudesmol on TSLP and inflammation-related factors in the AR animal model. (A–D) Inflammation-related factors in nasal mucosa were measured using the ELISA method. Dex (5 mg/kg) was used as a reference drug. PBS, OVA-unsensitized and then PBS-challenged mice; OVA, OVA-sensitized and then OVA-challenged mice. Data are presented as the mean $\pm$ S.E.M. of three independent experiments with $n = 4$ mice per group. # $P < 0.05$; significantly different from OVA-unsensitized mice. * $P < 0.05$; significantly different from OVA-sensitized mice.

activation (Fig. 5A). In addition, β -eudesmol inhibited the processing of pro-caspase-1 (Fig. 5A). Caspase-1 activates NF- κ B and NF- κ B activation by caspase-1 results in inflammatory cytokines gene expression [10–13]. Because Western blot analysis for NF- κ B in the supernatants of homogenized tissues revealed no differences between the stimulated and non-stimulated group [32], we measured NF- κ B DNA binding activity. The OVA significantly increased NF- κ B DNA binding activity; however, this increased activity was reduced by β -eudesmol administration ($P < 0.05$, Fig. 5B).

3.5. Toxicity profiles of β -eudesmol in mice

To evaluate the toxicity of β -eudesmol in mice, we weighed various organs including the heart, lung, liver, spleen, and kidneys. No mortality was observed in β -eudesmol-administered mice throughout the experimental period. The weights of all parameters (Table 1) as well as

the levels of LDH, SGOT, and creatinine (Fig. 6) were not changed by oral administration of β -eudesmol.

4. Discussion

Our results showed that β -eudesmol inhibited the scratching behavior, IgE and histamine serum levels, nasal levels of TSLP and inflammatory cytokines, and infiltration of eosinophils in AR mice. β -eudesmol also inhibited caspase-1 activation and NF- κ B DNA binding activity in AR mice.

The AR symptoms include nasal rubbing, rhinorrhea, sneezing, and nasal congestion [2,3]. These symptoms mainly originated from inflammatory cells in response to inflammatory cell-derived TSLP, IL-1 β , and TNF- α [39,40]. Thymic stromal lymphopoietin has been implicated as a key molecule for initiating AR [41]. Moreover, topical blockade of IL-1 β and TNF- α reduced pathological allergic inflammation in the

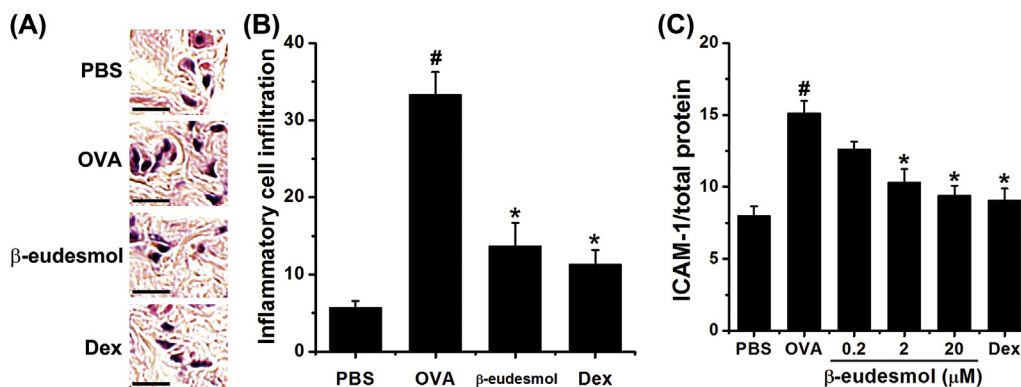


Fig. 4. Effects of β -eudesmol on the infiltration of eosinophils in AR nasal mucosa tissue. (A) Nasal mucosa tissue was stained with hematoxylin and eosin (H&E) for eosinophils. Original magnification $400\times$, scale bar = 20 μ m. (B) Eosinophils were counted by three individuals. Five randomly selected tissue sections per mouse were counted. (C) The level of ICAM-1 was measured using the ELISA method. Dex (5 mg/kg) was used as a reference drug. PBS, OVA-unsensitized and then PBS-challenged mice; OVA, OVA-sensitized and then OVA-challenged mice. Data are presented as the mean $\pm$ S.E.M. of three independent experiments with $n = 4$ mice per group. # $P < 0.05$; significantly different from OVA-unsensitized mice. * $P < 0.05$, significantly different from OVA-sensitized mice.

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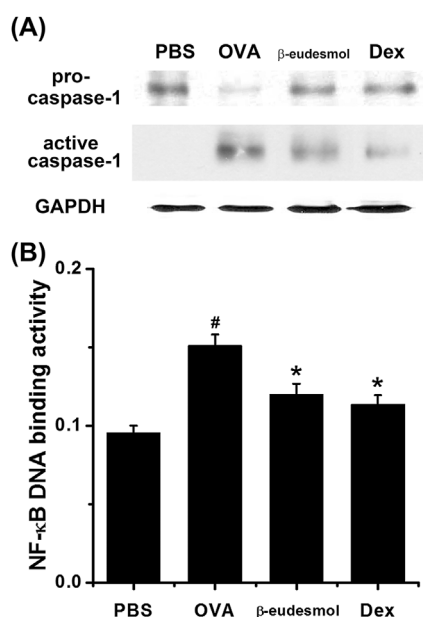


Fig. 5. Effects of β -eudesmol on the activation of caspase-1 and NF- κ B. (A) The expression of both pro-caspase-1 and cleaved active caspase-1 was measured by Western blot analysis. (B) NF- κ B DNA binding activity was measured with nasal mucosa tissue. Dex (5 mg/kg) was used as a reference drug. PBS, OVA-unsensitized and then PBS-challenged mice; OVA, OVA-sensitized and then OVA-challenged mice. Data are presented as the mean $\pm$ S.E.M. of three independent experiments with $n = 4$ mice per group. [#] $P < 0.05$; significantly different from OVA-unsensitized mice. ^{*} $P < 0.05$, significantly different from OVA-sensitized mice.

Table 1
Effects of β -eudesmol on body and organ weights in mice.

Parameters	DW	β -eudesmol
Initial body weight (g)	18.560 $\pm$ 0.206	18.600 $\pm$ 0.138
Final body weight (g)	20.280 $\pm$ 0.265	20.360 $\pm$ 0.333
Heart weight (g)	0.112 $\pm$ 0.004	0.114 $\pm$ 0.003
Lung weight (g)	0.130 $\pm$ 0.004	0.130 $\pm$ 0.004
Liver weight (g)	0.864 $\pm$ 0.031	0.868 $\pm$ 0.025
Spleen weight (g)	0.082 $\pm$ 0.002	0.082 $\pm$ 0.002
Kidneys weight (g)	0.264 $\pm$ 0.011	0.262 $\pm$ 0.005

β -eudesmol or DW was administered orally with a sonde once a day for 14 days. At 24 h after the last administration, body and organ weights were measured. No significant differences were shown between groups.

nasal mucosa and lung tissues of AR guinea pigs [42]. Our results showed that β -eudesmol inhibits nasal rubbing, as well as increases in serum levels of IgE, histamine, TSLP, IL-1 β , and TNF- α in OVA-

sensitized AR mice. Therefore, these results demonstrated that β -eudesmol exerts anti-inflammatory effects by suppressing inflammatory mediators.

Eosinophils play a crucial role in AR. When antigen provocation occurs, eosinophils in the tissue are activated, resulting in amplification of allergic reaction [43]. Eosinophils infiltration is an important characteristic of eosinophilic inflammation in the upper airways, such as occurs during allergic rhinitis [44], and ICAM-1 plays a central role in recruitment of inflammatory cells in the pathogenesis of asthma [36]. In a primate model of asthma, a monoclonal antibody to ICAM-1 prevented both the influx of eosinophils and airway hyperreactivity [45]. As shown in Fig. 4, β -eudesmol inhibited the infiltration of eosinophils and the level of ICAM-1 in AR mice. Thus, we can presume that β -eudesmol could decrease the infiltration of eosinophils, at least in part, by inhibition of ICAM-1 in AR.

In our previous study, TSLP was down-regulated by both caspase-1 and NF- κ B inhibitors. Furthermore, caspase-1 is an upstream factor than NF- κ B [12]. In addition, Lamkanfi and colleagues demonstrated that caspase-1 induces the activation of NF- κ B [11]. The results of the present study showed that β -eudesmol inhibits caspase-1 activation and NF- κ B activity in AR mice; therefore, it can be assumed that β -eudesmol could inhibit the level of TSLP through blockage of the caspase-1/NF- κ B signal cascade in AR.

To evaluate the toxicity of β -eudesmol in mice, an acute toxicity assay was conducted. In toxicology studies, organ weight can be a sensitive indicator [34]. Our results showed that β -eudesmol does not induce organ weight changes. LDH and SGOT are important serum toxicity markers [46]. LDH is a marker of cell injury [47–51], SGOT is used to confirm proper liver function [34], creatinine levels are used to determine kidney dysfunction [34], and the results of the present study showed that β -eudesmol did not induce any changes in the levels of these compounds, confirming that it does not exert toxic effects in mice.

In conclusion, our results demonstrated that β -eudesmol exerts an anti-inflammatory effect by improving rhinitis symptoms and inhibiting the release of pro-inflammatory mediators in AR mice. β -eudesmol also decreased the infiltration of eosinophils and caspase-1/NF- κ B signalling in the AR mice. These results suggest that β -eudesmol might be useful for the treatment of allergic and inflammatory diseases, such as AR, through the down-regulation of TSLP.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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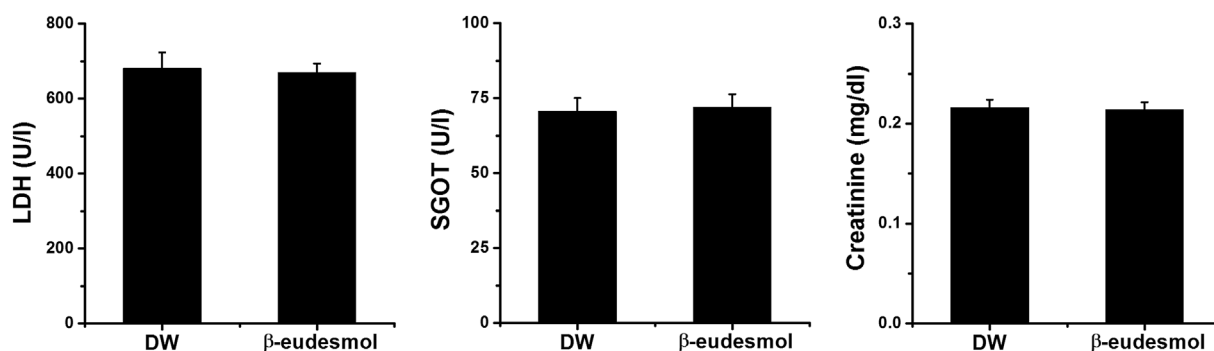


Fig. 6. Effects of β -eudesmol on serum biochemical parameters in mice. β -eudesmol or DW was administered orally with a sonde once a day for 14 days. At 24 h after the last administration, blood was collected, then measured using an automatic analyzer DRI-CHEM NX500i (FUJIFILM, Japan). No significant differences were shown between groups.

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