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The ameliorative effect of AST2017-01 in an ovalbumin-induced allergic rhinitis animal model

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Abstract

Objective AST2017-01 is developed to be used for treatment and prevention of allergic diseases and composed of processed-*Cordyceps militaris* and processed-*Rumex crispus*. But, effect of AST2017-01 remains unclear in an allergic rhinitis (AR). So, this study aimed to explore the effects of AST2017-01 in ovalbumin (OVA)-induced AR animal model.

Methods OVA-induced AR animals were orally administered AST2017-01 and chrysophanol, an active component of AST2017-01 for 10 days.

Results In mice with AR, AST2017-01 and chrysophanol markedly decreased number of rubs, IgE, histamine, thymic stromal lymphopoietin, tumor necrosis factor-α, interleukin (IL)-1β, IL-4, IL-5, and IL-13 in serum or nasal mucosa tissues. Moreover, activities and protein levels of caspase-1 were markedly diminished by oral administration of AST2017-01 and chrysophanol. Declines of macrophage inflammatory protein-2, intercellular adhesion molecules-1, eosinophil, and mast cells were also noted in nasal mucosa tissues of AST2017-01 and chrysophanol groups.

Conclusions Taken together, these findings indicate that AST2017-01 has an anti-allergic effect as a therapeutic agent or functional food for treating and preventing AR.

Keywords AST2017-01 · Chrysophanol · Allergic rhinitis animal model · Macrophage inflammatory protein-2 · Intercellular adhesion molecules-1 · Infiltration

Introduction

The presence of allergic rhinitis (AR) has spread widely in the general population worldwide of 10%, furthermore this disease is increasing in frequency [1]. This disease leads to unproductive or missed time at school, works, and sleep problems [2]. AR is defined as clinical symptoms of itching, allergic conjunctivitis, rhinorrhea, nasal congestion, and disturbed olfaction following provocation by a specific allergen [3]. AR is attributed to allergic mediators including inflammatory cytokines thymic stromal lymphopoietin (TSLP), interleukin (IL)-1β, tumor necrosis factor-α], T helper type 2 (Th2) cytokines (IL-4, IL-5, and IL-13), chemokines [macrophage inflammatory protein-2 (MIP-2), intercellular adhesion molecules-1 (ICAM-1)], histamine, and inflammatory cells (mast cell, eosinophil, and neutrophil) [4, 5]. Drug therapies of AR have been used anti-cholinergics, mast cell stabilizer, leukotriene receptor antagonists, and corticosteroids and recently many patients are using alternative and complementary treatments such as the use of medicinal herbs to regulate AR [6, 7].

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AST2017-01 was primarily formed of processed-*Cordyceps militaris* and processed-*Rumex crispus* and has been widely used in folk medicines in Korea and included cordycepin, xylitol, mannitol, and chrysophanol as ingredients [8, 9]. *Cordyceps militaris* is a well-known fungus with immuno-modulatory activity and modulate airway inflammation in asthma [10]. *Rumex crispus* is a perennial plant belonging to the Polygonaceae family and contains chrysophanol as a marker compound [8]. It is commonly consumed as a dried or processed herb or used as a medicinal product, and it is known to inhibit arachidonic acid-induced inflammation in mice [11, 12]. Moreover, *Rumex crispus* has anti-oxidant and anti-cancer effects [13, 14]. Recent data showed that inflammation is a critical component of tumor progression and anti-cancer agents has an anti-allergic inflammatory effect [15, 16]. Our previous studies found that AST2017-01 and chrysophanol have an anti-atopic dermatitis effect on in vitro and in vivo atopic dermatitis models [17, 18]. However, the potential effect of AST2017-01 and chrysophanol in the treatment of AR has been investigated only rarely. Therefore, we investigated the anti-allergic inflammatory effect of AST2017-01 and chrysophanol in ovalbumin (OVA)-induced AR animal model.

Materials and methods

Reagents

Chrysophanol (purity: ≥ 98%), avidin peroxidase, dexamethasone (DEX), OVA, and other reagents were obtained from Sigma (St. Louis, MO, USA). Mouse cytokine antibodies (Ab) and recombinant mouse IgE/IL-1β/TSLP/TNF-α/IL-4/IL-5/IL-13/MIP-2/ICAM-1 proteins were purchased from BD Pharmingen (San Diego, CA, USA). Ab for caspase-1(p10) and actin were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA). AST2017-01 was provided by Gahwa Well Food Co. (Chungbuk, Republic of Korea). AST2017-01 and chrysophanol were prepared according to previous report [17].

OVA-induced AR animal model

Female 4-week-old BALB/c mice were obtained from the Dae-Han Experimental animal center (Eumsung, Republic of Korea) and maintained under standard laboratory conditions. Mouse care and experimental procedures were performed with the approval of the animal care committee of Kyung Hee University [KHUASP (SE)-18-022]. Sensitization was performed three times (at 1, 5, and 14 day) by intraperitoneally (ip) injecting 100 μg of OVA emulsified in 100 μl phosphate-buffered saline (PBS) containing 20 mg aluminum hydroxide (Sigma Chemical Co, St. Louis, MO, USA). Intranasal challenges were performed using 1.5 mg of OVA in 2 μl PBS. Negative controls were challenged intranasally with PBS in an identical manner. AST2017-01 (0.5, 5, and 50 mg/kg), chrysophanol (0.06 mg/kg), and DEX (5 mg/kg) or a control vehicle (distilled water) was orally administrated before OVA intranasal challenge on days 15 to 24. Nasal rubs scoring was evaluated by counting the number of nasal itching motion (nasal rubbing) for 10 min after OVA intranasal challenge at 9 days. It was measured by a trained observer who was blind to the experimental treatments. Five mice were place in each group.

Histamine assay

Histamine release was measured as previously described [16].

Enzyme-linked immunosorbent assay (ELISA)

Cytokines levels in serum and intranasal tissues were measured according to the manufacturer's specification (BD Pharmingen, San Diego, CA, USA). Cytokine levels of intranasal tissues were normalized by the total protein amounts, which were calculated using a bicinchoninic acid (Sigma, St. Louis, MO, USA).

RNA extraction and quantitative real-time PCR

RNA extraction, cDNA synthesis, and quantitative real-time PCR were conducted as previously described [17]. Target cytokine mRNA levels were normalized versus GAPDH. Concentrations of amplified DNA were calculated using the ΔΔCT method.

Western blot analysis

Western blot analysis was used to confirm expression of protein caspase-1 in the intranasal tissues and was conducted as previously described [17].

Caspase-1 assay

Analysis of caspase-1 activity was performed using the Caspase-1 Colorimetric Assay Kit from R&D Systems (Minneapolis, Minnesota, USA) following the manufacturer's protocol.

Recruitment of eosinophils and mast cells

Intranasal tissues were immersed in 10% neutral formaldehyde. Tissues were embedded in paraffin and sectioned anterior to posterior at 4 μm thickness. Appearance of inflammatory cell recruitment was observed in sections

stained by hematoxylin and eosin (H&E, for eosinophils) and alcian blue and safranin O (A&S, for mast cells). Tissue samples were taken from the different sections of same nasal tissues for H&E and A&S staining. All tissue sections were investigated blindly with respect to the source of the tissue and cell counts were determined at seven different intranasal areas for each group.

Statistical analysis

Treatment effects were analyzed using one-way ANOVA followed by Turkey and the independent *t* test. All data are expressed as the mean ± standard error of the mean (SEM). Statistical significance was accepted for *P* values < 0.05.

Results

Ameliorative effect of AST2017-01 and chrysophanol on serum levels of OVA-induced AR biomarkers

Our previous study showed that AST2017-01 and chrysophanol have an anti-inflammatory effect by inhibition of mast cell activation in vitro model [17]. Here, we investigated whether AST2017-01 and chrysophanol have an anti-allergic inflammatory effect in AR in vivo model. To investigate the effect of AST2017-01 and chrysophanol on nasal mucosal symptoms, the numbers of rubs were measured for 10 min. The oral administration of AST2017-01 and chrysophanol significantly diminished the numbers of rubs compared with the OVA group (Fig. 1a, $P < 0.05$). The serum levels of IgE and histamine were markedly diminished in the AST2017-01

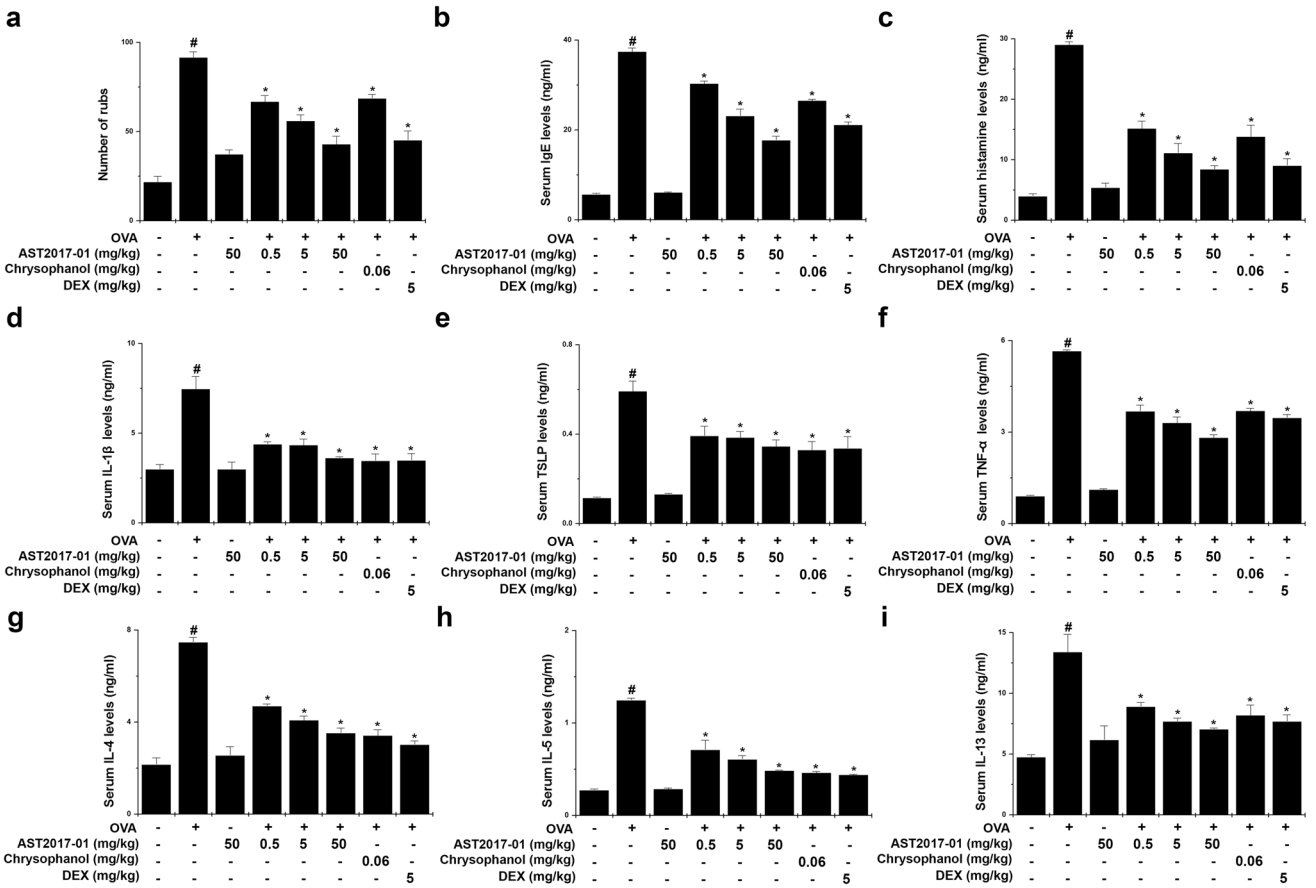

Fig. 1 Ameliorative effects of AST2017-01 and chrysophanol on OVA-induced AR biomarkers in serum. We sensitized mice on days 1, 5, and 14 by ip injections of 100 μg OVA emulsified in 20 mg of aluminum hydroxide and we challenged mice with 1.5 mg OVA. Mice received orally AST2017-01 (0.5, 5, and 50 mg/kg), chrysophanol (0.06 mg/kg) and DEX (5 mg/kg) before the OVA intranasal challenge for 10 days. **a** The number of the nasal rubs that occurred in the 10 min after the OVA intranasal challenge. Serum was isolated from blood and then assayed for **b** IgE, **c** histamine, **d** IL-1β, **e** TSLP, **f** TNF-α, **g** IL-4, **h** IL-5, and **i** IL-13 in the serum were measured by the ELISA method. $^{\#}P < 0.05$; significantly different from the normal control mice. $^{*}P < 0.05$; significantly different from the OVA-challenged mice. $N = 5$. *DEX* dexamethasone

and chrysophanol groups compared with the OVA group (Fig. 1b, c, $P<0.05$). IL-1β, TSLP, and TNF-α are inflammatory cytokines that induce the allergic disorder [19–21]. OVA significantly increased the IL-1β, TSLP, and TNF-α level in serum (Fig. 1d–f, $P<0.05$). The levels of IL-1β, TSLP, and TNF-α increased by OVA were regulated by AST2017-01 and chrysophanol (Fig. 1d–f, $P<0.05$). Allergic disorder was primarily indicated by up-regulation of activated Th2 cells-induced Th2 cytokines including IL-4, IL-5, and IL-13 [22]. AST2017-01 and chrysophanol significantly regulated the levels of these cytokines compared with the OVA group (Fig. 1g–i, $P<0.05$). DEX, as a positive control, significantly regulated the AR symptoms and biomarkers.

Ameliorative effect of AST2017-01 and chrysophanol on nasal mucosa tissues levels of OVA-induced inflammatory and Th2 cytokines

In sequence, we studied whether the levels of inflammatory and Th2 cytokines induced by OVA in the nasal mucosa tissues could be regulated by AST2017-01 and chrysophanol. AST2017-01 and chrysophanol significantly regulated the levels of IL-1β, TSLP, TNF-α, IL-4, IL-5, and IL-13 compared with the OVA group (Fig. 2, $P<0.05$). Furthermore, we sought to investigate the effect of AST2017-01 and chrysophanol in inflammatory cytokine mRNA expression of nasal mucosa tissue using a quantitative real-time PCR. AST2017-01 and chrysophanol significantly reduced the OVA-induced mRNA expression of IL-1β, TSLP, and TNF-α (Fig. 3, $P<0.05$).

Ameliorative effect of AST2017-01 and chrysophanol on OVA-induced caspase-1 activities

Caspase-1 is a member of a family of cysteine proteases and it generally become known IL-1β converting enzyme [23]. Caspase-1 accelerates the inflammatory reaction through maturation of cytokine such as IL-1β precursor [23]. To investigate whether AST2017-01 and chrysophanol could regulate the activity of caspase-1 increased by OVA, caspase-1 assay and Western blotting were conducted.

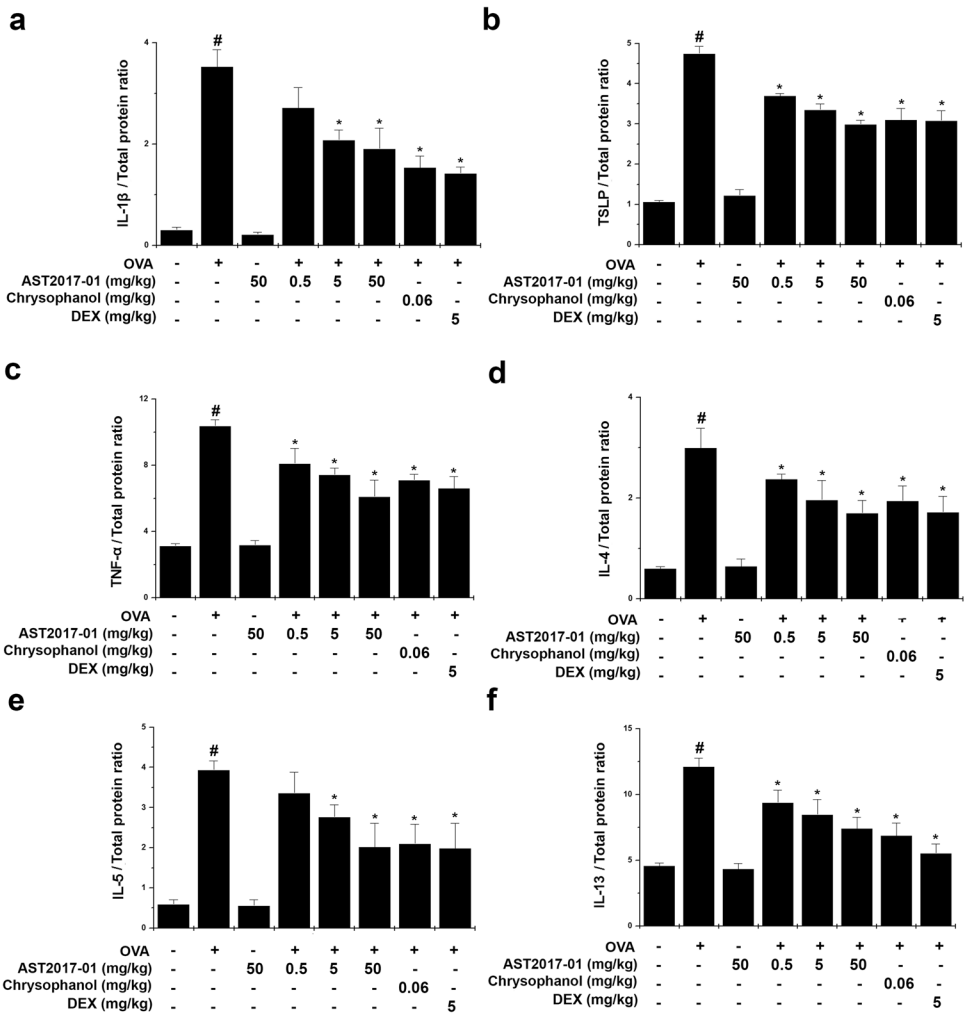

Fig. 2 Ameliorative effects of AST2017-01 and chrysophanol on OVA-induced AR biomarkers in intranasal tissues. **a** IL-1β, **b** TSLP IL-13, **c** TNF-α, **d** IL-4, **e** IL-5, and **f** IL-13 were measured by the ELISA method. All parameters measured in intranasal tissue homogenate were presented as a ratio to the total protein levels of the intranasal tissue. $^{\#}P<0.05$; significantly different from the normal control mice. $^{*}P<0.05$; significantly different from the OVA-challenged mice. $N=5$. *DEX* dexamethasone

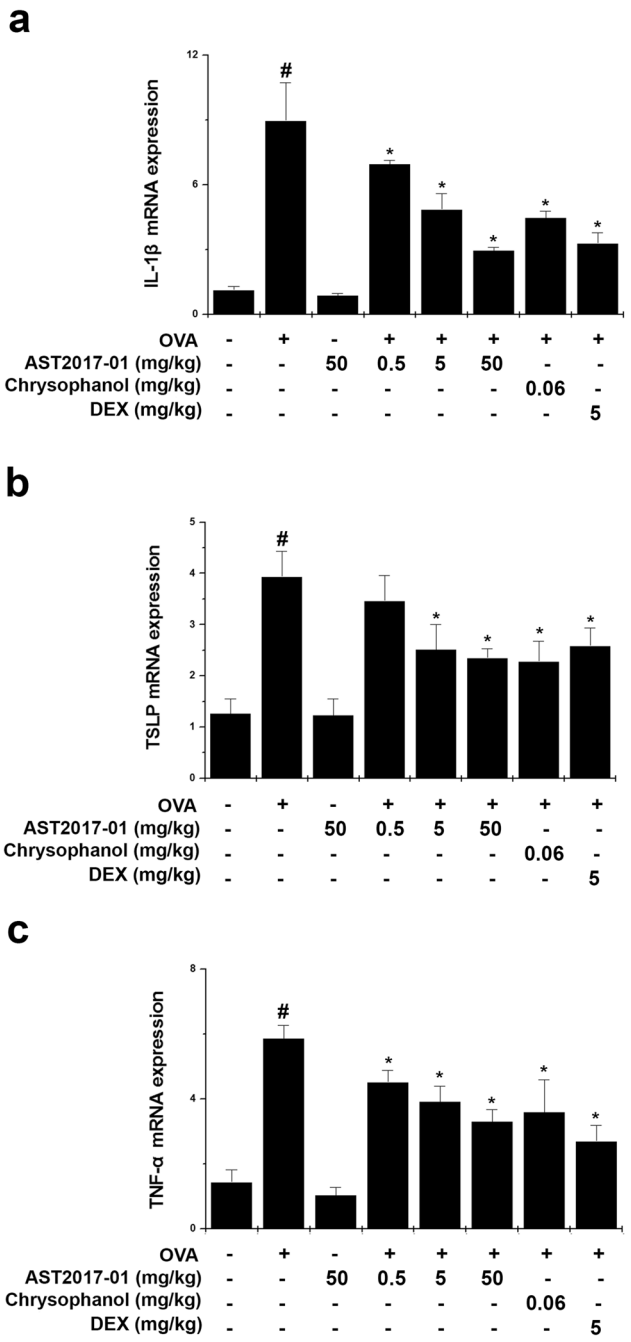

Fig. 3 Ameliorative effects of AST2017-01 and chrysophanol on OVA-induced inflammatory cytokines mRNA levels in intranasal tissues. Messenger RNA levels of **a** IL-1β, **b** TSLP, and **c** TNF-α were measured using the quantitative real-time PCR method. $^{\#}P<0.05$; significantly different from the normal control mice. $^{*}P<0.05$; significantly different from the OVA-challenged mice. $N=5$. *DEX* dexamethasone

As shown in Fig. 4a, AST2017-01 and chrysophanol suppressed the activation of caspase-1 compared with the OVA. In addition, we found that AST2017-01 and chrysophanol decreased the protein levels of active caspase-1.

Ameliorative effect of AST2017-01 and chrysophanol on OVA-induced the eosinophils and mast cells recruitment in intranasal tissues

Adhesion molecules and inflammatory chemokines are markedly up-regulated during inflammatory response lead to acute and chronic inflammatory diseases [24]. Moreover, the ability of chemokine is related to chemotaxis of mast cell, neutrophils, and eosinophils [25]. Next, to study whether levels of chemokine and adhesion molecule induced by OVA could be regulated by AST2017-01 and chrysophanol, we analyzed the protein levels of MIP-2 and ICAM-1 in the nasal mucosa tissues. The protein levels of MIP-2 and ICAM-1 induced by OVA were markedly reduced by the AST2017-01 and chrysophanol (Fig. 5a, b, $P<0.05$). Subsequently, we sought the efficacy of AST2017-01 and chrysophanol on recruitment of eosinophils and mast cells into the nasal mucosa tissues. The numbers of eosinophils and mast cells increased by OVA in the nasal mucosa tissue were markedly blocked by the AST2017-01 and chrysophanol (Fig. 5c–f, $P<0.05$).

Discussion

In the present study, we explored that AST2017-01 and chrysophanol effectively down-regulated the AR symptoms, AR biomarkers, and inflammatory cytokines. AST2017-01 and chrysophanol markedly down-regulated the activities of caspase-1. Additionally, reduction of chemokines levels and infiltrated inflammatory cells in the intranasal tissues was shown in the AST2017-01 and chrysophanol groups.

The function of Th2 cells in allergic diseases induces the release of allergen-specific IgE Ab by B cells and promotes the penetration of eosinophils and mast cells into the target tissues [26]. Activated Th2 cells produce IL-4, IL-5, and IL-13, which are involved in pathophysiological symptoms of allergic diseases [26]. IL-4 increases IgE synthesis in B cells and participates in the allergic reaction [27]. IL-5 is a major differentiation and maturation factor for eosinophils, concurrently it is crucial for supporting eosinophil activation, development, survival, and response to other cytokines [28]. IL-13 is released by activated T cells, B cells, and mast cell [29]. These factors escalated the allergic symptoms and reactions. In this study, our results showed that AST2017-01 and chrysophanol reduced the Th2 cytokines such as IL-4, IL-5, and IL-13 as well as AR clinical symptoms. Therefore, we deduced that AST2017-01 and chrysophanol exerts anti-allergic effects through regulating Th2 cytokines in AR responses.

Inflammatory cytokines play a principal role in the pathophysiological condition of allergic inflammation and allergic diseases. Several inflammatory cytokines such as IL-1β,

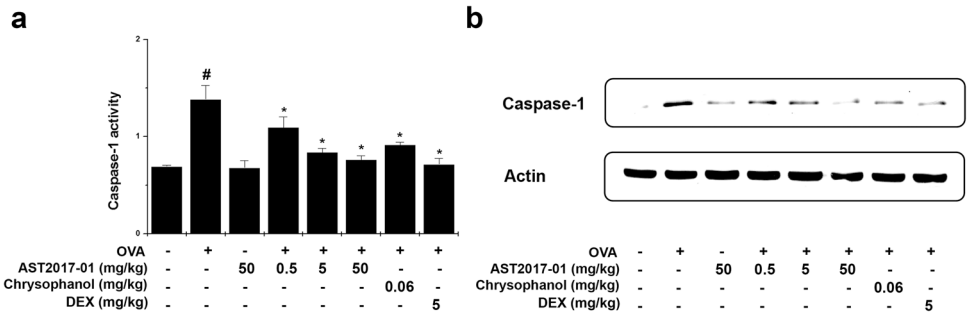

Fig. 4 Ameliorative effects of AST2017-01 and chrysophanol on OVA-induced caspase-1 activation in intranasal tissues. **a** Caspase-1 activity in the intranasal tissues was measured by a caspase-1 assay kit. **b** The protein levels of caspase-1 were assayed by Western blotting. Results are representative of three independent experiments. $^{\#}P<0.05$; significantly different from the normal control mice. $^{*}P<0.05$; significantly different from the OVA-challenged mice. $N=5$. *DEX* dexamethasone

TSLP, and TNF-α are known to stimulate a number of cells to produce inflammatory mediators including prostaglandins [30]. IL-1β can enhance mast cell-induced cytokine and histamine release in allergic responses [31]. TNF-α is produced from both macrophages and mast cells in allergic responses [32]. TSLP is an initiate cytokine of allergic reactions that triggers Th2-type inflammation. Co-stimulation with TSLP, IL-1β, and TNF-α synergistically stimulates mast cells and produces high levels of Th2 cytokines and chemokines [33]. The processing and maturation of inflammatory cytokines such as IL-1β was induced by caspase-1 activation, thus resulting in allergic symptoms in the sensitized mice [34]. So, caspase-1 activity is also closely associated with allergic inflammatory response [34]. Caspase-1 is activated by protein kinase C and OVA induces the activation of protein kinase C in allergic inflammatory animal model [35, 36]. Allergic reactions up-regulated by OVA were significantly down-regulated by the caspase-1 inhibitor [15]. Recently, we reported that AST2017-01 reduced the mast cell-mediated inflammatory reaction via inhibiting caspase-1 [17]. In this study, our results showed that AST2017-01 and chrysophanol decreased the levels of IL-1β, TSLP, and TNF-α and activation of caspase-1. Therefore, we deduced that AST2017-01 and chrysophanol exert anti-inflammatory effects through regulation of caspase-1 activation in AR responses.

Allergic responses concern many inflammatory cells, especially the two major cells operating this complex reaction are the eosinophils and the mast cells [37]. Mast cells are extensively dispersed in mucosal surfaces and connective tissues, and it also infiltrates the sites of inflammation associated with chronic atopic or allergic disease [38]. Furthermore, mast cells release several cytokines and modulate function of eosinophil [39]. In allergic inflammation, a number of eosinophil were markedly escalated in the tissues and blood near the inflammatory zone [40]. MIP-2 and ICAM-1 are concerned with allergic diseases such as asthma and AR and play a key role in the recruitment of leukocytes, synthesis of IgE, production of inflammatory cytokines, and promotion of Th2 responses [41]. In this study, our results showed that AST2017-01 and chrysophanol reduced the levels of MIP-2 and ICAM-1 and recruitment of mast cells and eosinophils. Therefore, we deduced that AST2017-01 and chrysophanol exert anti-allergic inflammatory effects through inhibition of inflammatory cells infiltration by decreasing MIP-2 and ICAM-1.

In conclusion, our study demonstrated that AST2017-01 and chrysophanol exert an anti-allergic inflammatory effect by regulation of Th2 cytokines, inflammatory cytokines, caspase-1, chemokines, and inflammatory cells in AR mice. These results suggest that AST2017-01 and chrysophanol might be useful therapeutic agents for treating AR.

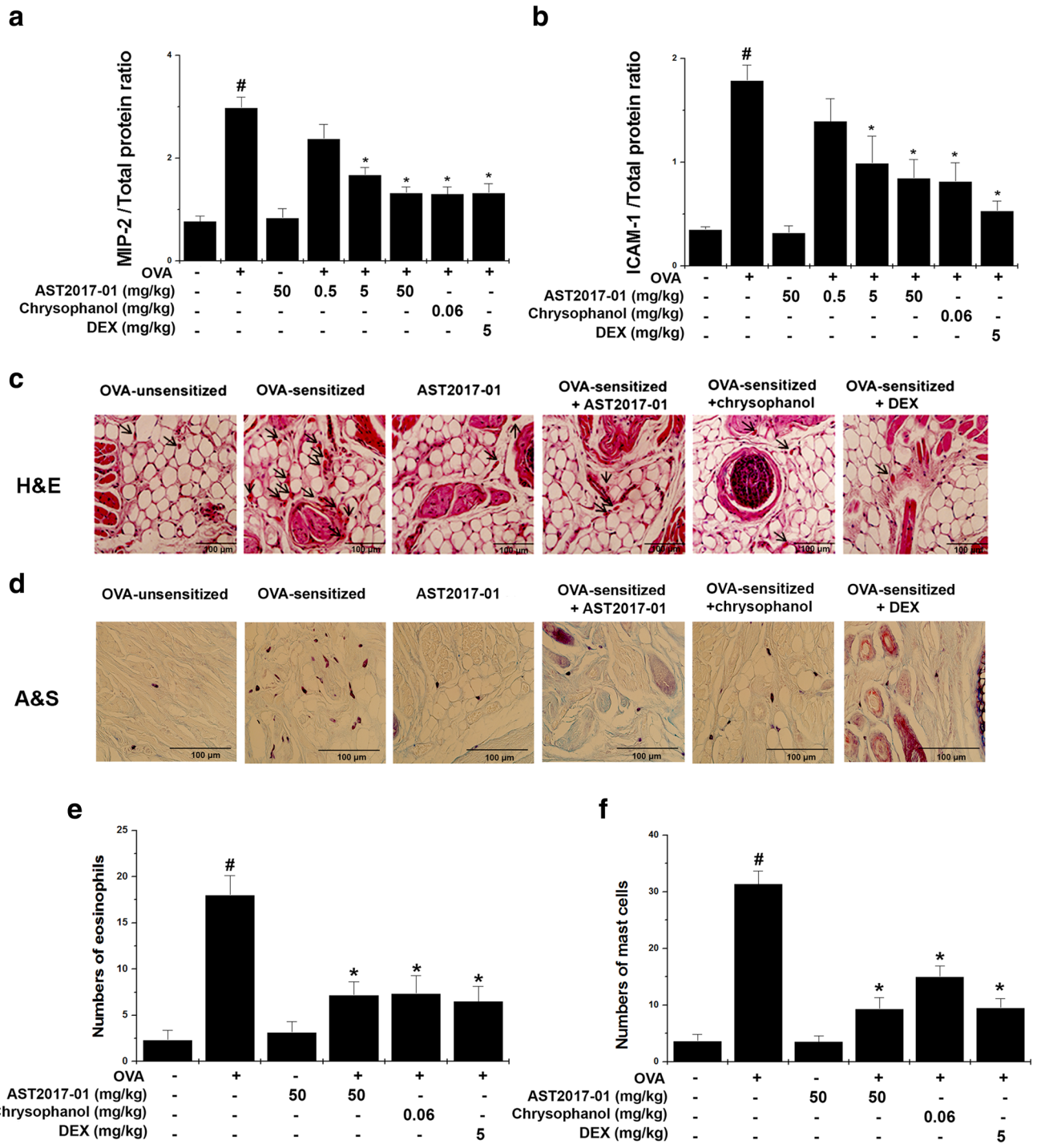

Fig. 5 Ameliorative effects of AST2017-01 and chrysophanol on levels of MIP-2 and ICAM-1 and recruitment of eosinophils and mast cells in intranasal tissues. Levels of **a** MIP-2 and **b** ICAM-1 in intranasal tissues were measured by the ELISA method. All parameters measured in the tissue homogenate were presented as a ratio to the total protein levels of intranasal tissues. **c** Intranasal tissues were stained with H&E (for eosinophils, arrows indicate eosinophils) (original magnification × 400, scale bar = 100 μm). **d** Intranasal tissues were stained with A&S (for mast cells) (original magnification × 200, scale bar = 100 μm). The numbers of **e** eosinophils and **f** mast cells were counted by two individuals. Afterwards, five randomly selected tissue sections per mouse were counted. The absolute number of cell was counted as the mean ± SEM. $^{\#}P < 0.05$; significantly different from the normal control mice. $^{*}P < 0.05$; significantly different from the OVA-challenged mice. $N = 5$. *DEX* dexamethasone

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical standards All procedures performed in studies involving murine tissues were in accordance with the ethical standards of the institution and/or national research.

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