doi: 10.4149/gpb_2026030

Cornuside attenuates inflammatory response injury in mice with ovalbumin-induced allergic rhinitis

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Abstract. Allergic rhinitis (AR) is characterized by inflammation of the nasal mucosa caused by an allergic reaction. Cornuside has been reported to possess anti-allergic properties. This study aims to investigate whether cornuside can suppress AR. Mice were induced by ovalbumin (OVA) to establish AR models. The AR symptoms including sneezing and nasal rubbing were recorded, and the eosinophils in mouse mucosal tissues were analyzed by hematoxylin and eosin staining. Total leucocytes in nasal lavage fluid (NLF) were quantified under a hemocytometer. Wright's Giemsa staining was utilized to quantify eosinophils, lymphocytes, and neutrophils in NLF. Enzyme-linked immunosorbent assay was conducted to detect histamine, serum cytokines (OVA-specific IgE, OVA-specific IgG1, interleukin-4, and leukotriene C4), and serum inflammation cytokines (tumor necrosis factor-α, interleukin-6, interleukin-13, and interleukin-17). Cornuside administration significantly reduced sneezing and nasal rubbing behaviors in mice with AR. Mice with AR exhibited more inflammatory cells and higher levels of histamine, serum cytokines, and inflammatory cytokines in the blood or NLF than the control group. However, these upregulations were all reversed by the administration of cornuside. In addition, we found that cornuside treatment improved the inflammatory condition of mice with AR dose-dependently Cornuside can attenuate the inflammatory response in mice with AR.

Key words: Cornuside — Inflammatory response — Allergic rhinitis — Ovalbumin

Introduction

Allergic rhinitis (AR) is a well-known chronic inflammatory disease Worldwide, the prevalence of allergic rhinitis varies enormously; there are significant differences between various countries and continents. The prevalence also varies in the population of adults and children. The incidence has increased significantly over much longer period than the last two decades (Canonica et al. 2008; Mortz et. al 2019). AR is triggered by exposure to allergens containing polluted air and its onset is closely associated with genetic factors and living environment (Luo et al. 2023). The diagnosis of allergic rhinitis is established through a comprehensive evaluation that includes medical history, clinical symptoms, physical examination, and allergen testing. Key diagnostic criteria encompass recurrent nasal symptoms such as sneezing, rhinorrhea, nasal congestion, and nasal pruritus, which confirmed sensitization to allergens *via* testing, and the exclusion of other conditions with similar presentations (Luo et al. 2022). Severe AR often results in sleep disturbance, impairment of work or daily activities, and reduces quality of life (Meltzer et al. 2009; Brożek et al. 2017).

Allergens could promote IgE production in the blood and lead mast cells to release histamine in the nasal mucosa (Ogulur et al. 2021). Moreover, the enrichment of immune cells such as leucocytes and eosinophils in nasal mucosa exacerbates the allergic symptoms and pathological status (Eckrich et al. 2020). Additionally, inflammation plays a significant role in AR progression. It has been reported

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that elevated levels of serum inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-13 (IL-13), and interleukin-17 (IL-17) were observed in AR patients' serum and NLF (Waśkiel-Burnat et al. 2021; Jiang et al. 2023). Hence, agents that attenuate the upregulation of these serum cytokines might be effective in treating AR.

Cornuside ($C_{24}H_{30}O_{14}$) is a monomeric component derived from *Cornus officinalis* (Tenuta et al. 2022). It is often used as a traditional Chinese medicine with various biological and pharmacological activities such as anti-apoptotic, antioxidant, and anti-inflammatory properties (Shi et al. 2022). Accumulating studies have demonstrated that cornuside could impede inflammation in various diseases. For instance, cornuside demonstrates anti-inflammatory effects in hampering psoriasis-like skin lesions in mice (Yan et al. 2024).

Moreover, cornuside also inhibited the inflammatory responses to alleviate gestational diabetes mellitus by reducing the inflammatory cytokines (Cui et al. 2024). Cornuside can also help regulate the immune system in certain diseases. Previous research pointed out that cornuside reduces the severity of autoimmune encephalomyelitis by blocking Th17 cells from entering the central nervous system (Zhang et al. 2021). In autoimmune hepatitis, cornuside can mediate T and natural killer T cells (immune cells) (Wang et al. 2023). However, the effect of cornuside on AR remains unclear. Hence, we hypothesized that cornuside protects against inflammatory responses in the AR progression. This study aims to investigate whether the effect of cornuside could be achieved via the regulation of immune cells and inflammatory cytokines.

Materials and Methods

Experimental mice and agents

A total of 40 male BALB/c mice aged 6–8 weeks obtained from the Jiangsu University Experimental Animal Center. Before induction of the AR model establishment, they were housed in the Maternal and Child Health Hospital of Hubei Province with free access to food and water and a 12/12 light/dark schedule for a week. The living conditions for mice were maintained at a controlled temperature of 22 ± 2°C and a humidity of 55 ± 15%. They were randomly divided into 5 groups (n = 8/group) to construct the AR model. The control group received normal food and water daily. The AR group received injections with ovalbumin (OVA, purity ≥ 98%, CAS: 9006-59-1, Bioss, Beijing, China) only The treatments (oral administration) of cornuside (purity ≥ 98%, CAS: 131189-57-6, Yeasen, Shanghai, China) at different concentrations were named Cornuside-L (50 mg/kg), Cornuside-M (100 mg/kg), and Cornuside-H (200 mg/kg) respectively (Li et al. 2016). To convert human doses to mice, the BSA-based method is commonly used (Blanchard and Smoliga 2015), with the formula: mouse dose (mg/kg) = human dose (mg/kg) × mouse BSA/human BSA. According to this formula, 045, 091 or 182 mg/kg of cornuside could be used as clinical dosages. However, the detailed clinical dosage of drugs in humans is typically calculated based on individual weight (mg/kg), body surface area (BSA), or disease severity, with standard doses for adults and adjusted for special populations.

Table 1. The evaluation of allergic rhinitis symptoms

Symptoms	Control	AR
Nasal secretion	0	2.2 ± 0.8**
Sneezing	0	1.6 ± 0.7**
Nasal rubbing	0	1.8 ± 0.8**
TNSS	0	6.1 ± 1.2**

The values are expressed as the mean ± SD. ** $p < 0.01$. TNSS, total nasal symptom score.

AR mouse model

On days 0, 7, 14, and 21, mice in the AR model were first subjected to systemic sensitization by intraperitoneal injection with 75 μg OVA and 2 mg aluminum hydroxide (CAS: 21645-51-2, Sigma-Aldrich, St Louis, MO, USA) that were diluted in 200 μl phosphate-buffered saline (PBS, Cat No: PB180327, Pricella, Wuhan, China). On days 23, 25, and 27, the mice received nasal challenge by nasal instillation with 20 μl PBS containing 500 μg OVA, using a precision microsprayer (Penn-Century Inc Beijing, China). AR symptoms were confirmed in the mice on the 28th day. Subsequently, they were fed with cornuside at doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg for the following two weeks. On day 43, mice were finally anesthetized with 200 mg/kg pentobarbital sodium (CAS: 57-33-0, Sigma-Aldrich). All experimental procedures were conducted in accordance with institutional guidelines for animal care and use and were approved by Maternal and Child Health Hospital of Hubei Province.

Evaluation of AR symptoms

AR symptoms were confirmed in the mice on the 28th day by evaluating the total nasal symptom score (TNSS) including nasal secretion/discharge, sneezing and nasal rubbing/scratching within 30 min (Table 1). (1) Nasal secretion/discharge - with the anterior nostril as the anatomical boundary, score 0 for no nasal cleansing, score 1 for flow limited to

the upper region, score 2 for flow extending downward, and score 3 for full-face discharge; (2) sneezing: score 0 for no sneezes, score 1 for 1–3 sneezes, score 2 for 4–10 sneezes, and score 3 for ≥10 sneezes; (3) nasal rubbing/scratching score 0 for no nasal scratching, score 1 for intermittent nose rubbing (several times), score 2 for persistent scratching of nose and face, and score 3 for continuous scratching/rubbing of nose and face. A total score of TNSS more than 5 indicated the success of model establishment (Liu et al. 2021). On the 42nd day, sneezing and nasal rubbing behaviors were recorded again within 10 min immediately after the mice received the last administration of cornuside. All animal AR symptoms were evaluated by researchers who were blinded to animal groups.

Sample preparation

On the 43rd day, the eyeball blood of mice was taken and centrifuged and the serum was reserved for enzyme-linked immunosorbent assay (ELISA) before sacrifice of mice. After the skin and mandible were removed, an incision was made along each group's midline of the maxilla. The nasal cavity was gently flushed with 10 ml of PBS at a low temperature, starting from the trachea and moving toward the nasopharynx. The nasal lavage fluid (NLF) was then promptly gathered. The mucosal tissue from the nasal cavity and paranasal sinuses were collected using micro tweezers. The tissue was then placed into cryopreservation tubes and immediately submerged in liquid nitrogen for the following experiments.

Hematoxylin-eosin (H&E) staining

The nasal mucosa of mice was fixed in 4% paraformaldehyde (CAS: 30525-89-4, Sigma-Aldrich) for 48 h, followed by dehydration with ethanol (CAS: 64-17-5, Sigma-Aldrich) at varying concentrations (50%, 70%, 80%, 90%, 95%, and 100%). The nasal mucosa tissue samples were then treated with xylene (CAS: 104-81-4, Sigma-Aldrich) at room temperature for 30 min and incubated with paraffin (CAS: 8002-74-2, Sigma-Aldrich) at 65°C overnight. Once embedded in wax, the tissues were sliced into sections measuring 5 μm thick using a microtome (Thermo Fisher Scientific, Waltham, MA, USA) and placed onto microscopy slides. These sections were dewaxed with fresh xylene for ten min, hydrated with gradient ethanol (100%, 90%, 80%, and 70%), and rinsed three times with DEPC water (Cat No: R0021, Beyotime, Shanghai, China). Finally, the samples were stained with hematoxylin staining solution (Cat No: C0107, Beyotime) for five min and eosin solution (Cat No: C0109, Beyotime) for one min at room temperature. The eosinophils were counted under a microscope (Nikon, Tokyo, Japan).

Assessment of inflammatory cells in nasal lavage fluid (NLF)

Total leucocytes were quantified under a hemocytometer (Mindray 3000, Shenzhen, China) Wright's Giemsa staining solution (Cat No: C0131, Beyotime) was utilized to quantify eosinophils, lymphocytes, and neutrophils based on the conventional method of Wright-Giemsa staining (Choi et al. 2021).

ELISA

Corresponding ELISA kits were utilized to detect the levels of histamine (Cat No: ab213975, Abcam, Cambridge, MA, USA), OVA-specific IgE (Cat No: KGEMC117-1, Keygentec, Nanjing, China), OVA-specific IgG1 (Cat No: D721096, Sangon Biotech, Shanghai, China), interleukin-4 (IL-4, Cat No: PI612, Beyotime), leukotriene C4 (LTC4, Cat No: AE90528Mu-96T, Lanso, Shanghai, China), TNF-α (Cat No: PT512, Beyotime), IL-6 (Cat No: PI326, Beyotime), IL-13 (Cat No: PI539, Beyotime), and IL-17 (Cat No: ab100702, Abcam) in mouse serum and histamine in mouse NLF In brief, 100 μl serum or NLF sample was added to each well of the experimental slabs and incubated at 36°C for 90 min. After washing the slabs with detergent three times, 100 μl of biotinylated antibodies were added to the sample and incubated at 36°C for 1 h. Subsequently, 100 μl of enzyme-labeled streptavidin was added to the serum and incubated at 36°C for 30 min in the dark. A mixture of 50 μl substrate solution A and 50 μl substrate solution B was added to each well and mixed for 30 s. The color was developed at 37°C for 15 min in the dark, and the reaction was terminated by adding 0.5 ml of 2 M H_2SO_4. Within 3 min after termination, the optical density (OD) at 450 nm was measured using a microplate reader (Infinite M200 PRO, Tecan Austria GmbH, Austria).

Statistical analysis

The data were analyzed using GraphPad Prism 10 software (GraphPad Software, San Diego, CA, USA) and SPSS 290 software (IBM, Armonk, NY, USA). The study results were presented as mean ± standard deviation (SD). Student's *t*-tests were used for comparisons between two groups, while analysis of variance (ANOVA) was employed to compare multiple groups with Tukey's *post hoc* test $^{###}p < 0001$ compared to the control group; $^{*}p < 005$, $^{**}p < 001$, $^{***}p <$ 0001 compared to the AR group.

Results

Cornuside inhibits histamine secretion and rhinitis symptoms

To investigate the effects of cornuside on AR, an ovalbumin-induced AR mouse model has been developed. Figure 1

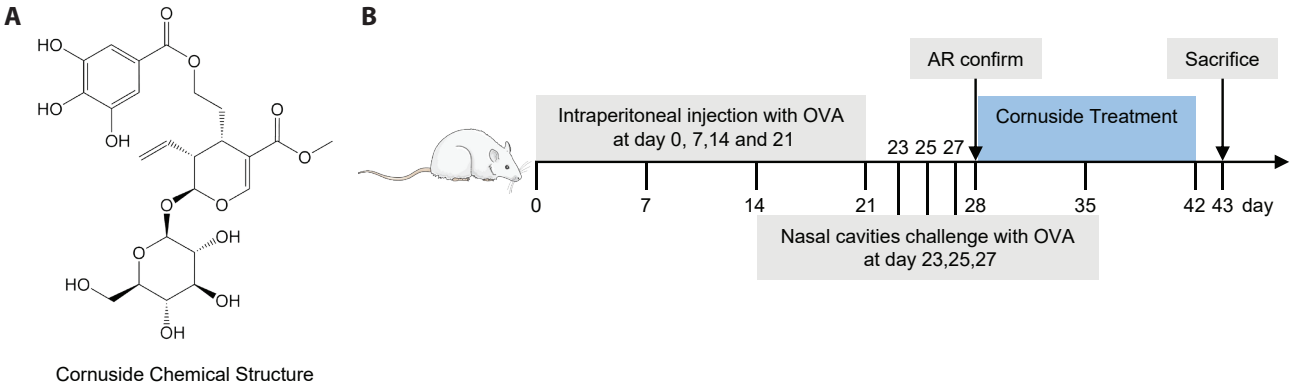

Figure 1. Experimental design mind map **A.** The chemical structure of cornuside. **B.** Schematic diagram of the experimental protocol for ovalbumin-induced allergic rhinitis mouse model.

presents the chemical structure of cornuside and the timeline of animal treatment. First, we recorded the incidence of sneezing and nasal rubbing in 10 min of each group of mice. It was found that mice with AR sneezed and experienced nasal rubbing more than 20 times on average, which exhibited a high frequency compared to the control group. However, the treatment with cornuside significantly reduced these AR symptoms (Fig. 2A,B). Histamine release is known to be important in AR progression. Herein, the histamine levels in serum and NLF of mice were detected. We found that histamine levels in serum and NLF were higher in AR-induced mice than in the control group. However, cornuside dose-dependently inhibited the AR-induced elevation of histamine secretion (Fig. 2C,D). Collectively, these results suggest that cornuside ameliorates AR symptoms in ovalbumin-induced mice.

Cornuside reduces eosinophils in nasal tissues

Next, we employed H&E staining to explore the effects of cornuside on eosinophils in nasal tissues. A significant increase in eosinophil numbers was observed in the AR

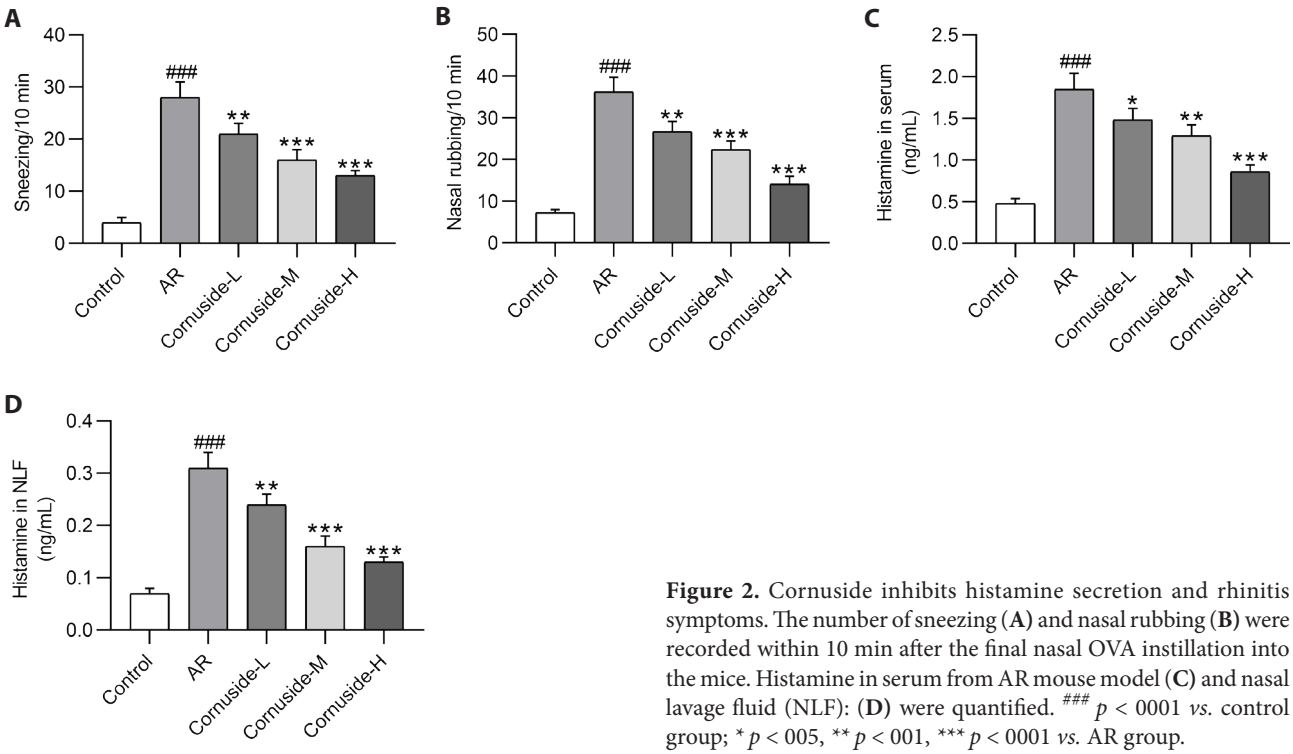

Figure 2. Cornuside inhibits histamine secretion and rhinitis symptoms. The number of sneezing (**A**) and nasal rubbing (**B**) were recorded within 10 min after the final nasal OVA instillation into the mice. Histamine in serum from AR mouse model (**C**) and nasal lavage fluid (NLF): (**D**) were quantified. $^{###}$ $p < 0001$ *vs.* control group; * $p < 005$, ** $p < 001$, *** $p < 0001$ *vs.* AR group.

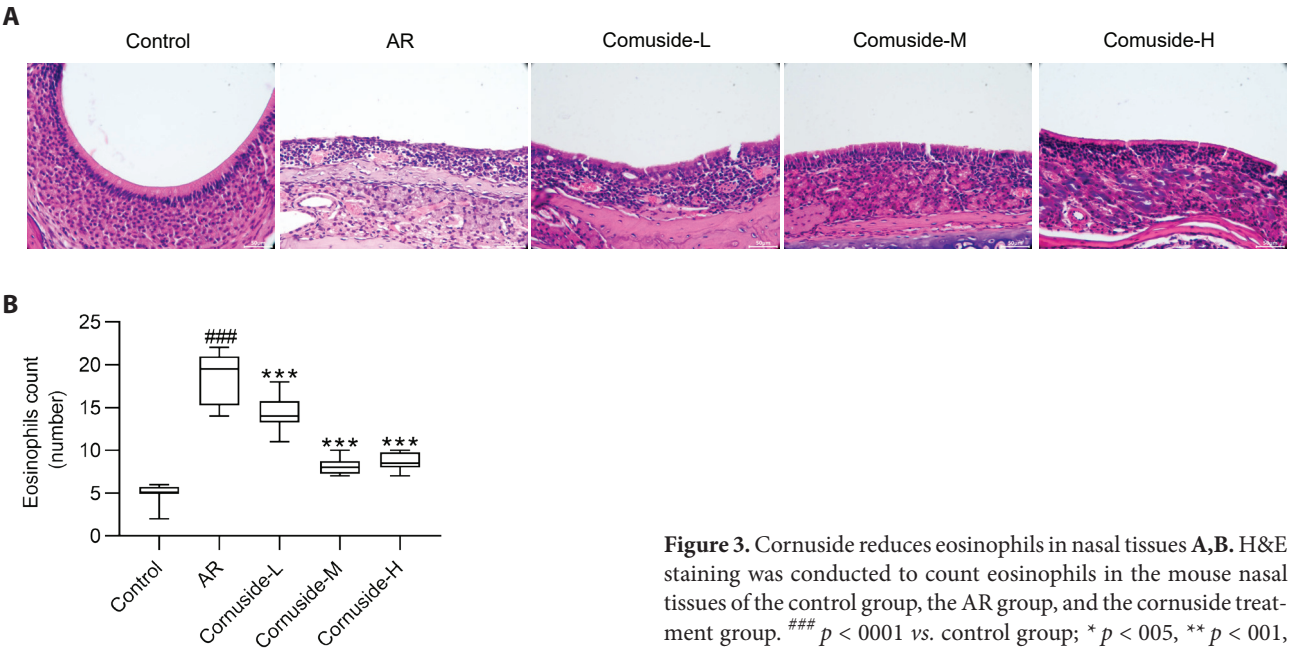

Figure 3. Cornuside reduces eosinophils in nasal tissues **A,B.** H&E staining was conducted to count eosinophils in the mouse nasal tissues of the control group, the AR group, and the cornuside treatment group. $^{###}p < 0001$ *vs.* control group; $^{*}p < 005$, $^{**}p < 001$, $^{***}p < 0001$ *vs.* AR group.

model group compared to the control group, while cornuside treatment effectively reduced eosinophil infiltration in AR-induced nasal tissues. Notably, the medium or high dose of cornuside further reduced the number of eosinophils (Fig. 3). These findings collectively indicated that cornuside exerted a dose-dependent inhibitory effect on eosinophil invasion into mouse nasal tissues.

Cornuside decreases inflammatory cells in NLF

During the development of AR, inflammatory cells including leucocytes, eosinophils, lymphocytes, and neutrophils often infiltrate into NLF. Hence, we researched these cells in the mouse model of AR. Compared to the control group, the number of leucocytes, eosinophils, lymphocytes, and neutrophils in NLF were all elevated in response to the AR induction. However, cornuside treatment rescued the increased number of these cells in the NLF of mice with AR (Fig. 4). It was also found that cornuside decreased the inflammatory cells in NLF in a dose-dependent manner.

Cornuside attenuates the inflammatory cytokines in the serum of mice with AR

To further confirm the effect of cornuside on inflammatory response, we evaluated the inflammatory cytokines including TNF-α, IL-6, IL-13, and IL-17 in the serum of mice with AR. Compared to the control group, the serum of AR-induced mice exhibited a significant increase in TNF-α, IL-6, IL-13, and IL-17, suggesting a serious inflammatory response. After varying cornuside doses treatment in mice with AR, these inflammatory cytokines in serum were reduced in a concentration-dependent manner (Fig. 5A–D). These results indicate that cornuside treatment attenuated the serum inflammatory response in AR mice in a dose-dependent manner. Moreover, the levels of OVA-specific IgE and IgG1 significantly increased compared to the control group. Treatment with cornuside at different doses resulted in a significant decrease in serum OVA-specific IgE and IgG1 (Fig. 5E,F). Similarly, the serum levels of two important cytokines, IL-4 and LTC4, were much higher in mice with AR than in control mice. After cornuside treatment, IL-4 and LTC4 levels significantly decreased (Fig. 5G,H). These results indicated that cornuside treatment effectively suppressed OVA-specific IgE and IgG1 levels as well as IL-4 and LTC4 levels in a dose-dependent manner.

Discussion

AR is a common respiratory disease that occurs in the nasal mucosa, affecting more than 300 million people worldwide (Nur Husna 2017; Tan et al. 2022). It was induced by exposure to environmental allergens leading to IgE-mediated inflammation (Ide et al. 2024). With environmental pollution, the incidence of AR will purportedly increase (Choi et al. 2021). Although AR is not life-threatening, AR does not exhibit a high mortality rate. Nevertheless, it substantially impairs patients' quality of

life. In this study, we identified cornuside as a potential therapeutic agent for AR.

It is widely known that OVA can induce allergic responses. Briefly, OVA activates dendritic cells to regulate the immune system, which promotes IgE and IgG1 secretion (Lin et al. 2022). The IgE triggers mast cells to release inflammatory mediators such as histamine, resulting in allergy (Vitte et al. 2022). Previous studies have shown that OVA is commonly used to induce AR in experimental mouse models (Ba et al. 2021; Zhang et al. 2023). The previous AR model was confirmed by the frequent behaviors including sneezing and nasal rubbing of experimental mice (Zhang et al. 2020; Zhang et al. 2023). Consistently, our study consistently demonstrated that OVA injections significantly increased the frequency of sneezing and nasal rubbing in mice compared with the control group.

Inflammation response is associated with AR. Mechanically, AR allergens increase the LTC4 levels and activate the inflammatory cytokines including the interleukin family (IL-4, IL-6, IL-13, and IL-17) and TNF-α (Drazdauskaitė et al. 2020). As a result, mast cells release excessive histamine, damaging epithelial cells in lab tests (Steelant et al. 2018). Concurrently, LTC4 promotes the infiltration to the nasal mucosa of inflammatory cells including eosinophils, neutrophils, leucocytes, and lymphocytes (Doherty et al. 2013). The results of this study demonstrated the increased inflammatory cell numbers (leucocytes, eosinophils, lymphocytes, and neutrophils), inflammatory cytokine level (TNF-α, IL-6, IL-13, and IL-17), and serum cytokine level (IgE, IgG1, IL-4, and LTC4). These results, consistent with previous theoretical frameworks, further support the successful establishment of our experimental model.

Recently, some scholars have been interested in traditional Chinese medicine (Liang et al. 2020; Yaqi et al. 2023). Cornus officinalis from which cornuside is derived has been reported to have anti-allergic, anti-inflammatory, and antioxidant activities (Quah et al. 2020). Existing studies have already revealed the anti-inflammatory effects of cornuside in various models (Li et al. 2023; Wang et al. 2023). For instance, cornuside suppresses inflammatory cytokines such as TNF-α and IL-6 in the septic mouse model (Kim et al. 2022). Similarly, we found that treatment with cornuside significantly reduced inflammatory cytokine levels including TNF-α, IL-6, IL-13, and IL-17 in NLF samples, implying its inhibitory effect on inflammation in mice with AR. It is well-known that mast cells are directly responsible for allergic symptoms. Previous researchers have discovered that mast cells exposed to cornuside release less histamine and inhibit the allergic response (Li et al. 2016). From the perspective of AR progression, allergens and IgE attached to mast cells cause the release of substances that widen small arteries, increase blood vessel permeability, and lead to symptoms like itching, runny nose, mucus production, and lung muscle constriction (Jafarinia et al. 2020). Meanwhile, mast cells produce TNF-α increasing endothelial immune cells such as leucocytes (Söderquist et al. 1999; Shi and Sun

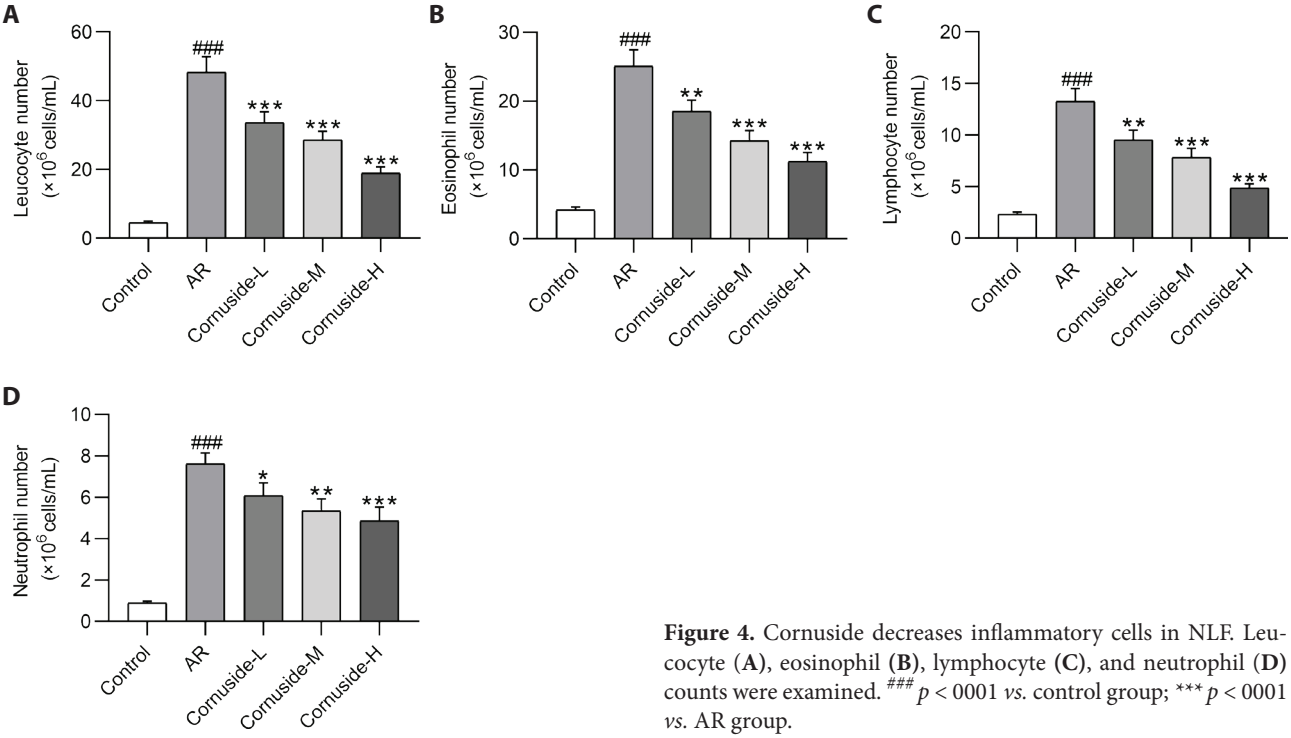

Figure 4. Cornuside decreases inflammatory cells in NLF. Leucocyte (**A**), eosinophil (**B**), lymphocyte (**C**), and neutrophil (**D**) counts were examined. $^{###}p < 0001$ *vs.* control group; $^{***}p < 0001$ *vs.* AR group.

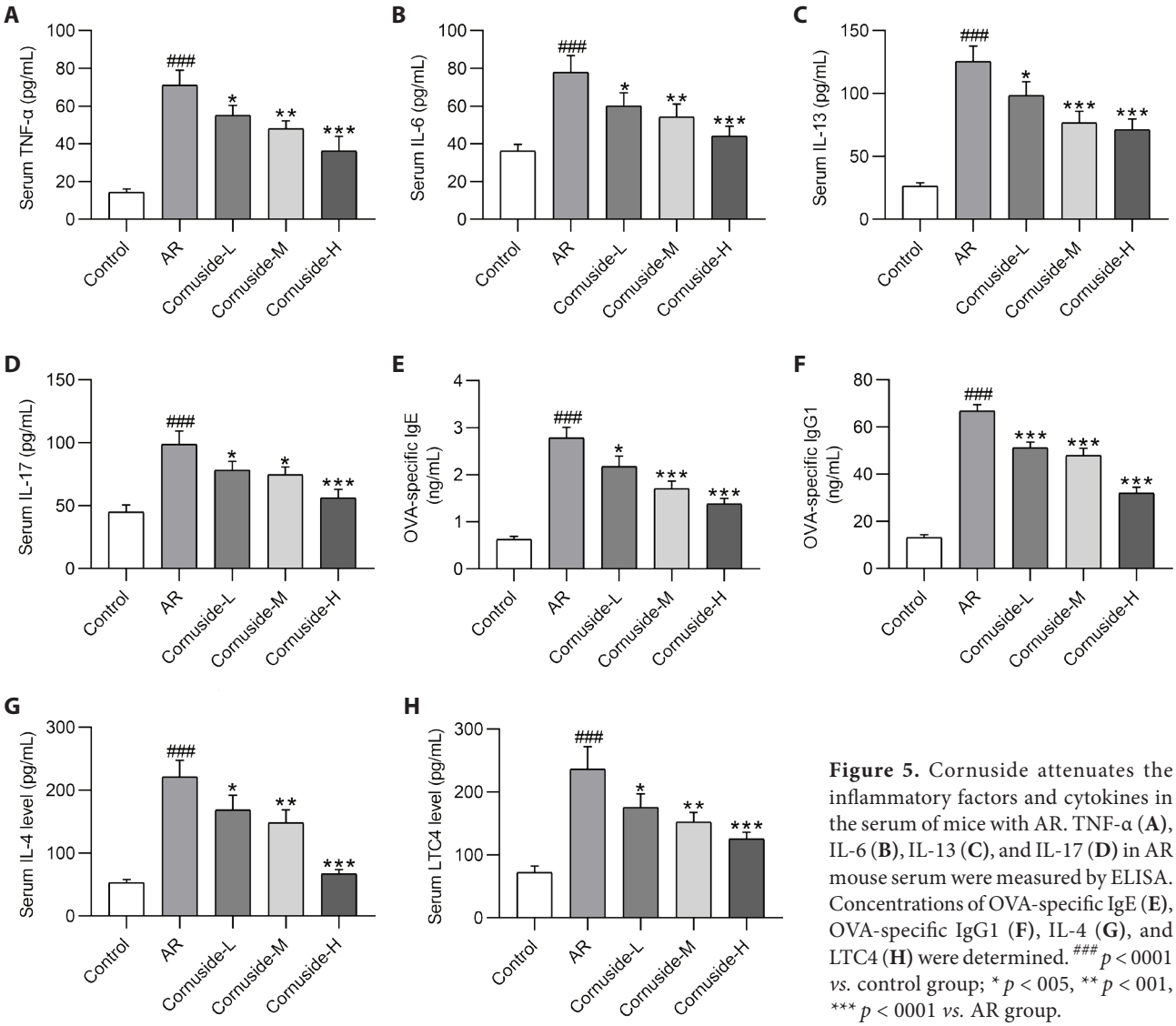

Figure 5. Cornuside attenuates the inflammatory factors and cytokines in the serum of mice with AR. TNF-α (**A**), IL-6 (**B**), IL-13 (**C**), and IL-17 (**D**) in AR mouse serum were measured by ELISA. Concentrations of OVA-specific IgE (**E**), OVA-specific IgG1 (**F**), IL-4 (**G**), and LTC4 (**H**) were determined. $^{###}p < 0001$ *vs.* control group; $^{*}p < 005$, $^{**}p < 001$, $^{***}p < 0001$ *vs.* AR group.

2018). Therefore, the late-phase allergic response is often characterized by the recruitment of immune cells including eosinophils, leucocytes, neutrophils, and lymphocytes into the lining of the nasal mucosa (Shamji et al. 2022). AR is also characterized by increased eosinophils in the nose and requires a management system to relieve symptoms (Kay 2001). Consistent with the previous study (Li et al. 2016), we found that cornuside remarkably reduced the excessive production of histamine in the serum and NLF from mouse model. However, we also found the inhibitory effect of cornuside on inflammatory cell infiltration in mice with AR, as evidenced by the decreasing number of leucocytes, eosinophils, lymphocytes, and neutrophils.

There are some limitations existing in the present study. First, only *in vivo* experiments were conducted, and the function of cornuside in nasal epithelial cells remains unclear. Establishing an appropriate *in vitro* model is necessary to further validate our findings. Moreover, the downstream signaling pathways and regulatory mechanisms of cornuside require additional investigation.

In conclusion, our study provides evidence that cornuside improves the AR symptoms in OVA-induced mice Cornuside administration reduces the number of inflammatory cells in NLF and serum inflammatory cytokines in Mice with AR. These results suggest that cornuside may serve as a potential therapeutic agent for AR.

Ethics approval. Experimental operations were all conducted following ethical standards for animal experimentation and were approved by Maternal and Child Health Hospital of Hubei Province.

Acknowledgement. We appreciate all participants who contribute to this work.

Conflict of interests. The authors have no conflicts of interest to declare.

Contribution of authors. HW conceived and designed the experiments; HW, LH analyzed the data; HW, LH drafted the manuscript. All authors agreed to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

Data availability. Data will be made available on reasonable request.

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Received: September 10, 2025
Final version accepted: April 24, 2026