Scientific African 23 (2024) e02004

Contents lists available at ScienceDirect

Scientific African

journal homepage: www.elsevier.com/locate/sciaf

Aurantio-obtusin alleviates allergic responses in ovalbumin-induced rhinitis

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ARTICLE INFO

Editor: DR B Gyampoh

Keywords:
Allergic rhinitis
Aurantio-obtusin

ABSTRACT

Allergic rhinitis (AR) is a growing global health concern. Despite being non-fatal, it has a detrimental effect on people's quality of life and poses a significant economic burden. In this study, we aimed to evaluate the anti-allergic effects of aurantio-obtusin against ovalbumin-induced murine model of allergic rhinitis. Aurantio-obtusin was administered to rats orally after sensitization to ovalbumin. Results of the study suggested that aurantio-obtusin causes a significant reduction in nose rubs and sneeze as compared to the vehicle-treated disease control group. The aurantio-obtusin treated group showed a dose-dependent significant reduction in serum TNF-α, IL-4, and IL-6 levels as well as histamine levels in the nasal mucosa. Additionally, it decreased neutrophil and eosinophil numbers in blood of AR rats'. In the nasal tissues of the vehicle-treated rats that were subjected to an OVA challenge, the histology of the nasal mucosa of AR rats revealed aberrant histological changes. A variety of histological abnormalities, including vascular congestion in the nasal mucosa, substantial inflammatory cell infiltration, and obvious alveolar wall oedema were present. In the rats treated with aurantio-obtusin, these characteristics were reversed. Collectively, the findings suggests that aurantio-obtusin could be used to enhance current AR treatment approaches.

Introduction

The mucosal tissue in the nasal cavity is impacted by allergic rhinitis (AR), a serious health problem that affects people all over the world [1,2]. It is characterized by signs of mucosal inflammation caused by Th2 cells and mediated by IgE, including nasal irritation, sneezing, watery discharges, and congestion [3]. Despite not being lethal, allergic rhinitis (AR), which affects more than 500 million people worldwide, has a tremendous impact. It can result in consequences like sinus infections, sleep issues, and asthma flare-ups, significantly reducing the quality of life for sufferers [4].

Allergens cause a hypersensitivity reaction that is facilitated by immunoglobulin E (IgE) antibodies in those who are affected by allergic rhinitis (AR), which is characterized by T helper type 2 cell-mediated allergic inflammation [5]. Interleukin 4 (IL-4), IL-5, and IL-13 thus play crucial roles in the reactions associated with allergic rhinitis [6]. Immunoglobulin E (IgE) is produced when Th2 cells, which are stimulated by IL-4, change the class of B cells. Elevated IgE levels are a major factor in allergic responses [7,8]. Th2 cells have been associated with the pathogenesis of allergic rhinitis, suggesting that their suppression could represent a potential therapeutic approach for treating allergic rhinitis. Inflammatory cells like basophils, eosinophils, mast cells, and mononuclear cells invade the nasal mucosa on allergen exposure. Numerous allergy mediators, including histamine, serotonin, cysteinyl leukotrienes,

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https://doi.org/10.1016/j.sciaf.2023.e02004
Received 28 July 2023; Received in revised form 10 September 2023; Accepted 29 November 2023
Available online 30 November 2023

prostaglandins, nucleotides, proteases, and tumor necrosis factor alpha (TNF-α), are released by these inflammatory cells. These mediators sustain the inflammatory response and contribute to the development of nasal symptoms such as sneezing, itching, rhinorrhea, and nasal congestion [9].

Antihistamines, corticosteroids, and mast cell stabilizers, either individually or in combination, are commonly used for managing allergic rhinitis [10,11]. However, these medications can have significant unwanted side effects that compromise their effectiveness in clinical practice. These side effects include urinary retention, dry mouth, blurred vision, constipation, rapid heart rate, and sedation [12,13]. As a result, there is a need to explore alternative treatments. Aurantio-obtusin is the major bioactive anthraquinone derivative from the dried seeds of *Cassia obtusifolia* and *Cassia tora*. It is a phytochemical marker of quality control in the Chinese Pharmacopeia (Version 2015) and exhibits a number of biological properties including anti-oxidative, anti-hypertension, anti-mutagenic, anti--genotoxic, anti-inflammatory and neuroprotective effects [14]. The potential of Aurantio-obtusin (AO) in modulating allergic rhinitis is not yet understood, despite its demonstrated anti-inflammatory effect on macrophages and its ability to reduce allergic reactions *in-vitro* studies [14,15]. In order to assess the anti-allergic effects of AO in rats, this section will make use of a well-researched murine model of allergic rhinitis caused by ovalbumin.

Materials and methods

Chemicals and reagents

The Aurantio-obtusin compound (98 % purity) was acquired from Ambeed, located in Arlington Heights, Illinois, USA. From St. Louis, Missouri, USA-based Sigma-Aldrich. A brand of Thermo Scientific called Pierce, located in Rockford, Maryland, and in the United States supplied the aluminum hydroxide adjuvant and Grade VI Ovalbumin (OVA). Dexamethasone (Dex) was sourced from the Innovative Research of America, with headquarters in Toledo, Ohio. The Netherlands' Oss branch of B. Braun Medical BV provided the phosphate buffered saline (PBS). To measure these markers in the experiment, OVA-sIgE, IL-4, IL-6, and TNF-alpha ELISA quantification kits for rats were purchased from MLBio Biotechnology Company Limited (Shanghai, China).

Animals and experimental protocol

Eight-week-old Wistar rats were purchased from the Centre for Plant Medicine Research in Mampong-Akuapem, Ghana, which were clear of infections that affect mice. Within the Animal House facility of the Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences at KNUST, the animals were kept in metal cages. They were kept in a 12 h cycle of light and darkness, at a temperature of 25 $\pm$ 2 °C, and with a relative humidity of 40–50 %. The animals spent one week in the facility to give them time to acclimate. Under ideal conditions, the rats received standard pellets every 8 h during the research and had unrestricted access to purified water. The KNUST Ethics Committee authorized all of the methods used in this study.

Methods

Ovalbumin-induced rhinitis; sensitization and challenge

The rats were injected intra-peritoneally with 200 μg of ovalbumin (OVA) dissolved in 200 μl of phosphate buffered saline (PBS) containing 2 mg of aluminum hydroxide to cause sensitization. This was done on days 0, 7, and 14. The rats were then given nasal instillations of OVA at a dosage of 10 mg/ml in 20 μL of PBS, delivered into both nasal cavities, over the course of days 21 to 27. In contrast, PBS was administered to the control group in place of OVA for sensitization and nasal challenge. The animals were placed into six groups, each with five rats, and given the following treatments for a period of seven days:

Group 1: "Control group (Con)", animals without sensitization and challenge; as a naive control, on days 15 to 27, animals received daily oral administration of polyethylene glycol (PEG).
Group 2: "OVA", after the sensitization phase, these rats were challenged with OVA (10 mg/mL, 20 μL/nostril) through intranasal instillation for seven days straight from day 21 to day 27. As a positive control, mice were given PEG via oral treatment once daily from days 15 to 27.
Group 3–5: "Aurantio-obtusin treated groups", Animals received oral administration of AO (10, 50, and 100 mg/kg, respectively) from days 15 to 27. Before each OVA challenge from days 21 to 27, AO was given one hour in advance.
Group 6: "Dexamethasone treated group (Dex)", Animals underwent the same immunization and challenge procedures as other groups. Animals were also given Dex (2 mg/kg) orally once a day from days 15 to 27. Dexamethasone was given one hour prior to each OVA challenge from days 21 to 27.

On day 28, 24 h following the final challenge, animals were sacrificed, and blood, nasal tissues, and nasal lavage fluid (NALF) were collected for analysis.

Evaluation of nasal symptoms

Evaluation and recording of the number of sneezing and nose rub motions occurring within a 15-minute period after each challenge

was conducted for the 7 days period. These recorded numbers were then compared to those of the control group. Nasal itch was defined as the act of rubbing one's nose with one or both forelimbs.

Nasal lavage fluid (NALF) collection and analysis

24 h after the last intranasal stimulation with OVA, nasal lavage fluid was collected. Following partial tracheal resection, an 18-gauge catheter was placed into the tracheal hole to collect the fluid. The nasopharynx and upper airway were the targets of the catheter's path. The fluid was collected in a tube after 1 mL of cold PBS was gently perfused into the nasal cavities. The collected fluid was then centrifuged at 2000 rpm for 7 min at 4 °C, and the supernatant that was produced was kept at 80 °C. An ELISA quantification kit that was used to measure the amounts of histamine in the nasal lavage fluid.

Measurement of OVA-Specific IgE and IL-4 in serum

Blood was drawn from the inferior vena cava twenty-four hours after the last intranasal stimulus. After centrifugation, serum was collected and kept at −80 °C. An ELISA assay kit was used to measure the concentrations of OVA-specific IgE, IL-4, and IL-6 in the serum.

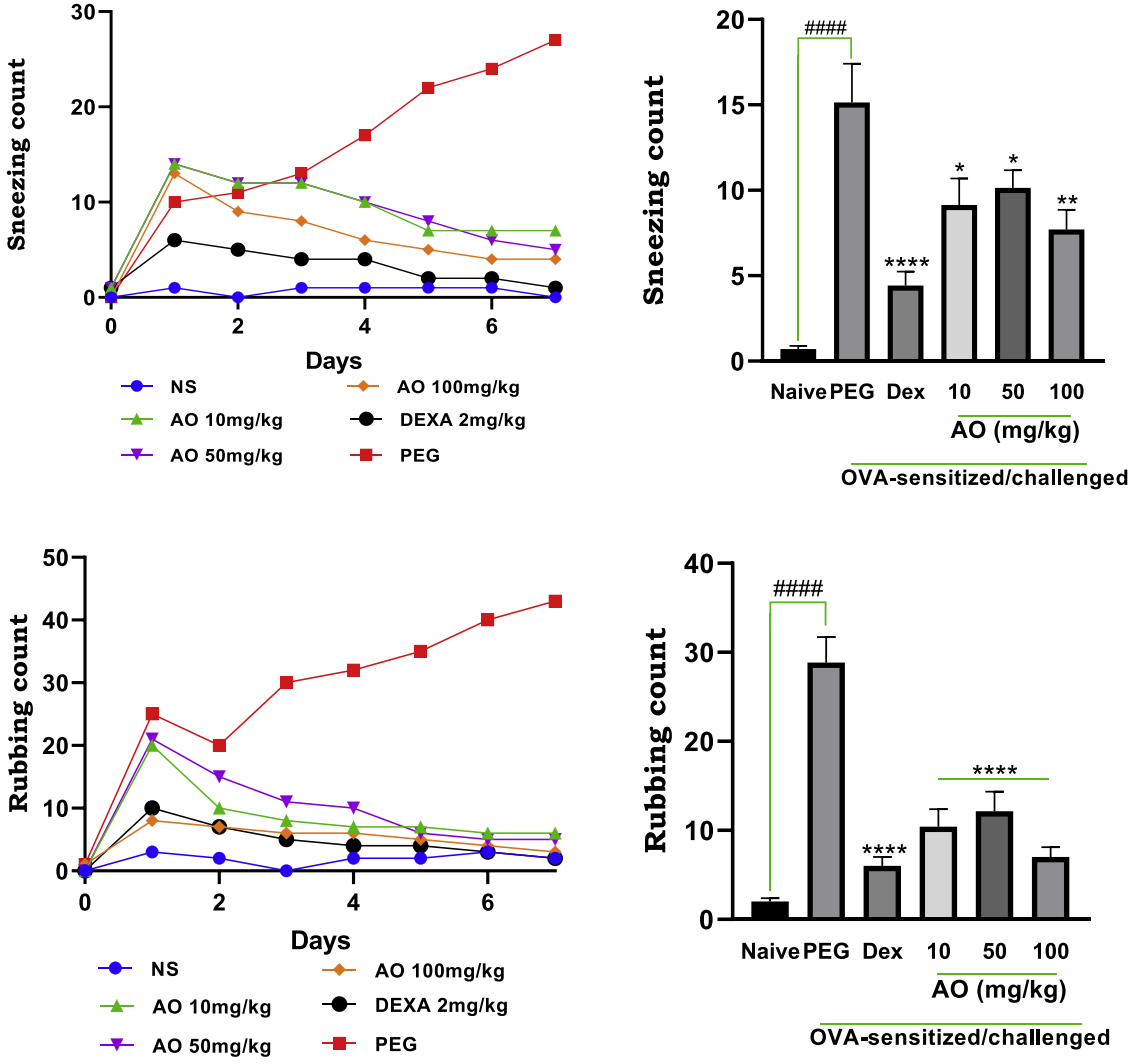

Fig. 1. Effect of aurantio obtusin (AO) on (A) sneezing trend and score and (B) nose-rub trend and score and (C) rhinorrhea trend and score, in AR rats. Data are presented as the mean ± S.E.M ($n = 5$). # $P < 0.05$: significantly different from sham, ****$P < 0.0001$, ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$: significantly different from PEG-treated OVA-sensitized and challenged rats.

Histological evaluation of nasal mucosa

All animals were euthanized with an intraperitoneal injection of pentobarbital at a dose of 80 mg/kg after blood and nasal lavage fluid (NALF) collection. 24 h following the last intranasal challenge, 400 ml of formaldehyde was then perfused via the left ventricle, followed by 100 ml of 0.9 % physiological saline. Rat heads were removed and let to dry in 10 % neutral buffered formalin for three days. The heads were decalcified for seven days with 5 % trichloroacetic acid. The nasal cavity was transversely sectioned at the level of the incisive papilla of the hard palate, and the tissue block was then embedded in paraffin to study the tissue histology. The sections were stained with haematoxylin and eosin (HE) to examine tissue histology.

The sections were carefully examined to determine a number of parameters, such as vascular obstruction and proliferation, inflammatory cell infiltration, cilia loss, nasal mucosa thickness, and the degree of chondrocyte hypertrophy. A trained individual performed a blinded study, evaluating a minimum of 5 fields per sample, to determine the severity of these changes. Each parameter was assigned a score based on the observed alterations: 0 for no change, 1 for mild change, 2 for moderate change, and 3 for severe change. The slides were examined under light microscopy (Leica microscope) and photographs were captured using an Olympus DP-70 digital camera.

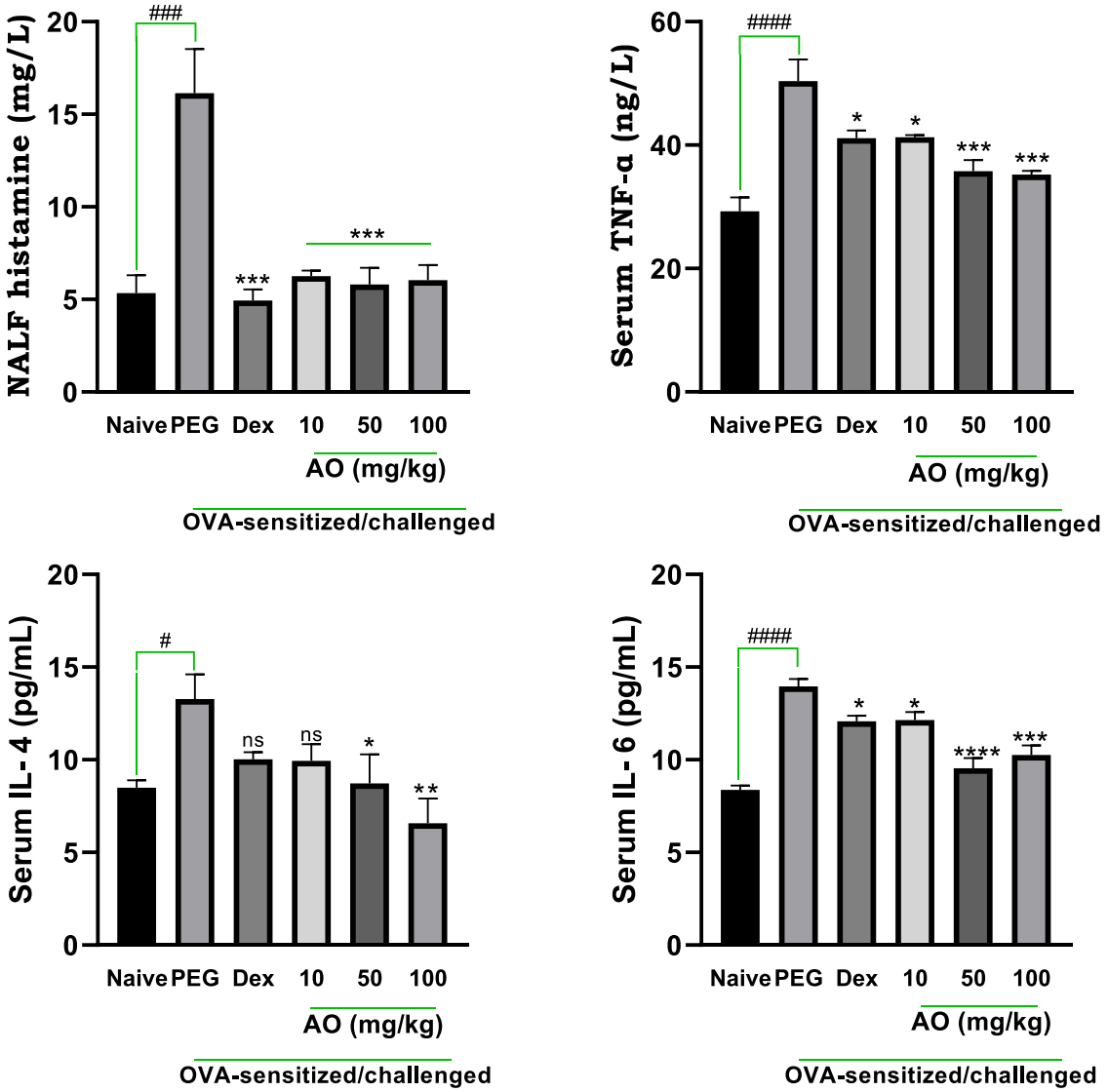

Fig. 2. Effect of aurantio-obtusin on various inflammatory biomarkers in AR rats. (A) OVA-sIgE, (B) TNF-α, (C) IL-4, and (D) IL-6. Data are presented as the mean ± S.E.M ($n = 5$) #$P < 0.05$: significantly different from PBS (control), *$P < 0.05$: significantly different from OVA-challenged rats.

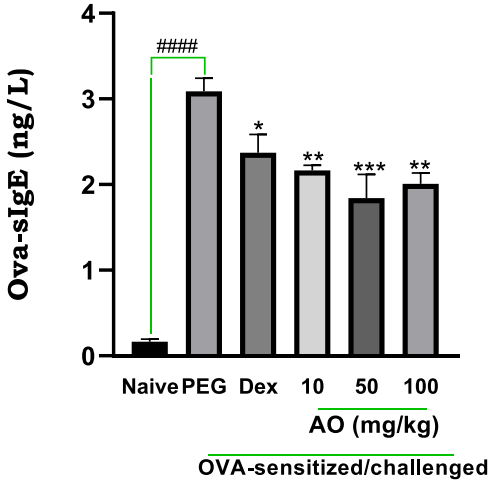

Fig. 3. Effect of aurantio obtusin (AO) on levels of OVA-sIgE in serum of AR rats. Data are presented as the mean ± S.E.M ($n = 5$). # $P < 0.05$: significantly different from sham, ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$: significantly different from PEG-treated OVA-sensitized and challenged rats.

Statistical analysis

Results were analyzed using the Graphpad Prism software version 8 and expressed as the mean ± standard error of mean (S.E.M). Statistical analysis consisted of ANOVA followed by Dunnet's post hoc test. The results were considered significant at a value of $P < 0.05$.

Results

Effect of aurantio-obtusin on the symptoms of OVA-induced allergic rhinitis in rat

As shown in Fig. 1, the frequency of nose-rubs found increased in OVA-sensitized rats with no-treatment, as compared to the sham. However, for rats that received treatment with AO, the frequency of nose-rubs decreased significantly in a dose-dependent manner.

Effect of AO on the levels of pro-inflammatory cytokines

The effect of AO was next investigated on various biochemical markers shown to play a critical role in the progression of AR. The release of various pro-inflammatory cytokines is a characteristic hallmark of AR following the exposure of allergens via inflammation. As shown in Fig. 2, the serum level of histamine was found significantly up-regulated in OVA rats as compared to control, which was reduced significantly upon administration of AO. Additionally, serum TNF-α, was significantly increased in the OVA control group as compared with the sham. Treatment with AO caused a significant reduction in a dose dependent manner. A similar trend was observed in the serum levels of IL-4. These observations suggest that AO might provide relief against AR possibly via modulation of serum IL-4, TNF-alpha and indirectly also of histamine release.

Effect of AO on the levels of OVA-sIgE

The serum levels of ovalbumin-specific immunoglobulin E (OVA-sIgE) was found higher in the vehicle-treated OVA-sensitized and challenged rats as compared to the sham. The level was found markedly reduced in AO treated group as compared to sham as shown in Fig. 3. Aurantio-obtusin administration significantly reduced serum levels of ovalbumin-specific immunoglobulin E (OVA-sIgE).

Effect of AO on the infiltration of leukocytes and eosinophils into the airways in a murine model of allergic airway inflammation

To determine whether AO has effects on allergic airway inflammation, its effect was then determined on total cell infiltration and eosinophilia in the blood of rats. As seen in Fig. 4, the OVA challenge in the vehicle-treated group caused a marked increase of inflammatory cells, especially eosinophils, which reflects the intensity of airway inflammation and the extent of cell infiltrates into nasal mucosa, as compared to the sham-treated group. This was absent in the sham challenged negative control group. Moreover, the number of eosinophils in the blood was also found reduced in AO treated group. Our findings indicate that AO reduces airway inflammation and prevents eosinophil infiltration into the airways in this allergy model.

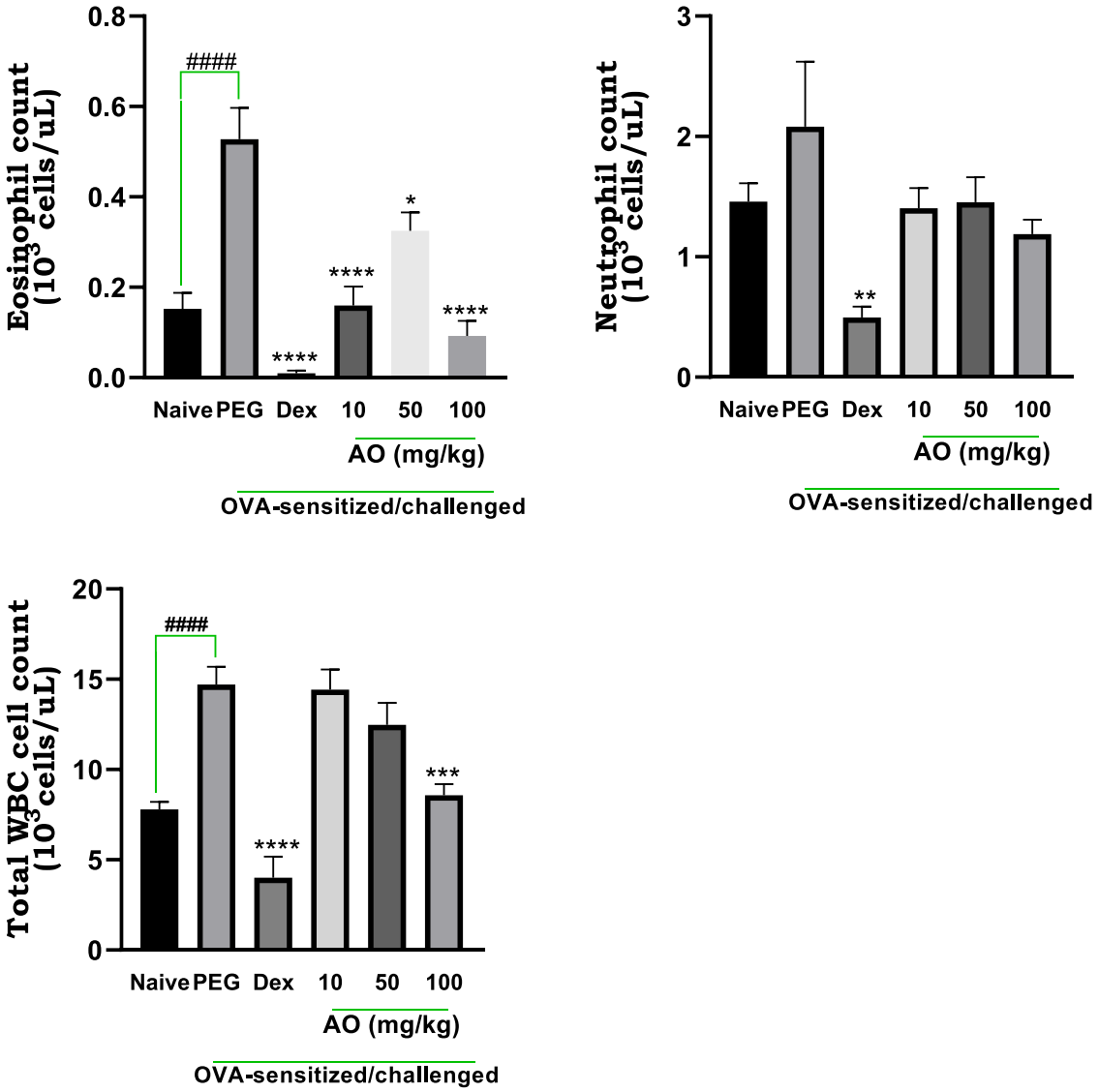

Fig. 4. Effect of aurantio-obtusin on the (A) eosinophil, (B) neutrophil and (C) total cells recruitment in AR rats. Data are presented as the mean ± S.E.M ($n = 5$). # $P < 0.05$: significantly different from sham, ****$P < 0.0001$, ***$P < 0.001$, **P 0.01, *$P < 0.05$: significantly different from OVA-challenged rats.

Histopathological examination of nasal tissues after AO administration

To further examine the effects of AO on nasal pathology, histological analyses of nasal mucosa were performed. As shown in Fig. 5, no apparent histological alteration was found in nasal tissues of the sham-treated group. However, the OVA challenged rats showed marked nasal injury suggested by a large number of infiltrations of inflammatory cells, nasal tissue damage, and marked alveolar wall edema as seen in Fig. 6. These changes were significantly improved by treatment with the AO in a dose-dependent manner.

Discussion

Inflammation of the upper respiratory tract is a defining feature of allergic rhinitis and is mediated by IgE [16]. Following contact with an allergen, the allergic inflammatory response occurs, primarily due to a shift in cytokine production by Th1 and Th2 cells, with a prevalence of Th2 cells [17]. Th2 cells discharge substances like IL-4 and IL-13, which, in conjuction with co-stimulatory signals, induce B-lymphocytes to generate specific gene products and plasma cells to produce IgE antibodies. Consequently, mast cells are triggered to release mediators, including histamine cytokines (IL-4, IL-5 and IL-6), chemotactic factors and enzymes [18,19]. In allergic rhinitis, the release of these mediators initiates the initial symptoms and stimulates the production of white blood cells, specifically eosinophils, which infiltrate the surrounding tissue. Experimental models using sensitized animals challenged with ovalbumin, an

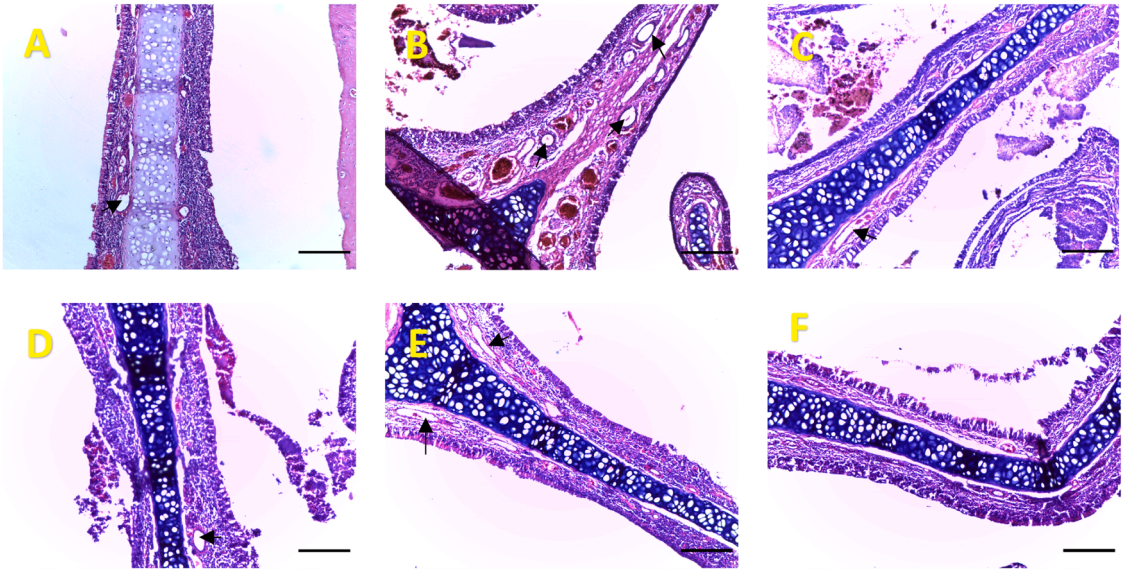

Fig. 5. Histological analysis of nasal mucosa of H&E stain in the (A) normal, (B) AR, (C) AR+Dex and (D) AR+AO 10 (E) AO 50 and (F) AO 100 mg/kg groups. Infiltration of inflammatory cells, ciliary loss, vascular congestion and proliferation, swelling of the mucosa, and chondrocyte hypertrophy in the nasal mucosa were all inhibited by systemic treatment with aurantio-obtusin (magnification, x10). The nasal mucosa in the PEG-treated ovalbumin sensitized and challenged group was severely inflamed, in contrast to the normal group, which exhibited no inflammatory alterations. Black arrows indicate vascular congestion. Micron bar represents 100 μm.

allergen, demonstrates an elevation of ovalbumin-specific IgE antibodies in the bloodstream, accompanied by the migration of inflammatory cells into the nasal mucosa's epithelium and sub-epithelium. The cascade of biochemical and cellular events triggered by ovalbumin exposure promotes the differentiation of Th2 cells, proliferation of T cells stimulated by IL-4 and activation of B cells to produce IgE through IL-4 induced isotype switching. Notably, the presence of eosinophils infiltrating the mucosal tissue is a distinctive characteristic of the inflammation observed in allergic rhinitis [20]. In this study, aurantio-obtusin (AO) treatment in rats resulted in a gradual reduction in eosinophil in serum. In addition, it also decreased the levels of ovalbumin-specific IgE antibodies in the blood. Furthermore, there was significant improvement in the observed nasal symptoms such as rubbing, sneezing and rhinorrhea. These findings suggest that aurantio-obtusin administration exhibits anti-allergic effects by inhibiting inflammatory cells, particularly eosinophils. In the initial phase of the allergic rhinitis response, histamine is released from mast cells and basophils in the nasal mucosa when IgE molecules crosslink with antigens. The participation of histamine in the early-phase response to allergens has been well established in individuals with allergic rhinitis, and its role in the late-phase response has also been acknowledged [21,22]. When histamine binds to H1 receptor, it triggers sensory nerve stimulation, leading to symptoms like sneezing and itching. Additionally, it causes vasodilation and increased vascular permeability, which cause congestion and rhinorrhea. Histamine may also be involved in the generation of leukotrienes and the release of interleukins by endothelial cells, as well as the attraction, adhesion, and activation of eosinophils and other inflammatory cells. This study found that giving aurantio-obtusin to participants significantly reduced the amount of histamine in the nasal mucosa. This reduction could partially explain the alleviation of nasal symptoms observed in the aurantio-obtusin-treated groups.

IL-1, IL-6, and TNF-α, are just a few of the pro-inflammatory cytokines that mast cells are known to emit. The migration of eosinophilic leukocytes increases during the late-phase reaction in allergic rhinitis. T helper cells additionally produce cytokines such as IL-5, and IL-6 in addition to IL-4. These cytokines support the development and spread of B lymphocytes, as well as the eosinophil and mast cell hypersensitivity. IL-6 plays a significant role in stimulating cell generation, growth, survival and migration during the inflammatory response. With regards to allergic reactions, it can also prevent the differentiation of Th1 cells and encourage the growth of Th2 cells [23,24]. Findings from this study suggests that rats treated with aurantio-obtusin had expressively lower serum levels of IL-4, IL-6, and TNF-α than those in the control group, which had only been exposed to ovalbumin without any additional treatment. These findings suggest that aurantio-obtusin may influence the production of these cytokines during antigen-specific IgE production. Thus it is possible to hypothesize that aurantio-obtusin exerts an inhibitory effect on allergic inflammation by suppressing humoral responses mediated by Th2 cells. Structural abnormalities observed in allergic rhinitis are ascribed to the activity of matrix metalloproteinases (MMPs) released by epithelial cells, fibroblasts and infiltrating inflammatory cells [25]. MMPs contribute to microvascular permeability, resulting in oedema, cell migration and remodeling of the extracellular matrix at the site of inflammation. Treatment for the symptoms of allergic illnesses, including allergic rhinitis, may involve employing anti-allergic drugs to modify MMP synthesis from epithelial cells, inflammatory cells, and fibroblasts.

In this study, rats with allergic rhinitis exhibited noticeable vascular congestion, significant chondrocyte hypertrophy and inflammatory cell infiltration. However, treatment with aurantio-obtusin demonstrated a significamnt reduction in the pathological

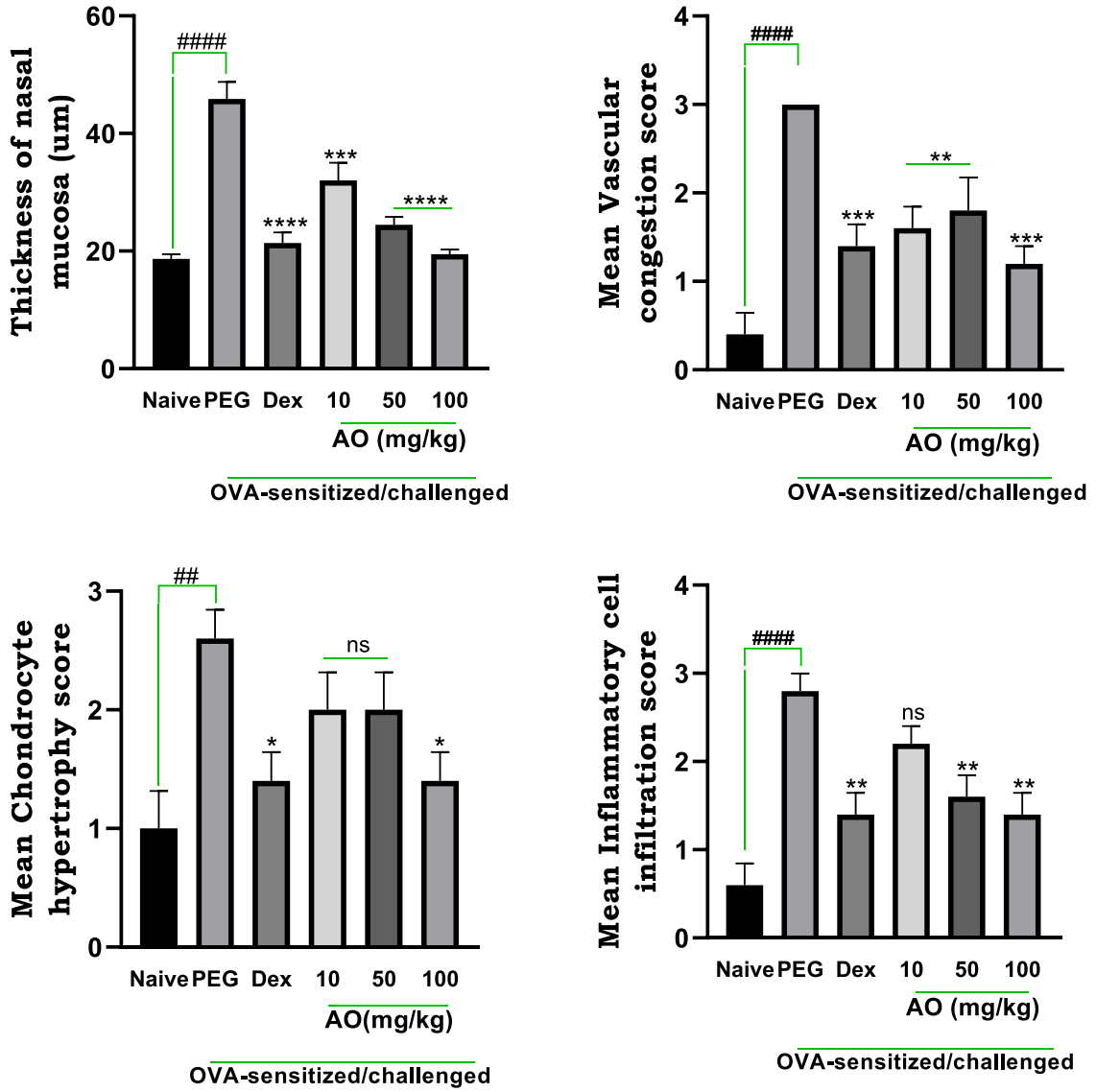

Fig. 6. Histopathological parameters scores in ovalbumin-induced allergic rhinitis in rat groups. Data are presented as the mean ± S.E.M ($n = 5$). $^{\#\#\#\#}P < 0.0001$: significantly different from sham, $^{****}P < 0.0001$, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$: significantly different from OVA-challenged rats, ns - not significant.

parameters assessed. These findings suggest that aurantio-obtusin may alleviate allergic symproms by suppressing the production of ovalbumin-specific IgE and histamine, inhibiting eosinophil infiltration and attenuating the proliferation of inflammatory cytokines.

Conclusion

The results of this study suggests that aurantio-obtusin has inhibitory effects on allergic reactions by decreasing the levels of IL-4, IL-6, TNF-α, and ovalbumin-specific IgE.

Data availability

Data is available upon request to authors.

Funding statement

The authors received no financial support for this research.

CRediT authorship contribution statement

Mavis Sersah Nyarko: Investigation, Formal analysis, Writing – original draft. **Cynthia Amaning Danquah:** Formal analysis, Supervision. **Aaron Opoku Antwi:** Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that there is no competing interest for this study.

Acknowledgment

Not applicable.

References

[1] J. Bousquet, H.J. Schünemann, A. Togias, C. Bachert, M. Erhola, P.W. Hellings, L. Klimek, O. Pfaar, D. Wallace, I. Ansotegui, Next-generation allergic rhinitis and its impact on asthma (ARIA) guidelines for allergic rhinitis based on grading of recommendations assessment, development and evaluation (GRADE) and real-world evidence, J. Allergy Clin. Immunol. 145 (1) (2020) 70–80, e73.
[2] A.N. Greiner, P.W. Hellings, G. Rotiroti, G.K. Scadding, Allergic rhinitis, Lancet North Am. Ed. 378 (9809) (2011) 2112–2122.
[3] S. Akasaki, K. Matsushita, Y. Kato, A. Fukuoka, N. Iwasaki, M. Nakahira, S. Fujieda, K. Yasuda, T. Yoshimoto, Murine allergic rhinitis and nasal T h2 activation are mediated via TSLP-and IL-33-signaling pathways, Int. Immunol. 28 (2) (2016) 65–76.
[4] B. Xiao, J.H. Wang, C.Y. Zhou, J.M. Chen, N. Zhang, N. Zhao, X.Y. Han, Y.X. Niu, Y.B. Feng, G.H. Du, Ethno-medicinal study of Artemisia ordosica Krasch. (traditional Chinese/Mongolian medicine) extracts for the treatment of allergic rhinitis and nasosinusitis, J. Ethnopharmacol. 248 (2020), 112262.
[5] C. Incorvaia, C. Cavaliere, F. Frati, S. Masieri, Allergic rhinitis, J. Biol. Regul. Homeost. Agents 32 (1 Suppl. 1) (2018) 61–66.
[6] Y.L. Zhang, H.J. Shin, J.H. Lee, J. Lee, Antiallergic effect of Hizikia fusiformis in an ovalbumin-induced allergic rhinitis mouse model, Clin. Exp. Otorhinolaryngol. 12 (2) (2019) 196.
[7] J.W. Lee, J.H. Min, M.G. Kim, S.M. Kim, O.K. Kwon, T.K. Oh, J.K. Lee, T.Y. Kim, S.W. Lee, S. Choi, Pistacia weinmannifolia root exerts a protective role in ovalbumin-induced lung inflammation in a mouse allergic asthma model, Int. J. Mol. Med. 44 (6) (2019) 2171–2180.
[8] W. Xu, M. Hu, Q. Zhang, J. Yu, W. Su, Effects of anthraquinones from Cassia occidentalis L. on ovalbumin-induced airways inflammation in a mouse model of allergic asthma, J. Ethnopharmacol. 221 (2018) 1–9.
[9] J. Bousquet, J.M. Anto, C. Bachert, I. Baiardini, S. Bosnic-Anticevich, G. Walter Canonica, E. Melén, O. Palomares, G.K. Scadding, A. Togias, Allergic rhinitis, Nat. Rev. Dis. Prim. 6 (1) (2020) 95.
[10] B.F. Asher, M.D. Seidman, W.D. Reddy, F.S. Omole, Integrative medical approaches to allergic rhinitis, Curr. Opin. Otolaryngol. Head Neck Surg. 23 (3) (2015) 221–225.
[11] K. Okubo, M. Gotoh, M. Asako, Y. Nomura, M. Togawa, A. Saito, T. Honda, Y. Ohashi, Efficacy and safety of bilastine in Japanese patients with perennial allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III study, Allergol. Int. 66 (1) (2017) 97–105.
[12] M.K. Church, D.S. Church, Pharmacology of antihistamines, Indian J. Dermatol. 58 (3) (2013) 219.
[13] M. Kapugi, K. Cunningham, Corticosteroids, Orthop. Nurs. 38 (5) (2019) 336–339.
[14] M. Kim, S.J. Lim, H.J. Lee, C.W. Nho, Cassia tora seed extract and its active compound aurantio-obtusin inhibit allergic responses in IgE-mediated mast cells and anaphylactic models, J. Agric. Food Chem. 63 (41) (2015) 9037–9046.
[15] K.H. Lee, J.H. Jang, K.W. Woo, J.H. Nho, H.K. Jung, H.W. Cho, J.H. Yong, B. An, Anti-inflammatory effects of Aurantio-obtusin isolated from cassia tora L. in RAW264. 7 cells, Korean J. Pharmacogn. 50 (1) (2019) 11–17.
[16] J. Chakir, M. Laviolette, H. Turcotte, M. Boutet, L.P. Boulet, Cytokine expression in the lower airways of nonasthmatic subjects with allergic rhinitis: influence of natural allergen exposure, J. Allergy Clin. Immunol. 106 (5) (2000) 904–910.
[17] S. Romagnani, Immunologic influences on allergy and the T_H1/T_H2 balance, J. Allergy Clin. Immunol. 113 (3) (2004) 395–400.
[18] M. Berker, L.J. Frank, A.L. Geßner, N. Grassl, A.V. Holtermann, S. Höppner, C. Kraef, M.D. Leclaire, P. Maier, D.A.C. Messerer, Allergies–AT cells perspective in the era beyond the T_H1/T_H2 paradigm, Clin. Immunol. 174 (2017) 73–83.
[19] G. Singh, P. Kaiser, M. Youssouf, S. Singh, A. Khajuria, A. Koul, S. Bani, B. Kapahi, N. Satti, K. Suri, Inhibition of early and late phase allergic reactions by Euphorbia hirta L, Phytother. Res. 20 (4) (2006) 316–321.
[20] S.H. Shin, M.K. Ye, J. Park, S.Y. Geum, Immunopathologic role of eosinophils in eosinophilic chronic rhinosinusitis, Int. J. Mol. Sci. 23 (21) (2022) 13313.
[21] R.M. Naclerio, The role of histamine in allergic rhinitis, J. Allergy Clin. Immunol. 86 (4) (1990) 628–632.
[22] B. Steelant, S.F. Seys, L. Van Gerven, M. Van Woensel, R. Farré, P. Wawrzyniak, I.K. Krohn, D.M. Bullens, K. Talavera, U. Raap, Histamine and T helper cytokine–driven epithelial barrier dysfunction in allergic rhinitis, J. Allergy Clin. Immunol. 141 (3) (2018) 951–963, e958.
[23] R. Fadaei, N. Bagheri, E. Heidarian, A. Nouri, Z. Hesari, N. Moradi, A. Ahmadi, R. Ahmadi, Serum levels of IL-32 in patients with type 2 diabetes mellitus and its relationship with TNF-α and IL-6, Cytokine 125 (2020), 154832.
[24] M. Rincon, C.G. Irvin, Role of IL-6 in asthma and other inflammatory pulmonary diseases, Int. J. Biol. Sci. 8 (9) (2012) 1281–1290, https://doi.org/10.7150/ijbs.4874.
[25] K. Samitas, A. Carter, H. Kariyawasam, G. Xanthou, Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: the one airway concept revisited, Allergy 73 (5) (2018) 993–1002.