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Boeravinone B ameliorates allergic nasal inflammation by modulating the GATA-3/T-bet signaling pathway in a mouse model of allergic rhinitis

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ABSTRACT

Objective: To evaluate the anti-allergic effect of boeravinone B against ovalbumin-induced allergic rhinitis in mice and explore its possible mechanism.

Methods: For the induction of allergic rhinitis, mice were intraperitoneally sensitized and intranasally challenged with ovalbumin, as well as orally received various concentrations of boeravinone B. Nasal mucosal inflammation, and the levels of nitric oxide, β -hexosaminidase, IFN- γ , LTC-4, myeloperoxidase, Nrf2, HO-1, GATA-3, ROR- γ , T-bet, antioxidant parameters, and allergen-specific cytokines were assessed.

Results: Boeravinone B markedly reduced ovalbumin-induced increase in the number of episodes of nasal sneezing, rubbing, and discharge, as well as the levels of IgE, IgG1, and β -hexosaminidase ($P < 0.05$). It also significantly reduced differential cell count, myeloperoxidase, oxide-nitrosative stress, and the levels of IL-1 β , IL-4, IL-5, IL-6, IL-13, IL-17, tumor necrosis factor- α , GATA-3, and ROR- γ while enhancing the level of T-bet.

Conclusions: Boeravinone B is a potential therapeutic agent for allergic rhinitis by modulating various inflammatory mediators and immune responses.

KEYWORDS: Allergic reaction; Boeravinone B; Oxidative stress; Inflammation; Ovalbumin

1. Introduction

An allergic reaction is induced by overreaction of the immune system to harmless substances such as food molecules and allergens like paints, dust, molds, pollens, and mites. This reaction triggers inflammation through immunoglobulin E (IgE), such as antibodies[1]. The allergic reactions are divided into four categories based on their mechanism of action[2,3]. Type I allergic reactions include allergic rhinitis (AR), food allergies, and hay fever, which involve a reaction called degranulation occurring in the basophils and mast cells[1,3].

AR affects the mucosal tissue of the nasal canal. The mucosal tissue of the nasal cavity is highly affected by allergic reactions. Millions of people worldwide are impacted by it, decreasing their quality of life and increasing their financial burdens even though it is not lethal[1,4]. AR affects individuals of all ages and genders but tends to occur frequently at early ages and persists throughout life. Allergens play a crucial role in the induction of AR, primarily responsible for the hypersensitivity reactions experienced by affected individuals[1]. Itching, rhinorrhea, and sneezing are among the clinical signs of AR, which are brought on by the infiltration and activation of inflammatory cells[5,6]. Eosinophils, mast cells, basophils, and other types of cells are involved in AR and play a key role in the development and progression of AR. Chemical mediators such as leukotrienes and histamine can induce allergic symptoms by stimulating the nerves and dilating the blood vessels[1,5,7].

Significance

Allergic rhinitis is associated with heightened nasal symptoms and elevated levels of inflammatory biomarkers. However, the specific molecular mechanisms underlying this condition and the potential therapeutic interventions still need to be further investigated. This study adds valuable insights into the therapeutic potential of boeravinone B in alleviating allergic rhinitis symptoms and modulating the associated inflammatory responses.

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During AR, inflammatory cells produce numerous inflammatory mediators such as serotonin, histamine, proteases, cytokines, and nucleotides. The clinical features of AR include inflammatory reactions in the nasal mucosa or airways, blood vessel enlargement, and serotonin and histamine secretion[5,6]. The nasal mucosa is a soft target for allergen exposure, inducing inflammatory reactions, and is a main feature of AR[4,7]. The pathophysiology involved in AR includes migrating and activating effector cells and secretion of cytokines, mediators, and chemokines from inflammatory cells, leading to injury in the nasal epithelium and nerve endings[5,8]. The mucosal epithelial cells release cytokines such as thymic stromal lymphopoietin, IL-25, and IL-33, after being activated by antigens[9–11]. Moreover, these cytokines further activate T-helper type 2 (Th2) cells to initiate the production of Th2-type cytokines like IL-4, IL-5, and IL-13, which actively participate in the expansion of allergic reactions[12]. Previous studies showed that the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), and nuclear transcription factor kappa B (NF- κ B) pathways are involved in the activation, differentiation, and functioning of T cells, resulting in an imbalance between Th1 and Th2 cells[5,6,12]. Additionally, treatment with inhibitors suppressed Th2 cytokine production and alleviated allergic symptoms. Moreover, improving T cell immune balance, and suppressing Th2 cytokine and histamine secretion could be considered protective therapeutic strategies for treating AR[5,6,8].

Various treatments, such as immunotherapy, leukotriene inhibitors, and steroids, are used for AR. However, these treatments may not be sufficient due to numerous side effects, including constipation, dry mouth, urinary retention, blurred vision, sedation, tachycardia, and others. Recently, antihistamine drugs such as chlorpheniramine, diphenhydramine, fexofenadine, cetirizine, and desloratadine are commonly used for AR treatment. However, they also have severe side effects such as drowsiness, cardiovascular effects, vomiting, fatigue, and headache[13,14]. Due to their high cost, long-term treatment requirements, and special storage needs, currently available treatments for AR are facing challenges. Researchers are now focusing on natural products due to their lower cost and fewer side effects, aiming to develop more protective therapeutics for the disease[8,15].

Plants and plant-based phytoconstituents can enhance both adaptive and innate immunity by targeting various mediators such as interleukins, IgE, cyclooxygenase (COX), prostaglandin E₂ (PGE₂), histamine, lipoxygenase, monocyte chemoattractant protein 1 (MCP-1), and NF- κ B[1]. Natural products have gained popularity in recent decades due to their preventive impacts against various diseases with few side effects *via* a variety of mechanisms[16,17]. A mouse model is widely used to evaluate numerous treatment options against AR[7,18]. Ovalbumin (OVA) is a protein allergen that triggers an IgE-facilitated allergic reaction after systemic administration, followed by sensitization with intranasal challenge in experimental mice[8,19,20]. OVA also induces the pathological symptoms of rhinitis, such as rubbing, nasal discharge, and sneezing, followed by increased levels of cytokines, IgE, inflammatory infiltration, and serum histamine[5,7]. The OVA-induced AR model is widely used to evaluate the anti-allergic effect of tested drugs. Therefore, the current study investigated the anti-allergic effect of boeravinone B against OVA-induced AR in mice.

2. Materials and methods

2.1. Chemical and drug

Boeravinone B (purity $\geq$ 98%), OVA (Grade V), and histamine dihydrochloride were purchased from Sigma-Aldrich (Sigma-Aldrich Company, St. Louis, MO, USA). Montelukast, OVA-specific IgE, TNF- α , IL-1 β , IL-4, IL-6, IL-13, and IFN- γ enzyme-linked immunosorbent kits were purchased from the R&D System, Minneapolis, USA.

2.2. Animals

In this investigation, BALB/c mice of both sexes (weighing 18.5 g, aged 8–10 weeks) were obtained from the animal house of our department. The mice were housed in standard conditions: a relative humidity of 60%–70%, a temperature of 22 °C, and a 12-hour light-dark cycle. Mice received standard pellet chow diet and water *ad libitum* throughout the experimental trial. The experimental study was conducted from 10:00 AM to 5:00 PM.

2.3. Experimental design

The mice were sensitized by intraperitoneal administration of OVA (100 μ g) emulsified with aluminum hydroxide [20 mg in 100 μ L of phosphate-buffered saline (PBS)] at regular intervals (1, 5, and 14 days). Subsequently, local immunization was induced by administering 1.5 mg OVA in PBS (2 μ L) into the nasal cavity once daily from day 15 to day 24[1]. The procedure mentioned above was carried out for normal mice (untreated mice) without using OVA. After AR induction by OVA administration, mice orally received boeravinone B (5, 10, and 20 mg/kg)[21,22] and montelukast (10 mg/kg) treatment, respectively. On day 28, the frequency of rubbing, discharge and sneezing was recorded for 20 min after challenge with PBS and OVA. On day 29, the mice were anesthetized using diethyl ether, and blood was collected from the retro-orbital plexus. Subsequently, the mice were sacrificed *via* cervical dislocation, and tissues were immediately removed.

On day 24, in a separate group of mice, we used histamine for induction of hypersensitivity. The number of nasal sneezing and rubbing was counted after intranasal challenge of 10 μ L histamine.

2.4. Nasal symptom assessment

The scores for nasal symptoms were assessed according to the previously published literature[18,20,21]. The number of sneezing and nasal rubbing was recorded for 15 min following the final OVA treatment in mice (days 21 to 27), and this experiment was recorded by blinded observation (28 days).

2.5. OVA specific immunoglobulins

Following the manufacturer's instructions, the ELISA kits were used to measure the OVA-specific IgE, IgG1, and IgG2a levels. Optical density was recorded at 450 nm (R&D System, Minneapolis, USA).

2.6. Nasal lavage fluid (NALF)

NALF was obtained by cannulating the upper section of the trachea in the direction of the nasal cavity following the administration of OVA (24 h), and the sample was then rinsed with saline (1 mL)[18]. Supernatants were collected to estimate biochemical parameters. The differential cell counts of lymphocytes, eosinophils, macrophages and neutrophils were analyzed from the centrifuged preparation, followed by DiQuik staining *via* counting 100 or more cells from each sample.

2.7. Determination of nitric oxide (NO), β -hexosaminidase, HO-1 and Nrf2

The levels of NO, β -hexosaminidase, HO-1 and Nrf2 were estimated *via* using the ELISA kits following the manufacturer's instructions (R&D System, Minneapolis, USA).

2.8. Determination of oxidative stress markers

Following the instructions of the test kit, the supernatant was used to assess lipid peroxidation (LPO) by measuring the level of malonaldehyde (MDA) (Bio-diagnostic, Egypt). The activities of superoxide dismutase (SOD)[22] and glutathione (GSH)[23] were estimated using the previously reported method with minor modifications.

2.9. Determination of cytokines and transcription factor expression as well as leukotriene C4 (LTC-4) and TGF- β 1

The levels of cytokines and transcription factors associated with Th1 (IFN- γ), Th2 (IL-4, IL-5, IL-13, and GATA-3), and Th17 [IL-17 and retinoic acid-related orphan receptor gamma (ROR- γ)], and T-bet, as well as TNF- α , IL-1 β , IL-6 were detected with corresponding ELISA kits in accordance with the manufacturer's instructions (R&D System, Minneapolis, USA).

Moreover, the levels of LTC-4, myeloperoxidase (MPO) and TGF- β 1 were estimated using the ELISA kits following the manufacturer's instruction (Bethyl Laboratories Inc., Montgomery, TX, USA).

2.10. Determination of CCL-11 and CCL-24

The levels of CCL-11 and CCL-24 were assessed according to the method of Wang *et al.*, with minor modifications[24].

2.11. STAT3 and p-STAT3

The levels of STAT3 and p-STAT3 were estimated using the ELISA kits (Abcam, USA) in accordance with the manufacturer's protocol.

2.12. Statistical analysis

The results were analyzed using the GraphPad Prism software (St. Louis, USA), and all the data are expressed as mean $\pm$ standard error of mean (SEM). The one way ANOVA followed by Dunnett's test was used for statistical analysis. Statistical significance was presented as $P < 0.05$.

2.13. Ethical statement

The institutional animal policies were strictly followed throughout the entire experimental process. The study was approved by Jinan Zhike Medical Science & Technology Medical Research Ethics Committee (Approval Number: B205668).

3. Results

3.1. Effect of boeravinone B on allergic symptoms

OVA-induced AR mice exhibited an increase in nasal symptoms including rubbing (Figure 1A), sneezing (Figure 1B), and discharge (Figure 1C). Boeravinone B treatment significantly ($P < 0.01$) alleviated rubbing, sneezing, and discharge in a concentration-dependent manner.

In addition, intranasal challenge with histamine caused a marked increase in nasal hypersensitivity evidenced by a rise in the number of rubbing (Figure 1D) and sneezing ($P < 0.01$) (Figure 1E). Boeravinone B treatment at all concentrations pronouncedly reduced the frequency of rubbing and sneezing ($P < 0.05$).

3.2. Effect of boeravinone B on total and differential cell count

OVA administration caused increased levels of macrophages (Figure 2A), eosinophils (Figure 2B), neutrophils (Figure 2C), and lymphocytes (Figure 2D) ($P < 0.01$). Treatment with boeravinone B (5, 10, and 20 mg/kg) significantly ($P < 0.05$) downregulated the levels of total and differential cell counts.

3.3. Effect of boeravinone B on NO and β -hexosaminidase

As shown in Figure 3, the levels of NO and β -hexosaminidase were heightened by OVA administration ($P < 0.01$). Boeravinone B treatment (5, 10, and 20 mg/kg) remarkably ($P < 0.05$) decreased NO and β -hexosaminidase levels.

3.4. Effect of boeravinone B on oxidative stress markers and LTC-4

OVA-administered mice exhibited enhanced oxidative stress, as evidenced by suppressed activities of SOD (Figure 4A) and GSH (Figure 4B), and increased MDA (Figure 4C), and LTC-4 (Figure 4D) ($P < 0.05$). In AR mice treated with boeravinone B, SOD and GSH activities were enhanced, along with decreased MDA and LTC-4 level ($P < 0.05$).

3.5. Effect of boeravinone B on immunoglobulins

OVA-induced AR mice exhibited higher levels of IgE (Figure 5A) and IgG1 (Figure 5B), and lower levels of IgG2a (Figure 5C) compared with the normal control ($P < 0.01$). In contrast, boeravinone B treatment normalized the levels of these immunoglobulins significantly ($P < 0.05$).

3.6. Effect of boeravinone B on cytokines

Figure 6 shows that the levels of TNF- α , IL-1 β , IL-4, IL-5, IL-

6, IL-13, and IL-17 were significantly increased in OVA-induced AR mice ($P<0.01$). Treatment with boeravinone B could suppress OVA-induced increased cytokines dose-dependently, with 20 mg/kg showing the superior effect ($P<0.01$).

3.7. Effect of boeravinone B on MPO

MPO level was noticeably enhanced by OVA administration, which was alleviated by boeravinone B treatment in a concentration-

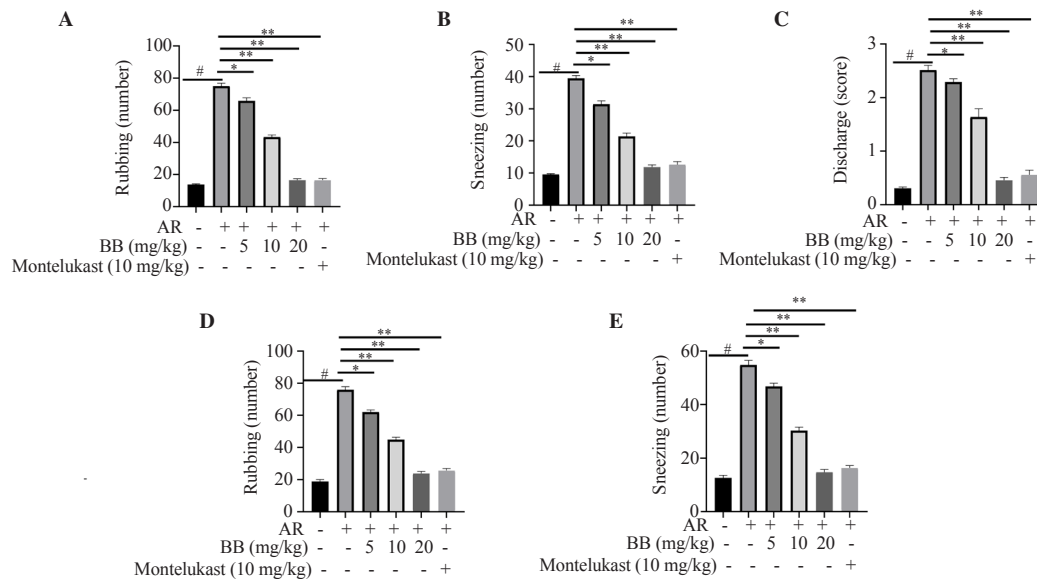


Figure 1. Effect of boeravinone B on nasal symptoms of mice with ovalbumin-induced allergic rhinitis. (A) rubbing, (B) sneezing, (C) discharge, (D) histamine-induced nasal symptoms including rubbing and (E) sneezing. The data are expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one way ANOVA followed by Dunnett's test. # $P<0.01$ compared with the normal control and * $P<0.05$ and ** $P<0.01$ compared with the ovalbumin-treated group. AR: allergic rhinitis; BB: boeravinone B.

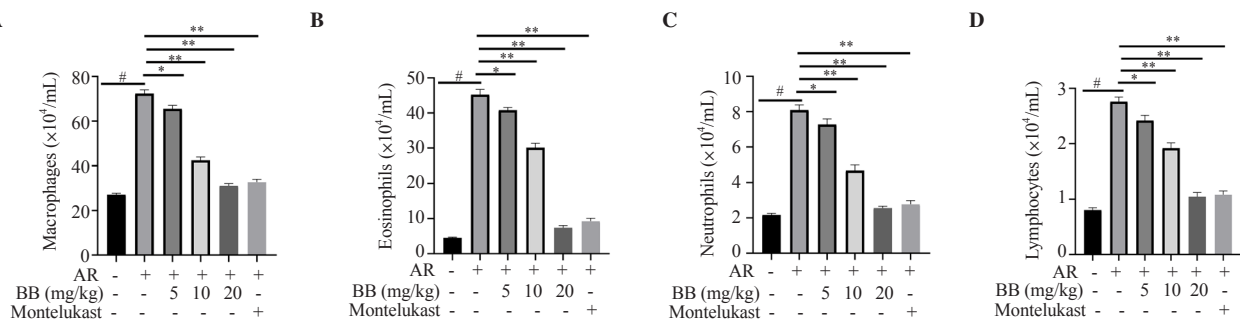


Figure 2. Effect of boeravinone B on total and differential cell count (A: macrophages, B: eosinophils, C: neutrophils and D: lymphocytes) in mice with ovalbumin-induced allergic rhinitis. The data are expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one way ANOVA followed by Dunnett's test. # $P<0.01$ compared with the normal control and * $P<0.05$ and ** $P<0.01$ compared with the ovalbumin-treated group.

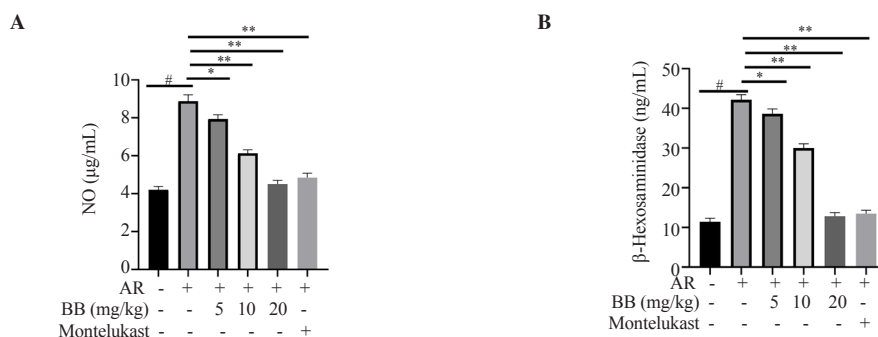


Figure 3. Effect of boeravinone B on the levels of NO and β -hexosaminidase in ovalbumin-administered mice. The data are expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one way ANOVA followed by Dunnett's test. # $P<0.01$ compared with the normal control and * $P<0.05$ and ** $P<0.01$ compared with the ovalbumin-treated group. NO: nitric oxide.

dependent manner ($P < 0.05$) (Supplementary Figure 1).

3.8. Effect of boeravinone B on Nrf2 and HO-1

Nrf2 (Supplementary Figure 2A) and HO-1 (Supplementary Figure 2B) levels were markedly suppressed in OVA-administered mice

($P < 0.05$). Boeravinone B at all concentrations significantly ($P < 0.05$) enhanced Nrf2 and HO-1 levels.

3.9. Effect of boeravinone B on GATA-3, ROR- γ and T-bet

OVA administration pronouncedly boosted the levels of GATA-3

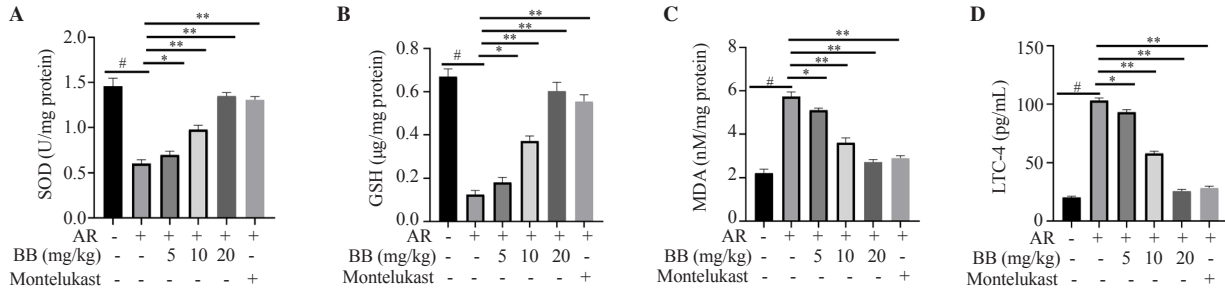


Figure 4. Effect of boeravinone B on (A) SOD, (B) GSH, (C) MDA and (D) LTC-4 levels in ovalbumin-administered mice. The data are expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one way ANOVA followed by Dunnett's test. $^{\#}P < 0.01$ compared with the normal control and $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the ovalbumin-treated group. MDA: malonaldehyde; SOD: superoxide dismutase; GSH: glutathione; LTC-4: leukotriene C4.

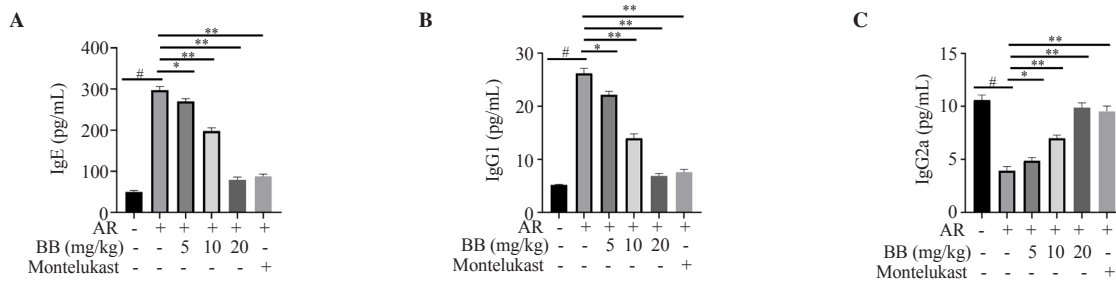


Figure 5. Effect of boeravinone B on (A) IgE, (B) IgG1 and (C) IgG2a in ovalbumin-administered mice. The data are expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one way ANOVA followed by Dunnett's test. $^{\#}P < 0.01$ compared with the normal control and $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the ovalbumin-treated group.

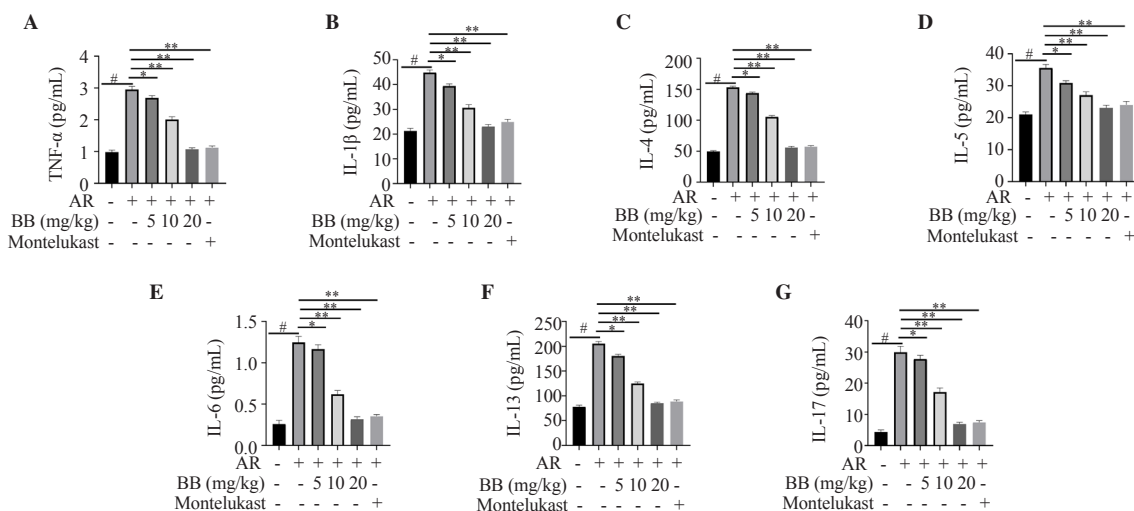


Figure 6. Effect of boeravinone B on (A) TNF- α , (B) IL-1 β , (C) IL-4, (D) IL-5, (E) IL-6, (F) IL-13 and (G) IL-17 in mice with ovalbumin-induced allergic rhinitis. The data are expressed as mean $\pm$ standard error of mean (SEM) and analyzed by one way ANOVA followed by Dunnett's test. $^{\#}P < 0.01$ compared with the normal control and $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the ovalbumin-treated group.

(Supplementary Figure 3A) and ROR- γ (Supplementary Figure 3B) while suppressing the level of T-bet ($P<0.01$) (Supplementary Figure 3C), which were all reversed by boeravinone B in a concentration-dependent manner.

3.10. Effect of boeravinone B on IFN- γ

The OVA-induced AR group showed reduced IFN- γ level. Boeravinone B treatment significantly ($P<0.05$) increased the level of IFN- γ (Supplementary Figure 4).

3.11. Effect of boeravinone B on CCL-11 and CCL-24

CCL-11 and CCL-24 are chemokines involved in immune responses and associated with allergic reactions. A remarkable rise was observed in the level of CCL-11 (Supplementary Figure 5A) and CCL-24 (Supplementary Figure 5B) in AR mice ($P<0.01$). In contrast, boeravinone B treatment at all concentrations significantly suppressed the increased level of CCL-11 and CCL-24 ($P<0.05$).

3.12. Effect of boeravinone B on TGF- β 1

OVA-induced AR mice exhibited a reduction in TGF- β 1 level (Supplementary Figure 6), while boeravinone B treatment significantly increased the level of TGF- β 1 ($P<0.05$).

3.13. Effect of boeravinone B on STAT3 and p-STAT3

STAT3 (Supplementary Figure 7A) and pSTAT3 (Supplementary Figure 7B) levels were upregulated by OVA administration in AR mice ($P<0.01$). However, all concentrations of boeravinone B significantly downregulated their levels, especially at 20 mg/kg ($P<0.05$).

4. Discussion

AR is a chronic immunological inflammatory disease affecting 20% of the global population[5]. The OVA-induced AR murine model can mimic certain types of typical allergic responses, wherein it suppresses the immunological response through alteration of Th1/Th2 cytokine levels[21]. In this investigation, we examine the anti-allergic efficacy of boeravinone B against OVA-induced AR in mice by modifying the balance of Th1/Th2 and oxidative stress responses. Boeravinone B treatment exhibited its anti-allergic potential *via* its inhibitory effects on multiple inflammatory mediators.

During allergic disease, Th2 cells play a critical role as they promote the secretion of allergen-specific IgE antibodies by B cells and increase the infiltration of mast cells and eosinophils into the target tissues[18]. The role of inflammatory cells, particularly mast cells, and eosinophils, in the inflammatory response during an allergic reaction is well documented[1,5]. Mast cells are commonly observed in the connective tissue and mucosal surfaces and their infiltration into inflamed areas is related to allergic diseases or chronic atopic

conditions[24,25]. The penetration of eosinophil is the hallmark of AR mucosal inflammation[25]. Our findings showed that the nasal mucosa structure was altered, increasing nasal symptoms, including sneezing and rubbing, mast cells and eosinophils infiltration, and the level of OVA-specific IgE in AR mice. Boeravinone B attenuated AR by inhibiting the infiltration of inflammatory cells and reducing nasal symptoms and immunoglobulin levels.

In OVA-induced AR mice, mediators such as mast cells and eosinophils are released, which participate in the secretion of cytokines, chemotactic factors, and enzymes[20]. All these mediators are involved in the AR reaction and circulating leukocytes, especially eosinophils in the inflamed tissue. IgE-mediated type-1 hypersensitivity reaction leads to the early phase of AR. OVA administration enhances the specific IgE and inflammatory cells in the circulation and ultimately induces the inflammatory reaction. By attaching to the mast cells' surface, allergens in sensitized individuals' nasal mucosa cause the fast production of stored mediators like histamine, which results in early-phase reactions like sneezing, nasal irritation, and watery nasal discharge[15].

According to recent reports, oxidative stress is a key factor in AR. The elevated level of ROS in the nasal mucosa is associated with mitochondrial dysfunction caused by oxidative damage[26]. The elevated amount of ROS in the nasal mucosa is associated with mitochondrial dysfunction caused by oxidative damage[21,27]. GSH and SOD are both natural antioxidant enzymes that are essential for preventing the generation of ROS[21]. Peroxynitrite [ONOO⁻] is produced when ROS interact with NO to further increase lipid oxidation and protein nitration[21,28]. Increased lipid oxidation, such as MDA, interferes with the mitochondrial respiratory chain and thus suppresses energy production[21]. The transactivation of genes that make detoxifying enzymes is regulated by the transcription factor Nrf2. Nrf2 maintains the equilibrium between oxidants and antioxidants. Therefore, the inhibition of Nrf2 activity contributes to the induction of AR[21]. It is widely acknowledged that Nrf2/HO-1 plays a critical role in controlling oxidative stress. The expression of Nrf2 and HO-1 is decreased during oxidative stress, and comparable results were shown in the OVA-induced AR animals. In the present study, OVA administration resulted in an increase in oxidative stress by increasing NO and MDA activity while decreasing SOD, Nrf2, HO-1, and GSH levels. Boeravinone B alleviated OVA-induced oxidative stress, as evidenced by noticeably increased levels of Nrf2, HO-1, SOD, and GSH, as well as decreased levels of MDA and NO.

It is widely known that IgE overproduction occurs during an allergic reaction, which contributes significantly to the development and onset of allergic disease. Previous reports suggest that basophils, Th2 cells, and mast cells can activate the IL-4 and IL-13 response, which further stimulates the signal transduction in B cells[29–32]. They cause the infiltration of eosinophils in the nasal mucosa due to the activation of cytokines. Walanj *et al.* showed that patients suffering from allergic reactions exhibited increased levels of mast cells, basophils, and eosinophils[33]. Mast cells and basophils are closely linked to IgE due to the high affinity of the immunoglobulin Fc epsilon receptor I (Fc ϵ RI), resulting in the degranulation of these cells and the release of cytokines[15]. In the current study,

boeravinone B dramatically lowered the level of TNF- α , IL-1 β , IL-4, IL-5, IL-6, IL-13 and IL-17 in mice.

The generation of inflammatory cytokines plays an essential role in activating innate immunity. Additionally, it has been demonstrated that allergen-specific IgG is essential for inducing the Th2-mediated allergic response[8,15]. The imbalance between the Th1 and Th2 is induced during AR, which further leads to AR development[18]. The production of cytokines is also increased by this imbalance[7,15]. IgE production in B cells is increased by IL-4, which also actively contributes to exacerbated allergic responses[15]. Th2 cytokines such as IL-4, responsible for the production of IgE, suppressed the systemic production of IL-4 and reduced the production of OVA-specific serum IgE[31]. IL-5 is a significant eosinophil maturation and differentiation factor and supports the other cytokines' initiation, activation, response, and survival. IL-13 is secreted from the mast, B, and T cells[18] and responsible for balancing the late-phase allergic inflammatory reaction. It is also related to mucous production *via* boosting the hyperplasia of goblet cells in the epithelium, secreting the mucopolysaccharide into the airway[31]. Cytokines like IL-4 and IL-13 play a crucial role in the transferring phase of IgM (IgM-generating B cells) to IgE-generating B cells.

Furthermore, previous reports suggest that patients who suffer from AR exhibited an increased level of IL-17 in the mucosa[32,33]. The research suggests that the level of IL-17 boosted during AR and exhibited increased levels of eosinophils and IgE[29]. The increased levels of IL-4, IL-5, IL-13, and IL-17 suggest the expansion of allergic reactions in mice. Th1 cytokines like IFN- γ play a crucial role in reducing Th2 immune response in the nasal mucosa *via* suppression of the production of mast cell-mediated IgE[32,33]. According to a previous investigation, NF- κ B is essential for controlling allergic inflammatory reactions. Degrading and phosphorylating I κ Ba during an inflammatory response causes NF- κ B to translocate into the nucleus form of NF- κ B p65, quickly increasing inflammatory cytokines like TNF- α and ILs[29]. Various cytokines are released from the macrophages. TNF- α is secreted from the activated phagocytes and plays a significant role in developing allergic reactions[12,34]. The findings of the current study align with those found in previous studies.

Furthermore, ILs are crucial for directly amplifying and activating NF- κ B, which exacerbates inflammatory responses. Previous reports reveal that the NF- κ B level is considerably boosted in AR patients [5,35–38]. The NF- κ B is a key target for the potential effect against the AR[29].

In conclusion, boeravinone B treatment remarkably suppressed the rubbing, sneezing, and discharge and reduced the production of macrophages, eosinophils, neutrophils, and lymphocytes. It also inhibited the production of NO, β -hexosaminidase, and LTC-4 and increased IFN- γ levels. Moreover, the levels of oxidative stress parameters, OVA-specific immunoglobulins, HO-1, Nrf2, GATA-3, ROR- γ , T-bet, and cytokines were improved by boeravinone B. These results suggest that boeravinone B attenuates allergic nasal inflammation by modulating the GATA-3/T-bet signaling pathways. However, the study has some limitations. The efficacy and safety of boeravinone B for allergic nasal inflammation still need to be verified in further studies. Its effect on other inflammation-associated

diseases should be investigated.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The study received no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

BY performed the experimental study. JZW designed the work, drafted the article, and reviewed the article. Both authors approved the final version of the published paper.

References

- [1] Wang J, Liu X, Liu Z, Ge Y, He S. Protective effect of Ellipticine in ovalbumin (OVA)-induced murine model of allergic rhinitis *via* dual inhibition of COX-2 and NF- κ B. *Isr J Plant Sci* 2021; **53**(9): 79-89.
- [2] Kamm GL, Hagmeyer KO. Allergic-type reactions to corticosteroids. *Ann Pharmacother* 1999; **33**(4): 451-460.
- [3] Polito V, Barbacki A, Isabwe G. Type I allergic reaction to rituximab upon first lifetime exposure: A case report. *Allergy Asthma Clin Immunol* 2020; **16**(1): 56.
- [4] Wei L, Ren D, Zhao G, Zhao L. Protective effect of corynoline in a murine allergic rhinitis model *via* inhibition of caspase-1/NF- κ B. *Arch Pharm (Weinheim)* 2021; **354**(2). doi: 10.1002/ardp.202000231.
- [5] Bae CH, Kim J, Nam W, Kim H, Kim J, Nam B, et al. Fermented red ginseng alleviates ovalbumin-induced inflammation in mice by suppressing interleukin-4 and immunoglobulin E expression. *J Med Food* 2021; **24**(6): 569-576.
- [6] Van Nguyen T, Piao CH, Fan YJ, Shin DU, Kim SY, Song HJ. Anti-allergic rhinitis activity of α -lipoic acid *via* balancing Th17/Treg expression and enhancing Nrf2/HO-1 pathway signaling. *Sci Rep* 2020; **10**(1): 12528. doi: 10.1038/s41598-020-69234-1.
- [7] Li K, Chen Y, Jiang R, Chen D, Wang H, Xiong W, et al. Protective effects of astragaloside IV against ovalbumin-induced allergic rhinitis are mediated by T-box protein expressed in T cells/GATA-3 and forkhead box protein 3/retinoic acid-related orphan nuclear receptor γ t. *Mol Med Rep* 2017; **16**(2): 1207-1215.
- [8] Chen S, Chen G, Shu S, Xu Y, Ma X. Metabolomics analysis of baicalin on ovalbumin-sensitized allergic rhinitis rats. *R Soc Open Sci* 2019; **6**(2).

- doi: 10.1098/rsos.181081.
- [9] Ohno T, Morita H, Arae K, Matsumoto K, Nakae S. Interleukin-33 in allergy. *Allergy Eur J Allergy Clin Immunol* 2012; **67**(10): 1203-1214.
- [10] Makrinioti H, Toussaint M, Jackson DJ, Walton RP, Johnston SL. Role of interleukin 33 in respiratory allergy and asthma. *Lancet Respir Med* 2014; **2**(3): 226-237.
- [11] Nakae S, Morita H, Ohno T, Arae K, Matsumoto K, Saito H. Role of interleukin-33 in innate-type immune cells in allergy. *Allergol Int* 2013; **62**(1): 13-20.
- [12] Shi YN, Su JZ, Wang J, Geng JQ. Myricetin alleviates ovalbumin-induced allergic rhinitis in mice by regulating Th1/Th2 balance. *Asian Pac J Trop Biomed* 2023; **13**(7): 306-314.
- [13] Bui TT, Fan Y, Piao CH, Nguyen TV, Shin D, Jung SY, et al. Piper nigrum extract improves OVA-induced nasal epithelial barrier dysfunction via activating Nrf2/HO-1 signaling. *Cell Immunol* 2020; **351**. doi: 10.1016/j.cellimm.2019.104035.
- [14] Jung HW, Jung JK, Park YK. Antiallergic effect of *Ostericum koreanum* root extract on ovalbumin-induced allergic rhinitis mouse model and mast cells. *Asian Pac J Allergy Immunol* 2011; **29**(4): 338-348.
- [15] Lee JE. *Hizikia fusiformis* ameliorates allergic inflammation in an OVA-induced allergic rhinitis mouse model. *J Allergy Clin Immunol* 2019; **143**(2). doi: 10.1016/j.jaci.2018.12.900.
- [16] Şahin A, Sakat MS, Kılıç K, Aktan B, Yildirim S, Kandemir FM, et al. The protective effect of naringenin against ovalbumin-induced allergic rhinitis in rats. *Eur Arch Otorhinolaryngol* 2021; **278**(12): 4839-4846.
- [17] Jena S, Kumar G, Singh D, Sethi A. Herbs used in dentistry: Need of the new era. *J Prim Care Dent Oral Heal* 2021; **2**(1): 11.
- [18] Kozlov V, Lavrenova G, Savlevich E, Bazarkina K. Evidence-based phytotherapy in allergic rhinitis. *Clin Phytosci* 2018; **4**(1): 12-23.
- [19] Piao CH, Fan YJ, Van Nguyen T, Song CH, Chai OH. Mangiferin alleviates ovalbumin-induced allergic rhinitis via Nrf2/HO-1/NF-κB signaling pathways. *Int J Mol Sci* 2020; **21**(10). doi: 10.3390/ijms21103415.
- [20] Liu T, Xu J, Wu Y, Li X, Ding D, Ma D, et al. Beneficial effects of baicalein on a model of allergic rhinitis. *Acta Pharm* 2020; **70**(1): 35-47.
- [21] Wang Z, Xiao S, Huang J, Liu S, Xue M, Lu F. Chemoprotective effect of boeravinone B against dmha/croton oil induced skin cancer via reduction of inflammation. *J Oleo Sci* 2021; **70**(7): 955-964.
- [22] Zhou C, Ou W, Xu Q, Lin L, Xu F, Chen R, et al. Chemoprotective effect of boeravinone B against 1,2-dimethyl hydrazine induced colorectal cancer in rats via suppression of oxidative stress and inflammatory reaction. *J Gastrointest Oncol* 2022; **13**(4): 1832-1841.
- [23] Liu Y, Wang F, Zhang D, Li Z. Anti-Inflammatory and immunomodulatory effects of hesperidin against the ovalbumin-induced allergic rhinitis in mice. *Int J Pharmacol* 2022; **18**(5): 1026-1037.
- [24] Wang J, Kandhare A, Mukherjee-Kandhare A, Bodhankar S. Chrysin ameliorates ovalbumin-induced allergic response in allergic rhinitis: Potential role of GATA-3, T-box protein expressed in T cells, nuclear factor-kappa B, and nuclear factor erythroid 2-related factor 2. *Pharmacogn Mag* 2020; **16**(70): 335-344.
- [25] Nishikimi M, Appaji Rao N, Yagi K. The occurrence of superoxide anion in the reaction of reduced phenazine methosulfate and molecular oxygen. *Biochem Biophys Res Commun* 1972; **46**(2): 849-854.
- [26] Beutler E, Duron O, Kelly BM. Improved method for the determination of blood glutathione. *J Lab Clin Med* 1963; **61**: 882-888.
- [27] Romagnani S. Cytokines and chemoattractants in allergic inflammation. *Mol Immunol* 2002; **38**(12-13): 881-885.
- [28] Possa SS, Leick EA, Prado CM, Martins MA, Tibério IFLC. Eosinophilic inflammation in allergic asthma. *Front Pharmacol* 2013; **4**. doi: 10.3389/fphar.2013.00046.
- [29] Sim CS, Lee JH, Kim SH, Han MW, Kim Y, Oh I, et al. Oxidative stress in schoolchildren with allergic rhinitis: Propensity score matching case-control study. *Ann Allergy Asthma Immunol* 2015; **115**(5): 391-395.
- [30] Fang S, Li X, Wei X, Zhang YU, Ma Z, Wei Y, et al. Beneficial effects of hydrogen gas inhalation on a murine model of allergic rhinitis. *Exp Ther Med* 2018; **16**(6): 5178-5184.
- [31] Pandhare RB, Sangameswaran B, Mohite PB, Khanage SG. Anti-hyperglycaemic and lipid lowering potential of *Adenanthera pavonina* Linn. in streptozotocin induced diabetic rats. *Orient Pharm Exp Med* 2012; **12**(3): 197-203.
- [32] Chen F, He D, Yan B. *Apigenin* attenuates allergic responses of ovalbumin-induced allergic rhinitis through modulation of Th1/Th2 responses in experimental mice. *Dose Response* 2020; **18**(1). doi: 10.1177/1559325820904799.
- [33] Walanj S, Walanj A, Mohan V, Thakurdesai PA. Efficacy and safety of the topical use of intranasal cinnamon bark extract in seasonal allergic rhinitis patients: A double-blind placebo-controlled pilot study. *J Herb Med* 2014; **4**(1): 37-47.
- [34] Zhang YL, Shin HJ, Lee JH, Lee J. Antiallergic effect of *Hizikia fusiformis* in an ovalbumin-induced allergic rhinitis mouse model. *Clin Exp Otorhinolaryngol* 2019; **12**(2): 196-205.
- [35] Carr VMM, Robinson AM, Kern RC. Tissue-specific effects of allergic rhinitis in mouse nasal epithelia. *Chem Senses* 2012; **37**(7): 655-668.
- [36] Bui TT, Piao CH, Hyeon E, Fan Y, Choi DW, Jung SY, et al. Preventive effect of *Bupleurum chinense* on nasal inflammation via suppressing T helper type 2, eosinophil and mast cell activation. *Am J Chin Med* 2019; **47**(2): 405-421.
- [37] Li J, Wang B, Luo Y, Zhang Q, Bian Y, Wang R. Resveratrol-mediated SIRT1 activation attenuates ovalbumin-induced allergic rhinitis in mice. *Mol Immunol* 2020; **122**: 156-162.
- [38] Nam SY, Kim HM, Jeong HJ. The potential protective role of taurine against experimental allergic inflammation. *Life Sci* 2017; **184**: 18-24.

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