Ind. J. Pharm. Edu. Res., 2025; 59(4):1366-1374.
https://www.ijper.org

Original Article

Anti-inflammatory and Anti-allergic Effects of Salvigenin in an Ovalbumin-Induced Allergic Rhinitis in Mice

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ABSTRACT

Background: Allergic Rhinitis (AR) is a prevalent inflammatory disorder of the nasal mucosa, often triggered by an IgE-mediated immune reaction to allergens. The underlying cause of AR can be attributed to the genetic predisposition and environmental causes that trigger an aberrant immune response. **Objectives:** The present work was performed to understand the salutary roles of salvigenin against allergen-initiated AR in mice. **Materials and Methods:** AR was initiated in BALB/c mice by intraperitoneally administering Ovalbumin (OVA) at a dose of 50 µg along with aluminum hydroxide. The salvigenin was administered at 10 and 20 mg/kg concentrations, respectively. The analyses of nasal symptoms (nasal rubbings and sneezing) were performed on the final day of OVA challenge. The histamine and allergen-specific IgE in the experimental mice were assessed using kits. Mouse airways Smooth Muscle Cells (SMCs) were extracted and sensitized with 20 µL OVA *in vitro*. Subsequently, they were treated with 10 and 20 mg/kg of salvigenin. The concentrations of pro-inflammatory cytokines were assessed in the experimental mice as well as OVA-induced SMCs using commercial assay kits. The commercial assay kits were employed for the analysis of oxidative stress biomarkers in the OVA-induced SMCs. **Results:** The treatment of salvigenin to the mice with AR was demonstrated a substantial diminution in nasal rubbings and sneezing incidences. In AR mice, salvigenin successfully diminished the levels of histone, allergen-specific IgE, eosinophils and inflammatory markers in the AR mice. The MDA and ROS were diminished, while the SOD was elevated in the OVA-challenged SMCs after the salvigenin treatment. The inflammatory cytokines were reduced in the OVA-challenged SMCs after the salvigenin treatment. **Conclusion:** The current results proved that salvigenin effectively decreased inflammatory and allergic reactions in the mice with OVA-induced AR. These outcomes highlight that salvigenin may be a talented salutary agent for treating AR.

Keywords: Allergic diseases, Histamine, Inflammation, Malondiadehyde, Salvigenin.

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Received: 19-10-2024;
Revised: 07-02-2025;
Accepted: 22-05-2025

INTRODUCTION

Allergic Rhinitis (AR), a common inflammatory disease affecting the nasal passages, has developed as a major public health issue worldwide, with a reported prevalence ranging from 10% to 30% of the global population. This chronic disorder, defined by sneezing, rhinorrhea and nasal itching, is particularly prevalent among children and adolescents.[1] The rising incidence of AR is due to the numerous causes, including environmental changes, urbanization and lifestyle modifications. Exposure to airborne allergens, like pollens, molds and dust mites triggers the body's immune response, leading to the inflammatory markers release and the subsequent development of the classic symptoms connected with AR.[2] The pathophysiology of AR involves interplay between genetic and environmental causes. Peoples with a family history of allergic conditions are at an elevated risk of AR due to inherited genetic susceptibilities.[3]

The underlying pathological mechanisms involve the mast cell activation, which release histamine and other inflammatory regulators upon exposure to allergens. This mast cell degranulation leads to the characteristic signs of itching, sneezing and nasal congestion. Additionally, the recruitment and activation of leukocytes further contribute to the inflammatory cascade, exacerbating the nasal mucosal response.[4] The inflammation associated with AR can also have significant physical and mental consequences for affected individuals, particularly in the pediatric population. Complications such as otitis media with effusion, chronic sinusitis, asthma and sleep disturbances can majorly affect the patient's life quality, academic performance and overall well-being.[5]

One widely used experimental model to study the pathogenesis and potential therapeutic interventions for AR is the Ovalbumin

DOI: 10.5530/ijper.20251122

(OVA)-induced AR model in rodents. The OVA-induced model involves sensitizing animals, typically mice or rats, to the egg protein OVA, followed by intranasal challenge with the same antigen.[6] This model recapitulates key features of human AR, including nasal congestion, rhinorrhea, sneezing and eosinophil infiltration into the nasal mucosa. BALB/c mice are commonly used, as they exhibit a robust allergic response to OVA sensitization and challenge.[7] This OVA-induced AR model has been extensively used in basic science research to elucidate the underlying pathophysiological mechanisms of the disease. In addition, the model serves as a valued tool for evaluating the efficacy of potential therapeutic interventions and other pharmacological agents that target various components of the allergic cascade.[8]

While conventional treatments like antihistamines and corticosteroids provide symptomatic relief, they may carry undesirable side effects and fail to address the underlying immune dysregulation.[9] However, recently, researchers have shifted their interests to the potential of plant-derived compounds as alternative or complementary therapies for this condition.[10] Plant-derived bioactive compounds have emerged as an alternative approach, with potential to modulate the immune response and provide a more comprehensive treatment.[11] While these alternative therapies hold promise, it is important to note that the evidence supporting their efficacy is still limited and more rigorous works are required to fully understand their effective applications. Furthermore, the underlying mechanisms by which these plant-derived compounds exert their potentials on the immune system and the nasal airways are not yet fully elucidated.[12] Salvigenin is a trimethoxylated flavone that found extensively numerous medicinal plants including Scutellariae radix and Scutellariae barbatae. It has been already reported that the salvigenin has several pharmacological properties.[13] Salvigenin showed lipid lowering effects,[14] immunomodulatory and antitumor effects,[15] anticancer,[16] and antioxidant properties.[17] Apart from these biological properties, the beneficial effects of salvigenin against AR was not studied yet. Henceforth, the present work was performed to understand the salutary roles of salvigenin against allergen-induced AR in mice.

MATERIALS AND METHODS

Chemicals

The salvigenin, aluminum hydroxide, OVA and other chemicals were acquired from Sigma-Aldrich, USA. The kits for biochemical studies were obtained from Elabscience, Abcam and Cayman Chemical Co., USA, respectively.

Experimental mice

The current study utilized BALB/c mice that were aged between 4 and 6 weeks. The experimental mice were kept in sanitary polypropylene enclosures. During the study, the mice were caged in a controlled condition with 23±5°C temperature; humidity levels between 50% and 60% and a light/dark sequence of 12 hr. Throughout the experiment, the mice were given unrestricted access to pellet diet. Prior to commencing the studies, the mice had a one-week period of acclimation to the laboratory setting.

Initiation of AR in mice and treatment protocols

After acclimation, the mice were distributed into five groups with 6 mice in each group (n=6): group I: control; group II: OVA; group III: OVA+SLGN (salvigenin) 10 mg/kg; group IV: OVA+SLGN (salvigenin) 20 mg/kg; and group V: OVA+DEX (dexamethasone) 2.5 mg/kg-treated groups. In order to induce a systemic immune response in the mice, they were administered intraperitoneally with OVA (50 µg) and Al $(OH)_3$ (1 mg) on 1, 8 and 15th days. From day 22nd to 28th a 20 µL solution of OVA (10 mg/mL) was administered into the nasal cavities of the mice from OVA, SLGN and DEX groups.

During the period of 16 to 28 days, the mice from SLGN groups were administered with 10 and 20 mg/kg of salvigenin orally, respectively. The mice from DEX group (positive control) received DEX (2.5 mg/kg). The control received a saline without being subjected to an OVA challenge. Following the last OVA exposure, the mice were euthanized and samples were obtained for further investigations. The nasal tissues were extracted and washed using a saline. The eosinophil levels were assessed in nasal tissues using a light microscope. The blood samples were utilized to generate the serum for further biochemical analyses.

Analysis of nasal rubbing and sneezing incidences

After the last OVA administration, the nasal signs of the experimental animals were examined within a 10-min timeframe following the OVA injection. The incidences of nasal rubbing and sneezing incidences were observed and recorded and the information was organized.

Nasal Lavage Fluid (NALF) preparation

Mice were exposed to pentobarbital (1%; 50 mg/kg) intramuscularly to initiate anesthesia, followed by a partial tracheotomy. A 22-gauge catheter was inserted via the nostrils starting at the tracheal entrance. The nasal apertures were irrigated with a clean saline (3 mL). NALF was collected from the front part of the nostril and then subjected to centrifugation at 220×g for 10 min. Afterward it was stored at -20°C for further studies.

Isolation of treatment of primary airway Smooth Muscle Cells (SMCs)

The mouse SMCs were cultured, which is obtained from the experimental mice using the same method described in a previous study.[18] The mouse tracheas were dissected in a cold saline solution. The epithelium was extracted, and the muscle layers

were carefully isolated from the underlying connective tissue in tiny bundles. These bundles were then immersed in a digestion solution consisting of 4 mg/mL collagenase-II and dispase for 60 min at 37ºC with a 5% CO_2. The cell suspension was centrifuged at 500 g for 15 min. Subsequently, the SMCs were cultivated in DMEM with the addition of 10% FBS and 2% antibiotic mixtures. A 10 µg/mL concentration of OVA was introduced into the wells to sensitize the cells and treated with 10 and 20 mg/kg of salvigenin for 24 hr.

Analysis of inflammatory biomarker levels

The histamine and allergen-specific IgE levels in the serum samples of treated mice were measured using the kits from Abcam (USA). An assay kits from Elabscience (USA) was used to measure the IL-4, -5, -6, -33, TNF-α and ECP levels in the NALF of the experimental mice. In order to measure the IL-4, -5, -6, -33 and TNF-α concentration in the treated SMCs, the kits were commercially procured from the Abcam, USA. The studies were conducted thrice, following the manufacturer's protocols.

Analysis of oxidative stress biomarker levels in the SMCs

The SOD activity and the MDA level in the SMCs were assessed using commercially purchased test kits, following the directions provided by the manufacturer (Elabscience, USA). In order to measure the build-up of endogenous ROS in the control and treated SMCs, the cells were treated with DCFH-DA (10 µL) dye and incubated for 30 min in darkness. Subsequently, the cells that had been stained were rinsed thrice with saline. The resulting fluorescence was then detected using a fluorescent microscope.

Statistical Analysis

The data was scrutinized using GraphPad software and the outcomes of the measurements were reported as the mean±SD of three replicates. A one-way ANOVA and Tukey's post hoc test was performed with $p<0.05$ as significant.

RESULTS

Effect of salvigenin on the sneezing and nasal rubbing incidences

Figure 1 displays the nasal symptoms like nasal rubbing and sneezing incidences of both control and experimental mice. The mice with OVA-induced AR exhibited a notable elevation in both nasal rubbing and sneezing incidences. Alternatively, following the treatment of salvigenin, mice with AR exhibited a notable reduction in both sneezing and nasal rubbing incidences. Comparable reductions in both sneezing and nasal rubbing incidences were also noted in the DEX-treated mice with AR (Figure 1).

Effect of salvigenin on the histamine and OVA-specific IgE in the experimental mice

Figure 2 illustrates the histamine and IgE contents in the serum of treated mice. The mice with AR exhibited a considerable elevation in both the histamine and IgE levels in their serum when compared with control. Whereas, the treatment of salvigenin (10 and 20 mg/kg) remarkably diminished both the histamine and IgE levels in the serum of AR mice. The DEX treatment also considerably decreased the histamine and IgE contents in the AR mice, which supported the activity of the salvigenin (Figure 2).

Effect of salvigenin on the ECP and inflammatory cytokine levels in the NALF

Figure 3 illustrates the impacts of salvigenin on the ECP and inflammatory cytokine levels in NALF of experimental mice. The NALF of mice with AR had significantly elevated amounts of ECP, IL-4, -5, -6, -33 and TNF-α when compared with control. Whereas, the salvigenin at 10 and 20 mg/kg dosages demonstrated the considerable reduction in the ECP, IL-4, -5, -6, -33 and TNF-α contents in the NALF of the AR mice. Similar outcomes were also noted when the standard drug DEX was treated to the mice with AR, resulting in a considerable reduction in ECP and inflammatory cytokine levels in the NALF. These outcomes witnessed the anti-inflammatory properties of the salvigenin (Figure 3).

Effect of salvigenin on the eosinophil counts in the nasal tissues

The eosinophils in the nasal tissues of the experimental mice were depicted in the Figure 4. The total eosinophil counts in the nasal tissues of the AR mice exhibited a considerable elevation. Interestingly, the salvigenin at the 10 and 20 mg/kg successfully reduced the total eosinophil counts in the nasal tissues of the AR mice. A comparable decrease in eosinophil counts were observed in the AR mice after treatment with standard drug DEX, thereby confirming the effectiveness of salvigenin (Figure 4).

Effect of salvigenin on the oxidative stress markers in the OVA-induced SMCs

The SOD, MDA and ROS levels were studied in the both control and treated SMCs and the outcomes are given in Figure 5. The MDA and ROS levels were substantially elevated while SOD activity was decreased in the OVA-challenged SMCs when compared with control. Whereas, the MDA and ROS levels was significantly decreased while the SOD activity was considerably elevated in the SMCs after treatment with the 10 and 20 mg/kg of the salvigenin. The results indicated that the outcomes were comparable to those of the DEX-treated group, providing evidence for the antioxidant property of the salvigenin (Figure 5).

Effect of salvigenin on the inflammatory cytokine levels in the OVA-induced SMCs

Figure 6 illustrates the influence of salvigenin treatment on the inflammatory markers in the OVA-challenged SMCs. The inflammatory cytokines, including IL-4, -5, -6, -33 and TNF-α in the OVA-induced SMCs were remarkably higher compared with control group. Meanwhile, the SMCs treated with 10 and 20 mg/kg of salvigenin successfully reduced these inflammatory cytokine levels. These anti-inflammatory properties of the salvigenin was further confirmed by the findings of standard drug DEX treatment, which also demonstrated a significant reduction in these inflammatory marker levels in the OVA-challenged SMCs (Figure 6).

DISCUSSION

AR is a prevalent inflammatory condition of the nasal mucosa, often initiated by an IgE-mediated immune response to the allergens. The underlying cause of AR can be attributed to the genetic predisposition and environmental causes that trigger an aberrant immune response.[19] The pathogenesis of AR is a complex cascade of events involving both immediate and late-phase reactions. Upon allergen exposure, the sensitized immune mechanism produces IgE antibodies, triggering the release of other chemical mediators. This immediate response is defined by signs like nasal congestion, rhinorrhea and sneezing.[20] The late-phase reaction involves the recruitment of inflammatory

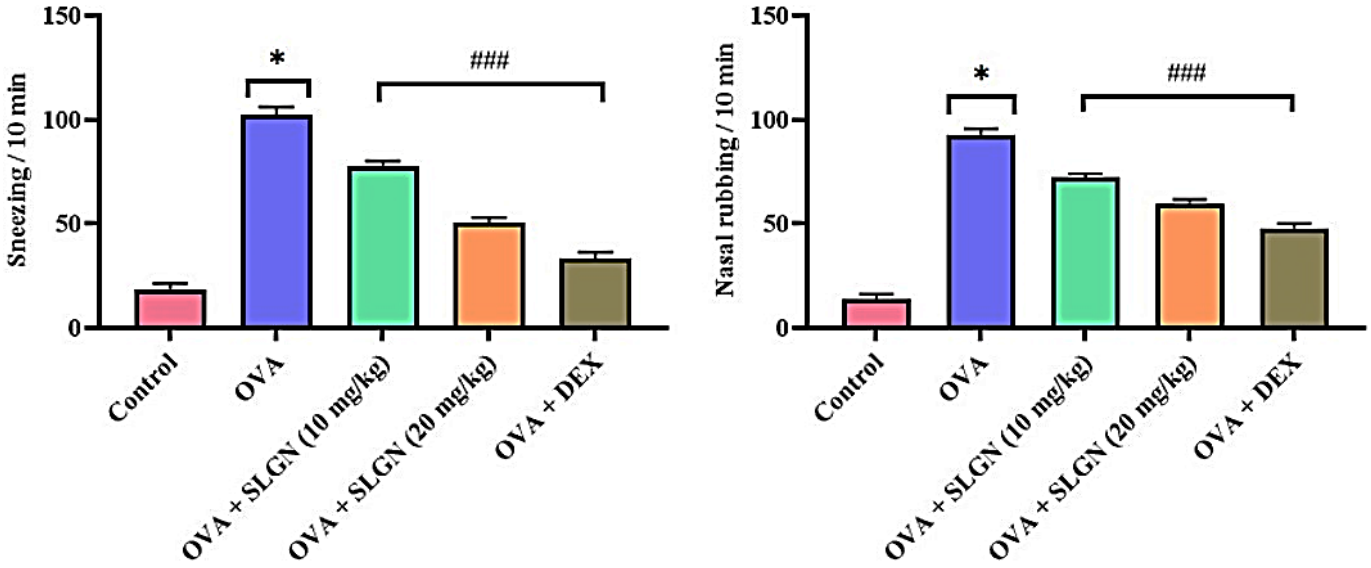

Figure 1: Effect of salvigenin on the nasal symptoms of the experimental mice. The data were portrayed as the mean±SD of three replicate experiments. An one-way ANOVA and Tukey's post hoc assay were utilized for statistical studies for the results. The marking '*' reveals that the values are significant at $p<0.01$ from the control group; '###' reveals that the values are significant at $p<0.05$ from OVA-induced AR group.

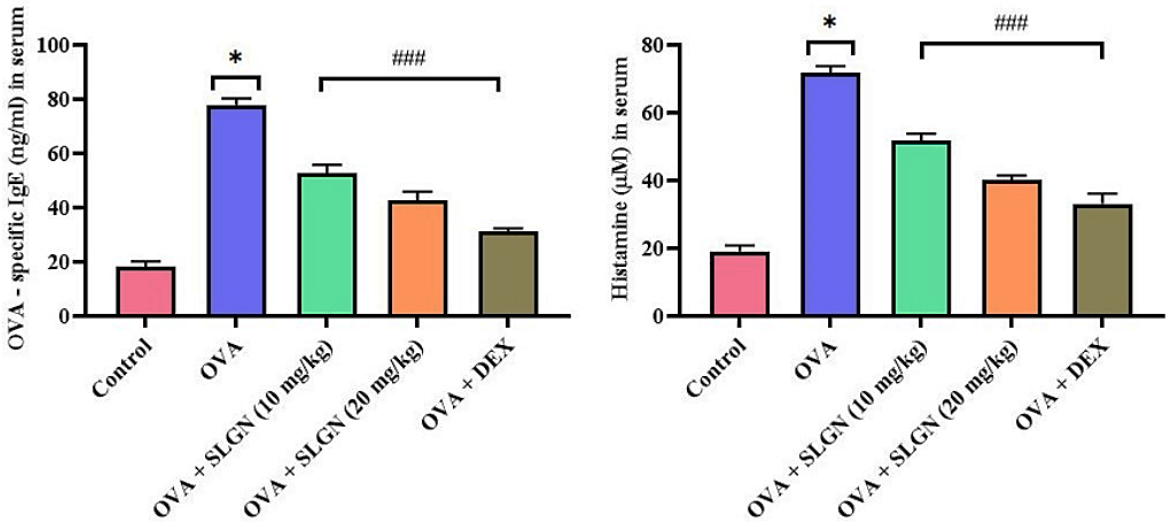

Figure 2: Effect of salvigenin on the histamine and OVA-specific IgE levels in the experimental mice. The data were portrayed as the mean±SD of three replicate experiments. An one-way ANOVA and Tukey's post hoc assay were utilized for statistical studies for the results. The marking '*' reveals that the values are significant at $p<0.01$ from the control group; '###' reveals that the values are significant at $p<0.05$ from OVA-induced AR group.

cells. This sustained inflammation can result in the progression of chronic rhinitis symptoms and potentially contribute to the progression of other allergic conditions, such as asthma.[21] In this work, we assessed the salutary potentials of the salvigenin against the OVA-induced AR in mice. Usually, the sensitization process involves intraperitoneal injections of OVA combined with an adjuvant, such as aluminium hydroxide, on multiple occasions over several weeks.[22] This urges the immunity to enhance an IgE-regulated reaction upon subsequent exposure to the allergen. Following the sensitization phase, the animals are challenged by intranasal instillation of OVA, which elicits the characteristic symptoms of AR. The severity of the allergic response can be assessed by quantifying nasal rubbing and sneezing behaviors, as well as measuring parameters such as histamine sensitivity and eosinophil infiltration in the nasal mucosa.[23] The present results demonstrated the increased incidences of the sneezing and nasal rubbing incidences, which supports the onset of AR in the mice. Whereas, the salvigenin treatment effectively decreased the nasal rubbing and sneezing incidences in the AR mice, which proves that the salvigenin decreased nasal symptoms.

The development of AR involves an interaction between numerous immune cells and inflammatory markers, including eosinophils, OVA-specific IgE and histamine. Eosinophils play a central role in the pathogenesis of AR. These cells are recruited to the nasal mucosa in response to chemo attractants such as eotaxin and IL-5, which are released during the late-phase reaction. Eosinophils release a variety of inflammatory markers, including leukotrienes, prostaglandins and cytokines, which contribute to the characteristic signs of AR, like nasal congestion, itching and rhinorrhea.[24] The occurrence of OVA-specific IgE is a hallmark of the allergic response in rhinitis. These antibodies bound to high-affinity IgE receptors of mast cells, leading to their activation and degranulation upon subsequent allergen exposure. The release of inflammatory regulators from mast cells is a key event in the development of the early-phase allergic reaction.[25] Histamine is a potent vasoactive amine that plays a central role in the AR progression. When released from mast cells and basophils, histamine binds to H1 receptors on vascular endothelial cells, leading to increased vascular permeability, vasodilation and the characteristic symptoms of AR.[26] Eosinophils contribute to the late-phase response, while OVA-specific IgE and histamine are key mediators of the early-phase response.[27] The present study evidenced the significant increment in the eosinophils, IgE and histamine contents in the AR mice. Fascinatingly, the salvigenin treatment successfully diminished the eosinophils, IgE and histamine contents in the mice with AR, which highlights its importance in mitigating the immune response in AR.

The intricate pathophysiology of the AR has been demonstrated to be regulated by the inflammation and inflammatory cytokines.[28] IL-33 is a crucial player in the advancement of allergic diseases, including AR. This cytokine is released by various immune cells during tissue damage or inflammatory conditions, enhancing the allergic severity. The increased levels of IL-33 in allergy and its positive correlation with severity of the disease, suggest that IL-33

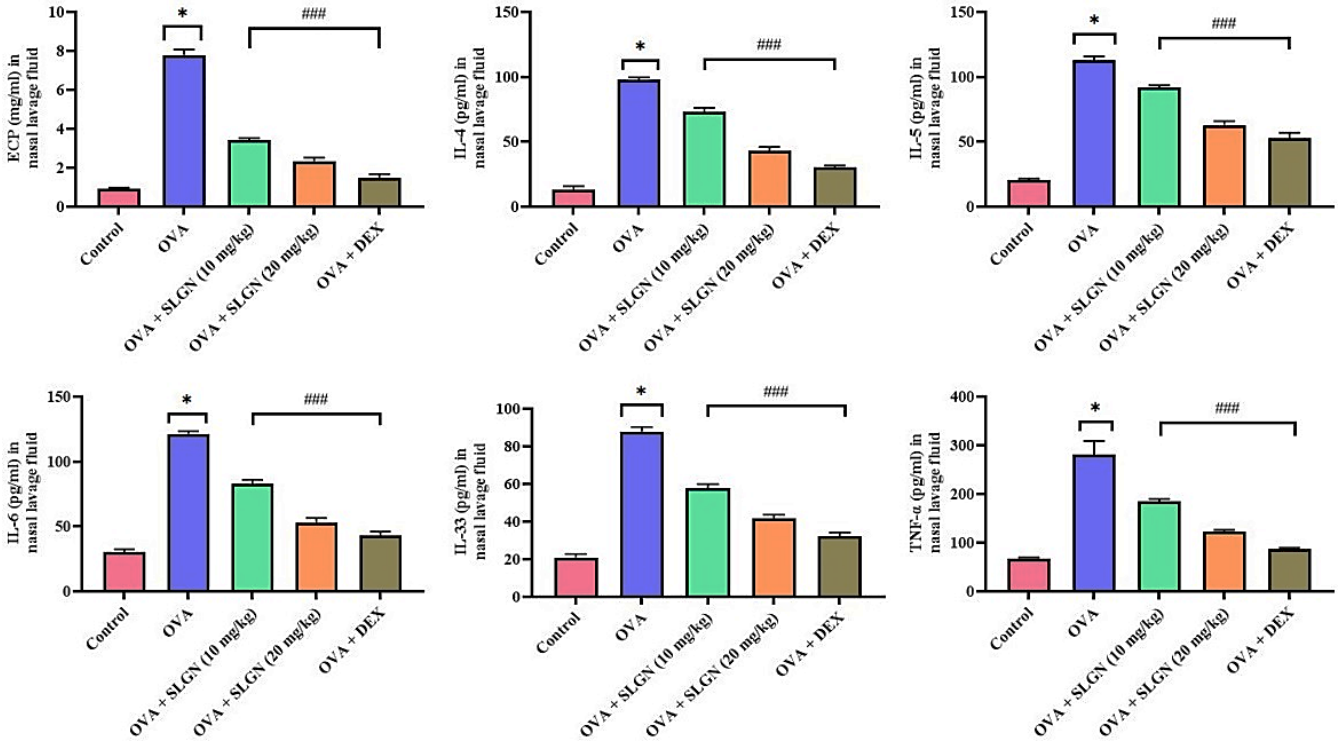

Figure 3: Effect of salvigenin on the ECP and inflammatory cytokine levels in the NALF of experimental mice. The data were portrayed as the mean±SD of three replicate experiments. An one-way ANOVA and Tukey's post hoc assay were utilized for statistical studies for the results. The marking '*' reveals that the values are significant at $p<0.01$ from the control group; '###' reveals that the values are significant at $p<0.05$ from OVA-induced AR group.

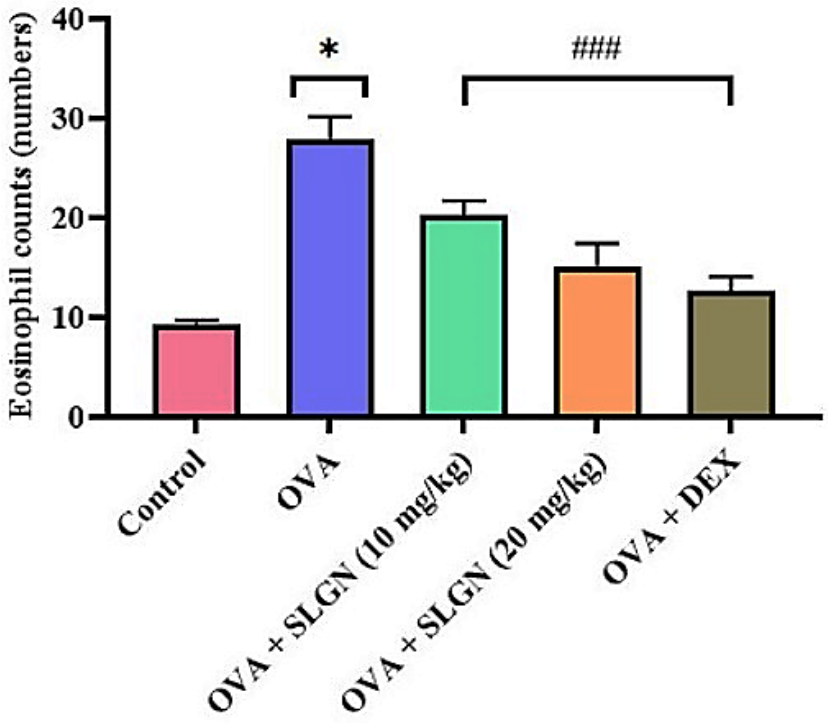

Figure 4: Effect of salvigenin on the eosinophil counts in the nasal tissues of the experimental mice. The data were portrayed as the mean±SD of three replicate experiments. An one-way ANOVA and Tukey's post hoc assay were utilized for statistical studies for the results. The marking '*' reveals that the values are significant at $p<0.01$ from the control group; '###' reveals that the values are significant at $p<0.05$ from OVA-induced AR group.

could be a promising target in addressing these hypersensitive conditions.[29] In addition to IL-33, other inflammatory cytokines like IL-4, -5, -6 and TNF-α also participate significantly to the pathophysiology of AR. These cytokines play essential roles in the differentiation of T helper cells, the promotion of inflammatory responses and the disruption of the epithelial barrier function.[30] The overproduction of Th2-dominant cytokines, including IL-4 and IL-5, results in the activation of eosinophils, mast cells and other effector cells, which in turn drive the characteristic signs of AR, like nasal congestion, rhinorrhea and itching.[31] Moreover, the dysregulation of the epithelial barrier function, facilitated by the actions of these inflammatory cytokines, further exacerbates the condition by allowing increased exposure to allergens and triggering a vicious cycle of inflammation.[32] To address the complex pathophysiology of AR, a multifaceted approach targeting the various inflammatory mediators and their signaling pathways may be necessary. By understanding the pivotal role of inflammation and inflammatory cytokines in the disease process, researchers and clinicians can develop more effective therapeutic strategies to alleviate the burden of this prevalent allergic disorder. The present study evidenced the significant elevation in the levels of IL-4, -5, -6, -33 and TNF-α in the NALF of the mice with AR and OVA-challenged SMCs. Interestingly, the salvigenin treatment potentially reduced these inflammatory cytokines in the NALF of the mice with AR and OVA-challenged SMCs. These outcomes are supported the anti-inflammatory properties of the salvigenin.

The relationship between oxidative stress and AR is complex and multifaceted. Exposure to environmental pollutants, such as particulate matter, can induce oxidative stress and participate in the aggravation of AR.[33] Furthermore, the inflammatory reaction connected with AR can exacerbate oxidative stress, creating a self-perpetuating cycle of inflammation and oxidative damage.[34] It has been already highlighted the role of oxidative stress in the AR progression. Oxidative stress, resulting from a disproportion between the ROS generation and the antioxidant mechanisms, has been participated in numerous inflammatory and respiratory conditions.[35] These reactive substances can induce cell injury, lipid peroxidation and inflammation, all of which may participate in the progression of AR.[36] MDA is a byproduct of lipid peroxidation and commonly used as a biomarker of oxidative stress and has been found to be augmented in individuals with AR.[37] In addition to ROS, the body's antioxidant mechanisms also plays a central role in controlling oxidative stress. SOD, an important antioxidant enzyme, has been shown to be diminished in patients with AR, indicating an impairment of the body's ability to neutralize ROS.[38] Targeting oxidative stress and its associated markers, such as ROS, MDA and SOD, may represent a promising therapeutic avenue for the management of AR.[39] By addressing the underlying oxidative imbalance, interventions that modulate redox mechanisms may help to alleviate the symptoms

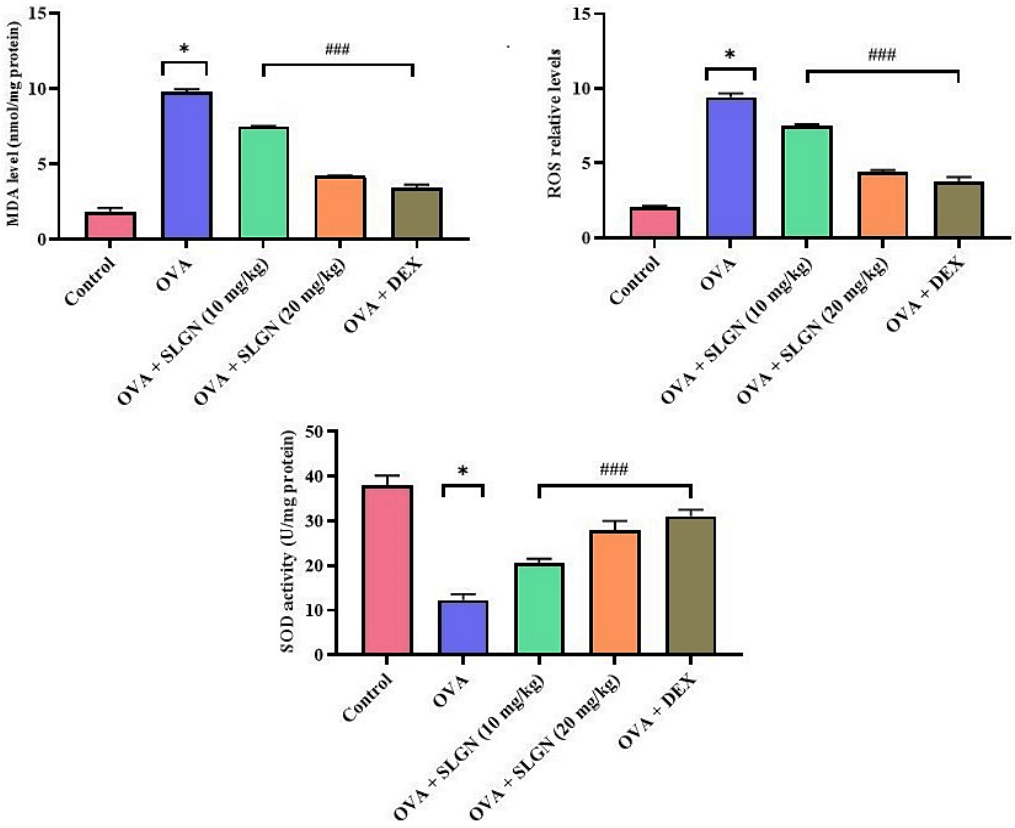

Figure 5: Effect of salvigenin on the oxidative stress markers in the OVA-induced SMCs. The data were portrayed as the mean±SD of three replicate experiments. An one-way ANOVA and Tukey's post hoc assay were utilized for statistical studies for the results. The marking '*' reveals that the values are significant at $p<0.01$ from the control group; '###' reveals that the values are significant at $p<0.05$ from OVA-induced AR group.

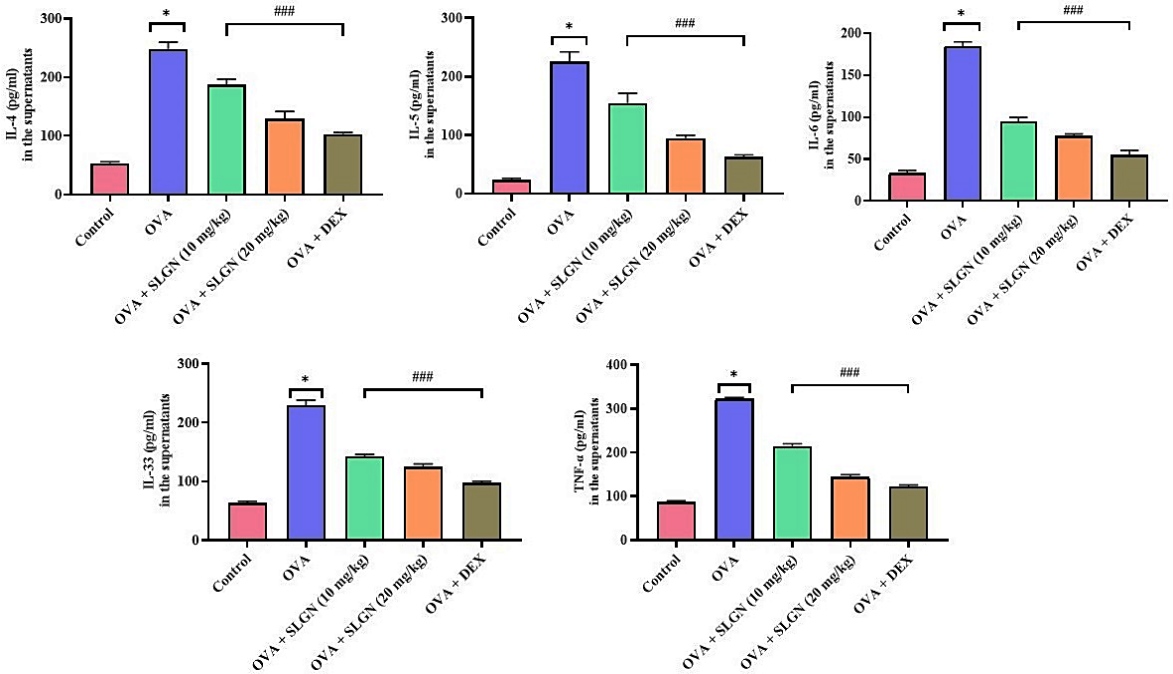

Figure 6: Effect of salvigenin on the inflammatory cytokine levels in the OVA-induced SMCs. The data were portrayed as the mean±SD of three replicate experiments. An one-way ANOVA and Tukey's post hoc assay were utilized for statistical studies for the results. The marking '*' reveals that the values are significant at $p<0.01$ from the control group; '###' reveals that the values are significant at $p<0.05$ from OVA-induced AR group.

and potentially slow the progression of the disease. Similarly, the present findings are revealed that the salvigenin treatment successfully diminished the MDA and ROS status while boosted the SOD in the OVA-induced SMCs. These outcomes indicate that salvigenin has the potential antioxidant properties in AR condition.

CONCLUSION

In conclusion, the present findings highlighted that salvigenin effectively decreased inflammatory and allergic reactions in the mice with AR. The treatment of salvigenin exhibited a remarkable diminution in nasal symptoms, allergen-specific IgE, histamine, eosinophils and inflammatory cytokine levels. Furthermore, the salvigenin treatment also reduced the inflammatory and oxidative stress biomarker levels in the OVA-specific SMCs. These outcomes highlight that salvigenin may be a talented salutary agent for treating AR. Furthermore, additional research is required to comprehensively recognize the mechanisms by which salvigenin demonstrates its therapeutic properties against AR.

ETHICAL STATEMENTS

The study was approved by the Ethics Committee of Xian Medical College (NO. XYYFY2022LSKY-026).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AR: Allergic rhinitis; **OVA:** Ovalbumin; **SMCs:** Smooth muscle cells; **MDA:** Malondiadehyde; **SOD:** Superoxide dismutase; **SLGN:** Salvigenin; **DEX:** Dexamethasone; **NALF:** Nasal lavage fluid.

SUMMARY

The present work was performed to understand the salutary roles of salvigenin against allergen-initiated Allergic Rhinitis (AR) in mice. AR was initiated in BALB/c mice by intraperitoneally administering Ovalbumin (OVA) at a dose of 50 µg along with aluminum hydroxide. The salvigenin was administered at 10 and 20 mg/kg concentrations, respectively. The analyses of nasal symptoms (nasal rubbings and sneezing) were performed on the final day of OVA challenge. The histamine and allergen-specific IgE in the experimental mice were assessed using kits. Mouse airway Smooth Muscle Cells (SMCs) were extracted and sensitized with 20 µL OVA *in vitro*. Subsequently, they were treated with 10 and 20 mg/kg of salvigenin. In AR mice, salvigenin successfully diminished the levels of histone, allergen-specific IgE, eosinophils and inflammatory markers in the AR mice. The MDA and ROS were diminished, while the SOD was elevated in the OVA-challenged SMCs after the salvigenin treatment. The inflammatory cytokines were reduced in the OVA-challenged SMCs after the salvigenin treatment. These outcomes indicate that salvigenin has the potential antioxidant properties in AR condition.

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Cite this article: Gong N, Chang H, He M, Zhang X, Li W. Anti-inflammatory and Anti-allergic Effects of Salvigenin in an Ovalbumin-Induced Allergic Rhinitis in Mice. Indian J of Pharmaceutical Education and Research. 2025;59(4):1366-74.