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Research Article
Anti-Inflammatory and Immunomodulatory Effects of Hesperidin against the Ovalbumin-Induced Allergic Rhinitis in Mice

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Abstract

Background and Objective: Allergic Rhinitis (AR), is a nasal mucosal inflammation that arises due to overreacts by the immune system to inhaled allergens and is a common and serious public health problem and affected a large number of the world population. The current experimental study scrutinizes the antiallergic effect of hesperidin against the Ovalbumin (OVA) induced Allergic Rhinitis (AR) in mice via anti-inflammatory and antioxidant parameters. **Materials and Methods:** Wistar mice were divided into six groups, non-sensitized, ovalbumin sensitized, sensitized treated with hesperidin (5, 10 and 20 mg kg^{-1}) and montelukast (10 mg kg^{-1}) for 21 days. On the day of 21, intranasal OVA was induced and end of the experimental protocol spleen weight, biochemical, physiological, Interleukin 4 (IL-4), Interleukin 6 (IL-6), Interleukin 10 (IL-10), Immunoglobulin-E (IgE), Interferon-gamma (IFN-γ), IFN-γ/IL-4 ratio, total protein, phospholipase A_2 (PLA_2) were estimated. However, the mRNA expression of GATA-3, T-bet, FOXP-3 and (ROR)-γt were also estimated. **Result:** Hesperidin significantly ($p<0.001$) showed the protection against sneezing, nose redness and nasal rubbing followed nasal challenge. Hesperidin considerably ($p<0.001$) down-regulated the histamine, nitric oxide production, IL-4, IL-6, IL-10, IgE, TP and PLA_2 as compared to the OVA-induced RA. Hesperidin considerably reduces the ratio of IFN-γ/IL-4 as compared to the OVA-induced RA. Hesperidin considerably down-regulated the mRNA expression of ROR-γt, GATA-3 and up-regulation of FOXP-3 and T-bet expression at concentration-dependent manner. **Conclusion:** Based on the result, we can conclude that hesperidin may ameliorate the OVA-induced AR condition via alteration of expression of ROR-γt, GATA-3, FOXP-3 and T-bet, which commit T helper cells to TH1 phenotype.

Key words: Hesperidin, allergic rhinitis, inflammation, GATA-3, FOXP-3, ROR-γt, antihistamines, leukotriene

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Allergic Rhinitis (AR) is an immune reaction exerted or stimulated by IgE antibody in which T-cell type 2 (TH2) expansion[1] triggers symptoms of normal allergy, comprises of sneezing, scratching, nasal inflammation, runny nose and red, watery and puffy eyes and Quality of Life (QOL) get worse[2]. Allergic Rhinitis (AR) is the overriding type and widespread chronic ailment which affects roughly 40% of the world populace[1,3]. Therefore, the cumulative social burden and the medical costs linked with allergic rhinitis is the main concern of area worldwide. Additionally, health care practitioners stated the various complications connected with AR progression, including anxiety, depression, memory loss, hyperactivity, less attention, bad performance in school, headache and reduction in sleeping process[4,5], primarily in infants and adolescent people. Further, it is also recorded in the literature that obstruction in the respiratory tract in various kids who suffers from AR may lead to producing abnormalities in craniofacial and orthodontic disorder because of chronic mouth breathers[6,7]. Recently, oral antihistamines are the main therapeutic agent for AR along with allergen[7]. Marketed available antihistamines medicines are diphenhydramine, chlorpheniramine, cetirizine, desloratadine, fexofenadine but have some side effects i.e. headache, fatigue, vomiting, diarrhoea, drowsiness and CVS effects also[6,8]. Additionally, there are other therapies for AR, i.e. intranasal corticosteroids, leukotriene receptor antagonists and immunotherapy for allergens, but such medications are expensive or have some undesirable side effects[6,9]. As a result, more affordable, safe medications with few side effects need to be discovered for treating AR.

Hesperidin (Fig. 1) is a flavonoid natural based product that is present in vegetables and fruits in large quantities[10]. The common name of hesperidin is 3′,5,7-trihydroxy-4'-methoxyflavanone-7-6-O-α-Lrhamnosyl-D-glucose. It is an economic byproduct that is processed from citrus fruits and the most effective bioflavonoids present in sweet orange and lemon[11,12]. It is a rich source of vitamin P and long dietary history in the world. This bioactive compound is prosperous in the skin of fruit and major compound included in the herbal medicine of China and used as a therapeutic agent for a long time[10,12,13]. In some countries such as Europe and Australia, it is utilized in the treatment of cardiovascular ailment whereas in the USA, widely used as a dietary supplement[14]. It possesses several activities such as antioxidant, anti-inflammatory[15], antiallergic, antidiabetic, etc[15,16].

Hesperidin already showed the antioxidant and anti-inflammatory effect and due to its potential effect against various inflammatory and oxidative stress diseases, this study aimed to explore the anti-inflammatory and immunomodulatory effects of hesperidin against the ovalbumin-induced allergic rhinitis in mice.

MATERIALS AND METHODS

Study area: The study was carried out in Shandong University, China From June-September, 2020.

Chemical

Drugs and chemicals: Hesperidin (purity 98%), Aluminum hydroxide, histamine dihydrochloride and ova-albumin (OVA, grade V) were purchased from Sigma Aldrich Co. (Sigma Aldrich Co, St Louis, Missouri). OVA-specific IgE, total IgG, total IgE, IL-1β, IL-4, TNF-α IL-5, IL-6, IL-13, IL-17, leukotriene C_4 and IFN-g Enzyme-Linked Immunosorbent Assay (ELISA) kits were purchased from the BD Biosciences, San Jose, CA, USA. All the chemicals and reagents used in the experimental study were analytical grade.

Animals: Total 108 Swiss BALB/c adults (gender-male, 20-25 g) were used in the current protocol. The mice were received from the animal house and quarantine for 7 days in the standard experimental condition such as temperature 20±5°C relative humidity 70% and 12/12 hrs dark and light cycle). All the experiments were performed between 9:00 AM and 4:00 PM. During the whole experimental study, the mice have received the standard food chew and water *ad libitum*. All the experimental study was carried out according to the University guidelines, which is in line with ethical principles, animal welfare, animal protection and is in line with relevant regulations of national experimental animal experimental ethics. During the experimental protocol, the experimental rodents were brought to the experimental laboratory before the 1 hr for adaptation purposes.

Induction of allergic rhinitis: For the induction of AR, the BALB/c mice have received the intraperitoneal injection of OVA (50 mg dissolved in 1000 mg of aluminium hydroxide soluble in saline (500 mL) on a regular time interval (1-13 days)[17]. On the 14 days, the mice were randomly divided into 6 groups and each group contains 18 mice) and received the treatment for the next 7 days (14–21 Days) as presented in Table 1.

The dose selection of hesperidin (5, 10 and 20 mg kg^{-1}) and montelukast (10 mg kg^{-1}) was done based on previous literature. The tested and standard drugs were given orally from day 14-21. At end of the experimental protocol (day 21),

Table 1: List of group and treatment

Groups	Treatments
Normal control	Received saline only
OVA control	OVA induced AR
Treated group	AR+hesperidin (5 mg kg^{-1})
Treated group	AR+hesperidin (10 mg kg^{-1})
Treated group	AR+hesperidin (20 mg kg^{-1})
Treated group	AR+montelukast (10 mg kg^{-1})

Table 2: List of primers

	Sequence (5-3)	
Primers	Forwarded	Reverse
GATA-3	ACAGAAGGCAGGGAGTGTGT	GGTAGAGTCCGCAGGCATT
ROR-γt	TGCGACTGGAGGACCTTCTA	TCACCTCCTCCCGTGAAAAG
T-bet	TACAACAGCCAGCCAAACAG	CACCCTTCAAACCCTTCCTC
FOXP-3	GCCCATCCAATAAACTGTGG	GTATCCGCTTTCTCCTGCTG
GAPDH	ACCCAGAAGACTGTGGACTT	TTCTAGACGGCAGGTCAGGT

1 hr after the last treatment, all group mice were intranasally administered 5% OVA (5 mL per nostril) and observed the mice.

Nasal symptoms: On the last day of the experiment (day 21), the nasal symptoms were scrutinized after the OVA administration (10 min later)[18]. The number of nasal rubbing (nasal itching motions) and sneezes were recorded. The nasal symptoms were estimated based on the scoring system such as no discharge-score 0, discharge reaches the anterior nasal aperture-score 1, discharge exceeds from the anterior nasal aperture-score 2 and discharge start to flow out-score 3.

Blood samples: At the end of the experimental study (on day 21), after the OVA administration (2 hrs), the blood sample of all group mice was collected via puncturing the retro-orbital plexus. The collected blood samples were centrifuged at 10000 g for 15 min at 4°C to get the clear plasma. The samples were stored at -20°C for further biochemical analysis[19].

Biochemical parameter estimation: OVA-specific total IgE, total IgG_1, b-hexosaminidase and IgE were estimated in the serum, while the cytokines IL-4, LTC-4 (leukotriene C_4), IL-5, IFN-γ, IL-13 and IL-17 were estimated using the mouse ELISA kit (Bethyl Laboratories Inc) via the following manufacture protocol.

Histamine level: For the estimation of histamine levels in the serum, the o-phthalaldehyde spectrofluorometric method was used. Briefly, the fluorescent intensity was estimated at 460 nm via using a spectrofluorometer and calculated the histamine content[17].

Real-time PCR: RT-PCR technique was used for the estimation of mRNA expression of T-bet, GATA-3, ROR-γt, FOXP-3 and signal transducer and activator of transcription-6 (STAT6) in the spleen were estimated in the spleen tissue via following the manufacture instruction. GAPDH mRNA was used for standardized the mRNAs intensity (Table 2).

Statistical analysis: All the results were presented as Means±Standard error of means and analysis were performed using GraphPad Prism (5.0 Software, GraphPad, San Diego, California, USA). The statistical analysis was made between the AR group and drug tested group. One way analysis of variance (ANOVA) followed via Dunnett's multiple tests. The score of sneezing, discharge and nasal rubbing were analyzed via nonparametric Kruskal-Wallis ANOVA followed via Mann Whitney's multiple comparison tests. $p<0.05$ consider being significant.

RESULT

Impact of hesperidin on body weight and spleen weight: The data in Fig. 1 showed the body weight and spleen weight of experimental mice. AR group mice showed decreased body weight as compared to normal control group mice. AR group mice treated with the hesperidin significantly ($p<0.001$) enhanced the bodyweight at dose-dependent manner (Fig. 1a). An opposite trend was observed in the spleen weight. AR control mice showed the increased spleen weight in AR group mice and hesperidin significantly ($p<0.001$) decreased the spleen weight (Fig. 1b).

Impact of hesperidin on nasal symptoms in mice: A general characteristic of AR is itching in the nasal, sneezing, chronic inflammation and nasal rhinorrhea. So our aim of the study is to find the impact of hesperidins (HP) on AR symptoms on nasal. In contrast to normal control mice, there was a significant elevation in the frequency of nasal rubbing, sneezing and discharge in the OVA-induced AR mice. Treatment with hesperidin at different dose levels significantly reduced the symptoms of nasal which was induced by OVA as compared to OVA-induced AR mice (Fig. 2). AR rats exhibited increased sneezing (Fig. 2a), nasal rubbing (Fig. 2b) and nasal discharge (Fig. 2c) as compared to other groups of mice. Conversely, administration of montelukast (10 mg kg^{-1}) also declined the OVA-induced nasal symptoms when compared to the hesperidin group. The consequences displayed the therapeutic role of hesperidin in OVA-induced AR.

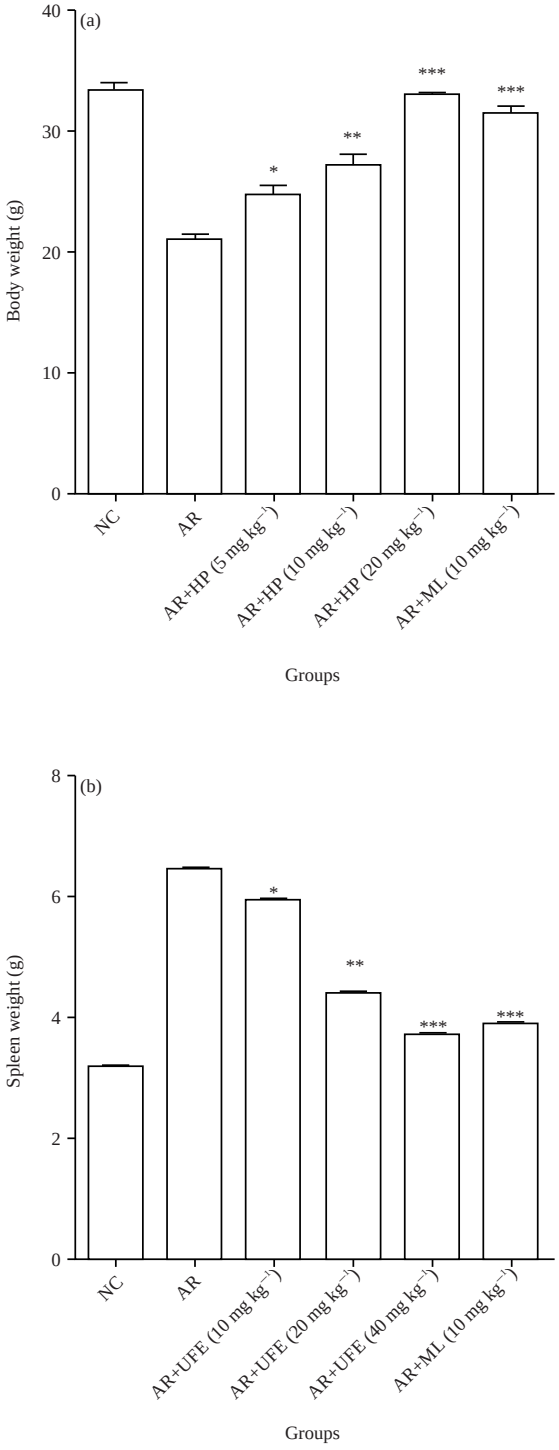

Fig. 1(a-b): Effect of hesperidin on the bodyweight of OVA-induced AR in the mice, (a) Body weight and (b) Spleen weight

Data for body weight and spleen weight were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

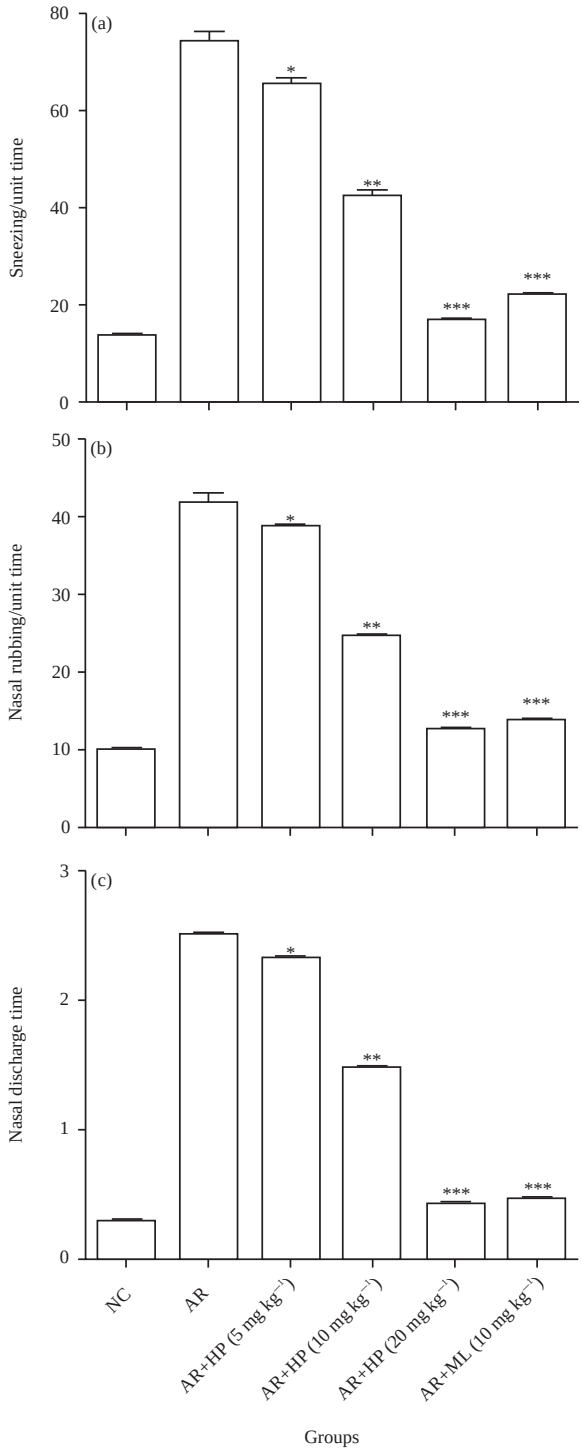

Fig. 2(a-c): Effect of hesperidin on the nasal parameters of OVA-induced AR in the mice, (a) Sneezing, (b) Nasal rubbing and (c) Nasal discharge

OVA and histamine treatment were analyzed by nonparametric Kruskal-Wallis test ANOVA followed by Mann-Whitney's multiple comparison tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

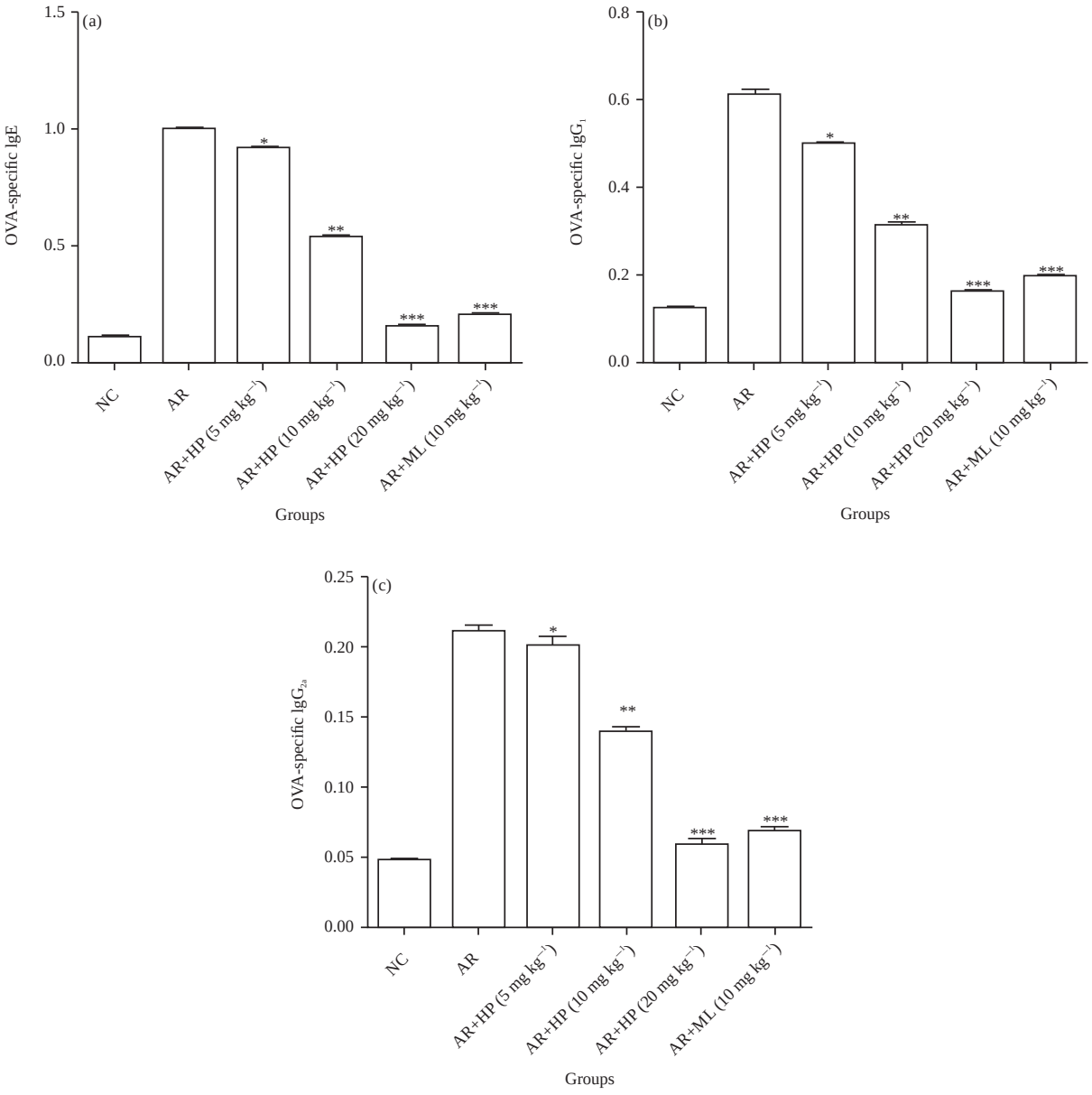

Fig. 3(a-c): Effect of hesperidin on the OVA-specific parameters of OVA-induced AR in the mice, (a) OVA-specific IgE, (b) OVA-specific IgG_1 and (c) OVA-specific IgG_{2a}

Data were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

Impact of hesperidin on levels of OVA-specific IgE, IgG_1 and IgG_{2a} in serum of mice: ELISA is used to determine inflammatory response (IgE, IgG_1 and IgG_{2a}) in the serum of OVA-induced AR. As illustrated in Fig. 3, OVA-specific immunoglobulins (IgE and IgG_1) were found to be higher in the serum of OVA-induced AR animals whereas IgG_{2a} levels were remarkably reduced as compared with normal control animals. Administration of hesperidin reduced the OVA-specific IgE and IgG_1 production in serum, on the other hand, lower dose level significantly enhanced the OVA-specific IgE (Fig. 3a), OVA-specific IgG_1 (Fig. 3b) and OVA-specific IgG_{2a} (Fig. 3c) as compared to the OVA-induced AR animals. An almost similar result was obtained when treated the montelukast (10 mg kg^{-1}). So the HP ameliorated the symptoms of AR via repressing the OVA-specific IgE and IgG_1 production and elevation in the OVA-specific IgG_{2a} immunoglobulin.

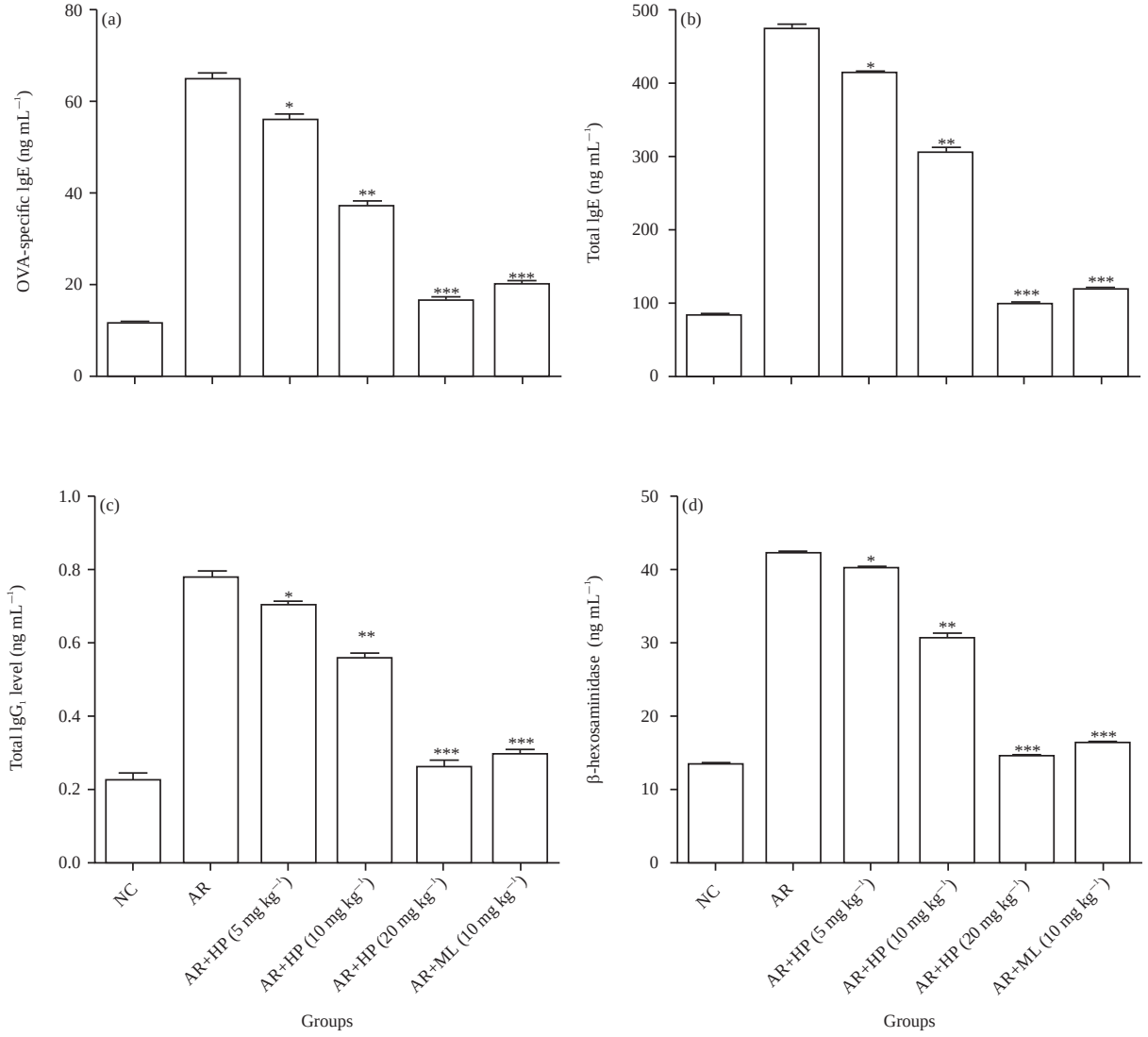

Fig. 4(a-d): The effect of hesperidin on the OVA-specific parameters of OVA-induced AR in the mice, (a) OVA-specific IgE, (b) Total IgE, (c) Total IgG_1 and (d) β-Hexosaminidase

Data were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

Impact of hesperidin on histamine, IgE, IgG_1 and β-hexosaminidase levels in serum of mice: OVA-induced AR group shows enhancement in the OVA-specific IgE (Fig. 4a), total IgG (Fig. 4b), total IgG_1 (Fig. 4c) and β-hexosaminidase (Fig. 4d) levels in contrast to the normal control mice. Treatment with HP at different dose levels significantly increased the levels of serum histamine, IgE, IgG_1 and β-hexosaminidase when compared to OVA-induced AR mice. A therapeutic dose of montelukast (10 mg kg^{-1}) markedly alleviates the level of serum histamine, IgE, IgG_1 and β-hexosaminidase as compared to the treatment with HP (Fig. 4).

Impact of hesperidin on IL-4, IL-5, IL-13, IL-17, IFN-γ and LTC-4 levels: We observed a significant elevation in the IL-4, IL-5, IL-13, IL-17 and LTC-4 of NLF and a significant reduction in the IFN-γ level of OVA-induced AR mice in contrast to the normal control mice. Dose dependently administration of HP significantly hampered the IL-4, IL-5, IL-13 and IFN-γ level but was unable to downregulate the levels of LTC-4 in the NLF as compared to the OVA-induced AR groups. Montelukast (10 mg kg^{-1}) administration considerably ameliorated the OVA-induced variation in the NLF IL-4 (Fig. 5a), IL-5 (Fig. 5b), IL-13 (Fig. 5c), IL-17 (Fig. 5d), IFN-γ (Fig. 5e) and IFN-γ (Fig. 5f) levels as compared to HP treated group.

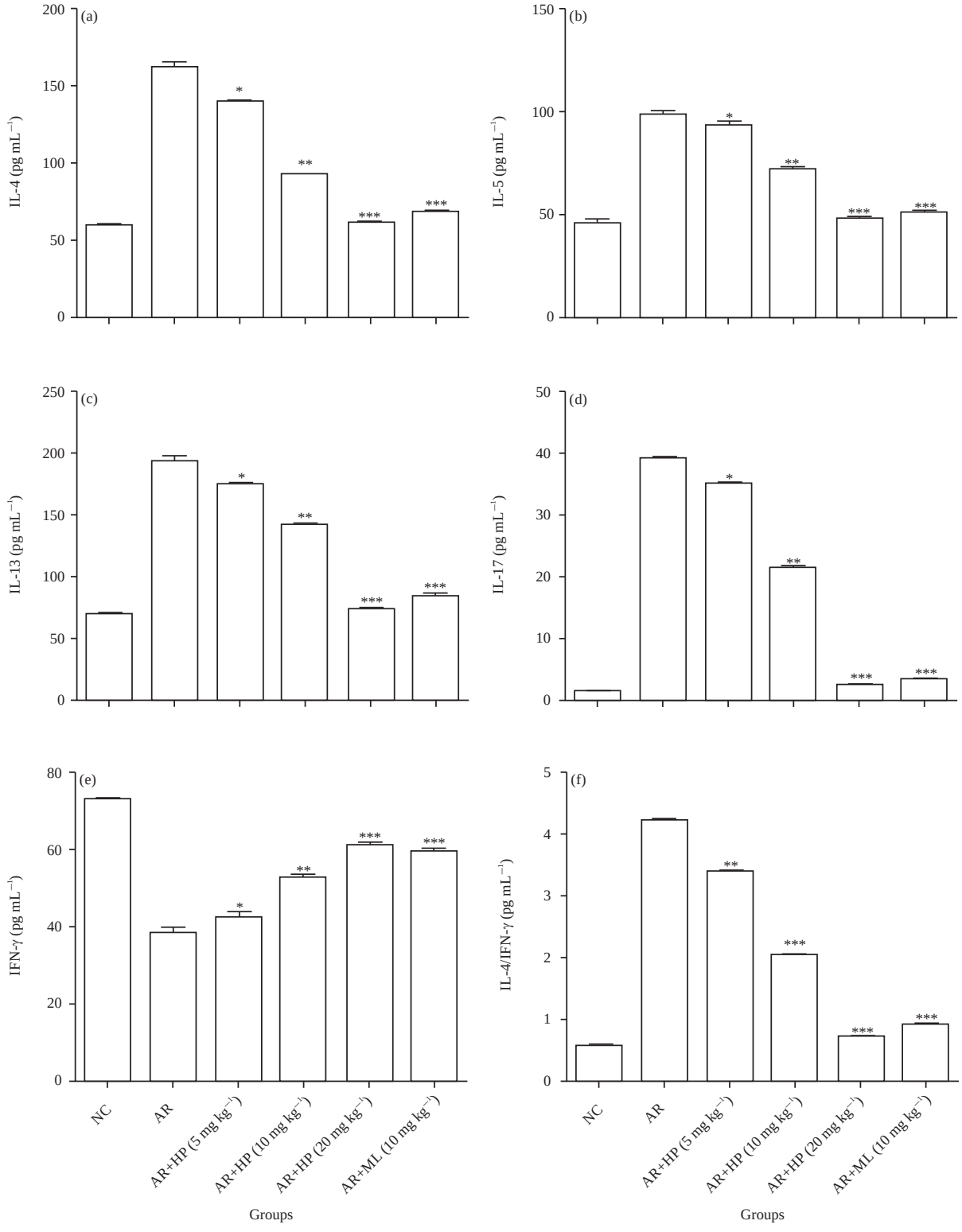

Fig. 5(a-f): Effect of hesperidin on the cytokines of OVA-induced AR in the mice, (a) IL-4, (b) IL-5, (c) IL-13, (d) IL-17, (e) INF-γ and (f) IL-4/INF-γ ratio

Data were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

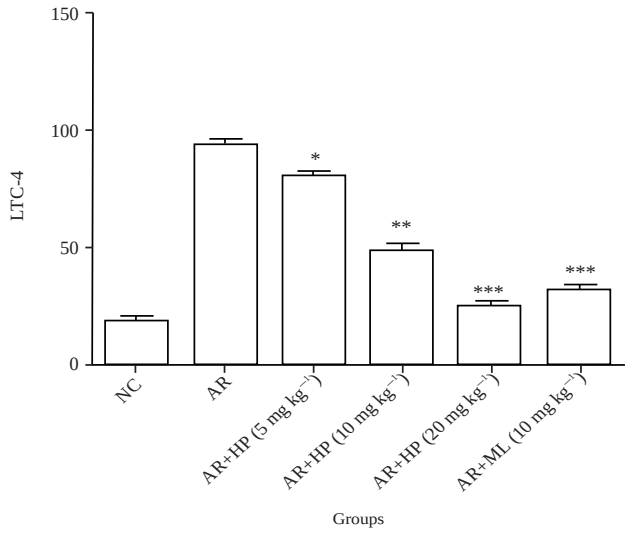

Fig. 6: Effect of hesperidin on the LTC-4 level of OVA-induced AR in the mice

Data were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

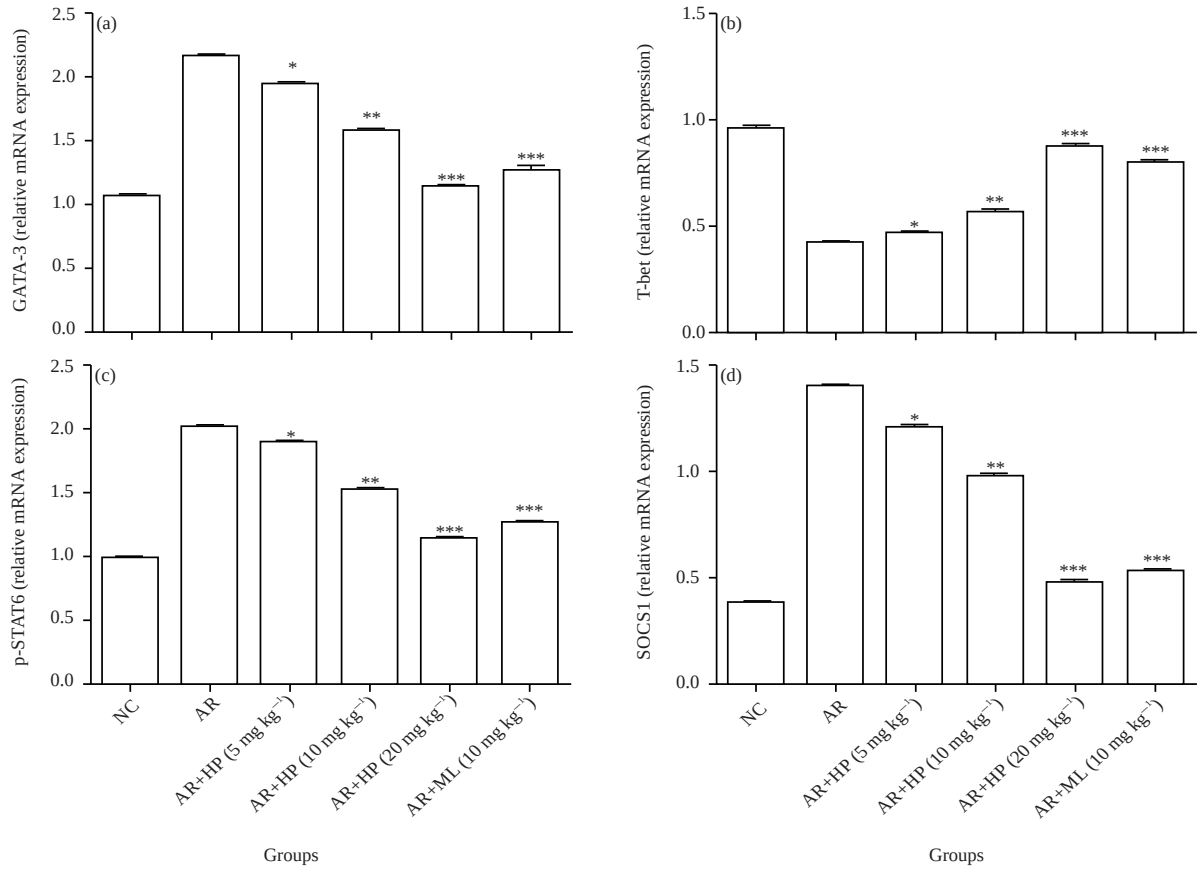

Fig. 7(a-d): Effect of hesperidin on the mRNA expression of OVA-induced AR in the mice, (a) GATA-3, (b) T-bet, (c) p-STAT6 and (d) SOCS-1

Data were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01, ***p<0.001 compared with the AR group mice

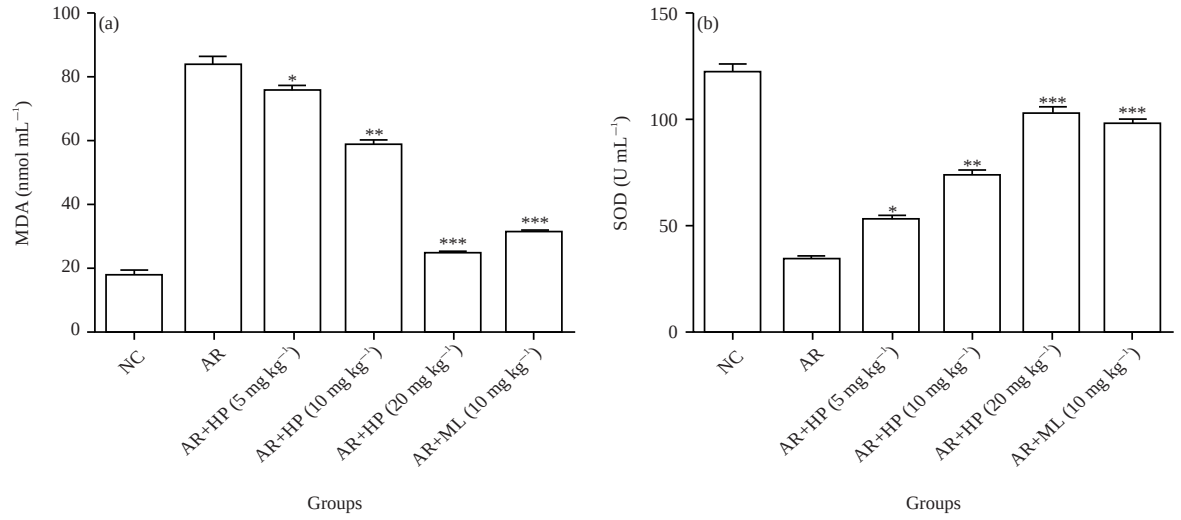

Fig. 8(a-b): Effect of hesperidin on the antioxidant parameters of OVA-induced AR in the mice, (a) MDA and (b) SOD

Data were analyzed by one-way ANOVA followed by Dunnett's multiple tests. Statistically, significant differences are indicated via asterisks and estimated via ANOVA. *p<0.05, **p<0.01 and ***p<0.001 compared with the AR group mice

Figure 6 showed the LTC-4 level of all group rats. AR treated group rats showed the enhancement of LTC-4 level and hesperidin treatment significantly ($p<0.001$) suppressed the level.

Impact of hesperidin on GATA-3, T-bet, STAT6 and SOCS-1 mRNA expressions of spleen of mice: OVA-induced AR group mice revealed the significant elevation of the mRNA expressions of GATA-3 (Fig. 7a), T-bet (Fig. 7b), p-STAT6 (Fig. 7c) and SOCS-1 (Fig. 7d) of spleen and significant reduction of the T-bet mRNA expression in contrast to the normal control group. Pharmacological doses of HP remarkably alleviates the OVA persuaded variation in mRNA expressions of GATA-3, STAT6, T-bet and SOCS-1 of spleen when compared to the AR negative mice. Treatment with HP resulted from a more significant reduction in the GATA mRNA expression in the spleen in comparison with the montelukast (10 mg kg^{-1}) treated group.

Impact of hesperidin on lipid peroxidation and antioxidant enzyme activity: To measure the underlying mechanism of antioxidant property of HP on OVA-induced AR, the estimation of MDA Level in NALF is necessary and identified via ELISA technique. Figures illustrated the LPO basal level via the formation of MDA (an indicator) which was significantly upregulated in the OVA-induced AR group as compared to the normal group. However, AR groups when treated with HP showed downregulation in the MDA concentration i.e. in the basal level of LPO in a dose-dependent manner. So the data point toward the strong association between HP and MDA concentration (Fig. 8a).

Treatment with HP significantly unregulated the SOD activity, an antioxidant enzyme and declined the oxidative stress when compared with OVA-induced AR groups. Administration of montelukast more significantly increased the SOD activity in comparison to the HP treatment and compared with OVA-induced AR groups. Outcomes confirmed the attenuation of the oxidative stress in mice which was induced by OVA via enhancement in the level of SOD (Fig. 8b).

DISCUSSION

Hesperidin is a bioactive component, a byproduct of citrus and accountable for anti-inflammatory and anti-oxidative properties[10,11]. The current study provides data about the impact of hesperidin on allergic rhinitis induced by OVA in mice. Our findings showed that treatment with hesperidin may stop the development and release of allergic cytokines i.e IL 4 and IL 10 and OVA-specific IgE in serum in NALF triggered by *in vivo* OVA induction. Furthermore, hesperidin also reduced the activation of OVA-induced goblet cells which was PAS-positive and nasal mucosal epithelial cells thickness. In addition, the treatment with hesperidin also considerably amended the rubbing and sneezing symptoms in mice who suffered from AR. The eosinophils infiltration numbers and the thickness of the nasal mucosa were remarkably less in the hesperidin treated group as compared to the OVA treated group. This study explains that treatment with hesperidin

amended the immune response after exposure to allergens in the AR model via declining the eosinophils infiltration. It indicates that the therapeutic drug used in the present study shows promising candidates to alleviate allergic rhinitis caused by OVA.

After the exposure to allergens and within the time the initiation of the allergic inflammatory response takes place[17,20]. This is mainly because of the liberation of mediators via mast cells which involves cytokines, enzymes and chemotactic factors[21]. These mediators involve in the production of the untimely AR symptoms and activate the generation and linkage of leukocytes that are circulating in the system, particularly eosinophils and their infiltration in the subsequent tissue[22]. In experimental models of animals, the sensitization and confront by OVA escort to elevation in the plasma OVA-specific IgE and epithelium inflammatory cells infiltration and lastly nasal mucosa subepithelial cells[23].

OVA-specific IgE and IgG_1 were appreciably elevated in our research with OVA sensitization, further decrease after treatment with hesperidin and montelukast. This may differ from earlier research that recorded administration of intranasal steroid or therapeutic agents, which reduced blood levels of OVA-specific IgE[24]. Amusingly, the levels of IL-4 in serum in the hesperidin treated groups were reduced as compared with the AR group as described above in the result.

The latest research suggested that serum-specific IgE may play a role in inducing allergic inflammation but may not serve an essential role in an AR rat model[25]. Local-specific IgE may therefore be better than serum-specific IgE in describing local nasal mucosa allergic inflammation[25]. Auxiliary work is required to elucidate the difference in the role of specific IgE and Th2 cytokines between the local and serum levels.

LPO is a well-recognized method to know about the damage of the cell. It generates various byproducts including aldehydes, MDA, lipid peroxides which cause lipid membrane destruction[26,27]. The last materials of the lipid peroxidation are Malondialdehyde (MDA) and are resultant of the breakdown of polyunsaturated fatty acids and related esters. Damage to the oxidative process is estimated via the exact and customary index of MDA[28,29]. A high level of LPO suggests the amassing of oxidative destruction via the process of inflammation. In the current study, the findings show the considerably hampering of oxidative stress induced by OVA by HP, as proven via reduced MDA and elevated levels of SOD. Such findings indicate that hesperidin defends with inflammatory and oxidative responses against AR caused by OVA. Nrf2 is a transcription factor involved in gene encoding transactivation which detoxifies enzymes[30]. The signalling pathways Nrf2/HO^{-1} are considered to play a vital role in regulating oxidative stress[31]. In the meantime, the antioxidant activity of HP was verified through increased expression of Nrf2 and HO^{-1} and was consistent with previously reported findings in a model of hepatotoxic[32,33].

Different research has reported that ILs are associated with the transcription of a variety of signalling pathways transcription is interrelated with the interleukins in sensitized airway ailment.9,13 IL-4 and IL-13 serve an important role throughout the process of transferring IgM-generating B cells to IgE-generating B cells[34]. IL-4 along with the chemoattractant plays an important role in mast cell growth factor[17]. Interleukin-13 serves in the control of pathogenesis of all airborne diseases by the immediate hypersensitivity augmentation[35]. IL-5 is concerned with late-phase allergic reactions and is accountable for eosinophilia infiltration in the respiratory tract[36,37].In addition, it is clinically predicted that AR patients are connected with the high range of IL-17 in the mucosa of the nasal[38]. Literature cited about the IL-17 deficient AR mice reveals the remarkably decline in symptoms of the nose, IgE serum levels and eosinophils levels when compared to mice having wild-type AR[38]. Therefore, IL-4, IL-5, IL-13 and IL-17 increased expression indicates the production of the allergic response in models of murine. Whereas, IFN-π, a Th1 cytokine act in the Th2 immune response inhibition of nasal mucosa through hindering the production of mast cell-mediated IgE[39,40]. As a result, increases in the IL-4 to IFN-γ ratio conclude the making of IgE following exposure to allergens. In the current study, allergic reactions caused by IgE were scrutinized by evaluating alterations in NLF expressions of these ILs[41]. The outcome of the study shows that hesperidin stimulates Th1 type response through IFN-π activation and restrain Th2 type response through IL-4, IL-5, IL-13 and IL-17 inhibition[42]. These results specified that in allergic responses illustrating its anti-allergic ability, hesperidin repressed production of mast cell-mediated IgE through controlling of the ratio of the IL-4 / IFN-ÿ[17]. An earlier study identified that hesperidin, a flavonoid extensively repressed IL-4 and IL-13 expression of both and as a result, a promising natural inhibitor of IgE and the outcome of this exploration are consistent with previous investigator findings.

CONCLUSION

In conclusion, the findings of this study demonstrated the anti-inflammatory and Immunomodulatory properties of hesperidin by reducing cytokines production in a rat model of AR. In this present research, we include *in vivo* evidence for the production of a successful and new natural therapeutic

agent for the management of AR. Conversely, further research works are needed to explicate its mechanism of action in detail.

SIGNIFICANCE STATEMENT

The study discovers the possible effect of hesperidin against the OVX induced AR. This study will help the researcher to uncover the critical area of allergic rhinitis. This, a new therapy on the hesperidin may have arrived.

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