Is resveratrol therapeutic when used to treat allergic rhinitis in rats?

Abstract

Purpose: Resveratrol has anti-infective, anti-inflammatory and antioxidant activities. The purpose of this study was to determine the effect of resveratrol in a rat experimental model of allergic rhinitis (AR).

Methods: Wistar albino rats were divided into three groups: control (n=7), AR with no treatment (AR+NoTr, n=7) and AR with resveratrol treatment (AR+Res, n=7). For AR+Res, AR was induced and resveratrol given on days 21-28. On day 28, the total blood IgE levels were measured. Allergic symptoms (sneezing, nose-rubbing, eye lacrimation and nasal congestion) were scored on a 0-3 point scale, and histopathological changes in the nasal mucosa were evaluated.

Results: Allergic symptom score of AR+NoTr was higher than the other two groups and the score of AR+Res was higher than the control group. Histopathologically, neither ciliary loss nor chondrocyte hypertrophy differed among the three groups; however, vascular congestion, inflammatory and plasma cell numbers, eosinophil and mast cell infiltration and goblet cell numbers were higher and mast cell infiltration was more prominent in AR+NoTr than in AR+Res and control. AR+Res and control did not differ significantly in any histological parameter.

In AR+NoTr, nasal mucosa exhibited ciliary loss, squamous epithelial metaplasia, inflammatory cell infiltration, vascular congestion of the lamina propria and goblet cell epithelial metaplasia. In AR+Res, goblet cell metaplasia was focal or absent and infiltration of the lamina propria by inflammatory cells, eosinophils, and plasma cells was reduced relative to AR+NoTr.

Conclusion: Allergic symptoms and tissue reactions were reduced by resveratrol treatment in rats with experimentally-induced AR.
Allergic rhinitis (AR) is an IgE-mediated inflammatory disease of the nasal mucosal membrane. It is characterized principally by early symptoms including sneezing, nasal rubbing, rhinorrea and lacrimation, and late symptoms of nasal congestion/obstruction and (less frequently) coughing [1].

The generation of inflammatory mediators, including chemotactic cytokines such as C5a and eotaxin, in response to tissue injury or inflammation triggers leukocyte chemotaxis and migration [2]. The release of such proinflammatory mediators induces rapid and severe changes in the adhesive properties of endothelial cells lining the walls of vessels of the surrounding vasculature, increasing adhesion of leukocytes to the endothelium. Recruitment of blood eosinophils by tissues is an important coordinated step in the inflammatory response [3].

Pharmacotherapy for rhinitis seeks to modify autonomic processes of the nasal mucosa to relieve symptoms, including congestion and secretions. Stimulation of $\alpha$-adrenergic receptors triggers vasoconstriction, decreasing blood flow and relieving nasal congestion, and antagonism of muscarinic receptors may reduce watery secretions [4].

Resveratrol (3,4,5-trihydroxy-trans-stilbene), a nonflavonoid polyphenolic antioxidant, is an extensively-investigated phytochemical with antioxidant, anticancer and anti-inflammatory properties [5–7]. Resveratrol belongs to the stilbene class of aromatic phytochemicals and exists in both cis and trans forms. The phytochemical is predominantly found in peanuts (Arachis hypogaea) [8] and grapes (Vitis vinifera) [9].

Resveratrol possesses anti-infective and anti-inflammatory activities [10]. The anti-inflammatory effects involve inhibition of the transcription factor NF-kB, principally the Ik-B kinase [11]. Moreover, resveratrol inhibits viral replication in general [12, 13], and rhinovirus (RV) in particular (the etiological agent of the common cold) in nasal epithelial cells. It also inhibits RV-dependent expression of ICAM-1 (the principal RV receptor) [14]. Resveratrol exhibited anti-inflammatory and antiasthmatic effects in a mouse model of allergic asthma, reducing IL-4 and IL-5 levels in both plasma and bronchoalveolar lavage fluid and suppressing bronchial hyper-reactivity, lung eosinophilia and mucus hypersecretion [15]. Piceatannol, a hydroxylated metabolite of trans-resveratrol, has anticancer properties similar to those of the unmetabolized molecule [16]. It may be possible to deliver trans-resveratrol nasally, as with steroids, but absorbance in the airway has not yet been studied [3].

In the present study, the effects of resveratrol were explored in a rat model of AR. Rats with AR were either untreated or received resveratrol.

Materials and Methods

This study was conducted in the Faculty of Medicine of Eskisehir Osmangazi University. Animal adaptation, care and experimental manipulation were performed at TICAM (the Experimental Studies Center of Eskisehir Osmangazi University). Animals were always treated in compliance with relevant principles of the Declaration of Helsinki.

Animals

Twenty-one healthy albino female Wistar rats weighing 190 to 220 g (15 months old) were used. The experimental protocol was reviewed and approved by the Committee of Ethics of Osmangazi University, Center of Medical and Surgical Experiments. All animal procedures were performed in accordance with the approved protocol.

All rats were housed under the same conditions in a room wherein both the temperature and humidity were controlled (20°C ± 1°C, 50% ± 10% relative humidity) under a 14/10-h to 16/8-h light/dark cycle. Tap water and standard pelleted food were provided ad libitum.

Experimental Design

Rats were randomly divided into three groups. Randomisation was performed as simple randomisation using a table of random digits [17]: (1) healthy rats (control group, n = 7); (2) AR with no treatment (AR+NoTr group, n = 7) in which AR was induced, but no treatment was given; and, (3) AR with resveratrol treatment (AR+Res group, n = 7) in which AR was induced, and resveratrol was given on days 21 - 28.

Methods

Induction of AR

The sensitizing solution was prepared by dissolving 0.3 mg ovalbumin (OVA) (Sigma, St. Louis, MO, USA) in 1 mL saline with 30 mg aluminum hydroxide (40 mg/mL) as adjuvant. Rats in the AR+NoTr and AR+Res groups were injected intraperitoneally with this agent every other day for 14 days (on days 1, 3, 5, 7, 9, 11 and 13; total of seven injections per rat). The rats in the control group were also given 1 mL saline plus 30 mg aluminum hydroxide intraperitoneally (total of seven injections per rat) on the same days. After 14 days of systemic sensitization, rats in the
AR+NoTr and AR+Res groups were given 50 µL 2% (w/v) OVA-saline solution in the form of intranasal drops into each nostril once daily for 14 days. Rats in the control group received saline drops [5, 18, 50]. Each nostril received 25 µL 2% (w/v) OVA-saline solution or saline [4, 18–20].

Treatment of AR+Res group

After the development of AR (day 21), rats in the AR+Res group received 20 µL resveratrol dissolved in distilled water (5 mg/mL) into each nostril twice daily for 7 days. Resveratrol was given 1 h before intranasal OVA.

Measurement of total IgE levels

On day 28, the total serum IgE levels were measured in all groups. Blood was collected by cardiac puncture. Blood samples (1 mL) were centrifuged for 20 min at 3,000 rpm and the supernatants stored at −20°C prior to analysis. Serum IgE levels were determined using a commercially available rat IgE ELISA kit (SunReed Biotechnology Co. Ltd., Shanghai, China) according to the manufacturer’s instructions. All results are expressed as kU/L.

Symptoms of AR

On day 28, the number of sneezes, duration of nose-rubbing, amount of lacrimation and difficulty in breathing (nasal congestion) were scored over 30 min (by K.B., M.A. and C.C.). A sneeze was defined as an explosive expiration just after a deep inspiration [21]; sneezing was scored on a scale of 0 to 3 (by K.B., M.A. and C.C.). Nose-rubbing was external perinasal scratching using either one or both forelimbs [21] and was scored on a scale of 0 to 3 (by K.B., M.A. and C.C.). Lacrimation was scored on a 0- to 3-point scale as follows: 0: none, 1: hazy eyes, 2: lacrimation, and 3: lacrimation with onset of conjunctivitis [20] (by K.B., M.A. and C.C.). Nasal congestion-obstruction was evaluated as follows: 0: no obstruction, 1: impaired inspiration, 2: nasal inflammation, and 3: severe breathing impairment [22] (by K.B., M.A. and C.C.).

Histology

The rats were intraperitoneally injected with 1% (w/v) pentobarbital sodium (50 mg/kg body weight) on day 28. Nasal mucosal samples were sliced into 5 µm-thick sections, transferred to adhesive slides, and dried at 37°C overnight and then at 60°C for 20 min. The slides were deparaffinized and dehydrated via xylene immersion twice for 10 min each time. After dehydration in an ascending series of increasingly ethanolic baths (70%, 80%, 96% and 100%), the samples were cleared in xylene and embedded in paraffin. The sections were stained with hematoxylin-eosin and Giemsa. A minimum of 10 fields/sample was examined and the severities of changes scored by an observer blinded to the treatment modality [19, 23]. Slides were examined using an Entella Olympus BH-2 light microscope and photographs were taken with an Olympus DP-70 digital camera.

Vascular congestion, ciliary loss, increased numbers of goblet cells, inflammatory cell infiltration, plasma cell infiltration, chondrocyte hypertrophy, eosinophil infiltration and mast cell infiltration were evaluated by light microscopy. The severities of changes were scored as none (−), mild (+), moderate (+++) or severe (++++) [4].

Statistical Analysis

SPSS software (version 16.0) was used for statistical calculations. Kruskal–Wallis variance analysis was used to explore differences among the three groups. If a statistically significant difference was apparent, the Mann–Whitney U-test with the Bonferroni correction was employed to identify the parameter causing the difference. A p value of <0.05 was considered to reflect statistical significance. If Bonferroni adjustment was performed, an adjusted p value of <0.0175 was considered to reflect statistical significance.

Results

The total serum IgE levels were 1,696.13, 2766.21, and 1302.25 kU/L in the control, AR+NoTr, and AR+Res groups, respectively, and were significantly different according to Kruskal–Wallis variance analysis (p< 0.05). To identify the parameter causing this difference, pairwise comparisons were performed using the Mann–Whitney U-test with Bonferroni adjustment. The total IgE level in the AR+NoTr was significantly higher than those of the other two groups, and the IgE level of the control group was significantly higher than that of the AR+Res group (adjusted p < 0.0175).

The allergic symptoms and histopathological findings of the three groups are shown in Table 1. Kruskal–Wallis analysis showed that the groups differed significantly in allergic symptoms (sneezing, nose-rubbing, lacrimation, and nasal congestion) (p < 0.05). To identify the parameters causing the observed differences, pairwise comparisons were performed using the Mann–Whitney U-test with the Bonferroni correction. All four allergic symptoms were more severe in the AR+NoTr group than in the other two groups.
(adjusted p < 0.0175). Additionally, the scores in the AR+Res group were significantly higher than those in the control group (adjusted p < 0.0175) (Table 2).

Differences in histopathological scores were examined using Kruskal–Wallis variance analysis. With the exceptions of ciliary loss and chondrocyte hypertrophy, all other items (vascular congestion, increased numbers of goblet cells and infiltration of inflammatory cells, plasma cells, eosinophils and mast cells) exhibited significant between-group differences (all p values < 0.05).

Mann–Whitney U-test with Bonferroni adjustment was used to conduct pairwise comparisons identifying parameters causing the observed differences. The level of mast cell infiltration in the AR+NoTr group was significantly higher than that of the control group. No significant differences in vascular congestion, increased number of goblet cells or infiltration of inflammatory cells, plasma cells, or eosinophils were observed between the AR+Res and control groups (adjusted p > 0.0175). All parameters in the AR+NoTr group were significantly higher than those in the other two groups (adjusted p < 0.0175) (Table 2).

**Histopathological results**

The nasal mucosa of the rats in the control group was normal (Figures 1 and 2). In the AR+NoTr group, the nasal mucosa exhibited ciliary loss, squamous metaplasia of the epithelium, inflammatory cell infiltration and vascular congestion in the lamina propria (Figure 3), and goblet cell metaplasia of the epithelium (Figure 4). In the AR+Res group, focal goblet cell metaplasia was evident on the surface of the respiratory epithelium and inflammatory cell infiltration, eosinophils and plasma cells were evident in the lamina propria (Figure 5). The extent of goblet cell metaplasia and inflammatory cell infiltration of the lamina propria was lower in the AR+Res group than in the AR+NoTr group (Figure 6).

| Table 1: Allergic symptoms and histopathological findings in the three groups |
|-----------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                                                | Median | Min | Max | Mean Rank | Median | Min | Max | Mean Rank | Median | Min | Max | Mean Rank | p*    |
| **Allergic symptoms**                         |       |     |     |           |       |     |     |           |       |     |     |           |      |
| Sneezing                                      | 2.0   | 0.0 | 4.0 | 4.0       | 37.0  | 26.0 | 50.0 | 18.0      | 15.0  | 10.0 | 22.0 | 11.0      | 0.000 |
| Nose rubbing                                  | 5.0   | 4.0 | 8.0 | 4.0       | 51.0  | 35.0 | 70.0 | 18.0      | 20.0  | 18.0 | 32.0 | 11.0      | 0.000 |
| Eye lacrimation                               | 1.0   | 0.0 | 1.0 | 4.86      | 3.0   | 2.0  | 3.0  | 17.71     | 2.0   | 1.0  | 2.0  | 10.43     | 0.000 |
| Nasal congestion                              | 0.0   | 0.0 | 1.0 | 4.57      | 3.0   | 2.0  | 3.0  | 17.36     | 1.0   | 1.0  | 2.0  | 11.07     | 0.000 |
| **Histopathologic examination results**        |       |     |     |           |       |     |     |           |       |     |     |           |      |
| Vascular congestion                           | 1.0   | 1.0 | 2.0 | 8.21      | 2.0   | 2.0  | 3.0  | 16.57     | 1.0   | 1.0  | 2.0  | 8.21      | 0.006 |
| Cilia loss                                    | 2.0   | 1.0 | 3.0 | 8.86      | 3.0   | 2.0  | 3.0  | 15.29     | 2.0   | 1.0  | 3.0  | 8.86      | 0.057 |
| Increase of goblet cells                      | 1.0   | 1.0 | 2.0 | 7.36      | 2.0   | 2.0  | 3.0  | 16.93     | 1.0   | 1.0  | 1.0  | 8.71      | 0.010 |
| Inflammatory cell infiltration                | 1.0   | 1.0 | 2.0 | 8.29      | 2.0   | 2.0  | 3.0  | 17.71     | 1.0   | 1.0  | 1.0  | 7.00      | 0.000 |
| Plasma cell infiltration                      | 1.0   | 1.0 | 2.0 | 8.57      | 2.0   | 2.0  | 3.0  | 16.43     | 1.0   | 1.0  | 3.0  | 8.00      | 0.007 |
| Chondrosit hypertrophy                        | 2.0   | 1.0 | 2.0 | 8.36      | 2.0   | 2.0  | 3.0  | 14.14     | 2.0   | 1.0  | 3.0  | 10.50     | 0.153 |
| Eosinophil infiltration                       | 1.0   | 1.0 | 2.0 | 7.79      | 2.0   | 2.0  | 3.0  | 17.43     | 1.0   | 1.0  | 2.0  | 7.79      | 0.001 |
| Mast cell infiltration                        | 1.0   | 0.0 | 1.0 | 5.43      | 2.0   | 1.0  | 3.0  | 16.14     | 1.0   | 1.0  | 2.0  | 11.43     | 0.003 |

*p values derived via Kruskal–Wallis variance analysis. A p value of <0.05 was considered to reflect statistical significance.
TABLE 2. Pairwise comparisons using the Mann–Whitney U-test with Bonferroni adjustment.

<table>
<thead>
<tr>
<th>Allergic symptoms</th>
<th>Pairwise comparison</th>
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<tbody>
<tr>
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<td>Group 1-Group2</td>
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<td></td>
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<tr>
<td>Sneezing</td>
<td>-3.148</td>
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<tr>
<td>Nose rubbing</td>
<td>-3.141</td>
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<td>Eye lassication</td>
<td>-3.314</td>
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<tr>
<td>Nasal congestion</td>
<td>-3.258</td>
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<tr>
<td>Vascular congestion</td>
<td>-2.734</td>
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<tr>
<td>Increase of goblet cells</td>
<td>-3.060</td>
</tr>
<tr>
<td>Inflammatory cell infiltration</td>
<td>-3.082</td>
</tr>
<tr>
<td>Plasma cell infiltration</td>
<td>-2.734</td>
</tr>
<tr>
<td>Eosinophil infiltration</td>
<td>-3.082</td>
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<tr>
<td>Mast cell infiltration</td>
<td>-2.992</td>
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$p_{\text{adjusted}}$: Mann–Whitney U-test/ Bonferroni adjustment data. $p_{\text{adjusted}} < 0.0175$ was considered to reflect statistical significance.

**Discussion**

In sensitive individuals, an allergen initiates a cascade of biochemical and cellular events culminating in IgE synthesis and release. Subsequent allergen exposure triggers mast cell degranulation, causing the release of allergenic mediators including histamine, tryptase, cysteinyl leukotrienes (CysLTs), cytokines (IL-4, IL-5 and TNF-α), platelet-activating factor and prostaglandins [24]. The late-phase response is primarily a cellular event involving an influx of eosinophils, basophils and lymphocytes, which then become activated and release materials promoting nasal congestion, local edema and tissue damage [4]. Certain symptoms of rhinitis, including sneezing, nose-rubbing, nasal blockage and rhinorrhea, can be modelled in experimental animals [25].

Polyphenols are natural products, principally of fruits and vegetables. The principal classes are flavonoids (flavonols, flavones, isoflavones, flavanones and flavan-3-ols) and non-flavonoid compounds, including the stilbenoids, resveratrol [26]. Th-2 cytokines, including IL-4, IL-5 and IL-13, play important roles in allergic reactions, either triggering IgE production or attracting mast cells and eosinophils to inflammatory sites [27]. Polyphenol consumption attenuates allergic re-exposure by inhibiting the adhesion and migration of peripheral B-cells, suppressing IgE and IgG1 levels and abrogating Th-2 cytokine production in sensitized mice [28-30]. In patients with asthma and other allergic diseases, functional deficits in Treg cells may be corrected by consumption of polyphenols as an alternative to other treatments such as corticosteroid use, allergen immunotherapy, vitamin D3 consumption, or prescription of long-acting β-agonists [26].

In this study, we explored the effects of resveratrol in an experimental rat model of AR. The allergic symptom scores for sneezing, nose-rubbing, lacrimation and nasal congestion were higher in the AR+NoTr group than in the AR+Res and control groups. The symptom scores of the AR+Res group were higher than those of the control group.

In our study, IgE levels were studied on the 28th day of the study in all groups. The total IgE level of the AR+NoTr group was significantly higher than that of the other two groups, and the IgE level of the Control group was significantly higher than that of the AR+Res group.

In the present study, histopathological evaluation showed that neither ciliary loss nor chondrocyte hypertrophy differed among the groups. Vascular congestion, inflammatory cell, plasma cell, eosinophil and mast cell infiltration and goblet cell increases were higher in the AR+NoTr group than in the other two groups. No significant difference between the AR+Res and control groups was evident. The level of mast cell...
infiltration was higher in the AR+NoTr group than in the control group. No significant difference was evident between the AR+Res and control groups.

Mast cells have a high-affinity receptor (FcεRI) for the Fc region of IgE, and IgE binds irreversibly to such cells. Re-exposure to the same antigen results in the binding of that antigen to sites on the variable regions of IgE molecules on mast cell membranes. Cross-linking of two or more of these molecules triggers a sequence of reactions culminating in degranulation of the mast cells and, finally, release of inflammatory mediators into the nasal mucosa. Sneezing, itching and watery discharge follow [18, 29]. Released IgE triggers increased production of leukotrienes and prostaglandins, which attract eosinophils, increase microvascular leakage, enhance edema, trigger mucous secretion, and augment kinin action [32]. Levels of mast cell infiltration were found to be similar in the AR+Res and control groups; thus, resveratrol prevented mast cell infiltration in rats with AR.
Eosinophils play important roles in the development of many allergic diseases, including asthma, dermatitis and rhinitis. Activation and recruitment of eosinophils into sites of allergic inflammation are hallmarks of allergic disease [33]. Eosinophils are a rich source of CysLTs, which are released in large amounts when cells are activated via the 5-lipoxygenase pathway [34]. CysLTs have been implicated in the pathophysiology of asthma, where they stimulate mucus hypersecretion, increase microvascular permeability, enhance inflammatory cell recruitment, and trigger edema [35]. In the present study, the extent of eosinophil infiltration did not differ between the AR+Res and Control groups; thus, resveratrol prevented eosinophil infiltration in rats with AR.

Trans-resveratrol inhibits human eosinophil activation and degranulation at concentrations of <100 μM, but does not induce apoptosis. Such potent anti-inflammatory activities of trans-resveratrol (and possibly the associated metabolites) may be useful in the treatment of eosinophil-related allergic diseases [3].

Trans-resveratrol is strongly cardioprotective and possesses chemopreventative, chemotherapeutic, neuroprotective and anti-inflammatory properties [36]. Trans-resveratrol inhibits the release of inflammatory cytokines, formation of reactive oxygen species, inflammatory gene expression [37, 38] and chemotaxis of neutrophils and monocytes. Trans-resveratrol may be useful to treat asthma and chronic obstructive pulmonary disease because it inhibits the release of IL-8 and granulocyte-macrophage colony-stimulating factor [39].

In the AR+NoTr group, ciliary loss, squamous metaplasia of the epithelium, inflammatory cell infiltration, vascular congestion of the lamina propria and goblet cell metaplasia of the epithelium were observed in the nasal mucosa. In the AR+Res group, goblet cell metaplasia was either focal or absent. Inflammatory cell, eosinophil and plasma cell infiltration of the lamina propria decreased; thus, resveratrol appears to prevent the mucosal changes characteristic of AR. In the AR+NoTr rats, ciliary loss, inflammatory cell infiltration, vascular congestion and goblet cell metaplasia were evident; however, when rats with AR were given resveratrol, goblet cell metaplasia was eliminated and inflammatory cell infiltration in the lamina propria was less than that seen in AR+NoTr rats.

In a study by Del Giudice et al. [40], 68 children were given resveratrol plus β-glucan or placebo (as diluents of the active drug) via two sprays (100 μL/spray) into each nostril three times a day for 2 months. Nasal symptoms, including itching, sneezing, rhinorrhea and obstruction, were assessed at baseline and after treatment. The need for rescue medication, such as cetirizine syrup, was also evaluated. Children treated with resveratrol achieved significant reductions in all nasal symptoms, namely itching (p = 0.0001), sneezing (p = 0.0009), rhinorrhea (p = 0.009) and obstruction (0.002), as well as antihistamine use (p = 0.003). Placebo did not affect the levels of nasal complaints or extent of cetirizine use. Intergroup analysis showed that active treatment was
significantly superior to placebo in terms of reducing AR symptoms and the need for rescue medication. The authors concluded that intranasal resveratrol with carboxymethyl-β-glucan significantly improved the nasal symptoms of children with pollen-induced AR. Similarly, we found that resveratrol reduced allergic symptoms (sneezing, nose-rubbing, lacrimation and nasal congestion) and the histopathological profile of AR in the rat nasal mucosa.

Kim *et al.* [41] explored the therapeutic effects of resveratrol in a mouse model of chronic rhinosinusitis with nasal polyps (CRSwNP) and the mechanism of action. Both eosinophilic infiltration and subepithelial fibrosis were significantly decreased by high-dose resveratrol; the potency of which was similar to that of triamcinolone acetonide. The levels of IL-4, IL-5, prostaglandin D synthase, and leukotriene C4 synthase were significantly reduced by administration of either low- or high-dose resveratrol. Production of 5-lipoxygenase was strongly inhibited by high-dose resveratrol. The authors concluded that resveratrol may prevent eosinophilic CRSwNP via a key mechanism of action that is believed to be anti-inflammatory in nature. Eosinophils were particularly affected, and the lipoxygenase pathway was inhibited.

Crowell *et al.* [42] found that rats given resveratrol at 300 mg/day for 4 weeks showed no adverse effects, suggesting that this chemopreventative phytochemical may be safe [43]. Del Giudice *et al.* [40] tested resveratrol in humans and found that it may be valuable for patients with AR. In this study, resveratrol was given with β-glucan to children with AR and resulted in significant symptom improvement.

We found that allergic symptoms were reduced upon resveratrol treatment: the symptoms in the AR+Res group were less severe than those of the AR+NoTr group. Similarly, allergic tissue reactions were reduced by resveratrol. Histopathologically, we found no difference between the AR+Res and control groups. The allergic reactions and cellular response values were higher in the AR+NoTr group than in the other two groups. It may be said that, resveratrol improved the symptoms of AR. In our study, resveratrol also reduced ciliary loss and inflammatory cell, mast cell and eosinophil infiltration and reduced or eliminated goblet cell metaplasia of the nasal mucosa, as revealed histopathologically.

Limitations of our study include the following: 1) the absence of a control treatment group (i.e., intranasal treatment with distilled water), 2) the researchers who evaluated the allergy symptoms were not blinded to the experimental groups and 3) baseline serum IgE levels were not measured.

Allergic symptoms and allergic tissue reactions were reduced by resveratrol treatment in rats, suggesting that resveratrol may effectively treat experimentally-induced AR in rats.

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**References**