

Preliminary Clinical Effect Evaluation of Resveratrol in Adults with Allergic Rhinitis

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Keywords

Resveratrol · Allergic rhinitis · Adult · Nasal symptoms · Eosinophils

Abstract

Background: Resveratrol is a natural, nonflavonoid polyphenol, exerting anti-inflammatory activity. It has been reported that resveratrol, together with carboxymethyl- β -glucan, can reduce nasal symptoms in children with allergic rhinitis (AR). In this study, the effect of resveratrol on nasal symptoms in adults with AR was investigated. **Methods:** We conducted a placebo-controlled, double-blinded study. One hundred and fifty-one adults (aged 18–60 years) with severe persistent AR were divided into a placebo-treated group ($n = 50$), a positive control budesonide-treated group ($n = 50$), and a resveratrol-treated group ($n = 51$). They were then treated with 2 sprays (100 μ L/spray) in each nostril 3 times/day for 1 month. Nasal symptoms including obstruction, itching, sneezing, and rhinorrhea, and the levels of IgE, IL-4, TNF- α , and eosinophils in the blood were assessed at baseline and after treatment. **Results:** Adults treated with resveratrol or budesonide achieved a significant reduction in nasal symptoms compared to the placebo-treated group. The resvera-

tol treatment significantly decreased the IgE, IL-4, TNF- α , and eosinophil levels in the blood. In addition, the resveratrol treatment was found to improve the quality of life of adults with AR. **Conclusion:** Our preliminary study showed that intranasal resveratrol is capable of significantly improving nasal symptoms in adults with AR.

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Introduction

Allergic rhinitis (AR) is a prevalent yet underappreciated inflammatory disorder of the nasal mucosa, characterized by pruritus, sneezing, rhinorrhea, and nasal congestion [1]. It is a common disorder that affects up to 40% of the population [2]. It is mediated by early- and late-phase hypersensitivity responses, similar to those of allergic asthma, to indoor and outdoor environmental allergens. AR is caused by an IgE-mediated inflammatory reaction as a consequence of exposure to the causal allergen. The allergy is sustained by a functional defect of al-

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lergen-specific T regulatory cells that allows T helper 2 (Th2) cell polarization. Th2 cells produce interleukin (IL)-4, IL-5, and IL-13 to drive allergic inflammation which, in turn, promotes immunoglobulin E (IgE) synthesis and the production, recruitment, and activation of eosinophils at the nasal level [3]. In addition, Th2 cytokines upregulate the endothelial and epithelial expression of adhesion (and other) molecules to promote eosinophil mucosal infiltration. Allergic inflammation causes typical AR symptoms to occur, such as itching, sneezing, rhinorrhea, and nasal obstruction, and can impair the quality of life [4].

AR is usually a long-standing condition that often goes undetected in the primary-care setting. Patients suffering from the disorder often fail to recognize its impact on their quality of life and daily functioning, and so do not often seek medical attention. In addition, physicians fail to regularly question patients about the disorder during routine visits [5]. Therefore, screening for rhinitis is recommended, particularly in asthmatic patients, since studies have shown that rhinitis is present in up to 95% of patients with asthma [6]. A thorough history and physical examination are the cornerstones of establishing the diagnosis of AR. Allergy testing is also important for confirming that underlying allergies cause the rhinitis. Referral to an allergist should be considered if the diagnosis of AR is in question.

Several medications have been used to treat AR, such as antihistamines, nasal corticosteroids, and decongestants [7–9]. These medications may have adverse side effects. For example, antihistamines may cause sleepiness and result in physical limitations. The number of people is growing who prefer to use complementary medicines, such as herbal medicine [10]. A lot of effort has also been put into searching for new natural cures which are not detrimental, as opposed to the chemical compounds used to treat AR.

Resveratrol (trans-3, 4, 5-trihydroxystilbene) is a natural, nonflavonoid polyphenol, and belongs to a subclass of stilbenes. It is found in significant amounts in grapes, berries, peanuts, other plant sources, and in red wine [11]. It functions as a phytoalexin (a class of vegetal antibiotics), protecting the plant from environmental stress or infection. It has become very popular due to its anticancer potential, first reported in 1997 [12]. Since then, researchers have paid attention to this compound, owing to its promising role in mediating inflammation [13] and tumorigenesis [14] as well as its cardioprotective effects [15]. Resveratrol exerts anti-inflammatory activity by inhibiting NF- κ B, mainly via I κ B kinase. NF- κ B activation

regulates several pro-inflammatory cytokines and proteins including IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), cyclooxygenase (COX)-1, COX-2, and inducible nitric oxide synthase. Resveratrol also exerts antitumor activity. It has been reported that it inhibits the proliferation of multiple cancer cell lines, such as colorectal cancer HT-29 and HCT116 cells, ovarian cancer SKOV3 cells, and breast cancer MCF-7 cells, both in vitro and in vivo.

In a mouse model of allergic asthma, resveratrol has been shown to exert anti-inflammatory and antiasthma effects. It significantly reduces IL-4 and IL-5 in both the plasma and bronchoalveolar lavage fluid, and suppresses bronchial hyperreactivity, lung eosinophilia, and mucus hypersecretion [16]. Kim et al. [17] showed that high doses of resveratrol decrease IL-4 and IL-5 gene expression. In an experimentally induced AR rat model, Bozdemir et al. [18] showed that resveratrol treatment reduced allergic symptoms and tissue reactions. These data strongly suggested the potential of resveratrol to treat AR. Recently, Miraglia Del Giudice et al. [4] reported that resveratrol reduced nasal symptoms in children with pollen-induced AR. In this study, we investigated the effect of resveratrol on nasal symptoms in adults with AR. We found that adults treated with resveratrol achieved a significant reduction in nasal symptoms, together with decreased levels of IgE, IL-4, TNF- α , and eosinophils. Our data shed light on the application of resveratrol to treat AR.

Materials and Methods

Patients

We conducted a double-blinded, placebo-controlled, randomized study. One hundred and fifty-one adults aged 18–60 years were enrolled at the Second People's Hospital of Wuxi, Nanjing Medical University. AR diagnosis was performed, according to validated criteria. All patients had positive skin prick tests and specific IgE tests and nasal symptoms (sneezing, itching, and rhinorrhea) for at least 1 month, >4 days/week. These patients were able to complete our scale survey.

The patients were randomly divided into a placebo-treated group (50 adults), a resveratrol-treated group (51 adults), and a budesonide-treated group (50 adults). Budesonide is a medication of the corticosteroid type used for AR (400 μ g/spray) [19]; it was used here as a positive control. Resveratrol was extracted from *Polygonum cuspidatum*. Patients were treated with an isotonic solution containing resveratrol 0.1%. The placebo was an isotonic solution, i.e., the diluent of an active drug. Patients were instructed to spray twice (100 μ L/spray) in each nostril 3 times/day for a month.

Nasal symptoms (itching, sneezing, rhinorrhea, and obstruction) were scored using a 4-point scale (0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe). Symptoms were assessed at baseline, and 2 and 4 weeks after treatment initiation. After treatment, a medical

outcomes study short-form 36-item health survey (SF-36) and a rhinoconjunctivitis quality of life questionnaire (RQLQ) were assigned to each patient for evaluation before and after treatment. For comparison, 51 healthy adults were also asked to complete the SF-36. This study was approved by the local ethical review board of the hospital and written informed consent was obtained from all patients.

ELISA

The levels of IL-4, IL-5, and TNF- α in patients' serum were tested using ELISA kits from R&D Systems, following the manufacturer's protocol.

Detection and Quantitation of Eosinophils

The eosinophils from patients' blood were detected and quantitated by flow cytometry following the protocol described before [20]. CCR3 was used as the specific marker for eosinophils. Anti-CCR3-APC antibody was purchased from BioLegend (San Diego, CA, USA).

Statistical Analysis

Data were presented as mean $\pm$ standard deviation. Statistical analysis was performed by the ANOVA analysis, followed by the Tukey post hoc test, which considered $p < 0.05$ as statistically significant.

Results

We recruited 151 adults with AR based on the clinical practice guideline. After being divided into the 3 groups, they were treated, and then nasal symptoms were analyzed after 2 and 4 weeks. Symptoms scores were compared with baseline. As shown in Figure 1, actively treated patients reported a significant reduction in nasal symptoms after 2 or 4 weeks. Budesonide, an effective medication for AR, also significantly reduced nasal symptoms. In contrast, the placebo group did not show any change in nasal symptoms from treatment.

All 151 patients, together with another 51 healthy adults (Health group), completed the SF-36, so that we could monitor their quality of life. As shown in Table 1, AR significantly impaired all 8 items. The placebo group scores were similar to severe persistent allergic rhinitis (SPAR) group scores and significantly different from the Health group, indicating that mock treatment did not change the quality of life. In contrast, we can see the obviously increased scores in the resveratrol-treated group, significantly higher than in the SPAR or placebo group, and close to the Health group. This result suggested that resveratrol treatment improved health. All 151 patients completed the RQLQ. As shown in Table 2, the resveratrol-treated group showed a significantly improved quality of life compared to the SPAR group. Our data suggest

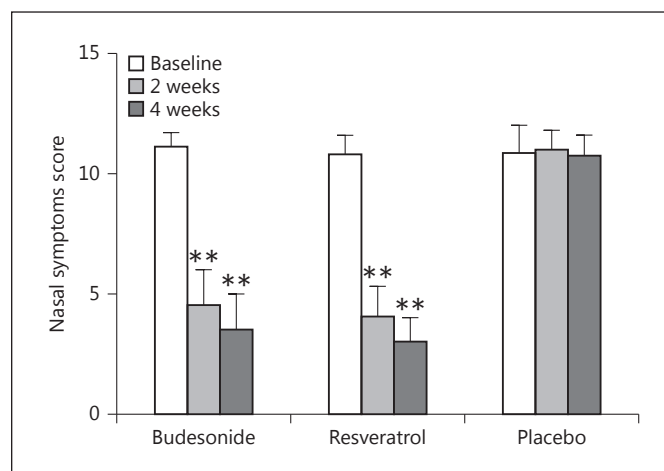


Fig. 1. Nasal symptoms severity score at baseline, week 2, and week 4 visits after initial treatment. ** $p < 0.01$ compared with baseline.

Table 1. Medical outcomes study short-form 36-item health survey, SF-36

	Health (n = 51)	SPAR (n = 50)	Resveratrol (n = 51)	Placebo (n = 50)
PF	94.2 $\pm$ 7.7	89.3 $\pm$ 10.1 ^b	91.7 $\pm$ 5.3 ^a	90.2 $\pm$ 9.1 ^b
RP	90.5 $\pm$ 15.6	72.1 $\pm$ 30.9 ^b	85.6 $\pm$ 25.4 ^a	73.3 $\pm$ 27.2 ^b
BP	87.1 $\pm$ 19.3	80.4 $\pm$ 21.3 ^b	85.7 $\pm$ 20.5	78.9 $\pm$ 18.5 ^b
GH	65.3 $\pm$ 22.2	53.1 $\pm$ 20.5 ^b	60.3 $\pm$ 25.7 ^a	51.7 $\pm$ 17.4 ^b
VT	73.1 $\pm$ 16.7	63.9 $\pm$ 15.9 ^b	71.8 $\pm$ 16.3	65.7 $\pm$ 17.3 ^b
SF	90.8 $\pm$ 17.7	75.2 $\pm$ 17.5 ^b	83.7 $\pm$ 15.4 ^a	74.8 $\pm$ 18.8 ^b
RE	84.5 $\pm$ 28.2	53.3 $\pm$ 35.7 ^b	77.6 $\pm$ 30.3 ^a	61.8 $\pm$ 39.6 ^b
MH	78.4 $\pm$ 13.4	66.7 $\pm$ 15.3 ^b	73.1 $\pm$ 14.9 ^a	68.3 $\pm$ 13.7 ^b

Values are expressed as means $\pm$ SD. PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; SPAR, severe persistent allergic rhinitis; Health, healthy adults (control group).

^a $p < 0.05$; ^b $p < 0.01$ compared with the Health group.

that resveratrol treatment significantly reduced AR symptoms and improved the quality of life of AR patients.

IgE, IL-4, the proinflammatory cytokine TNF- α , and eosinophils play an essential role in AR development [21–24]. As resveratrol reduced AR symptoms, we further compared the cytokine and eosinophil levels in patients' peripheral blood. As shown in Table 3, we detected a significantly increased IgE level in subjects from the SPAR and placebo groups, when compared to the Health group. The IgE level in resveratrol-treated patients was signifi-

Fig. 2. The level of serum IL-4 and TNF- α decreased in resveratrol-treated SPAR patients. Each value represents the mean $\pm$ SEM. ** $p < 0.01$ compared with the SPAR group. Health, healthy control group; SPAR, severe persistent allergic rhinitis; Res, resveratrol; Pla, placebo.

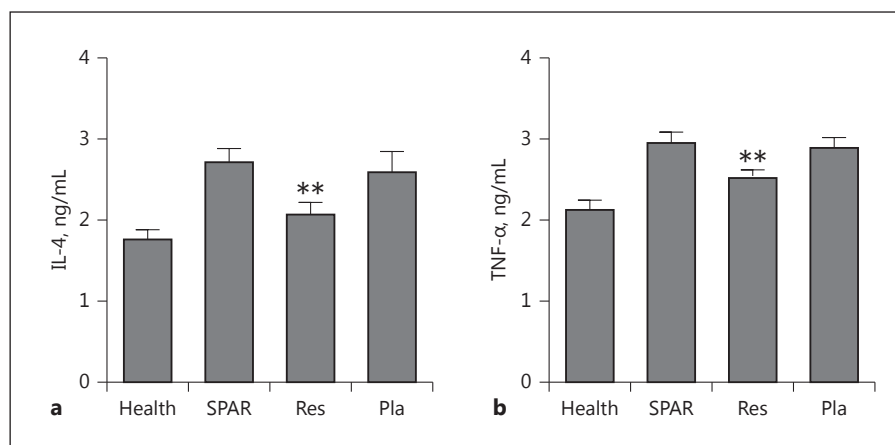


Table 2. Rhinoconjunctivitis quality of life questionnaire

	SPAR (n = 50)	Resveratrol (n = 51)	Placebo (n = 50)
Activities	2.01 $\pm$ 1.13	1.13 $\pm$ 0.98 ^b	2.10 $\pm$ 1.09
Sleep	2.16 $\pm$ 1.20	1.21 $\pm$ 0.89 ^a	2.06 $\pm$ 1.87
Non-nose/eye symptoms	2.13 $\pm$ 1.15	0.97 $\pm$ 0.52 ^b	2.27 $\pm$ 1.05
Practical symptoms	3.15 $\pm$ 1.21	2.11 $\pm$ 1.15 ^a	3.09 $\pm$ 1.37
Nose symptoms	3.27 $\pm$ 1.38	2.03 $\pm$ 1.22 ^a	3.11 $\pm$ 1.23
Eye symptoms	1.64 $\pm$ 0.99	1.04 $\pm$ 0.73 ^a	1.77 $\pm$ 1.54
Emotions	2.43 $\pm$ 1.09	1.18 $\pm$ 1.06 ^b	2.61 $\pm$ 1.17

Values are expressed as means $\pm$ SD. SPAR, severe persistent allergic rhinitis.

^a $p < 0.05$; ^b $p < 0.01$ compared with the SPAR group.

Table 3. Levels of serum IgE and eosinophils

	Health (n = 51)	SPAR (n = 50)	Resveratrol (n = 51)	Placebo (n = 50)
IgE, g/L	0.15 $\pm$ 0.10	0.42 $\pm$ 0.13 ^b	0.27 $\pm$ 0.16 ^a	0.39 $\pm$ 0.18 ^b
EOS				
0.5–1.5 $\times 10^9$ /L	50 (98.0)	2 (4)	11 (21.6)	3 (6)
1.5–2.5 $\times 10^9$ /L	1 (2.0)	16 (32)	31 (60.8)	12 (24)
>2.5 $\times 10^9$ /L	0 (0)	32 (64)	9 (17.6)	35 (70)

Values are expressed as means $\pm$ SD or n (%). EOS, eosinophils; SPAR, severe persistent allergic rhinitis.

^a $p < 0.05$; ^b $p < 0.01$, compared with the Health group.

cantly reduced compared to in subjects from the SPAR or placebo groups. Similarly, the concentration of eosinophils in the peripheral blood of resveratrol-treated patients was also decreased (Table 2). The resveratrol treatment also significantly reduced IL-4 and TNF- α levels in patients' serum (Fig. 2). Our data suggest that resveratrol reduced AR symptoms by decreasing the levels of IgE, IL-4, TNF- α , and eosinophils.

Discussion

AR is a very common atopic disorder. Patients with AR are bothered both by the nasal symptoms and associated symptoms such as headache and fatigue, which impair quality of life. Although effective medication such as antihistamines and intranasal corticosteroids are available to treat AR, the associated adverse events, including

drowsiness and confusion, have led to efforts to search for new medications.

We investigated the effect of resveratrol on AR in adult patients. Our data show that nasal application of resveratrol significantly reduced AR symptoms including itching, sneezing, rhinorrhea, and obstruction, reflected in the decreased overall symptom scores in the resveratrol-treated group (Fig. 1).

Our data are consistent with a similar study in which the effect of resveratrol was evaluated in children with AR [4] treated with resveratrol plus β -glucan (2 sprays in each nostril 3 times/day for 2 months). Nasal symptoms, including itching, sneezing, rhinorrhea, and obstruction were assessed at baseline and after treatment. Children treated with the active drug achieved a significant reduction in all nasal symptoms. Our study showed that resveratrol alone is sufficient to reduce AR symptoms in adult patients, consistent with previous studies in children. It is

worth noting that different dosages of resveratrol were employed across studies, likely due to the different ages of the patients. In our study, besides reducing the nasal symptoms of the AR patients, the resveratrol treatment also improved their quality of life (Tables 1, 2). Together with previous findings, our data strongly suggest the potential of resveratrol as a new medication for AR.

AR is an IgE-mediated inflammatory disease of the nasal mucous membranes caused by the interaction of allergens characterized by an inflammatory infiltrate made up of eosinophils, T cells, mast cells, and basophils, which release several mediators, chemokines, and cytokines (among these, histamine and cysteinyl-leukotrienes are the major vasoactive mediators) for the regulation of local and systemic IgE synthesis [25]. Nasal mast cells and T cells are important sources of Th2-type cytokines like IL-4 and IL-13, and can induce IgE synthesis [26].

AR is characterized by a 2-phase allergic reaction, an initial sensitization phase and a late phase. The initial sensitization phase is where allergen exposure results in IgE formation as well as the induction of humoral response [27]. After the deposition and elution of allergens into the mucus layer, they are taken up by antigen-presenting cells, processed, and then presented to Th2 lymphocytes. Activated Th2 lymphocytes release cytokines like IL-4 and IL-13, and interact with B lymphocytes to induce the synthesis of allergen-specific IgE. Thereafter, the allergen-specific IgE binds to the high-affinity receptor for IgE on the surface of the mast cells. In addition to the conventionally known mast cell mediators released upon activation by an IgE-dependent mechanism in AR, mast cells also induce IgE synthesis in B cells [28]. Thus, IgE and cytokines (including IL-4) play an essential role in initiating AR. In this study, we found that patients treated with resveratrol had significantly decreased IgE and IL-4 levels in the blood, suggesting that resveratrol inhibited IgE and IL-4 production. Han et al. [29] reported that resveratrol inhibits IgE-mediated basophilic mast cell degranulation. This could be another mechanism that contributes to inhibition of AR.

The early-phase response in AR is usually followed by a late-phase response which occurs 4–6 h after antigen stimulation. The late-phase response is essentially a cellular event [30], characterized by an inflammatory cellular influx comprised of, predominantly, T lymphocytes, basophils, and eosinophils [25]. Inflammatory cells become activated and release their mediators, promoting local edema and damage, and perpetuation of the overall inflammatory process [30]. Symptomatically, late-phase AR is characterized by nasal congestion and obstruction,

as opposed to sneezing and rhinorrhea which are characteristic of the early-phase response [31]. The key to the orchestration of the late-phase response lies in the production and release of a variety of chemokines and cytokines (like TNF- α and IL-13). These cytokines can up-regulate the expression of adhesion molecules like vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells, facilitating the infiltration of eosinophils, T lymphocytes, and basophils into the nasal mucosa. In addition, chemokines like RANTES and eotaxin, released from the epithelial cells, serve as chemoattractants for eosinophils, basophils, and T lymphocytes [27].

In this study, we analyzed the levels of TNF- α and eosinophils in the patients' blood, and found that the resveratrol-treated group had significantly decreased levels. Our findings elucidated another mechanism by which resveratrol can reduce AR symptoms. It has been demonstrated that resveratrol has anti-inflammatory activity and functions as a natural anti-TNF- α molecule [32]. It has also been shown to inhibit human eosinophil activation and degranulation [33]. It is altogether not surprising that resveratrol reduces nasal symptoms in adults with AR. This study was the first to be conducted on adults using resveratrol in the treatment of AR. We demonstrated the efficiency of resveratrol to treat AR in adults, but the small number and lack of diversity of patients were limitations. More patients, of different ages and clinical backgrounds, need to be recruited for such a study.

Conclusions

Our preliminary study shows that intranasal resveratrol is capable of significantly reducing AR symptoms in adults.

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None.

Disclosure Statement

The authors declare that they have no conflict of interests.

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