

Effect of curcumin on nasal symptoms and airflow in patients with perennial allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) is a common disorder that can significantly affect patient quality of life. Previous studies have found that curcumin had anti-inflammatory and antioxidant effects and clinical benefits in cancer and asthma.

Objective: To determine the efficacy of curcumin in the treatment of AR and to explore the molecular mechanisms involved.

Methods: In a randomized, double-blind study, 241 patients with AR received either placebo or oral curcumin for 2 months. The therapeutic effects of curcumin were evaluated by nasal symptoms and nasal airflow resistance. In addition, the production of interferon γ , interleukin (IL) 4, IL-10, and tumor necrosis factor α from mononuclear cells and IL-8, soluble intercellular adhesion molecule, polyethylene glycol 2, and leukotriene C_4 from polymorphonuclear neutrophils were compared before and after curcumin treatment.

Results: Curcumin alleviated nasal symptoms (sneezing and rhinorrhea) and nasal congestion through reduction of nasal airflow resistance. Curcumin was found to exert diverse immunomodulatory effects, including suppression of IL-4, IL-8, and tumor necrosis factor α and increased production of IL-10 and soluble intercellular adhesion molecule. However, curcumin did not affect the release of prostaglandin E_2 and leukotriene C_4 from polymorphonuclear neutrophils.

Conclusion: This pilot study provides the first evidence of the capability of curcumin of improving nasal airflow and modulating immune response in patients with AR.

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Introduction

Allergic rhinitis (AR) is associated with a symptom complex characterized by nasal congestion, rhinorrhea, sneezing, and nasal itching secondary to IgE-mediated inflammation of the nasal mucosa. The most common causative allergens include pollens, dust mites, molds, and insects. Patients with AR have an increased risk of developing asthma. A report from the World Allergy Organization reported that more than 40% of patients with AR have asthma and more than 80% of patients with asthma have concomitant rhinitis.¹ Other comorbidities of AR include sinusitis, nasal polyposis, conjunctivitis, otitis media with effusion, upper respiratory tract infections, breathing through the mouth, sleep disorders, and decreased quality of life. AR has psychological effects, interferes with social interactions, and creates an economic burden not only for the affected person but also for the family and society at large.

The prevalence of allergic diseases and asthma is increasing worldwide, particularly in low- and middle-income countries. AR is

the most common form of noninfectious rhinitis, affecting 10% to 30% of all adults and as many as 40% of children. Epidemiologic studies have found that the prevalence of AR continues to increase worldwide. The World Health Organization has estimated that 400 million people in the world have AR and 300 million have asthma.

Successful treatment of AR can involve allergen avoidance, pharmacotherapy, and immunotherapy. More pharmacotherapy for satisfactory symptom control became available. Oral antihistamines are often used as first-line therapy in patients with rhinitis symptoms. The use of these histamine₁-receptor antagonists had long been limited because of sedating adverse effects; however, the newer second-generation drugs are extremely safe and efficacious with far less sedation. These drugs block the effects of released histamine that is present in high concentrations during allergic reactions. The intranasal antihistamines work similarly to oral antihistamines, blocking the histamine receptor and thus decreasing rhinorrhea, itch, and sneeze. Intranasal antihistamines also are effective at reducing congestion, probably because topical application places a much higher concentration of antihistamine on the nasal mucosa than is possible with oral antihistamines. Nasal corticosteroids are the mainstay of therapy for both nonallergic and AR. With potent but local anti-inflammatory effects, they are efficacious in treating most rhinitis syndromes regardless of origin. By

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decreasing inflammation, nasal corticosteroids decrease mucosal edema and vascular leak, improving the symptoms of rhinorrhea and nasal congestion. Nasal corticosteroids are extremely safe and well tolerated, and systemic steroid effects are rare. The most frequent adverse effects are local irritation and epistaxis, both of which can typically be lessened by using proper spray technique and thus avoiding the nasal septum.²

Curcumin is the active ingredient of turmeric. It exerts potent anti-inflammatory and antioxidant effects, and these effects seem to be protective against cancer progression.^{3,4} Curcumin was reported to improved rhinitis symptoms via decreasing the IgE, tumor necrosis factor (TNF) α , interleukin (IL) 1 β , IL-6, and IL-8 in the mouse model.⁵ Thakare et al⁶ also reported that curcumin treatment prevented significant elevation of serum IgE, IL-4, nitric oxide in nasal lavage, and eosinophil peroxidase in nasal homogenate in the AR guinea pig model. Clinical studies indicated its benefits in patients with rheumatoid arthritis,⁷ osteoarthritis,⁸ and atopic asthma.⁹ In the present study, a randomized, double-blind clinical trial, we suggest that curcumin is a promising antiallergic agent that may be useful in the clinical management of AR.

Methods

Patient Recruitment

The present randomized, single-center trial was performed to assess the efficacy of curcumin capsules for the treatment of perennial AR. This study was double-blind and placebo-controlled. Clinical protocol was approved by the Second People's Hospital of Wuxi Ethical Committee. Written informed consent was received from all patients. Curcumin (500 mg/d; ORGANIKA Health Products, Richmond, British Columbia, Canada) was orally administered once a day for a consecutive 2 months according to previous human studies.^{10,11} No other pharmacologic treatments were allowed during this study.

A total of 313 adult patients with perennial AR were screened according to international guidelines.¹² All patients had at least a 2-year history of seasonal AR and positive skin prick test results to multiple allergens. The main exclusion criteria included asthma that required long-term inhaled or systemic corticosteroids within the previous 30 days, topical or systemic treatment with corticosteroids caused by other diseases within the previous 30 days, nasal polyps, respiratory tract infection, and pregnancy. Well-controlled asthma with corticosteroid nasal sprays, decongestants, and antihistamines were prepared as rescue medications for the entire study.

Finally, 241 patients were enrolled in the trial and randomized into 2 groups: 111 patients (54 males and 58 females) in placebo group and 129 patients (61 male and 68 females) in curcumin treatment group (Fig 1). The placebos were packed with starch in capsules of the same size and same color. The demographic and clinical/laboratory characteristics of the 2 groups were compatible (Table 1).

Nasal Symptom Evaluation

The typical nasal symptoms of sneezing, itchy, rhinorrhea, and obstruction were evaluated in all patients on the following scale: 0, absent; 1, mild (symptom was present but was not annoying or troublesome); 2, moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep); and 3, severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep).^{13,14} The sum of the total symptom score and each individual symptom score was recorded to assess the severity before and after treatment.

Nasal Airflow and Decongestion Test by Rhinomanometry

Rhinomanometry was used to measure air pressure and the rate of airflow during breath. Patients wore a tightly fitting facemask and

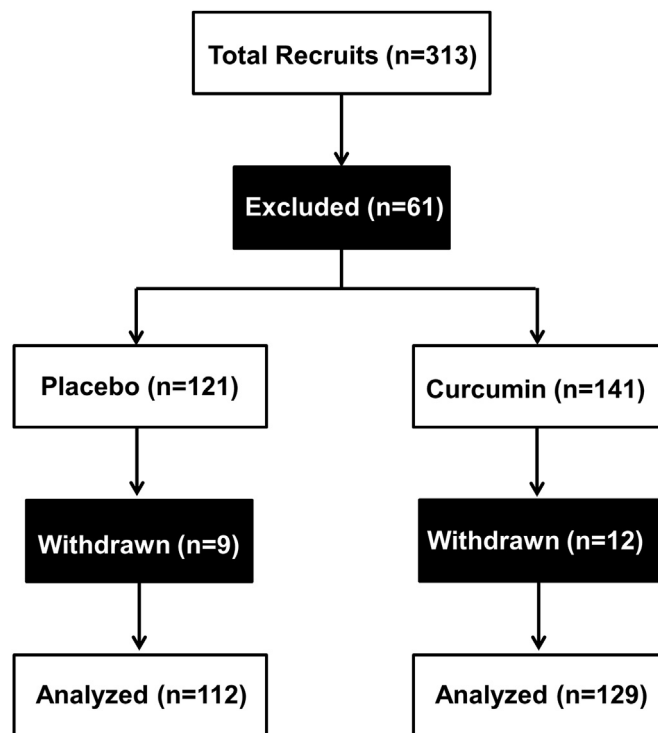


Figure 1. Flow diagram of the study design.

breathed through one nostril with their mouth closed. A sensor, placed in the contralateral nostril, recorded data of prenasal and postnasal pressures via airflow and pressure transducers. The signals of transnasal airflow and pressure were amplified, digitized, and saved for statistical analysis. Nasal airflow was reported as the sum of recorded airflow through the right and left nostrils in milliliters per second at a pressure difference of 150 Pa across the nasal passage. Four or more airflow measurements were performed for each patient, and the mean was recorded when reproducible values were achieved.

A decongestion test was performed following the method by Ciprandi et al.^{14,15} After baseline rhinomanometry, the nostril was administered 2 sprays of naphazoline (adrenal stimulator, 1 mg/mL) that rapidly induced vasoconstriction. Rhinomanometry was performed 5 and 10 minutes later. Total nasal airflow before and after naphazoline was measured to evaluate the reversibility in nasal resistance attributable to mucosal congestion.

Isolation of MNCs and PMNs From Peripheral Blood

The mononuclear cells (MNCs) and polymorphonuclear neutrophils (PMNs) were isolated from patient whole blood as described by Yang et al.¹³ Briefly, heparinized venous blood was mixed with 4 $\times$ volume of 2% dextran (467 kDa; Sigma-Aldrich, St Louis, Missouri) for 30 minutes at room temperature. The

Table 1

Baseline Characteristics of the Study Patients^a

Characteristic	Placebo (n = 112)	Curcumin (n = 129)	P Value
Sex, M/F	54/58	61/68	NA
Age, mean (SD), y	33.3 (6.1)	31.9 (6.7)	.43
Smoker	25 (22.3)	27 (20.9)	NA
Asthma history	10 (8.9)	12 (9.3)	NA
Atopic dermatitis history	5 (4.5)	5 (3.9)	NA
Drug allergy history	35 (31.3)	38 (29.5)	NA
Food allergy history	23 (20.5)	28 (21.7)	NA

Abbreviation: NA, not applicable.

^aData are presented as number (percentage) unless otherwise indicated.

leukocyte-enriched supernatant was diluted with $2 \times$ volume of Hanks' buffer and carefully layered over Ficoll-Hypaque (specific gravity, 1.077) for density gradient centrifugation (150g for 25 minutes). The MNCs were aspirated from the interphase, and the PMNs were obtained from the bottom. The isolated MNCs and PMNs were then washed and suspended in RPMI-1640 medium that contained 10% fetal bovine serum. Trypan blue exclusion test was conducted to confirm that the cell viability of MNCs and PMNs was greater than 95%.

The isolated cells (1 million cells per milliliter) were cultured in serum-free medium and stimulated with monoclonal antibodies against CD3 (1 μ g/mL) and CD28 (0.5 μ g/mL). For MNCs (R&D Systems, Minneapolis, Minnesota) and 10 ng/mL of IL-4 (R&D Systems) for PMNs for 24 hours at 37°C in 5% carbon dioxide, respectively. The supernatants were collected by centrifuging the cells and stored at -20°C until use.

Cytokines Assessment by Enzyme-Linked Immunosorbent Assay

Cytokines from stimulated MNCs and PMNs were measured by enzyme-linked immunosorbent assay kits (R&D Systems). Interferon (IFN) γ , TNF α , IL-4, and IL-10 from MNCs and IL-8, soluble intercellular adhesion molecule 1 (sICAM-1), polyethylene glycol 2 (PEG₂), and leukotriene C₄ (LTC₄) from PMNs were determined.

Statistical Analysis

Data are presented as mean (SD). Differences on evaluated parameters at baseline and after treatment were assessed within groups by the Wilcoxon signed rank test and between groups by the Mann-Whitney test. $P < .05$ was considered statistically significant.

Results

Effects of Curcumin on Nasal Symptoms

All patients tolerated the prescribed therapy. As shown in Figure 2A, patients receiving curcumin had a significant reduction in nasal symptom scores (from 8.03 [1.31] to 2.76 [0.51]; $P < .001$), whereas there is no difference in the placebo treatment group (from 8.11 [1.24] to 8.22 [1.37]; $P > .05$). Improvement in the nasal single symptom was also demonstrated in the curcumin group (Fig 2C): sneezing was significantly reduced from 1.94 (0.31) to 0.63 (0.14) ($P < .001$), itching from 1.63 (0.27) to 0.54 (0.13) ($P < .001$), rhinorrhea from 2.13 (0.32) to 0.47 (0.17) ($P < .001$), and obstruction from 2.33 (0.31) to 1.12 (0.23) ($P < .001$). Expectably, placebo treatment failed to improve the nasal single symptom (Fig 2B) with sneezing from 1.83 (0.25) to 1.97 (0.32) ($P > .05$), itching from 1.52 (0.24) to 1.46 (0.28) ($P > .05$), rhinorrhea from 2.21 (0.37) to 2.35 (0.39) ($P > .05$), obstruction from 2.55 (0.35) to 2.44 (0.36) ($P > .05$). In the clinical trial, curcumin greatly relieved nasal symptoms in patients with AR.

Effects of Curcumin on Nasal Airflow Resistance

There was no difference in airflow baseline between the 2 groups (placebo: 455.5 [73.2] mL/s; curcumin: 463.7 [67.8] mL/s; $P > .05$) (Fig 2A). Placebo treatment did not improve nasal airflow when compared with baseline (471.2 [78.6] mL/s, $P > .05$), whereas curcumin treatment significantly increased the nasal airflow from baseline to 625.3 (79.2) mL/s ($P < .01$). In the decongestion test, placebo did not affect the percentage of reversibility (before treatment: 54.4% [5.5%], after treatment: 51.0% [5.6%], $P > .05$) (Fig 2B). Before curcumin treatment, the percentage of reversibility was similar as placebo group (50.2% [5.7%], $P > .05$ vs the placebo group). After treatment, curcumin induced lower reversibility (19.9% [2.9%]) compared with pretreatment values with statistical significance ($P < .01$) (Fig 3C). The intergroup analysis revealed that curcumin significantly affected reversibility than placebo.

Effects of Curcumin Treatment on T_H1/T_H2 Cytokine Production in Activated MNC

T_H1 (represented by IFN- γ) and T_H2 (represented by IL-4, IL-10, and TNF- α) cytokine generated by stimulated MNCs were determined to elucidate the molecular mechanism underlying the immunomodulatory effects of curcumin. Placebo treatment had no obvious effect on cytokines production, including IL-4 (before treatment: 13.5 [2.7] pg/mL; after treatment: 14.1 [2.9] pg/mL; $P > .05$) (Fig 4A), TNF- α (before treatment: 5.5 [0.8] pg/mL; after treatment: 5.2 [0.9] pg/mL; $P > .05$) (Fig 4B), IL-10 (before treatment: 75.4 [10.5] pg/mL; after treatment: 80.8 [11.1] pg/mL; $P > .05$) (Fig 4C), and IFN- γ (before treatment: 784.7 [103.5]; after treatment: 750.5 [96.7] pg/mL; $P > .05$) (Fig 4D). Curcumin treatment did not influence IFN- γ levels (before treatment: 793.6 [108.4] pg/mL; after treatment: 825.7 [112.3] pg/mL; $P > .05$) (Fig 4D). However, IL-10 was significantly elevated by curcumin treatment (before treatment: 77.5 [10.6] pg/mL; after treatment: 93.2 [12.1] pg/mL; $P < .05$) (Fig 4C). Meanwhile, TNF- α (before treatment: 5.7 [0.9] pg/mL; after treatment: 3.4 [0.7] pg/mL; $P < .01$) (Fig 4B) and IL-4 (before treatment: 14.2 [2.8] pg/mL; after treatment: 9.4 [2.1] pg/mL; $P < .01$) (Fig 4A) were observed to be markedly decreased in curcumin-treated MNCs. Of note, neither the placebo nor curcumin treatment could alter IL-17 production (eFig 1).

Effects of Curcumin on the Production of Inflammation-Related Factors in Activated PMNs

To investigate the effects of curcumin on nasal inflammation, we assessed the inflammation-related molecules, including sICAM-1, IL-8, and prostaglandin E₂ (PGE₂) and LTC₄ released from IL-4-stimulated PMN cells before and after treatment. Placebo had no effects on these molecules (IL-8: from 2.5 [0.3] ng/mL to 2.3 [0.3] ng/mL, $P > .05$; sICAM-1: from 4.3 [0.5] ng/mL to 4.1 [0.6] ng/mL,

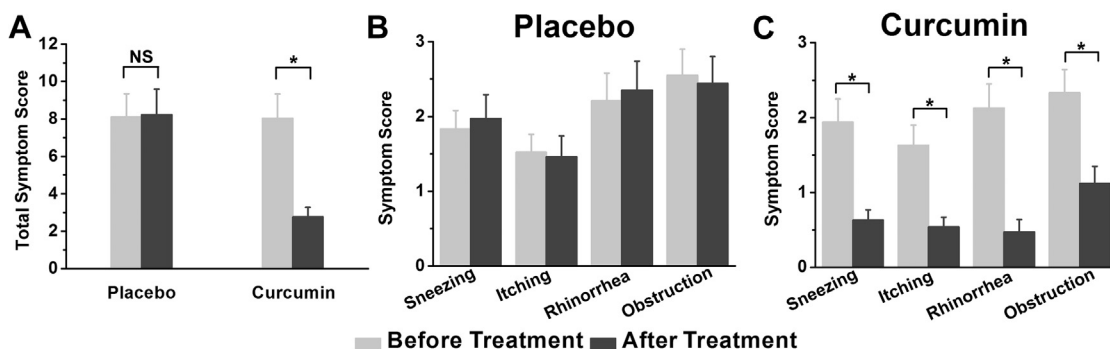


Figure 2. Effects of curcumin treatment on nasal symptoms, including total symptom score (A); symptom score for sneezing, itching, rhinorrhea, and obstruction in placebo (B); and curcumin treatment groups (C). Data are given as mean (SD). NS indicates nonsignificant. * $P < .001$.

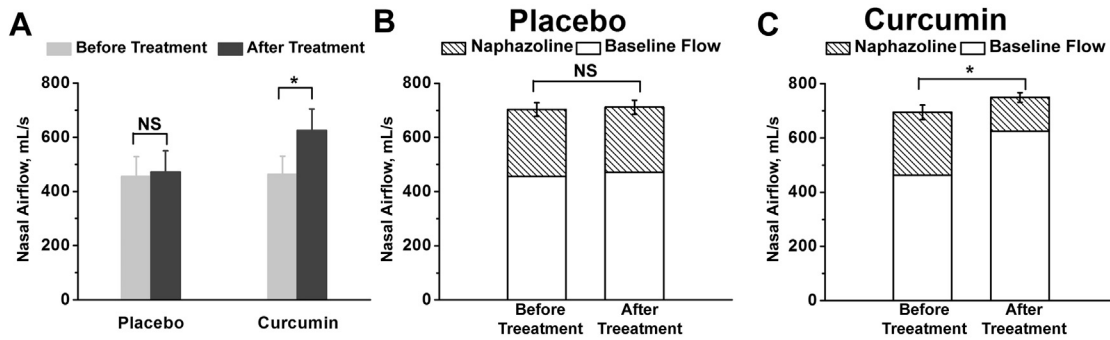


Figure 3. Curcumin treatment improves nasal airflow as measured by active anterior rhinomanometry (A) and decongestion test (B and C). Data are given as mean (SD). NS indicates no significance. * $P < .01$.

$P > .05$; PEG₂: from 4.3 [0.5] ng/mL to 4.7 [0.5] ng/mL, $P > .05$; LTC₄: from 63.5 [8.1] pg/mL to 58.7 [7.9] pg/mL, $P > .05$). With curcumin treatment, IL-8 decreased from 2.6 (0.4) ng/mL to 1.8 (0.2) ng/mL ($P < .01$) (Fig 5A), sICAM-1 increased from 4.5 (0.6) ng/mL to 5.7 (0.7) ng/mL ($P < .05$) (Fig 5B), and PGE₂ (4.5 [0.5] ng/mL to 4.2 [0.5] ng/mL, $P > .05$) (Fig 5C) and LTC₄ (68.3 [9.2] pg/mL to 72.4 [9.1] pg/mL, $P > .05$) (Fig 5D) did not change.

Discussion

AR is a common disorder that can significantly affect patient quality of life. Rhinitis is broadly defined as inflammation of the nasal mucosa that accounts for nasal symptoms.¹⁶ Therapeutic intervention in AR has often focused on blocking the nasal

symptoms. In the present clinical study, patients with AR were administered curcumin orally at 500 mg/d for 2 months. Compared with placebo treatment, curcumin greatly relieved the nasal symptoms, including sneezing, itching, rhinorrhea, and obstruction, in patients with AR. Moreover, curcumin treatment markedly improved the nasal airflow. The data indicate the therapeutic effect of curcumin for patients with AR.

To investigate the mechanism of the action of curcumin in AR, we assessed the production of T_H1/T_H2 cytokines and different inflammatory mediators. The AR immunopathologic mechanisms are characterized by T_H2-dependent inflammation and T_H1 response impairment.^{17,18} The inflammatory response in the nasal mucosa in patients with AR challenged intranasally with an allergen includes an immediate IgE-mediated mast cell response

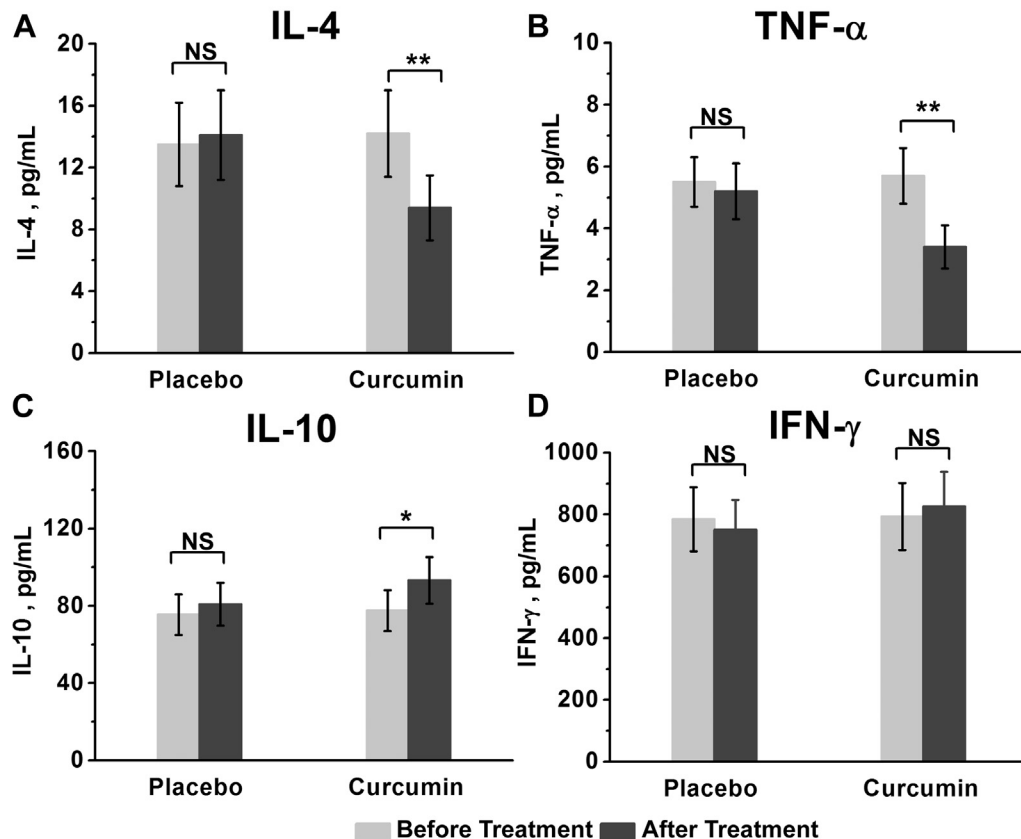


Figure 4. Effects of curcumin treatment on T_H1/T_H2 cytokine production in activated peripheral blood mononuclear cells isolated from patients. Cytokine production, including interleukin (IL) 4 (A), tumor necrosis factor (TNF) α (B), IL-10 (C), and interferon (IFN) γ (D), were determined by corresponding enzyme-linked immunosorbent assays. Data are given as mean (SD). NS indicates no significance. * $P < .05$ and ** $P < .01$.

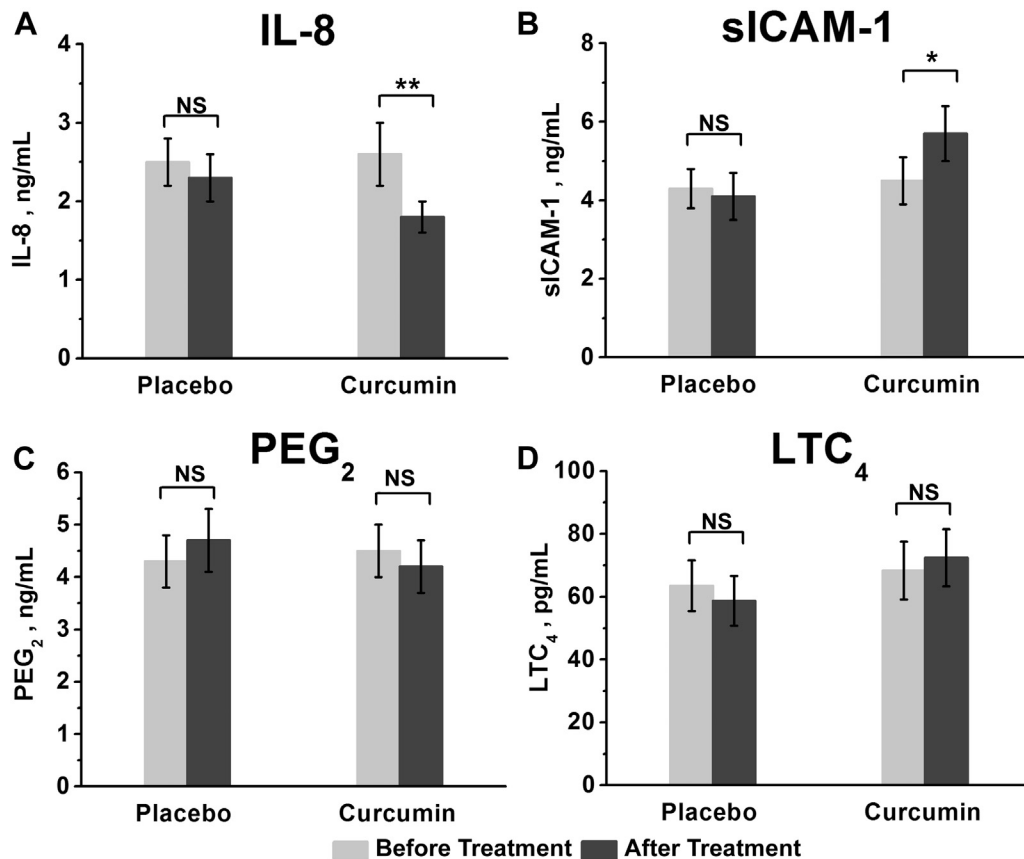


Figure 5. Effects of curcumin treatment on the production of inflammation-related factors in activated polymorphonuclear neutrophils isolated from patients. The expression of inflammation-related factors, including interleukin (IL) 8, soluble intercellular adhesion molecule 1 (sICAM-1), polyethylene glycol 2 (PEG₂), and leukotriene C₄ (LTC₄), were analyzed by corresponding enzyme-linked immunosorbent assays. Data are given as mean (SD). NS indicates no significance. **P* < .05 and ***P* < .01.

and a late-phase response characterized by recruitment of eosinophils, basophils, and T cells expressing mediators and cytokines, including IL-4, IL-8, IL-10, IL-13, and TNF- α .^{19,20} We found that curcumin significantly reduced IL-4 and TNF- α levels and significantly increased IL-10 levels in the CD³/CD²⁸ stimulated MNCs from curcumin-treated patients with AR. Of note, curcumin treatment increased IL-10 production and decreased the levels of other proinflammatory cytokines (IL-4 and TNF- α). These results are conceivable because elevation of IL-10 may downregulate T_H1 cytokine production.²¹ IL-10 and transforming growth factor β can be produced by regulatory T (Treg) cells and are important for Treg operability, which may robustly suppress IgE production and other different effector cells (mast cells, basophils, and eosinophils) in AR. However, no conclusive statements on the effects of curcumin in Treg cells can be drawn because IL-10 may be produced by other cell types, such as T_H2 cells, as well. Meanwhile, increasing evidence reveals the elevated levels of IL-17 in patients with AR, suggesting the possible involvement of IL-17 and T_H17 (IL-17-producing cells) in AR.^{22,23} In this study, curcumin treatment failed to induce obvious change in IL-17 production, indicating that T_H17 may not be biological target of curcumin.

Patients with AR exhibit a significant influx of eosinophils and neutrophils into the nasal cavity. Leukocyte emigration into tissue requires the involvement of adhesion molecules and chemotactic factors. Patients with AR have a significant influx of eosinophils and neutrophils into the nasal cavity. The release of inflammation-related molecules, including sICAM-1, IL-8, PEG₂, and LTC₄, plays an important role in the recruitment and activation of neutrophils in modulating the severity of AR.²⁴ In the present study, we found that the increased sICAM-1 and decreased IL-8, but not PGE₂ or

LTC₄, are observed by IL-4-stimulated PMN in patients with AR. After 2 months of treatment with curcumin. Taken together, this pilot study provides the first evidence of the capability of curcumin to improve nasal airflow and modulate immune response in patients with AR.

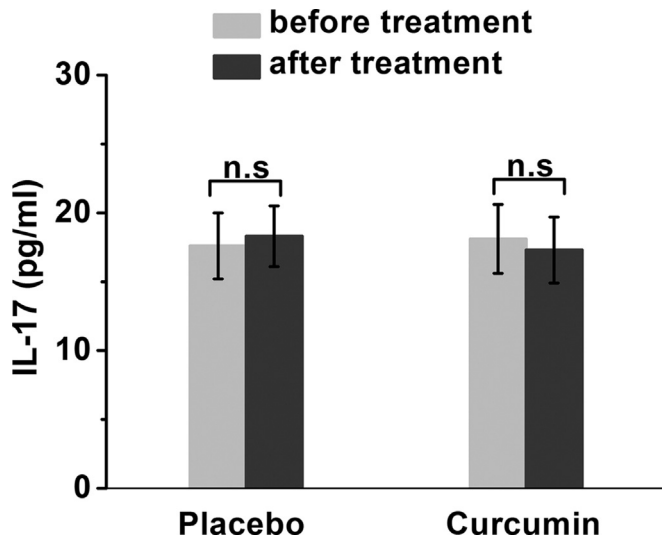
Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.09.427>.

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eFigure 1. Effects of curcumin treatment on IL-17 production in activated peripheral blood mononuclear cells isolated from patients. IL-17 levels were determined by the corresponding ELISA assays. Data were given as mean $\pm$ SD. n.s indicates no significance.