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What is This?
Effect of Silymarin in the Treatment of Allergic Rhinitis

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. Although the role of oxidative stresses has been confirmed in the pathophysiology of allergic rhinitis and the protective effect of silymarin against oxidative stresses has been proven in different organs, no study has yet been conducted on the impact of silymarin on allergic rhinitis treatment.

Study Design. A randomized clinical trial study.

Setting. Two tertiary referral centers with otorhinolaryngology–head and neck surgery and allergy and immunology departments.

Patients and Methods. In a randomized clinical trial, 94 patients with the signs and symptoms of allergic rhinitis and a positive skin prick test were selected and randomly divided into 2 groups. Their signs and symptoms, eosinophil percentage on nasal smear, serum IgE, and interleukin (IL-4, IL-5, interferon-γ) levels were recorded. The study group was treated with silymarin, whereas the control group received placebo, both for 1 month, along with routine antihistamine treatment. At the end of the treatment course, clinical and laboratory findings were statistically analyzed.

Results. Sixty patients completed the trial. Based on the Sino-Nasal Outcome Test 20 (SNOT-20), a significant improvement in clinical symptom severity was observed in both groups (9.23 ± 5.14 vs 2.20 ± 2.69; P < .001), which was statistically significantly higher in the study group (P < .001). Posttreatment percentage of nasal eosinophils and cytokine levels showed no significant difference (P > .05). Rise in serum IgE level was seen after treatment with silymarin (P = .003).

Conclusion. Considering the statistically effective role of silymarin in alleviating the severity of allergic rhinitis symptoms, applying this herbal antioxidant along with other medications may result in better management.

Keywords
allergic rhinitis, silymarin, cytokine

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In the wide range of allergic diseases, allergic rhinitis, with a 20% prevalence rate in the general population of Western countries, is the most common type.²³ Apart from trauma and malignancies, allergy is the first or second etiology in up to half of the patients referred to ear, nose, and throat clinics.² Its financial costs and influence on life quality are substantial issues.³

Typically, allergic rhinitis is caused by natural pollens or house-dust mites, and it manifests with a runny nose, nasal itching, sneezing, nasal congestion, conjunctivitis, and smelling disorder. Previous findings introduce it as a major risk factor for developing future asthma;⁴ therefore, its effective treatment would be of great value. Persistent allergic rhinitis is defined as having allergic symptoms present for more than 4 days a week and for more than 4 consecutive weeks. During recent years, significant changes have occurred in the management of allergic
rhinitis. The role of oxidants and oxidative stresses in the pathophysiology of allergic rhinitis has been confirmed in several studies, yet in one study, the use of antioxidants has been introduced as the cause of the ever-increasing prevalence of allergic diseases. Many studies have also been conducted on the role of antioxidants in the treatment of allergic rhinitis in which a mixture of medicinal plants has been used as the antioxidant drug, leading to desired outcomes through various mechanisms.

Silymarin, extracted from milk thistle and scientifically named *Silybum marianum*, is a mixture of mainly 3 flavonolignans (silibinin, silydianine, and silychristine). Silymarin is a polyphenol compound with well-proven hepatoprotective effects. Its products have been in practice for more than 200 years, and it has been widely used clinically since 1969 in European countries. Silymarin is absorbed in the intestine and is concentrated in the biliary system followed by the hepatic cycle. Silymarin is a reductant of free radicals and a stabilizer of the cell membrane; increases the intercellular concentration of glutathione, which is responsible for detoxification and elimination of free radicals from the body; and prevents lipo-peroxidation, which causes cell membrane injury. Today, silymarin is well known for its anti-inflammatory, antioxidant, cytoprotective, and anticarcinogenic effects. In 1 study that measured the antioxidant nature of many known compounds, silymarin was the best. Recent studies have shown that silymarin also has other properties such as therapeutic effects on fatty liver, hepatic cirrhosis, diabetes, hyperlipidemia, cataract, osteoporosis, and cancer.

Based on several studies, the side effects of silymarin include minor gastrointestinal disorders, and a mild laxative effect is usually seen with its usage. It is of very low toxicity, and its highest tolerated dosage has been 300 mg/kg in dogs.

Although during the past decade, silymarin has been used as a strong antioxidant in various studies and different diseases, including cardiovascular disease, diabetes, cancer, toxic and alcoholic hepatitis, and so on, it has not yet been applied in allergic rhinitis. Therefore, considering the growing body of research suggesting a role for antioxidants as well as anti-inflammatory drugs in treating allergic rhinitis, in a novel approach, we aimed to survey the exact effect of silymarin in the management of clinical and laboratory signs and symptoms of allergic rhinitis.

**Patients and Methods**

This randomized clinical trial evaluated the added effect of silymarin on reducing the signs and symptoms of allergic rhinitis. In total, 106 patients with allergic rhinitis who visited the allergy or ear, nose, and throat (ENT) clinics of Qaem educational hospital, Mashad, Iran, from March 2009 to January 2010 were assessed as eligible. Of the 94 patients who fully met the inclusion criteria and gave informed consent, 60 completed the trial and performed laboratory tests at both time points (Figure 1). Because the present work was a pilot study at the time of initiation, we chose the sample size based on the number of referral cases to our clinic and the available material for performing such a study.

The inclusion criteria for this study included having the clinical signs/symptoms of allergic rhinitis plus a positive allergy skin test for at least one of the tested allergens (in total, 18 common regional allergens according to studies that investigated the prevalence of allergy and common allergens in this region were tested and reported in 4 groups: tree, mixed grass, *Salsola* [weed], and *Alternaria* [mold]).

Persistent allergic rhinitis was defined as related symptoms present for more than 4 days a week and for more than 4 consecutive weeks, with the realization that patients usually suffer almost every day. For all these patients, oral antihistamines (H1 type) and also inhaled corticosteroids had been previously administered according to the standard treatment protocol of allergic rhinitis, but patients had shown no or very little clinical response. By employing a simple randomization method, the cases were divided into 2 groups (47 cases each); both groups also received the routine daily treatment for allergic rhinitis, ceterizine 10 mg daily. Along with antihistamine therapy, a 1-month treatment course of silymarin was administered as 140-mg tablets prescribed 3 times daily for the study group. The control group received placebo for the same duration. It was prepared from excipients that were used as conservatvies or carriers besides the main therapeutic components and matched for size, shape, and volume of contents and manufactured by the same company.

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences; all patients were fully informed about the study protocol, and a signed informed consent was obtained from each of them.

Patients with any other etiology for rhinitis, or with other underlying systemic diseases, and those taking any kind of herbal drugs with antioxidant effects were excluded from the study.

The clinical symptom severity of the patients was evaluated by the standard Sino-Nasal Outcome Test 20 (SNOT-20) questionnaire. A skin test for all the common regional aeroallergens—tree, mixed grass, *Salsola* (weed), and *Alternaria* (mold)—was also performed for each case to confirm the allergic base of the disease. The percentage of eosinophils on the nasal smear was then measured under a high-power field microscope (HPF 4); a 5-mL blood sample was collected from each patient at baseline and after 4 weeks (end of study period). Plasma was frozen and then stored for analysis at completion of the study. Level of total IgE was obtained by enzyme-linked immunosorbent assay (ELISA) kits (manufactured by Pishbaz Teb Diagnostics, Tehran, Iran) both at baseline and at the end of the study. Blood samples were also used to determine the concentration of Th1/Th2 cytokines, interleukin (IL)–4 and IL–5, and interferon (IFN)–γ, and at each time point, a 2-cc blood sample was sent to Bu-Ali immunologic research center (Meshhad, Iran), where the lymphocytes were initially separated and cultured for 48 hours under polyclonal stimulation by using the Phycol method (DiFo, Bacto Laboratories Pty Ltd, Liverpool, England). After being stimulated with the mitogen agent of Phyto Mito Antigen (PMA, which increases the concentration of cytokines and facilitates their measurement), the supernatant was collected and stored at –80°C pending further analysis. After study completion, cell supernatants were
assessed by the ELISA technique for quantifying cytokine concentrations based on the kit’s instructions (Sanquin Blood Supply Foundation, Amsterdam, the Netherlands). Cytokine data are expressed as the difference between the spontaneous culture and the control (pg/mL).

After taking the first blood sample by a single physician, the patients were randomly and in a double-blind manner divided into the study and control groups. A simple randomization method was used where the consecutive patients were divided into the study or control group intermittently. The first patient group was selected by chance (coin flip). At the end of the treatment period, clinical and laboratory signs and symptoms were once again recorded for each patient. Data were then analyzed by applying the SPSS software (version 13; SPSS, Inc, an IBM Company, Chicago, Illinois). The pre- and posttreatment changes in each group and between the 2 groups were compared by using the paired samples t test and independent samples t test, respectively.

**Results**

In this study, the clinical and laboratory findings of 94 allergic rhinitis patients divided into 2 groups, before and after treatment with silymarin, were recorded, whereas the final statistical analysis was performed on 60 patients who completed the trial (30 patients in each group). No significant difference in age and sex was seen between the 2 groups; 12 (40%) patients and 11 (36.7%) controls were men, whereas 18 (60%) and 19 (63.3%) were women, respectively. Mean (SD) age of the study and control groups was 29.03 (10.17) years and 28.4 (8.41) years, respectively.

**Figure 1.** Flow diagram of the patients in the study and control groups.
In total, 7 (8.57%) patients were smokers, including 4 cases and 3 controls; 42% (25 of 60) had a positive family history of allergy.

The most prevalent clinical symptoms among all the studied cases are shown in Table 1.

Applying the paired samples t test showed a significant decrease in symptom severity following treatment in the study group (P < .001); also, a statistically significant difference in mean IgE was observed (P = .003), which, despite our expectations, showed a meaningful rise in IgE after treatment with silymarin. Nevertheless, comparing the mean cytokine levels in the study group before and after treatment with silymarin showed no significant difference (P > 1).

Mean clinical symptom severity based on SNOT-20 before and after treatment showed a statistically significant decrease following treatment in the control group (P < .001).

Mean posttreatment nasal smear eosinophil count showed no significant difference in the control group (P = .683). Pre- and posttreatment mean serum IgE and cytokine levels in the control group also showed no meaningful difference after placebo treatment (P > .1).

### Intergroup Pre- and Posttreatment Clinical and Laboratory Findings

A significant decrease in the mean clinical symptom severity was detected in both groups following treatment. Considering a 95% confidence interval, this drop was markedly higher in the study group (9.23 ± 5.14 vs 2.20 ± 2.69). Therefore, a significant difference in posttreatment changes of mean symptom severity between the 2 groups was revealed (P < .001; Table 2).

The difference in pre- and posttreatment mean IgE serum level with the 95% confidence interval was –602.50 ± 1004.60 µg/mL and –3.80 ± 1004.90 µg/mL in the study and control groups, respectively. It shows a significant rise in serum IgE level in the study group but no rise in the control group. Therefore, a remarkable difference was seen in the posttreatment serum IgE level between the 2 groups (P = .027). Table 2 also indicates no significant difference in pre- and posttreatment changes of anti-inflammatory markers (IFN-γ, IL-4, IL-5) and nasal smear eosinophil percentage between the 2 groups (P = .993, P = .327, P = .202, and P = .929, respectively).

### Discussion

The dominant symptoms of allergic rhinitis recorded in our patients were similar to those of previous studies, mainly including nasal congestion; clear, watery rhinorrhea; and sneezing. Sleep pattern disorder was also widely seen in these patients.

Although the current study did show some effects of silymarin in the management of allergic rhinitis on controlling the symptoms based on the SNOT-20, the severity of clinical symptoms based on the patients’ sex showed no significant difference between the 2 genders. This factor has not been separately included in previous studies.

To the best of our knowledge, the current study is the first to evaluate the effect of silymarin on allergic rhinitis. Although the role of antioxidants and oxidative stresses has been proven in several studies, no study has yet been performed on the impact of silymarin (with the proven antioxidant and anti-inflammatory effects) in the treatment of allergic rhinitis. It should be noted that other herbal products with confirmed antioxidant and anti-inflammatory effects have been examined in this disease, and a desired outcome mostly in relieving major symptoms and improving the quality of life of such patients has been achieved.

Although silymarin’s biochemical mechanisms have not yet been fully understood, many experimental studies have shown that they are mainly caused by the scavenging of free radicals from the body, which is verified by stabilizing the cell membrane and adjusting the body’s glutathione level. However, the protective effects of silymarin (flavonoids) could be accomplished through other various mechanisms that result in inducing antioxidant production through triggering protein synthesis.

In numerous studies, herbal mixtures (eg, Aller-7) have been used in treating allergic rhinitis. A significant improvement has been observed in major symptoms, life quality, total

### Table 2. Comparing Intergroup Pre- and Posttreatment Clinical and Laboratory Findings

<table>
<thead>
<tr>
<th></th>
<th>Study Group</th>
<th>Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in pre- and posttreatment symptom severity(SNOT-20)</td>
<td>9.23 ± 5.14</td>
<td>2.20 ± 2.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Difference in pre- and posttreatment nasal smear eosinophil, %</td>
<td>–0.89 ± 38.20</td>
<td>–1.62 ± 21.18</td>
<td>.929</td>
</tr>
<tr>
<td>Difference in pre- and posttreatment serum IgE level</td>
<td>–602.50 ± 1004.60</td>
<td>3.80 ± 1004.90</td>
<td>.027</td>
</tr>
<tr>
<td>Difference in pre- and posttreatment interferon-γ level</td>
<td>9.52 ± 211.80</td>
<td>9.08 ± 213.30</td>
<td>.993</td>
</tr>
<tr>
<td>Difference in pre- and posttreatment interleukin-4 level</td>
<td>1.71 ± 15.93</td>
<td>–2.12 ± 13.17</td>
<td>.327</td>
</tr>
<tr>
<td>Difference in pre- and posttreatment interleukin-5 level</td>
<td>0.70 ± 6.29</td>
<td>–1.47 ± 6.42</td>
<td>.202</td>
</tr>
</tbody>
</table>

Abbreviation: SNOT-20, Sino-Nasal Outcome Test 20. Values presented as mean ± SD.
eosinophil count, mucociliary cleansing time, exhalation air speed, and nasal air circulation.\textsuperscript{11,13} In the current study, silymarin administration for a month besides other routine treatments for allergic rhinitis showed a significant improvement in the severity of clinical symptoms based on the SNOT-20. The progress in clinical symptoms was also observed in the control group, which solely received the routine treatments for allergic rhinitis. Still, the degree of improvement was significantly higher in the study group. As mentioned before, there is no similar study to compare the results. However, Saxena et al\textsuperscript{12} reported a significant decrease in the total eosinophil count after treatment with an herbal mixture of Aller-7 with antioxidant properties. In our study, the posttreatment nasal smear eosinophil percentage showed no significant difference ($P > .1$). Nonetheless, nasal smear eosinophil percentage is not a reliable variable in the diagnosis or treatment follow-up of allergic rhinitis.

Serum IgE level should have decreased but instead showed a significant rise after treatment with silymarin. Serum IgE level has not been measured in any previous study that has administered antioxidant agents for the treatment of allergic rhinitis. Considering that the disease’s symptoms had markedly improved in cases in comparison with controls based on the SNOT-20, the rise in IgE level could also be defined as a probable allergic reaction to the drug. Nevertheless, differential diagnoses for elevated serum IgE are numerous (fungal and parasite infections, immunologic syndromes, neoplastic diseases, burns and dermatitis, liver diseases, etc). Respectfully, in the cases treated with silymarin and having shown a uniform increase in serum IgE level, these diagnoses are out of the frame as the history and physical examination of the studied patients were fully reviewed.

Cytokine levels have also not been evaluated in previous studies investigating the effect of antioxidants on allergic rhinitis. In the current study, their posttreatment level showed no significant difference in either group, despite the fact that IL-5, which is responsible for eosinophil accumulation, and IL-4, which is the main cytokine of Th2 cells, decrease after effective treatment of allergic rhinitis, and at the same time, IFN-\gamma, the main cytokine of Th1 cells, increases. Therefore, the nonchanging condition in cytokine levels after silymarin treatment could be the result of the inefficiency of this drug, particularly for the laboratory and immunologic findings of this disease.

This study had its own limitations. Its main limitation was not using silymarin individually for controlling the patients’ symptoms; this was due to ethical considerations and the patients’ probable dissatisfaction in using a single experimental drug. Therefore, silymarin was applied along with other routine treatments.

Because of limited facilities, we evaluated the immunologic condition of the patients by studying serum IgE and cytokine levels, whereas measuring such indexes in the nasal discharge has a much higher specificity and accuracy in evaluating an allergic condition limited to the upper airway system. This is because other simultaneous systemic inflammatory disorders can also affect serum IgE and cytokine levels.

Furthermore, the difference in response rates could be due to remarkable differences in oxidative stress laboratory tests, which were not investigated in the current study because of some limitations but would be highly recommended for future research in this field.

**Conclusion**

Silymarin is a safe medicinal plant with proven antioxidant properties in various studies; it is being increasingly administered in different diseases. Because it also has statistically alleviated the severity of clinical symptoms in allergic rhinitis and led to a high rate of patient satisfaction, the application of this antioxidant drug, which has numerous protective effects on various body organs, especially in neoplastic and inflammatory disorders, is recommended in the treatment of allergic rhinitis. Knowing that allergic diseases, including allergic rhinitis, are mostly multifactorial, control and prevention of oxidative stresses cannot be fully overcome individually. Therefore, the use of such drugs besides other routine treatments is advisable in most cases.

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**Author Contributions**

Mehdi Bakhshaei, study design and conduct; Farahzad Jabbari, study design and conduct, analysis; Saeed Hoseini, data collection; Reza Farid, study design; Mohammad Hadi Sadeghian, conduct; Mohsen Rajati, editing; Amir Houshang Mohamadpour, interpretation of data; Rahman Movahhed, writing; Mohammad Ali Zamani, data collection.

**Disclosures**

**Competing interests:** None.

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