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Assessment of Change in Cytokine and Chemokine Profile with Antioxidant Therapy in Allergic Rhinitis

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ABSTRACT

Allergic rhinitis (AR) is a common disorder that affects people of all ages and is associated with significant impairments in quality of life, sleep and work performance. The prevalence of AR is approximately 10-40%, 1 in 6 individuals are affected by allergic rhinitis across the globe. A total of 64 patients attending the outpatient section of Otorhinolaryngology department, diagnosed with persistent moderate-severe allergic rhinitis as per ARIA guidelines, fulfilling the inclusion and exclusion criteria were included in this study. The patients were randomly assigned to two groups of 32 patients each. After the initiation of the therapy, patients were followed up at 2 weeks, 4 weeks and 8 weeks. The mean age of the test group was 28.06±8.4 years, while the control group's mean age was significantly higher at 34.62±8.3 years, with a P value of 0.006 indicating a significant difference. The gender distribution between the test and control groups was not significantly different. The distribution of most common allergens showed similar trends between the test and control groups. The most common allergen was Dermatophagoides farinae. The mean TNSS score before therapy in the test group was 8.09±1.532, which significantly reduced to 4.25±1.524 after therapy while in the control group, it decreased from 7.81±1.148 before therapy to 6.66±1.516 after therapy. In the test group, the mean IL-4 declined by 20.39% after therapy while the mean IL-13 level showed 9.48% reduction. On the other hand, in the control group both mean IL-4 and IL-13 levels slightly increased. The significant decrease in IL-4 and IL-13 levels in test group as compared to control group indicate that the therapy was effective in study subjects. Thus, we can conclude that antioxidants may play a major role in the prevention and treatment of AR. However more studies with a larger sample size are needed to further confirm these findings.

INTRODUCTION

The prevalence of AR is around 10-40%, depending on geographic location[1]. It is an atopic disorder having symptoms of nasal congestion, rhinorrhea, sneezing, postnasal drip and nasal pruritus. It can also have other symptoms like non-productive cough, chronic rhino sinusitis, eustachian tube dysfunction, aural fullness, itching and allergic conjunctivitis[2,3]. Allergic Rhinitis is per se a Type I Hypersensitivity reaction. A complex of reactions involving components of the immune system -cells, mediators, cytokines, neuropeptides, adhesion molecules etc. are involved in manifestation of the disease symptoms. Mainly the cytokines interleukin-4 (IL-4), interleukin-5 (IL5) and interleukin-13 play a critical role in the production of atopic allergic rhinitis[4,5]. The routine therapies for Allergic rhinitis include nasal steroid sprays and oral antihistamines or antileukotriene drugs, such as cetirizine, montelukast, and desloratadine citrate desmodium[6]. Inhalational Nasal Steroids (INS) are recommended as first-line treatment for patients with moderate-to severe symptoms of Allergic rhinitis (AR)and has been proven to improve all nasal symptoms and patients' quality of life. However, a study has indicated that only 60% of subjects achieve relief from INS, which indicates the need for additional treatment to improve its efficacy[7]. Anti-histamines and inhalational nasal steroids have demonstrated impressive effects on AR, yet issues such as the length of treatment and poor patient compliance persist. There are few studies in which alternative treatment options like antioxidant therapy, vitamin D have been tried in the treatment of allergic rhinitis. Chauhan *et al.,* studied the effect on the clinical outcome of perennial allergic rhinitis patients with anti-oxidant therapy and demonstrated marked improvement in the mean total daytime and night time nasal symptom scores and composite symptom scores[8]. But there is no study in which effect of antioxidant therapy on the cytokine profile of allergic rhinitis has been done. In this study we aim to analyze the change in cytokine and chemokine profile in patients with persistent moderate-severe allergic rhinitis patients after anti-oxidant therapy.

MATERIALS AND METHODS

This was a prospective, randomized, open label Case-Control study conducted in the Department of ENT-HNS together with the Department of Biochemistry at a postgraduate teaching Institution in India between August' 22 to July 24 after obtaining clearance from the Institutional Ethics Committee (letter number HIMSR/IEC/0066/2022) All patients diagnosed with Allergic rhinitis, as per ARIA guidelines, were evaluated comprehensively and based on the inclusion, exclusion criteria for recruitment in the study.

Inclusion Criteria:

- Subjects between 18 and 55 years of age.
- Diagnosis of Persistent Moderate-severe allergic rhinitis.
- Giving consent for participating in the study.

Exclusion Criteria:

- Non-Allergic Rhinitis.
- Treatment with antibiotics or anti-histaminics (within 4 weeks).
- Respiratory tract infection within 2 weeks.
- Chronic rhino sinusitis.
- Gross structural abnormalities of the nasal airway
- Immune deficiency disorder.
- Systemic disease like HTN, DM, Renal, Liver, or cardiovascular disease.
- Pregnancy or lactation.

The Patients Who Fulfilled the Inclusion Criteria Were Randomized into two Groups: Group A, receiving 110 mcg FF (Fluticasone Furoate) nasal spray along with oral administration of Antioxidants in the following dose-Vitamin A 25,000 IU once a week., Vitamin C (ascorbic acid) 1000 mg, Vitamin E 200 mg (200 IU), and Selenium 40 mcg daily and group B, receiving 110 mcg of FF (Fluticasone Furoate) nasal spray once daily with the first dose administered at the clinic after device demonstration. Also, blood samples were taken to see the complete blood counts, Absolute eosinophil count, serum specific-IgE as well as to measure the serum levels of cytokines and chemokines, namely IL-4, IL-13 and MIP-1ß at the start of treatment. After initiation of therapy, patients were called for follow-up at 2, 4 and 8 weeks. At each visit, they were evaluated on TNS Score and findings noted. The clinical examination at each visit was done by the same clinician to eliminate inter observer variations and to enhance the credibility of the nasal examinations of the subjects. Nasal endoscopy for nasal secretions and turbinate swelling were done. Repeat blood tests were done at 8 weeks follow-up only.

Assay Procedure for Cytokines and Chemokines:

- 100 µL of diluted standard or sample was put in each well. The analysis was carried out in duplicate.
- The micro plate was covered and incubated for 2 h at room temperature.
- The liquid in each well was removed and washed, repeating the process for a total of three washes. Wash is done by filling each well with 1×Wash buffer (250 µL) using an automated micro plate, and let it stand for 1-2 min. Complete removal of liquid at each step is essential for good test performance. After the last wash, any remaining 1×Wash Buffer was removed by inverting the plate and blotting it against clean blotting paper.

- Then, 100 µL of 1×Human IL-4 was added to each well to detect antibody. Plate is covered and incubated for 1 h at room temperature.
- Washes are repeated as in step 3.
- Now, 100 µL of 1×Streptavidin-HRP was added to each well.Again the plate was covered and incubated for 30 min at room temperature, taking care not to expose the plate to direct light.
- The wash process is repeated for five times as in step 3.
- Then, 100 µL of HRP Substrate (TMB) is added to each well, plate covered and incubated for 15 min at room temperature, protecting it from expose to light.
- Finally, 50 µL of Stop solution is added in each well and colour change noted. The colour in the wells should change from blue to yellow. If the colour in the wells is green or if the colour change does not appear uniform, plates can be gently tapped so as to ensure thorough mixing.
- The Optical Density of each well was measured, within 30 min, using a micro plate reader at 450nm wavelength.

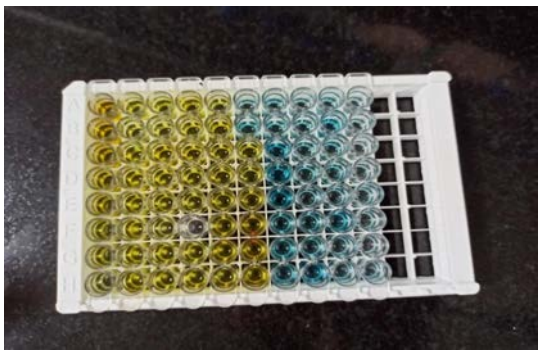

Fig. 1: Assay Procedure for Cytokines and Chemokines

RESULTS AND DISCUSSIONS

This study was conducted on 64 age and sex matched individuals, 32 in each group. The study aimed to evaluate the effectiveness of our novel therapeutic regime in patients with allergic rhinitis by comparing various parameters between a test group and a control group. Key aspects assessed included demographics, diagnostic nasal endoscopy findings, allergen sensitization, TNS scores and cytokine levels. Allergen sensitization profiles were compared to understand the allergic burden in each group. Symptom scores, including total nasal symptom scores (TNSS), nasal blockage, rhinitis, sneezing and pruritus, were measured before and after therapy to determine symptomatic improvements after 8 weeks. Furthermore, cytokine levels of IL-4, IL-13 and MIP-1ß were analyzed pre-and post-therapy to evaluate immunological responses. The percentage improvement in symptom scores and cytokine levels was calculated to quantify therapeutic benefits. This comprehensive assessment provides a detailed comparison of the therapeutic outcomes between the test and control groups, highlighting significant findings and their implications for allergic rhinitis management. Here is the section wise review of the results.

Age Range: The mean age of the test group was 28.06±8.4 years, while the control group's mean age was significantly higher at 34.62±8.3 years, with a P value of 0.006 indicating a significant difference.

Gender: The gender distribution between the test and control groups was not significantly different, with a P value of 0.601. In the test group, 18 participants (56.25%) were male and 14 (43.75%) were female. In the control group, 20 participants (62.5%) were male and 12 (37.5%) were female.

Smoking Incidence: In the test group, 50% of male patients (9 out of 18) had a history of smoking, while the remaining 50% did not. Similarly, in the control group, 49% of male patients (10 out of 20) reported a smoking history, with 51% being non-smokers. Notably, no female patients in either group had a history of smoking. In the test group, all 14 female patients (100%) were non-smokers, and in the control group, all 12 female patients (100%) also had no smoking history.

Sensitized Number of Allergens Via IgE/SPT: The test group had a wider range of sensitization to allergens compared to the control group. In the test group, 17 patients had sensitivity against 5 or more allergens while in the control group such patients were only 6. Sensitivity against 4 allergens was more prevalent in the control group,50%. Pearson Chi-Square P values were 0.347 for the test group and 0.238 for the control group, suggesting no significant statistical difference. This distribution has been presented in the following chart.

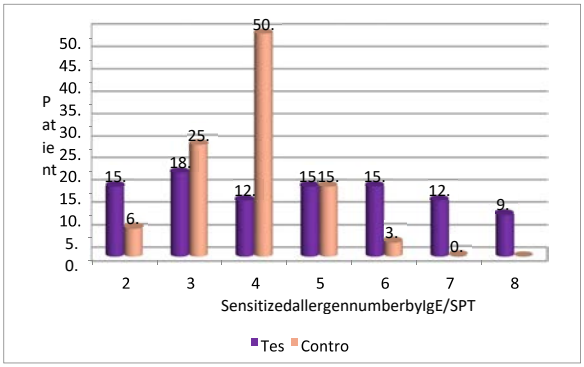

Fig. 2: Allergen Sensitization Via IgE/SPT

Top Allergens: The distribution of top allergens showed similar trends between the test and control groups. The most common allergen was Dermatophagoides farinae, affecting 12 patients (37.5%) in the test group and 11 patients (34.4%) in the control group. Other common allergens included Chenopodium album, Aspergillus fumigatus and Hay dust. Some allergens like Dermatophagoides pteronyssinus were present only in the control group, affecting 4 patients (12.5%). The test group showed a broader range of allergens, including those not present in the control group.

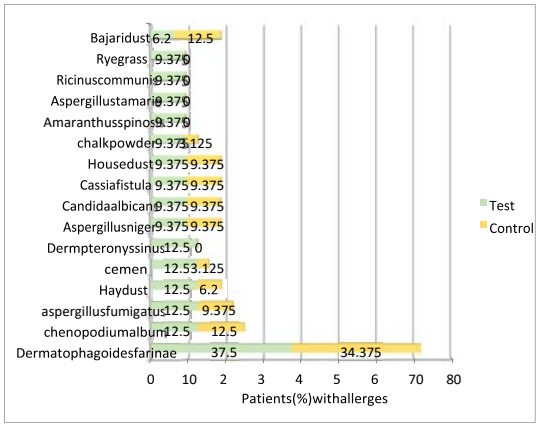

Fig. 3: Sensitization of Top Allergens of Patients in Both Groups

Symptom Scores: In the test group, the Total Nasal Symptom Score (TNSS) and individual symptoms were assessed before and after an 8-week therapy period. The mean TNSS score before therapy was 8.09±1.532, which significantly reduced to 4.25±1.524 after therapy, demonstrating a notable improvement with a P value of 0.0001, indicating strong statistical significance. The test group exhibited greater improvement across all symptoms compared to the control group. The TNSS score improved by 47% in the test group versus 15% in the control group. Nasal blockage improved by 54% in the test group compared to 17% in the control group. Rhinitis, sneezing and pruritus showed similar trends, with improvements of 45%, 42% and 44% respectively in the test group, compared to 11%, 14% and 19% in the control group.

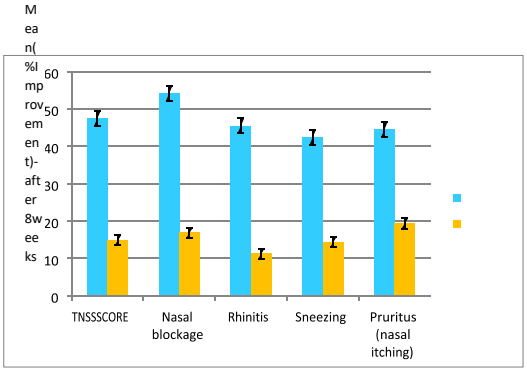

Fig. 4: Percentage Improvement in Symptom Scores After 8 Weeks

Analysis of Cytokine Levels Before and After Treatment: In the study group, the levels of two cytokines-Interleukin-4 (IL-4), Interleukin-13 (IL-13), and one chemokine Macrophage Inflammatory Protein-1 Beta (MIP-1ß)-were measured before and after the 8week period to assess the immunological impact of therapy.

Interleukin-4 (IL-4): Before therapy, the mean IL-4 level was 3.3±2.4 pg/ml. After 8 weeks of therapy, the mean IL-4 level decreased to 2.6±2.1 pg/ml. This reduction was statistically significant, with a P value of 0.036. The 20.39% decrease in IL-4 levels indicates that the therapy effectively reduced this cytokine, which is often associated with allergic responses and inflammation. However, in control group, the mean IL-4 level was 5.2±6.5 pg/ml. After the 8-week period, the IL-4 levels slightly increased to 5.3±5.0 pg/ml. This change was not statistically significant, with a p-value of 0.934. The slight increase of 1.75% in IL-4 levels indicates that the control treatment does not effectively reduce IL-4 levels.

Interleukin-13 (IL-13): The mean IL-13 level before therapy was 33.8±5.4 pg/ml. Following therapy, the IL-13 levels dropped to 30.6±7.2 pg/ml. This change was statistically significant, with a P value of 0.047. The 9.48% reduction in IL-13 levels suggests that the therapy had a beneficial effect in lowering this cytokine, which plays a role in allergic inflammation and asthma. Further, IL-13 level in control group was 29.0±5.7 pg/ml before therapy and after 8 weeks of follow-up the IL-13 levels rose to 35.0±17.8 pg/ml. Although this change was not statistically significant (p-value of 0.073), the 20.66% increase in IL-13 levels suggests that the control treatment might have inadvertently elevated this cytokine, which could potentially worsen allergic inflammation.

Macrophage Inflammatory Protein-1 Beta (MIP-1ß): Interestingly, the MIP-1ß levels in the test group increased from 106.5±67.7 pg/ml before therapy to 126.5±113.2 pg/ml after therapy. This increase was not statistically significant, as indicated by a P value of 0.36. The 18.79% increase in MIP-1ß levels suggests a complex immune response, possibly indicating a shift in the inflammatory profile that may not be directly beneficial or detrimental without further context. However, MIP-1ß levels in the control group showed a minor decrease from 121.4±99.7 pg/ml before therapy to 116.8±103.8 pg/ml after therapy, with a non-significant P value of 0.834. The 3.85% decrease suggests a negligible impact of the control treatment on this cytokine. Although there is an increase in MIP-1ß levels in the test group and a slight decrease in the control group, these changes are not sufficient to draw definitive conclusions about the efficacy or

impact of the therapies on MIP-1ß levels. The significant decrease in IL-4 and IL-13 levels in test group as compared to control group indicate that the therapy was effective in study subjects.

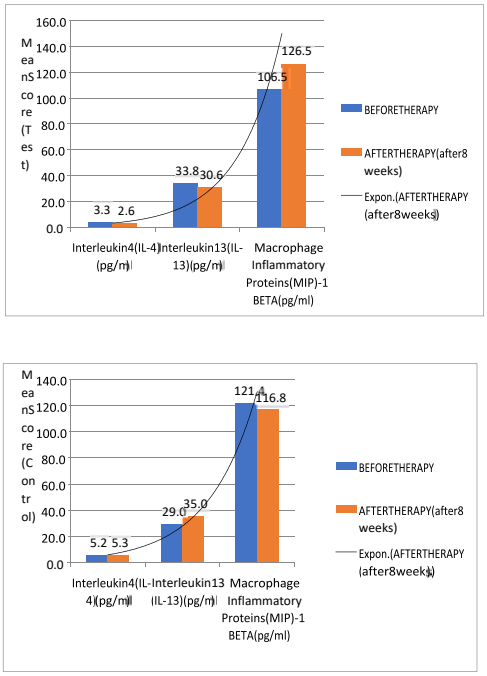

Fig. 5: Cytokine Levels Before and After Therapy, (a) Test Group and (b) Control Group

Mean (% Improvement) in Cytokine Levels: The analysis of mean percentage improvement in cytokine levels provides insight into the effectiveness of the therapy administered to the test group compared to the control group. Specifically, it examines the changes in levels of three key cytokines: Interleukin-4 (IL-4), Interleukin-13 (IL-13) and Macrophage Inflammatory Protein-1 Beta (MIP-1ß). The mean percentage improvement in cytokine levels highlights the differential impact of the therapies administered to the test and control groups. The test group showed significant reductions in IL-4 and IL-13 levels, indicative of a successful anti-inflammatory and immuno modulator effect of the therapy. The increase in MIP-1ß in the test group, however, points to a more complex immunological response that warrants further exploration. On the other hand, the control group exhibited negligible or negative improvements in cytokine levels, with increases in IL-4 and IL-13 suggesting an exacerbation of inflammatory responses. The slight decrease in MIP-1ß in the control group was not substantial enough to indicate any meaningful therapeutic effect. These results underscore the efficacy of the therapy used in the test group in reducing key cytokines associated with allergic inflammation, compared to the control treatment.

Percentage Improvement in Cytokine Levels After 8 Weeks

Mean (% Improvement)	Test	Control
IL-4 (pg/ml)	20.39	-1.75
IL-13 (pg/ml)	9.48	-20.66
Macrophage Inflammatory Proteins (MIP)-1 BETA (pg/ml)	-18.79	3.85

Understanding the prevalent allergens in allergic rhinitis is crucial for effective management and treatment strategies. In our study, in the test group, Dermatophagoidesfarinae was identified as the most common allergen, sensitizing 37.5% of individuals. Additionally, chenopodium album, Aspergillus fumigatus and hay dust were prevalent allergens, each sensitizing 12.5% of patients. Similar allergens dominated the sensitization profiles of the control group, with Dermatophagoidesfarinae remaining prominent, sensitizing 34.4% of patients. These findings emphasize the importance of house dust mites as primary allergens in allergic rhinitis which is similar to the findings observed in many other studies[9-11]. Chenopodium album, Aspergillus fumigatus and hay dust were also common allergens in this group, consistent with their prevalence in the test group. Comparing allergen profiles between the test and control groups reveals consistency in sensitization patterns. The overlap in prevalent allergens suggests similar environmental exposures in both groups, supporting the internal validity of the study. This consistency strengthens the reliability of the findings and ensures that any observed treatment effects can be attributed to the interventions rather than variations in allergen exposure. In Group A, despite the high incidence of smoking among males, the combination of FF and antioxidants resulted in substantial improvements in symptom scores and reductions in inflammatory cytokines. This suggests that the addition of antioxidants might help mitigate the negative effects of smoking by reducing oxidative stress and inflammation, thereby enhancing the overall treatment efficacy. The significant improvements in Total Nasal Symptom Score (TNSS), nasal blockage, rhinitis, sneezing and pruritus in Group A (Test) patients indicate that the combined therapy can be effective even in patients with a smoking history. Conversely, in Group B, which was treated with FF alone, the improvements in symptom scores were less pronounced. The modest improvements in TNSS, nasal blockage, rhinitis, sneezing and pruritus suggest that FF alone may not be as effective in patients with a history of smoking. The persistence of high cytokine levels, particularly IL-4 and IL-13, in the control group further underscores the potential limitations of FF mono therapy in addressing the inflammation and oxidative stress associated with smoking[12]. The mean percentage improvement in symptom scores of TNSS over eight weeks further emphasizes the efficacy

differences between the two treatment regimens. Group A showed a remarkable 47% improvement in TNSS, 54% in nasal blockage, 45% in rhinitis, 42% in sneezing and 44% in pruritus. These substantial improvements demonstrate the superior efficacy of the combined FF and antioxidant therapy in alleviating allergic rhinitis symptoms. Conversely, Group B showed modest improvements with a 15% improvement in TNSS, 17% in nasal blockage, 11% in rhinitis, 14% in sneezing and 19% in pruritus. While FF alone is effective, the addition of antioxidants significantly enhances symptom relief, as reflected by the higher improvement percentages in Group A. In another study by Kaiser *et al.,* Fluticasone furoate, substantially decreased nasal symptoms compared to placebo, with an observed TNSS difference of-1.473 (P and lt.001) for the whole treatment period[13]. In a study by Mirmoezzi *et al.,* the changes in total nasal symptom scores from baseline (W0) for individual symptoms in two treatment groups: Fluticasone propionate and Mometasone furoate. Both treatments showed significant reductions in nasal symptoms across all evaluated parameters[14]. There have been few studies on the role of anti-oxidants in AR. However most of these studies demonstrated subjective improvement. In none of these studies improvement in the level of cytokine was analyzed. Wang and Pan *et al.* in their study demonstrated the association of low serum levels of Vitamin E in children with allergic rhinitis. Vitamin E is a major lipid soluble antioxidant present in all cellular membranes and can act directly against a variety of oxygen free radicals, including peroxy radicals, super oxide radicals and singlet oxygen and which thereby protects against lipid peroxidation[15]. Farid *et al.* demonstrated serum selenium levels in 33 patients with allergic rhinitis and 21 cases of allergic asthma using spectrophotometer method (atomic absorption). The mean serum selenium levels in patients of allergic rhinitis and asthma were much lower than the control group with similar age and sex[16]. In an observational study conducted by Vollbracht *et al.*, the interim sub-group analysis proved that in patients of allergies, high dose of vitamin C intravenously reduced both specific symptoms (respiratory and cutaneous symptoms) and non-specific symptoms (fatigue, depression, disturbed sleep, poor concentration)[17]. Feng *et al,* in a study on the effects of vitamin A on the severity of allergic rhinitis and asthma in animal models showed decreased total IgE, IL-4, IL-17, IL-33 after vitamin A administration[18]. These findings align with our research demonstrating the efficacy of intra nasal corticosteroids along with antioxidants in enhancing the therapeutic effect, providing substantial relief from allergic rhinitis symptoms. The changes in cytokine levels corroborate the symptom score improvements. Group A exhibited a 20.39% reduction in IL-4 levels and a 9.48% reduction in IL-13 levels, indicating a substantial decrease in Th2-mediated inflammation. However, the 18.79% increase in MIP-1ß levels suggests a complex inflammatory response, possibly involving regulatory mechanisms that need further exploration. In contrast, Group B showed a 1.75% increase in IL-4 levels and a 20.66% increase in IL-13 levels, reflecting persistent allergic inflammation. The modest 3.85% decrease in MIP-1ß levels in Group B is not significant enough to suggest a strong anti-inflammatory effect. These cytokine level changes highlight the additional anti-inflammatory benefits provided by antioxidants when combined with FF therapy. In a study done by Nur Husna *et al.*, they found that IL-4, IL-5, IL-6 and IL-13 blood levels were significantly higher in AR patients, as was the expression of IL13RA1 transcripts in AR patient's nasal epithelial cells compared to non-allergic controls[19]. In another study, it has been observed that consuming thyme, which has antioxidants that reduce IL-5 and raise the anti-inflammatory cytokine IL-4, helps to reduce inflammation and alleviate the symptoms of allergic rhinitis[20]. The findings from this study align with and expand upon previous research by Chauhan *et al* demonstrating the benefits of combining FF with antioxidants for managing allergic rhinitis. For instance, antioxidants such as vitamin C and E have shown to reduce oxidative stress and inflammation in respiratory diseases, supporting the observed efficacy in Group A. The significant reductions in IL-4 and IL-13 levels in Group A are consistent with studies indicating that antioxidants can modulate cytokine production and reduce Th2-mediated allergic responses. In contrast, the control group's persistent cytokine levels align with findings that FF alone, while effective, may not fully address the oxidative stress and inflammation underlying allergic rhinitis. In another study when antioxidants and FF were used together, the PAR symptoms were much reduced as opposed to when FF was used alone[8]. Previous research by Dhanawat *et al* showed the effectiveness of adding antioxidants to INS (FF) in the treatment of AR produced similar results. Overall, no problems with tolerability and safety that were clinically significant were found. Sneezing, burning sensation were a few minor side effects of the medication that were comparable to those seen in past research. Overall, our study underscores the potential of integrating antioxidants into standard FF therapy for allergic rhinitis. The combined treatment not only provides superior symptom relief but also achieves significant reductions in key inflammatory cytokines, offering a comprehensive approach to managing this chronic condition. These results suggest a promising

avenue for enhancing allergic rhinitis treatment protocols and improving patient outcomes.

CONCLUSION

This study was conducted to analyze the change in cytokine and chemokine profile after antioxidant therapy along with standard treatment in Allergic Rhinitis patients. The study also compared the Total Nasal Symptom Score (TNSS) in patients with allergic rhinitis before and after therapy. The most common allergen found in AR patients in our study was Dermatophagoides farinae. Analysis of study data suggests that adding antioxidants results in a significant improvement in clinical outcome of AR patients. The significant decrease in IL-4 and IL-13 levels in test group as compared to control group further indicate that the antioxidant therapy was effective in AR patients. Thus, we can conclude that antioxidants play a major role in the prevention and treatment of AR. However more studies with a larger sample size are needed to further confirm these findings.

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