Allergic Respiratory Disorders: Role of Bresol

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INTRODUCTION

Immunologically, there are two important phases in a child in-utero and postnatal. In the 18th week of gestation, T_h (T helper) cells appear in the blood. These cells prepare the child’s immune system for postnatal life. When there is a balance between T_h1 and T_h2 cells, interleukin-2 (IL-2), interferon-γ, tumor necrosis factor (TNF), and natural killer (NK) cells—which give protection against viruses, bacteria, and other microorganisms—are produced in the body. However, inheritance of certain genes in children results in the production of excessive T_h2 cells in the immune system. When such children are exposed to allergens, they develop allergic diseases.¹

The immune system consists of two types of immune responses: specific and nonspecific. Specific response is characterized by its ability to recognize specific invaders (antigens); cells of specific response include T cells, B cells, and NK cells. Some of these cells destroy antigens directly, whereas others secrete antibodies to destroy them. Nonspecific immune mechanisms help eliminate infections by rapidly killing bacteria and viruses upon first contact.

Allergy is an overreaction of the immune system induced by exposure to a particular

<table>
<thead>
<tr>
<th>Table 1. The road to allergy</th>
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<tbody>
<tr>
<td>15-16 weeks of gestation</td>
</tr>
<tr>
<td>17-18 weeks of gestation</td>
</tr>
<tr>
<td>2nd-3rd trimester</td>
</tr>
<tr>
<td>Birth</td>
</tr>
<tr>
<td>Infancy</td>
</tr>
<tr>
<td>No T cells can be identified</td>
</tr>
<tr>
<td>T_h1 + T_h2 (normal)</td>
</tr>
<tr>
<td>IL-2</td>
</tr>
<tr>
<td>Protective effect</td>
</tr>
<tr>
<td>Interferon-γ</td>
</tr>
<tr>
<td>TNF</td>
</tr>
<tr>
<td>Natural (innate) immunity</td>
</tr>
</tbody>
</table>

¹
An allergen is a substance that the body perceives as foreign and dangerous, and causes an allergic reaction. Common allergens include pollen, animal dander, feathers, mites, chemicals, drugs, and a variety of foods.

Allergy develops after repeated exposure to the causative allergen. Sensitization takes place on initial exposure to the allergen, a process that may take up to 6 weeks to develop; no adverse reaction seems to occur during this stage. During sensitisation, immunoglobulin E (IgE) antibodies are produced by white blood cells and on reexposure, IgE antibodies bind the allergen and attach to mast cells, which release histamine. This triggers the beginning of the allergic reaction causing wheezing, sneezing, itchy skin, red and watery eyes, ache, fatigue, fever, diarrhoea, stomachache, and vomiting. Symptoms could be seasonal or chronic depending on the allergen involved.

Allergy of the respiratory tract occurs when airborne allergens enter the respiratory tract and elicit an adverse immunological response. The nature of the airway immune response depends on the nature of the allergen, the antigen-processing pathway, and the microenvironment which dictates the phenotype of available T lymphocytes.

Respiratory allergic diseases (rhinitis and bronchial asthma) have become serious health issue affecting a major chunk of global population.

ALLERGIC RHINITIS

Allergic rhinitis (AR) is a symptomatic disorder of the nose induced, after allergen exposure, by an IgE-mediated inflammation of the membranes lining the nose. The peak incidence of 37 per 1000 occurs at 10 to 15 years of age with a decrease in its incidence with age.7

The pathology of AR can be divided into early- and late-phase reactions. Early-phase symptoms occur within minutes of allergen exposure and are characterised by rhinorrhea, nasal obstruction, sneezing, and pruritus.3 IgE-mediated activation of mast cells and basophils release mediators (histamine and leukotriene), which activate their respective receptors and induce the symptoms of AR. Histamine is the major mediator of the early-phase reaction.4 Both mast cells and T cells release cytokines (ILs), which induce IgE synthesis.5 Approximately 30% to 40% of patients develop a late-phase reaction occurring 4 to 5 hours after the initial allergen exposure characterized by congestion and nasal obstruction.6 Other symptoms such as impaired sense of smell, postnasal drip, sore throat, hoarseness, and watery eyes may also occur. AR has traditionally been divided into seasonal (caused by airborne plant pollens) and perennial (caused by indoor allergens). The causative allergens of perennial AR commonly include house-dust mites, indoor molds, cockroaches, and animal dander.7

AR is characterised by continuous or periodic nasal congestion; rhinorrhea; sneezing; pruritus of the conjunctiva, nasal mucosa, and oropharynx; lacrimation; and fatigue. Predisposing factors include family history of similar symptoms and a personal history of collateral allergy manifested as eczematous dermatitis, urticaria, and/or asthma. Clinical presentation may include nasal polyps, pale and boggy (reddened or excoriated) nasal passages, congested and edematous conjunctiva, injected pharynx, and swelling of the turbinates.8

Management

Allergen avoidance is the first line of management for AR. Keeping the house clean, using effective air filtering system, washing the beddings with hot water, replacing carpets with hard flooring, and wiping surfaces regularly with wet clothes are some of the measures that will eradicate most allergens. However, total exclusion of allergens from the environment is difficult. Therefore, treatment to control the symptoms of AR is frequently used.
Antihistamines
The first-generation antihistamines (e.g., chlorpheniramine, diphenhydramine) are effective in reducing the symptoms such as sneezing, itching, and rhinorrhea. Adverse effects include sedation and decreased reaction time. The second-generation antihistamines (e.g., loratadine, cetirizine, fexofendaine, desloratadine, and levocetirizine) are much better tolerated than the first-generation antihistamines. Adverse reactions associated with all types of antihistamines include dryness, stuffiness, sedation, fatigue, headache, and psychomotor impairment.

Decongestants
Decongestants are $\alpha$-adrenergic agonists that reduce nasal swelling, thus relieving congestion. Rebound congestion is the major adverse effect associated with decongestants. Other adverse effects include anxiety, irritability, insomnia, and palpitations. e.g., pseudoephedrine, phenylephrine, oxymetazoline, and xylometazoline.

Intranasal corticosteroids
Corticosteroids are beneficial in AR due to their ability to decrease inflammation caused by exposure to an allergen. Adverse effects include sneezing, stinging, headache, and nose bleeds. E.g., budesonide, fluticasone, beclomethasone, and flunisolide.

Mast cell stabilizers
Cromolyn, a mast cell stabilizer, acts by stabilising the mast cell, thereby preventing the release of mediators, particularly histamine. Because of this unique mechanism, it must be initiated before the onset of symptoms. Adverse effects include increase in sneezing, nasal burning, or stinging.

Leukotriene inhibitors
Leukotriene inhibitors block the action of leukotrienes in the lungs and bronchial tubes by binding to them, and reduce the bronchoconstriction caused by leukotrienes resulting in reduction of inflammation. Adverse effects include gastrointestinal disturbances, hypersensitivity reactions, sleep disorders, and increased bleeding tendency. e.g., montelukast, zafirlukast, and zileuton.

ASTHMA
Numerous factors such as alteration in the number or type of infections early in life, widespread use of antibiotics, adoption of unhealthy lifestyle, and repeated exposure to allergens, may affect the balance between $T_{h1}$-type and $T_{h2}$-type cytokine responses and increase the likelihood that the immune response will be dominated by $T_{h2}$ cells, resulting in allergic diseases such as asthma, a chronic inflammatory disorder of the airways. Airflow obstruction is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

Inhaled antigen activates the mast cells and $T_{h2}$ cells in the airway. They in turn induce the production of mediators of inflammation (such as histamine and leukotrienes) and cytokines (such as IL-4 and IL-5). IL-5 travels to the bone marrow and causes terminal differentiation of eosinophils. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with selectins, and eventually adhering to endothelium through the binding of integrins to members of the immunoglobulin superfamily of adhesion proteins: vascular-cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). As eosinophils enter in to the matrix of airway through the influence of various chemokines and cytokines, their survival is prolonged by IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). On activation, the eosinophil releases inflammatory mediators, such as
leukotrienes and granule proteins, to injure airway tissues. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and contribute to persistent airway inflammation.

Symptoms such as tightness of chest, breathlessness, and wheezing may be caused by dust, cold air, and changes in the environment. Based on the symptoms and pulmonary function tests, asthma can be graded as follows.

Diagnosis of asthma is mainly done by pulmonary function test in which reversible airway obstruction is observed before and after the administration of short-acting bronchodilator.12

Management
The aim of the treatment include minimal chronic symptoms, minimal exacerbations, minimal need for use of β2-agonist, no limitations on activities, including exercise and PEFR variability of less than 20%. The drugs can be divided into maintenance medication (anti-inflammatory) and rescue medication (bronchodilator). Inhaled route is the best route of treatment.13 (Table 2)

**Table 2. Management of asthma**

<table>
<thead>
<tr>
<th>Maintenance medication</th>
<th>Rescue medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled corticosteroids</td>
<td>Inhaled short-acting β2 agonist</td>
</tr>
<tr>
<td>Long-acting β agonists</td>
<td>Inhaled anticholinergics</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>Oral theophyllines (short acting)</td>
</tr>
<tr>
<td>Sustained release theophyllines</td>
<td></td>
</tr>
</tbody>
</table>

**ROLE OF BRESOL IN THE MANAGEMENT OF ALLERGIC RESPIRATORY CONDITIONS**

The treatment options currently available for respiratory allergic conditions have major limitations such as low efficacy, associated adverse events, and patient compliance. Bresol, a phytopharmaceutical formulation recommended for allergic respiratory disorders, has antihistaminic, mast cell stabilizing, IL down-regulating, bronchodilatory, antitussive, mucolytic, antimicrobial, anti-inflammatory, and antioxidant properties, which synergistically act to provide symptomatic relief in allergic respiratory conditions. Table 3 depicts the composition of bresol syrup.

The antihistaminic property of Bresol helps in controlling the symptoms associated with respiratory
disorders, whereas the mucolytic and bronchodilatory properties help in liquefying sputum and easing expectoration, relieving nasal and bronchial congestion. Its antimicrobial action combats the infections caused by gram-positive and gram-negative bacteria.

**CLINICAL TRIAL 1**

Evaluation of the efficacy and safety of Bresol tablets in allergic rhinitis.\(^\text{15}\)

**Aim**

To evaluate the clinical efficacy and short- and long-term safety of Bresol tablets in the management of AR.

**Patients and Method**

**Inclusion criteria**

Patients with a history of being reactive to inhaled allergens and who had been diagnosed with AR, for more than 1 year, were included in the study.

**Exclusion criteria**

Patients with obstruction-causing nasal abnormalities, acute respiratory infection, or severe concomitant disease and who were away from their usual environment for more than a week during the trial were excluded from the study.

**Study procedure**

A total of 100 patients (including 9 children) with clinical symptoms of AR were included into the study. They were administered Bresol at a dosage of 1 tablet twice daily; in severe cases, the dosage was increased to 2 tablets twice daily. The drug was administered for a period of 2 weeks and the treatment was continued for another 2 weeks if no response was observed. Total duration of the study was 3 months.

**Results and Conclusion**

Results of the study showed significant improvement in haematological parameters. On subjective evaluation of the overall effectiveness of the drug, 22% of patients rated it “fair,” 31% “good,” 27% “very good,” and 20% “excellent.” It also prevented the recurrence of AR during the entire study period. None of the patients experienced any adverse effects. Therefore, it can be

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**Table 3. Composition of bresol syrup each 5 ml/each tablet contains:**

<table>
<thead>
<tr>
<th>Exts.</th>
<th>Sanskrit name</th>
<th>Botanical name</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haridra</td>
<td>Curcuma longa</td>
<td>100.5</td>
<td></td>
</tr>
<tr>
<td>Tulsi</td>
<td>Ocimum sanctum</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Vasaka</td>
<td>Adhatoda vasica</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Trikatu</td>
<td>----------------</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Triphala</td>
<td>----------------</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Vidanga</td>
<td>Embelia ribes</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Musta</td>
<td>Cyperus rotundus</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Tvak</td>
<td>Cinnamomum zeylanicum</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ela</td>
<td>Elettaria cardamomum</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Patra</td>
<td>Cinnamomum tamala</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nagakesara</td>
<td>Mesua ferrea</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Other ingredients: Methylparaben sodium, propylparaben sodium, and sodium benzoate

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**Asthma grades**

<table>
<thead>
<tr>
<th>Asthma grades</th>
<th>First choice</th>
<th>Other options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4</td>
<td>Medium to high dose inhaled steroid + LABA. If needed, add oral steroid</td>
<td>Low/medium dose steroid + Leukotriene receptor antagonist/ SR theophylline</td>
</tr>
<tr>
<td>Grade 3</td>
<td>LABA or medium dose inhaled steroid. If recurring severe Exacerbation Medium dose inhaled steroid and LABA</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Low dose inhaled steroid</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>No daily medication</td>
<td></td>
</tr>
</tbody>
</table>
concluded that Bresol tablet is safe and effective in the management of AR.

**CLINICAL TRIAL 2**

Evaluation of the efficacy and safety of Bresol syrup in pediatric allergic rhinitis.

**Aim**
To evaluate the efficacy and safety (short- and long- term) of Bresol syrup among children (in the age group of 3 to 12 years) with AR using an open, noncomparative, phase III clinical trial.

**Patients and Method**

**Inclusion criteria**
Children in the age group of 3 to 12 years with AR were included in the study.

**Exclusion criteria**
Children with severe malnutrition and severe systemic illness were excluded from the study.

**Study procedure**
A total of 105 children were included in the study. They were administered 1 teaspoonful Bresol syrup twice daily for a period of 4 weeks. All children were followed-up on a weekly basis for a period of 1 month and were investigated for haematological and biochemical parameters (Hb, TLC, DLC, and ESR) on entry and at the end of 1 month of treatment.

**Results and Conclusion**
Results of the study showed excellent symptomatic control of AR. Changes in haematological and biochemical parameters noted at the time of the enrollment were also renormalized without any significant adverse events. Therefore, it can be concluded that Bresol syrup is clinically effective and safe in children with AR.

**CLINICAL TRIAL 3**

Evaluation of the efficacy and safety of Bresol tablets in children with upper and lower respiratory tract allergic diseases.

**Aim**
To evaluate the clinical efficacy and safety (short- and long-term) of Bresol tablets in children with AR or allergic bronchitis or asthmatic bronchitis using an open, noncomparative phase III clinical trial.

**Patients and Method**

**Inclusion criteria**
Children in the age group of 3 to 12 years who were presented with symptoms (such as tightness of chest, wheezing, productive cough, and nocturnal asthma) of rhinitis and bronchitis were included in the study.

**Exclusion criteria**
Children with severe malnutrition and severe systemic illness were excluded from the study.

**Study procedure**
A total of 105 children were included in the study; they were divided into three groups: group A (children with AR), group B (children with allergic bronchitis), and group C (children with asthmatic bronchitis). Bresol tablets were administered according to the following dosage schedule: 1 tablet twice daily for 2 weeks for children with AR and allergic bronchitis, whereas 1 tablet twice daily for 12 weeks for children with asthmatic bronchitis.

**Results and Conclusion**
Results of the study showed a significant reduction in the mean scores of rhinitis, bronchitis, tightness of chest, daily asthmatic symptoms, wheezing, cough, shortness of breath, and sputum production at the end of the treatment. Significant improvement in mean
scores of PEFR was also observed. Therefore, it can be concluded that Bresol tablets are clinically effective and safe in children with AR, allergic bronchitis, and asthmatic bronchitis.

**CLINICAL TRIAL 4**

Evaluation of the efficacy and safety of Bresol tablets and syrup in allergic rhinitis. 16

**Aim**

To evaluate the clinical efficacy and safety (short- and long-term) of Bresol tablets and syrup in the management of AR.

**Patients and Method**

*Inclusion criteria*

Patients in the age group of 3 to 60 years with AR were included.

*Exclusion criteria*

Patients suffering from severe systemic comorbid illness, which necessitated the use of other medications, were excluded from the study.

**Study procedure**

Adolescents and adults were administered Bresol at a dosage of 1 tablet twice daily for 6 weeks, whereas children were administered Bresol syrup at a dosage of 1 teaspoonful twice daily for 6 weeks. All the patients were followed up fortnightly for a period of 6 weeks.

**Results and Conclusion**

Results of the study showed a significant reduction in the mean scores of sneezing, nasal congestion, itching of nose, postnasal drip, and rhinorrhea at the end of 2, 4, and 6 weeks compared with their respective baseline scores. There was also a significant reduction in the haematological and biochemical parameters.

**CONCLUSION**

Results of the above studies showed a significant reduction in the clinical symptoms and haematological values after the treatment. There was no recurrence of allergic episodes. The efficacy of Bresol could be attributed to the synergistic effects of all the ingredients present in the formulation. No clinically significant adverse events were observed during the entire study period, indicating the safety of Bresol. Therefore, it can be concluded that Bresol tablets and syrup are effective and safe in the management of respiratory allergic conditions.

**About the Authors**

Dr. Bharat J Parmar is a Associate Professor of Paediatrics, B J Medical College, Civil Hospital, Ahmedabad

**REFERENCES**

10. Section 2, definition, pathophysiology and pathogenesis of Asthma, and natural history of asthma 2007.