Evaluation of efficacy and safety of Bresol (HK-07) tablets and syrup in allergic rhinitis

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ABSTRACT
Increasing prevalence of AR is a global health issue and although AR may have its onset at any age, the incidence is greatest in children and there is a decrease in the incidence with advancing age. Currently available therapeutic options in the management of AR have major limitations due to low clinical efficacy and associated adverse events. This study was planned to evaluate the clinical efficacy and safety (short- and long-term) of Bresol (HK-07) tablets and syrup in AR. The study was an open, non-comparative, phase III clinical trial conducted as per the ethical guidelines of Declaration of Helsinki. One hundred patients from the age group of 3 to 60 years who presented with symptoms of AR were included in the study. Patients suffering from severe systemic comorbid illness, which necessitated the use of other medications, were excluded from the study. Informed written consent was obtained from all included patients/parents/guardians and a witness, who was unrelated to the clinical trial attested the same.

At the initial visit, a detailed medical history was obtained by interviewing the patients, which was followed by thorough clinical examination and all the patients were investigated by hematological and biochemical tests. Adolescent and adult patients were advised to consume one Bresol (HK-07) tablet, twice-daily for 6 weeks and for children the Bresol (HK-07) syrup was administered in a dose of one teaspoon twice-daily for 6 weeks. All adverse events either reported or observed by patients/parents/guardians were recorded in CRF with information about severity, onset, duration and action taken regarding the study drug. The predefined primary endpoints were proportion of patients with rapid symptomatic control and clinical improvement, alongwith renormalization of laboratory parameters. The predefined secondary endpoints were incidences of adverse events and overall compliance to the drug therapy. An intent-to-treat analysis was performed for all efficacy evaluations.
A total of 100 patients were enrolled in the study and the age of enrolled patients ranged from 3 to 60 years. The mean score for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea decreased significantly at the end of 2, 4 and 6 weeks, when compared to their respective baseline values. There was a highly significant reduction in the TLC, DLC, ESR and AEC at the end of 6 weeks, when compared to their respective baseline values. There were no clinically significant adverse reactions; either reported or observed during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported.

Therefore, it may be concluded that Bresol (HK-07) tablets and syrup are effective and safe in the management of AR.

INTRODUCTION

Epidemiological studies suggest that the prevalence of AR is increasing globally and the contributing factors are higher concentrations of airborne pollution, rising dust mite populations, dietary factors and a trend towards sedentary lifestyle.

The prevalence of AR has been estimated to range from as low as 4% to more than 40% and an accurate estimate of the incidence of AR is difficult to obtain. Although AR may have its onset at any age, the incidence is greatest in children and there is a decrease in the incidence with advancing age. Occasionally, symptoms may appear first in middle age and AR has been reported in infants as young as 6 months of age.

The term ‘rhinitis’ describes the inflammation of nasal membrane and is characterized by rhinorrhea, sneezing and congestion, which persist for a period of at least an hour per day. Rhinitis is classified into 2 major types: infectious and noninfectious. Infectious rhinitis is characterized by presence of whitish, yellowish or greenish nasal secretions, while noninfectious rhinitis is characterized by clear, watery discharge. The noninfectious group is further subdivided into “SAR”, “PAR” and “PNAR”. Seasonal allergic rhinitis is a specific allergic reaction of the nasal mucosa and is characterized by watery rhinorrhea, nasal congestion, sneezing and pruritus of the eyes, nose, ears and throat. Perennial allergic rhinitis is characterized by intermittent or continuous nasal symptoms resulting from an allergic reaction without seasonal variation.

Currently available therapeutic options in the management of AR have major limitations due to low clinical efficacy and associated adverse events. Antihistamines, sympathomimetics and xanthine derivatives are commonly used as the first-line treatments for symptomatic management, but they fail to prevent recurrent episodes. Use of glucocorticosteroids and anticholinergics is questionable due to long-term adverse effects and prophylactic use of mast cell stabilizers has the disadvantage of frequent administration. Decongestant drugs are effective in the treatment of nasal obstruction; however do not improve other symptoms of rhinitis and they have a high incidence of adverse effects. Studies with the LT receptor antagonist as a sole therapy in AR have proved disappointing.

Bresol (HK-07) tablets and syrup are polyherbal formulations indicated for the management of AR. Bresol (HK-07) tablets and syrup contains extracts of Curcuma longa, Ocimum sanctum, Adhatoda vasica, Trikatu, Triphala, Embelia ribes, Cyperus rotundus, Cinnamomum zeylanicum, Elettaria cardamomum, Cinnamomum tamala, and Mesua ferrea. This study was planned to evaluate the efficacy and safety of Bresol (HK-07) tablets and syrup in AR.
Aim of the study
This study was planned to evaluate the clinical efficacy and safety (short- and long-term) of Bresol (HK-07) tablets and syrup in AR.

Study design
The study was an open, non-comparative, phase III clinical trial conducted at the CDR Medical Center, Bangalore from March to June 2002, as per the ethical guidelines of Declaration of Helsinki. The study protocol, CRFs, regulatory clearance documents, product related information and informed consent form (in Kannada and English) were submitted to the Institutional Ethics Committee and were approved by the same.

MATERIALS AND METHODS
Inclusion criteria
One hundred patients from the age group of 3 to 60 years who presented with symptoms of AR (sneezing, nasal congestion, itching of the nose, postnasal drip and rhinorrhoea) were included in the study.

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

Study procedures
All patients/parents/guardians were informed about the study drug, its effects, duration of the study, patient’s responsibilities, importance of compliance, patient’s rights, ethical aspects and overall plan of the study. Informed written consent was obtained from all included patients/parents/guardians and a witness, who was unrelated to the clinical trial attested the same.

At initial visit, a detailed medical history was obtained by interviewing the patients, which was followed by through clinical examination and special emphasis was laid on respiratory system examination. The details of the clinical examination were recorded in the structured CRF. All patients were investigated by hematological and biochemical tests, which included Hb, TLC, DLC, ESR and AEC. Adolescent and adult patients were advised to consume one Bresol (HK-07) tablet, twice-daily for 6 weeks and for children, the Bresol (HK-07) syrup was administered in a dose of one teaspoon twice-daily for 6 weeks.

Follow-up and monitoring
All patients were followed up every fortnightly for a period of 6 weeks. At each follow-up visit, clinical examination was done for evaluating symptomatic improvement of AR (sneezing, nasal congestion, itching of the nose, postnasal drip and rhinorrhea). All patients were investigated by hematological and biochemical tests at the end of the study period.

Adverse events
All adverse events, either reported or observed by patients/parents/guardians were recorded in the CRF with information about severity, onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as “Unrelated” (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), “Possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to
the patient), and “Probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Primary and secondary end points
The predefined primary endpoints were proportion of patients with rapid symptomatic control and clinical improvement, along with renormalization of laboratory parameters. The predefined secondary endpoints were incidences of adverse events (short- and long-term) and overall compliance to the drug therapy.

Statistical analysis
An intent-to-treat analysis was performed for all efficacy evaluations. Changes in various parameters from baseline values and values after the 2, 4 and 6 weeks were analyzed by “Repeated Measures ANOVA Test”, followed by “Bonferroni’s Multiple Comparison Test”. The changes in the values, before the initiation of study and at the end of the study were analyzed by “Paired t Test”. The minimum level of significance was fixed at 99% confidence limit and a 2-sided ‘p’ value of <0.0001 was considered significant. All values were expressed as Mean ± SEM.

Table 1: Reduction in mean scores for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea (Repeated measures ANOVA with Bonferroni’s Multiple Comparison Test Statistics)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Parameter</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
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<tbody>
<tr>
<td>Sneezing</td>
<td>Mean</td>
<td>1.34</td>
<td>1.06</td>
<td>0.78</td>
<td>0.01</td>
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<tr>
<td></td>
<td>Std. Deviation</td>
<td>1.224</td>
<td>0.9829</td>
<td>0.8828</td>
<td>0.1</td>
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<tr>
<td></td>
<td>Std. Error</td>
<td>0.1224</td>
<td>0.09829</td>
<td>0.08828</td>
<td>0.01</td>
</tr>
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<td></td>
<td>Lower 99% CI of mean</td>
<td>1.018</td>
<td>0.8013</td>
<td>0.5476</td>
<td>-0.01632</td>
</tr>
<tr>
<td></td>
<td>Upper 99% CI of mean</td>
<td>1.662</td>
<td>1.319</td>
<td>1.012</td>
<td>0.03632</td>
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<td></td>
<td>F=82.26, R squared=0.4538, p&lt;0.0001, Highly significant</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>Mean</td>
<td>1.89</td>
<td>1.5</td>
<td>1.04</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>1.014</td>
<td>0.8933</td>
<td>0.8278</td>
<td>0.3712</td>
</tr>
<tr>
<td></td>
<td>Std. Error</td>
<td>0.1014</td>
<td>0.08933</td>
<td>0.08278</td>
<td>0.03712</td>
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<tr>
<td></td>
<td>Lower 99% CI of mean</td>
<td>1.623</td>
<td>1.265</td>
<td>0.8221</td>
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<td>Upper 99% CI of mean</td>
<td>2.157</td>
<td>1.735</td>
<td>1.258</td>
<td>0.1577</td>
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<tr>
<td></td>
<td>F=140, R squared=0.5858, p&lt;0.0001, Highly significant</td>
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<tr>
<td>Itching of nose</td>
<td>Mean</td>
<td>0.96</td>
<td>0.75</td>
<td>0.56</td>
<td>0.03</td>
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<tr>
<td></td>
<td>Std. Deviation</td>
<td>1.118</td>
<td>0.9143</td>
<td>0.8566</td>
<td>0.3</td>
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<tr>
<td></td>
<td>Std. Error</td>
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<td>0.09143</td>
<td>0.08566</td>
<td>0.03</td>
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<tr>
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<td>Lower 99% CI of mean</td>
<td>0.6656</td>
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<td>Upper 99% CI of mean</td>
<td>1.254</td>
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<td>Postnasal drip</td>
<td>Mean</td>
<td>1.73</td>
<td>1.43</td>
<td>1.07</td>
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<td></td>
<td>Std. Deviation</td>
<td>0.9625</td>
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<td>0.8675</td>
<td>0.3</td>
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<td></td>
<td>Std. Error</td>
<td>0.09625</td>
<td>0.09348</td>
<td>0.08675</td>
<td>0.03</td>
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<tr>
<td></td>
<td>Lower 99% CI of mean</td>
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<td></td>
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<tr>
<td>Rhinorrhea</td>
<td>Mean</td>
<td>1.89</td>
<td>1.58</td>
<td>1.1</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>0.9417</td>
<td>0.8782</td>
<td>0.9156</td>
<td>0.3</td>
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<tr>
<td></td>
<td>Std. Error</td>
<td>0.09417</td>
<td>0.08782</td>
<td>0.09156</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Lower 99% CI of mean</td>
<td>1.642</td>
<td>1.349</td>
<td>0.859</td>
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<td>Upper 99% CI of mean</td>
<td>2.138</td>
<td>1.811</td>
<td>1.341</td>
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<tr>
<td></td>
<td>F=148, R squared=0.5992, p&lt;0.0001, Highly significant</td>
<td></td>
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</tr>
</tbody>
</table>
RESULTS
A total of 100 patients were enrolled in the study and the age of the enrolled patients ranged from 3 to 60 years (Median=33, M=31.65, SD=13.6, SEM=1.367, Lower 99% CI of mean=28.05, Upper 99% CI of mean=35.25).

The mean score for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea decreased significantly at the end of 2, 4 and 6 weeks, when compared to their respective baseline values (Table 1).

There was a highly significant reduction in the TLC (M=9074 ± 140.5 to 8276 ± 148.7, t=6.667, Mean of differences=797.5, 99% CI=482.6 to 1112, R squared=0.3098, r=0.6591, p<0.0001, S) (Figure 1), polymorph count (M=58.58 ± 0.4951 to 55.71 ± 0.7395, t=6.399, Mean of differences=2.87, 99% CI=1.690 to 4.050, R squared=0.2926, r=0.7153, p<0.0001, S) (Figure 2), lymphocyte count (M=39.30 ± 0.5676 to 37.21 ± 0.5721, t=7.792, Mean of differences=2.09, 99% CI=1.384 to 2.796, R squared=0.2133, r=0.5935, p<0.0001, S) (Figure 3), monocyte count (M=0.70 ± 0.0659 to 0.38 ± 0.05081, t=5.181, Mean of differences=0.32, 99% CI=0.1574 to 0.4826, R squared=0.5348, r=0.8083, p<0.0001, S) (Figure 4) and ESR (M=19.36 ± 1.079 to 12.20 ± 0.6561, t=10.67, Mean of differences=7.16, 99% CI=5.393 to 8.927, R squared=0.4432, r=0.6323, p<0.0001, S) (Figure 5), at the end of 6 weeks when compared to their respective baseline values.

There was highly significant reduction in eosinophil count (M=3.490 ± 0.1720 to 2.150 ± 0.08572, t=9.611, Mean of differences=1.34, 99% CI=0.9730 to 1.707, R squared=0.4827, r=0.5935, p<0.0001, S) (Figure 6) and AEC (M=323.7 ± 16.82 to 206.1 ± 8.261, t=8.878, Mean of differences=117.6, 99% CI=82.73 to 152.50, R squared=0.4432, r=0.6323, p<0.0001, S) (Figure 7) at the end of 6 weeks when compared to their respective baseline values.

There were no clinically significant adverse reactions; either reported or observed during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported.
DISCUSSION

Pollen and mold spores are the most common allergens responsible for AR and chronic antigen challenge results in recurring (almost continuous) symptoms throughout the year and the other perennial allergens are house dust mites, feather pillows, animal dander and cockroaches. Occasionally, AR may be the result of exposure to an occupational allergen and occupational allergic rhinitis has been described in flour industry workers, detergent workers, and wood workers. Nonspecific irritants (tobacco smoke, air pollutants and chemical fumes) and infections influence the course of AR. A direct immunologic relationship between ingested foods and persistent rhinitis symptoms has been difficult to establish, but hypersensitivity to dietary proteins may induce nonseasonal AR and cow’s milk has been the most associated food, which precipitates or aggravates upper respiratory symptoms.

The major symptoms of AR are sneezing, rhinorrhea, nasal pruritus and nasal congestion. Sneezing is the most characteristic symptom and activation of the nasal lacrimal reflex leads to the tearing of the eyes. The skin covering the nose and the upper lip becomes tender because of the rhinorrhea and nasal congestion resulting from swollen turbinates occurs frequently. Itching of the nose may be a prominent feature, inducing frequent rubbing of the nose and ocular symptoms such as pruritus, erythema and lacrimation. A characteristic feature of the symptom complex is the periodicity of its appearance and there is an increased reactivity of the nasal mucosa after repeated exposure to the allergen. This local and nonspecific increased reactivity has been termed the “priming effect”, which accounts for the presence of symptoms in some patients even after the pollinating season. Patients with AR have IgE antibodies that bind to high-affinity receptors (on mast cells and basophils) and low-affinity receptors (on monocytes, eosinophils, and platelets). On re-exposure to antigen, the mast cells degranulate, releasing a number of inflammatory chemomediators like histamine, LT, PG, platelet-activating factor and bradykinin. These chemomediators are responsible for
vasodilation, increased vascular permeability, glandular secretion and stimulation of afferent nerves. All these changes culminate in the immediate-type rhinitis symptoms.\textsuperscript{23-25}

Mast cells and mast cell–derived mediators (histamine, LT-C4 and PG-D2) play the central role in the pathogenesis of the early response of AR.\textsuperscript{26} In addition to mast cell mediators, the early response is associated with an increase in neuropeptides (calcitonin gene–related peptide, substance P, and vasoactive intestinal peptide) and cytokines (IL-1, IL-3, IL-4, IL-5, IL-6, GM-CSF and TNF-\(\alpha\)). There is a subsequent accumulation of CD4+ T-lymphocytes, eosinophils, neutrophils and basophils.\textsuperscript{27,28} Eosinophils release ‘major basic protein’, which further disrupts the epithelium and promotes further mast cell mediator release.\textsuperscript{29} Recent studies involving nasal mucosal biopsy confirm an increase in CD4+ and CD25 T-lymphocytes, in addition to neutrophils and eosinophils, during late responses. These CD4 T-lymphocytes help promote the late-phase allergic reaction as they express messenger RNA (mRNA) for IL-3, IL-4, IL-5, and GM-CSF. Interleukin-5 participates in eosinophil chemotaxis and growth, whereas IL-4 helps mediate IgE production and upregulates adhesion molecules (vascular cell adhesion molecule on vascular endothelium). Overall, the late-phase reaction of AR is characterized by the infiltration of the nasal cavity with basophils, lymphocytes, eosinophils and neutrophils, as well as the release of the same mediators involved in the early response (except PG-D2 and tryptase). The absence of the mast cell–derived mediators PG-D2 and tryptase during the late-phase reaction is consistent with basophil-derived histamine release rather than mast cell involvement. In patients with AR, a continuous allergen exposure results in persistent inflammation that upregulates the expression of ICAM-1/CD54 in the inflamed epithelium. Because ICAM-1 is the ligand for rhinoviruses, its upregulation may be responsible for the increased viral respiratory infections in these patients.\textsuperscript{30}

The only characteristic laboratory finding in AR is the presence of large numbers of eosinophils in the nasal secretions. Peripheral blood eosinophilia (4% to 12%) may be present in active AR. A significantly elevated level of serum IgE may occur in the serum of some patients with AR.\textsuperscript{31}

Because of a variety of factors (geographic location, allergen load and climate) the clinical course and prognosis for any single patient cannot be predicted. About 30% of patients with AR who have not been treated with specific immunotherapy eventually develop allergic asthma and patients with AR may develop other complications such as recurrent otitis media, impaired speech development, chronic sinusitis, nasal polyps, sleep apnea and aggravation of the existing asthma. Poorly controlled symptoms of AR contribute to sleep loss, secondary daytime fatigue, learning impairment, decreased cognitive functioning and decreased quality of life.

The currently available options for the management of AR are avoidance therapy, symptomatic therapy and immunotherapy. Complete avoidance of an allergen results in a cure, when there is only a single allergen, but in most cases of AR, complete avoidance therapy is difficult, because of widely distributed aeroallergens.
Antihistamines are useful in controlling some of the symptoms (sneezing, rhinorrhea and pruritus) of AR, but they are less effective in relieving the nasal obstruction and ocular symptoms. Antihistamines are most effective when given early, because they do not abolish existing effects of histamine, but rather prevent the development of new symptoms caused by further histamine release. Many antihistamines also have anticholinergic effects, which account for adverse effects (blurred vision, dryness of the mouth, vertigo and gastrointestinal upset) and central nervous system depression is the major limiting side effect. Because of fatal cardiac arrhythmias with the newer second-generation antihistamines (when given concomitantly with erythromycin, imidazole antifungal agents or drugs that inhibit the cytochrome P-450 system), these drugs have been removed from the United States market.32

Sympathomimetic agents stimulate alpha-receptors and reduce the edema of the nasal mucous membranes in AR, but these drugs may induce elevated blood pressure, nervousness and insomnia.33,34 The topical application of sympathomimetics is often followed by a “rebound” phenomenon in which the nasal mucous membranes become more congested and edematous. This leads the patient to use the drops or spray more frequently and in higher doses, to obtain relief from nasal obstruction. The condition resulting from the overuse of topical sympathomimetics is called “rhinitis medicamentosa”. Intranasal corticosteroids have been demonstrated to have specific effects on the inflammatory cells and chemomediators involved in the allergic process, but the major adverse effects of intranasal steroids include local dryness or irritation in the form of stinging, burning or sneezing.35 Systemic adverse effects are a serious risk associated with intranasal steroids and some studies of intranasal dexamethasone administration at dosages used in AR have revealed mild to moderate adrenal suppression36,37 and bilateral posterior subcapsular cataracts have been reported in association with nasal or oral inhalation of beclomethasone dipropionate.38

Intranasal corticosteroid injections also have major adverse effects such as adrenal suppression, which may lead to transient or permanent loss of vision.39 Systemic corticosteroids are an inappropriate therapy for patients with mild to moderate AR. Mast cell stabilizers have little effect on the mucociliary transport and the adverse effects are frequent (sneezing, nasal stinging, nasal burning, transient headache and an unpleasant aftertaste). Though anticholinergics decrease the watery rhinorrhea in patients with AR and reduce nasal drainage in patients with vasomotor rhinitis, they have no appreciable effect on obstruction or sneezing in patients with rhinitis.40

Immunotherapy increases the threshold level for symptom appearance after exposure to the aeroallergen and this altered degree of sensitivity may be the result of either the induction of a new antibody, a decrease in allergic antibody, a change in the cellular histamine release phenomenon or interplay of all the three possibilities. A recent study reported that traditional allergen immunotherapy, administered for 3 to 4 years, induced a clinical remission that persisted for 3 years after treatment was discontinued.41

This study observed significant reduction in the mean symptom score for sneezing, nasal congestion, itching of nose, postnasal drip and runny nose. The increased levels of TLC, DLC (polymorphs, lymphocytes, monocytes, eosinophil), ESR and AEC also reduced significantly. These excellent results might be due to the synergistic activities of the ingredients of Bresol (HK-07) tablets and syrup, which have been studied in depth by various researchers.
In various studies, curcumins - I, II and III (components of *Curcuma longa*) have been shown to inhibit chemomediators of inflammation (phospholipase, LO, COX-1 and -2, LT, TX, PG, NO, collagenase, elastase, hyaluronidase, monocyte chemottractant protein-1, interferon-inducible protein, TNF-α, and IL-12. Inhibition of these inflammatory chemomediators was shown to be due to the ability of curcumins to bind with phosphatidylcholine micelles. Enhanced suppression of COX-2 expression was observed due to extracellular signal-regulated kinase activity and NF-kappaB activation inhibition, which might be the molecular mechanisms of actions of curcumins. Kang et al. observed that curcumins significantly inhibited the production of IL-12, reduced induction of γ-IFN, IL-4 in CD4+ T-lymphocytes by macrophages, leading to the inhibition of T-helper cells-1 cytokine profile (↑IFN-γ and ↓IL-4 production) in CD4+ T-cells. Curcumins are potent antioxidants and inhibit Ca^{2+} entry and PK-C activity. Curcumin also have an immunostimulatory activity, which increases circulating antibody titer, plaque forming cells, alpha-esterase positive cells and phagocytosis. Ram et al. observed the antiallergic property of curcumin in an *in vitro* model of airway hyperresponsiveness.

Gingerols and diarylheptanoids, the principle active ingredients of *Zingiber officinale* are potent inhibitors of PG synthetase enzyme and 5-LOX enzymes. Umeda et al. reported the potent inhibition of biotransformation of AA (comparable to indomethacin) by *Zingiber officinale*. The other active ingredients of *Zingiber officinale* (oleoresins-[8]-paradol and [8]-shogaol), have inhibitory effects on COX-2 enzymes and the mechanism of action was hypothesized by the inhibition of COX-1 / TX synthase enzymes. Cyclo-oxygenase-1 and -2 (regulated by the eukaryotic transcription factor NF-kappaB) is the molecular target for the actions of *Zingiber officinale*, and it acts by interfering with the intracellular signaling cascades, those involving NF-kappaB and mitogen-activated PK. Thomson et al. documented significant inhibitory effects of *Zingiber officinale* on PG-E2 production. Ahmed et al. observed that the antioxidant effect of *Zingiber officinale* was comparable to that of ascorbic acid as demonstrated by lowered lipid peroxidation, while maintaining the activities of other antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase). [6]-gingerol was found to be a potent inhibitor of iNOS and also an effective protector against peroxynitrite-mediated damage. Wilarusmee et al. reported the immunosuppressive effects of *Zingiber officinale* in vitro as evidenced by the decreased responsiveness in lymphocyte culture. The *Zingiber officinale* extract had been shown to raise the thymus index, spleen index, phagocytosis, and the rate of α-ANAE+ and titer of IgM.

The principle anti-inflammatory ingredients of *Piper longum* are dihydrokawain, yangonin and methysticin. Choudhary et al. documented that *Piper longum* inhibits the lipid peroxidation process effectively by its ability to scavenge free radicals involved in initiation and propagation steps. Chiou et al. observed *Piper longum* retards the macrophage recruitment and suppress cytokines production. Hashimoto et al. isolated kawapyrones from *Piper longum* and recorded the inhibition of TNF-α release.

The principle ingredients of *Embllica officinalis* are tannoids (emblicanin A and B, punigluconin, and pedunculagin). In addition to the antitussive activity, it was observed that *Embllica officinalis* has anti-inflammatory, antispasmodic and antioxidant efficacy and it reduces the mucus secretion in the airways. Khanom et al. identified the strong superoxide-scavenging and prolyl endopeptidase inhibitory activity of *Embllica officinalis*. Sai Ram et al. observed that *Embllica officinalis* significantly inhibited the free radical production, restored the anti-oxidant status, inhibited apoptosis and DNA fragmentation, relieved the
immunosuppressive effects on lymphocyte proliferation and even restored the IL-2 and γ-IFN production.\textsuperscript{67} In another study, it was observed that \textit{Emblica officinalis} acts as an immunomodulator and decreases the induction of iNOS.\textsuperscript{68} Sai Ram et al. reported that \textit{Emblica officinalis} enhanced the cell survival, decreased free radical production and higher antioxidant levels, inhibited induced immunosuppression and restored both phagocytosis and γ-IFN production by macrophages.\textsuperscript{69}

Tasaduq et al. demonstrated potent anti-peroxidative activity of \textit{Terminalia belerica}.\textsuperscript{70} \textit{Terminalia belerica} inhibited lipid peroxide formation by scavenging hydroxyl and superoxide radicals \textit{in vitro}.\textsuperscript{71} Saleem et al. observed the antioxidant potential of \textit{Terminalia belerica} (stronger than alpha-tocopherol), which was attributed to hydroxybenzoic acid and hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides.\textsuperscript{72}

Godhwani et al. documented that \textit{Ocimum sanctum} has an immunostimulatory effect on the humoral immunologic response (an increase in antibody titer), as well as of the CMI response (E-rosette formation and lymphocytosis).\textsuperscript{73} Another study documented a decrease in histamine release from mast cells (humoral immune response) and a decrease in leucocyte migration inhibition (CMI response). This immunomodulatory effect was postulated as mediated by GABAergic pathways.\textsuperscript{74} Kelm et al. documented an anti-oxidant bioassay of \textit{Ocimum sanctum} (which yielded cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid and eugenol) and in addition observed a potent anti-inflammatory (COX-1 and -2 inhibitory) activity.\textsuperscript{75} \textit{Ocimum sanctum} was found to possess significant anti-inflammatory activity against PG-E2, LT and AA, and the results suggested that \textit{Ocimum sanctum} has the capacity to block both the COX and LOX pathways of AA metabolism.\textsuperscript{76} Singh et al. observed a significant inhibition of leucocyte migration in the pleural exudates, which suggest that the \textit{Ocimum sanctum} inhibits the enhancement of the vascular permeability and leucocyte migration following inflammatory stimulus.\textsuperscript{77} Analgesic action of \textit{Ocimum sanctum} is exerted both centrally as well as peripherally.\textsuperscript{78} Balanehru et al. observed the free radical scavenging potential of ursolic acid isolated from \textit{Ocimum sanctum} against lipid peroxidation \textit{in vitro}.\textsuperscript{79} Maulik et al. demonstrated the potent free radical scavenging activity of \textit{Ocimum sanctum}.\textsuperscript{80} Orientin and vicenin (isolated from \textit{Ocimum sanctum}) have strong antioxidant activity.\textsuperscript{81}

Paliwa et al. documented the potent antiallergic activity of “Compound 73/602 (AA)” (a structural analogue of vasicinone, an alkaloid of \textit{Adhatoda vasica}).\textsuperscript{82} The widely used mucolytics, namely benzylamines (bromhexine and ambroxol) are the semi-synthetic derivatives of vasicine, extracted from \textit{Adhatoda vasica} and these benzylamines enhance lysozyme levels in the respiratory-tract secretions and clear bacilli-laden mucus.\textsuperscript{83} Chakraborty et al. reported that the potent antiinflammatory activity of \textit{Adhatoda vasica} was equivalent to that of hydrocortisone.\textsuperscript{84} Dhuley et al. reported the antitussive activity of \textit{Adhatoda vasica} to be similar to that of codeine, \textit{in vitro}.\textsuperscript{85}

The principle ingredients of \textit{Cyperus rotundus} are sesquiterpenes (beta-selinene, isocurcumenol, nootkatone and aristolone) and a triterpene (oleanolic acid).\textsuperscript{86} Seo et al. observed inhibition of NO and O\(_2\)\(_-\) production \textit{in vitro} by \textit{Cyperus rotundus} and the inhibition was found to be due to the suppression of iNOS protein and iNOS mRNA expression.\textsuperscript{87}

Embelin, a benzoquinone-derivative isolated from Embelia ribes, when tested for its antibacterial potential exhibits significant inhibition against five and moderate activity against three stains of 12 bacteria tested.\textsuperscript{88} Embelin and its 2, 5-isobutylmine salts have been reported
to possess anti-inflammatory activity in carrageenan-induced paw edema and cotton pellet granuloma formation.\textsuperscript{89}

The aqueous fruit extract of \textit{Terminalia chebula} has been investigated for its effect on cell-mediated and humoral components of the immune system in mice. Administration of \textit{Terminalia chebula} extract produced an increase in humoral antibody titer and delayed-type hypersensitivity in mice. It was concluded that the \textit{Terminalia chebula} extract is a promising drug with immunostimulastin properties.\textsuperscript{90}

Aqueous extract of \textit{Terminalia chebula} was tested for potential antioxidant activity by examining its ability to inhibit γ-radiation-induced lipid peroxidation in rat liver microsomes and damage to superoxide dismutase enzyme in rat liver mitochondria. The antimitagenic activity of the extract has been examined by following the inhibition of γ-radiation-induced strand breaks formation in plasmid pBR322 DNA, which showed the presence of compounds such as ascorbate, gallic acid and ellagic acid. The extract inhibits xanthine/xanthine oxidase activity and is also an excellent scavenger of DPPH radicals.\textsuperscript{91}

The extracts show antimicrobial activity against two dental caries causing bacteria i.e. \textit{S. mutans} and \textit{S. aureus}. Highest mean diameter of inhibition zone was produced by the acetone extracts(25.32 mm) and a MIC of 25 mg/ml against \textit{S. mutans} and 32.97 mm and a MIC of 12.5 mg/ml against \textit{S. aureus}.\textsuperscript{92}

In the present study, the effect of isolated piperine from \textit{Piper nigrum} fruits on memory and behavior mediated via monoamine neurotransmitters was investigated. Piperine isolated from \textit{Piper nigrum} exhibited prominent nootropic activity, reversed clonidine-induced hypothermia, decreased lithium induced head twitches and significantly delayed haloperidol induced catalepsy at a dose of 10 mg/kg. The alkaloid modified 5-HT and NA mediated behavior. Hence, piperine from the fruits of \textit{Piper nigrum} can be employed as a potential nootropic agent.\textsuperscript{93}

The various biological determinants such as oxidative stress markers (reactive oxygen species and GSH), Bcl-2 protein expression, mitochondrial membrane potential, caspase-3 activity, DNA damage, splenic B and T cell population, blastogenesis and cytokines (Interleukin-2 and gamma-Interferon) were measured to ascertain its cell protective potential The reported free radical scavenging property of piperine and its antioxidant potential could be responsible for the modulation of intracellular oxidative stress signals. These in turn appear to mitigate the apoptotic pathway and other cellular responses altered by cadmium.\textsuperscript{94}

The bark of \textit{Cinnamomum zeylanicum}, showed a very low inhibitory concentration value ranging from 0.14 to 0.26 mg/ml, efficiency concentration value from 6.1 to 11.6 mg/mg DPPH and reducing power value from 0.6 to 2.8 ascorbic acid equivalents (ASE/ml), and reasonably high values (8.5–16.2) of anti-radical power (ARP), indicating their strong Free radical scavenging activity. They also showed better inhibition of hydroxyl radical induced deoxyribose degradation.\textsuperscript{95}

The high dose of cinnamon bark (100 mg/kg p.o.) decreased \textit{Pasteurella multocida}-induced mortality by 17%, increased the phagocytic index in carbon clearance test, increased neutrophil adhesion, increased serum immunoglobulin levels and antibody titer values.\textsuperscript{96}
CONCLUSION
Increasing prevalence of AR is a global health issue and AR has a severe impact due to associated long-term compromises in the quality of life. The available treatment options for AR have major limitations due to less efficacy and associated adverse events. This study observed a highly significant reduction in the mean scores for sneezing, nasal congestion, itching of nose, postnasal drip and rhinorrhea. The increased levels of TLC, DLC (polymorphs, lymphocytes, monocytes, eosinophil), ESR, and AEC reduced significantly at the end of the study. These excellent results might be due to the synergistic activities of the ingredients of Bresol (HK-07) tablets and syrup. There were no clinically significant adverse reactions during the entire study period. The overall compliance to the treatment was good and no treatment discontinuations were reported. Therefore, it may be concluded that Bresol (HK-07) tablets and syrup are effective and safe in the management of AR.

REFERENCES


