Asthma is a common disease, which affects 5% of the population in Western countries. Pharmacological treatment of asthma includes two categories of drugs: Bronchodilators and anti-inflammatory medications. Anti-inflammatory drugs such as corticosteroids, which are administered through local or systemic route, target inflammatory process in asthmatic bronchi. Several studies have shown corticosteroids to be effective in the management of asthma by reducing the severity of the disease and decreasing the need for symptomatic medications. Widespread use of corticosteroids is, however, still advised with some caution, since side effects may occur, with both oral and inhaled formulations, as a consequence of low specificity of action. This has stimulated considerable efforts to produce anti-inflammatory agents with improved risk-benefit ratios. Inhalation and oral agents that might inhibit the effects of proinflammatory mediators are also the focus of research interest. Disodium cromoglycate, a nonsteroidal inhalation agent, was discovered as an alternative to corticosteroids. Despite encouraging results from earlier studies, more recent data tend to question its efficacy in the treatment of asthma. Histamine exhibits numerous actions of relevance to asthma, such as bronchoconstriction, enhanced mucus secretion and increased vascular permeability; these actions are partly mediated by \( H_1 \)-receptor. New antihistamines are considered to be less sedating than older compounds, leading to the use of higher doses. This property, combined with early reports that new antihistamines may have specific anti-allergic properties in addition to \( H_1 \)-blocking activity, has led to development in asthma therapy. To date, clinical trials have delivered contradictory results and the matter is still the subject of debate.

Bresol, a polyherbal formulation, is claimed to be useful in bronchial asthma. The principal herbs of Bresol tablets are listed in Table 1.

**Aim of the Study**

The aim of this open study was to evaluate the efficacy of Bresol in the management of bronchial asthma and its adverse effects, if any, and to determine patient compliance with the study drug.

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**Pediatric Consultant
GAIL India Ltd., Dvypur, Uttar Pradesh
Material and Methods

Study Design

An open label study was conducted in 10 bronchial asthma patients (with complaints of breathing difficulty, cough, wheezing and tightness of chest) from the Outpatient Department of Babu Ram Memorial Hospital, Divyapur, U.P., India. The study was approved by the Ethics Committee of the institution and all the patients gave a witnessed written informed consent before enrollment. The study was conducted in accordance with Declaration of Helsinki and GCP Guidelines issued by the Ministry of Health, Government of India.

In order to ensure appropriate and consistent quality of medicinal plant/herbal substances good agricultural and collection practice (GACP) was followed during the collection, manufacture, processing and packaging of the herbal formulation. Botanical identification and ayurvedic criteria of the desired quality were in accordance with the guidelines of Pharmacopoeial Standards of Ayurvedic Formulations (1987).

Inclusion Criteria

- Patients of either sex, who have been diagnosed and objectively proved as a patient of bronchial asthma, who require long-term maintenance therapy
- Age above 12 years
- Willing to sign the informed consent form and comply with the study procedures

Exclusion Criteria

- Severe cardiovascular, renal or hepatic disorders, metabolic or endocrinial disorders
- Female patients either pregnant or lactating
- Severe respiratory complications like severe infection or respiratory distress, pneumonia

Study Procedures

Ten patients with complaints of difficulty in breathing, cough, wheezing and tightness of chest wall were selected from the Outpatient Department of Babu Ram Memorial Hospital, Divyapur, U.P., India between December 2009 and February 2010. All the patients underwent complete examinations according to both Ayurvedic and Medical Methods. Patients fulfilling the inclusion criteria were enrolled into the study.

Patients were administered Bresol tablets at a dosage of two tablets twice daily for a period of 30 days in adults and one tablet twice daily for the same period in children in the age group of 12-18 years.

Patients were evaluated on Days 0, 15 and 30 for subjective improvements in cough, dyspnea, tightness of chest and rhonchus and general well being. Objective improvements were also evaluated during all the visits.

There were no specific diet recommendations; patients were allowed to take any type of food except for the ones that may trigger asthma symptoms. No other adjuvant treatment was given except for bronchodilators and steroid inhalers during acute exacerbations of asthma but did not exceed for more than three days.

Drug safety was assessed primarily on the basis of adverse events and changes in hematological and biochemical parameters. Adverse effects, if any, were noted in the case report forms. Patients were free to withdraw from the study, if they desired.

Primary and Secondary Outcome Measures

Primary predefined outcomes were clinical recovery from the symptoms and signs of bronchial asthma. Secondary end points are to evaluate the safety and compliance to Bresol tablets.

Adverse Effects

The incidence and type of adverse events reported by various studies were also tabulated separately. All

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Table 1. Composition of Bresol Tablets

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Tulasi</td>
<td>Ocimum sanctum</td>
<td>50</td>
</tr>
<tr>
<td>Vasaka</td>
<td>Adhatoda vasica</td>
<td>50</td>
</tr>
<tr>
<td>Trikatu</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Triphala</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Vidanga</td>
<td>Embelia ribes</td>
<td>8</td>
</tr>
<tr>
<td>Musta</td>
<td>Cyperus rotundus</td>
<td>8</td>
</tr>
<tr>
<td>Tvak</td>
<td>Cinnamomum zeylanicum</td>
<td>5</td>
</tr>
<tr>
<td>Ela</td>
<td>Elettaria cardamomum</td>
<td>5</td>
</tr>
<tr>
<td>Patra</td>
<td>Cinnamomum tamala</td>
<td>5</td>
</tr>
<tr>
<td>Nagakesara</td>
<td>Mesua ferrea</td>
<td>5</td>
</tr>
</tbody>
</table>

*Note: Drug safety was assessed primarily on the basis of adverse events and changes in hematological and biochemical parameters. Adverse effects, if any, were noted in the case report forms. Patients were free to withdraw from the study, if they desired.*
adverse events, either reported or observed by patients, were recorded with information about severity, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as 'Unrelated' (a reaction that does not follow a reasonable temporal sequence from the 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), '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) and 'Certain' (the adverse events must have definitive relationship to the study drug, which cannot be explained by concurrent disease or any other agent).

Statistical Analysis

Statistical analysis was done according to the intention-to-treat principles using GraphPad Prism Version 4.03 for Windows, GraphPad Software, San Diego, California, United States (www.graphpad.com). Changes in various parameters from values at the baseline level to values at the end of the study were pooled and analyzed cumulatively using Fisher’s exact test. Values were expressed as incidences of patients with or without symptoms. Minimum level of significance was fixed at 95% confidence limit and a two-sided p < 0.05 was considered significant.

Results

All the 10 enrolled patients completed the study. The effects of Bresol treatment on clinical parameters are shown in Table 2. Of the 10 patients presenting with dyspnea, cough, tightness of the chest, eight responded after treatment with Bresol, showing 80% protection (p < 0.0007). Out of the 10 patients with wheezing and rhonchus, seven patients responded with 70% improvement (p < 0.0031).

Sneezing, paroxysmal nocturnal dyspnea and general weakness showed improvement in 75% of patients following Bresol treatment. Symptomatic improvement in sneezing and paroxysmal nocturnal dyspnea was significant at p < 0.007, but was not significant in general weakness, which may be due to small sample size of the patients presenting with the symptoms at baseline.

Fever presented in four patients showed complete 100% protection. Insomnia presented by two patients improved showing 100% improvement.

Patients presenting with difficulty in expectoration and rhinitis, responded to the treatment with significant improvement of 88% (p < 0.014) and 71% (p < 0.0210), respectively.

Table 2. Effect of Bresol Tablets on Clinical Parameters of Bronchial Asthma

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>No. of patients presenting with symptoms</th>
<th>Significance (p)</th>
<th>Protection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>2</td>
<td>&lt;0.0007</td>
</tr>
<tr>
<td>Cough</td>
<td>10</td>
<td>2</td>
<td>&lt;0.0007</td>
</tr>
<tr>
<td>Wheezing</td>
<td>10</td>
<td>3</td>
<td>&lt;0.0031</td>
</tr>
<tr>
<td>Rhonchus</td>
<td>10</td>
<td>3</td>
<td>&lt;0.0031</td>
</tr>
<tr>
<td>Tightness of the chest</td>
<td>10</td>
<td>2</td>
<td>&lt;0.0007</td>
</tr>
<tr>
<td>Difficulty in expectoration</td>
<td>8</td>
<td>1</td>
<td>&lt;0.014</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7</td>
<td>2</td>
<td>&lt;0.0210</td>
</tr>
<tr>
<td>Sneezing</td>
<td>8</td>
<td>2</td>
<td>&lt;0.0070</td>
</tr>
<tr>
<td>Fever</td>
<td>4</td>
<td>0</td>
<td>&lt;0.0286</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>8</td>
<td>2</td>
<td>&lt;0.0070</td>
</tr>
<tr>
<td>General weakness</td>
<td>4</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Not significant.
Discussion

The present study indicates the significant clinical efficacy of Bresol in the management of bronchial asthma. A significant improvement was observed in all the clinical parameters of asthma like dyspnea, cough, wheezing, rhonchus, tightness of the chest, difficulty in expectoration, rhinitis, sneezing, fever, insomnia, paroxysmal nocturnal dyspnea and in general weakness. None of the patients presented with any adverse effects.

Curcumin is reported to have anti-allergic property, as tested in an in vitro model of airway hyperresponsiveness. In various studies, Curcuminoids - I, II and III (components of Curcuma longa) have been shown to inhibit a number of molecules involved in inflammation [phospholipase, lipooxygenase (LOX), cyclooxygenase (COX) -1 and -2, leukotrienes (LT), thromboxane (TX), prostaglandins (PG), nitric oxide (NO), collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF) and interleukins 12 (IL-12)]. Inhibition of LOX-1 was found to be due to the ability of curcumins to bind with phosphatidylcholine micelles. Enhanced suppression of COX-2 expression was observed due to extracellular regulated receptor kinase (ERK) activity and NF-κB activation inhibition, which might be the molecular mechanisms of the antitumor promoting effects of curcumins. Curcuminoids significantly inhibited production of IL-12, reduced induction of interferon γ (IFN-γ) and IL-4 in CD4+ T cells by macrophages, leading to the inhibition of TH1 cytokine profile (↓IFN-γ and ↑IL-4 production) in CD4+ T cells. Curcumnios are potent antioxidants and inhibit Ca2+ entry and protein kinase activity, the antioxidation effects might provide an explanation for their anti-mutagenic action. Curcuminoids inhibit angiogenesis by preventing proliferation and migration of endothelial cells. They also have an immunostimulatory activity, which increases circulating antibody titer, plaque forming cells, α-esterase positive cells and phagocytosis.

Gingerols and diarylheptanoids, the active ingredients of Zingiber officinale, are potent inhibitors of prostaglandin biosynthesizing enzyme (PG synthetase). The chemical structures of these compounds indicate that the inhibitors would also be active against arachidonate 5-lipoxygenase (an enzyme of LT biosynthesis). The inhibition of biotransformation of arachidonic acid (AA) comparable to indomethacin is also being reported for Z. officinale. The other ingredients of Z. officinale, oleoresins ([8]-paradol, [8]-shogaol), have inhibitory effects on COX-2 enzymes and the mechanism of action was hypothesized by the attenuation of COX-1/TX synthase enzymatic activity. COX-1 and -2 (regulated by the eukaryotic transcription factor NF-κB) is the molecular target for actions of Z. officinale. [6]-gingerol acts by interfering with intracellular signaling cascades, which involves NF-κB and mitogen-activated protein kinases. Z. officinale exerts inhibitory effect on prostaglandin-E2 (PGE2) production. Ahmed et al observed that the antioxidant effect of Z. officinale extract 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 NO synthesis and also an effective protector against peroxynitrite-mediated damage. Wilaarsrumee et al reported immunosuppressive effects of Z. officinale in vitro as evidenced by the decreased responsiveness in mixed lymphocyte culture. The Z. officinale extract had been shown to raise the thymus and spleen indices, phagocytosis, rate of α-ANAE+ and titer of IgM.

The principle COX-1 and -2 inhibitory ingredients of Piper longum are dihydrokawain, yangonin and methysticin. Choudhary et al documented that P. longum inhibits the lipid peroxidation process effectively by its ability to scavenge free radicals involved in initiation and propagation steps. Chiou et al observed that P. longum retards macrophage recruitment and suppresses cytokines production. Hashimoto et al isolated 6-kawapyrones from P. longum that recorded inhibition of TNF-α release. Sunila et al observed that the administration of P. longum inhibited tumor development, increased life span, increased bone marrow cellularity and α-esterase positive cells, in vitro.

The principle ingredients of Emblica officinalis are tannoids (emblicanin A and B, punigluconin and pedunculagin). In addition to the antitussive activity,
it was observed that *E. officinalis* has antiphlogistic, antispasmodic and antioxidant properties and it reduces the mucus secretion in the airways.³⁷ Khanom et al identified the strong superoxide-scavenging and prolyl endopeptidase inhibitory activity of *E. officinalis*.³⁸ Sai Ram et al observed that *E. officinalis* significantly inhibited free radical production, restored antioxidant status, inhibited apoptosis and DNA fragmentation, relieved immunosuppressive effects on lymphocyte proliferation and restored the IL-2 and γ-IFN production.³⁹ In another study, immunosuppression in the early phase with mild hyperplasia, infiltration of few mononuclear cells and reduction in the inducibility of NO synthase was observed.⁴⁰ One study reported that *E. officinalis* enhanced cell survival, decreased free radical production and higher antioxidant levels, inhibited immunosuppression and restored both phagocytosis and γ-IFN production by macrophages.³¹

*Terminalia belerica* has potent antifungal activity.⁴² Tasaduq et al demonstrated potent antiperoxidative activity of *T. belerica*.⁴³ *T. belerica* inhibited lipid peroxide formation with scavenging of hydroxyl and superoxide radicals in vitro.⁴⁴ Saleem et al observed antioxidant potential of *T. belerica* stronger than α-tocopherol, which was attributed to hydroxybenzoic acid and hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides.⁴⁵

The principle ingredients of *Cyperus rotundus* are four sesquiterpenes (β-selinene, isocurcumanol, nootkatone and aristolone) and a triterpene (oleanolic acid).⁴⁶ Seo et al observed inhibition of NO and O₂⁻ production in vitro by *C. rotundus* and the inhibition was due to the suppression of iNOS protein, as well as iNOS mRNA expression.⁴⁷

Godhwani et al documented that *Ocimum sanctum* has an immunostimulatory effect on the humoral immunologic response (an increase in antibody titer) and on the cellular immunologic response (E-rosette formation and lymphocytosis).⁴⁸ The study also documented a decrease in histamine release from mast cells (humoral immune responses) and leukocyte migration inhibition (cell-mediated immune responses). This immunomodulatory effect was postulated as mediated by GABAergic pathways.⁴⁹ Kelm et al reported antioxidant bioassay of *O. sanctum* yielded cirsilineol, cirsimaritin, isothymusin, isothymonin, apigenin, rosmarinic acid and eugenol and also observed potent anti-inflammatory (COX-1 and -2 inhibitory) activity.⁵⁰ *O. sanctum* fixed oil was found to possess significant anti-inflammatory activity against PGE₂, LT and AA and the results suggested that linolenic acid present in *O. sanctum* has the capacity to block both the COX and LOX pathways of arachidonate metabolism.⁵¹ Singh et al observed significant inhibition of leukocyte migration in the pleural exudates, which suggests that the *O. sanctum* inhibits enhancement of vascular permeability and leukocyte migration following inflammatory stimulus.⁵² Analgesic action of *O. sanctum* is exerted both centrally as well as peripherally.⁵³ Balanerhu et al observed the free radical scavenging potential of ursolic acid isolated from *O. sanctum* against lipid peroxidation in vitro.⁵⁴ Maulik et al demonstrated potent free radical scavenging activity.⁵⁵ Orientin and vicenin (isolated from *O. sanctum*) have strong antioxidant activity.⁵⁶

Widely used as mucolytics, benzylamines (bromhexine and ambroxol) are the semi-synthetic derivatives of vasicine extracted from *Adhatoda vasica* and these benzylamines enhance the lysozyme levels in respiratory tract secretions and clear bacilli-laden mucus.⁵⁷ Chakraborty et al reported that the potent anti-allergic activity of *A. vasica* was equivalent to that of hydrocortisone.⁵⁸ Paliwa et al documented the potent anti-allergic activity of ‘Compound 73/602 (AA)’, a structural analog of vasicinone (an alkaloid of *A. vasica*).⁵⁹ Dhuley et al reported the antitussive activity of *A. vasica* similar to that of codeine, in vitro.⁶⁰ Embelin, a benzoquinone-derivative isolated from *Embelia ribes*, when tested for its antibacterial potential exhibited significant activity against five strains and moderate activity against three of the 12 bacterial strains tested.⁶¹ 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.⁶²

The aqueous fruit extract of *Terminalia chebula* has been investigated for its effect on cell-mediated and humoral components of the immune system in mice. Administration of *T. chebula* extract produced an increase in humoral antibody titer and
delayed-type hypersensitivity in mice, indicating the immunostimulant properties. Aqueous extract of *T. chebula* was tested for potential antioxidant activity by examining its ability to inhibit $\gamma$ radiation-induced lipid peroxidation in rat liver microsomes and damage to superoxide dismutase enzyme in rat liver mitochondria. The antimutagenic activity of the extract has been examined by following the inhibition of $\gamma$ radiation-induced strand breaks 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.

The bark of *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/ml DPPH, reducing power value from 0.6 to 2.8 ascobic acid equivalents (ASE/ml) and reasonably high values (8.5-16.2) of antiradical power (ARP) indicating their strong free radical scavenging activity. It also showed better inhibition of hydroxyl radical induced deoxyribose degradation.

The high dose of cinnamon bark (100 mg/kg PO) decreased *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.

Principal herbs such as *C. longa*, *Z. officinalis* and *P. longum* exhibit anti-inflammatory actions through COX and LOX pathways. They also exhibit immuno-modulatory, anti-allergic and phagocytic activities. *E. officinalis* because of its antitussive, antioxidant, antibacterial and phagocytic activities and by decreasing the mucus secretion contributes to the management of bronchial asthma. *A. vasica* with its mucolytic property helps in easy expectoration. *T. chebula* and *O. sanctum* also possess immuno-modulatory and antioxidant property. The effect of Bresol tablets in the management of bronchial asthma is thus the resultant synergistic actions of the individual ingredients.

**Conclusion**

Increasing prevalence of bronchial asthma is a global issue of concern. The available treatment options for these diseases have major limitations due to low efficacy, long-term administration, associated adverse events and compliance to drugs. The study showed a significant improvement in all the clinical parameters of asthma such as dyspnea, cough, wheezing, rhonchus, tightness of the chest, difficulty in expectoration, rhinitis, sneezing, fever, insomnia and paroxysmal nocturnal dyspnea and in general weakness. None of the patients presented with any adverse effects. All the patients completed the treatment and compliance to the study drug was good without any dropouts. Therefore, it can be concluded that Bresol tablet is clinically effective and safe in patients with bronchial asthma.

**References**