

# Clinical Validation of Efficacy and Safety of Herbal Cough Formula: Study of Herbal Cough Syrup

Tanuja Nesari, MD  
B. K. Bhagwat, MD  
Jasmin Johnson, MD  
Narendra S. Bhatt, MD  
Deepa Chitre, MD

**ABSTRACT.** *Objective of the Study:* To clinically validate the efficacy and safety of herbal cough formula CORSHE-E of ayurvedic origin.

*Procedure:* An open label, uncontrolled clinical study was done on thirty patients with history of cough. The patients were given the cough syrup after they were enrolled in the study and were followed up for a period of seven days. The cough severity, frequency (as recorded on Visual Analogue Scale from 0 to 10 cm), chest discomfort, quantity and type of sputum were recorded at screening, on the fourth day and on the seventh day of treatment. The patient recorded the severity and frequency of cough on a Visual Analogue Scale which was divided into ten equal parts of 1 cm each. The patient marked the extent of symptoms on this

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Tanuja Nesari is Head of Department, and B. K. Bhagwat is Principal and Superintendent, Tilak Ayurvedic Mahavidyalaya and Tarachand Hospital, Rasta Peth, Pune-411011, India.

Jasmin Johnson is Assistant Director, Pharmacology, Narendra S. Bhatt is President and Executive Director, and Deepa Chitre is Chief Executive Officer, Bio-Ved Pharmaceuticals Pvt. Ltd., Z-Wing, Warje-Malvadi, Pune 411052, India.

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scale at screening and after four days of consumption of the cough syrup. The scores were marked on these days and reduction in score was examined for efficacy evaluation of the cough syrup. The clinical and hematological safety parameters and parameters for acceptability of cough syrup (palatability, color, odor and consistency) were also studied. Global assessment by the patient and the physician was also carried out on the fourth day.

*Results:* Twenty-six of the thirty patients studied showed a significant decrease in the frequency and severity of cough (on Visual Analogue Scale). The sputum quantity and consistency also showed steady decrease and liquefaction respectively.

Four patients who had longer duration of did not respond adequately to treatment. These patients had history of sub-acute to chronic cough with mean duration of cough being forty days ( $40 \pm 34$  days), sore-throat and fever, highly suggestive of bacterial upper respiratory tract infection and a long duration of cough before initiation of therapy.

Most of the patients found the cough syrup to be acceptable in terms of these criteria. Nineteen patients rated the cough syrup as excellent in palatability, two in color, four in odor and five in consistency. Six patients rated the syrup as good to taste, twenty-eight patients rated the natural color as good and twenty five and twenty patients rated the odor and consistency as good, respectively. Five patients described the taste as bad, none described the color as bad, one patient found the odor bad and five described the consistency as bad. All patients described a soothing effect of the study drug and appreciated the natural color and flavor of the same.

Global assessment was based on improvement in symptoms, acceptability and overall efficacy and safety as reported by the physician and the patient. Thirteen of the thirty patients rated the trial medicine as excellent, thirteen rated it as good and four considered it poor. The investigator in charge of the patients rated the trial medicine as excellent in eighteen cases, good in eight cases, fair in two cases and poor in two cases.

*Conclusion:* The test drug CORSHE-E is an effective and safe cough syrup that is highly acceptable for patients with cough of short duration. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2004 by The Haworth Press, Inc. All rights reserved.]

**KEYWORDS.** Cough expectorant, herbal, clinical trial

## INTRODUCTION

There is an increasing interest in use of plants in health care for its claimed safety and benefits. Clinical relevance and evidence have been the basis of phytomedicine developments in the past. Standardization, quality control and methods for validation of single or multiple claims of medicinal plants or their derivatives, are newer challenges that we now face in order to provide scientific bases to them.<sup>1</sup>

CORSHE-E is a combination of standardized herbs, derived from the ayurvedic practice, in asyrup base. CORSHE-E contains extracts of *Adhatoda vasica*, *Glycyrrhiza glabra*, *Terminalia bellerica*, *Solanum xanthocarpum* and *Ocimum sanctum*. The chemical constitution, raw material (sourced from 'Plantex-Manufacturers and exporters of herbal extracts and plant products,' Vijayawada, India) and available herb product ratio of extracts have been studied to develop a pleasant tasting, and standardized cough syrup. CORSHE-E being a poly-herbal formulation consisting of five herbs, the method of standardization is based on qualitative identification for presence of each extract in the finished product. The identification is carried out by High Performance Thin Layer Chromatography (HPTLC). The quality of each of the five constituent extracts is also checked by similar technique, i.e., HPTLC.

All the developed specifications have been confirmed by analyzing several batches of raw material and finished product. The formulation was studied for stability at room temperature and accelerated temperature conditions and found to remain as per specifications in the finished product. The specifications included color of the syrup which is brown, pH, the limits being 3.8 to 4.8, weight per millilitre at 1.14 to 1.20 and identification of individual plant ingredients by HPTLC.

An acute toxicity study was done on ten (five male and five female) Swiss albino mice following single oral administration of CORSHE-E in the dose 20 ml/kg. The mice exhibited a normal pattern of body weight gain ( $20 \pm 1.31$  gms at initiation of study,  $28 \pm 1.83$  at end of 7 days and  $37 \pm 1.55$  at end of 14 days) during the observation period. No mortality was observed in any of the treated mice after 14 days of administration of the syrup. The treated mice did not show any abnormal clinical signs or pathological changes in any organs (as observed after necropsy on the 14th day).

### **OBJECTIVES**

The objective of the study was to evaluate the efficacy and safety of CORSHE-E, a new herbal cough syrup.

### **METHODS**

The trial was uncontrolled and open label. The trial was conducted on 30 patients between 15-65 years of age, suffering from cough and requiring symptomatic treatment, after obtaining their informed consent. The patients were recruited from those attending the General Medicine clinics of the hospital. All patients already taking medicines for the current episode of cough were excluded from the study. Those with acute exacerbation of chronic bronchitis (requiring additional treatment with antibiotics),<sup>2</sup> pregnant or lactating women, patients with congestive cardiac failure or conditions like narrow angle glaucoma, obstructive gastrointestinal disorders, prostatic hypertrophy and urinary tract disorders were also excluded from the study.<sup>3</sup> History of smoking was not an enrollment criterion.

The treatment was administered for a period of four to seven days.<sup>4</sup> Two teaspoons (10 ml) of CORSHE-E syrup was taken orally three times a day for four days after breakfast, lunch and dinner. If cough was not relieved completely, the syrup was continued for an additional three days, and the patient followed up on the 7th day. Patients were advised to avoid taking any other cough syrup, opioid containing drugs, sedatives and anti-histaminics. A note was made in the Case Record Form of any antibiotics or bronchodilators or any other drug that the patient received during the course of treatment. Each patient underwent hematological investigations (haemoglobin, complete blood count, erythrocyte sedimentation rate) and routine urine examination (urine albumin and microscopy) at the beginning and end of the trial.

Treatment compliance was assured by visual inspection of the drug container, which was carried by the patient at every visit made to the hospital.

Statistical analysis of data was done using the t-test for significance of difference in means. Significance was defined as  $P < 0.05$ .

### **RESULTS AND OBSERVATIONS**

Twenty-six of the thirty patients studied were between 15 and 30 years of age. This age group is constantly exposed to viral upper respiratory tract infections and also very likely to demand fast relief consider-

ing the discomfort at study and work place. eight out of 30 patients complained predominantly of rhinorrhoea, bodyache, and headache associated with cough with expectoration. Sputum was mucoid and white in color in these patients. Twelve patients complained of dry cough. These patients also showed elevated eosinophil count ( $3.5 \pm 1.4\%$ ) of total WBC count, as compared to ( $2.8 \pm 0.9\%$  in) the other eighteen patients. Ten of the thirty patients had sore throat associated with cough and white to yellow to green sputum. Cough before enrollment in the trial lasted for two to one hundred and twenty days.

Three patients had history of smoking 1-3 cigarettes per day and one patient smoked approximately 10 bidis per day. The patients elicited no history of tuberculosis, asthma or other major illness.

The vital parameters inclusive of body weight, temperature, pulse and blood pressure did not show a significant difference pre and post treatment. The respiratory rate decreased though not significantly after treatment (Table 1).

The improvement in Visual Analogue Scale (VAS) score<sup>5</sup> was found to be significant ( $P < 0.001$ ). Frequency of cough and quantity of sputum also reduced significantly at end of four days of treatment ( $P < 0.001$ ). The frequency of cough showed a statistically significant further reduction on day seven as compared to day four ( $P < 0.01$ ). However, a similar reduction was not seen with the quantity of sputum (Tables 2 and 3).

The consistency of sputum also showed a significant improvement from viscous or mucoid to a watery consistency ( $P < 0.01$ ) (Table 3).

Chest discomfort was only seen in seven patients at initiation of trial and was absent in all patients at the end of four days of therapy.

The mean duration for relief of symptoms was derived after questioning each patient for the same and was found to be after  $6 \pm 2$  doses, i.e., after the 2nd day.

TABLE 1. Vital Parameters of Patients Before and at End of Treatment (n = 30)

Parameter	Before treatment	After treatment	Level of significance
Body weight	$55.02 \pm 8.8$	$54.9 \pm 8.7$	$P > 0.05$
Temperature	$98.5 \pm 0.5$	$98.2 \pm 0.3$	$P > 0.05$
Pulse	$85 \pm 7.7$	$82 \pm 6.5$	$P > 0.05$
Blood pressure	$177 \pm 7/77 \pm 5$	$177 \pm 7/77 \pm 5$	$P > 0.05$
Respiratory rate	$17.53 \pm 1.36$	$16.7 \pm 1.1$	$P > 0.05$

TABLE 2. Mean Values of Efficacy Parameters in Patients (n = 30)

Parameter	At screening	After four days of treatment	After seven days of treatment	Level of significance
Visual analogue scale	5.7 ± 1.4	1.6 ± 2.5		P < 0.001
Frequency of cough (number of bouts/day)	8 ± 3	3 ± 3	1 ± 3	P < 0.001
Quantity of sputum per bout of cough in teaspoonfuls	2.5 ± 2.7	0.6 ± 1.6	0.6 ± 1.6	P < 0.01

TABLE 3. Numbers of Patients with Changes in the Efficacy Parameters

Parameter at End of 4 Days		Decrease	No Change	Increase	Total
VAS Score		27	1	2	30
Frequency of cough (bouts/day)		27	2	1	30
Quantity of Sputum	Wet Cough	16	2	0	18
	Dry Cough	--	11	1	12
Thickness of Sputum	Wet Cough	13	4	1	18
	Dry Cough	--	11	1	12

Seventeen patients of the thirty studied were completely relieved of cough within four days and thirteen patients required additional three days of therapy for complete remission of cough.

There was no improvement in symptoms in four patients. There was however no increase in cough frequency and chest discomfort in these patients.

An observation that could be made on evaluation of clinical findings is that four patients did not show significant improvement in terms of decrease in severity and frequency of cough and global impression of patient and physician. These patients had yellow to green sputum, fever and sore throat and a longer duration of cough lasting from twenty to ninety days.

Among the haematological parameters, the hemoglobin, RBC and total WBC counts remained more or less constant. The erythrocyte sedimentation rate (ESR) and eosinophil counts showed improvement by the end of treatment with statistical significance at P < 0.05 for ESR and

$P < 0.01$  for the eosinophil count. Urine examination did not show any significant changes in the study patients (Table 4).

No side effects or adverse events were reported. No concomitant medication was required by any of the patients.

Acceptability of cough syrup based on palatability, color, odor, and consistency was recorded. Patient acceptance is influenced by a combination of sensory perceptions including *taste* and *smell*, and to a lesser extent *texture*, *appearance*, and *temperature* of the oral liquid products.<sup>6</sup> Most of the patients found the cough syrup to be acceptable in terms of these criteria. Nineteen patients rated the cough syrup as excellent in palatability, two in color, four in odor and five in consistency. Six patients rated the syrup as good to taste, twenty-eight patients rated the natural color as good and twenty-five and twenty patients rated the odor and consistency as good, respectively. Five patients described the taste as bad, none described the color as bad, one patient found the odor bad and five described the consistency as bad (Table 5).

*Global assessment* was done on day four and was based on improvement in symptoms, acceptability and overall efficacy and safety as re-

TABLE 4. Hematological Findings for Assessment of Safety (n = 30)

Parameter	At screening	At end of treatment	Level of significance
Hemoglobin (g/dl)	13.3 ± 1.5	14 ± 1.5	P > 0.05
Red Blood Cell count ( $\times 10^6$ )/mm <sup>3</sup>	4.5 ± 0.6	4.6 ± 0.6	P > 0.05
White Blood Cell (WBC) count/mm <sup>3</sup>	8000 ± 1547	7951 ± 1325	P > 0.05
Eosinophil count (% of WBC count)	3 ± 1.1	2.4 ± 0.9	P < 0.01
Erythrocyte sedimentation rate-Westergen method (mm in 1 hr)	17.7 ± 8.5	14.5 ± 8.6	P < 0.05

TABLE 5. Rating of Acceptability Parameters by the Patients (n = 30)

Rating	Palatability	Color	Odor	Consistency
EXCELLENT (Number of patients)	19	2	4	5
GOOD (Number of patients)	6	28	25	20
BAD (Number of patients)	5	0	1	5

ported by the physician and the patient. The global assessments have found place in the primary efficacy criteria in studies on management of respiratory symptoms.<sup>7</sup> The physician and the patients rated the cough syrup as Excellent, Good, Fair, or Bad. Thirteen of the thirty patients rated the trial medicine as excellent, thirteen rated it as good and four considered it poor. The investigator in charge of the patients rated the trial medicine as excellent in eighteen cases, good in eight cases, fair in two cases and poor in two cases.

### DISCUSSION

Cough is the most common symptom for which patients seek medical attention, because cough can so profoundly and adversely affect their quality life.<sup>8</sup> Some patients—especially women, but also men who had undergone transurethral prostatectomy experience urinary incontinence every time they cough, and a few even had fecal incontinence. Other complaints include frequent retching, dizziness, sweating, and even broken ribs. The majority are concerned that something is seriously wrong. For many, the coughing causes embarrassment and self-consciousness in public and tries the patience of their spouses. They have difficulty in speaking on the telephone and can no longer sing or go to movies.<sup>9,10</sup>

Cough syrups provide immediate symptomatic relief and improve to some extent the quality of life of patients.<sup>11</sup>

The polyherbal combination in CORSHE-E plays a multifaceted role in the management of cough. The soothing, anti-inflammatory, and expectorant effect of *Solanum xanthocarpum*, *Glycyrrhiza glabra*,<sup>12</sup> and Menthol<sup>12</sup> relieve the irritation of the respiratory tract. *Solanum xanthocarpum*<sup>12</sup> is anti-histaminic, bronchodilating, and antipyretic. *Adhatoda vasica*<sup>12</sup> leaf extract has been used for treatment of bronchitis and asthma for centuries. It liquefies the respiratory secretions thus easing expectoration and preventing further complications. *Ocimum sanctum*<sup>8</sup> has antiseptic and immunomodulating properties and *Terminalia bellerica*<sup>12</sup> apart from enhancing the body defense mechanism also has bronchodilatory, expectorant, antipyretic, and sedative properties. The natural flavor and color of CORSHE-E add further credentials to its acceptability.

CORSHE-E, which has mucolytic, antihistaminic, anti-inflammatory and soothing components was, therefore, expected to improve cough efficiency by improving mucociliary clearance, mobilizing secre-

tions, increasing water content of mucus and/or decreasing viscosity of mucus. It was also expected to decrease irritation of the upper respiratory tract by a soothing effect, decrease the cough frequency, discomfort, and severity.

It was further expected that CORSHE-E would have fewer side effects as compared to the combinations of anti-histaminics, decongestants, and mucolytics that are available over the counter for relief of cough, if any.

Eight of the thirty patients, complained of rhinorrhoea, bodyache, and headache associated with productive cough. The sputum was mucoid and white in color in these patients. Viral upper respiratory tract infection is the most common cause of this clinical presentation.<sup>8</sup> Ten of the thirty patients had sore throat associated with cough and white to yellow to green sputum. A bacterial etiology or secondary bacterial infection is likely in these patients.<sup>13</sup> Twelve patients complained of dry cough. These patients also showed elevated eosinophil count ( $3.5 \pm 1.4\%$ ) of total WBC count, as compared to ( $2.8 \pm 0.9\%$  in) the other eighteen patients. The probable etiology in these patients is postnasal drip, allergic, or parasitic.<sup>14</sup>

Cough before enrollment in the trial was present for a period ranging from two days to one hundred-twenty days with a mean duration of sixteen days ( $16 \pm 26$  days). Cough has been divided into three categories: acute, defined as lasting less than three weeks; subacute, lasting three to eight weeks; and chronic, lasting more than eight weeks.<sup>8</sup> Based on these definitions, the cough could be defined as acute or sub-acute in all but two of the patients.<sup>8</sup> Acute and sub acute cough commonly have viral, allergic or acute bacterial etiology or maybe acute exacerbation of an obstructive pathology.<sup>5</sup> One patient had history of cough since three months and another patient complained of cough since six months. These patients did not respond to the treatment and required specific management of underlying cause in addition.

A significant improvement was seen in severity, frequency and discomfort associated with cough ( $P < 0.001$ ). The severity of cough was gauged on the Visual Analogue Scale.<sup>4</sup> This improvement can be attributed to the mucolytic and demulcent properties of the formulation.<sup>15</sup>

The consistency of sputum showed a significant improvement from viscous and mucoid to watery secretion suggestive of liquefaction of sputum by the cough syrup ( $P < 0.01$ ).<sup>16</sup>

The mean duration for relief of symptoms due to drug action was after the 6th ( $6 \pm 2.42$ ) dose, i.e., after two days of treatment suggesting an

early response to treatment. Comparison of the efficacy parameters on days four and seven was done to evaluate the benefit of longer duration of use of the study drug and any adverse events or plateau effect. The frequency of cough in patients with persistence of symptoms though reduced showed a statistically significant further reduction on day seven as compared to day four ( $P < 0.01$ ).

Though most of the patients showed a remarkable improvement in the efficacy parameters, four patients did not respond adequately to the study drug. These patients had history of sub-acute to chronic cough with mean duration of cough being forty days ( $40 \pm 34$  days), sore-throat and fever, highly suggestive of bacterial upper respiratory tract infection and a long duration of cough before initiation of therapy. The patients were non smokers. Upper respiratory tract inflammation or irritation of long duration is known to hamper the defense mechanism and may precede a number of cases of bacterial infection which may even manifest as pneumonia.<sup>17</sup> These patients should be treated with a specific agent to eliminate the cause of cough in addition to symptomatic treatment.

The hematological parameters, i.e., the RBC, total and differential WBC counts and hemoglobin count showed no change before and after therapy ( $P > 0.05$ ) except in the eosinophil count and the ESR. Eosinophil count is a good marker of allergic disorders irrespective of the source of the allergen, whether extrinsic or intrinsic. Pharyngeal, tracheal or bronchial irritations that are associated with extrinsic provoking factors manifests as dry cough. Raised eosinophil count is a common finding in these conditions.<sup>14</sup> The initial eosinophil count in the study patients was not pathological, defined as greater than 500 per microliter of blood.<sup>14</sup> A fall in the counts could be observed, from initial value of  $240 \pm 123$  per microliter to  $193 \pm 89$  per microliter of blood ( $P < 0.01$ ) at end of treatment. This finding has two implications. One, the study drug does not probably provoke an allergic response in the users. Two, the formulation may have a role in modulation of the local/systemic immune response so as to suppress/alleviate any allergic manifestations. ESR is a non-specific marker of chronic inflammatory diseases. A reduction in ESR therefore points towards anti-inflammatory activity of the study drug.<sup>18</sup>

The safety of the formulation has been established with no reports of adverse effects. The acceptability of the study drug in terms of palatability, color, odor, and consistency was also good. All patients de-

scribed a soothing effect of the study drug and appreciated the natural color and flavor of the same.

Subjective measures in investigation of cough syrups best reflect the severity of cough from the patient's perspective because a subjective response most likely integrates both cough frequency and intensity.<sup>19</sup> The study drug was rated as excellent to good by all patients except for the four patients who did not respond to treatment. The study investigator also rated the cough syrup as fair in two of the four patients, who did not respond to treatment and poor in the other two.

### ***Key Points for Clinicians***

- CORSHE-E contains extracts of *Adhatoda vasica*, *Glycyrrhiza glabra*, *Terminalia belerica*, *Solanum xanthocarpum*, and *Ocimum sanctum*.
- It is an effective and safe cough syrup for use both in patients with dry cough and cough with expectoration.
- It is an effective mucolytic agent and has a soothing effect on the upper respiratory tract.

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