Clinical Investigations

Respiration

Respiration 2006;73:457–463
DOI: 10.1159/000089922

Received: May 18, 2005
Accepted after revision: August 10, 2005
Published online: November 22, 2005

Plant-Based Formulation for Bronchial Asthma: A Controlled Clinical Trial to Compare Its Efficacy with Oral Salbutamol and Theophylline

P.M. Murali S. Rajasekaran O.R. Krishnarajasekar T. Perumal K. Nalini
S. Lakshmisubramanian C.N. Deivanayagam

Dalmia Centre for Research and Development, Coimbatore, India

Key Words
Asthma · Clinical trial · Forced expiratory volume in 1 s · Herbal medicine · Phytomedicine · Salbutamol · Theophylline

Abstract
Background: Plant-based medicine is the 3rd most popular choice of both adults (11%) and children (6%) suffering from Asthma. While several plant-based formulations have been reported for the treatment of asthma in the past, many authors have published their reservations on clinical trials carried out using complementary and alternative medicines. ***Objectives:*** The authors desired to eliminate the shortcomings of the earlier clinical trials carried out by many investigators in a structured study. Therefore, a 12-week randomized double-blind placebo-controlled clinical study was conducted to investigate the efficacy of a plant-based formulation (DCBT4567-Astha-15) in comparison with oral salbutamol, salbutamol + theophylline and a matching placebo in patients with reversible asthma. ***Methods:*** Ninety-four patients between 15 and 50 years of age, showing 15% improvement in forced expiratory volume in 1 s (FEV_1) 15 min after a bronchial challenge of inhaled salbutamol (200 μg) were recruited, and the end point of the study was determined as a 15% improvement in FEV_1 and clinical symptoms like dyspnoea, wheezing, cough, expectoration, disability, sleep disturbances and respiration rate. ***Results:*** DCBT4567-Astha-15, salbutamol and salbutamol + theophylline patients showed statistically significant improvement in FEV_1, while placebo patients did not show any improvement. Fifty percent of DCBT4567-Astha-15, 48% of salbutamol, 58% of salbutamol + theophylline and 26% of placebo patients showed the desired 15% improvement in FEV_1. Improved mean FEV_1 values at the end of the trial indicated that the salbutamol - theophylline combination was superior followed by salbutamol and DCBT4567-Astha-15. Clinical symptoms like dyspnoea, wheezing, cough, expectoration, disability, and sleep disturbances were significantly reduced in DCBT4567-Astha-15 patients compared to patients of the other three arms. ***Conclusions:*** DCBT4567-Astha-15 was as efficacious as salbutamol (12 mg/day) or salbutamol (12 mg/day) in combination with theophylline (200 mg/day) in the treatment of reversible asthmatics. Quality of life of patients also improved with DCBT4567-Astha-15 drug treatment.

Introduction

Asthma is the most common inflammatory chronic disease of the airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli such as immunologic and environmental features. It is defined by the National Asthma Education Program of the National Heart, Blood and Lung Institute as (1) airway obstruction that is at least partially

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0025–7931/06/0734–0457$23.50/0

Accessible online at:
www.karger.com/res

Dalmia Centre for Research and Development
B-133,134 Sirvani Main Road, Kalampalayam
Coimbatore 641 010 (India)
Tel. +91 422 2605216, Fax +91 422 2607688, E-Mail dalmiabiotechnology@vsnl.com

reversible, (2) airway inflammation and (3) increased airway responsiveness to a variety of stimuli [1]. The diagnosis of asthma is established by demonstrating reversible airway obstruction. Reversibility is traditionally defined as a 15% or greater increase in FEV_1 following two puffs of a β-adrenergic agonist [2, 3].

A survey by the National Asthma Campaign in the United States of America found that 60% of the patients with moderate asthma and 70% with severe asthma have had complementary and alternative medicine to treat their children [4]. Plant-based medicine is the 3rd most popular choice of both adults (11%) and children (6%) suffering from asthma. Several alternative and plant-based formulations have been reported for the treatment of asthma in the past [5, 6]. However, many authors have published their reservations on clinical trials done using complimentary and alternative medicines [7, 8]. This study group desired to eliminate the shortcomings of conducting a clinical trial with a plant-based formulation so that if found efficacious at the end of the study, a plant-based formulation for the treatment of asthma would have passed one important milestone in its development for the treatment of asthmatics.

An earlier double-blind randomized placebo-controlled trial to assess the safety and efficacy with three arms (biomedical, DCBT4567-Astha-15) totaling 90 patients, 30 in each arm, with the end points being a 15% increase in FEV_1 and improved clinical symptoms like dyspnoea, cough, expectoration, wheezing, disability and respiration rate, on volunteers showed that the plant-based formulation was well tolerated by the patients, the formulation was as efficacious as salbutamol (9 mg/day) and was better than placebo [9, 10].

In this study, DCBT4567-Astha-15 was compared with salbutamol treatment (12 mg/day) with or without theophylline (200 mg/day) for asthma along with a placebo arm. The primary objective of the study was to observe a 15% improvement in FEV_1 and the secondary objective to record improvement in clinical symptoms.

Patients and Methods

Patients

The study was conducted at the specialty Government Hospital of Thoracic Medicine, Chennai, India. Several weeks prior to the study, the hospital notice board clearly envisaged the scope of the trial and sought volunteers for the study. Volunteers, between 15 and 50 years of age, having asthma with moderate and stable symptoms during the previous month, maintained on usual oral and/or inhalation drugs like salbutamol, theophylline or prednisolone, or combinations thereof, without the requirement of hospitalization were selected for this trial. Patients showing a minimum of 15% improvement in FEV_1 compared to the baseline recordings 15 min after the administration of 200 μg (2 puffs) of inhaled salbutamol with a gap of 5 min between the puffs after stopping the usual drugs for 12 h were included into the study. Steroid dependence was not a contraindication for the admission into the trial. Pregnant patients, patients having chronic bronchitis and/or emphysema, or patients suffering from concurrent systemic diseases, with cardiopulmonary tuberculosis, pulmonary eosinophilia, bronchiectasis, cancer, congestive heart failure, hepatic dysfunction, neurological disorders and diarrhoeal disorders or having a hemoglobin level <10 g/dl were excluded from the study. Present smokers and brittle asthmatics with wide fluctuations in symptoms and pulmonary function test values within a month were also excluded. The hospital ethics committee approved a 2-week run-in period without medication to volunteers before they were given the trial medication.

Study Design

Volunteers inducted into the study signed the informed consent form in 'Tamil', which is the local Indian language where the hospital is located. The hospital ethics committee approved the study protocol. The study design was double blind for 12 weeks and had four arms; DCBT4567-Astha-15, two modern biomedical arms and a placebo arm. The two biomedical arms were salbutamol (12 mg/day) and salbutamol (12 mg) plus theophylline (200 mg). Earlier the statistician determined the sample size for the clinical trial by a factor analysis with a provision for 20% dropout.

For randomization, each arm was named as A, B, C and D. The lottery method was used for the randomization sequence generation. A bag containing numbered identical plastic tokens was drawn out and assigned to A, B, C and D. The numbers were pasted according to this randomization on the fours groups of identical medication strips and handed over to the hospital.

Study Medication

The biomedical drugs were identical capsules of uniform color and shape to that of placebo and DCBT4567-Astha-15 packed in uniform strips separately. The generic salbutamol and theophylline were filled in capsules with each capsule containing 3 mg equivalent of salbutamol or 3 mg equivalent of salbutamol plus 50 mg theophylline for the two biomedical arms. Lactose was used as a filler to arrive at uniform weight for the biomedical and plant drugs. Placebo contained lactose only.

All patients admitted to the trial were de-wormed, as out-patients, by administering a tablet of albendazole 400 mg, before the commencement of the trial. Only 1 patient from one family was enrolled into the trial. Patients were instructed to avoid the use of all drugs, by themselves, for any ailment. They were advised to consult the treating physician for any symptom or complaint. The physician made a record of all the details of the complaints and dispensed any essential medication.

Patients were advised to visit the hospital daily during the 1st week. Subsequently they visited every week for follow-up and collection of medication. The patients were instructed to take three capsules every day, one each after breakfast, lunch and dinner.

Patients were instructed to bring during each visit the drug strip supplied during the previous attendance, along with any unconsumed capsules. The physician interrogated the patient regarding

Table 1. Composition of plant extracts per capsule

Sl. No.	Botanical name	Parts used	Weight per capsule, mg
1	*Woodfordia fruticosa*	dried flower	57.1
2	*Solanum xanthocarpum*	dried fruit	35.9
3	*Adathoda vasika*	dried leaf	177.7
4	*Acacia arabica*	dried bark	16.3
5	*Ellateria cardamomum*	dried fruit	0.2
6	*Piper nigrum*	dried unripened fruit	15.5
7	*Achyranthus aspera*	dried root	48.7
8	*Zingiber officinalis*	dried rhizome	6.6
9	*Hollarhena antidysenterica*	dried seed	3.0
10	*Curcuma longa*	dried rhizome	11.0
11	*Syzygium aromaticum*	dried bud	16.0
12	*Syzygium aromaticum*	dried bud oil	16.7
13	*Calotropis procera*	dried root	4.3
14	*Enicostemma littorale*	dried whole plant	8.5
15	*Piper longum*	dried unripened fruit	6.0
Total			423.5
Q.S (lactose)			76.5
Total weight per capsule			500.0

the regularity of drug intake and also recorded the number of unconsumed tablets in the container if any. A new container with drugs (for the next week) was issued each week. The investigating centre provided direct access facility for the patient round the clock for any emergency.

Before signing the consent form, information and details of the trial were given to each patient and they were informed of the option to withdraw from the study at anytime without assigning any reason. The principal investigator could withdraw any patient from the trial if the patient showed any deterioration of vital signs of kidney function or elevated liver or cardiac enzymes. Fortnightly review meetings between the investigators, physicians and the trial coordinators were conducted to monitor the progress and compliance of the trial.

Study Visits

Comprehensive assessment comprising history, clinical assessment, laboratory investigations and lung function tests were recorded before the medication dispensation. Clinical assessment was done daily in the 1st week and at weekly intervals thereafter. The laboratory investigations were performed on the 7th day, 6th week and at the end of the 12th week. Lung function tests were recorded twice a day in the 1st week and then fortnightly thereafter.

Examinations

Clinical assessments of dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances were recorded daily in the 1st week and subsequently every week. They were assessed individually as absent, mild, moderate and severe with scores of 0, 1, 2 and 3. Lung function tests were recorded weekly during the 1st month and fortnightly during the remaining period of the study at the out-patient department of the hospital. Spirometry was done using a Transfer Test C model lung function machine (P.K. Morgan, UK).

Statistical and Other Analyses

Scores of 0, 1, 2 and 3 were used in clinical symptoms such as dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances that were assessed as absent, mild, moderate and severe, respectively. The mean baseline values in comparison to the values on completion of the study for each of the arms for the above parameters were computed, and standard deviations were determined. The Mann-Whitney test was performed to determine baseline variations if any. Respiration rate and pulmonary function values are expressed as means ± SD. Paired t test was used to analyze the improvement in clinical symptoms and FEV_1 in the patients before and after the trial. Analysis of variance (ANOVA) was used for between-group comparisons, and a p value <0.05 was considered as statistically significant improvement.

Composition of DCBT4567-Astha-15

The composition of the plant-based formulation, DCBT4567-Astha-15, is listed in table 1.

Results

Ninety-four patients were recruited within a period of 4 months based on a 15% or more improvement in FEV_1 upon a bronchial challenge. Except for the DCBT4567-Astha-15 arm which had 22 patients, the remaining three arms had each 24 patients. Patients in the DCBT4567-Astha-15 arm completed the trial, whereas 3 patients in the salbutamol arm and 5 patients each in the placebo and salbutamol + theophylline arms did not complete the trial and were lost to follow-up (table 2).

Table 2. Demographic data

Characteristics	DCBT4567-Astha-15 (n = 22)	Salbutamol + theophylline (n = 24)	Salbutamol (n = 24)	Placebo (n = 24)
Mean age, years	30	32	29	31
Aged 30 years or below, %	52	46	62	40
Females, %	65	55	62	64
Exposed to dust, %	14	14	12	12
Childhood asthma, %	15	10	0	5
Past IP treatment, %	7	9	4	0
Past OP treatment, %	93	91	96	100
Use of steroids, %	22	29	19	24
Patients lost during follow-up, n	0	5	3	5
Peak expiratory flow rate, l/min[a]	308.6 ± 71.6	329.2 ± 64.7	343.3 ± 71.4	322.1 ± 61.4
FEV_1, liters				
Before bronchodilator use	1.51 ± 0.35	1.57 ± 0.46	1.66 ± 0.49	1.51 ± 0.38
After bronchodilator use	1.95 ± 0.43	2.07 ± 0.49	2.10 ± 0.47	1.96 ± 0.37
Forced vital capacity, liters	2.06 ± 0.37	2.31 ± 0.56	2.22 ± 0.61	2.16 ± 0.54
$FEF_{25-75\%}$, l/s	1.57 ± 0.74	1.48 ± 0.82	1.79 ± 1.19	1.61 ± 0.67

$FEF_{25-75\%}$ = Forced expiratory rate between 25 and 75% of FVC. p = 0.52, 0.85, 0.43 and 0.82 for peak expiratory flow rate, FEV_1, forced vital capacity and $FEF_{25-75\%}$. Lung function tests were performed before bronchodilator use unless stated otherwise. Baseline values of FEV_1 before bronchodilator use were similar in all four.

Table 3. Clinical symptoms and FEV_1 in patients

Parameters	DCBT4567-Astha-15 (n = 22)	Salbutamol + theophylline (n = 19)	Salbutamol (n = 21)	Placebo (n = 19)
Dyspnoea				
Baseline	0.17 ± 0.46	0.15 ± 0.36	0.15 ± 0.36	0.16 ± 0.37
End of the trial	0.06 ± 0.25*	0.33 ± 0.46^{NS}	0.23 ± 0.42^{NS}	0.32 ± 0.55^{NS}
Wheezing				
Baseline	0.24 ± 0.51	0.23 ± 0.53	0.30 ± 0.47	0.28 ± 0.48
End of the trial	0.20 ± 0.41*	0.47 ± 0.51^{NS}	0.34 ± 0.56^{NS}	0.48 ± 0.58^{NS}
Cough				
Baseline	0.24 ± 0.43	0.09 ± 0.30	0.19 ± 0.40	0.20 ± 0.40
End of the trial	0.20 ± 0.41*	0.38 ± 0.49^{NS}	0.07 ± 0.27*	0.40 ± 0.57^{NS}
Expectoration				
Baseline	0.31 ± 0.47	0.14 ± 0.35	0.19 ± 0.40	0.16 ± 0.37
End of the trial	0.17 ± 0.38*	0.33 ± 0.57^{NS}	0.23 ± 0.42^{NS}	0.36 ± 0.48^{NS}
Disability				
Baseline	0.10 ± 0.30	0.14 ± 0.33	0.07 ± 0.27	0.04 ± 0.02
End of the trial	0.00 ± 0.00*	0.35 ± 0.57^{NS}	0.23 ± 0.42^{NS}	0.08 ± 0.27^{NS}
Disturbances in sleep				
Baseline	0.10 ± 0.30	0.09 ± 0.04	0.11 ± 0.32	0.16 ± 0.37
End of the trial	0.00 ± 0.00*	0.30 ± 0.21^{NS}	0.07 ± 0.27*	0.04 ± 0.02*
Respiration rate				
Baseline	22.89 ± 6.91	24.4 ± 2.24	22.54 ± 7.73	22.90 ± 2.74
End of the trial	21.00 ± 3.09*	24.4 ± 2.24^{NS}	23.09 ± 1.60^{NS}	23.27 ± 2.09^{NS}
FEV_1				
Baseline	1.51 ± 0.35	1.57 ± 0.50	1.66 ± 0.47	1.51 ± 0.35
End of the trial	1.69 ± 0.52*	1.80 ± 0.50*	1.95 ± 0.64*	1.50 ± 0.51^{NS}

* $p < 0.05$. NS = Non-significant.

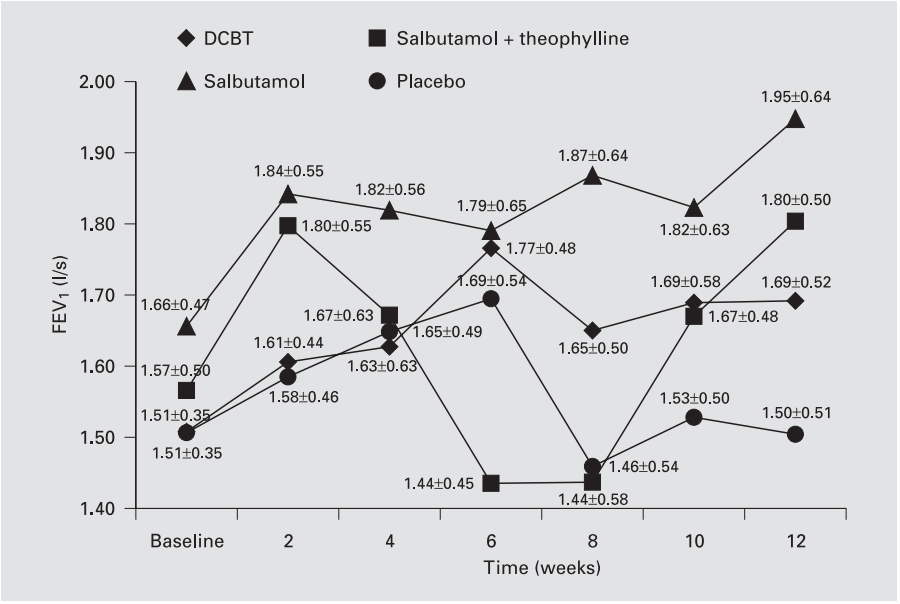

Fig. 1. FEV_1 values (±SD) during treatment.

Table 4. Patients showing improvement in FEV_1

Drug type	Patients showing ≥15% improvement after β_2-agonist use	Patients who dropped out	Patients showing ≥15% improvement in FEV_1 after 12 weeks
DCBT4567-Astha-15	22	0	11
Salbutamol	24	3	10
Salbutamol + theophylline	24	5	11
Placebo	24	5	5
Total	94	13	38

Table 2 outlines the medical history and the baseline demographic data of the patients. The mean age of the study population and exposure to dust were similar in all the four arms. The distribution of female patients was lower in the salbutamol + theophylline arm than in the other three arms. The DCBT4567-Astha-15 group had more childhood asthma patients. Though the salbutamol arm had slightly higher mean values in the pulmonary function tests followed by salbutamol + theophylline, placebo and DCBT4567-Astha-15 arms, the Mann-Whitney test indicated that all the four groups had similar baseline values (table 2).

Clinical Symptoms

Clinical symptoms were analyzed individually, and the mean baseline (initial) and 12th-week (final) values are represented in table 3. It is evident that DCBT4567-Astha-15 patients had significantly reduced ($p < 0.05$; 95% significance) dyspnoea, wheezing, cough, expectoration, disability and sleep disturbances. The salbutamol (12 mg/day) patients recorded reduction in cough and reduced sleep disturbances, while salbutamol + theophylline and placebo patients showed reduction in sleep disturbances only (table 3).

Pulmonary Function Tests

Mean FEV_1 values at baseline and at the end of the trial showed statistically significant improvement ($p < 0.05$; 95% significance) in the three arms, namely DCBT4567-Astha-15, salbutamol and salbutamol + theophylline. Analysis of FEV_1 between the groups by ANOVA revealed that the three drug arms showed similar improvement. The placebo arm did not show any improvement (fig. 1; table 3). The number of patients who have shown the desired 15% improvement in FEV_1 demonstrated in all the three drug arms were found to be similar (table 4; fig. 2).

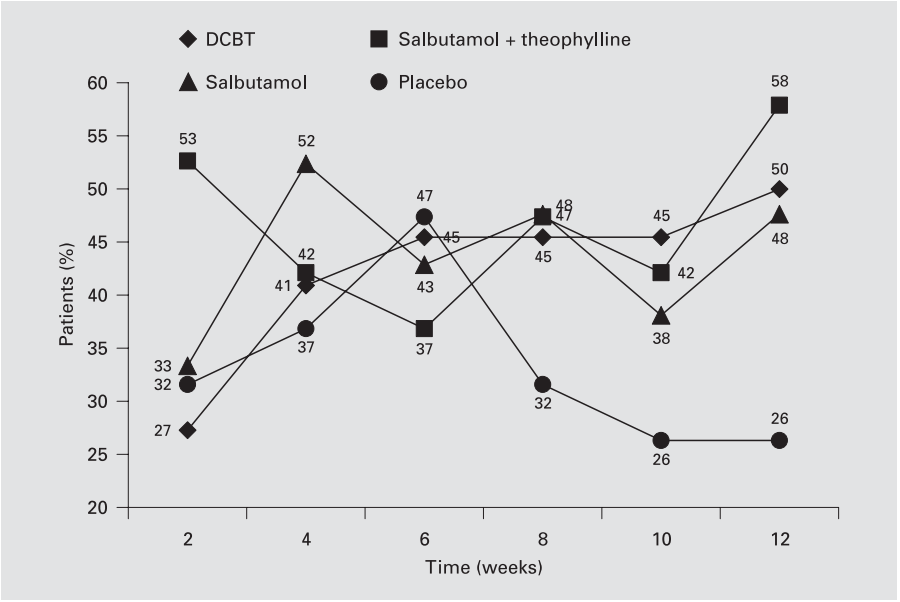

Fig. 2. Percentage of patients showing improvement during treatment.

Table 5. Adverse events

	DCBT4567-Astha-15 (n = 22)	Salbutamol + theophylline (n = 19)	Salbutamol (n = 21)	Placebo (n = 19)
Headache	2	2	3	4
Nausea	1			
Nervousness				
Insomnia				
Asthma				3
Anxiety				
Dizziness		1	1	
Palpitations				
Dyspepsia				
Itching	2	2	1	1
Loss of appetite	1	4	2	
Increased appetite		1	1	
Diarrhoea		2	1	
Chest pain		1	1	
Thinking abnormal				
Loss of hair		1		
Tremor		3		
Overdose				
Abdominal pain	2	5	3	2
Vasodilation				
Gastritis	1	2	2	
No drug effect				
Dyspnoea				
Decreased lung function				2
Total	9	24	15	12

Adverse Events

The DCBT4567-Astha-15 drug group recorded the least adverse events in comparison with salbutamol and salbutamol + theophylline groups (table 5). Headache, itching and abdominal pain were recorded in all the four arms studied. Decreased lung function with symptoms of asthma was observed in 5 patients in the placebo arm. Loss of appetite and gastritis were reported in the other three arms except for the placebo arm. One patient complained of nausea in the DCBT4567-Astha-15 group, which lasted 1 day only.

Discussion

Clinical trials using complimentary medicines have been reviewed by many authors with reservations. Most of these trials have either not been carried out for a minimum period of 12 weeks or did not use standard measures of improvement such as the pulmonary function test or FEV_1. A few of these trials had ethical flaws with patients not signing the consent form or the trial not being approved by an ethical committee [7, 8].

The importance of a 15% or more improvement in FEV_1 values, the marker determining the efficacy of a drug in the treatment of asthma patients, has been described by several authors [1, 2]. In India, salbutamol and theophylline are used in the treatment of asthma, as their synergistic effect was noticed and found superior to other forms of

treatment for over a decade [11]. The objective of this group was to design a structured study which does not have the above-cited shortcomings and also make a direct comparison of the plant-based formulation with the existing biomedical drugs used in the treatment of asthma. An earlier double-blind placebo-controlled study conducted by this group had demonstrated the efficacy and tolerability of DCBT4567-Astha-15, a plant-based formulation.

In this study, clinical symptoms analyzed have unequivocally demonstrated greater improvement in the DCBT4567-Astha-15 arm than in the two biomedical arms (table 2). However, FEV_1 improvement was similar in all the three drug arms (tables 3, 4). The plant-based formulation appears to have considerable potential to be used as a substitute for the drugs used in the biomedical arms of this study.

The drug-related adverse events recorded were in agreement with two recent studies published on asthma [2] and COPD [12]. The DCBT4567-Astha-15 formulation showed minimal side-effects. Some of the side-effects like nervousness, insomnia, anxiety, palpitations, dyspepsia or abnormal thinking, were not observed during this study, though being reported earlier with salbutamol and theophylline [2, 13].

Several interesting publications by a number of authors on the likely mechanism of action of the individual plants used in DCBT4567-Astha-15, e.g. immunomodulation [14–18], anti-inflammatory [19–21] and bronchodilatory properties [22], have been reported. This study did not investigate in detail the mechanism of action of this multi-plant-based formulation. However, results from this study being encouraging, it has now opened up the possibility for further investigation.

Acknowledgements

The authors are grateful for the cooperation and support of the Dalmia Brothers Private Limited, New Delhi, India, and of the Government Hospital for Thoracic Medicine, Chennai, India, for carrying out this clinical study. The advice of Dr. Gupte, TRC, Chennai, and the support of Mr. Kishore for carrying out the statistical analyses are also hereby acknowledged.

References

1 National Heart, Lung and Blood Institute: National Asthma Education Program Expert Panel Report: Guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol 1991;88:425–533.
2 Goldstein MF, Chervinsky P: Efficacy and safety of doxofylline as compared to theophylline in chronic reversible asthma – a double-blind randomized placebo-controlled multicentre clinical trial. Med Sci Monit 2002;8:CR297–CR304.
3 Ouksel H, Meslier N, Badatcheff-Coat A, Racineux JL: Influence of predicted FEV_1 on bronchodilator response in asthmatic patients. Respiration 2003;70:54–59.
4 Ernst E: Complementary therapies in asthma: What patients use? J Asthma 1998;35:667–671.
5 Villani F, Comazzi R, De Maria P, Galimberti M: Effect of dietary supplementation with polyunsaturated fatty acids on bronchial hyperreactivity in subjects with seasonal asthma. Respiration 1998;65:265–269.
6 Huntley A, Ernst E: Herbal medicines for asthma: a systematic review. Thorax 2000;55:925–929.
7 Steurer-Stey C, Russi EW, Steurer J: Complementary and alternative medicine in asthma – do they work? Swiss Med Weekly 2002;132:338–344.
8 Linde K, Jonas WB, Melchart D, Willich S: The methodological quality of randomized controlled trials of homoeopathy, herbal medicines and acupuncture. Int J Epidemiol 2001;30:526–531.
9 Murali PM, Lakshmisubramanian S, Nalini K, Augustus GDPS, Perumal T, Krishnarajasekar OR, Rajasekaran S, Paramesh P, Deivanayagam CN: Proof of concept study of a herbal formulation for the treatment of asthma (abstract OP-02). Kochi, World Ayurvedic Congress, November 1–4, 2002.
10 Deivanayagam CN, Sridhar CB, Rajasekaran S, Paramesh P, Krishnarajasekar OR, Perumal T, Vasudevan S, Lakshmisubramanian S, Nalini K, Murali PM: Promising plant-based formulation in the treatment of chronic obstructive pulmonary disease and asthma. New Delhi, National Symposium on Pulmonary and Critical Care Medicine, August 30 to September 1, 2002.
11 Niphadkar PV, Ghamande AR, Shah MU, Mehta AK, Odak VV: Combination of salbutamol (2 mg)/theophylline (100 mg) in perennial bronchial asthma: a critical assessment. Lung India 1984;2:307–311.
12 Murali PM, Rajasekaran S, Paramesh P, Krishnarajasekar OR, Vasudevan S, Nalini K, Lakshmisubramanian S, Deivanayagam CN: Plant-based formulation in the management of chronic obstructive pulmonary disease: a randomized double-blind study. Respir Med, in press.
13 Wood AJJ: Theophylline in asthma. N Engl J Med 1996;334:1380–1388.
14 Antony S, Kuttan R, Kuttan G: Immunomodulatory activity of curcumin. Immunol Invest 1999;28:291–303.
15 Kroes BH, Van den Berg AJJ, De Silva KTD, Labadie RP: Investigation of *Nimba arishta*, an immunomodulating ayurvedic drug obtained by fermentation. J Eur Ayurved Soc 1992;2:123–133.
16 Puri A, Sahai R, Singh KL, Saxena RP, Tandon JS, Saxena KC: Immunostimulant activity of dry fruits and plant materials used in Indian traditional medical system for mothers after child birth and invalids. J Ethnopharmacol 2000;71:89–92.
17 Atal CK, Sharma KL, Kaul A, Khajuria A: Immunomodulatory agents of plant origin. I. Preliminary screening. J Ethnopharmacol 1986;18:133–141.
18 Srivasthva KC, Malhotra N: Acetyl eugenol, a component of oil of cloves (*Syzygium aromaticum* L.) inhibits aggregation and alters arachidonic acid metabolism in human blood platelets. Prostoglandins Leukot Essent Fatty Acids 1991;42:73–81.
19 Srinivas L, Shalini VK, Shylaja M: Turmerin: a water-soluble antioxidant peptide from turmeric. Arch Biochem Biophys 1992;292:617–623.
20 Basu A, Chaudhuri AK: Preliminary studies on the anti-inflammatory and analgesic activities of *Calotropis procera* root extract. J Ethnopharmacol 1991;31:319–324.
21 Sadique J, Chandra T, Thenmozhi V, Elango V: The anti-inflammatory activity of *Enicostemma littorale* and *Mollugo cerviana*. Biochem Med Metabol Biol 1987;37:167–176.
22 Amin AH, Mehta DR: Bronchodilator alkaloid (vasicinone) from *Adhatoda vasica* Nees. Nature 1959;184:1317.