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Chambá (*Justicia pectoralis*) syrup for the treatment of cough and respiratory symptoms: A randomized clinical trial

Wilcare de Medeiros Cordeiro Nascimento¹, Francisco Plácido Nogueira Arcanjo^{2*}, Mary Anne Medeiros Bandeira¹, Bruna Linhares Prado², Maria Ester Frota Fernandes¹, Elayne Cristina Oliveira Brito³, Bianca Frota Monte³, Aristides Avilo do Nascimento³, Antonio Flávio Queiroz de Oliveira², Leandro Cordeiro Portela² and Cecília Costa Arcanjo²

¹ Department of Research and Postgraduation, Faculty of Pharmaceutical Sciences, Federal University of Ceará, Brazil.

² Department of Postgraduation in Health Sciences, Faculty of Medicine, Federal University of Ceará, Brazil.

³ Department of Health Sciences, Faculty of Pharmacy, Centro Universitário INTA, Brazil.

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Cough is a common pediatric complaint, resulting in frequent doctor's office or hospital visits. In Brazil, the leaves of chambá (*Justicia pectoralis*) have been used extensively in herbal preparations for the treatment of many respiratory problems such as cough, bronchitis, and asthma. Thus, this study aimed to assess the effectiveness of chambá syrup for the treatment of cough and respiratory symptoms in children. Between November 2017 and February 2018, patients aged 1 to 12 years with respiratory symptoms and cough, and onset of symptoms greater than 48 h were enrolled in this trial. Participants were randomized to receive either chambá syrup in three daily doses or placebo. Effectiveness was assessed through a questionnaire, to measure the intensity of cough and respiratory symptoms, before the intervention and 48 h after, using Likert scale responses. A total of 114 children, 56 in the chambá group and 58 in the placebo group, participated in the study. After 48 h, there was a significant reduction in frequency of cough, severity of cough, severity of nasal congestion, and in improvement in the ability to sleep for both the child and caregiver in the chambá group ($p < .0001$ for all variables); for participants in the placebo group, there were no significant differences after intervention, in comparison with baseline. In this study population, chambá syrup was effective in the treatment of cough and respiratory symptoms, providing an overall improvement of symptoms when compared to placebo, as well as improving the ability to sleep.

Key words: Cough, clinical trial, pediatrics, *Justicia pectoralis*.

INTRODUCTION

Cough is one of the most common pediatric problems for which parents seek medical attention. To treat coughs,

parents frequently administer over the counter (OTC) drugs, however the efficacy of most of these drugs has

*Corresponding author. E-mail: franciscoplacidoarcanjo@gmail.com.

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not been proven, and in fact several studies have shown that these drugs are ineffective (Smith et al., 2012).

In recent decades, interest in phytotherapy has increased considerably among users, researchers, and health services (Rosa et al., 2011). Many plant species are traditionally used for the treatment of respiratory diseases, and some of these plants have been investigated for their effectiveness, presenting promising results (Bussmann and Glenn, 2010). The family Acanthaceae has a wide morphological and ecological variety, consisting of about 250 genera and more than 4000 species and is largely distributed in the tropics all over the world (Wasshausen, 1995; Mabberley, 1997). According to Barroso et al. (1991), Brazil represents one of the largest centers of diversity of this family with approximately 40 genera and 550 species. *Justicia pectoralis* var. *stenophylla* Leonard is a medicinal plant with a long history of traditional use in South and Central America. In Brazil, *Justicia pectoralis* var. *stenophylla* Leonard is popularly known as chambá, anador, trevo-cumaru, trevo-do-Pará ou cachambá (Morton, 1977; Matos, 2000). The leaves are simple, membranous, green, transversely opposite, measuring 4-6 cm in length. Leaf blade has petiole, lanceolate, acute or attenuated apex, acute or narrow base and whole margin with trichomes on both sides. It has small, sessile flowers with green goblet and white or lilac corolla. The whole plant and freshly harvested leaves dried or after boiling, exhale a sweet odor due to the presence of coumarin (Oliveira and Andrade, 2000; Trueba et al., 2001). In Brazil, the leaves of *Justicia pectoralis* are popularly used in homemade preparations for treatment of respiratory tract disorders, such as cough, bronchitis, and asthma. Its syrup is widely produced and distributed by the public phytotherapy program called “Farmácias Vivas” (Living Pharmacies). In addition, this species belongs to the National Record of Plants of Interest to the National Health System (Ministry of Health, 2009) and the national phytotherapy formulary (Leal et al., 2017).

Chambá (*Justicia pectoralis* var. *stenophylla* Leonard) has several biological effects, including its therapeutic potential for the treatment of inflammatory diseases, such as asthma (Leal et al., 2017). Clinical studies with chambá syrup or extracts containing coumarins are scarce in one clinical trial. It was shown that the use of chambá syrup for two weeks improved the obstructive and symptomatic clinical profile of patients with intermittent, mild or persistent moderate asthma, revealing a bronchodilator action of this herbal medicine (Santana et al., 2012). In a double-blind randomized controlled trial with 35 asthmatic patients, the therapeutic use of *J. pectoralis*, *P. amboinicus* and *M. arvensis* syrup as complementary therapy in asthma treatment associated with inhaled beclomethasone dipropionate 250 mg combined with salbutamol spray 100 mg was observed. The syrup did not cause alterations in the parameters of pulmonary function tests through spirometry nor did it cause toxicity or adverse events

(Linhares, 2012). A strong collaboration between preclinical and clinical studies is still necessary for the development of an herbal medicine from aerial parts of *J. pectoralis* (Leal et al., 2018). Since there are only a few clinical studies, and no randomized trials with chambá (*J. Pectoralis*) syrup, this study aimed to assess the effectiveness of this syrup when compared to a placebo in the treatment of cough and respiratory symptoms in children.

MATERIALS AND METHODS

Study design, setting and participants

A randomized, double-blind study that was carried out between November 2017 and February 2018, in the pediatric unit at the *Unimed Sobral Regional Hospital*, Ceará, Brazil, where two groups were studied simultaneously, one of which received the intervention of interest and the other a control group receiving placebo. The cohort consisted of patients aged 1 to 12 years with respiratory symptoms and cough, and onset of symptoms greater than 48 h, and who had had these symptoms for a maximum of 7 days. Eligibility criteria were analyzed at the time of hospital admittance. Patients with a clinical picture suggestive of asthma, pneumonia, laryngitis, and patients with a history of asthma, chronic lung disease or other chronic conditions were excluded from the study. Patients taking other medications, in addition to antipyretics, in the last 48 h, and whose legal guardians did not grant permission were also excluded.

Sample size calculation

The sample size was calculated by using the G*Power 3.1 sample size calculation program with an effect size of 0.3 for difference between two dependent means (matched pairs), $\alpha = 0.05$, power of 80%. The total sample size is 90 participants (45 participants per group). However, allowing for an attrition rate of 10%, the minimum sample size was increased to 100 participants in total (50 participants in the control group and 50 participants in the intervention group).

Intervention

Double-blind masking was achieved and maintained during the study; the identity of the intervention syrup and placebo was masked from the investigator and the subject in the following manner: all participants received medication from a 100 ml amber-glass flask, with a dosage cup, the flasks were differentiated by means of a label, one was identified as syrup A and the other as syrup B, with no reference to the specific content.

The quantity in milliliters (ml) was prescribed according to the age of each participant and based on the phytotherapy guide from the State Phytotherapy Program in the State of Ceará (Matos et al., 2001). For children aged between 1 and 4 years, a dose of 5 ml was administered three times a day, and for children aged between 5 and 12 years, a dose of 10 ml was administered three times a day.

Preparation of syrup

Justicia pectoralis var. *stenophylla* Leonard originates in shaded understory regions with a humid climate, in Tropical America and is

Table 1. Composition of chambá syrup and placebo (100 ml).

Chambá syrup at 50 mg/ml		Placebo syrup	
Ingredient	Quantity	Ingredient	Quantity
Dry leaves <i>J. pectoralis</i>	5 g	-	-
77 GL alcohol	2.8 ml	77 GL alcohol	2.8 ml
White crystal sugar	66 g	white crystal sugar	66 g
Nipagin (methylparaben)	0.15 g	Nipagin (methylparaben)	0.15 g
Mint Essence	0.1 ml	Mint Essence	0.1 ml
Purified water	25.95 ml	Purified water	30.95 ml

Source: Guia Fitoterápico do Programa Estadual de Fitoterapia do Estado do Ceará, 2001.

cultivated in several regions of Brazil (Matos, 2007). The aerial parts grown in the medicinal plant garden at the Family Health Center in the Sumaré neighborhood (Sobral, Ceará) were used. The primary processing of the leaves was carried out at a pharmacy facility (*Farmácia Viva*) in the municipality. Facilities in the *Farmácia Viva* project in the state of Ceará are organized in such a way that they have control over all stages from botanical certification, the cultivation of medicinal plants, to the preparation of herbal medicines and their dispensation in health centers with a medical prescription (Ceará, 2015).

The pharmaceutical forms and formulas of herbal medicines prepared and used in *Farmácia Viva* project were selected and made possible with pharmacotechnical support from the Federal University of Ceará (UFC) and from the Phytotherapeutic Center (NUFITO) of the Pharmaceutical Assistance Coordination of the Health Department of State of Ceará (Ministry of Health, 2013). The formulation of *Justicia pectoralis* syrup is described in the Phytotherapy Guide of the State Phytotherapy Program of the State of Ceará (Matos et al., 2001). This syrup is the only formulation produced from Chambá by governmental phytotherapy program in the Northeast region of Brazil, known as the *Farmácia Viva* project, and in its composition there is 5% of *J. pectoralis*, water, sucrose, methylparaben and mint essence (Table 1). The syrups (intervention and control) were produced following Good Manufacturing Practice (GMP), regulated according to RDC N. 18/2013, which determines the minimum requirements for the preparation of medicinal and phytotherapeutic plants. The syrup used in the study was prepared and provided without charge by the *Farmácia Viva* project. For this study, two standardized syrups were produced, one containing the leaves of *J. pectoralis* (intervention) and the other without (control); the composition is described in Table 1.

Randomization

After the parents or legal guardians accepted participation in the study, the children were randomly assigned by means of sequentially numbered, opaque, sealed envelopes, into two groups: group A (placebo) and group B (chambá syrup).

Data collection instrument

At the time of the prescription, a data collection instrument and questionnaire were administered to parents or legal guardians of children, and once more 48 h later by the researcher. The data collection instrument consisted of patient identification, length of time since the onset of symptoms, use of medication prior to treatment, any adverse reactions to prescribed treatment, use of any other medication during treatment, and a questionnaire with a

Likert scale to measure the intensity of cough and respiratory symptoms (Hartnick et al., 2009). Scale responses ranged from the most severe symptoms (7 points) to no symptoms (1 point) (Figure 1).

Statistical analysis

To compare the means between the groups, at baseline and endpoint, we used the unpaired student's t-test; and the paired student's t-test to assess the difference in study variables before and after intervention within the groups. Data had normal distribution. The statistical software package SPSS for Windows, version 23.0, was used for all analyses (SPSS Inc., Chicago, IL). The limit for statistical significance was set at $p \leq .05$. Analyses were by intention to treat.

Ethical considerations

The study was approved by Research Ethics Committee of the Federal University of Ceará (protocol number: 2.365.956). Written informed consent was obtained from parents or legal guardians of all participants before enrollment, and literate children authorized their collaboration through a term of assent. The study was conducted in compliance with the Brazilian National Health Council (CNS) Resolution 466/12, which establishes the ethical standards for conducting research involving human beings.

RESULTS

One hundred and fourteen children were randomized into two groups, where 58 children received syrup A (placebo), and 56 received syrup B (chambá). For the patients who received placebo 36 were females and 22 were males, and for the patients who received the chambá syrup, 30 were females and 26 were males. There was no statistical difference regarding gender or age between groups ($p=0.45$, and 0.30 , respectively).

In the analysis prior to the intervention, there were no significant differences for the study variables between the groups (Table 2). A Likert scale was used to assess respiratory symptoms before and after treatment in both groups. For the group A (placebo), there was no significant reduction for cough frequency after treatment ($p=0.31$), cough severity ($p=0.12$), severity of nasal

In responding to the questions, please mark the appropriate box next to your answer choice with an "x".						
1. How OFTEN did you child COUGH in the last 24 hours?						
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
Not at all		Half of the time			Most of the time	
2. How SEVERE was your child's COUGH in the last 24 hours?						
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
Not at all		Moderate			Very intense	
3. How SEVERE was your child's STUFFY NOSE in the last 24 hours?						
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
Not at all		Moderate			Very intense	
4. How SEVERE was your child's RUNNY NOSE in the last 24 hours?						
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
Not at all		Moderate			Very intense	
5. How much did last night's cough and cold symptoms affect your CHILD'S ABILITY TO SLEEP?						
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
Not at all		Moderately			Very intensely	
6. How much did your child cough and cold symptoms affect your OWN ABILITY TO SLEEP?						
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6	<input type="checkbox"/> 7
Not at all		Moderately			Very intensely	

Figure 1. Questionnaire to assess cough and respiratory symptoms.

Table 2. Baseline analysis between groups.

Variables	Syrup A (Placebo)	Syrup B (Chambá)	p-value ^a
	(n=58)	(n=56)	
	(mean±SD)	(mean±SD)	
Frequency of cough	40.45±10.49	40.57±10.65	0.68
Severity of cough	40.48±10.49	40.61±10.58	0.67
Severity of nasal congestion	30.17±10.91	30.64±20.08	0.21
Severity rhinorrhea	20.72±10.65	30.21±20.15	0.17
Effect on child's ability to sleep	30.76±10.89	30.39±10.89	0.30
Effect on caregivers' ability to sleep	40.07±20.15	30.79±20.04	0.47

Mean values based on Likert scale. SD Standard deviation. ^aBased on unpaired student's t-test.

congestion (p= 0.48), rhinorrhea severity (p=0.89), or disrupted children's and parents' sleep patterns (p= 0.48

and 0.22, respectively) (Table 3). For group B (chambá syrup), cough frequency before treatment was 4.57±1.65,

Table 3. Effect of Chambá syrup on cough and respiratory symptoms compared to placebo in children aged 1 to 12 years.

Variables	Syrup A (Placebo) (n=58)			Syrup B (Chambá) (n=56)			p-value ^b between groups
	Before (mean±SD)	After (mean±SD)	p-value ^a	Before (mean±SD)	After (mean±SD)	p-value ^a	
	Frequency of cough	4.45±1.49		4.10±1.97	0.31		
Severity of cough	4.48±1.49	4.07±2.07	0.12	4.61±1.58	2.18±1.08	<0.0001	<0.0001
Severity of nasal congestion	3.17±1.91	2.97±1.97	0.48	3.64±2.08	1.54±0.91	<0.0001	<0.0001
Severity rhinorrhea	2.72±1.65	2.76±1.92	0.89	3.21±2.15	1.86±1.10	<0.0001	0.0028
Effect on child's ability to sleep	3.76±1.89	3.55±2.19	0.48	3.39±1.89	1.39±0.87	<0.0001	<0.0001
Effect on caregivers' ability to sleep	4.07±2.15	3.69±2.30	0.22	3.79±2.04	1.29±0.71	<0.0001	<0.0001

Mean values based on Likert scale. SD Standard deviation. ^a Based on paired student's t-test. ^b Based on unpaired student's t-test at the end of the intervention.

and 2.07±0.97 after; cough severity was 4.61±1.58 at the beginning of the study and 2.18±1.08 after intervention; severity of nasal congestion was 3.64±2.08 before, and 1.54±0.91 after; rhinorrhea severity was 3.21±2.15 before, and 1.86±1.10 after; effect of the cough of children's sleep patterns was 3.39±1.89 before intervention, and 1.39±0.87 after; and effect on parents' sleep patterns was 3.79±2.04 before, and 1.29±0.71 after intervention. All results were statistically significant different, in the before and after comparisons for chambá syrup group, ($p < .0001$ for all comparisons) (Table 3).

In the comparison between groups at the endpoint, all study variables presented statistical significance (Table 3). As for the time since the onset of symptoms, in the placebo group 42 children reported the onset of symptoms within the last 4 days, and in the intervention group 40 children reported the onset of symptoms during the same period, $p=0.53$. Regarding the appearance of other symptoms after starting treatment, 12 patients reported having a fever, and diarrhea and abdominal pain by other 2 patients in the placebo group; in the intervention group, 2 patients reported a fever, with no other

symptoms (Data not shown). No adverse reactions associated with the use of chambá syrup were reported.

DISCUSSION

Many plant species are traditionally used for the treatment of respiratory diseases, and some of these plants have been investigated for their effectiveness, with promising results (Bussmann and Glenn, 2010). The results of the present study indicate that *J. pectoralis* was effective in the symptomatic relief of cough, nasal congestion and rhinorrhea, as well as improving the ability to sleep of children and their caregivers, probably due to the comfort provided by the global relief of symptoms.

The anti-inflammatory properties of coumarins may be responsible for a decrease in irritation that is due to inflammatory process and excess mucus. Studies on rats, with the hydroalcoholic extract of coumarin-rich plants have demonstrated antinociceptive, anti-inflammatory and bronchodilator activities, which could justify its traditional use for the treatment of respiratory tract

disorders (Leal et al., 2000). Coumarin is one of the main phytochemical compounds present in the extracts obtained from this plant (Kostova, 2005). In this context, it has been demonstrated that umbelliferone, a compound found in chambá syrup, suppressed pneumonia in mice infected with the influenza virus, not through antiviral action but by reducing the production of pro-inflammatory cytokines (Kurokawa et al., 2010). Furthermore, it was reported that umbelliferone is able to suppress inflammatory response in asthmatic mice by reducing leukocyte accumulation and production of IL-4, IL-5 and IL-13 in the bronchoalveolar lavage of animals (Vasconcelos et al., 2009). The effects of chambá syrup may have been responsible for an improvement in the frequency and intensity of cough and respiratory symptoms of the children in the intervention group in our study.

Another species rich in coumarin, which is traditionally used in the treatment of respiratory diseases is cumaru (*Amburana cearensis*).

In a randomized, double-blind, placebo-controlled clinical trial ($n=42$), the efficacy and safety of cumaru syrup as adjunctive therapy for mild persistent asthma was evaluated.

There was a statistically significant improvement in asthma symptoms as measured by the “Asthma Quality of Life Questionnaire”, and spirometric parameters (Carvalho et al, 2012).

Another preliminary clinical assessment was conducted with asthmatic patients (n=21) who took chambá syrup for two weeks. Through clinical, physical and spirometric examination before and after intervention, researchers identified an improvement in clinical symptoms and pulmonary obstruction measured by spirometry, revealing a bronchodilator action of the herbal remedy (Santana et al., 2012).

In our study, parents favorably rated chambá syrup for the symptomatic relief of cough and respiratory symptoms, thus allowing both the children and their caregivers to have a quieter night's sleep, presenting results that were significantly higher when compared to placebo group, $p < 0.0001$. The sensation of irritation that precedes the motor act of coughing allows inferring the concept of cough hypersensitivity syndrome after acute respiratory viral infection, which in some patients becomes a refractory and exhaustive cough due to inflammation and excess mucus. In viral infection, there is an increased release of cytokines, neurotransmitters and leukotrienes that induce an increase in neural receptor levels, with transient stimulus of afferent neural activity, mucus hypersecretion and possibly exacerbation of cholinergic motor effects (Dicpinigaitis, 2014). According to Leal et al. (2017), the oral administration in rats of the standardized hydroalcoholic extract of *J. pectoralis* reduced showed an anti-inflammatory activity, as observed by its ability to significantly inhibit the increase of the levels of TNF- and IL-1, pro-inflammatory cytokines, in bronchoalveolar lavage of rats. The anti-inflammatory action of *J. pectoralis* syrup may be responsible for a decrease in the enhanced release of cytokines, thus reducing the intensity and frequency of cough, in addition to reducing nasal obstruction and coryza, thus providing an overall improvement of respiratory symptoms. The joint actions of the two main compounds present in *J. Pectoralis*, coumarin and umbelliferone may represent an advance in the symptomatic treatment of cough and respiratory symptoms, possibly by blocking the triggering mechanisms of cough due to viral or irritative conditions.

In a clinical assessment, it was observed that the drugs most used in the management of irritative cough, dextromethorphan and diphenhydramine, were not superior to placebo when the frequency and intensity of coughing were analyzed (Paul et al., 2004). Some studies report a significant placebo effect in the treatment of children with cough and respiratory symptoms. In another trial, agave nectar was used in one group, and placebo in the other; both resulted in a significant improvement of symptoms compared to the group without any treatment (Paul et al., 2014). In pediatric clinical trials that seek to investigate treatments for treating the

symptoms of coughs and colds, placebo effects are common (Hutton et al., 1991; Unuvar et al., 2007). However, in our study, there was no significant improvement in cough or respiratory symptoms with placebo. No adverse effects were reported by participants assigned to the use of chambá syrup in our study. These data are consistent with another study, in which a sample of 110 patients taking this syrup did not present toxicity or adverse reactions related to this herbal medicine (Silva, 2015).

In the clinical aspect, more studies are needed to consolidate the efficacy and safety of products derived from *J. pectoralis*, since most of the clinical studies already performed involved a small group of patients, did not use a control group, and plants other than chambá. Just as the study of Linhares (2012), which employed syrup such as Cuban oregano or Mexican mint (*Plectranthus amboinicus*) and Wild mint (*Mentha arvensis*).

CONCLUSION AND PROSPECT

This study showed that chambá syrup (*Justicia pectoralis*) was effective in the treatment of cough and respiratory symptoms, providing an overall improvement of symptoms when compared to placebo, with decreased frequency and intensity of cough, obstruction, nasal congestion and rhinorrhea. Some limitations need to be acknowledged and addressed regarding the present study. First, many confounding factors, which may affect the outcome of cough and respiratory symptoms in children, such as chilling, air pollution, crowding, irritants, fluids, etc., were not accounted for. Secondly, its necessary to do a phytochemical test to check for the presence of coumarins and umbelliferone in the composition of chambá syrup produced by the *Farmácias Vivas* project. Another important fact is that the period of intervention was short; a longer period may have presented more conclusive results. Furthermore, the sample was restricted to patients from a single private hospital; therefore, the results cannot be generalized to all hospitals. However, despite these limitations, it should be emphasized that this study was able to identify significant differences in all the variables analyzed.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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