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Curcuma longa L. ameliorates asthma control in children and adolescents: A randomized, double-blind, controlled trial

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ABSTRACT

Ethnopharmacological relevance: Roots of *Curcuma longa* L. are used as medicine for millennia. They possess several pharmacological properties, including anti-inflammatory action, and can be suitable for asthma treatment.

Aim of the study: We aimed to test the hypothesis that, in children and adolescents with persistent asthma, the administration of powdered roots of *C. longa* for 6 months, in addition to standard treatment, compared to placebo, will result in better disease control.

Patients and methods: We conducted a randomized, double-blind, placebo-controlled, phase II clinical trial. Patients were randomly assigned to receive 30 mg/kg/day of *C. longa* for 6 months, or placebo. Data were collected prospectively. All patients were categorized for asthma severity and control according to GINA-2016 and underwent pulmonary function tests.

Results: Overall, both groups experienced amelioration of their frequency of symptoms and interference with normal activity, but no differences were found between the two treatment groups. However, patients receiving *C. longa* experienced less frequent nighttime awakenings, less frequent use of short-acting β-adrenergic agonists, and better disease control after 3 and 6 months.

Conclusion: The powdered roots of *C. longa* led to less frequent nighttime awakenings, less frequent use of short-acting β-adrenergic agonists, and better disease control after 3 and 6 months, when compared to placebo.

1. Introduction

Asthma is a highly prevalent chronic inflammatory disease whose main characteristics are bronchial hyper-responsiveness, variable limitation of air flow, and airway remodeling. Symptoms include episodes of wheezing, dyspnea, and cough (Global Initiative for Asthma, 2016). The disease leads to significant morbidity worldwide, and its prevalence is increasing in the last 20 years.

The treatment for asthma aims at controlling inflammation in the long term, while keeping symptoms at minimum and ameliorating the lung function. The main drugs used for long-term control are: inhaled corticosteroids and inhaled long-acting beta-adrenergic agonists (LAβAA). Oral corticosteroids and short-acting beta-adrenergic agonists (SAβAA) are used for asthma attacks. Although most patients experience good disease control, many patients do not (Global Initiative for Asthma, 2016). In addition, chronic exposure to corticosteroids can cause serious adverse effects, especially in children. Therefore, new, safe and effective drugs for asthma are needed.

Curcuma longa L. (turmeric, Zingiberaceae) is a perennial plant, extensively grown in Asia and tropical countries, like Brazil. Roots of *C. longa* have been used for millennia as medicine for many purposes, including respiratory diseases (Jagetia and Aggarwal, 2007) and, more specifically, asthma (WHO, 1999). However, its traditional use for asthma lacks scientific validation.

The characteristic yellow, golden color is due to the presence of curcuminoids [curcumin (75–81%), demethoxycurcumin (15–19%), and bisdemethoxycurcumin (2.2–6.6%)] (Patil et al., 2009). There is evidence that the mixture of curcuminoids is more effective than each one alone (Balaji and Chempakam, 2010). Curcumin possessed several biological activities, including: anti-inflammatory, antibacterial, antiviral, antifungal, antioxidant, wound healing, among many others (Jagetia and Aggarwal, 2007). Curcumin modulates the inflammatory response and release of cytokines by suppressing nuclear factor kappa-B (NF-κB) activation, through inhibition of phosphorylation and

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degradation of NF-κB inhibitor alpha (I-κBα) and blockade of phosphorylation of I-κBα kinase (IKKα) (Jagetia and Aggarwal, 2007; Wongcharoen and Phrommintikul, 2009; Yeh et al., 2005). These properties make curcumin into a promising drug for treatment of many inflammatory diseases, including asthma. In fact, there is evidence that curcumin is beneficial on controlling inflammation and hyper-responsiveness in animal models of asthma (Karaman et al., 2012; Oh et al., 2011; Ram et al., 2003).

Therefore, the objective of this study was to test the hypothesis that, in children and adolescents with persistent asthma, the oral administration of encapsulated powdered roots of *C. longa* for 6 months, in addition to standard treatment, compared to placebo, will result in better disease control.

1.1. Patients and Methods

This was a phase 2, double-blind, randomized, placebo-controlled clinical trial. The study was approved by a local institutional review board (protocol #17207213.4.0000.5440), and signed informed consent was required. This study conforms to the standards of the Helsinki Declaration of 1975, as revised in 1983. The study was registered in the Brazilian Registry of Clinical Trials (http://www.ensaiosclinicos.gov.br/) under protocol RBR-9f3wwp, UTN number U1111-1147-8036. This study followed the recommendations of the CONSORT Statement for herbal interventions (Gagnier et al., 2006). Children and adolescents between 7 and 18 years of age with persistent asthma were eligible. They were recruited at the Allergy Clinics from Hospital das Clinicas, Ribeirao Preto Medical School, University of Sao Paulo. Patients with history of allergy or hypersensitivity to turmeric or other plants from the Zingiberaceae family were not included. Exclusion criteria were: parental request, severe allergy or adverse reaction that could be attributable to the plant, and significant non-adherence to treatment, judged by the researchers.

1.2. Preparation of drug and placebo

C. longa was grown at the rural area of Jardinopolis, Sao Paulo, Brazil (latitude 21°4′33″ S, longitude 47°44′48″ W). The plant was identified by Dr. Lin Chau Ming (State University of Sao Paulo, Botucatu, SP, Brazil). *C. longa* is acknowledged as medicine in Brazil by the National Sanitary Surveillance Agency (Agencia Nacional de Vigilancia Sanitaria, ANVISA). Rhizomes of *C. longa*, cultivated in the region of Jardinopolis (Sao Paulo, Brazil, latitude: 21°01′04″, longitude: 47°45′50″, altitude: 590 m). The roots were harvested in 2012, at 9 a.m., and a voucher specimen was deposited in the Herbarium of Medicinal Plants at UNAERP (voucher HPMU-3215). The roots were washed in water, sliced, dried in a circulating-air oven at 45 °C for 36 h, and sieved up to particle size of 40 mesh. The resulting powder is called powdered plant material. The powdered plant material of *C. longa* was encapsulated (250 mg, corresponding to 11 mg of curcumin and 2 mg of demethoxycurcumin). Placebo was maltodextrin, encapsulated identically.

1.3. Quality control

The content of curcuminoids were determined in the powdered roots by high-performance liquid chromatography (HPLC), at the Laboratory of Medicinal Plants, Department of Plant Biotechnology, University of Ribeirao Preto. Curcumin and demethoxycurcumin standards were obtained from the rhizomes following previously described methodology (Jayaprakasha et al., 2002) and validated by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Phytocomplexes (5 mg) were mixed to methanol (1 mL) and sonicated for 15 min in ultrasound (Eco-sonics Q - 5.9/37, W 154 and 37 kHz). The supernatant was filtered through Millipore filter (0.22 μm pore size) and injected in HPLC.

The HPLC used was a Shimadzu™ (Kyoto, Japan) model LC-10-AVP equipped with a SIL-10AF autoinjector, a SPD-M20A photodiode array detector and a Phenomenex™ (Torrance, CA, USA) Luna C18 column (250 × 4.6 mm i.d.; 5 μm particle size). The injection system (Shimadzu™) used was a 20 μL sample loop. A Shimadzu SPD-M10A VP series variable-wavelength detector set at 420 nm was used for detection. A Millipore® (Bangalore, India) membrane filter (0.22 μm pore size) was used for filtration.

1.3.1. Chromatographic conditions

The mobile phase comprised of (A) water/methanol/acetic acid (93:5:2; v/v/v) and (B) acetonitrile/methanol (95:5; v/v) and gradient elution was performed for 30 min at a flow rate of 1 mL min^{-1}. Quantitative levels of curcuminoids were determined using the above solvents programmed linearly from 48 to 68% in B for 0–15 min. The gradient went then from 68 to 48% in B for 15.01–30min. The injection volume was 20 μL and the detection wavelength at 420 nm, as previously described (Jayaprakasha et al., 2002).

1.3.2. Preparation of stock solutions for HPLC

Methanolic stock solutions of curcumin and demethoxycurcumin were prepared separately at a concentration of 250–15.625 μg mL^{-1}.

1.3.3. Determination of curcumin and demethoxycurcumin in samples

Samples (25 μL) were injected in the HPLC. Curcuminoids concentration was determined using linear equation considering dilution factors. Curcumin and demethoxycurcumin contents were expressed as mg.g^{-1} dry weight (DW).

1.3.4. Ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) analysis of the methanolic extract of C. longa, curcumin and demethoxycurcumin

The identities of curcumin and demethoxycurcumin present in the methanolic extract of *C. longa* roots were confirmed by UPLC-MS-MS analysis using a Waters (Milford, MA, USA) Acquity UPLCH-Class system equipped with a PAD and a Waters Xevo TQ-S tandem quadrupole mass spectrophotometer and fitted with a Supelco Ascentis Express C18 column (100 × 4.6 mm i.d.; 2.7 μm particle size) (Fig. 1).

The mobile phase used for gradient elution consisted of 0.1% formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B) at a flow rate of 0.5 mL min^{-1}. The gradient elution program started with 40% B, increased B to 90% up to 10 min remaining in that condition for 5 min and returned to the initial condition (40% B) within the next 4 min. The total time of analysis was 20 min at a flow rate of 500 μL min^{-1}. Wavelengths from 220 to 600 nm were employed to monitor the targeted compounds in diode array detector (DAD). The source and operating parameters were optimized as follows: capilar voltage = 3.2 kV, source temperature = 150 °C, desolvation temperature (N_2) = 350 C, desolvation gas flow = 600 L h^{-1}, and mass range from *m/z* 150 to 800 in the full-scan mode.

1.4. Study protocol

Patients were randomized to one of two groups: *C. longa* or placebo. A randomization list was generated at www.sealedenvelope.com, in blocks of random size (4 or 6). The list was generated by a researcher who did not take part in randomization or patient assessment. The list was uploaded to a software for allocation concealment. Researchers, clinicians, and patients were all concealed and blinded to allocation.

The dose of powdered roots of *C. longa* recommended by the World Health Organization (WHO) for adults is 1.5–3.0 g/day (WHO, 1999), which corresponds to 30–60 mg/kg/day, considering an average adult with 1.73 m^2 of body surface area. In Brazil, ANVISA recommends a dose of 2.5–5.0 mL of a 10% tincture, up to three times a day (BRASIL, 2011), corresponding to a dose of 6–36 mg/kg/day of the powdered roots, considering an adult with 1.73 m^2 of body surface area. We opted

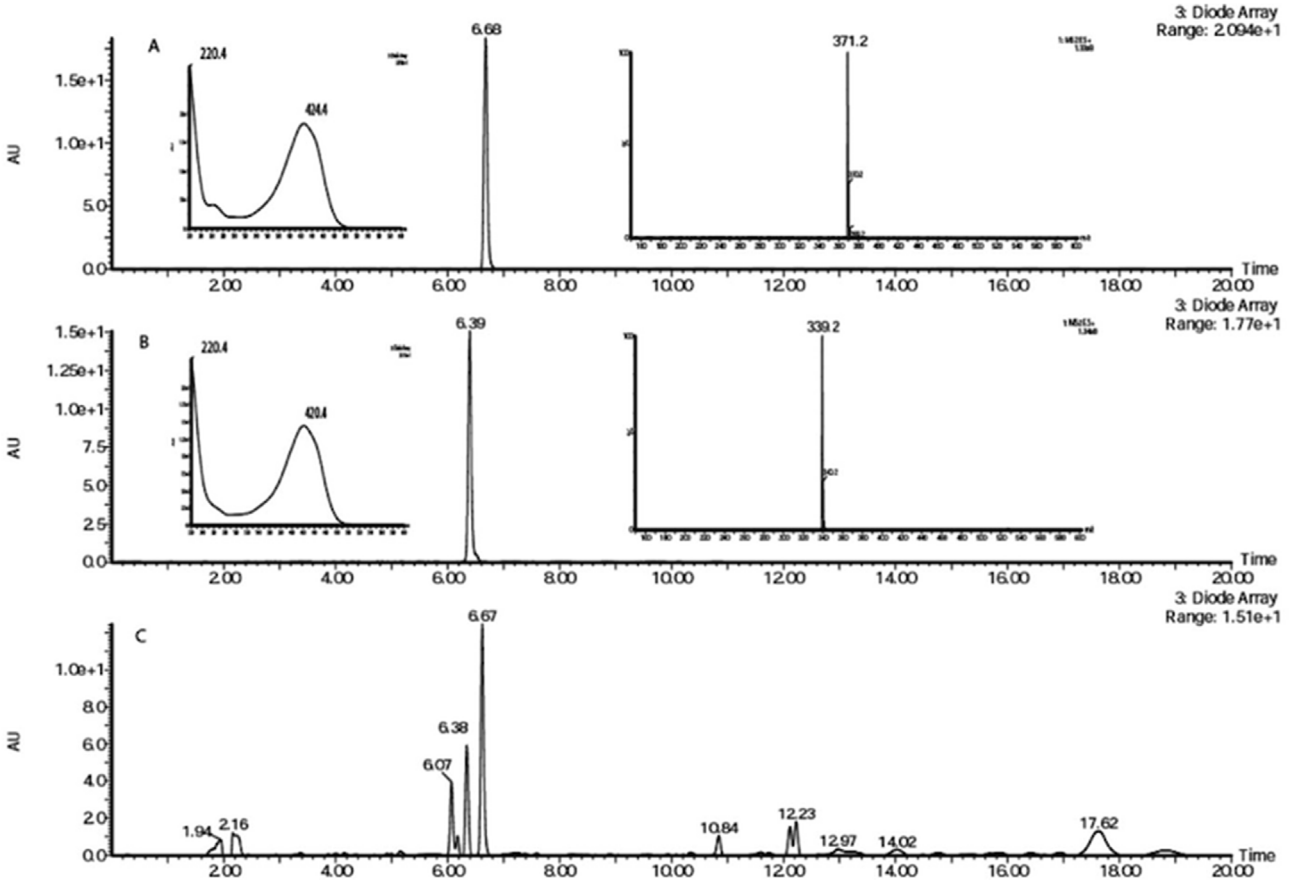

Fig. 1. UPLC-DAD-MS chromatograms of curcumin (A), demethoxycurcumin (B), and methanolic extract of *Curcuma longa* (C) rhizomes.

to use an approximated dose of 30 mg/kg/day. Therefore, patients received either *C. longa* powdered roots or placebo (approximately 30 mg/kg/day, twice daily) for 6 months, as follows: 7–10 years-old, 500 mg/day; 11–14 years-old, 750 mg/day; and 15–18 years-old, 1000 mg/day. These doses yielded approximately 20, 30, and 40 mg/kg/day of curcuminoids, respectively. There were no protocol deviations.

1.4.1. Clinical assessment

Clinical and demographical data were collected from medical records and interviews. All patients were categorized for asthma severity and asthma control (primary outcome) according to GINA-2016 (Global Initiative for Asthma, 2016). They also underwent a pulmonary function test (spirometry) for determination of forced expiratory volume in 1 s (FEV_1).

All data were collected in standardized paper forms and then typed into REDCap (Research Electronic Data Capture, https://projectredcap.org) forms. Our instance of REDCap is hosted in a cloud server provided by USP (InterNuvem, https://internuvem.usp.br) as infrastructure-as-a-service (IaaS). Briefly, REDCap allows safe, regulation-compliant storage of research data (Harris et al., 2009). Paper forms were stored in a locked room at the hospital and were destroyed.

1.5. Statistical analysis

There are no methods for computing sample sizes for multinomial outcomes. In a simpler approach, assuming a binary outcome (disease control yes/no) and considering the maximum difference between these proportions at baseline and after 6 months, if 20% of patients have a well-controlled disease and one wishes to take this proportion to 50%, with 80% power and 5% significance, a total of 17 patients per group would need to be included. We opted to augment this number and planned to enroll 48 patients (24 per group).

The primary outcome was disease control, according to GINA-2016 (Global Initiative for Asthma, 2016): frequency of respiratory symptoms, nighttime awakenings, and use of SAβAA for symptom control, and interference with normal activity. The secondary outcome was FEV_1.

The clinical outcomes and determination of FEV_1 were assessed by a single researcher, blinded to allocation, who was trained by specialists on asthma. Randomization was done by another researcher, who did not assess outcomes.

Results were expressed as means ± standard deviations, medians (ranges), or counts (proportions). Comparisons between the two treatment groups were made with Fisher's exact test, Student's *t*-test, or Mann-Whitney's *U* test, as appropriate, using softwares Stata SE 14.2 (StataCorp, College Station, TX) and Prism 6.0 (GraphPad, LaJolla, CA). A significance level of 5% was adopted. Interim analyses were not planned. All analyses were per-protocol.

2. Results

Phytochemical analysis showed that the powdered roots of *C. longa* contained 45.31 ± 3.1 mg/g of curcumin and 6.94 ± 0.4 mg/g of demethoxycurcumin (Table 1 and Fig. 1).

Between February 2013 and November 2015, 55 patients met inclusion criteria and were randomized. Of these, 21 were excluded (38%), because of loss to follow-up, hindering a total of 34 patients completing the study, 17 in each group (Fig. 2). Their baseline characteristics are shown in Table 2. Patients that received *C. longa* were lighter, shorter, and leaner than those receiving placebo. However, z-scores for height-for-age and BMI-for-age were not different between

Table 1
Concentration of curcuminoids in *Curcuma longa* samples analyzed by HPLC.

Analyte (mg.g^{-1} DW)		
Sample	Curcumin	Demethoxycurcumin
	45.31 ± 3.1	6.94 ± 0.4

Legend: DW, dry weight; HPLC, high-performance liquid chromatography.

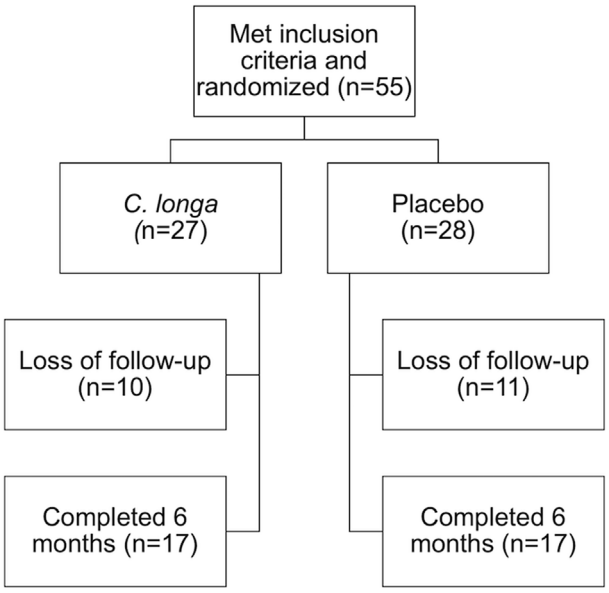

Fig. 2. Flow diagram of the study.

Table 2
Baseline characteristics of patients.

Variable	*C. longa* (n = 17)	Placebo (n = 17)	p-value
Age (years)	11.4 ± 3.3	12.6 ± 3.4	0.3104
Gender (male)	12 (70%)	10 (58%)	0.7210
Weight (kg)	37.8 ± 12.2	53.7 ± 22.8	0.0193
Height (m)	1.45 ± 0.15	1.54 ± 0.15	0.1074
Height-for-age z-scores[a]	−0.15 ± 0.99	0.08 ± 0.87	0.4867
BMI[b] (kg/m^2)	17.4 + 3.1	21.9 ± 5.7	0.0103
BMI[b]-for-age z-scores[a]	0.04 ± 0.90	0.73 ± 1.36	0.1133
Asthma severity			0.4650
Mild	1 (6%)	0	
Moderate	12 (71%)	10 (59%)	
Severe	4 (23%)	7 (41%)	

Legend.
[a] , the references were WHO 2006 Child Growth Charts and WHO Reference 2007 Charts (http://www.who.int/childgrowth/en/), and weight-for-age z-scores were not calculated because they are only available for children younger than 10 years-old (WHO, 2019).
[b] , body mass index.

groups. There was no difference in asthma severity between the two groups.

All patients were on nasal plus inhaled corticosteroids (fluticasone, mometasone, budesonide or beclometasone). Oral anti-histamines (loratadine, desloratadine, cetirizine, or levocetirizine) were used by 28 patients. Inhaled LAβAA (formoterol) was used by 26 patients, and SAβAA (salbutamol) was used by 42 patients. Another two patients used oral leukotriene inhibitors and two patients used oral corticosteroid (prednisolone). There were no significant differences on treatment regimens between the two groups.

Overall, both groups experienced amelioration of their frequency of symptoms (Fig. 3A) and interference with normal activity (Fig. 3C), but no differences were found between the groups. However, despite also ameliorating in the placebo group, patients receiving *C. longa* experienced less frequent nighttime awakenings (Fig. 3B), less frequent use of SAβAA (Fig. 3D), and, consequently, better disease control (Fig. 3E) after 3 and 6 months of treatment. None of the treatments affected FEV_1 after 6 months (Fig. 3F). Of note, no patients receiving *C. longa* reported use of SAβAA many times a day or had uncontrolled disease, conversely to the placebo group.

Only one patient, from placebo group, reported adverse symptoms (nausea), which resolved after adjusting the time of medicine intake. No other side effects were reported in any of the groups.

3. Discussion

We have shown that the powdered roots of *C. longa*, administered to children and adolescents with asthma, in addition to the standard treatment, compared to placebo, led to less frequent nighttime awakenings, less frequent use of SAβAA, and better disease control after 3 and 6 months.

In animal models of asthma, administration *C. longa* or curcumin resulted in significant anti-inflammatory and antioxidant effects (Shakeri et al., 2017; Shakeri and Boskabady, 2017), and ameliorated bronchial hyper-responsiveness (Karaman et al., 2012; Oh et al., 2011). *C. longa* and curcumin attenuate allergic airway inflammation and hyper-responsiveness through inhibition of cyclooxygenase 2 (COX-2), lipoxygenase (LOS), nitric oxide inducible synthase (iNOS), decreasing levels of inflammatory cytokines (Jagetia and Aggarwal, 2007; Jurenka, 2009), inhibition of NF-κB activation (Oh et al., 2011), inhibition of the via Wnt/β-catenin signaling (Yang et al., 2017), activation of nuclear factor-E2-related factor 2/haem oxygenase (HO)-1 signaling pathway (Liu et al., 2015), regulation of $CD4^+CD25^+$ (Ma et al., 2013) and inhibition of Notch1-GATA3 signaling pathway (Chong et al., 2014). There is also evidence that intranasal curcumin prevents airway inflammation, obstruction, and remodeling in acute and chronic models of asthma in animals by regulating MAPKinase activation (p38, Erk and JNK) and prostaglandin D2 release (Chauhan et al., 2014; Subhashini et al., 2016a, 2016b, 2013). Curcumin also inhibited smooth muscle cell proliferation in the airways, *in vitro* and *in vivo*, possibly by upregulating the expression of caveolin-1 and blocking the activation of the ERK pathway (Zeng et al., 2013).

Surprisingly, despite the encouraging preclinical evidence of effectiveness, clinical studies are scarce. In a population-based survey, 2478 Chinese older adults (aged 55 years or more) were assessed for curry (in which turmeric is a major ingredient) intake, smoking status and pulmonary function. A curry intake of at least once monthly was significantly associated with better pulmonary function in multivariable analysis controlling for gender, age, anthropometric measures, smoking status, occupational exposure, history of asthma/chronic obstructive pulmonary disease and intake of other supplements. The effect was more pronounced among smokers (Ng et al., 2012).

In a preliminary clinical study, 15 adult patients with stable, persistent asthma with evidence of allergic sensitization were randomized to receive curcumin (1000 mg, twice daily, n = 9) or placebo (n = 6), for 6 months. The treatment did not affect post-bronchodilator FEV_1 (primary endpoint), nor asthma control test scores, rescue use of bronchodilators, doses of corticosteroids, exhaled nitric oxide (NO), serum IgE, or blood counts of leukocytes or eosinophils (Kim et al., 2011). In another, bigger study, 77 patients with asthma were enrolled in a randomized clinical trial to receive curcumin (500 mg, twice daily, for 30 days) or nothing, in addition to standard treatment. Treatment with curcumin resulted in higher FEV_1 measurements, without any adverse events (Abidi et al., 2014).

Curcumin was also studied for the treatment of allergic rhinitis, in which 241 patients with perennial allergic rhinitis were enrolled in a randomized, double-blind clinical trial that compared the effect of oral curcumin or placebo, for 2 months, on nasal symptoms and nasal airflow resistance, and on production of cytokines. Patients receiving

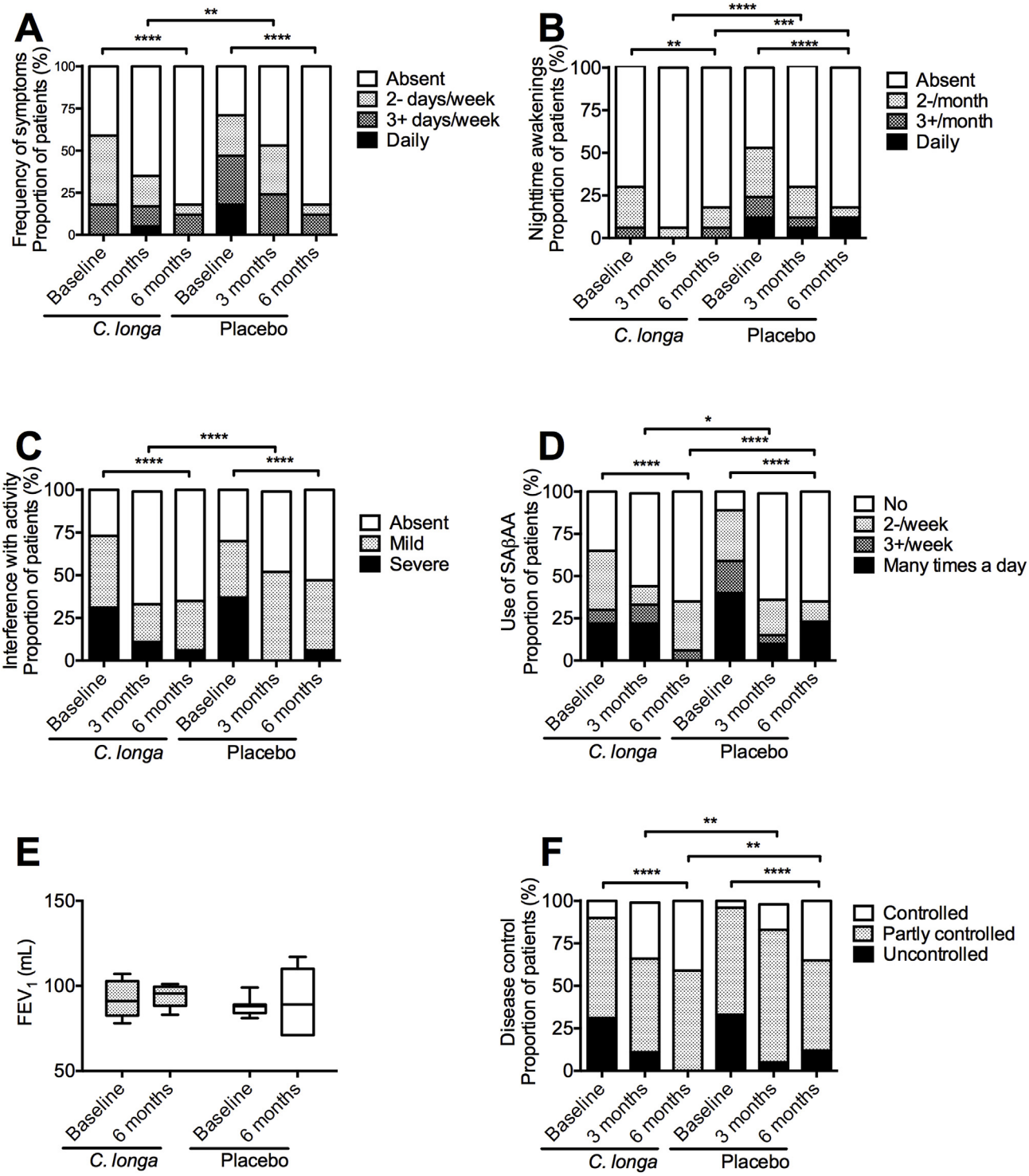

Fig. 3. Proportions of patients in each category of (A) asthma symptoms, (B) nighttime awakenings, (C) interference with normal activity, (D) use of short-acting β-adrenergic agonists (SAβAA), and (F) disease control; and (E) forced expiratory volume in 1 s (FEV_1); all according to treatment and time. Only significant differences are marked. Legend: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$. In (F) boxes are interquartile ranges, with median at center, and whiskers are minimum and maximum.

curcumin experienced less nasal symptoms (sneezing and rhinorrhea) and lower nasal airflow resistance, and lower concentrations of interleukins (IL)-4, IL-8, tumor necrosis factor alpha (TNF-α), and higher concentrations of IL-10 and intercellular adhesion molecule (ICAM) (Wu and Xiao, 2016).

Curcumin is a very promising drug, since it has minimal toxicity, and no adverse effects were reported with doses up to 12 g/day (Bisht and Maitra, 2009; Jagetia and Aggarwal, 2007; Patil et al., 2009; Wongcharoen and Phrommintikul, 2009). Many products sold over-the-counter advertised as curcumin contain, in fact, a mixture of curcuminoids (Patil et al., 2009). There have been some concerns regarding its bioavailability (Jurenka, 2009), but it can be increased up to 20-fold with concomitant administration of piperine (from black pepper, *Piper nigrum* L.). Interestingly, the best bioavailability of curcumin was

obtained when mixed with other compounds found in the roots of *C. longa* (Kiefer, 2007).

The major limitation of our study was the high rate of patients lost to follow up (21/55 patients, 38%). The dropouts were similar between the two treatment groups, and excluded patients were not different from those retained. We did not assess the reasons for dropping out. Another limitation is that we used a low dose of *C. longa* roots. One can speculate that, should a larger dose be used, differences on other aspects could be observed. Finally, our results should be generalized with caution to asthmatic patients in other settings since our population consisted mostly of patients with moderate and severe asthma.

4. Conclusion

In conclusion, the powdered roots of *C. longa*, administered to children and adolescents with moderate and severe asthma, in addition to the standard treatment, compared to placebo, led to less frequent nighttime awakenings, less frequent use of SAβAA, and better disease control after 3 and 6 months.

Authors' contributions

- GM participated in study design, data collection and patient assessment.
- DA participated in data collection and patient assessment.
- JMS participated in study design, data collection and patient assessment.
- JSC participated in chemical analysis of the powdered plant material.
- PRJ participated in study design and writing and revising the final manuscript.
- AMSP participated in study design, preparation of the powdered plant material, chemical analysis of the powdered plant material and writing and revising the final manuscript.
- FC participated in study design, ethics, randomization, data analysis and writing and revising the final manuscript.

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