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Clinical evolution of acute bronchitis in Colombian children between 2 and 14 years treated with *Hedera helix* EA575 syrup

Danitza Madero Oróstegui[1], Guillermo Sánchez-Vanegas[2*], Fernando Vera Castro[3], Andrés Bastidas Manzanares[4], Angélica Monterrosa-Blanco[5], Gloria Esperanza Castro[6a], Alvaro Guillermo Vallejos Narvaez[6b]

[1]Hospital Santa Clara, Cra. 14b #1-45 sur, Bogotá D.C., Colombia.

[2]Hospital Universitario Mayor Mederi (Universidad del Rosario), Cl. 24 #29-45, Bogotá D.C., Colombia.

[3]Universidad del Quindio, Manizales, Colombia.

[4]Clínica Imbanaco, Quiron Salud, Cra. 38 Bis #5B2-04, Cali, Colombia.

[5]SIIES Consultores SAS, Cl. 106 #54-15, Of. 602, Bogotá D.C., Colombia.

[6]Megalabs Colombia SAS, Cl. 106 #18A-45, Bogotá D.C., Colombia.

Correos electrónicos:

[1]danymadero1@gmail.com, [2]guillermosanchezvanegas@gmail.com, [4]doctor.bastidas@gmail.com, [5]ammonterrosa@fucsalud.edu.co, [6a]gcastro@megalabs.com.co, [6b]avallejos@megalabs.com.co

*Corresponding author

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Summary

Aim: To describe the experience of use and clinical evolution of patients with acute bronchitis treated with *Hedera helix* EA575 syrup for seven days. **Methods:** A descriptive observational study based on clinical records, which included patients between 2-14 years old with acute bronchitis prescribed by their doctor *Hedera helix* EA575 syrup. Sociodemographic data and the time of evolution of the cough were taken from the baseline consultation. Treatment-related variables, BSS-Pediatric Scale, visual analogue cough scale, and verbal descriptive cough score were taken from the follow-up. The satisfaction with the treatment and its success were evaluated after 14 days. **Results:** 80 patients between 2 and 12 years old were included. The median number of cough days was eight days. After 7 and 14 days of treatment, 50% and 76% had resolved the cough, respectively. On day 14, coughing

was frequent without interfering with activities in 1 patient. The BSS-pediatric score decreased at each follow-up. Median day-and-night cough VAS was zero for day 14. Awakenings due to coughing decreased from 3 at baseline to 0 per week. 98.75% of the patients were satisfied with the treatment, and none presented adverse events. **Conclusions:** After seven days of treatment, half of the patients had resolved cough and night awakenings; it is suggested that treatment with *Hedera helix* EA575 could be beneficial and of low risk.

Keywords: Bronchitis, cough, hedera, phytotherapy, child.

Resumen

Evolución clínica de la bronquitis aguda en niños colombianos entre 2 y 14 años tratados con jarabe *Hedera helix* EA575

Objetivos: describir la experiencia de uso y la evolución clínica de pacientes con bronquitis aguda tratados con *Hedera helix* EA575 jarabe durante 7 días. **Métodos:** estudio observacional descriptivo basado en registros clínicos, incluyó pacientes entre 2-14 años con bronquitis aguda a quienes su médico les prescribió *Hedera helix* EA575 jarabe. De la consulta basal se tomaron datos sociodemográficos y el tiempo de evolución de la tos. De los seguimientos se tomaron variables relacionadas con el tratamiento, la escala BSS-pediátrica, escala visual análoga de la tos y el puntaje de categoría verbal descriptiva de la tos. A los 14 días de evaluó la satisfacción con el tratamiento y el éxito del mismo. **Resultados:** se incluyeron 80 pacientes entre 2 y 12 años. La mediana de días de tos fue 8 días, después de 7 y 14 días de tratamiento el 50%y 76% había resuelto la tos, respectivamente. Al día 14 la tos era frecuente en 1 paciente, esta no interfería con sus las actividades. El puntaje del BSS-pediátrico disminuyó en cada seguimiento. La mediana de la EVA de tos día y noche fue cero para el día 14. Los despertares por tos pasaron de 3 en el momento basal a 0 a la semana. El 98,75% de los pacientes estuvieron satisfechos con el tratamiento y ninguno presentó eventos adversos. **Conclusiones:** al completar los 7 días de tratamiento, la mitad de los pacientes había resuelto la tos y los despertares nocturnos, se sugiere que el tratamiento con *Hedera helix* EA575 podría ser beneficioso y de bajo riesgo.

Palabras clave: Bronquitis, tos, hedera, fitoterapia, niños.

Resumo

Evolução clínica da bronquite aguda em crianças colombianas entre 2 e 14 anos tratadas com xarope *Hedera helix* EA575

Objetivo: descrever a experiência de uso e a evolução clínica de pacientes com bronquite aguda tratados com *Hedera helix* EA575 xarope por 7 dias. **Métodos:** estudo observacional descritivo baseado em registros clínicos, incluiu pacientes entre 2-14 anos de idade com bronquite aguda que receberam prescrição de *Hedera helix* EA575 xarope por seu médico. Os dados sociodemográficos e a duração da evolução da tosse foram retirados da consulta inicial. Variáveis relacionadas ao tratamento, a escala BSS-pediátrica, a escala visual analógica de tosse e o escore descritivo de categoria verbal da tosse foram retirados dos acompanhamentos. Após 14 dias, foi avaliada a satisfação com o tratamento e seu sucesso. **Resultados:** foram incluídos 80 pacientes entre 2 e 12 anos. O número médio de dias de tosse foi de 8 dias, após 7 e 14 dias de tratamento 50% e 76% haviam resolvido a tosse, respectivamente. No 14º dia, a tosse foi frequente em 1 paciente sem interferir nas atividades. A pontuação pediátrica da BSS diminuiu a cada acompanhamento. A EVA mediana para tosse diurna e noturna foi zero no dia 14. Os despertares devido à tosse aumentaram de 3 no início do estudo para 0 por semana. 98,75% dos pacientes ficaram satisfeitos com o tratamento e nenhum apresentou eventos adversos. **Conclusões:** ao completar os 7 dias de tratamento, metade dos pacientes havia resolvido a tosse e os despertares noturnos, sugerindo que o tratamento com *Hedera helix* EA575 pode ser benéfico e de baixo risco.

Palavras-chave: Bronquite, tosse, hedera, fitoterapia, crianças.

Introduction

Infections of the respiratory system are considered a prevalent public health problem and are one of the most frequent reasons for consultation in the pediatric population [1]. Among the most common is acute bronchitis, caused by inflammation of the lining of the bronchi that tends to be recurrent and self-limiting for up to three weeks, surpassing the five days of expected symptoms in the common cold and making it possible to differentiate the diagnosis of bronchitis. The main symptom is cough, associated with odynophagia, nasal discharge, and sometimes fever [2]. It is estimated that annually, 5% of the general population reports an episode of acute bronchitis, of which 90% go to a health professional [2].

External, environmental, age and family-inherited factors are related to increased cases of acute bronchitis. These occur more frequently in winter than in summer, as climate changes between indoor and outdoor spaces and rainfall increase mucosal vulnerability to pathogens. Likewise, air pollution, exposure to smoke, poor access to public services, inadequate hand washing, and a family history of bronchial asthma and allergies increase the incidence of acute bronchitis [3, 4].

Specifically, in children, this bronchial inflammation generates an important repercussion on the quality of life. When coughing is frequent and intense, it may affect daily activities, interfere with sleep, modify the family dynamics, generate school absenteeism in children and work in parents, produce mood changes, and increase the direct and indirect costs related to bronchial pathology [1]. Therefore, a symptomatic therapeutic intervention must prioritize its effect on controlling the cough's intensity, frequency, and duration.

In 90% of cases, acute bronchitis occurs due to viral etiology, most commonly involving respiratory syncytial virus, adenovirus, influenza A and B, parainfluenza, coronavirus, and rhinovirus [3, 5]. Even so, 8 out of 10 patients are treated with antibiotic therapy, constituting an inappropriate and ineffective therapy, which increases antimicrobial resistance and the appearance of adverse events, making management symptomatic [2, 6, 7]. Phytopharmaceuticals and alternative medicine have been used for over 50 years and have demonstrated clinical effectiveness and acceptability by patients, mainly due to their natural components [8]. In addition, in Europe, using the dry extract of ivy leaves EA575 for treating acute bronchitis is common, and more than 65,000 patients in 20 studies have demonstrated its effectiveness [9-13].

Hedera helix EA575 syrup, obtained from ivy EA575 leaves, is available. This syrup is a mucolytic, expectorant, and bronchodilator and works as an anti-inflammatory at the level of the lungs and airways [8, 11, 14-18]. The above is why it has been indicated for the symptomatic management of adult and pediatric patients with acute bronchitis and has INVIMA registration. Latin American literature demonstrates its effectiveness and safety; however, no local research was found [13]. This study was conducted to document the syrup's user experience in a real-life scenario in Colombia and to describe the clinical evolution of a cohort of patients aged 2 to 14 years with a diagnosis of acute bronchitis treated with *Hedera Helix* EA575 syrup for seven days.

Methodology

Design: A retrospective descriptive observational study based on the clinical records of a cohort of patients diagnosed with acute bronchitis who were prescribed *Hedera helix* EA575 syrup as part of their treatment.

Population and sampling: Using sequential convenience sampling, we included all available clinical records (N=80) of patients between 2 and 14 years with a clinical diagnosis of acute bronchitis with dry or productive cough, with or without bronchospasm, who had symptoms for at least three days, who were or were not using concomitant pharmacological management with antibiotics, antihistamines or inhaled B2 agonists, and who had been prescribed *Hedera helix* EA575 syrup by their treating physician. We excluded records of patients who (or whose legal representative) did not authorize the use of their data. In addition, we excluded patients with a confirmed diagnosis of COVID-19, those under corticosteroid, antitussive, or mucolytic management, and those with other diseases such as allergic asthma or bronchial hyperreactivity, chronic bronchitis, chronic or inherited lung diseases, or severe heart, liver, or kidney disorders.

Procedure: From the private consultation of three pediatricians in Bogotá, Cali, and Cúcuta, we identified patients who had a prescription for *Hedera helix* EA575 syrup as part of the treatment for acute bronchitis and who met the selection criteria. From the selected patients' clinical history records, we obtained the evolution of the clinical parameters of interest, previously filled out by the treating physician during an initial consultation and in the follow-ups at seven days (or – 2 days) and at 14 days (or – 2 days) of having started the use of *Hedera helix* EA575 syrup. This information was later documented in an information collection application designed for research.

Variables of interest: The variables identified in the patient's clinical history at baseline were sociodemographic variables such as age and sex and the time of evolution of the cough in days. The need for concomitant antibiotic treatment, the presence of adverse events, the discontinuation of treatment, and the following scales related to the patient's condition, were identified at baseline and follow-ups 7 and 14 days after the start of treatment. The presence of cough, pulmonary rales, and dyspnea was evaluated with the BSS-pediatric scale, which rates each item from 0 to 4 (0-absent, 1-mild, 2-moderate, 3-severe, 4-very severe). Then, these scores are added together, resulting in a total score between 0 and 12. The cough evaluation was conducted by quantifying the number of times the child woke up the night before due to cough, and with the Visual Analogue Scale (VAS) of cough during the day and night, measured in millimeters, which ranges between 0 and 100, where 0 indicates no cough and 100 mm the

worst possible cough in the last 24 hours. The cough impact was determined with the Verbal Cough Descriptive Category Score (VCD), where 0 = no cough, 1 = cough for one or two short periods, 2 = cough for more than two short periods, 3 = cough that is frequent but doesn't interfere with the patient's activities, 4 = frequent cough that interferes with the patient's activities, and 5 = the patient is unable to perform most activities.

Additionally, satisfaction with the treatment was measured during the last follow-up appointment. This satisfaction was determined with the *Integrative Medicine Patient Satisfaction Scale* (IMPSS), in which 1 = very satisfied, 2 = satisfied, 3 = neutral, 4 = dissatisfied, and 5 = very dissatisfied. The degree of success or failure of the treatment was also established with the scale *Integrative Medicine Outcomes Scale* (IMOS) from the perspective of the doctor and the patient, where 1 = complete recovery, 2 = important improvement, 3 =slight to moderate improvement, 4 = no change, and 5 = deterioration.

Analysis: The variables were analyzed according to their nature; the quantitative variables were described using measures of central tendency and dispersion according to the symmetry of the data distribution. For qualitative variables, frequency tables with absolute and relative values were used. For the three components of the BSS-pediatric scale (cough, rales, dyspnea) and the VCD scale, the absolute number and percentage of subjects in each category were established for each of the three measurement times. Likewise, the IMPSS and IMOS scales were thoroughly analyzed according to the information from the last follow-up appointment (Day 14). For the overall scale score BSS-pediatric and the VAS score, central tendency statistics and dispersion were calculated at baseline, seven days, and 14 days, as presented in summary tables.

Ethics: For the development of this research, national and international guidelines were followed, including the Helsinki Declaration and the Belmont Report. Per the regulations issued by the Colombian Ministry of Health (Resolution 08430), this study was classified as risk-free research. Its execution had the approval of an independent ethics committee (CEISH - Comité de Ética en Investigación con Seres Humanos. Sociedad de Cirugía de Bogotá, Hospital de San José).

Results

The study included eighty patients, between 2 and 12 years old, 37.5% were girls (n=30) and 62.5% boys (n=50). The median number of cough days was 8, with 50% of patients between 6 and 12 days. No adverse events were reported during therapy in any of the participants. In one patient, suspension of treatment was reported on day seven

due to complete improvement. At admission, 23.8% had concomitant management with antibiotics (n=19). On day 7 of follow-up, this management was described in 11 patients (13.75%) and at 14 days in only two patients (2.5%). Tables 1 and 2 show the details of all the qualitative and quantitative measurements.

Table 1. BSS (cough, dyspnea, and rales) and VCD

SYMPTOM AND SEVERITY	BASAL	7 DAYS	14 DAYS
	N (%)		
BSS: Cough			
Absent	0	40 (50)	61 (76.25)
Light	25 (31.3)	35 (43.8)	18 (22.5)
Moderate	32 (40.0)	5 (6.3)	1 (1.3)
Severe	23 (28.8)	0	0
BSS: Dyspnea:			
Absent	60 (75)	78 (97.5)	80 (100)
Light	19 (23.8)	2 (2.5)	0
Moderate	1 (1.3)	0	0
Severe	0	0	0
BSS: Rales:			
Absent	46 (57.5)	76 (95)	79 (98.75)
Light	30 (37.5)	4 (5.0)	1 (1.25)
Moderate	4 (5.0)	0	0
Severe	0	0	0
VCD			
No cough	0	40 (50.0)	61 (76.3)
1 or 2 short coughing periods	33 (41.3)	11 (13.8)	7 (8.8)
More than two short periods of coughing	4 (5.0)	24 (30.0)	11 (13.8)
Frequent cough but does not interfere	29 (36.3)	5 (6.3)	1 (1.3)
Frequent cough interferes	14 (17.5)	0	0
Unable to perform activities	0	0	0

Table 2. Global BSS score, cough VAS (day and night), and episodes of nocturnal awakening.

SCALE OR SYMPTOM	BASAL	7 DAYS	14 DAYS
	MEDIAN (IQR)		
Pediatric BSS (0 to 12)	3 (2- 3)	1 (0- 1)	0 (0- 0.5)
Pediatric BSS (concomitant AB)	3 (2- 3)	1 (0- 1)	0 (0-0)
Pediatric BSS (Without concomitant AB)	3 (2- 3)	1 (0- 1)	0 (0- 1)
VAS day cough (0 to 100)	70 (60- 80)	20 (10- 27.5)	0 (0- 2)
VAS night cough (0 to 100)	70 (50- 80)	10 (5.5- 20)	0 (0-0)
Awakening from cough	3 (2- 4)	0 (0- 1)	0 (0-0)

Evolution of the Pediatric BSS with its three components

Cough: At the time of the baseline measurement, 100% of the patients had a cough; 25 classified it as mild, 32 moderate and, 23 severe. After seven days of treatment, 35 patients reported mild cough, 5 reported moderate cough, and the cough in 40 (50%) patients had disappeared. After 14 days of follow-up, in 61 patients (76.2%), the cough was controlled entirely; in 18 cases, it was mild, and only in one case it was reported as moderate (Figure 1)

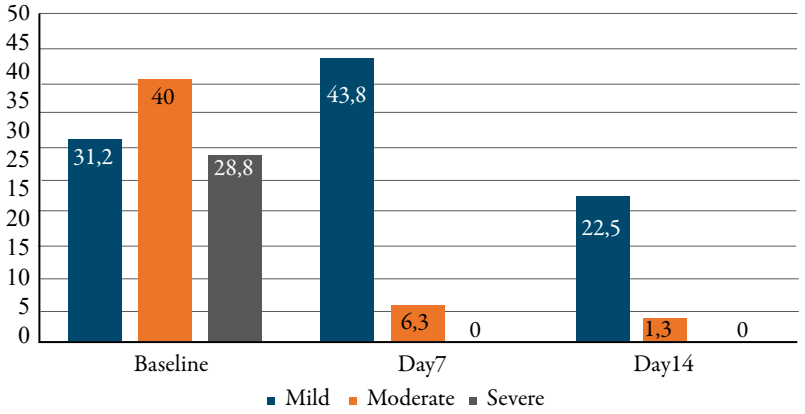

Figure 1. Evolution of the pediatric BSS. Cough component

Dyspnea: At the start of treatment, 20 patients reported symptoms of dyspnea (25%), classified as mild by 19 of them (23.7%) and, in one case, as moderate (1.25%).

On day 7, this symptom was present in two patients (2.5%); on day 14, no patient reported dyspnea.

Rales: According to the medical examination, at baseline, 30 patients had mild rales (37.5%), and four had moderate rales (5%); on the seventh day, four patients had rales (5%), and on day 14 they were present in 1 patient (1.2%).

Overall score: At admission, the median of the Pediatric BSS was 3 points (IQR: 2-3), moving to a point on day seven (IQR: 0-1) and zero points on day 14 (0-0.5). The baseline and follow-up pediatric BSS medians were the same in the group that received concomitant antibiotics and those that did not (see Table 2).

Evolution of cough

As reported in the VAS of cough during the day and at night in the initial measurement, the median was 70 points with IQR: 60-80 and IQR: 50-80, respectively; going to 20 points for the day VAS, and 10 points for the night VAS on day 7, and reaching a median of zero at 14 days, both the day and night EVA.

Regarding the number of times the children woke up due to cough, the initial median was three occasions, reaching zero at seven days and zero at 14 days.

Using the VCD scale as a reference, at baseline, 43 patients (53.8%) reported episodes of frequent coughing, including 14 patients in whom the cough interfered with daily activities (17.5%). After seven days of treatment, in five patients, the cough was frequent (6.3%), and in no case did it interfere with activities. On day 14 of follow-up, the cough was frequent in one patient (1.3%) and did not interfere with activities.

Overall satisfaction level with treatment - IMPSS

After 14 days, 67.5% of the patients considered themselves very satisfied (n=54), and 31.25% reported being satisfied (n=25). In summary, 98.75% (n=79) reported satisfaction with the treatment. Only one patient reported neutral satisfaction. In no case was dissatisfaction reported.

Treatment success – IMOS

After 14 days, patient-reported treatment success was complete recovery in 55 patients (68.7%), major improvement in 23 patients (28.75%), and mild to moderate improvement in two patients (2.5%). From the physician's perspective, the treatment success report was complete recovery in 55 patients (68.7%) and significant improvement in 25 patients (31.25%). No change or deterioration in health status was reported in any case.

Discussion

Eighty children with acute bronchitis received symptomatic management with the extract of *Hedera helix* EA575, an over-the-counter phytopharmaceutical in Colombia, for seven days and were monitored for seven more days. The presence of cough was 100% in the initial measurement; after seven days, it disappeared in 50% of the participant, and at 14 days, 76.2% of the patients were free of cough. According to the VDC, in 14 days, the cough went from being frequent in 43 patients to only one. There was also a decrease in this impact: from day 7 of treatment, no patient reported interference in daily activities due to cough. The median of the pediatric-BSS was three, one, and zero at each of the three measurement times. After seven days of follow-up, a reduction in the median cough VAS of 50 and 60 points during both day and night was documented. By day 14, the median for both scales was zero. The median awakenings from cough increased from 3 at baseline to 0 at 7 and 14 days. Due to clinical improvement, 98.75% of patients reported being satisfied with the treatment. The patients and the doctors agreed that 68.7% of the patients achieved complete recovery with management with *Hedera helix* EA575 syrup. None of the patients presented adverse events during the use of the treatment.

Phytotherapy refers to using plant substances, parts of plants, or products thereof after being subjected to different treatments to obtain their properties for therapeutic purposes. Currently, there are two types of phytopharmaceuticals, ancestral and medicines; the latter have standardized extraction and purification processes, ensuring that this characterization is maintained and are those that have demonstrated effectiveness [19]. The extract from *Hedera Helix* EA575 is a product with complex structures that are difficult to copy because it is a phytomedicine. The available evidence on efficacy and safety comes from using *Hedera Helix* EA575 specifically; to the best of our knowledge, no other product with *Hedera helix* has shown phytosimilarity [9,11,12,16]. Therefore, the abundant and overwhelming evidence favoring *Hedera Helix* EA575 cannot be extrapolated to other substances with different components.

A multicenter clinical trial in 11 Latin American countries determined the efficacy [13], tolerance, and safety of the syrup with extract of *H.helix* EA575 in patients with bronchitis administered for seven days. It included 9,657 patients, 5,181 of whom were children. The mean duration of symptoms was four days, improvement or disappearance of cough and expectoration occurred in 93%, tolerance to the syrup was described as good or very good by 96.6%, and 2.1% of the participants presented an adverse event predominantly of gastrointestinal origin. In contrast, in the present study, the median number of cough days was eight, and no adverse events occurred. Additionally, it is

important to highlight that in the Latin American study by Fazio *et al.*, has was shown that the concomitant use of antibiotics or other medications did not show a benefit in terms of efficacy but instead increased the risk of adverse events. In our study, the outcomes of interest were also the same for those who used concomitant treatments compared to those who did not.

Schaefer *et al.*, in two randomized clinical trials conducted in 2016 [9] and 2019 [10] in German adult patients, reiterates the effectiveness of EA575 ivy leaf extract compared to placebo. As in the present study, through the application of the Bronchitis Severity Score (BSS), the VAS of cough, and the VCD scale, a significant reduction in their scores was identified in the intervention group compared to the control group. Based on the BSS and VCD scores, the statistical superiority of the *H. helix* EA575 against placebo was obtained on the second and the third day of treatment, respectively. Additionally, this effect was maintained until the end of the observation period, established at 14 days, suggesting a symptomatic effect even one week after the end of treatment.

In the pediatric population, rales, and dyspnea tend to be infrequent, which could explain the low scores in these two components of the BSS-pediatric and the global score obtained in the present study. Greater relevance should be given to the clinical evaluation of cough, considered the most important symptom of acute bronchitis and, consequently, the outcome in which the most significant impact is expected. According to the cough component score of the pediatric BSS, the cough VAS and the VCD found in this study, *H. helix* EA575 syrup stands out for its symptomatic relief capacity, improving the intensity, frequency, and duration of cough, as well as the commitment of daily activities.

It is also important to note that the results of this study agree with the results found by Lang *et al.* [11]. Their study observed a cohort of 1,066 schoolchildren aged 6 to 12 years with a diagnosis of acute bronchitis who received management with ivy leaf extract EA575 for seven days and evaluated its effectiveness according to the BSS clinical score. This study recorded an improvement in 79.3% of patients regardless of using additional concomitant therapy or variable administration of the product. Regarding the assessment made by the patients and their parents, the study showed an improvement in the symptoms caused by bronchitis by up to 58.1%. The incidence of daily coughing fits decreased considerably, from 15-20 per day to around 5 per day. Nighttime awakenings were also less frequent at the end of treatment, reducing from 7 times per night to approximately two per night.

The clinical effectiveness of ivy Leaf extract can be explained by its well-studied effects at the pulmonary and bronchial levels. Oleanolic saponins, represented by heder-

agenin, α-hederin, and hederacoside C, are the main components of the extract of *H. helix,* which according to research, could have an indirect mimetic β2 effect. This effect allows for bronchodilator activity, increased production of pulmonary surfactant, maintenance of alveolar function, antitussive effect, and ease of expectoration of bronchial secretions, leading to a resolution of the clinical picture and prolonging its effects even up to a week after the end of the treatment, as has been found in different studies and this study [8, 14, 20].

The results showed a significant reduction in the presence, frequency, impact, and repercussions of the main symptom of acute bronchitis in the pediatric age, which translates into clinical improvement, quality of life, normal development of daily activities, tolerability, satisfaction with treatment, and adherence to it. Additionally, due to the absence of adverse events, evidence is added to that currently available that supports the use of *H. helix* EA575 safely in this age group [8, 11, 13, 18, 21].

The results obtained should be interpreted considering the limitations of this study, which has descriptive observational designs, where it is impossible to establish causality, association, or extrapolation of the results. On the contrary, using several validated and widely validated measurement tools to determine clinical evolution is a strength. It is also worth highlighting the generation of local evidence on the use of Hedera helix EA575 syrup in children from a study conducted under conditions of routine clinical practice of Colombian pediatricians. Having a follow-up for 14 days allowed us to describe the clinical course of the disease and establish the absence of adverse events during this period, emphasizing the product's safety, which is an aspect of great importance, especially when treating the pediatric population.

Conclusion

After seven days of treatment with *Hedera helix* EA575 syrup, 50% of the patients presented complete improvement of the cough, and in the remaining 50%, the condition progressed with clear improvement. After 14 days, the percentage of improvement exceeded 76%, and the remaining patients had mild symptoms without the cough affecting their daily activities. With this treatment, there was a marked improvement in nocturnal awakening episodes, reaching a median of zero from day seven. Other symptoms, such as dyspnea or rales, were significantly controlled by day seven and completely controlled by day 14. Due to the results and the satisfaction found in physicians and patients, it is suggested that this treatment could be beneficial and of low risk for the management of acute bronchitis. Further experimental studies are required for a complete characterization of *Hedera helix's* efficacy and safety profile.

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Conflicts of interest

G.E.C and A.G.V have employment ties with Megalabs Colombia SAS.

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