Efficacy and tolerability of SEDIFLÙ® in treating dry or productive cough in the paediatric population (SEPEDIA). A pilot, randomized, double blind, placebo-controlled, multicentre clinical trial.

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Research Article

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Abstract

Background: Nonpharmacological interventions, such as throat and pharynx demulcents and emollients, are an alternative for cough management and mucosa protection, especially in children, who experience upper respiratory infection-associated acute cough almost four times more than adults. The aim of this trial was to assess the effectiveness of Sediflù®️, a medical device containing active herbal ingredients, on nocturnal and diurnal persistent coughs in children, with a duration of 3 to 7 days.

Methods: Children with a dry and/or productive cough were enrolled in this prospective, interventional, multicentre, placebo-controlled, double-blind, randomized clinical study. Clinical efficacy was assessed through the evaluation of the soothing action of Sediflù®️ against dry and/or productive coughing, both at night and during the day and other effects of coughing associated with quality of sleep: frequency, child's quality of sleep, parental quality of sleep, severity and bothersomeness.

Results: Treatment with Sediflù®️ improved both night- and day-time cough scores from D2. The improvement of the night-time cough score is statistically significantly higher in the Sediflù®️ group (28% and 71% lower) at D4 and D7, respectively, in comparison to the placebo group (p<0.05). The diurnal score improved significantly in the Sediflù®️ group (22% and 71% lower) at D3 and D7, respectively, in comparison to the placebo group (p<0.05 and p<0.01, respectively).

There was also a significant decrease in the scores of five nocturnal variables associated with sleep quality (frequency, severity, bothersomeness, child's and parental quality of sleep) from D2, and it was maintained throughout the rest of the days (D3-D7). Considering the inter-group analysis, Sediflù®️ showed a more significant improvement for frequency, severity, bothersomeness, child's and parental quality of sleep (70%, 51%, 52%, 58% and 66% lower, respectively) at D7, in comparison to the placebo group (p<0.01).

The analysis of a subgroup of children, with cough scores ≥ 3, showed a significant reduction of both frequency and severity scores from the first day of treatment with Sediflù®️ (p<0.05).

Conclusions: Sediflù®️ syrup can be considered a valid treatment for cough management, especially in younger children with upper respiratory tract infections, shortening the cough duration in children, with a very good safety profile.


Background

Coughing and irritation of the mucosa are mainly associated with upper respiratory tract infections, such as the common cold. In young children, respiratory tract infections are extremely common and frequently recurrent [1]. Pathogens often colonize the upper respiratory tract (nose or mouth) prior to causing lower
respiratory infections or invasive diseases. The oral mucosa and epithelium play a protective role against the entry of microorganisms into the body [2]. This mucosa is the main target tissue of microorganisms such as viruses. Normally, primary infection results in viral replication at mucosal surfaces.

Upper respiratory tract infection is very frequent. Adult subjects experience 2 to 5 episodes per year, whereas school children suffer 7 to 10 episodes per year, coughing up 140 days per year. Children are almost four times more likely to experience upper respiratory infection-associated acute coughs than adults [3]. In this context, coughing is the most common symptom of many inflammatory diseases.

Coughing is a physiological response to airway irritation. It has two main functions: (1) to prevent the entry of food and fluids into the lower airways and (2) to favour the removal of material which exceeds the transport capacity of the mucociliary system. Coughing can be initiated by pharyngeal stimulation or mucosal dehydration. A cough may be classified according to its duration and characteristics. It is considered to be occasional when it lasts less than three days. Persistent coughs that last more than seven days are usually treated with medicinal products. However, persistent coughs lasting more than three days but less than seven can be particularly bothersome and their appropriate management might help to improve symptoms, without compromising the patient's natural cough recovery mechanisms. Coughs may be wet, such as a productive cough associated with secretion, or dry, such as an irritative cough [3].

An acute cough consequent to an upper respiratory tract infection may persist in children for many days. A cough, mainly when prolonged, can impact quality of life, cause anxiety and distress, and affect the sleep of children and their parents or cohabitants [3–4]. Coughing, especially during the night, can be particularly troubling to children and to their parents, as it often results in discomfort to the child and loss of sleep for both the child and their parents. In addition, there have been very few assessments of the associated sensations: irritation, the urge to cough and even pain, yet these may be more important symptoms for patients with laryngitis or a post-viral cough than the actual coughing [5]. In addition, a sore throat represents inflammation or irritation. Throat irritation also dehydrates the pharyngeal mucosa and is commonly accompanied by a dry cough, aggravating the irritative state.

No treatment option has been associated with clear benefits in terms of cough recovery [6]. Given that some therapeutic options exhibit low effectiveness and also produce undesirable adverse effects, they are not optimal treatments [7]. Nonpharmacological interventions, such as throat and pharynx demulcents and emollients, are an alternative for cough management and mucosa protection and do not have side effects.

A suitable strategy to treat coughing and irritation is to form a protective barrier by a formulation able to adhere to and reside on the mucosal surface, in the oral cavity as far as the pharynx. This protective barrier can be achieved with a demulcent and/or emollient effect. A demulcent is a substance that forms a soothing film over a mucous membrane to relieve minor pain and inflammation. Emollients are the ingredients responsible for the smooth feel of the skin or mucosa.
The demulcent capacity is a physical action that confers a protective effect on the mucous membranes. This action can lead to decreased coughing, and its efficacy has been demonstrated in clinical studies elsewhere [8]. Furthermore, the formation of this layer on the epithelial surface or the oral cavity allows rehydration, increasing saliva production, desensitization and a decrease in local inflammation and the cough reflex [8]. Demulcent, emollient and lubricant effects are reinforced by a mucoadhesive effect.

The ideal physical and chemical characteristics for a cough syrup can be obtained by a complex mixture of natural substances exerting lubricant, demulcent and protective barrier effects [3]. The optimal combination of ingredients to produce a humectant action is natural sweetness, such as honey, which stimulates salivation, and herbal extracts associated with complementary actions. Up to 85% of the benefit of cough syrups may be due to the physical and chemical effects of the syrup, which contribute to its demulcent action.

The syrup tested in this study is a Class IIa medical device containing different active herbal ingredients: eucalyptus honey and dry extracts of horehound flowers (*Marrubium vulgare* L.), sundew flowers (*Drosera rotundifolia* L.), ivy leaves (*Hedera helix* L.) and plantain leaves (*Plantago lanceolata* L.).

The ingredients of this syrup involve a combination of actions with a potential benefit for cold symptoms. Sedìfu® uses two main mechanisms to produce the desired effects: a) mucolytic and expectorant actions (moisturizing and fluidifying action of mucus that favours its physiological elimination), and b) demulcent effect (soothing and protective effects against external irritants by forming a protective barrier and increasing saliva production to reduce the cough reflex) [8]. Due to this double action, it is recommended both for productive coughs (due to its mucolytic and expectorant effect, as well as its demulcent action) and for dry coughs (due to its demulcent effect).

The aim of this randomized trial was to assess the effectiveness of this medical device, as compared to a placebo, on nocturnal and diurnal persistent coughs in children, with a duration of three to seven days.

**Methodology**

**Study treatment**

The product administered to the treatment group is a vegetable extracts-based medical device manufactured by Sakura Italia Srl and marketed in different EU territories with their corresponding brand names (Seditus® tos, Sedìfu® tosse, Actirub® toux and Complexe expert® Sirop toux sèche et grasse). It is a syrup containing eucalyptus honey, dry extract of horehound flowers (*Marrubium vulgare* L.), dry extract of sundew flowers (*Drosera rotundifolia* L.), dry extract of ivy leaves (*Hedera helix* L., 10% hederacoside C) and dry extract of plantain leaves (*Plantago lanceolata* L., 5% total phenols and 1% verbascoside). The placebo product was an inactive syrup, without the active components listed above, with the same appearance, density, brix and flavour as Seditus®.
Either the treatment or the placebo was administered in two doses per day (morning and evening), 10 ml each, for seven days, as recommended in the instructions for use of the marketed product.

**Design**

The study was conducted as a prospective, interventional, multicentre, placebo-controlled, double-blind, randomized clinical study to evaluate the clinical response and tolerance of the medical device in patients aged five to eleven, with a dry and/or productive cough.

**Study Population**

Children were recruited, between November 2020 and March 2021, in two primary care centres in Madrid (Consultorio local de Brunete, Brunete, Madrid, Spain and Pediatría Dr. Carlos Núñez de Prado Aparicio, Majadahonda, Madrid). The criteria for inclusion were the signature of informed consent by their parents, having an age ranging from five to eleven and suffering at the time of study initiation from a dry and/or productive cough, with a duration of three to seven days.

Patients were excluded if they were under therapies that could interfere with the evaluation of the product under test, especially other antitussives or cough relief products, or if the children suffered from serious lung, kidney and/or liver diseases, neoplasms of any kind, allergy, hypersensitivity or any other type of incompatibility with some of the components of the product under study. Other exclusion criteria were participation in another clinical study in the last month, any surgery scheduled during their participation in the study or any other cause that, in the opinion of the investigator, could compromise compliance with the protocol.

A simple balanced randomization (1:1) was carried out, in which the random distribution of each group (either treatment or placebo) was ensured. The purpose of randomization was to ensure that each patient had an equal chance of being assigned to either of the two treatment groups.

**Ethical Considerations**

The study was conducted in compliance with the ICH-GCP Guideline and appropriate procedures were always followed to ensure compliance with Regulation (EU) 2016/679. It was approved by the local Ethics Committee of Madrid (CEIm). The participants’ parents gave their written informed consent before the study was carried out.

**Primary And Secondary Endpoints**

The primary endpoint of the study was to assess the clinical efficacy of Seditus® through the evaluation of its soothing action against dry and/or productive coughing, both at night and during the day.
The following clinical findings were documented during visits in accordance with both the Cough Clinical Score (CCS) (modified from Chung, 2002) [9] and Paul's Night Cough Questionnaire [10].

CCS provides the primary endpoint, and it is composed of two variables: night-time cough score and day-time cough score. This severity perception method includes not only severity criteria, but also intensity and impact of cough as a whole (Table 1).

Table 1
Day- and night-time cough clinical scores (CCS) (Chung modification, 2002)

<table>
<thead>
<tr>
<th>Cough score</th>
<th>Symptom for day-time</th>
<th>Symptom for night-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>For a short period (approximately a few minutes)</td>
<td>Only at awakening/only before falling asleep</td>
</tr>
<tr>
<td>2</td>
<td>For 2 short periods (approximately 10 minutes)</td>
<td>Awaken once/early awaken due to cough</td>
</tr>
<tr>
<td>3</td>
<td>Frequent cough that does not interfere with normal activities</td>
<td>Frequently awaken due to cough</td>
</tr>
<tr>
<td>4</td>
<td>Frequent cough that interferes with normal activities</td>
<td>Frequent cough for the most part of the night</td>
</tr>
<tr>
<td>5</td>
<td>Disturbing cough for the most part of the day</td>
<td>Disturbing cough</td>
</tr>
</tbody>
</table>

The secondary endpoints were the evaluation of the tolerability of Seditus® in accordance with Paul's Night Cough Questionnaire, a survey that specifically assesses the effects of coughing on several variables associated with quality of sleep: frequency, child's quality of sleep, parental quality of sleep, severity and bothersomeness (Table 2).

Table 2
Evaluation of tolerability according to Paul’s Night Cough Questionnaire (Paul et al., 2007).

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How frequent was your child’s coughing last night?</td>
<td>0: Not at all</td>
</tr>
<tr>
<td>2. How severe was your child’s cough last night?</td>
<td>1: Not much</td>
</tr>
<tr>
<td>3. How bothersome was last night’s cough to your child?</td>
<td>2: A little</td>
</tr>
<tr>
<td>4. How much did last night’s cough affect your child’s ability to sleep?</td>
<td>3: Somewhat</td>
</tr>
<tr>
<td>5. How much did last night’s cough affect your (parental) ability to sleep?</td>
<td>4: A lot</td>
</tr>
<tr>
<td></td>
<td>5: Very much</td>
</tr>
<tr>
<td></td>
<td>6: Extremely</td>
</tr>
</tbody>
</table>
The clinical safety was evaluated through the registration of adverse effects in patients and the identification of those that are device-related adverse effects.

The duration of the study was 14 days per patient, with a screening visit (or visit one), where either Seditus® or a placebo was provided to the patients, 1 week of treatment (visit two at day 7) and 1 follow-up week (through a phone call to monitor the product’s safety) (Fig. 1). The assessment was continuous (from day 0 to day 7) through the subject’s diary. At the end of the treatment period (visit 2), the bottles of the administered products (both treatment and placebo) were returned to the principal investigators so that they could assess compliance with the posology described in the protocol.

Statistical analysis

A descriptive statistical analysis of the results of quantitative biometric variables at different experimental times was carried out, including basic descriptive parameters (central tendency and variation) that reliably expose the distribution of the main variable at each time. Night- and day-time cough scores are considered qualitative variables, ranging from 0 (absent) to 5 (the most disturbing cough). A subgroup analysis was performed for each variable, according to data ≥ 3 and < 3, in order to assess the effects in children with more intense symptoms.

Cumulative logit mixed-effects models (CLMMs) were used, adjusting them to the data distributions in each response variable (Day-time cough score, Night-time cough score, Frequency score, Child’s sleep score, Parental sleep score, Severity score and Bothersomeness score), with the aim of evaluating the clinical response of the product at each experimental time (D0, D1, D2, D3, D4, D5, D6 and D7). The effect of the product on the values of the main variables in the statistical analyses is interpreted with reference to the initial time (D0), which corresponds to the screening and first administration of the treatment, and between treatment groups at each experimental time. All the models used in the study for data analysis are present in the “clmm” function of the “ordinal” package of the R software.

The performance of multiple biometric measurements over time (volunteers evaluated during different time points), and therefore correlated, was taken into account by including random effects at the level of each individual, allowing the interception of the models to vary randomly between individuals in the trial. The value of significance established for all the statistical tests of the study is p < 0.05.

Results

Baseline characteristics

60 children with a dry and/or productive cough were recruited in the study. Of them, 56 were enrolled, randomized to either the treatment (n = 27) or placebo (n = 29) group and completed the study. The mean age of the children was 8.65 ± a standard deviation (SD) of 2.14, with similar baseline characteristics for the two treatment groups (Table 3). Boys and girls accounted for 53% and 47%, respectively, of the total sample of enrolled children.
Table 3
Baseline characteristics of children enrolled for the study.

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sediù® (n = 27)</td>
<td>Age (years)</td>
<td>8.82</td>
<td>2.44</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>33.64</td>
<td>12.94</td>
<td>17</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>135.17</td>
<td>16.77</td>
<td>107</td>
<td>172</td>
</tr>
<tr>
<td>Placebo (n = 29)</td>
<td>Age (years)</td>
<td>8.47</td>
<td>1.82</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>31.66</td>
<td>12.93</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>131.02</td>
<td>14.43</td>
<td>111</td>
<td>163</td>
</tr>
<tr>
<td>Total (n = 56)</td>
<td>Age (years)</td>
<td>8.65</td>
<td>2.14</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>32.65</td>
<td>12.87</td>
<td>17</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Height (cm)</td>
<td>133.09</td>
<td>15.65</td>
<td>107</td>
<td>172</td>
</tr>
</tbody>
</table>

Efficacy Of The Product: Cough Score

According to the primary endpoint of the study, the changes in night-time and day-time cough scores were evaluated between D0 (visit 1, basal time) and the other experimental times (D1 to D7). There is a decrease in night- and day-time cough scores in the Sediù® group between the experimental times and the baseline from the second day (D2) to the last day (D7) (Fig. 2). The difference between D2 and D0 is statistically significant, and it is maintained throughout the rest of days (D3-D7) (p < 0.01).

Significant differences were also detected favouring the Sediù® group, in the inter-group analysis, for both scores. The improvement of the night-time cough score is statistically significantly higher in the Sediù® group (28% lower) at D4, in comparison to the placebo group (p < 0.05). Similarly, at D5, D6 and D7, patients in the Sediù® group also reduced the score by 36%, 44% and 71%, respectively, as compared to the placebo group (p < 0.05) (Fig. 3). In line with these findings, the diurnal score improved significantly in the Sediù® group (22% lower) at D3, in comparison to the placebo group (p < 0.05) as well as at D4, D5, D6 and D7, with a reduction of 36%, 43%, 58% and 71%, respectively, in comparison to the placebo group (p < 0.01).

As per the day- and night-time cough score, the variables studied with Paul’s questionnaire rapidly improved after treatment with Sediù®. In fact, there was a significant decrease in the scores of the five nocturnal variables associated with the quality of sleep (frequency, severity, bothersomeness, and child’s quality of sleep and parental quality of sleep) from D2 (Fig. 4). The difference between D2 and D0 is statistically significant, and it is maintained throughout the rest of the days (D3-D7).
Considering the intra-group analysis, at D7 the Sediflù® group causes a reduction in the frequency score of 89% in comparison to D0 ($p < 0.001$). For the severity score, the Sediflù® group showed a decrease of 87% ($p < 0.001$) from D0. The bothersomeness score also suffered a significant decrease at D2 in the Sediflù® group, going down to 87% at D7, as compared to the baseline values at D0.

In relation to the intra-group analysis of the child’s quality of sleep score, a significant improvement was observed from D2 in the Sediflù® group, with a score reduction of 30% ($p < 0.001$), reaching an improvement of 89% (as compared to the baseline values) at D7. Similarly, the parental sleep score showed a significant reduction ($p < 0.01$) of 30% in the Sediflù® group at D2. This score reduction reached 92% at D7, having the original values as the reference.

To further evaluate the effect of Sediflù® in children with a more severe cough (i.e., children with cough scores $\geq 3$), a subgroup analysis was conducted, dividing all the participants into two subgroups ($\geq 3$ and $< 3$). The intra-group analysis showed a significant reduction of both frequency and severity scores from first day (D1) of treatment in children that received Sediflù® ($p < 0.05$).

Considering the inter-group analysis for frequency, severity, bothersomeness, child’s sleep and parental sleep, Sediflù® showed a significant improvement, for all variables (70%, 51%, 52%, 58%, 66% lower, respectively) at D7, in comparison to the placebo group ($p < 0.01$). These percentages are particularly relevant taking into consideration that the baseline scores of all the variables in the Sediflù® group were higher than those present in the placebo group, thus reinforcing the effect of the treatment with Sediflù® syrup, in comparison to placebo (Fig. 5).

**Safety**

No adverse effects were observed either in the treatment or placebo group.

**Discussion**

This study corresponds to a prospective, interventional, multicentre, randomized, placebo-controlled, double-blind clinical investigation designed to evaluate the potential benefits of Sediflù® syrup for children with a dry or productive cough that persists for seven days. Children without known severe underlying diseases commonly suffer, particularly during the cold months, from several respiratory infections involving mainly the upper respiratory tract. Therefore, effective and safe therapeutics are needed. There is no scientific evidence to justify the use of over-the-counter cough medicinal products (antitussives, mucolytic and/or antihistamines), as they could have potentially serious side effects, and thus should not be prescribed to children on a regular basis. Products with honey and herbal extracts, such as Sediflù® syrup, are an effective and safe alternative treatment to drugs. In these upper respiratory tract infections, coughing is a functional disorder frequent in children and it is one of the most frequent reasons for consultation in daily paediatric practice [11–13].
Sediù® syrup is a medical device containing eucalyptus honey and dry extracts of plantain leaves (*Plantago lanceolata* L.), horehound flowers (*Marrubium vulgare* L.), sundew flowers (*Drosera rotundifolia* L.) and ivy leaves (*Hedera helix* L.). The aerial part of plantain or ribwort plantain (*Plantago lanceolata* L.) has been used for centuries by traditional medicine in the treatment of infectious disorders of the respiratory tract. Its beneficial properties are due to the significant content of mucilaginous polysaccharides, mainly rhamnogalacturonans, galactans, arabinogalactans and xylogalacturonans [14]. Horehound flowers (*Marrubium vulgare* L.) have also been traditionally used in Europe as well as in Southern and Eastern Mediterranean countries, and one of their therapeutic uses is treatment of respiratory diseases [15]. Ivy leaves (*Hedera helix* L.) showed effectiveness for treating symptoms of respiratory tract infections and improving the respiratory function, mainly for paediatric coughs, by reducing their frequency and intensity, with high tolerability [16–20]. Finally, sundew flowers (*Drosera rotundifolia* L.) have a long history as a remedy for coughs, being probably one of the most widely distributed carnivorous plant species [21].

The results of this clinical trial show a significant reduction in night-time and day-time cough symptoms in children that received Sediù® syrup, as measured using a specific and validated evaluation scale. Antitussive effects, in night and day times, improved significantly at day 2 and they continued ameliorating during the 7 days of treatment, with a significant difference favouring the Sediù® treatment, in comparison to the placebo.

Similar findings were observed in cough frequency, severity and bothersomeness, as well as in the child’s quality of sleep and parental quality of sleep, which are variables specifically designed to assess nocturnal coughing. Indeed, the reduction of disturbances in night-time coughing is a very important topic in cough management, as it causes considerable discomfort and sleep disturbances both in children and their parents.

Sediù® syrup reduces the frequency and severity of coughing from the first day of treatment in a subset of children that had more severe coughs (i.e., CCS ≥ 3). Rapid recovery, 24 hours after the first administration of Sediù®, is of extreme interest, provided that these variables are recognized as the two main disturbances associated with coughing. Concerning bothersomeness and the quality of sleep of children and their parents, significant improvements were also observed for these variables in the Sediù® group.

The effectiveness Sediù® is a consequence of the combined action of its ingredients. This syrup treats coughing through a mechanical mode of action related to demulcent, bioadhesive, protective and expectorant characteristics of the combination of honey with these herbal extracts, without an action similar to antitussive drugs that acts either on the cough centre of central nervous system that controls coughing or on the peripheral cough receptor, mainly located in the trachea and pharynx.

The active components of Sediù® syrup, in addition to honey, include mainly mucilaginous polysaccharides from plantain, lactones and phenolic compounds from horehound, saponins from ivy and naphthoquinones from sundew.
The ingredients of Sefidů® syrup create a protective film on the mucosa, calming coughing and protecting the upper respiratory tract. In an inflammatory process of the throat and pharynx, the function of the epithelial surface is altered causing subsequent physical irritation of the membranes. Adhesion to the mucosa limits contact with external irritating agents, promotes hydration and reduces damage caused by the mucosal contact of microorganisms and other irritant agents [22–24].

Honey is used to treat upper respiratory tract symptoms and it is generally believed to be safe outside of the paediatric population. Honey is a lay remedy for upper respiratory tract infections and has an emerging evidence base for its use [25]. The World Health Organization (WHO) considered the use of honey of interest in the treatment of coughs, due to its demulcent properties [26] (WHO, 2001). The WHO reports that demulcents may soothe the throat and can be recommended to provide some relief from coughing in children. As evidenced by some previous studies, honey products may have a beneficial effect for symptomatic relief of coughing, even nocturnal coughing, associated with upper respiratory tract infections [4, 25, 27–28].

Mucilaginous polysaccharide-containing plants are widely used for therapeutic treatment of irritations of mucous membranes in the pharynx regions. In addition to the demulcent activity of honey, these polysaccharides adhere to the oral and pharynx mucosa and exert a mechanical barrier effect. In fact, polysaccharides are related to a protective effect on irritation of the mucosa and with a cough-reduction effect mediated by chemical or mechanical changes [22–23]. It is a protective effect produced mechanically but not pharmacologically, due to the demulcent effect of polysaccharides. Moreover, the bioadhesive effect allows the formation of a protective layer of polysaccharides due to the mucoadhesive effect of their hydrophilic macromolecular structures. Polysaccharides have a high number of hydroxyl groups, allowing a high binding capacity with water and causing hydration [22, 24]. The formation of this layer on the epithelial surface allows rehydration, desensitization, a decrease in local inflammation and a reduction in dry coughing. Hydration is one of the recognized non-pharmacological interventions in the cough approach and is causally related to the reduction of the sensitivity of the cough reflex [29]. Furthermore, the effect on the reduction of local inflammation is produced by a mechanical barrier effect related to mucoadhesive capacity.

Extracts obtained from Plantago sp. are characterized by their mucilaginous polysaccharide content [14]. Their effect is complemented with lactones from horehound, mainly marrubiin, a labdane diterpene, which is characteristic for the genus, and it acts as a good antioxidant agent in conjunction with various phenolic compounds [30]. Ivy leaves contain saponins (hederacosides) and produce a secretolytic effect, inducing type II alveolar epithelial cells to generate more surfactant yielding for reduction of mucus viscosity, a physicochemical effect [17].

Moreover, the sweet taste and palatability provided by honey, and its physical and chemical properties, are responsible for modulating cough sensitivity [31–33]. It is an effect related to the stimulation of sensory pathways that influence the normal response of the body, contributing to reflex processes such
as salivation. These sensory pathways are also associated with those that participate in the cough process, being able to inhibit their reflex, without pharmacological mechanisms.

The study was conducted between November 2020 and March 2021, when the use of masks was compulsory in Spain as a result of the COVID-19 pandemic. Due to this fact, cough episodes have been milder and less frequent than in previous years. This is the main limitation of this study, since the cough-associated disturbances of the children enrolled were lower than expected. Additionally, children in the Sediflu® group had baseline scores for all the variables studies slightly higher than those present in the placebo group. Despite these limitations, Sediflu® syrup proved to be effective in reducing all the variables associated with both diurnal and nocturnal coughing in children and confirmed its safety profile as well as its tolerability. Further studies should be conducted with a larger sample size and a wider age range of the participants.

Conclusion

Sediflu® syrup exerts positive effects by reducing the main disturbances associated with day-time and night-time cough scores, shortening the duration of coughs in children. Cough severity and frequency are significantly reduced from day 1 of treatment with Sediflu®, which showed a very good safety profile. Based on these findings, Sediflu® syrup can be considered a valid treatment for cough management, especially in younger children with upper respiratory tract infections, thanks to the creation of a protective mechanical barrier on oropharyngeal mucosa and its complementary physicochemical effects.

Abbreviations

D0 (visit 1, basal time) and the other experimental days (D1 to D7).

Declarations

Availability of data and materials: The full data set and other materials related to about this study can be obtained from the corresponding author on reasonable request.

Ethical approval and consent to participate

All methods of this study were carried out in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or compa- rable ethical standards. The study was conducted in compliance with the ICH-GCP Guideline and appropriate procedures were always followed to ensure compliance with Regulation (EU) 2016/679. It was approved by the local Ethics Committee of Madrid (CEIm). The participants’ parents gave their written informed consent before the study was carried out.

Consent for publication
Not applicable

**Competing interest**

CR and ERR have been scientific advisors for Cinfa and speakers outside the objective of this work. CR has worked as principal investigator in clinical studies promotes by Cinfa. CN and MCC are principal investigator in this trial. The other author declare that they have no competing interest.

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Cinfa Laboratories was the sponsor of the trial; however, it played any role in the design of the study, data collection and analysis and interpretation, and writing the manuscript.

**Authors’ contributions**

CN and MC were responsible for data acquisition; FT and CC reviewing the manuscript; ER reviewed the protocol of the study and drafted the manuscript. All authors read and approved the final manuscript.

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Not applicable.

**References**


**Figures**
Figure 1

Study schedule.

Figure 2

Evolution of the day-time and night-time cough scores ± standard error over time of Sediflu®. *p<0.05; **p<0.01.
Figure 3

Average variation (%) among treatment group in comparison with placebo by the day-time and night-time cough score ± standard error over time. Negative values correspond to a greater efficacy of the treatment with Sediflu®. *p<0.05; **p<0.01.
Figure 4

Evolution of the frequency, severity, bothersomeness, child's sleep and parental sleep scores ± standard error over time of Sediflu®. *p<0.05; **p<0.01.
Figure 5

Average variation (%) of the treatment group as compared to placebo in the frequency, severity, bothersomeness, child’s sleep and parental sleep scores ± standard error over time. Negative values correspond to a greater efficacy of the treatment with Sediﬂu®. *p<0.05; **p<0.01.