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Research Article

Efficacy of a Medical Device Based on Plant Extracts for the Symptomatic Treatment of Cough in Children and Adults. A Clinical Study

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Abstract

Cough is one of the most common medical situations that leads to seek medical attention. The present study was carried out to evaluate the efficacy and tolerability in the treatment of cough in adults and children of a sugar-free syrup containing glycerol and extracts from roots of Althaea officinalis and from leaves of Plantago lanceolata (FTP 65 Cough syrup sugar free: Manufacturer Labomar SPA). One hundred and twenty subjects (60 children and 60 adults) were recruited. Participants received for 7 days one of the following dosage schedules:

a) Adult: " Cough Syrup REF FTP 65" in single-dose containers of 10 ml, to be taken daily in 3 administrations

b) Children: " Cough Syrup REF FTP 65" with a daily dosage of 10 ml/day for 2–6-year-old children, and of 20 ml/day, for 7–12-year-old children. The survey included three visits: a first visit (V0) of enrollment, a second visit (V1) after 3 days from the V0 and a third visit (V2) carried out after 7 days of therapy. The results of this study confirm the evidence that the medical device Cough Syrup REF FTP 65 may represent a valid choice as a treatment for coughing in adults and children

Keywords: Cough; mucociliary clearance; Althaea officinalis; Plantago lanceolata; moisturizing film

Introduction

Cough is one of the most common medical situations that leads to seek medical attention. It is an archaic reflex act that aims to protect the respiratory tract from foreign materials. Despite its frequency, there are still no objective methods to quantify the cough whose assessment remains, therefore, eminently subjective. Due to the vagueness of the nature of this symptom, together with a strong impact on the quality of life, the absence of objective tools and the possibility that it is expression of an insidious pathology, the cough should be considered and cured as a major problem until a harmless etiology is identified. The cough is a reflex act, essentially uncontrollable, capable to facilitate the mucociliary clearance and to determine the removal of excess secretions from the airways. The mucociliary clearance depends on the presence on inner surface of the respiratory tree, from the trachea to the terminal bronchioles, of a ciliated respiratory epithelium. Every single epithelial cell has about 200 cilia (each cilium is about 7 μm in length) that protrude towards the lumen and that constantly beat at a speed of 10-20 Hz.

The cilia are surrounded by a layer of periciliary fluid formed by a deeper, very fluid layer, in turn dominated by a mucous layer, together forming the epithelial lining fluid that, in addition to keeping the epithelium moist, traps the particulate material that has penetrated the respiratory tract. The cilia beat with a coordinated movement directed towards the pharynx where the transported mucus is swallowed or eliminated with the cough. An effective mucociliary clearance depends on a number of factors, including the number of cilia, their structure, the frequency with

which they oscillate, and the quality of the mucus produced which must be maintained at a correct humidity, temperature and acidity. The cilia must be able to move freely in the layer of periciliar fluid and when this is compromised, the mucus cannot be correctly removed from the respiratory tract [1]. The cough reflex act is characterized by the simultaneous closure of the glottis and activation of an expiratory act with the resulting increase in the intrathoracic pressure that can even exceed 300 mm Hg. The strong increase in intrapulmonary pressure causes the violent expulsion of the airway contents through the glottis into the pharyngeal space and, therefore, out of the respiratory system. Due to the high intensity of this process, in which the velocity of the expired air can exceed 800 km/h, mucous secretions are detached from the airway and expelled. In normal conditions, the cough is a protective mechanism, but under certain circumstances can occur alterations in the system's physiology capable to generate situations that are often unfavorable and exasperating for the patient.

The cough reflex is initiated by the activation of sensory receptors located mainly, but not exclusively, in the pharynx, in the larynx and along the entire tracheobronchial tree. Some of these receptors are activated by chemical stimuli while others by mechanical ones. Chemical type receptors, located mainly in the respiratory tract, are activated by acids, heat and capsaicin-like molecules that act on capsaicin type-1 receptors. The mechanical type receptors are located not only in the respiratory tract but also in the in the paranasal sinuses, eardrum, external auditory canal, in pleura, pericardium, diaphragm, and stomach [2]. The different types of sensory receptors are connected to the CNS through afferent fibers that travel in the Vagus nerve (cranial nerve X) to the respiratory centers located in the brainstem. The exact location of the hypothetical cough center is not known, but it is likely that the cough, rather than the effect of the activation of a single structure, is the consequence of the modulation of the different respiratory centers located in the brainstem [3]. Traditionally, the cough's mechanism is divided into 3 successive phases: the inspiratory phase, the compression phase and the expiratory phase. The first has the task of making a sufficient amount of air enter the lung to produce an efficient cough. The compression phase is characterized by the closure of the glottis and the simultaneous contraction of the expiratory musculature that leads to a strong increase in intrapulmonary pressure. Finally, the expiratory phase is characterized by a rapid opening of the glottis resulting in an explosive outflow of air. At the end of the exhalation, an inspiration usually occurs to compensate for the developed hypoxia.

As mentioned above, in addition to the use of pharmacological treatments based on antitussives, antihistamines or fluidizers, cough can be treated by using plant extracts rich in polysaccharides. In fact, they, with a purely mechanical action, form a moisturizing and protective film [4] with a barrier effect that, on the one hand, limits contact with irritating agents and, on the other one, moisturizes the mucus so favoring a physiological expectoration. The present medical device is a sugar-free syrup containing glycerol and polysaccharide-rich aqueous extracts from roots of Althaea officinalis and from leaves of Plantago lanceolata. Althaea officinalis is traditionally used for the treatment of cough and inflammation of the upper respiratory tract. Its roots are known to contain relatively high mucilage content that makes this herb excellent demulcent, emollient, expectorant [5]. Plantago lanceolata is indicated for the treatment of cough for the presence of components such as mucilages with an emollient and soothing action [6]. Glycerol or glycerine is an ingredient found in many cough preparations for its lubricant, emollient, and humectant properties [7]. The aim of the present study was to confirm the efficacy and tolerability of the syrup in the treatment of cough in adults and children from 2 years of age.

Materials and Methods

Study design

In the period between March and May 2019, a multicenter post-marketing study was carried out. The study was conducted at two primary care clinics, the first of general practitioner and the second of family pediatrician, involving: adults, males and females, with an age between 18 and 65 years, and children, male and female, with an ages between 2 and 12 years. A total of 120 subjects were recruited: 60 children and 60 adults. The used product was Cough Syrup REF FTP 65 (Labomar SPA, Istrana , TV, Italy) a medical device already available on the European market under different brand names and composed of extract of Plantago lanceolata, extract of Althaea officinalis, vegetable glycerin, thyme extract, sorbitol, water, xanthan gum, natural flavors, citric acid, potassium sorbate, sugar-free and gluten-free. The experimental protocol "Study Code: SFT2018" was approved by the Ethical Committee "Catania 2", in the session of 11/13/2018. All adult subjects signed the Informed Consent approved by the Ethics Committee, while for children the Informed Consent was signed by both parents and children over 5-year-old. After Informed Consent and basic evaluations, patients, considered suitable for enrollment in the study, received one of the following dosage schedules according to the instructions for use of manufacturer:

a) **Adult:** "Cough Syrup REF FTP 65" in single-dose containers of 10 ml, to be taken daily in 3 administrations.

b) **Children:** "Cough Syrup REF FTP 65" with a daily dosage of 10 ml/day for 2–6-year-old children, and of 20 ml/day, for 7–12-year-old children.

The overall duration of the survey for each subject was seven days.

Inclusion criteria

Subjects were admitted to the survey:

a. Females and males' adults, suffering from cough associated with sore throat or upper respiratory tract infections.

b. Females and males' children, suffering from cough also associated with sore throat or upper respiratory tract infections

Exclusion criteria

Subjects were not included in the survey if:

a. Presenting contraindications indicated in the instructions for use of the product " Cough Syrup REF FTP 65";

b. Presenting presumed or ascertained hypersensitivity to one or more of the ingredients present in the formulation

c. Having a history of anaphylaxis or allergic reactions in general or serious food intolerances, which the doctor may deem relevant for inclusion in the study with concomitant conditions that do not guarantee participation / participation in the study according to the investigator's opinion.

d. Were children affected by chronic pathologies with serious respiratory compromises (cystic fibrosis, Spinal muscular atrophy, dystrophies, cerebral palsy or oncological pathologies).

e. Were adults with an overly complicated clinical picture for which the investigating doctor believes that participation in the study may be in some way harmful.

f. Were adults and children already in therapy with other preparations for cough treatment in acute respiratory infections.

Concomitant therapies

The subject had to follow an adequate diet; subjects in therapy with other cough preparations including cough suppressants and mucolytics were not included in the study. Any assumption of concurrent permitted and non-permitted drugs was reported in the Data Collection Form (DCF) and used for the final evaluation.

Study procedures

The survey included three visits. A first visit (V0) of enrollment, a second visit (V1) carried out after 3 days from the V0 and a third visit (V2) carried out after 7 days of therapy, i.e., at the end of the study therapy.

V0 (enrollment): first enrollment visits and compilation of the SRD:

a. explanation of the investigation to the subject if adult or to the parent / legal representative and obtaining written Informed Consent before each investigation procedure.

b. medical history and verification of inclusion and exclusion criteria and clinical evaluation.

c. evaluation of the cough by using a questionnaire.

d. assessment of associated symptoms:

e. for adults: general conditions (poor, satisfactory good), fatigue, vomiting, hoarseness, difficulty breathing, chest pain, vertigo and urine leakage; all these parameters were evaluated in mild, moderate, severe.

f. for children: general conditions (poor, satisfactory good), fever (Celsius degrees, °C), headache, vomiting, hoarseness, stuffy nose, ear pain, assessed in mild, moderate, severe, and respiratory sounds (wheezes, rhonchi, and rales).

g. assessment of psychophysical well-being for adults, with questions as: do you feel depressed? Do you feel irritated? Do you feel tired? Do you consider yourself sick?

h. evaluation of daily activities such as: loss of school days, loss of days of work of parents, reduction of appetite and sense of discomfort.

i. any concomitant therapy and the type of drug used were recorded.

j. setting of therapy with " Cough Syrup REF FTP 65" and delivery of product.

k. programming of visit 1 (V1).

V1: second visit:

a) review of inclusion and exclusion criteria.

b) evaluation of the symptom cough based on the questionnaire.

c) clinical evaluation and associated symptoms.

d) evaluation of the parameters of psychophysical wellbeing for adults and those of daily activities for children.

e) registration of any adverse effects.

V2: final visit, conclusion of the study

a) review of inclusion and exclusion criteria.

b) evaluation of the symptom cough based on the questionnaire.

c) assessment of the patient's general condition.

d) evaluation of efficacy, tolerability and compliance of the medical device.

e) assessment of patient satisfaction.

f) evaluation of the parameters of psychophysical wellbeing for adults and those of daily activities for children.

g) assessment of any adverse effects incurred.

h) completion of the end of study procedures.

Study endpoints

The primary endpoint was the evaluation of the efficacy of the medical device Cough Syrup REF FTP 65 to reduce the symptom cough in adults and children with acute respiratory diseases. To assess the cough's intensity and its impact on the patient's daily life we used a questionnaire taken from validated cough measurement instruments such as cough scales (Table 1). The result was given by

the variation from baseline (V0) to the intermediate visit (V1) and at the end of the treatment (V2). The secondary endpoints included the evaluation of the clinical status, the evaluation of efficacy and tolerability of the medical device Cough Syrup REF FTP 65 obtained from the variation from baseline (V0) to the intermediate visit (V1) and at the end of treatment (V2).

Table 1: Casuistry and characteristics of the cough in the sample.

Sample		Adults		Children	
AGE (years)		54.0 (38.3-59.8)		5.0 (3.0-7.0)	
		N	%	N	%
Males		34	56.7	24	40
Females		26	43.3	36	60
Opposite conditions		-	-	-	-
Hypersensitivity		-	-	-	-
History of anaphylaxis		-	-	-	-
Cough		60	100	60	100
Features	dry	19	31.7	21	35
	wet	41	68.3	39	65
Period	day	2	3.3	5	8,3
	night	10	16.7	9	15
	indifferent	48	80	46	76,7

Data analysis

The sample used was considered adequate for the purpose of the study, namely: observation and description of the efficacy and safety characteristics of the product under study in the post-marketing follow-up. The intention-to-treat population was used for the analysis of the raw data. Comparisons between the groups, openly treated, were of a descriptive nature and data were reported in terms of means and standard deviations (SD) for quantitative variables and in terms of absolute frequencies and percentages for qualitative variables. To detect significant differences in changes in primary and secondary efficacy endpoints from baseline (V0) to the end of treatment (V2) the exact Fisher test, Chi square test with Yates's correction, McNemar test and Mann-Witney test were used.

Results

Children

The 60 children had a median age of 5 years (range 3-7 years), 24 were males (40%) and 36 females (60%); all had coughs and had no contraindications to the use of medical device Cough Syrup REF FTP 65, nor conditions that hindered the taking. The cough was dry in 21 (35%) and wet in 39 (65%) children. Only 5 (8.3%) children had daytime cough, 9 (15%) had nocturnal cough, all the other 46 (76.7%) children had either daytime or night cough. Concerning the associated symptoms, at the time of diagnosis (V0) 40 children (66.7%) had poor general conditions, 17 (28.3%) satisfactory conditions, 3 (5%) very poor conditions and non-good conditions. Forty-three children (71.7%) had fever with a median value of 38 °C (38 - 38.5 °C); 51 children (64.7%) had headaches, most of them mild (33, 64.7%), 18 moderate (35.3%); 6 children (10%) had mild vomiting. Fifty-two children (86.7%) had hoarseness, 36 (69.2%) moderate, 13 (25%) mild and only 3 (5.8%) severe. Fifty-three children (88.3%) had coryza, out of which 11 (20.8%) mild, 38 (71.7%) moderate, 4 (7.5%) severe. Eight children (13.3%) had ear pain, out of which the majority were mild (6, 75%), 1 moderate (12.5%) and 1 severe (12.5%). Finally, 54 children (90%) had positive respiratory sounds, 7 children (13%) had wheezing, 31 (57.4%) Ronchi and 16 (29.6%) rales (Table 2).

Table 2: Changes of the cough during the study.

Cough		V1				V2			
		Adults		Children		Adults		Children	
		N	%	N	%	N	%	N	%
Changed	yes	52	86,7	56	93.3	58	96.7	60	100
	no	8	13.3	4	6.7	2	3.3	0	0
Modality	increased	1	1.9	1	1.8	0	0	0	0
	decreased	50	96.2	39	69.6	36	62.1	7	11.7
	disappeared	1	1.9	16	28.6	22	37.9	53	88.3

Features	dry	9	15.3	8	18.2	1	2.8	2	28.6
	wet	50	84.7	36	81.8	35	97.2	5	71.4
Period	day	4	6.8	1	2.3	2	5.6	0	0
	night	6	10.2	13	29.5	2	5.6	2	28.6
	indifferent	49	83	30	68.2	32	88.8	5	71.4

As regards the influence on activities, at the time of diagnosis only 4 children (6.7%) declared that cough did not affect their activities while 56 children (93.3%) sometimes felt compelled to interrupt them. Fifty-two children (86.7%) stated that sometimes they did not have a restful sleep, 2 (3.3%) always, 6 (10%) never; 35 children (48.3%) stated that sometimes he had difficulty concentrating, 10 (16.7%) always, 15 (25%) never. Thirty-five children (58.3%) declared that, when sick, they always stopped eating, 15 (25%) sometimes, 10 (16.7%) ever (Table 3). As for daily activities, at the time of diagnosis 52 children (86.7%) had constant loss of school days and 8 (13.3%) only sometimes. The parents of 23 children had always lost working days, 34 (56.7%) sometimes, only the parents of 3 children (5%) had not lost working days; 46 children (76.7%) had always lost their appetite, 6 (10%) sometimes, 7 (13.3%) never; finally, 48 children (80%) always had a sense of malaise, 8 (13.3%) sometimes, 4 (6.7%) never.

Table 3: Changes on the daily activities of children during the study.

Daily Activities		V0		V1		V2	
		N	%	N	%	N	%
Lack of school	yes	52	86,7	8	13,3	–	–
	sometimes	8	13,3	37	61,7	6	10
	no	-	-	15	25	54	90
Lack of parent's work	yes	23	38,3	-	-	–	–
	sometimes	34	56,7	42	70	1	1,7
	no	3	5	18	30	59	98,3
Lack of appetite	yes	46	76,7	1	1,7	–	–
	sometimes	6	10	10	16,7	-	-
	no	8	13,3	49	81,6	60	100
Illness	yes	48	80	2	3,3	-	-
	sometimes	8	13,3	7	11,7	-	-
	no	4	6,7	51	85	60	100
activity stoppage	always	52	86,7	4	6,7		
	sometimes	8	13,3	41	68,3	7	11,7
	never	-	-	15	25	53	88,3
Sleep no restful	always	48	80	1	1,7	–	–
	sometimes	10	16,7	43	71,1	1	1,7
	never	2	3,3	16	26,7	59	98,3
Hard enforcement	always	48	80	1	1,7	–	–
	sometimes	8	13,3	9	15	-	-
	never	4	6,7	50	83,3	60	100
Lack of drink and eat	always	46	76,7	1	1,7	–	–
	sometimes	6	10	8	13,3	-	-
	never	8	13,3	51	85	60	100

At the time of the first visit, in addition to the product being tested, 29 children (47.1%) received another drug, most often salbutamol (13 children, 44.8%), 6 children (10%) received an antibiotic, 6 children (20.7%) the combination paracetamol-chlorphenamine, 1 child (3.4%) beclomethasone for inhalation, 1 child (3.4%) cetirizine and, finally, 3 children (10.3%) other preparations for cough. The endpoints evaluation showed that already at V1, after only 3 days of therapy, 56 children (93.3%) showed a change in cough and only 4 (6.7%) had no change; those in which the coughing had changed, 39 children (69.6%) had

decrease, in 16 (28.6%) cough disappeared and only in 1 (1.8%) cough increased. Concerning the characteristics, the cough was kept wet in 36 children (81.8%) and dry in 8 (18.2 &); the cough remained both diurnal and nocturnal in 30 (68.2%), while 13 (29.5%) still presented it nocturnal and only 1 (2.3%) diurnal. At the final visit all the children (100%) had modified cough, in 7 (11.7%) cough decreased, while in the other 53 (88.3%) cough disappeared. The characteristics had remained the same: predominantly wet (71.4%) and indifferent (71.4%). As for the associated symptoms, these showed, already at V1, an improving trend, with the exception of the general conditions that remained unchanged with respect to the initial visit. On the contrary, fever persisted in only 3 children (5%), a mild headache was present only in 12 (20%), vomiting only in 1 (1.7%), while hoarseness persisted in 15 (25 %). In 19 children (31.7%) persisted the coryza, out of which 16 (84.2) was mild; in 3 (5%) persisted ear pain and in 12 (20 %) respiratory sounds, more often ronchi (10, 83.4%). At V2 the improvement was evident with good general conditions in all 60 children (100%); only 1 (1.7%) persisted headache, none vomited, only 2 (3.3%) had hoarseness, 2 (2.2%) coryza, none had more ear pain, and none had abnormal respiratory sounds.

As for the influence on daily activities, already at V1 only 4 (6.7%) and none at V2, had been forced to interrupt them. Forty-one (68.3%) were sometimes at V1 and 7 (11.7%) at V2, 15 (25%) and 53 (88.3%) at V2 were no longer; only 1 (1.7%) and none at V2, had no restful sleep, 43 (71.7%) had sometimes not and 16 (26.7%) had never at V1 and only 1 (1.7%) at V2, mind the other 59 (98.3%) never. Fifty children (83.7%) at V1 and all 60 (100%) at V2 had no more difficulty in concentrating; only 1 (1.7%) always had it and 9 (15%) sometimes at V1. Finally, already 51 children (85%) had no more difficulties in eating and drinking in V1 and 15 (25%) in V2, 10 (16.7%) and 45 (76.7%) in V2 were no more; 11 subjects (6.7%) and only 1 (1.7%) always had difficulties and 8 (13.3%) sometimes, in V2 nobody had any more. As far as the daily functions, already at V1 were concerned, only 8 (13.3%) and none at V2, had lost their schooling, 37 (61.7%) had lost it sometimes at V1 and 6 (10%) at V2, 15 (25%) and 54 (90%) at V2 had not lost it anymore. In 42 children (70%) at V1 and only 1 (1.7%) at V2, the parents had sometimes lost their job, while 18 (30%) at V1 and 59 (98.3%) at V2, had not lost it anymore. Only 1 child (1.7%) and none at V2 had a reduction in appetite, 10 children (16.7%) at V1 and none at V2 had sometimes a reduction in appetite, while 49 children (81.6%) at V1 and all (100%) at V2 had no reduction in appetite. Finally, only 2 children (3.3%) at V1 and none at V2 had a reduction in appetite, 7 (11.7%) at V1 and none at V2 had sometimes a reduction in appetite, 51 children (85%) at V1 and none at V2 had a reduction in appetite.

Nineteen children out of the initial 29 had maintained the associated drug therapy, as was logical to think, but at V2 still 10 children were taking an associated drug.

In terms of efficacy, 53 children (88.3%) assessed it as good at V1, 2 children (3.3%) as satisfactory and 5 (8.4&) as excellent, while at V2 all 60 children (100%) assessed it as excellent. Tolerability was considered good by 59 children (98.3%) already at V1, only 1 (1.7%) satisfactory, while at V2, all 60 children (100%) considered it very good. Only one child (1.7%) was agitated when taking the syrup, which lasted a few days during the therapy, which did not need to be suspended, and disappeared immediately after the suspension of the therapy. All subjects took all the doses (8 to V1 and 14 to V2) and followed the therapy. 25 children (41.7%) found the taste of the syrup very good, 17 (28.3%) good, 13 (21.7%) bad and 5 (8.3%) very bad; 38 children (63.3%) considered the syrup very easy to swallow, 17 (28.3%) easy, 3 (5.1%) difficult, 2 (3.3%) very difficult. The statistical analysis showed high statistical significance (chi2 $p<0.001$) for all the variables already considered at the intermediate visit and especially at the final visit. The following associated symptoms also showed a statistically highly significant reduction ($p<0.001$) in McNamar's test at both V1 and V2: fever, headache, hoarseness, coryza and chest pain; at V2 the reduction was statistically significant for vomiting ($p<0.05$) and otalgia ($p<0.01$) because they already started from a small number of subjects (Figures 1 & 2).

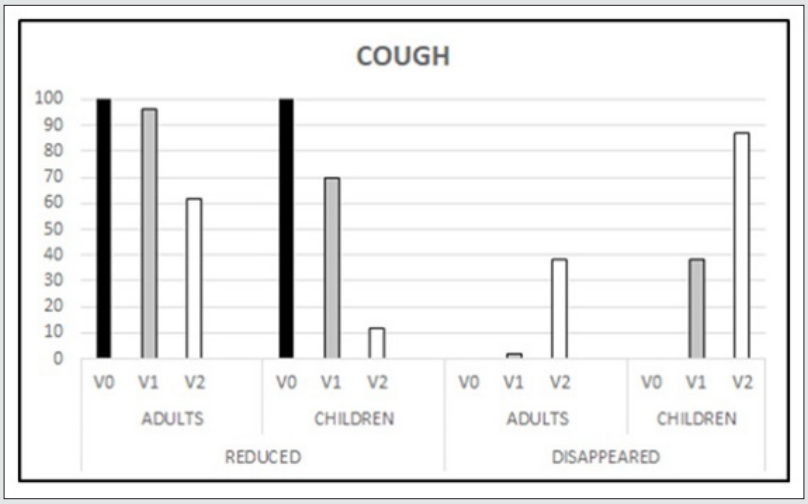

Figure 1: Behavior of the cough during the study * $p<0.001$.

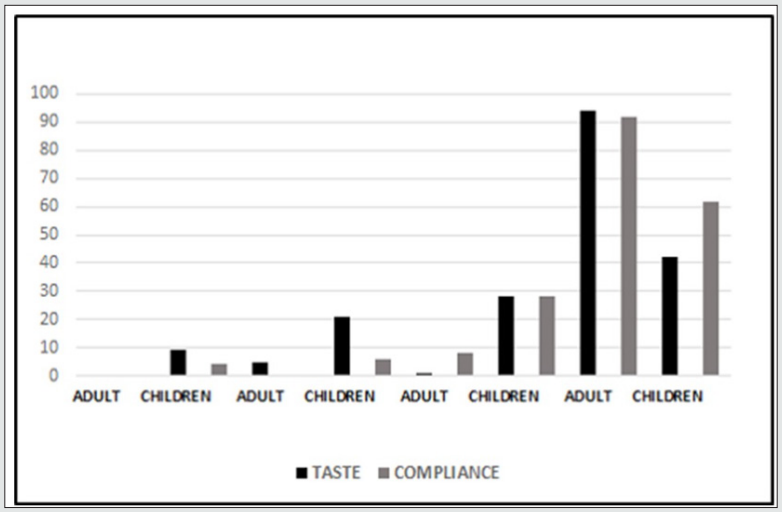

Figure 2: Results of Taste and Compliance of the studied device.

Adults

The 60 adults had a median age of 54 years (range 38-60 years), 34 were males (57%) and 26 females (43%), all had coughs and had neither contraindications to the preparation nor conditions that hindered its intake. The cough was dry in 19 subjects (32%), wet in 41 (68%) subjects. Only 2 (3%) adults had daytime cough, 10 (17%) had nighttime cough, all the other 48 (80%) had both daytime and nighttime cough. Concerning the associated symptoms, at the time of diagnosis 31 (51.7%) had poor general conditions, 24 (40%) satisfactory, 1 (1.7%) poor and 4 (6.6%) good. Fifty-three adults (88.3%) experienced fatigue, although the majority (39, 73.6%) experienced mild fatigue; 42 adults (70%) suffered from headache, the majority of which were mild (36, 85.7%), 6 subjects (10%) had vomiting and 9 (15%) hoarseness. Forty-two subjects (70%) had difficulty breathing, of which 22 (52.4%) were mild; 40 subjects (66.7%) had chest pain, the majority of which were mild (25, 62.6%); only 3 subjects (5%) had dizziness and 6 (10%) slight loss of urine (Table 2). As regards the influence on physical well-being, at the time of diagnosis 41 subjects (68.3%) sometimes felt depressed, 17 (28.3%) always felt depressed, 2 (3.3%) never. Forty subjects (66.7%) sometimes felt irritated, 18 (30%) always, 2 (3.3%) never; 40 subjects (66.7%) sometimes felt tired, 18 (30%) always, 2 (3.3%) never; 39 subjects (65%) sometimes felt sick, 19 (31.7%) always, 2 (3.3%) never.

Concerning daily activities, at the time of diagnosis 47 subjects (78.3%) sometimes interrupted their work, 8 (13.4%) always, 5 (8.3%) never; 39 subjects (65%) had sometimes no restful sleep, 16 (26.7%) always, 5 (8.3%) never. Forty-one subjects (68.3%) sometimes had difficulty concentrating, 12 (20%) always, 7 (11.7%) never; finally, 40 subjects (66.7%) sometimes stopped drinking and eating, 10 (16.7%) always, 10 (16.7%) never (Table 4). At the first visit and in conjunction with the investigational product 21 subjects (35%) received another drug, more often an antibiotic (8, 13.3%), than a steroid (6, 10%), someone an antihistamine. The evaluation of endpoints showed that already at V1, after 3 days of therapy, 52 subjects (86.7%) showed a modification of the cough and 8 (13.3%) a stationarity; of those in which it was modified, 50 (96.2%) had shown a decrease, 1 (1.9%) disappeared and 1 (1.9%) increased. As far as its characteristics were concerned, the cough remained wet (84.7%) and indifferent between day and night (83%). At the final visit the same trend was maintained with 58 (96.7%) subjects in which it had changed and of these 36 (62.1%) showed a decrease and 22 (37.9%) disappeared. The characteristics had remained the same: mainly wet (97.2%) and indifferent (88.8%).

Table 4: Changes on the wellness and daily activities of adults during the study.

Wellness and Daily Activities		V0		V1		V2	
N		%	N	%	N	%	
Feel down	yes	17	28,3	4	6,7	–	–
	sometimes	41	68,4	44	73,3	14	23,3
	no	2	3,3	12	20	46	76,7
Feel sore	yes	18	30	4	6,7	–	–
	sometimes	40	66,7	42	70	13	21,7
	no	2	3,3	14	23,3	47	78,3

Feel tired	yes	18	30	4	6,7	–	–
	sometimes	40	66,7	46	76,6	15	25
	no	2	3,3	10	16,7	45	75
Feel sick	yes	19	31,7	11	18,3	1	1,7
	sometimes	39	65	39	65	14	23,3
	no	2	3,3	10	16,7	45	75
work stoppage	always	8	13,4	1	1,7		
	sometimes	47	78,3	47	78,3	18	30
	never	5	8,3	12	20	42	70
Sleep no restful	always	16	26,7	2	3,3	–	–
	sometimes	39	65	51	85	23	38,3
	never	5	8,3	7	11,7	37	61,7
Hard enforcement	always	12	20	1	1,7	–	–
	sometimes	41	68,3	44	73,3	16	26,7
	never	7	11,7	15	25	44	73,3
Lack of drink and eat	always	10	16,7	1	1,7	–	–
	sometimes	40	66,6	38	63,3	12	20
	never	10	16,7	21	35	48	80

Regarding the associated symptoms, they showed, already at V1, an improving trend. General conditions were satisfactory in 43 (71.7%) and good in 13 (21.7%), headache was present only in 19 (31.7%), vomiting and hoarseness only in 3 (5%), difficulty in breathing persisted in 34 (56.7%) subjects and chest pain in 25 (41.7%), no one had dizziness and only 2 (3.3%) loss of urine. At V2 the improvement was evident with good general conditions in 55 (91.7%), only 4 (6.7%) had headaches, no one vomited, only 3 (5%) had hoarseness, 16 (23.7%) had difficulty breathing, 3 (5%) chest pain and only 1 (1.7%) dizziness.

As for the influence on physical well-being, already at V1 only 4 (6.7%) and none at V2, still felt depressed, 44 (73.3%) were sometimes depressed at V1 and 14 (23.3%) at V2, 12 (20%) and 46 (76.7%) at V2 were no longer. Only 4 (6.7%) and none at V2, still felt irritated, 42 (70%) were sometimes at V1 and 13 (21.7%) at V2, 14 (23.3%) and 47 (78.3%) at V2 were no longer irritated. Only 4 (6.7%) and none at V2, still felt tired, 46 (76.6%) were sometimes at V1 and 15 (25%) at V2, 10 (16.7%) and 45 (76.7%) at V2 were no longer tired. Eleven subjects (6.7%) and only 1 (1.7%) at V2, still felt sick, 39 (65%) were sometimes at V1 and 14 (23.3%) at V2, 10 (16.7%) and 45 (75%) were no longer sick. Regarding daily activities, already at V1, only 1 (1.7%) and none at V2, had interrupted work, 47 (78.3%) had sometimes done so at V1 and 18 (30%) at V2, 12 (20%) and 42 (70%) at V2 had not interrupted it anymore. Only 2 participants (3.3%) and none at V2 had a restful sleep, 51 (85%) had sometimes at V1 and 23 (38.3%) at V2, 7 (11.7%) and 37 (61.7%) at V2 had a restful sleep. Only one participant (1.7%) and none at V2, had difficulty concentrating, 44 (73.3%) had it sometimes at V1 and 16 (26.7%) at V2, 15 (25%) and 44 (73.3%) at V2 had it no more. Finally, only 1 subject (1.7%) and none at V2, had stopped drinking and eating, 38 (63.3%) had it sometimes at V1 and 12 (20%) at V2, 21 (35%) and 48 (80%) had it no more.

Seventeen subjects out of the initial 21 maintained the associated drug therapy, as was logical to think, but at V2 only 5 were still taking an associated drug. Concerning effectiveness of treatment, 30 subjects (50%) assessed it as good at V1 and 6 (10%) at V2, 27 (45%) assessed it as excellent at V1 and 53 (88.3%) at V2, only 2 (3.3%) at V1 and 1 (1.7%) at V2 considered it satisfactory and 1 subject (1.7%) at V1 considered it poor. Tolerability was considered good by 14 subjects (23.3%) to V1 and 2 (3.3%) to V2, excellent by 45 subjects (75%) to V1 and 56 subjects (93.4%) to V2, only 1 (1.7%) to V1 and 2 (3.3%) considered it poor. All subjects took all the doses (9 to V1 and 20 to V2) and followed the therapy. 57 subjects (95%) found the taste of the syrup very good, 1 (1.7%) good and only 2 (3.3%) bad; 56 subjects (93.3%) considered it very easy to swallow the syrup and 4 (6.7%) easy, nobody found it difficult. The statistical analysis showed high statistical significance (chi2 $p<0.001$) for all the variables considered already at the intermediate visit and especially at the final visit. Also, the associated symptoms showed statistically significant difference to McNemar's test already at V1 headache ($p<0.001$) and chest pain ($p<0.01$), but a bit all at V2: headache ($p<0.001$), vomiting ($p<0.01$), difficulty breathing ($p<0.001$), chest pain ($p<0.001$) and loss of urine ($p<0.01$). Only hoarseness and dizziness did not show significant differences, probably because they already started from a small number of subjects (Figures 1 & 2).

Discussion

Coughing at any age has to be dealt with different approaches. It is always necessary to go back to the initial cause and remove it, either from infectious causes, identifying the agent in question and starting the specific therapy, you know allergic or from irritating substances by removing the cause (allergens, smoke, pollutants, etc.). However, at the same time, it is essential to improve the symptom, to improve the quality of life and bring daily benefits. If it can be useful to alleviate the course of an annoying cough that lasts a few days, it is always necessary to intervene when the cough is caused by an identified etiological agent [8].

A specific treatment of the cough symptom is of great importance both for the adult, because it improves the mood, the perception of health and the evaluation of one's own state of health, and in the child, because seeing his or her own little cough creates fear and discomfort in the whole family. In any case, if the cough does not pass within a few days, it is necessary to initiate more specific diagnostic investigations to make a precise diagnosis. The treatment of the symptom cough has always relied on sedatives, i.e., substances that, by suppressing the cough reflex, prevent coughing [9]. Unfortunately, some act on the central nervous system and derive from morphine (codeine, etc.), others with central action do not derive from morphine (dextromethorphan, cloperastine, etc.), others are peripheral sedatives (levodropropizine, etc.), acting on sensory fibres afferent to the center of the cough. Many of these cough sedatives cannot be used in children under 2 years of age and in any case both in older children and adults, they are all of dubious efficacy and have presented, depending on the different points of action, important side effects, mainly represented by restlessness and drowsiness [10-15].

Banned expectorant syrups, never indicated in children under 12 years of age and working badly in adults with few exceptions [16], the alternative is to use natural preparations. Most of the preparations did not fail the most important test of effectiveness and showed to reduce the discomfort of coughing. The active ingredients used for these preparations have been many over time, starting with thyme, ivy, etc., all plants that nature makes available to us to soothe the problems of the first airways and in cases of coughing.

In this context is inserted the medical device object of the present clinical investigation which, thanks to its components (glycerol, marshmallow and plantain), has a calming action on the irritation and protective action of the respiratory tract mucosa. The results of the present study showed that the medical device used by us is highly effective in improving the cough symptom, even after only 3 days of therapy in the adult (86.7%) and after 4 days of therapy in the child (93.3%). In addition to the change of cough all symptoms improve after the first days of therapy and this allows a rapid resumption of daily functions, work activities and overall perception of health status. The combined action of Alhtea, Plantago and glycerol has allowed our device to act completely on all kind of cough (wet, dry) presented by both adults and children, resulting effective. It is worth noting that a recent review confirmed the efficacy of Alhtea officinalis extracts alone in treatment of dry cough, while in combination with other extracts improved all kinds of cough [17]. The cough is a symptom that is very annoying to the patient and his family, since it is linked to diseases important for severity and danger, its improvement is therefore able to determine serenity and tranquility important for a good course of the disease. In any case, a product, be it a drug or a device, must be not only effective but also well tolerated and agreeable. In the present study, we have noticed differences between adults and children. Adults consider Cough Syrup REF FTP 65 almost unanimously good/very good (97%), children a little less (70%). Only one child presented a side effect (agitation) which, in any case, was mild and did not require therapy to be discontinued.

Conclusions

The results of this study confirm the evidence that the medical device Cough Syrup REF FTP 65, with its content in natural functional components and its efficacy and safety profile, may represent a valid choice as a treatment for coughing in adults and children. It allows reducing the traditional therapy, with a faster return to school and to normal, working life of adults. In addition, the good taste and ease of administration of the product make it practical and easily accepted.

Statement of Ethics

All procedures in this study were performed in accordance with the of the Declaration of Helsinki and were approved by the Ethical Committee "Catania 2" of Catania (Italy).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Vincenzo Perciavalle is the corresponding authors of this article. All authors planned and designed the study; Gaetano Bottaro and Benedetta Veruska Costanzo performed the experiment. Tiziana Percora and Filippo Palermo are responsible for data collection. All authors contributed to the interpretation of the analysis. Vincenzo Perciavalle wrote the paper, and all authors critically revised the manuscript.

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