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THE EFFECT OF A THYME-IVY FLUID EXTRACT COMBINATION ON THE SEVERITY OF COUGH IN CHILDREN: RANDOMIZED CONTROLLED TRIAL

Sharif M.R.[1], Safari A.[2], Baghshahi H.[3]*, Akbari H.[4]*, Memarzadeh M.R.[3], Rezaii Hajiabad H.[5], Mehran M.[3], Kianipour P.[3]

[1] Infectious Diseases Research Center, Department of Pediatrics, School of Medicine, Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran

[2] Department of Pediatrics, School of Medicine, Shahid Beheshti Hospital, Kashan University of Medical Sciences, Kashan, Iran

[3] Barij Essence Medicinal Plants Research Center, Kashan, Iran

[4] Social Determinants of Health (SDH) Research Center, Department of Biostatistics and Epidemiology, School of Public Health, Kashan University of Medical Sciences, Kashan, Iran

[5] School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

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Abstract

Thyme and ivy leaves contain anti-inflammatory, mucolytic, and bronchospasmolytic properties, resulting in anti-cough benefits. There are no extensive studies conducted on the efficacy of thyme and ivy in children with acute cough.

The purpose of the study was to investigate the efficiency and safety of thyme and ivy in reducing the severity of cough in children.

This study was a randomized, controlled, double-blind clinical experiment on children aged 1 to 12-year old who had an acute cough with no identified etiology. One hundred and forty-two patients were randomly assigned to dextromethorphan or herbal groups, and frequency and severity were measured using a visual analog scale. After the initiation of therapy, recovery trends were assessed at 24, 48, and 96 hours. Eighty-three patients, including 43 patients in the dextromethorphan group and 40 in the herbal group, were followed for 96 hours. Cough severity was decreased by 80.7% in the dextromethorphan group and 87.4% in the herbal syrup group. In addition, there was a significant interaction effect of time and groups on changes in cough severity. In the groups of dextromethorphan and herbal after 96 hours of complete treatment, the efficacy was 72.1% and 75%, respectively, which showed the beneficial effects of both drugs. In children, a mixture of thyme and ivy extracts can help to reduce the severity and length of the cough.

As a result, this combination has the potential to be an effective cough therapy for children.

Keywords: *Hedera helix, herbal medicine, respiratory tract diseases, thymus vulgaris.*

Introduction

Cough is one of the most commonly reported symptoms of respiratory infections in both children and adults. Upper respiratory tract infections and acute bronchitis are the most prevalent causes of cough [*Murgia V et al., 2020*]. The disorder is mainly viral and self-limiting, taking about 1-2 weeks to recover [*Khan E et al., 2020*]. In the human body, the mechanism of spontaneous airway clearing is likewise quite delicate. When microorganisms or foreign substances enter the air-

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Address for Correspondence:

Hojjat Baghshahi
Barij Medicinal Plants Research Center
Mashhad Ardehal, Kashan 3795191916, Iran
Tel.: +989159031196
E-mail: Baghshahi_h1989@yahoo.com

Hossein Akbari
Department of Biostatistics and Epidemiology, Kashan University of Medical Sciences, 15th Khordad Square, Abazar Street, Kashan, P.O.Box: 87137.81147, Iran
Tel.: +983155540111
E-mail: akbari1350_h@yahoo.com

ways, they can induce respiratory tract inflammation [*Prat C, Lacoma A, 2016*]. Increased sputum production occurs because of the inflammation, and the lashes of the respiratory system cannot clear the airways, resulting in coughing [*Shen Y et al., 2018*]. In addition, the secretions adhere to the respiratory system, providing an appropriate environment for harmful microorganisms to multiply [*Invernizzi R et al., 2020*]. Frequent coughing usually reduces the quality of life for patients and might lead to consequences [*Decalmer S et al., 2007*]. Chemical drugs used to treat cough are not only not cost-efficient, but they can also induce dizziness, restlessness, irritability, drowsiness, and other side effects. These medications may interact with other chemical drugs [*Miller S, 2005; Romanelli F, Smith K, 2009*]. Using medicinal plants to cure different diseases has been investigated in recent years [*Panahi Y et al., 2012*]. Herbal remedies have few side effects and help lower and halt coughs [*Ekor M, 2014; Taghizadeh M et al., 2017a; b*]. The dried leaves of ivy (*Hedera helix L.*) contain various compounds, including saponins, flavonoids, phenolic acids, and essential oils, with saponins accounting for most of the ivy's therapeutic properties [*Conrad F, Kemmerich B, 2006; Holzinger F, Chenot J, 2011*]. The ivy extract possesses anti-inflammatory, mucolytic, and bronchospasmolytic characteristics, making it anti-cough. Because of its expectorant properties, ivy leaf preparations are used in pediatrics to treat cold coughs. It has been reported that ivy extract can be effective and safe for treating cough in patients with respiratory diseases with productive cough [*Schmidt M et al., 2012; Sierocinski E et al., 2021*].

Thyme (*Thymus vulgaris*) is an antispasmodic, antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant plant used to treat respiratory disorders [*Conrad F, Kemmerich B, 2006*]. Several studies have been shown that thyme and thymol essential oils have antifungal and antibacterial properties against Cryptococcus neoformans, Aspergillus, Saprolegnia, and Zygorhynchus species, as well as Salmonella typhimurium, Staphylococcus aureus, Escherichia coli, and other bacteria [*Keyhanmanesh R et al., 2016; El-Sherbeny E et al., 2018; Jung K et al., 2021*]. Thymol has a 25-fold antibacterial action and has fewer side effects than phenol. Thymol and carvacrol are the most effective therapeutic compounds in thyme [*Hosseini F et al., 2016*]. Thyme extract has been confirmed in guinea pig trachea rings to have a bronchodilator action similar to theophylline [*Boskabady M et al., 2006*]. In vitro experiments revealed that flavonoids and thyme extract suppress the responses of specific receptor agonists such as acetylcholine, histamine, and norepinephrine, and also non-specific cellular activities like barium chloride [*Boskabady M et al., 2006*]. In a clinical study, thyme extract was compared with diphenhydramine to treat coughs induced by colds in children. They discovered that thyme extracts dramatically relieved cold and cough symptoms with no adverse effects [*Hosseini F et al., 2016*].

This study aimed to investigate the impact of a combination of *Thyme vulgaris* and *Hedrea helix L.* extracts on the severity of cough in children.

MATERIALS AND METHODS

Aerial parts of Thymus vulgaris were collected from Golestan province, Iran. Leaves of Hedera helix L. were collected from Mazandaran province, Iran. The collected plants were dried in a shade-ventilated place for 72 hours. Thyme with number 209-1 and Ivy with number 244-1 are kept in the herbarium of Research Barij Essence Pharmaceutical Company, Iran.

Extraction and preparation of extract: One kilogram of the dried plant was ground and extracted with 50% ethanol by the percolation method. The liquid extract was concentrated at 40°C by rotary apparatus and finally dried at 120°C by a spray dryer.

Preparation of formulation: To prepare the syrup, dry extracts of ivy and thyme were combined based on United States Pharmacopeia so that the amount of hederacoside C and the sum of thymol and carvacrol in the syrup is 0.3 and 0.13 *mg/ml*, respectively.

Standardization: Standardization was done by determining hederacoside C and the sum of thymol and carvacrol. Four standard concentrations range 40-200 *µg/ml* hederacoside C were prepared in methanol and injected into high-performance liquid chromatography. The calibration curve for hederacoside C was constructed at five concentration levels. To develop the calibration curve for thymol, solutions of pure thymol in ethanol (25-100 *µg/ml*) were used. The absorbance of thymol at 455 *nm* was measured after the reaction to potassium hexacyanoferrate and then extraction with chloroform. The calibration curve was drawn according to the absorbance of thymol at 455 *nm*.

Method and features of the device: The high-performance liquid chromatography analysis was performed using a Knauer Azura system, equipped with a binary pump, column compartment, and UV detector. The high-performance liquid chromatography separation was achieved on a Nucleodur-C18 (250×4.6 *mm*, 5*μm*) at ambient temperature. Optimal separation of hederacoside C was achieved using linear gradient elution with Acetonitrile: Phosphoric acid (99.8:0.2) (eluent A) and Water: Acetonitrile: 0.2 M Phosphoric acid (88:14:2.4) (eluent B). The gradient elution was started with A, from 8 to 27% in 40 *min* and then 27 to 100% in 10 *min* at a flow rate of 1.0 *ml/min*. The chromatogram was obtained at 205 *nm*.

Study participants, inclusion and exclusion criteria: This study was a randomized, controlled, double-blind clinical experiment on children aged 1 to 12 years who had an unexplained cough. Patients were referred to the pediatric clinic at Kashan's Shahid Beheshti Hospital to have their clinical symptoms assessed. The patients and their parents were then informed about the study procedure, length, and research aims and offered the chance to fill out a written informed consent if they so desired. The inclusion criteria were acute cough lasting fewer than three weeks and ranging from 1 to 12 years of age. Exclusion criteria included allergies to dextromethorphan or thyme and ivy, the need for specific and aggressive remedies, fever, taking antibiotics, and participation in other studies within the previous 15 days. The patients had the right to withdraw throughout the research and did not pay any fees associated with the visit and medicine.

Ethical considerations: This research was approved by the Medical Ethics Committee of Kashan University, Iran (IR.KAUMS.NUHEPM.REC.1398.055) and registered in Iranian Registry of Clinical Trials with the number IRCT20200908048662N1.

Sample size: The sample size was determined using the Hosseini et al. study [*Hosseini F et al., 2016*]. The percentage of children who were completely free from cough in the diphenhydramine group was 11.5 percent (P1) and 38.5 percent (P2) in the herbal syrup group with 95% confidence and 90% test power computed as 46 people.

Study design: One hundred and forty-two patients were allocated to herbal treatment or control groups using the replacement block method (block size four) hidden in consecutively numbered envelopes [*Behbahani M et al., 2018*]. Patients received 5 *mL* every eight hours for four days. The drugs were packed, formed, and tested identically in both treatment groups. The content of the medicine was unknown to both the patient and the physician. At the start of the experiment, 24, 48, and 96 hours later, the frequency and severity of cough were evaluated using a visual analog scale, with scores ranging from 0 to 10 (0 = no discomfort, 10 = maximum pain). Outcomes of recovery rate were classified into three patterns: fully, partially, or no recovery. A physician conducted clinical evaluations of patients at the start and end of the experiment, with additional assessments completed over the phone.

Statistical analysis: The Kolmogorov-Smirnov test was applied to examine the normal distribution of data. Independent chi-square and t-tests were used to compare two groups, while repeated measures analysis of variance was used for multivariate analysis using SPSS v17.0 software (SPSS, Inc.).

Results

Standard curve: The standard curve of hederacoside C was obtained using high-performance liquid chromatography within the concentration of 40 to 200 *μg/ml* (y=26157.6x+133274, R2=0.999). According to the absorption values of thymol in the spectrophotometer, the standard curve was drawn in the concentration range of 25 to 100 *μg/ml* (y=1.3705x+0.055, R2=0.998). The quantity of hederacoside C and the total of thymol and carvacrol in one milliliter of the syrup were determined to be 0.36 and 0.17 *mg*, respectively, using the standard curve.

Formulation uniformity: Analysis of organoleptic properties (e.g. color, taste, odor) and visual inspection of physical stability (e.g. signs of caking, ease of pouring/redistribution, microbial growth), analysis of pH and assay was evaluated during six months under accelerated conditions (40°C and 75% humidity). The results revealed no significant changes throughout the storage period.

Microbial control: The results of microbial tests of the syrup were the same in the zero, third, and sixth months. Salmonella and Escherichia coli tests were negative. Total aerobic microbial count and total molds and yeast enumeration were $n \leq 10^2$ and $n \leq 10$, respectively.

Demographic characteristics: Finally, this study followed 83 children with acute cough, including 38 girls and 45 boys, until the end of the

study (Fig. 1). There was no significant difference in the demographic characteristics of children and parents between the two groups (Table 1).

Frequency and severity of cough: At the beginning of treatment, 69.8% of patients in the dextromethorphan syrup group and 57.5% in the herbal group had a single cough. Both groups had 20.9% and 35.1% of sputum cough, respectively. In addition, 23.3% and 47.5% of patients in the dextromethorphan and herbal groups used antibiotics, respectively.

The results of the initial examination showed that the frequency of cough, duration of cough, type of cough, fever, and cough episodes were not statistically significant between the two groups ($p<0.2$), while there were considerable differences in antibiotic use ($p=0.02$; table 2).

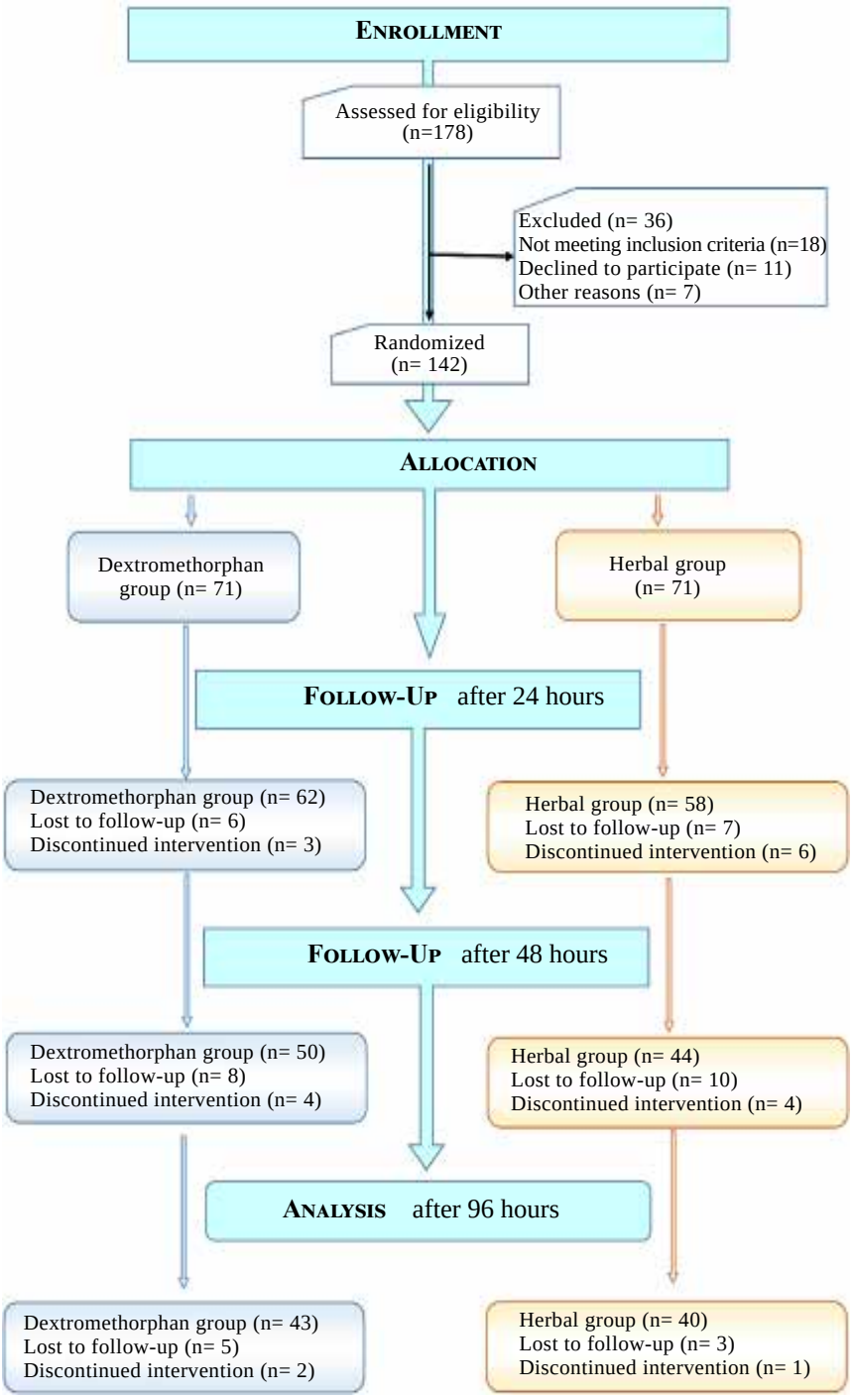

FIGURE 1. *The CONSORT flow diagram of participants*

The mean score of cough severity in the dextromethorphan syrup group was 5.19 at the start, decreasing to 3.45, 1.88, and 1 at 24, 48, and 96 following hours, respectively. In the herbal group, the mean cough severity score was 5.8 at the beginning of the study, but it dropped to 4.6, 2.6, and 0.73 at 24, 48, and 96 hours, respectively. Data analysis showed that the effect of time on changes in cough severity score was significant ($p<0.001$). In addition, there was a significant interaction effect of time and groups on changes in cough severity ($p=0.004$). The cure rate of cough in the dextromethorphan syrup group after 96 hours was 80.7%, while this efficacy was 87.4% in the herbal group (Table 3; fig. 2).

After 24 hours of treatment, 14% complete recovery was seen in the dextromethorphan group, and after 48 and 96 hours, it increased to 44.2% and 72.1%, respectively. In the herbal group, complete recovery at the mentioned times was 2.5%, 27.5%, and 75%, respectively. There was no statistically significant difference between the recovery rates of the two treatment groups after 24, 48, and 96- hour treatment ($p<0.14$; table 4). Using antibiotics was 37.2%, 37.2%, and

Table 1

Children's and parents' sociodemographic characteristics in the dextromethorphan and herbal groups

Status	Groups Parameters n(%)		p-value
	Dextro-methorphan	Herbal	
Age (months)[a]	56.07 ± 34.4	58.4 ±30.1	0.74**
Gender			
Female	18 (41.9)	20 (50)	0.51*
Male	25 (58.1)	20 (50)	
Paternal education			
Illiterate	0 (0)	1 (2.5)	0.66*
Elementary school	6 (14)	4 (10)	
Middle school	11 (25.6)	9 (22.5)	
High school	8 (18.6)	12 (30)	
University studies	18 (41.9)	14 (35)	
Maternal education			
Illiterate	0 (0)	1 (2.5)	0.49*
Elementary school	5 (11.6)	3 (7.5)	
Middle school	3 (7)	7 (17.5)	
High school	17 (39.5)	14 (35)	
University studies	18 (41.9)	15 (37.5)	
Paternal employment			
Unemployed	1 (2.3)	0 (0)	0.88*
Self-employed	26 (60.5)	23 (57.5)	
Government employee	11 (25.6)	13 (32.5)	
Worker	1 (2.3)	2 (5)	
Military	3 (7)	2 (5)	
Other	1 (2.3)	0 (0)	
Maternal employment			
Homemaker	31 (72.1)	36 (90)	0.05*
Self-employed	2 (4.7)	2 (5)	
Government employee	10 (32/3)	2 (5)	
Smoking status			
Yes	0 (0)	1 (2.5)	0.48*
No	43 (100)	39 (97.5)	
Parental smoking status			
Yes	4 (9.3)	4 (10)	N.S*
No	39 (90.7)	36 (90)	

Notes: ** - Chi Square test, ** - Independent T test, N.S - Not Significant,* ***a*** *- the average age of patients is represented by "Mean±SD"*

Table 2

Frequency and severity of cough in the dextromethorphan and herbal groups

Variables and Status	Groupsn (%)		p-value*
	Dextro-methorphan	Herbal	
Frequent			
Single	30 (69.8)	23 (57.5)	0.26
Continuous	13 (30.2)	17 (42.5)	
Type of cough			
Sputum cough	9 (20.9)	14 (35)	0.22
Dry cough	34 (79.1)	26 (65)	
Cough time			
Nighttime	13 (30.2)	11 (27.5)	0.92
Daytime	13 (30.2)	14 (35)	
Always	17 (39.5)	15 (37.5)	
Fever			
Yes	14 (33.3)	8 (20)	0.22
No	28 (66.7)	32 (80)	
Taking antibiotics			
Yes	10 (23.3)	19 (47.5)	0.02
No	33 (76.7)	21 (52.5)	
Cough episode			
Second	0 (0)	1 (2.5)	0.22
Minute	18 (41.9)	22 (55)	
Hour	25 (58.1)	17 (42.5)	

Note: ** Chi Square test*

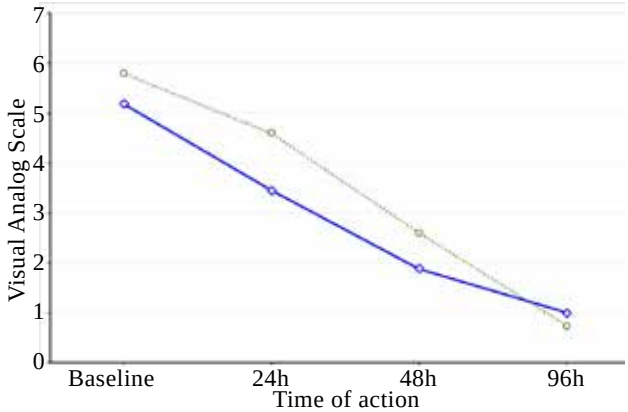

Figure 2. *The mean and standard deviation of the cough severity score in the dextromethorphan (solid line) and herbal (dotted line) groups at 24, 48, and 96-hour treatment.*

TABLE 3

The mean (M) and standard deviation (m) of the cough severity score in the dextromethorphan and herbal groups during the study (*Repeated Measure Test*)

Variable	Dextromethorphan		Herbal	
	IP	M ± m	IP	M ± m
Start	-	5.19 ± 1.75		5.8 ± 1.36
After 24 hours	33.5	3.45 ± 2.21	20.7	4.60 ± 1.82
After 48 hours	63.8	1.88 ± 2.22	55.2	2.60 ± 2.15
After 96 hours	80.7	1.00 ± 2.14	87.4	0.73 ± 1.41
Time effect	<0.001			
The group × time interaction	0.004			

NOTE: *IP - Improvement percent*

25.6% in the dextromethorphan syrup group at 24, 48, and 96 hours, respectively. In addition, this parameter was 52.5%, 52.5%, and 42.5% in the plant group. There was no difference in antibiotic use between the two groups (p<0.11) (data not shown).

DISCUSSION

According to the findings, dextromethorphan and herbal groups significantly reduced the severity of the cough. However, the herbal groups had better effects than dextromethorphan on reducing cough. Although the difference between the two groups was not statistically significant (p=0.139), the dextromethorphan group had a better effect on complete recovery in the first 24 hours of treatment. After four days, the herbal group reached its full potential.

Thyme (*Thymus vulgaris*) and ivy (*Hedera helix*) extracts were the components of the herbal group used in this study. In addition to improving the function of the respiratory system, thyme has anti-inflammatory, analgesic, antimicrobial, relaxing, and immune-boosting effects. In some studies, the combination of thyme and ivy reported similar efficiency [*Mahboubi M, 2018*].

Anti-cough effects of these two plants have been investigated and validated in several studies. The study showed that the efficacy of cough syrup containing thyme extract was 84.6%, while diphenhydramine syrup was 65.4% [*Hosseini F et al., 2016*].

Aqueous alcoholic extract of thyme affected histamine receptors and relaxed airway smooth muscle. These effects may be due to its effect as a competitive antagonist on H1 receptors and stimulation of beta-adrenoceptors [*Shakeri F et al., 2018*].

Schmidt et al. (2012) investigated the effect of syrup containing ivy extract on children with cough and bronchitis using two types of syrup and drops. After 14 days of treatment, the efficacy of the herbal composition on rhinitis, cough, and sputum was 93%, 94.2%, and 97.7%, respectively. The acceptance and tolerance of the drug were 99% in the form of syrup and 100% in the form of drops [*Schmidt M et al., 2012*].

Another study compared the effect of a syrup containing ivy extract as an expectorant to a placebo in children with respiratory diseases associated with sputum cough. The results showed that dry ivy extract improved respiratory capacity and several lung function parameters such as vital capacity, expiratory flow at 25% of forced vital capacity (MEF25), forced mid expiratory flow (MEF25-75) factors [*Zeil S et al., 2014*]. Conrad F. and Kemmerich B. (2006) evaluated the effect of thyme and ivy extracts in patients with acute bronchitis. The effectiveness was measured by counting the number of coughs per day, which after nine days of treatment in the herbal composition group was 68.7%, while in the placebo group was 47.6%. Bronchitis severity scores improved rapidly in both groups. However, the severity score of bronchitis in the two studied groups four days after treatment was 83% against 53.9%, respectively, with 96.2% and 74.7% after ten days. There were no severe side effects [*Conrad F, Kemmerich B, 2006*].

In line with the present study, Schaefer et al. (2016) explored the effects of a dry extract of ivy leaf on cough in adults. They measured cough severity using a visual analog scale. There was a sig-

TABLE 4

Patients' recovery status in the dextromethorphan and herbal groups during the study

Time	Status (%)	Groups		
		Dextro-methorphan	Herbal	p value*
After 24 hours	Complete recovery	6 (14)	1 (2.5)	0.14
	Partial recovery	26 (60.5)	24 (60)	
	No improvement	11 (25.6)	15 (37.5)	
After 48 hours	Complete recovery	19 (44.2)	11 (27.5)	0.31
	Partial recovery	19 (44.2)	23 (57.5)	
	No improvement	5 (11.6)	6 (15)	
After 96 hours	Complete recovery	31 (72.1)	30 (75)	0.36
	Partial recovery	6 (14)	8 (20)	
	No improvement	6 (14)	2 (5)	

NOTE: ** Chi Square test*

nificant reduction in the cough severity in the herbal group compared with the placebo. In addition, no adverse side was observed [*Schaefer A et al., 2016*]. However, studies of the effect of different plants on cough are contradictory. Sutovska et al. (2011) found that the impacts of Althaea officinalis on cough in animal models were negligible compared to codeine. In addition, the biological effects of rhamnogalacturonan isolated from Althaea officinalis root in vitro and in vitro on citric acid-induced cough reflex were different. However, the reactivity of airway smooth muscle was not significantly impressed by rhamnogalacturonan [*Šutovská M et al., 2009; Sutovska M et al., 2011*].

Conclusion

An extract combination of thyme and ivy leaves can minimize the severity and duration of cough in children. As a result, this combination has the potential to be an effective treatment for children's cough.

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CONTENTS

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Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37493 588697 Editor-in-Chief
Fax: (+37410) 582532
E-mail:namj.ysmu@gmail.com, ysmiu@mail.ru
URL:http//www.ysmu.am

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