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Thymus vulgaris ameliorates cough in children with asthma exacerbation: a randomized, triple-blind, placebo-controlled clinical trial

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Abstract
Background: Asthma is one of the most common chronic respiratory diseases with inflammatory involvement and has a high burden worldwide. This study aimed to determine the effect of *Thymus vulgaris* (TV) on cough in children between 5 and 12 years old with mild to moderate asthma exacerbation.
Methods: In this randomized, triple-blind clinical trial, 60 children between the ages of 5 and 12 with asthma exacerbations were randomly divided into two groups. The intervention group (n = 30) was given TV powder at a dose of 20 mg/kg every 8 hours, prepared as syrup, along with routine medical treatment for a week, and the control group (n = 30) received only routine medical treatment with placebo syrup. At the end of the week, clinical and laboratory symptoms, and spirometry data were re-recorded for both groups. Finally, the recorded factors were compared and statistically analyzed.
Results: The results showed that after the intervention, activity-induced cough reduced, and difference was statistically significant between the two groups (p = 0.042), but the reduction in wheezing and breathlessness had no statistically significant difference. Spirometry data showed a significant difference in forced expiratory volume in 1 second (FEV1) between the two groups after intervention (p = 0.048), but this difference was not significant in FEV1/FVC (forced vital capacity), peak expiratory flow (PEF), and forced expiratory flow at 25–75% of the vital capacity (FEF25–75%).
Conclusion: The results show that TV syrup may be useful as an adjuvant treatment in children with asthma exacerbations.

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Introduction

Asthma is a chronic inflammatory disease of the airways in which immune cells, such as mast cells, eosinophils, and lymphocytes, play a pivotal role in its development. Recently, its prevalence has increased in several countries. This disease is one of the most significant causes of student absences and leads to academic failure. Inflammation creates recurrent symptoms, such as wheezing, breathlessness, chest tightness, and coughing in sensitive individuals. Asthma is one of the main causes of chronic cough in both children and adults.[1-4] Various plants have been used as antitussives since ancient times, and their effects and side effects should be investigated.[5] Thymus vulgaris (TV) is a herbal medicine belonging to the *Lamiaceae* family that has several pharmacological properties. TV is a herb with many branches and goes up to 30 centimeters in height. It grows in hilly regions between stones and in European countries in particular. Fourteen Thymus species grow in many mountainous regions of Iran.[6]

The flower and its leaves are the most useful parts of a TV plant.[7] The plant's most important component is its essential oil, which is found in its leaves at a rate of 1–2.5%. Thymol and carvacrol are the two major components of its essential oil, accounting for 30–70% and 15–30% of the oil, respectively.[8] The essential oil has antibacterial, antitussive, and expectorant properties.[9] It also has an anti-inflammatory effect on the tracheal smooth muscle, and a spasmolytic effect on the bronchial tissue, and even increases mucociliary activity.[10] According to several pharmacological properties, due to its therapeutic effects on the respiratory system, many products, such as syrups, have been prepared from it.[9] Considering the effect of asthma on physical health, the present study was conducted to investigate the effects of TV on cough in children with asthma attacks aged between 5 and 12 years who were referred to the Asthma and Allergy Clinic of Ardabil University of Medical Sciences.

Materials and methods

Study design, setting, and participants

This study was a randomized, triple-blind, placebo-controlled clinical trial on 60 children aged 5–12 years with asthma exacerbations from March 2020 to March 2021 at the Asthma and Allergy Clinic of Ardabil University of Medical Sciences. The inclusion criteria included children of 5–12 years of age suffering from an asthma exacerbation, and the consent of the children's parents was also obtained to participate in the study. Children with severe asthma exacerbations and severe dyspnea who needed to be admitted to the hospital were excluded from the study. It was due to the lack of permission of the "Ethical Committee" and because of probable unknown risks in this group. Also, children with a history of cardiac, metabolic, neurologic, and other chronic illnesses were also excluded. This study was approved by the Ethics Committee of Ardabil University of Medical Sciences, Ardabil, Iran, with Ethics code: IR.ARUMS.REC.1398.242 and IRCTID: IRCT20200505047310N1.

Sample size

The participants were enrolled in the study by using convenience sampling. The sample size with a 95% confidence level and an error of 0.04 was considered for 48 patients. To make it more prominent, the sample size was increased to 60 patients, a 20% increase.

Randomization and Concealment

Fixed-size block randomization was used to divide the patients into either TV or placebo groups (30 participants each). A random sequence was produced by the Randlist 11 software package. The drugs and the placebos were given in the form of syrups of similar size, shape, and color by Etemad Tabiat Peyk Shafa Co. To maintain secrecy, a person not from the research team coded the syrups (A and B), put them in the closed and dark packet, and in accordance with the randomization list, numbered them sequentially. In this research, the participants, the physician (clinical evaluator), and the statistician were not disclosed to the types of medication.

Preparation of TV syrup

The plant used in this study was "Thymus vulgaris L." from the "Lamiaceae" family, and its leaves were used to prepare the syrup. First, the plant was bought, identified by a pharmacognosy professor, from a local market in Ardabil (northwest of Iran). The plant was cleaned, washed, and dried in shadow and a coarse powder was prepared from it. The total aqueous extract of the plant was prepared by the maceration method.[11]

The coarse powder of the plant material was soaked in a solvent in a container. After 3 days, the macerated mixture was filtered to separate the plant material from the liquid. The solution was then homogenized and finally pasteurized. The thyme syrup was obtained after the process. Thyme syrup was stored in dark-colored bottles. The dose of the plant was determined and standardized based on its aqueous extract. After preparing the syrup, microbial examinations were done to ensure their safety for clinical use at Ardabil University of Medical Sciences (ARUMS). A voucher specimen (ARD-L1) has been deposited in the herbarium of the School of Pharmacy at ARUMS, Ardabil, Iran. Non-absorbable stevia drops, sweetener, and permitted food colors were used to prepare placebo syrup.

Herbal and placebo syrup components

Thyme syrup contained an aqueous extract of *Thymus vulgaris* leaves that was standardized by the phenolic compound based on thymol (0.2 mg/cc) and sugar (3 g/120 cc). The placebo syrup contained sugar (3 g/120 cc), brown coloring additive, and 1% thyme distillate.

Standardization

The thyme syrup was standardized by the phenolic compound based on thymol via the high-performance liquid

chromatography-ultra-violet (HPLC-UV) method.[12] Based on the HPLC-UV method, the total phenol content (thymol-based) in the thyme aqueous extract was 0.2 mg/cc.

Study protocol

In this randomized triple-blind clinical trial, 60 children, between 5 and 12 years of age, with asthma attacks were randomly divided into two groups (30 for the intervention group and 30 for the control group). After obtaining written consent from the parents, general and anthropometric information (height and weight) and cough, fever, wheezing, and other symptoms of the respiratory system were collected. The stepping of previous asthma maintenance therapy and the definition of the severity of asthma exacerbations for each patient were according to the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3).[13]

According to the severity of dyspnea, physical examination parameters and spirometry parameters (FEV1/PEF) and the condition of exacerbation in patients were divided into mild, moderate, and severe

At the beginning of the study, a spirometry test was performed on the patients. To definitively confirm asthma, salbutamol spray was used, and after half an hour, spirometry was performed again. If confirmed, the patients were included in the study. Then, for one week, the intervention group was given the prepared TV syrup at a dose of 20 mg/kg every 8 hours a day along with the routine medical treatment (salbutamol ± prednisolone), and the control group only received the routine medical treatment along with a placebo. At the end of one week, the changes in clinical symptoms and spirometry data were re-recorded in both groups. The consolidated standards of reporting trials (CONSORT) flow diagram of the study is illustrated in Figure 1.

Data collection tools

Demographic data, and medical and clinical characteristics of participants were collected through an interview with patients, which included taking a medical history, a physical examination, and a test of pulmonary function by spirometry. The collected data were noted in a researcher-made questionnaire.

Statistical analysis

SPSS version 25 software was used to perform statistical calculations. Age-related information was expressed as the

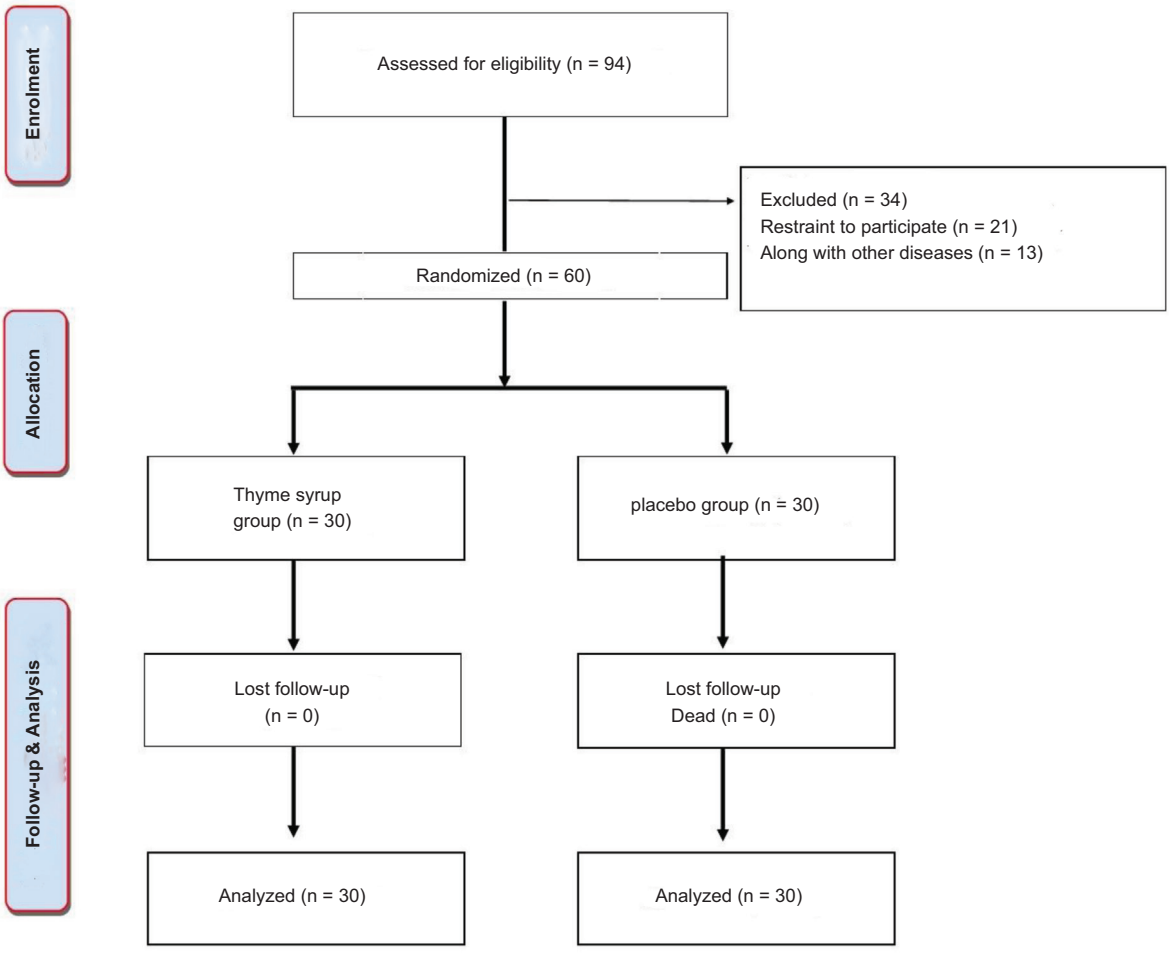

Figure 1 Consolidated standards of reporting trials (CONSORT) flow diagram of the study.

mean ± standard deviation. The normal distribution of data was checked by the Kolmogorov–Smirnov test.[14] A comparison of two groups with a normal distribution was made using an independent T-test, and an intra-group comparison before and after was done with a paired T-test. Furthermore, Mann–Whitney and McNemar tests were used for variables with a non-normal distribution. The Chi-square test was also used to check the relationship between treatment results and qualitative variables. The significance of the results was accepted with a $P < 0.05$.

Results

In this study, 60 patients were included. The mean age of the children was 8.1 ± 2.06 years. The minimum age of the patients was 5, and the maximum was 12. The mean age of children in the TV group was 8.07±2.1 and the placebo group was 8.13±2.047 years. Thirty-three (55%) of the participants were boys, and 27 (45%) were girls. Sixty percent of placebo-group patients were boys, while there was no gender difference in the TV group (50% boys and 50% girls). The mean body mass index (BMI) of children in the TV group was 18.06±2.38 and in the placebo group was 18.79±2.81. The average diagnosis time period of children in the TV group was 2.48 ± 1.50 years, and in the placebo group it was 2.88 ± 1.89 years.

Of the studied patients, included: 6 (10%) were skin prick test positive (of the 10 tested patients), 33 (55%) patients had a history of parental asthma, 55 (91.7%) patients had allergic rhinitis symptoms, 9 (15%) patients had an atopic eczema history, and 34 (56.7%) patients had a history of gastroesophageal reflux. Also, 32 (53.3%) patients had a history of exposure to smoking. Asthma maintenance therapy among the studied patients: 5 STEP 1 (8.3%), 14 STEP 2 (23.3%), 19 STEP 3 (31.7%), 10 STEP 4 (16.7%), and 12 (20%) patients were newly identified. According to the Mann–Whitney test, the two groups did not have a statistically significant difference in terms of the STEP of the disease ($p = 0.64$).

Coughs after activity

Patients were evaluated at the beginning and at the end of the study in terms of their coughs after the activity. At the beginning of the intervention, all patients had a cough after moderate physical activity. At the end of the intervention, 5 patients in the case group (16.7%) and 12 patients in the control group (40%) had a cough after moderate physical activity. According to the McNemar test, cough after activity in both groups was significantly reduced compared to the beginning of the study. When comparing the changes between the two groups, the chi-square value obtained by comparing the frequencies of both groups at the end of the intervention in the variable of cough after an activity is equal to 4.02, which is statistically significant ($p = 0.042$). The results are presented in Table 1.

Shortness of breath

At the beginning of the intervention, all patients had shortness of breath. At the end of the intervention, 5 patients in the TV group (16.7%) and 7 patients in the placebo group (23.3%) had mild shortness of breath. According to the McNemar test, shortness of breath in both groups was significantly reduced compared to the beginning of the study. In the comparison of the changes between the two groups, the chi-square value obtained by comparing the frequencies of the TV and placebo groups at the end of the intervention is equal to 0.42, which is not statistically significant ($p = 0.37$). The results are presented in Table 2.

Table 1 Cough after moderate activity at the end of the intervention in the groups.

Groups		Cough		x2	P-value*
		Yes	No		
Placebo	Frequency	12	18	4.02	0.042
	Percentage	40%	60%		
Thyme	Frequency	5	25		
	Percentage	16.7%	83.3%		

*P<0.05 was significant

Table 2 Shortness of breath at the end of the intervention in the thyme and placebo groups.

Groups		Results		x2	P-value*
		Yes	No		
Placebo	Frequency	7	23	0.42	0.37
	Percentage	23.3%	76.6%		
Thyme	Frequency	5	25		
	Percentage	16.7%	83.3%		

*P<0.05 was significant

Wheezing

When comparing the changes between the two groups, the chi-square value obtained by comparing the frequencies of the case and control groups at the end of the intervention in the wheezing variable is equal to 0.88, which was not statistically significant (p = 0.266).

Spirometry parameters

Spirometry was performed at the beginning and end of the intervention for the patients, as shown in Table 3. The presented results show that based on the independent t-test at the beginning of the intervention, there was no significant difference in FEV1 (Forced Expiratory Volume in the First Second), FEV1/FVC (Forced Vital Capacity) PEF and FEF25-75 in the two study groups, while at the end of the intervention, there was a significant difference in FEV1 between the two groups (p = 0.048). There was no significant difference in other variables. Also, based on the paired t-test, the results of all spirometry findings were significantly increased compared to the beginning of the treatment. The results are presented in Table 3.

Discussion

In this randomized, triple-blind, placebo-controlled clinical trial study, 60 patients (30 people in each control and placebo group) were included. The results showed a statistically significant difference between the two groups after the intervention in cough after activity. In this study, the results of spirometry after the intervention showed a significant difference in FEV1 between the two groups, but this difference was not significant in FEV1/FVC, PEF, and FEF25-75. It is probably due to the short duration of the study or the simultaneous use of other prescribed drugs. In line with the present study, Boskabady et al.[15] study aimed to investigate the bronchodilatory effect of TV extract compared to theophylline in children with asthma and showed that thyme extract significantly increased all PFT values. According to the results of this study, TV showed a bronchodilatory effect in asthma patients comparable to the effect of theophylline, but with a longer duration, which is consistent with the results of the present study. In line with the present study, the study of Korani et al.[16] to investigate the effects of TV on clinical symptoms, pulmonary function tests, and oxidative stress in patients with chronic obstructive pulmonary disease (COPD) showed that FEV1 increased significantly after two months of treatment. This is consistent with the results of the present study on improving clinical symptoms and increasing FEV1 in asthmatic children. In line with the results of the present study, the clinical trial of Ranjbar et al.[3] in patients with acute and dry cough showed that TV essential oil has an acceptable therapeutic effect in suppressing acute cough. In line with our study, Alizade et al. analyzed the effectiveness of long-term (two months) use of Shirazi Thyme on spirometry parameters and inflammatory cytokine levels in asthmatic patients in a randomized clinical trial.[17] They confirmed the significant effectiveness of long-term use of thyme in asthma maintenance therapy, as we showed the effectiveness in asthma exacerbations.

Although asthma and bronchitis have different pathophysiologic and inflammatory conditions, many studies have investigated the therapeutic effect of thyme on cough and its anti-inflammatory effect on acute bronchitis. In a clinical trial study,[9] which was conducted to investigate the therapeutic effect of the combination of TV and primrose root in the treatment of acute bronchitis symptoms in adults, a decrease of 67.1% in the average cough after treatment with this combination was observed. In another similar study,[18] where the combination of ivy leaves with TV was used in the form of syrup in the treatment of acute bronchitis, a 68.7% decrease was observed in the average cough after 7–9 days of treatment with this combination, which was statistically significant. In contrast, Bayat et al.[19] showed that consumption of TV drops by 60 patients with chemical bronchitis was not helpful in improving the clinical symptoms, such as cough, sputum, shortness of breath, and spirometry values. The result of this study was not consistent with the results of the present study, which can be due to the difference in the statistical population of the two studies. It seems that the creation of fibrotic changes in the airways has prevented the effect of TV in these patients. TV extract improves antioxidant potential and thus helps prevent oxidative stress.[20,21] Research shows that

Table 3 Comparison of the average spirometry parameters of patients with asthma exacerbations between the two study groups.

Variables	Measurement steps	Thyme group	Placebo group	P-value*
FEV1 (liter)	At the beginning	1.65±0.36	1.59±0.18	0.43
	At the end	1.98±0.38	1.77±0.45	0.048*
P-value		0.002**	0.049**	
FEV1/FVC (%)	At the beginning	0.88±0.09	0.88±0.07	0.99
	end of study	0.95±0.07	0.94±0.16	0.99
P-value		0.002**	0.044**	
PEF	At the beginning	2.77±0.66	2.89±0.96	0.56
	At the end	3.99±0.83	3.68±1.11	0.22
P-value		0.001**	0.00**	

*P<0.05 was significant

there are compounds in TV extract that inhibit cyclooxygenase enzymes and reduce oxidative stress.[22] It also has an anti-inflammatory effect on tracheal smooth muscle, and a spasmolytic effect on bronchial tissue, and even increases mucociliary activity.[10,23,24] Zhou et al. also stated that thymol reduces hyperreactivity and allergic inflammation of respiratory tracts by reducing the infiltration of inflammatory cells, Th2 cytokines, and ovalbumin (OVA)-specific IgE and suppressing NF-κB.[25]

These findings indicate that thymol in TV can potentially be used as a drug in the treatment and reduction of asthma symptoms. But the limitations of the present study were the lack of adequate direct monitoring of the correct use of drugs in patients (study was outpatient) and receiving a full dose of salbutamol± prednisolon by the patients (since the patients were in the attack phase). Maybe because of the latter limitation, there was no significant difference between the two groups at the end of the intervention regarding the FEV1/FVC, PEF, and FEF25-75 variables.

Conclusion

The present study showed that TV syrup improved clinical symptoms of asthma exacerbation in children, including cough after activity and spirometry findings as FEV1, but had no significant effect on FEV1/FVC, PEF, and FEF25-75. However, further investigations are suggested to elucidate the effect of herbal medicine on the treatment of asthma manifestations.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author up on reasonable request.

Ethical considerations

This study was approved by the Ethics Committee of Ardabil University of Medical Sciences, Ardabil, Iran with Ethics code: IR.ARUMS.REC.1398.242 and IRCTID: IRCT20200505047310N1.

Competing interests

The authors declare that there are no competing interests.

Funding

Not applicable.

Authors' Contributions

RM conceived the study; EE, AMJ, AA, and RNDA had substantial contributions to the acquisition, analysis, and interpretation of the data. RM and EE drafted the first manuscript. RM supervised the study. RM critically revised the final manuscript for important intellectual content. All authors read and approved the final manuscript.

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