

# Comparison of *Zataria multiflora* Extract Syrup and Diphenhydramine in the Treatment of Common Cold-Induced Cough in Children: A Double-Blind, Randomized, Clinical Trial

Firozeh Hosseini,<sup>1</sup> Hossein Mahjoub,<sup>2</sup> Ali Amanati,<sup>3</sup> Mohammad Mehdi Fazlian,<sup>4</sup> and Iraj Sedighi<sup>1\*</sup>

<sup>1</sup>Department of Pediatrics, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, IR Iran

<sup>2</sup>Department of Statistics, Faculty of Health, Hamadan University of Medical Sciences, Hamadan, IR Iran

<sup>3</sup>Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran

<sup>4</sup>Department of Emergency, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, IR Iran

\*Corresponding author: Iraj Sedighi, Department of Pediatrics, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, IR Iran. Tel: +98-8112640081, Fax: +98-8112640016, E-mail: sedighi@umsha.ac.ir

Received 2015 December 13; Revised 2016 February 26; Accepted 2016 April 17.

## Abstract

**Background:** Management of cold-associated cough is a challenging aspect of supportive care for the common cold for pediatricians and parents worldwide. Herbal compounds have traditionally been used for the treatment of cold-related cough. Among these compounds, *Zataria multiflora* (ZM) has been found to be effective for cough relief.

**Objectives:** The aim of this study is to compare a thyme mixture with diphenhydramine in the treatment of cold-related cough in a double-blind, randomized, clinical trial.

**Patients and Methods:** A total of 52 pediatric patients (2-12 years old) with common colds were included in the study. The patients were randomly divided into two treatment groups: one group received diphenhydramine compound and the other received ZM syrup, each for five days. The severity of cold-related symptoms and the efficacy of each drug were determined seven days later by asking the parents to complete a prepared questionnaire. Sedation, sleepiness, a four-point scale of cough status, and a two-point scale of consumption convenience were also evaluated in these questionnaires.

**Results:** Our results showed that sedation and sleepiness occurred in 30.8% and 19.2% of the patients in the diphenhydramine and ZM groups, respectively ( $P = 0.54$ ). Also, 65.4% and 84.6% of the patients in the diphenhydramine and ZM groups, respectively, reported convenient usage ( $P = 0.10$ ). The patients who received ZM syrup had significantly better outcomes ( $P = 0.036$ ).

**Conclusions:** Herbal compounds, such as ZM mixtures, are acceptably efficacious in cough relief with fewer adverse effects than chemical compounds in the treatment of cold-related cough, especially in infants and younger children.

**Keywords:** Common Cold, *Zataria Multiflora*, Cough, Children

## 1. Background

The cold is one of the most common reasons for pediatric visits to clinics, and it is estimated that each child suffers from an average of 6-8 colds per year. Cough is one of the most frequent complications of a cold, especially in children (1). Herbal compounds and other non-chemical agents are frequently used for symptom relief as an alternative option for patients with a poor response to conventional drugs (2). In the United States, there is a public trend toward the use of these agents for cough or cold (3). These products are currently used to an extent that causes concern about adverse effects and interactions with other agents (4, 5). Many homemade indigenous herb preparations for colds have been weakly evaluated. Previous studies showed inconclusive results for the efficacy of cough medicines in the treatment of cold-related cough in adults and children, and it seems that high-quality research is still

needed to provide evidence-based recommendations for herbal agents (6-8). There have been only four clinical trials that compared cough medicines with placebo in children (9-12).

Among both over-the-counter (OTC) and homemade preparations, thyme has been shown to be effective in the treatment of cold-related cough. The most common variety is *Thymus vulgaris*, which is indigenous in many countries in Europe. *T. vulgaris* is not native to Iran, but is presently cultivated in several parts of this country (especially in the outskirts of the Zagros Mountains in western Iran), and it is widely refined as a tea, spice, and herbal medicine (13, 14). *Zataria multiflora* (ZM; Shirazi thyme) is a thyme-like flowering plant of the Lamiaceae family, and is native to Iran (15). ZM is chemically similar to *T. vulgaris*, and its leaf is listed in the Herbal Pharmacopoeia (15). Many studies have demonstrated the antibacterial and anti-inflammatory effects of ZM extract (16-19). Al-

though there are inconclusive results about ZM products used for the relief of gastrointestinal syndromes, few studies have been carried out on the antitussive effects of this indigenous plant (20, 21).

## 2. Objectives

We conducted the present study to compare a ZM mixture with diphenhydramine in the treatment of cold-related cough in children, using a double-blind, randomized, placebo-controlled clinical trial.

## 3. Patients and Methods

A total of 52 children aged 2 - 12 years with common colds, who were referred to the outpatient pediatric clinics of Hamadan University of Medical Sciences, Hamadan, Iran, were enrolled. We included children with typical signs and symptoms of common cold, after ruling out any similar conditions, such as acute sinusitis or other respiratory tract infections. Additional exclusion criteria included a previous history of antibiotic treatment, chronic concomitant disorders (e.g., asthma), and other coexisting conditions that interfered with our patients' cough self-evaluation (e.g., mental retardation) or with evaluation by their parents (e.g., failure of close observation).

The patients were randomly allocated to one of two treatment groups. One group (n = 26) was given diphenhydramine compound (1.25 mg/kg three times a day) and the other group (n = 26) was given ZM syrup (2 mg/kg three times a day), each prescribed for five consecutive days. The ZM extract was provided by Tolid-Darou, Tehran, Iran. Each child received the drug in an unlabeled bottle. The bottles were pre-numbered in consecutive order according to the patient's time of enrollment. The patients were blinded to the drugs until the end of the study. All clinical evaluations were performed by a single pediatrician who was blinded to the contents of the drugs used.

The parents were asked to complete a questionnaire seven days later about the severity of their child's cold-related symptoms and the efficacy of each drug. These questionnaires also contained parameters such as the induction of sedation and sleepiness (mild to severe), a five-point scale of cough status (completely improved, moderately improved, somewhat improved, not improved, and worsened), and a two-point scale of consumption convenience (good or bad). Demographic data was also obtained.

This study was approved by the ethics committee of Hamadan University of Medical Sciences and Health Services, and informed consent was obtained from all parents.

Statistical analyses were performed on all collected data using SPSS version 13 (SPSS, Chicago, IL, USA). The chi-square test, the Mann-Whitney U test, and student's t-test were used for non-parametric and parametric variables, respectively. P values of 0.05 or lower were considered statistically significant.

## 4. Results

A total of 52 patients (22 females, 30 males) were randomized, and half received the trial medication. The patients had an average age of  $52.55 \pm 28.55$  months, and there was no difference between the genders ( $P = 0.70$ ). The parents' education levels did not differ statistically significantly between the two groups ( $P > 0.05$ ). The patients' weights were  $16.78 \pm 5.6$  kg, with no significant difference between the two groups ( $P = 0.77$ ).

Our results showed that sedation and sleepiness occurred in 30.8% and 19.2% of the patients in the diphenhydramine and ZM groups, respectively ( $P = 0.54$ ). Meanwhile, 65.4% and 84.6% of the patients in the diphenhydramine and ZM groups, respectively, reported convenient usage ( $P = 0.10$ ). In comparison to the diphenhydramine group, cough status statistically significantly improved ( $P = 0.036$ ) in the ZM group (Table 1).

## 5. Discussion

Our data confirmed that the clinical efficacy of *Zataria multiflora* (Shirazi thyme) extract syrup was statistically significant and clinically relevant in decreasing the severity of cold-related cough in children. Herbal compounds with antitussive properties are widely used for the treatment of cold-related symptoms (8, 22). There are considerable differences between countries with regard to the availability and recommended use of traditional and complementary medicine (T&CM), which continues to be a challenging issue in other aspects, such as safety, effectiveness, and quality (8, 23). However, there is an increasing trend toward the use of T&CM in developed countries (24, 25). Despite the worldwide popularity of T&CM, there is little evidence to support its use based on satisfactory clinical trials that evaluate safety and efficacy (8, 26). As previously noted, there have been only a few studies on the use of non-chemical agents in children (4, 8, 27).

The immunopharmacological potential of *T. vulgaris* has been established by various in vitro and in vivo models (28). Meanwhile, in a clinical evaluation, Buechi et al. concluded that thyme herbs are useful for reducing cough in the symptom-score system, with acceptable tolerability for the treatment of common cold, bronchitis, and other

**Table 1.** Cough Status in the Diphenhydramine and ZM Groups<sup>a</sup>

Group	Cough Status				
	Worsened	Not Improved	Somewhat Improved	Moderately Improved	Completely Improved
Diphen hydramine	6 (23.1)	6 (23.1)	4 (15.4)	7 (26.9)	3 (11.5)
Zataria multiflora	0	4 (15.4)	5 (19.2)	7 (26.9)	10 (38.5)

<sup>a</sup>P Value = 0.036.

respiratory tract diseases (29). In contrast, the results of a study by Taylor did not support the use of certain herbs (such as *Echinacea purpurea*) for the treatment of URI symptoms in children (30).

The most recent Cochrane review re-emphasized previous conclusions (22, 31) that there is a “lack of good evidence for or against the effectiveness of over the counter (OTC) medications in acute cough” (8). Some authors explicitly recommend against the use of these medications (7).

To the best of our knowledge, there have been few studies on the usefulness of thyme extract for upper respiratory tract infections. The present study is the first double-blind, randomized, clinical trial of the antitussive effects of *Zataria multiflora* in children (32, 33).

Our study found no side effects from ZM in the treatment of cough in the interventional group, and the parents were satisfied with using ZM for their children.

### 5.1. Conclusion

The results of this prospective randomized clinical trial confirmed the efficacy and safety of ZM in the treatment of cough caused by the common cold.

### Acknowledgments

We would like to thank all of the individuals who participated in this study.

### Footnotes

**Authors' Contribution:** Firozeh Hosseini and Hossein Mahjoub designed the study; Firozeh Hosseini substantially contributed to the data acquisition; Firozeh Hosseini, Hossein Mahjoub, Mohammad Mehdi Fazlian, Iraj Sedighi, and Ali Amanati performed data interpretation and drafted the manuscript.

**Financial Disclosure:** There is no financial disclosure in relation to this study.

**Funding/Support:** This study was financially supported by the Hamadan University of Medical Sciences.

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