Journal of Integrative Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Integrative Medicine

journal homepage: www.jcimjournal.com/jim
www.journals.elsevier.com/journal-of-integrative-medicine

Review

Management of acute cough by *Zataria multiflora* Boiss as an alternative treatment

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ARTICLE INFO

Article history:
Received 28 June 2017
Accepted 22 August 2017
Available online xxxx

Keywords:
Zataria multiflora
Foeniculum vulgare
Althaea officinalis
Cough
Medicine, Iranian traditional

ABSTRACT

Cough, as a defensive reflux mechanism, removes foreign objects and secretions from bronchi and bronchioles of airways. *Zataria multiflora* is a popular plant for treatment of cough in Iranian traditional medicine. The aim of this review was to evaluate the potency of *Z. multiflora* as an alternative treatment in management of acute cough and its possible mechanisms of action. Here the authors compiled information about *Z. multiflora* in the treatment of cough from all accessible resources and books. The results of this investigation showed that there were five clinical studies that evaluated the efficacy of *Z. multiflora* essential oil or extract alone ($n = 1$), in combination with *Althaea officinalis* ($n = 2$) or *Foeniculum vulgare* essential oil ($n = 1$), in the form of syrup ($n = 3$), oral drop ($n = 1$) and soft capsule ($n = 1$), for the treatment of acute cough in comparison with placebo or synthetic drugs (bromhexine, dextromethorphan and clobutinol). All clinical studies confirmed the efficacy of *Z. multiflora* in the amelioration of acute cough in pediatric ($n = 1$) and adult patients ($n = 4$) without any adverse effects. Different mechanisms, such as anti-inflammatory, analgesic, antimicrobial, relaxant and immune-enhancement, may be responsible for the efficacy of *Z. multiflora* in cough relief. Other clinical trials can be performed with *Z. multiflora* in combination with ivy leaf extract or primrose root extract on patients with cough.

Please cite this article as: Mahboubi M. Management of acute cough by *Zataria multiflora* Boiss as an alternative treatment. *J Integr Med.* 2017; xx(x): xxx–xxx

Contents

1. Introduction

The respiratory system's special structure (pharynx, nasal cavity, trachea, larynx, bronchi, bronchioles and lungs) facilitates the passage of oxygen into the body, and therefore, it plays a critical role in obtaining energy and maintaining active metabolism in all tissues. Respiratory diseases can impact public health and quality of life and in some cases, cause death. Colds, sinusitis, pharyngitis, tracheitis, epiglottitis, bronchitis, chronic obstructive pulmonary diseases (COPD) and asthma are the most common diseases that adversely affect a nation's economy.

Cough is one clinical symptom common to these diseases that need medical attention and annually imposes high expense. Cough is an essential function of the respiratory system and protects the airways and lungs from contamination and pollution. Cough receptors of the respiratory tract are sensitive to mechanical and

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https://doi.org/10.1016/j.joim.2017.12.006
2095-4964/

chemical stimuli. Without cough, the body cannot expel mucous discharge, infections and atelectasis. Cough is the reason for 10%–38% of visits to pulmonologists. Cough is categorized into acute, subacute and chronic groups. Acute cough is frequently due to upper respiratory tract infections with durations of less than three weeks; chronic cough is persistent, continuing more than three weeks. Postnasal drip or *catarrh* is the most common reason for chronic cough, while viral common cold, acute bacterial sinusitis, pertussis, exacerbation of COPD and allergic rhinitis are the most common causes of acute cough [1]. Viral infections of the upper respiratory system are the most common cause of cough. Antitussives, antihistamines, bronchodilators, pharyngeal demulcents, expectorants, mucokinetics and mucolytics are used for the treatment of cough. Treatment of cough with chemical agents is often associated with disagreeable symptoms such as dizziness, drowsiness, nausea and vomiting [2] and many expensive treatments do not have better effects than placebo. Finding suitable alternative natural treatments is one approach to managing cough. Therefore, the aim of this review was to evaluate the efficacy of *Zataria multiflora* Boiss in management of acute cough and explore its possible mechanism of action.

2. Cough definition in Iranian traditional medicine

In Iranian traditional medicine, cough was called *Seal* and described as a movement from the chest and lung that sought to expel anything that annoyed the body. Also, Iranian traditional practitioners believed that diseases in other organs, including the stomach, liver, spleen, etc. could cause cough. They sometimes treated other organs to resolve symptoms of cough. The formation of a cough involves the lung and other organs (esophagus, lower esophagus sphincter, liver, spleen and breast), and may be stimulated by many external causes such as cold weather, cold water, warm weather, dry weather, smoke and food taste (sour, spicy and astringent) [2]. Cough could be the result of warming the blood in the liver and sending this blood to the lungs. Dry cough is the result of cold, hot temperament and simple constipation. Sometimes, it can occur in the early phase of hot edema in the lungs or liver, but rarely in spleen. Entrance of dust and smoke into lungs is the cause of dry coughs [3–5]. According to Avicenna (Ibn Sina) (980–1037), cough appears in three forms: sudden cough, continuous cough and old cough [6].

3. *Z. multiflora*

Ephedra sinica Staph, *Thymus vulgaris* L., *Echinacea purpurea* L., *Echinacea angustifolia* DC. and *Z. multiflora* can be used for treatment of respiratory infections and cough [7]. Among them, *Z. multiflora* is the most well known for its use in the treatment of cough. *Z. multiflora* has the same property as *T. vulgaris* [8,9]. *Z. multiflora* of best quality comes from Iran.

According to Iranian traditional medicine, there is a strong relationship between warm and cold temperament and activity of sym pathetic–parasympathetic systems. Therefore, the food temperament can have an effect on chemical, hormonal and functional factors of body [10]. *Z. multiflora*, in Iranian traditional medicine, was considered to be a warm tempered spice and had a typical dose of 5 g [6]. For improving the efficacy of herbal medications, *Z. multiflora* is prescribed alone or with other plants. In Iran, *Z. multiflora* aerial parts were traditionally used as anthelmintic, antiasthmatic and carminative and for the treatment of colic, sinusitis, menstrual pains, dysmenorrheal and dyspnea conditions [11]. *Z. multiflora* leaves were also used as an antitussive and for the treatment of early stage asthma and hiccup [12]. *Z. multiflora* is traditionally used for fever, flatulence, pregnancy pain, rupture, bone pain, gastrodynia, headache, common cold, migraine, hemostatic, diarrhea, vomiting and joint pain [13]. Although the uses of *Z. multiflora* have been synthesized in one review [14], there has been insufficient focus on the potency of this valuable plant in treatment of cough. In this review, we explored the potencies of *Z. multiflora* extracts (essential oil and ethanol-aqueous extract) in the treatment of cough, especially its therapeutic effects on cough owing to common cold, laryngitis, tonsillitis, bronchitis and pertussis.

4. *Z. multiflora* for treatment of cough

The efficacy of cough treatment with *Z. multiflora* essential oil or its aqueous-ethanol extract, in combination with other plant extracts, was the subject of some clinical studies [15–19].

In one clinical trial [19], the efficacy of *Z. multiflora* aqueous-ethanol extract syrup (2 mg/kg, 3 times per day) and diphenhydramine (1.25 mg/kg, 3 times per day) for 5 d were evaluated on 52 pediatric patients (2–12 years old) with acute cough related to the common cold. The questionnaire including cold-related symptoms, the mild to severe sedation and sleeplessness, the status of cough improvement and the patient's satisfaction was used. There was no difference in age, gender or education levels at the baseline. After treatment, the corresponding patient's satisfaction rates were 65.4% and 84.6% ($P = 0.1$), respectively. Cough status significantly improved in *Z. multiflora* extract syrup group compared with diphenhydramine group ($P = 0.036$). About 23.1% of patients in the diphenhydramine group reported exaggerated cough, 23.1% reported no improvement, and only 11.5% and 26.5% of patients improved completely or moderately, respectively. The corresponding amounts for exaggerated, no improvement, complete or moderate improvement were 0%, 15.4%, 38.5% and 26.9% in *Z. multiflora* extract syrup groups, respectively. No side effects were reported among patients in *Z. multiflora* extract syrup groups.

In another study [15], the efficacy of *Z. multiflora* extract in combination with *Althaea officinalis* extract (*Bronchobarij* syrup, Barij Essence Pharmaceutical Company, Kashan, Iran) has been evaluated in the treatment of cough. A syrup was made from *Z. multiflora* aqueous-ethanol extract and *A. officinalis* extract; it was standardized to contain 2.6–3.1 mg thymol and 24.3–29.3 mg amino acid in each 5 mL of syrup. The antitussive activity of polysaccharides from *A. officinalis* is higher than in dropropizine, a peripherally acting non-narcotic drug [20]. Rhamnogalacturonan is one biological compound from *A. officinalis* that has relaxant effects on the citric acid-induced cough reflex and on airway smooth muscle. The dose-dependent cough suppression effect of rhamnogalacturonan is comparable to the opioid agonist codeine. Also, it has been shown that the antitussive effects of rhamnogalacturonan are independent of its bronchodilatory effects. Although K^+/ATP ion channels are not involved in its antitussive effects, these effects are associated with serotonergic 5-hydroxytryptamine 2 receptors [21]. The efficacy of treatment with herbal or dextromethorphan syrups (3 times a day for 4 d) was evaluated in 200 patients with cough due to common cold. The improvements in cough symptoms were 65.5% and 39.4% in herbal and dextromethorphan syrups ($P = 0.001$), respectively. The results of the study showed that *Bronchobarij* syrup was more effective than dextromethorphan in ameliorating acute cough [18].

In another clinical study, the efficacy of 5 mL syrup from *Bronchobarij* syrup ($n = 78$) on cough was compared with dextromethorphan syrup ($n = 79$). And 157 patients (10–85 years old) with persecutor and idiopathic cough were divided into 2 groups. The severity of cough was evaluated using the Visual Analog Scale (VAS) and a questionnaire at 24, 48 and 72 h after the beginning of treatment. In each stage, complete improvement (cessation of cough), partial recovery (reduction in cough), and

Please cite this article in press as: Mahboubi M. Management of acute cough by *Zataria multiflora* Boiss as an alternative treatment. J Integr Med. (2017), https://doi.org/10.1016/j.joim.2017.12.006