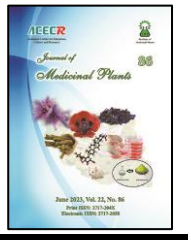
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Research Article

The effect of an Iranian polyherbal formulation on the management of allergic asthma in mice

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ABSTRACT

Background: Asthma is a chronic respiratory ailment characterized by bronchospasm, airway inflammation and hyperresponsiveness, and recurrent episodes of breathing complications. Due to the high incidence of this disease, there has been a surge in the use of complementary branches of medicine such as Iranian traditional medicine (ITM) in recent times. **Objectives:** In this study, the efficacy of an ITM polyherbal formulation (Compound Honey Syrup) in the management of allergic asthma was explored. **Methods:** 60 Balb/c mice were divided into five groups (n = 12) as follows: G1, ovalbumin (OVA)-sensitized; G2, PBS-treated; G3, OVA + oral Compound Honey Syrup; G4, OVA + inhalational compound honey; G5, OVA + inhalational Budesonide. Subsequently, airway hyperresponsiveness (AHR) was assessed using methacholine test, cytokines levels were determined in bronchoalveolar lavage fluid (BALF) and eosinophilia was assayed in blood and BALF. Also, histological transformation of the lungs was analyzed. **Results:** Oral Compound Honey Syrup prevented the development of AHR. Both oral and inhalational Compound Honey Syrup significantly diminished eosinophil counts in blood and BALF specimens. Moreover, both types of Compound Honey Syrup treatments remarkably reduced the levels of IL-5 and IL-13 in BALF and blood samples in comparison to the OVA-received animals ($P < 0.05$). **Conclusion:** The present data show that Compound Honey Syrup is an effective herbal formulation to alleviate asthma-induced inflammatory response and therefore can be a promising remedy for the management of this disease.

Abbreviations: ITM, Iranian Traditional Medicine; OVA, Ovalbumin; AHR, Airway Hyperresponsiveness; BALF, Bronchoalveolar Lavage Fluid; IL-5, Interleukin-5; IL-13, Interleukin-13; CAM, Complementary and Alternative Medicine; PBS, Phosphate-Buffered Saline; H&E, Hematoxylin and Eosin; PAS, Periodic Acid Schiff; TAPP, Type-A Procyanidin Polyphenols; ACA, 19-Acetoxychavicol Acetate; ACQ, Asthma Control Questionnaire

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1. Introduction

Asthma is a serious inflammatory airway disease of chronic nature [1]. In terms of prevalence, 5 to 10 percent of the US population and about 300 million individuals throughout the world suffer from asthma [2, 3]. It is becoming a significant cause of death in developed countries. Patients usually complain of recurring episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and early morning [4]. The disease is associated with variable degrees of chronic inflammation, mucosal hypersecretion, airways obstruction and bronchial hyperresponsiveness [5]. There are other features such as increased smooth muscle mass, enlargement of the bronchial gland, hyperplasia, and metaplasia of goblet cells [6].

The most common approach for asthma management is drug therapy. Short-acting β-agonists, long-acting β-agonists, and inhaled corticosteroids are the major drugs for asthma management. Despite their antiasthmatic use, the underlying pathology of the disease will remain unchanged, which explains the recurrent attacks of asthma in the patients [7]. On the other hand, continued use of these medications can result in a range of side effects such as growth failure, accelerated loss of bone mass, oral candidiasis, dysphonia, tachyphylaxis, and elevated intraocular pressure [8]. These complications have encouraged researchers to find alternative treatments with fewer side effects for asthma. Interestingly, 4 % to 79 % of adults and 33 % to 89 % of children with asthma profit from complementary and alternative medicine (CAM) with breathing techniques and plant-based products being most widely used [9]. Iranian traditional medicine (ITM) is a branch of CAM, which has been practiced in Iran for centuries. It is based on the theory of four humors (Dam, Balgham, Safra, and Sauda). In ITM, the clinical symptoms and pathophysiology of a condition called "*Rabv Balghami*" have been described by ancient scholars in such a way that it conforms to asthma [10, 11].

In ITM, honey has been used for medical purposes since ancient times. The combination of honey, water, and some herbs and spices, known as Compound Honey Syrup, is used for various ailments. The Persian scholars have prepared Compound Honey Syrup with ingredients such as *Zingiber officinale* Roscoe, *Cinnamomum verum* J.Presl, *Crocus sativus* L., *Elettaria cardamomum* (L.) Maton, *Alpinia galanga* (L.) Willd., *Pistacia lentiscus* L., *Myristica fragrans* Houtt., honey, and water for the management of fevers, colic, stomach ailments of cold nature, and the diseases that affect lungs especially "*Rabv Balghami*" or asthma [12, 13]. According to Avicenna recommendations, Compound Honey Syrup has been used as a popular beverage for the treatment of asthma complications [14].

Kaveh, et al. conducted a randomized, double-blinded, placebo-controlled clinical study on 80 patients with asthma to evaluate the therapeutic efficacy of Compound Honey Syrup on the symptoms of these patients [15]. They reported that intervention group had significantly lower asthma-related symptoms than the control group, suggesting the potential anti-asthmatic activity of this drug in adult patients with asthma [15]. Therefore, the goal of this study was to examine the effect of Compound Honey Syrup on histopathological changes of the lungs and inflammatory response of the airways and blood in a mouse model of ovalbumin-triggered asthma (Fig. 1).

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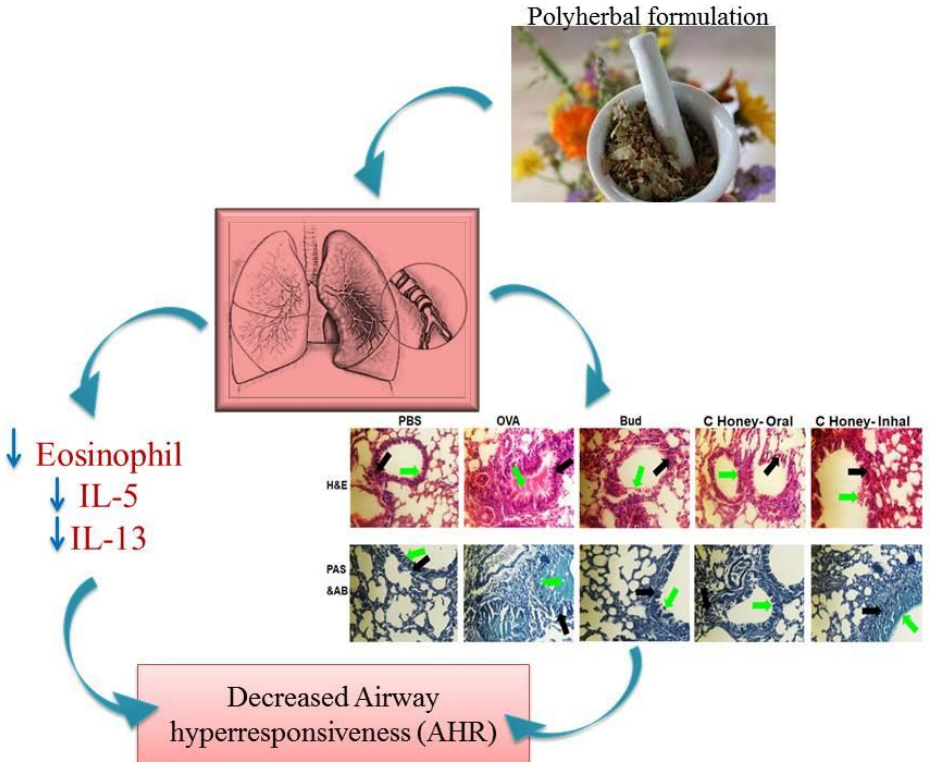


Fig. 1. Graphical representation of the main outcomes of the study.

2. Materials and methods

2.1. Compound Honey Syrup Preparation

Based on ITM recommendations, the type of Compound Honey Syrup used for the management of asthma was commonly made of Honey, Water, *Z. officinale*, *C. verum*, *C. sativus*, *E. cardamomum*, *A. galanga*, *P. lentiscus*, and *M. fragrans* [11, 16, 17]. Fine honey and spices including *Z. officinale*, *C. verum*, *C. sativus*, *E. cardamomum*, *A. galanga*, *P. lentiscus*, and *M. fragrans* were purchased from market of Iran. Thereafter, Physicochemical tests including accurate identification of the herbal materials, determination of total ash, acid insoluble ash as well as microbial tests were performed in accordance with authentic Herbal Pharmacopoeia. The final product was then evaluated based on physical appearance, PH, density, viscosity, mixture dry weight, as well as microbial and fungal control. According to the described daily dosage of the above-mentioned spices in various references such as PDR for herbal medicines, Iranian Herbal Pharmacopoeia, and traditional medicine manuscripts based on ITM practitioner views and current medical findings, the product (Compound Honey Syrup) was prepared. As recommended in PDR, a daily dosage of different herbs was administered as follows: *Z. officinale*, 0.5 g; *C. verum*, 1 g; *C. sativus*, 0.5 g; *E. cardamomum*, 1 g; *A. galanga*, 1 g; *P. lentiscus*, 1 g, and *M. fragrans*, 1 g [15].

For the preparation of Compound Honey Syrup, 1 kg of fine honey plus 2 kg of water were mixed and heated mildly. The foam on the surface was then removed. The process continued until approximately one-third of the mixture evaporated. 37.5 g of each of *C. verum* and *E. cardamomum*, 18.75 g of each of *A. galangal*, *P. lentiscus*, *M. fragrans*, and

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Z. officinale, and 3.75 g of *C. sativus* were mixed and half-grinded. Then, all plant materials were extracted in the boiling water (100 ºC) for 4 hours. The extracts were placed into a cotton cloth and suspended in a container containing water and honey to be fully absorbed by the mixture. The cloth was finally removed; the product was filtered and packed in 250 cc bottles until use.

2.2. Animal model of asthma

60 mice (sex: female, age: 6-8 weeks, breed: BALB/c mice, weight: 20-25 g) were obtained from Pasteur **Institute** of **Iran**. All mice were maintained in an animal house with standard housing temperature, humidity, and 12h light-dark cycle with access to a standard and sufficient diet. Since female mice are more vulnerable to the development of allergic asthma than males, they were selected for our study. This study was approved by ethics committee of Shahid Beheshti University of Medical Sciences (Reference number: IR.SBMU.RETECH.REC. 1396.106).

2.3. Animal treatment schedule

Sixty mice were randomly divided into 5 groups of 12 mice [six mice for histopathological analysis and bronchoalveolar lavage (BAL), six mice for airway hyperresponsiveness (AHR) measurements] follows: G1, PBS challenge (negative control); G2, ovalbumin (OVA) challenge (positive control); G3, OVA challenge + Compound Honey Syrup administrated orally; G4, OVA challenge + inhaled Compound Honey Syrup; G5, OVA challenge + inhaled budesonide administration. The induction of inflammation in the airways of mice was performed in 4 groups by OVA (Sigma-Aldrich, Netherlands), according to a standard program. This process was carried out for 30 continuous days. Initially, the mice in groups G2-G5 were sensitized with an intraperitoneal injection of a solution containing 50 µl of sterile alum solution (adjuvant aluminum hydroxide), 20 µg of OVA, and 30µg of sterile saline on day 1, and 14. Then, the mice were treated with inhaled OVA (8 ml 1 % ovalbumin in saline solution) for 20 minutes by an ultrasonic nebulizer (NE-U07, Omron, Japan) on the 24th, 26th, 28th, and 30th days of the experiment. The mice in the negative control group inhaled PBS solution. Treatment groups (G3-G5) also experienced asthma induction, and then received Compound Honey Syrup and budesonide on days 25, 27, and 29. Group 3 mice received 1 ml/kg Compound Honey Syrup orally, but groups 4 and 5 inhaled 1 % Compound Honey Syrup and 1 % inhaled budesonide solution using an ultrasonic nebulizer for 20 minutes, respectively. Budesonide is a corticosteroid that was used as a standard drug for comparison with the anti-inflammatory effect of Compound Honey Syrup. On the 31st day, half of the mice in each group were anesthetized to collect their blood, BALF, and lung tissues for further analyses. The rest of the animals were used for the Methacholine challenge test. Figure 2 represents a diagram of experimental protocol for animal sensitization and treatments.

2.4. Measurement of airway responsiveness

48 hours after the last OVA or PBS challenge, the Methacholine challenge test was carried out for all groups of animals [18]. The determination of the AHR to Methacholine challenge was done by the estimation of enhanced pause (Penh). In order to obtain a reference Penh value, each mouse was first subjected to Phosphate-buffered saline (PBS) aerosol and then to double concentrations of aerosolized Methacholine [19]. Therefore, a percentage of the PBS Penh value was measured as the relative Penh values.

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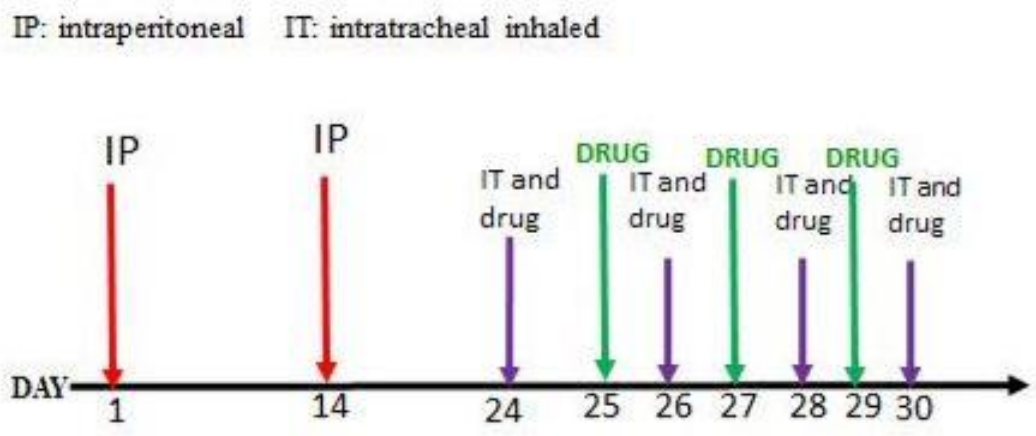


Fig. 2. Diagram of experiment for animal sensitization and treatment. Mice were sensitized by intraperitoneal (IP) injection of 20 µg of ovalbumin along with 50 µl aluminum hydroxide on day 1. The same procedure was repeated at day 14. The sensitized groups of mice were subsequently challenged with inhaled (IT) ovalbumin solution aerosolized on days: 24, 26, 28 and 30. Animals were treated with inhalational Compound Honey, oral Compound Honey Syrup and Budesonide on days: 25, 27 and 29.

2.5. Collection of BALF and measurement of its cytokines level

Urethane (Sigma-Aldrich, USA) was utilized in order to anesthetize the mice. Then, each mouse was tracheotomized and a catheter was inserted into the trachea for the collection of BALF specimens by irrigation of the lung through the trachea with 1 ml of PBS. Thereafter, the BALF cells were collected over cytospin slides, stained with Wright's solution, and differential cell count was done. For the purpose of cytokine analysis, supernatants that were isolated from BALF were subjected to ELISA technique to measure the concentrations of IL-5 and IL-13 in line with the manufacturer's instructions (Abcam, USA).

2.6. Histological Analysis

The lung tissues from euthanized mice were kept apart and fixed in 10 % neutral buffered formalin followed by trimming and embedding in paraffin. The tissue sections were prepared and stained with hematoxylin and eosin (H&E) and periodic acid Schiff (PAS). The ratio of mucus secretion was determined by two pathologists by scoring the intensity of PAS stain in 10 microscopic fields. Using an Olympus B ×50 microscope supplied with a Leica DFC 320 digital camera the photomicrographs were taken.

2.7. Statistical analysis

The results of all experiments represent as means ± SD. The statistical tests used in this current investigation were two-tailed, non-paired, student's *t*-test. Analyses were performed by SPSS software (version 22). The data were considered statistically significant when $P < 0.05$.

3. Results

3.1. Effect of Compound Honey Syrup on airway hyperresponsiveness

According to Figure 3, AHR was significantly augmented ($P < 0.05$) in the OVA-received mice (9.8 ± 0.70) in comparison to negative control (2.5 ± 0.08). On the other hand, oral Compound Honey Syrup was successful in the prevention of AHR development in the OVA-sensitized animals and showed that it acts more effective than budesonide (5.4 ± 0.45) or inhaled Compound Honey Syrup (5.2 ± 0.60).

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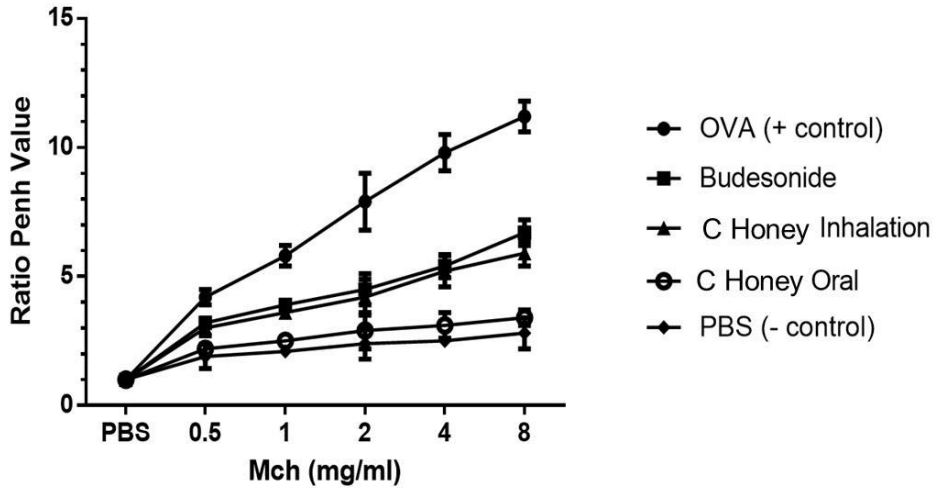


Fig. 3. Effect of drugs on airway hyperresponsiveness measured by enhanced pause (Penh) in response to increasing doses of Methacholine (Mch). Penh values showed an elevation in the ovalbumin (OVA) sensitized mice (OVA, +ve control) versus negative control mice (PBS, -ve control). The effects of oral Compound Honey Syrup, inhalational Compound Honey and Budesonide on airway responsiveness in sensitized and challenged mice are presented. The results are displayed as the means ± S.D. ($P < 0.05$).

3.2. Effect of Compound Honey Syrup on blood and BALF eosinophilia

The occurrence of eosinophilia in the blood and BALF specimens was quantified after staining (Figures 4A and B). OVA sensitization caused a significant amplification in the number of blood eosinophils (5 ± 1.26 versus 0.33 ± 0.51, $P < 0.05$) and BALF eosinophils (68.16 ± 4.87 versus 1.16 ± 1.16, $P < 0.05$) as compared with PBS-treated negative controls mice. On the other hand, the blood eosinophil counts were considerably declined following the administration of oral Compound Honey Syrup (1.33 ± 0.81, $P < 0.05$), inhaled Compound Honey Syrup (2.5 ± 0.54, $P < 0.05$), and budesonide (3 ± 0.63, $P < 0.05$). In addition, OVA-triggered eosinophilia in BALF samples was diminished after treatment of mice with oral Compound Honey Syrup (17.83 ± 5.19 $P < 0.05$), inhaled Compound Honey Syrup (45.66 ± 10.28, $P < 0.05$), and budesonide (37.83 ± 5.6, $P < 0.05$).

3.3. Effect of Compound Honey Syrup on lung histology

As shown in Figure 5, mucus level (3.7 ± 0.19 fold) and goblet cell hyperplasia (Score: 3.7) were significantly higher in the airways of OVA-challenged mice than the PBS-treated mice (mucus secretion: 1.4 ± 0.1) (goblet cell score: 0). Oral consumption of Compound Honey Syrup conversely decreased mucus hypersecretion (1.86 ± 0.3) in the lung tissue compared to inhaled Compound Honey Syrup-administered (2.85 ± 0.1) and budesonide-received groups (2.63 ± 0.2) ($P < 0.05$). The effects of OVA on the induction of pathological changes in lungs were more prominent than the negative control group. The group treated with oral Compound Honey Syrup had a remarkably lower score of eosinophil infiltration (perivascular: 1.85 ± 0.16, peribronchial: 1.6 ± 0.24) compared to the budesonide-treated group (perivascular: 2.76 ± 0.08, peribronchial: 2.66 ± 0.16). The budesonide-administered group also had a lower degree of eosinophil infiltration when compared to inhaled Compound Honey Syrup-used group (perivascular: 2.73 ± 0.27, peribronchial: 2.86 ± 0.16).

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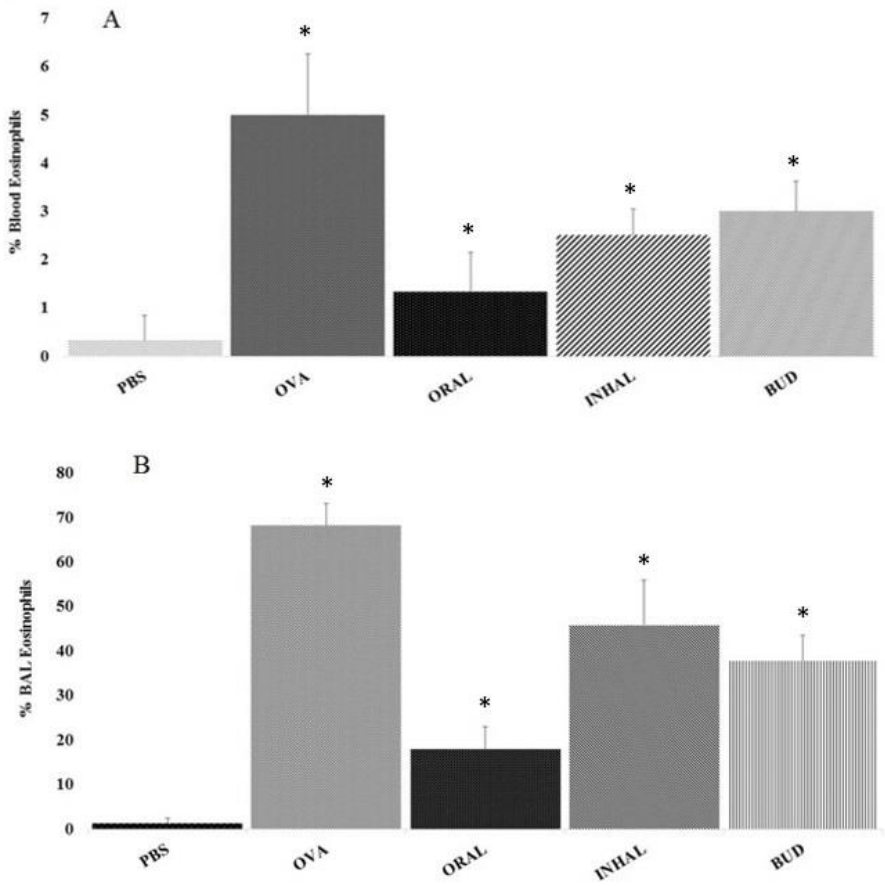


Fig. 4. Effect of different treatments on ovalbumin-induced eosinophilia in blood and bronchoalveolar lavage fluid (BALF). Effect of oral Compound Honey Syrup, inhalational Compound Honey, and Budesonide on peripheral blood eosinophil (A) and BALF eosinophil percentage (B). All data are presented as means ± S.D. ($p<0.05$).

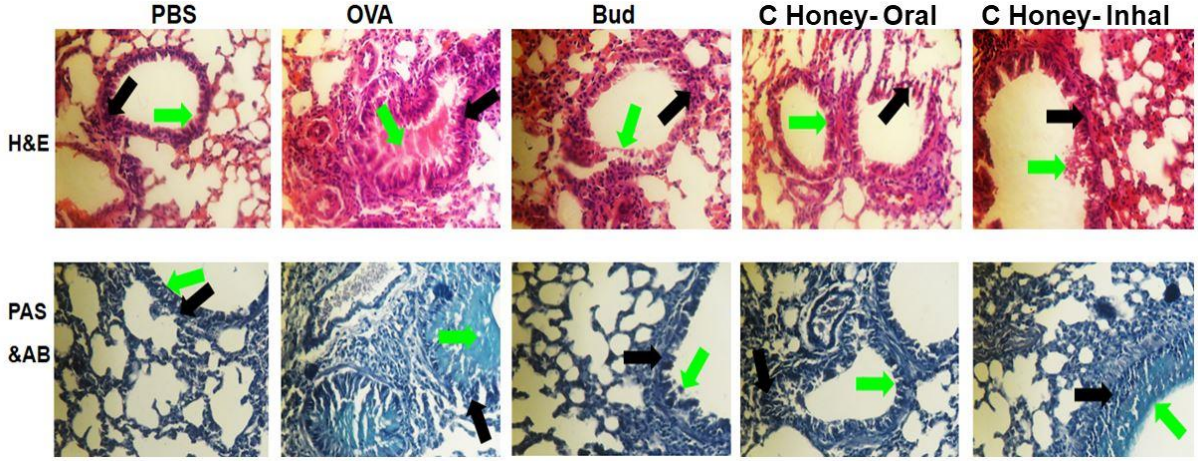


Fig. 5. The histological examination of tissues stained with Hematoxylin-Eosin (H&E) and Alcian blue-Periodic acid Schiff (AB-PAS) showed the peribronchial inflammation, goblet cell hyperplasia within the airway epithelium and mucus hypersecretion in lung sections. Through PAS staining it was possible to show mucus and goblet cells (they show the presence of mucus in their cytoplasm). Goblet cells are shown with black arrows and mucus is shown with green arrows. OVA-challenged group shows hyperplasia of goblet cells and mucus hypersecretion. PBS-challenged group showed no airway obstruction and mucus hypersecretion. In the inhalational Compound Honey-treated group, the mucus hypersecretion was reduced compared to positive control group, but increased compared to negative control group. In OVA-challenged mice that were treated with budesonide, mucus hypersecretion and goblet cell hyperplasia were less prominent compared to the group treated with inhalational Compound Honey. Oral Compound Honey Syrup treatment of asthmatic mice reduced mucus hypersecretion and goblet cell hyperplasia compared to budesonide group.

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3.4. Effect of Compound Honey Syrup on cytokines levels of BALF

OVA sensitization led to the diminution of IL-5 (99.11 ± 5.32 versus 20.66 ± 2.61 pg/ml, $P < 0.05$) and IL-13 (152.23 ± 4.51 versus 48.71 ± 2.87 pg/ml, $P < 0.05$) levels compared to the PBS-challenged mice (negative control) (Figures 6A and B). On the other hand, oral Compound Honey Syrup, inhaled Compound Honey Syrup, and budesonide treatments remarkably decreased the BALF levels of IL-5 (oral Compound Honey Syrup: 26.5 ± 2.94, aerosolized Compound Honey Syrup: 52.01 ± 4.99, budesonide: 58.38 ± 7.49) and IL-13 (oral Compound Honey Syrup: 54.15 ± 7.06, aerosolized Compound Honey Syrup: 80.63 ± 4.93, budesonide: 91.65 ± 3.26).

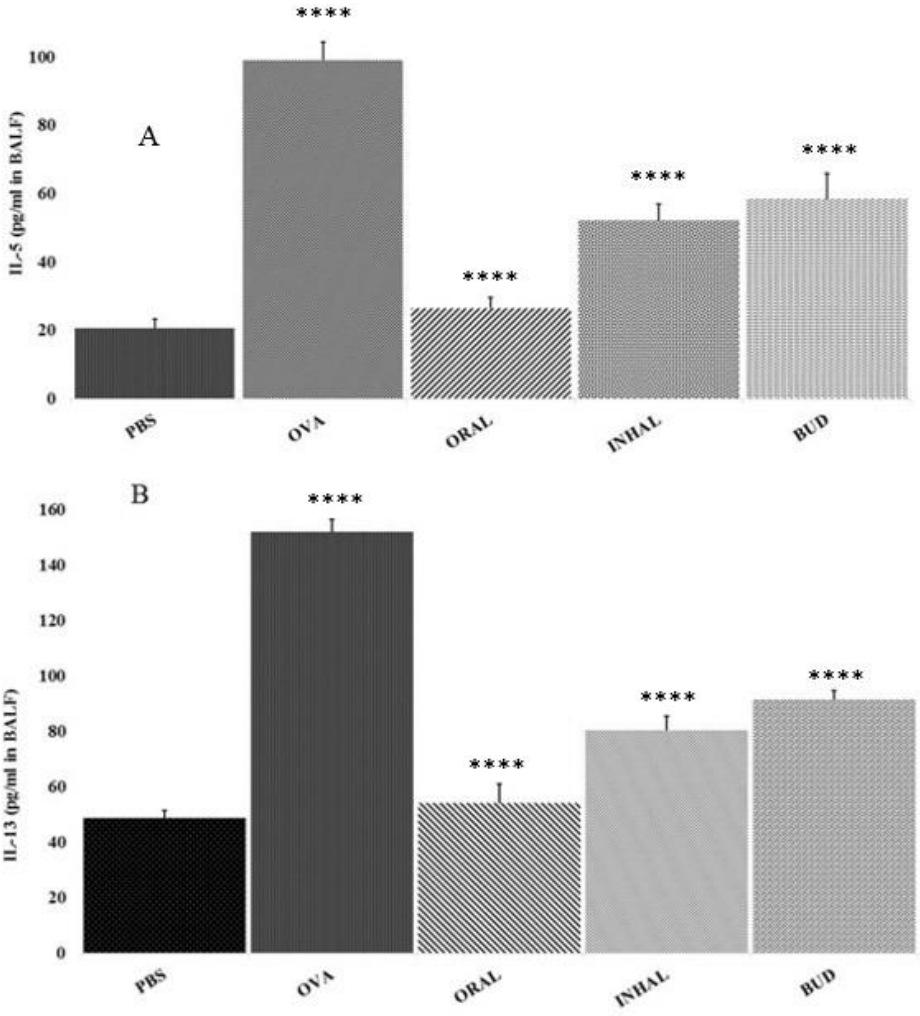


Fig. 6. The effects of various treatments on the levels of cytokines in bronchoalveolar lavage fluid (BALF) of ovalbumin (OVA)-sensitized animals. First, the mice were sensitized and challenged with OVA (positive control) or PBS (negative control). Then, using ELISA method, the levels of IL-5 and IL-13 in BALF were measured. We observed the elevation of IL-5 (A) and IL-13 (B) levels in OVA-treated animals in comparison to negative controls. On the other hand, treatment with oral Compound Honey Syrup, inhalational Compound Honey and Budesonide decreased the levels of IL-5 (A) and IL-13 (B). The results are presented as means ± S.D. ($P < 0.001$).

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4. Discussion

According to ITM, the accumulation of thick Balgham in the lungs results in the overproduction of sticky sputum, narrowing and obstruction of airways, and the inflammatory process, which can lead to further contraction of the airways. This is the most common type of *"rabv"* known as *"rabv balghami"* [10, 11].

The ITM scholars believed that Compound Honey Syrup can attenuate, dissolve, and collect Balgham and therefore is an ideal remedy for the amelioration of respiratory problems especially *"rabv balghami"* (asthma) [10, 20].

In this study, Compound Honey Syrup was proved as an effective remedy for the treatment of allergic asthma by rendering both immunomodulatory and anti-allergic activities. Compound Honey Syrup reduced the AHR to Methacholine. Also, using histopathological analysis, we demonstrated that Compound Honey Syrup significantly prohibited OVA-stimulated eosinophilia in BALF as well as in peribronchial and perivascular areas of the lungs of our animal models.

Compound Honey Syrup also prevented the oversecretion of mucus in the lung tissue and goblet cell hyperplasia in the airways of OVA-treated mice. Moreover, oral Compound Honey Syrup was more effective than aerosolized Compound Honey Syrup in hindering asthma-related cytokine production. In addition, treatment of OVA-sensitized mice with oral Compound Honey Syrup was at least as effective as budesonide.

Kamaruzaman, et al reported the inhibitory effects of Compound Honey Syrup ingredients on AHR and the inflammatory process of asthma. They reported that aerosolized honey decreased the number of inflammatory cells of BALF (eosinophils, mononuclear cells, neutrophils, and macrophages) and suppressed the goblet cell hyperplasia in the rabbit model of OVA-induced asthma [21]. The use of the oral extract of *C. sativus* in OVA-sensitized guinea pigs caused a significant decline in AHR and serum levels of inflammatory mediators such as IL-4, total NO, and nitrite as well as a rise in the ratio of Th1/Th2 cells [22]. *Z. officinale* aqueous extract has been unraveled to prevent the accumulation of eosinophils in the lungs of OVA-sensitized mice. Moreover, the levels of eotaxin, IL-4, and IL-5 in BALF, lung, and sera were significantly suppressed, which indicates the ability of *Z. officinale* extract in blocking the Th2-mediated inflammation [23]. *E. cardamomum* treatment of rats with carbachol-mediated bronchoconstriction resulted in the suppression of the carbachol-induced increase in the inspiratory pressure. The outcomes have evidenced a bronchodilator activity for *E. cardamomum*, which was exerted by its calcium antagonist action [24]. In another investigation, oral use of type-A procyanidin polyphenols (TAPP) isolated from *Cinnamomum zeylanicum* bark significantly decreased the levels of total protein (lung and BALF), albumin (serum, BALF, and lung) as well as hyperplastic goblet cells and infiltration of inflammatory cells into lung tissue in a male Wistar rat model of OVA-sensitized asthma. This preparation also markedly suppressed the AHR [25].

19-acetoxychavicol acetate (ACA) derived from *A. galanga* rhizome had positive effects on OVA-induced asthma in a murine model. ACA showed a reduced eosinophilia and IgE level in the lungs as well as decreased histopathological findings such as airway remodeling, goblet-cell hyperplasia, and eosinophil infiltration. Furthermore, ACA inhibited the concentrations of IL-4, IL-13, IL-12α, and interferon-γ but did not changed IL-5 [26]. Cytokines have a key role in airway inflammation. Among them, IL-5 plays a pivotal role in a variety of biological aspects of eosinophil activity [27]. IL-13 is implicated in

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AHR, mucus overproduction, and airway alterations. It is also well-known that IL-13 augmentation may induce resistance to corticosteroid treatment in some patients [28].

Among different components of Compound Honey Syrup, *Z. officinale* was shown as an effective plant in suppressing IL-4 and IL-5. In addition, *A. galanga* could diminish the level of IL-13 but had no significant activity against IL-5. In our study, Compound Honey Syrup remarkably repressed both IL-5 and IL-13 secretion. Interestingly, in a recent study, Kaveh, et al explored the impacts of Compound Honey Syrup on patients with mild to moderate asthma using an asthma control questionnaire (ACQ) before and after the consumption of oral Compound Honey Syrup, which resulted in favorable effects. However, underlying mechanism of action was not unraveled for Compound Honey Syrup anti-asthmatic effects [29]. In terms of histopathological changes, our prepared Oral Compound Honey Syrup was more efficient than inhaled Compound Honey Syrup in hampering infiltrated cells, mucus production, and presence of hyperplastic goblet cells. Furthermore, Oral Compound Honey Syrup was more potent than the inhaled formulation in lowering the eosinophilia in blood and BALF samples. As indicated before, the reduction in IL-5 and IL-13 levels were also more significant in the Oral Compound Honey Syrup group. This finding complies with the ITM concepts that the stomach, as the organ of first the step of digestion, is responsible for the preparation of suitable nutrients for other organs such as the lungs. In other words, if the production of abnormal *Balgham* in the stomach results in the accumulation of *Balgham* in the lungs, Oral Compound Honey Syrup, by dissolving the *Balgham* in both the stomach and lung, can be more effective than the inhaled drug which dissolves the *Balgham* in lungs only. There were a number of limitations in our study as follows: We used an acute model of asthma and we did not investigate the duration of the Compound Honey Syrup effect as well as single doses in prophylactic form.

5. Conclusion

In summary, Oral Compound Honey Syrup showed more effectiveness than the inhaled syrup and budesonide in the reversal of asthma complications in our experimental mouse model. This indicates that Compound Honey Syrup, as an effective natural remedy with feasible production, can be considered a promising therapeutic formulation for the management of asthma.

Author Contribution

S.S., M.M. and R.C. designed the experiments and methodology; S.D. prepared the draft of the manuscript and performed the experiment; S.S.A supervised the project and analyzed; S.R. assisted in data analysis and interpretation along with writing the draft and editing the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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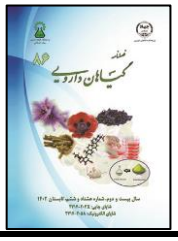
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مقاله تحقیقاتی

بررسی اثر یک فرمولاسیون چند گیاهی ایرانی بر درمان آسم آلرژیک در موش سوری

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اطلاعات مقاله

گل‌واژگان:
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پاسخ ضدالتهابی
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شربت عسل ترکیبی
موش

چکیده

مقدمه: آسم یک بیماری مزمن تنفسی است که با اسپاسم برونش، التهاب راه‌های هوایی و مشکلات تنفسی مشخص می‌شود. با توجه به شیوع بالای این بیماری، استفاده از طب سنتی ایران (ITM) در سال‌های اخیر افزایش یافته است. **هدف:** در این مطالعه، اثر یک فرمول چند گیاهی (شربت عسل مرکب) در درمان آسم آلرژیک مورد بررسی قرار گرفت. **روش بررسی:** ۶۰ موش Balb/c به پنج گروه ۱۲ تایی به شرح زیر تقسیم شدند: گروه ۱، حساس شده با اوالبومین. گروه ۲، دریافت کننده PBS. گروه ۳، تیمار با شربت عسل ترکیبی خوراکی، گروه ۴، تیمار با شربت عسل ترکیبی استنشاقی و گروه ۵، تیمار با بودزونید استنشاقی. سپس، واکنش بیش از حد راه هوایی (AHR) با استفاده از تست متاکولین و سطح سیتوکین‌ها در مایع لاواژ برونش آلوئولار (BALF) و ائوزینوفیل‌ها در خون و BALF اندازه‌گیری شد. تغییرات بافت شناسی ریه‌ها نیز بررسی شد. **نتایج:** شربت عسل ترکیبی خوراکی از ایجاد AHR جلوگیری کرد. شربت عسل ترکیبی خوراکی و استنشاقی به طور قابل توجهی تعداد ائوزینوفیل‌ها را در خون و نمونه‌های BALF کاهش داد. علاوه بر این، هر دو نوع خوراکی و استنشاقی شربت به طور قابل توجهی سطوح IL-5 و IL-13 را در نمونه‌های BALF و خون در مقایسه با حیوانات دریافت شده با OVA کاهش دادند ($P < ۰/۰۵$). **نتیجه‌گیری:** داده‌های حاضر نشان می‌دهد که شربت عسل ترکیبی یک فرمول گیاهی مؤثر برای کاهش پاسخ التهابی ناشی از آسم است و بنابراین می‌تواند درمانی امیدوارکننده برای مدیریت این بیماری باشد.

مخففها: ITM، طب سنتی ایران؛ OVA، اووالبومین؛ AHR، واکنش بیش از حد راه هوایی؛ BALF، مایع لاواژ برونکوآلوئولار؛ IL-5، اینترلوکین-۵؛ IL-13، اینترلوکین-۱۳؛ CAM، طب مکمل و جایگزین؛ PBS، سالین بافر فسفات؛ H&E، هماتوکسیلین و ائوزین؛ PAS، پریودیک اسید شیف؛ TAPP، پلی فنل‌های پروسیانیدین نوع A؛ ACA، 19-استوکسی چاویکول استات؛ ACQ، پرسشنامه کنترل آسم

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