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# The Effect of Compound Honey Syrup on Clinical Manifestation of the Adult Asthma Patients: A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial

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## Abstract

Asthma is a chronic inflammatory disease of the respiratory tract which includes inflammation and obstruction of the airways. Modern medical treatment has side effects in addition to therapeutic effects. According to the high incidence of asthma, the use of complementary therapies has risen, such as compound honey syrup in Traditional Persian medicine and Integrative medicine as a treatment for asthma. Therefore, the aim of this study was to evaluate the effect of compound honey syrup in improving the clinical symptoms of adult asthma referred to Loghman hospital. This randomized, double-blinded, controlled trial was performed on 80 patients with asthma symptoms. Patients were divided into two groups of 40 and the study was conducted for 12 weeks. The intervention group received classic asthma treatment and compound honey syrup. The control group also received classic asthma treatments plus placebo. The questionnaire was done by individuals at the beginning and end of the study. At the end of study some factors like night symptoms, morning symptoms, activity limitation, shortness of breath, wheezing, and use of Short Acting Beta Agonist (SABA) were significantly decreased in both groups, but it had a greater extent in the intervention group than in the control group. Difference in total scores and some items of Asthma Control Test (ACT) were significant between groups ($P < 0.05$). No serious adverse effects were observed in any of the groups. The results of this study demonstrate that compound honey syrup can be a safe and effective drug for the treatment of asthma in adults.

**Keywords:** Asthma; Asthma control test; Traditional persian medicine; Integrative medicine; Compound honey syrup

## Introduction

Asthma is a chronic inflammatory disease that occurs as a result of interactions between genetic and environmental factors [1], which include inflammation, chronic obstruction, increased secretions, and increased airway irritability. Asthma symptoms are wheezing, coughing, shortness of breath, and a feeling of heaviness or pain in the chest [2]. There are about 339 million asthmatic people in the world [3], which may increase to 400 million by 2025 [4,5]. The prevalence of asthma in Iran was about 8.9% in total population [6]. According to WHO, about 417,000 deaths occur annually due to asthma disease [3].

There are several conventional treatments for asthma

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and they have side effects, but they vary depending on their dose and duration. Some of them include nausea, vomiting, headache, diuresis, palpitations, muscle tremors, dry mouth, oral candidiasis, osteoporosis, diabetes, hypertension, gastric ulcer, glaucoma, and urinary retention [7,8]. The average cost for an adult with asthma for one year is 300-1300 $ [8,9]. Also, about 42% of patients with asthma in Iran do not use inhaled sprays for various reasons, including side effects, fear of dependence and pessimistic beliefs about the medicine [10].

Due to the economic condition, high prevalence of the disease, the wrong beliefs about inhaled sprays, the lack of knowledge about treatment, and the side effects of these medications, a lot of research is being done to find a treatment with better effectiveness and fewer side effects. One of the treatment methods in different parts of the world is traditional and complementary medicine. About 80% of the populations in developed countries use traditional medicine to stay healthy. Each culture has its own traditional and indigenous medicinal materials, including plants, animals, and minerals for treatment of different disorders [11-14]. Traditional Persian medicine (TPM) is one of the most ancient traditional medical doctrines all over the world. One of the medicines mentioned in TPM books for the treatment of asthma is honey [15]. Different methods have been recommended for preparing honey-based products in different books of TPM. Still, the most common ingredient used in all is a combination of honey and water, mixed in different proportions of other materials such as ginger, cinnamon, mastic, saffron, cloves, pepper, rose, and cardamom [15-17]. Honey can be an excellent medicine for excretion of lung moisture and sputum. It has a special application in treating pulmonary disorders and has been used in pneumonia, pleurisy, cough, shortness of breath, and hoarseness [15]. Thus, we decided to design a randomized clinical trial to evaluate the efficacy and safety of compound honey syrup in adult patients with asthma.

## Materials and Methods

### *Patients*

In this randomized double-blinded, placebo-controlled clinical trial, the subjects were 80 patients with diagnosis of asthma (age: 18-60 years) who came to Loghman hospital for follow-up treatment; they were recruited from August to October 2018. A sample size of 80 patients (40 patients each in the intervention and the control group) was considered a 30% possibility of withdrawal rate.

### *Inclusion and exclusion criteria*

Inclusion criteria were as follows: being 18 to 60 years of age; having mild to moderate asthma which are diagnosed by an expert pulmonologist after taking a history, clinical examination and spirometry. Patients with mild asthma having cough or wheezing more than twice per week, but less than once a day were considered for the study. Nocturnal symptoms of cough or wheeze occur no more than 3 to 4 times per month, and pulmonary function (forced expiratory volume in one second [FEV1] and FEV1/FVC [forced vital capacity]) is in the normal range. Patients with mild asthma may also have two or more exacerbations per year. Patients with moderate asthma have symptoms during most days and nocturnal symptoms at least weekly, and they may report frequent occurrence of slowed play and missed school days. The FEV1 and FEV1/FVC measures are often in the range of mild obstructive lung disease (60%-80% of predicted). As with patients with mild asthma, those categorized as moderate asthma may also have two or more serious exacerbations per year [18]; understanding the research protocol and consent to participate.

Exclusion criteria were patients with severe asthma and required hospitalization or patients with an asthma attack; being under 18 or over 80 years, having underlying diseases such as cystic fibrosis, bronchopulmonary dysplasia, heart failure, tracheobronchomalacia, gastroesophageal reflux disease, bronchiectasis, pulmonary embolism, sarcoidosis, allergy or intolerance to compound honey syrup; use of medications such as aspirin, beta blockers, and nonsteroidal anti-inflammatory drugs, other acute diseases during the study, and patients who have decided to leave the study at their request.

### *Ethical considerations*

The experiment was explained to potential subjects, and they were asked to provide written informed consent before participating in the study. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.828) and registered in the Iranian Registry of Clinical Trials (IRCT20181115041664N1).

### *Randomization and blinding*

The randomization method was performed using quadruple blocks and individual randomization unit and also the randomization tool was a table of random numbers.

To make a sequence, in the table of random numbers, a number was randomly selected from the table and the next numbers were selected in a row or column in the up, down, left or right direction.

Because the number of modes of 4 blocks for two groups was 6 modes, numbers higher than 6 and zero were ignored in the table and each digit specifies the desired block.

The study was double-blinded, patients enter the study

after completing informed consent and knowing that the drug and placebo are not known.
The researcher also does not know the drug codes whether it is a drug or a placebo.

### *Drug preparation*

Compound honey syrup is a popular beverage in TPM used for asthma for many years [15]. In our study, the compound honey syrup was prepared according to documented pharmaceutical TPM manuscripts [15-17] with slight modifications. Compound honey syrup is a TPM product that has a license from the Iranian Food and Drug Administration (IFDA) affiliated to The Ministry of Health of Iran (license number: S-94-0425). Plants used in compound honey syrup are considered as well-known medicinal plants that were prepared by Niak Company and were controlled by using standard methods at quality control laboratory, Niak Company. Compound honey syrup with the batch number 94230, 10.08.2015 was given to each patient in the intervention group. This product has two years' expiry date. As a syrup formulation, compound honey syrup is a mixture of honey, water and an extract of herbs of *Zingiber officinale* Roscoe (root), *Cinnamomum verum* Presl (bark), *Crocus sativus* L (stigma), *Elettaria cardamomum* (L) Maton (fruit), and *Alpinia galanga* (L) Willd (root), *Pistacia lentiscus* L. (oleogum resin), *Myristica fragrans* Houtt. (mace). Each 100 mL of compound honey syrup consisted of ginger, saffron, mastic, nutmeg and galangal (1 g), cinnamon and cardamom (2 g), and honey (40 g).

### *Sample size calculation*

Based on statistical calculations with the default power (1- β) 0.95, type I error (α) 0.05, 20% improvement in drug efficacy variables ($\bar{X}1$ - $\bar{X}2$), and the group variance (S1 and 2) of about 25%, and with the overall sample size formula,

**Equation 1.**

$$n = \frac{(S_1^2 + S_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})2}{(\bar{X}_1 - \bar{X}_2)^2}$$

the estimated sample size was 60 subjects. A sample size of 80 patients (40 patients in the experimental group and 40 patients in the control group) was considered with a 30% possibility of withdrawal rate.

### *Study design*

Eligible subjects were randomly assigned into two groups (intervention and control groups, [n = 40] in each group) that received classical treatment of asthma with one puff of fluticasone/ Salmeterol spray 250/25 µg every 12 h. In addition to the conventional treatment, the intervention group also received 10 mL of compound honey syrup in 100 mL of warm water, three times per day after meal for 12 weeks. Furthermore, the control group received 10 mL of placebo in 100 mL of warm water, three times per day after meal for 12 weeks.
During the first visit for both groups, the investigator completed Asthma Control Test (ACT). In weeks 2, 6, and 10, patients were monitored by the researcher, and in weeks 4, 8, and 12, they were observed by a specialist. At week 12, ACT was completed by the investigator and then the findings before and after the intervention were compared within and between groups.

### *Statistical analysis*

All analyses of baseline and treatment effects were performed by using Statistical Package for the Social Sciences (SPSS), version 22. $P < 0.05$ was considered statistically significant, and all tests were 2-tailed. The Kolmogorov-Smirnov test of normality of data was employed. On the basis of the nature of the results, we used nonparametric methods (descriptive statistics, Wilcoxon, and Mann-Whitney test) for symptom scores and number of puffs of short-acting bronchodilator were used per day. For all other variables, we tested the assumptions of equal variances and normality used in the analysis of differences between groups with respect to changes from baseline. We employed the independent sample t test to analyze these changes if these assumptions were satisfied, and the Mann-Whitney test if otherwise. Analysis of within-group differences from baseline was usually not a problem because the results were very obvious, and our policy was to use the paired t test if the analysis of differences between groups (which involved an examination of assumptions) was based on the independent sample t test.

## Results

### *Patient enrollment and exclusion*

A total of 80 patients participated in the study from August to October 2018 and 40 patients each were randomized in both the intervention and the control groups. During the 12-week study, 9 patients were excluded from the study population, all from the placebo group, because of unwillingness to take medication. The number of patients who completed the survey and were analyzed was 71 (22 (31%) male, 49 (69%) female) (Figure 1).

### *Baseline data*

The difference between variables such as night symptoms, morning symptoms, activity limitation, short-

ness of breath, wheeze, use of SABA, control asthma activity, and ACT scores before the treatment, according to statistics were not significant between intervention and control groups (P > 0.05) (Table 1).

### *Efficacy*

After 4 weeks, night symptoms, morning symptoms, wheezing and total scores of ACT were significantly different between the groups (P < 0.05) (Table 1). After 12 weeks, night symptoms, morning symptoms, activity limitation, shortness of breath, wheezing, controlling asthma activity and total scores of ACT were significantly different between the two groups (P < 0.05) (Table 1).

In the intervention group, there was a significant differ-

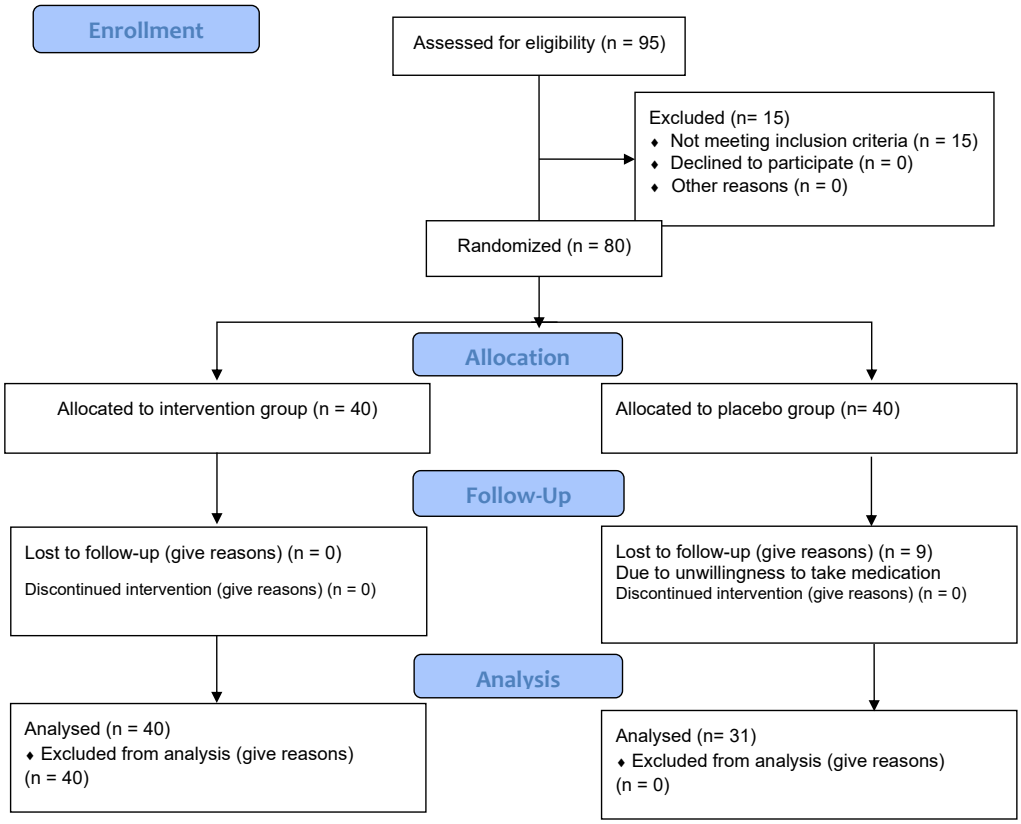


**Figure 1.** Consolidated standards of reporting trials (CONSORT) flowchart of the study

**Table 1.** Baseline demographic and clinical characteristics of participants in the two groups

| Variables | Placebo group (n = 31) | Drug group (n = 40) | P-value |
|---|---|---|---|
| Male/ Female (n) | 9/22 | 13/27 | |
| Night symptoms, Mean (± SD) | 3.16 ± 1.67 | 1.15 ± 2.87 | 0.398 |
| Morning symptoms, Mean (± SD) | 3.16 ± 1.67 | 1.15 ± 2.87 | 0.398 |
| Activity limitation, Mean (± SD) | 3.25 ± 1.69 | 1.27 ± 2.60 | 0.066 |
| Shortness of breath, Mean (± SD) | 2.54 ± 1.60 | 1.31 ± 2.40 | 0.670 |
| Wheeze, Mean (± SD) | 3.16 ± 1.67 | 1.15 ± 2.95 | 0.532 |
| Puffs of SABA, Mean (± SD) | 4.12 ± 1.47 | 1.41 ± 3.57 | 0.113 |
| Asthma control, Mean (± SD) | 2.38 ± 1.17 | 0.87 ± 2.41 | 0.876 |
| Total score of ACT, Mean (± SD) | 21.81 ± 8.72 | 5.14 ± 19.70 | 0.208 |

SD: Standard deviation, SABA: Short Acting Beta Agonist, ACT: Asthma Control Test

**Table 2.** Changes in the all variables of ACT questionnaire, comparing mean values before and after trial within groups, and mean differences between groups

| Variables | Study group | Before (Mean ± SD) | After (Mean ± SD) | P-value | Statistical test | Mean difference | P-value | Statistical test |
|---|---|---|---|---|---|---|---|---|
| Night symptoms | Drug | 1.15 ± 2.87 | 0.26 ± 4.92 | <0.0001 | Paired t-test | Before: -0.29 ± 0.34 (CI 95% -0.95 ± 0.38) | 0.039 | Independent t-test |
| | Placebo | 1.67 ± 3.16 | 0.99 ± 4.58 | <0.0001 | Paired t-test | After: 0.34 ± 0.16 (CI 95% 0.02 ± 0.67) | | |
| Morning symptoms | Drug | 1.15 ± 2.87 | 0.26 ± 4.92 | <0.0001 | Paired t-test | Before: -0.29 ± 0.34 (CI 95% -0.95 ± 0.38) | 0.039 | Independent t-test |
| | Placebo | 1.67 ± 3.16 | 0.99 ± 4.58 | <0.0001 | Paired t-test | After: 0.34 ± 0.16 (CI 95% 0.02 ± 0.67) | | |
| Activity limitation | Drug | 1.27 ± 2.60 | 0.33 ± 4.87 | <0.0001 | Paired t-test | Before: -0.65 ± 0.35 (CI 95% -1.36 ± 0.04) | 0.012 | Independent t-test |
| | Placebo | 1.69 ± 3.25 | 0.96 ± 4.45 | <0.0001 | Paired t-test | After: 0.42 ± 0.16 (CI 95% 0.09 ± 0.74) | | |
| Shortness of breath | Drug | 1.31 ± 2.40 | 0.45 ± 4.72 | <0.0001 | Paired t-test | Before: -0.14 ± 0.35 (CI 95% -0.84 ± 0.54) | 0.005 | Independent t-test |
| | Placebo | 1.60 ± 2.54 | 1.12 ± 4.16 | <0.0001 | Paired t-test | After: 0.56 ± 0.19 (CI 95% 0.17 ± 0.95) | | |
| Wheeze | Drug | 1.15 ± 2.95 | 0.22 ± 4.95 | <0.0001 | Paired t-test | Before: -0.21 ± 0.34 (CI 95% -0.88 ± 0.46) | 0.025 | Independent t-test |
| | Placebo | 1.67 ± 3.16 | 0.99 ± 4.58 | <0.0001 | Paired t-test | After: 0.37 ± 0.16 (CI 95% 0.04 ± 0.69) | | |
| Puffs of SABA | Drug | 1.41 ± 3.57 | 0.34 ± 4.92 | <0.0001 | Paired t-test | Before: -0.55 ± 0.34 (CI 95% -1.24 ± 0.13) | 0.888 | Independent t-test |
| | Placebo | 1.47 ± 4.12 | 0.24 ± 4.93 | 0.003 | Paired t-test | After: -0.01 ± 0.07 (CI 95% -0.15 ± 0.13) | | |
| Asthma control | Drug | 0.87 ± 2.41 | 0.36 ± 4.85 | <0.0001 | Paired t-test | Before: 0.03 ± 0.24 (CI 95% -0.44 ± 0.52) | <0.0001 | Independent t-test |
| | Placebo | 1.17 ± 2.38 | 0.88 3.87± | <0.0001 | Paired t-test | After: 0.98 ± 0.15 (CI 95% 0.67 ± 1.28) | | |
| Total score of ACT | Drug | 5.14 ± 19.70 | ± 34.18 1.25 | <0.0001 | Paired t-test | Before: -2.11 ± 1.65 (CI 95% -5.41 ± 1.20) | 0.001 | Independent t-test |
| | Placebo | 8.72 ± 21.81 | ± 31.13 5.14 | <0.0001 | Paired t-test | After: 3.05 ± 0.84 (CI 95% 1.36 ± 4.72) | | |

SD: Standard deviation, SABA: Short Acting Beta Agonist, ACT: Asthma Control Test, CI 95%: 95% Confidence Interval

ence between all questionnaire variables before the intervention and 12 weeks after the intervention ($P < 0.05$). In the control group, there was a significant difference between all variables before the intervention and 12 weeks after the intervention ($P < 0.05$).

### *Side effects*

No serious adverse effects were observed in both groups.

## Discussion

Honey is a common food and widely used as a treatment for cough, inflammation and infections [19] and has some biological effects like anti-inflammatory, antibacterial, antioxidant, and immunomodulatory properties [20,21]. It was suggested that compound honey syrup is effective in treating asthma in patients and decreasing both symptoms and frequency of asthma attacks [22,23]. Compound honey syrup, containing honey, ginger, cinnamon, saffron, cardamom and galangal, mastic and nutmeg can be effective in asthma [24]. Our results illustrated that compound honey syrup could positively affect the symptoms of asthma (activity limitation, shortness of breath, wheezing, use of SABA, and control asthma). This study also

demonstrated the symptoms were reduced to a greater extent in the intervention group than in the control group.

The most popular ingredient in literature was honey. All studies which used this agent have revealed that honey is an effective natural medicine for relieving respiratory symptoms like night symptoms, morning symptoms, activity limitation, shortness of breath, wheezing and the use of SABA in children [24]. Sadr et al., investigated the effect of compound honey on the clinical symptoms of asthma in children aged 6 to 16 years. In this study, asthma symptoms were assessed based on the ACQ questionnaire. Their results showed night symptoms, morning symptoms, activity limitation, chest tightness, shortness of breath, the short-acting dosage of bronchodilator spray, and overall ACQ score significantly improved in the compound honey recipient group compared with the control group [24]. The results of our study were consistent with the results of the aforementioned study. One of the strengths of our study is the use of a placebo group. Another strength is the duration of the study which was longer than the study on above.

In another study, the intake of a high-dose honey supplement, in addition to standard medications, was investigated on allergic rhinitis. It was demonstrated that there was no significant difference between the mean total symptom score of the intervention and the control groups at the beginning of the study. At week 4, both groups showed progressive improvement in the symptoms; while at week 8, only the intervention group showed a continuous improvement in the symptom score. The improvement persisted for a month after the cessation of the treatment [25]. A study by Cohen et al. [26], found that honey was much more effective in treating night coughs arising from upper respiratory tract infections than conventional therapies. Paul et al. [27], depicted that in a comparison between honey, dextromethorphan and no treatment, parents rated honey as the most effective symptom reliever for their child's nocturnal cough and sleep difficulty due to upper respiratory tract infection. Honey may be a preferable treatment for the cough and sleep difficulty associated with childhood upper respiratory tract infection. A meta-analysis in 2014 indicated that the combination of honey and coffee has a positive effect on cough [28].

The results of the mentioned studies were consistent with our study, because coughing is a clinical symptom of asthma and is an item in the ACT questionnaire, had significant improvement in both groups. However, in our study, in addition to honey, other compounds were used to increase the effect of honey.

Many studies have examined the effect of ginger on asthma symptoms and respiratory diseases. It has demonstrated an anti-inflammatory effect on respiratory infections, suppression of Th2-mediated immunity and reduction of LPS-induced interleukin 8 (IL-8) secretion. Therefore, it can be effective in improving the clinical symptoms of asthma, an inflammatory disease of the airways. Moreover, due to its beta-2 agonist properties, it can also act as a bronchodilator in order to improve the clinical symptoms of asthma [29-32]. Rouhi et al. examined the effect of ginger on asthma recovery. Their results revealed that the ginger was effective in reducing asthmatic symptoms, but not effective in changing the stage of the disease and spirometry findings [33]. However, in addition to ginger, there were other ingredients in our study, but the results of the Rouhi et al. study were consistent with our study. Both studies were performed in adults and both had control and intervention groups. Both groups received conventional asthma treatment, except that our control group also received a placebo.

In Rouhi's study, a valid questionnaire was not used; while in our study, a valid ACT questionnaire was used. Also, the duration of the study was one month, which was 3 months in our study.

Some studies indicated that cinnamon extract had anti-inflammatory effect that could reduce TNF-α, IL-6 and also has anti-asthmatic effects; therefore, it can be useful in the treatment of asthma [34-38]. Saffron had anti-inflammatory, antitussive and antioxidant effects that can reduce the hyper responsiveness of airways, inducible nitric oxide synthase (iNOS) production, apoptosis of the bronchial epithelial cells and the production of Th2 type cytokines in the lungs [39,40].

Cardamom is another component of compound honey syrup and due to its bronchodilator mechanism, it improves asthma symptoms [41,42]. Alpinia officinarum also has anti-inflammatory effect and improves asthma symptoms by inhibiting the expression of Th2 cytokines, including IL-4 and IL-13, Th1 cytokines such as IL-12α and interferon gamma and it also reduces IgE production [43,44]. Recently, some reports suggested mastic and nutmeg have anti-inflammatory and bronchodilator effects [45-48].

Although the mechanisms of compound honey syrup on asthma are not quite clear, our study confirmed the effect of honey with other spices in improving asthma and respiratory symptoms.

It was suggested in this study that this drug can be used to improve clinical manifestations of asthma.

Our limitation in this study was the provision of inhaled sprays due to the sudden increase in prices and the decrease in drug imports because of sanctions.

## Conclusions

The results of this study demonstrate that compound honey syrup can be a safe and effective complementary drug for the treatment of asthma. Therefore, compound honey syrup can be used to improve clinical

manifestations of asthma. Future studies with a larger sample size and a longer follow-up period are recommended to confirm the safety and efficacy of this product in respiratory disorders.

## Conflict of Interests

The authors declare that there was no conflict of interest.

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