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Review Article (Pages: 18180-18188)

Efficacy of Compound Honey Syrup on Pulmonary Symptoms and Body Mass Index in Cystic Fibrosis Patients: A Clinical Trial

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Abstract

Background: Patients with Cystic Fibrosis (CF) often have respiratory tract infections and bacterial colonization requiring antibiotic treatment. The use of complementary treatments such as Compound Honey Syrup (CHS) in Persian medicine is increasing in the treatment of diseases. This study aimed to assess the effects of Compound Honey Syrup (CHS) on CF-induced changes in pulmonary symptoms, and Body Mass Index (BMI) in children.

Method: In a before/after clinical trial, 44 children aged ≥6 suffering from CF were included. They were referred to Mofid children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, between March 2020 and March 2021. The patients received their standard treatment, plus CHS (prescribed at 5-10 cc dose twice daily according to the weight of children (weight over 30 kg 10 ccs and under 30 kg 5 ccs) for 12 weeks. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) was used to determine the Severity of pulmonary symptoms. Moreover, BMIs were compared before and after CHS intervention.

Results: CHS administration for 12 weeks improved daily cough (P=0.000), sputum production (P=0.003), wheezing (P=0.000), difficulty breathing (P=0.002), and night-time cough scores (P=0.004) considerably in CF patients after intervention. Moreover, CHS consumption increased BMI (P=0.000) in these patients.

Conclusion: It can be concluded that compound honey syrup can be a safe and effective complementary medicine to improve pulmonary symptoms and nutritional status of cystic fibrosis patients. In order to confirm these results, it is recommended to conduct more studies with larger sample sizes in order to evaluate the effect of CHS on pulmonary symptoms and BMI in cystic fibrosis patients.

Key Words: Body Mass Index (BMI), Compound Honey Syrup (CHS), Cystic Fibrosis, Respiratory Symptoms.

* Please cite this article as: Sadr S, Kaveh S, Fadavi N, Tahermohammadi H, Tabatabaei SA, Khanbabaei G, Eshghi A, Pourghasem M, Honarpisheh P, Nikpendar M. Efficacy of Compound Honey Syrup on Pulmonary Symptoms and Body Mass Index in Cystic Fibrosis Patients: A Clinical Trial. Int J Pediatr 2023; 11 (08):18180-18188. DOI: **10.22038/ijp.2023.72361.5269**

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Received date: May.14,2023; Accepted date: Aug.18,2023

1- INTRODUCTION

Cystic fibrosis (CF) is a rare and autosomal recessive disorder, occurring due to a mutation in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene (1). A chloride channel is formed by the CFTR protein, which is indispensable for efficient mucus transport (2). When CFTR is disrupted or absent, sticky mucus builds up in the pulmonary and gastrointestinal tracts. This abnormal fluid consistency causes infection, inflammation, malnutrition, and ultimately, multiple organ dysfunction (3).

Digestive and nutritional disorders are the earliest manifestations of the disease. Acinar pancreatic tissue demolition, obstruction of pancreatic duct and subsequent lack of enzyme activity cause malabsorption of fats, proteins and as a result lack of growth (4, 5). Common clinical pulmonary manifestations of patients with CF include the persistent cough, increased respiratory rate, wheeze, crackles, and cyanosis. Among the paraclinical pulmonary findings, hyperinflation of the lung fields on chest radiography, minor accentuation of broncho-vascular markings, atelectasis, bronchiectasis, obstructive airway disease pattern on spirometry, and airway colonization with pathogens such as staphylococcus aureus and pseudomonas aeruginosa have been reported (6). The onset and progression of clinical presentations of pulmonary disease in CF are varying (7). Although increased knowledge about the pathogenesis of cystic fibrosis (CF) has led to therapeutic approaches that have improved lung health, progressive pulmonary involvement remains a major cause of morbidity and mortality in CF patients (8).

Other non-pulmonary clinical signs include recurrent pancreatitis, electrolyte imbalance, male infertility, rectal prolapse, and diabetes mellitus (9).

Currently, the assessment of nutritional status in CF patients has emphasized on the percentile of body mass index (BMI) (10). CF patients with low BMI are susceptible to poorer lung function, higher number of acute exacerbations, increased systemic inflammation, chronic colonization of the respiratory system by Pseudomonas aeruginosa, and higher rates of hospitalization as well as death (11).

In order to treat the CF patients, a multidisciplinary approach is used (12). CF Patients usually have little compliance with their therapeutic regimen and experience failure due to the complexity of the drug regimen, lack of interest in inhaled therapies, and resistance to antibiotics (13). The prolongation of the disease period and the lack of preventive and therapeutic measures have motivated CF patients to choose Complementary and Alternative Medicines (CAM) (14). In some studies, the effectiveness of CAM in children with lung disorders has been mentioned (14, 15).

Compound Honey Syrup (CHS), as part of CAM, the combination of honey and an extract of five medicinal plants, which include Zingiber officinale Roscoe (Zingiberaceae) or ginger, Cinnamomum Verum J Presl (Lauraceae) or cinnamon, Crocus sativus L (Iridaceae) or saffron, Elettaria cardamomum (L) Maton (Zingibera-ceae) or cardamom, and Alpinia galanga (L) Willd (Zingib-eraceae) or galangal medicinal plants (16). Each of the CHS compounds has useful properties in the treatment of lung diseases, which can be named as anti-inflammatory, antibacterial, anti-cough, antioxidant properties, bronchodilator, and anticholinergic effects (16-19). To the best of our knowledge, no clinical trial has investigated the effectiveness of CHS on the clinical manifestations of CF. Therefore, the present study aimed at evaluating the effectiveness of CHS on

pulmonary symptoms and BMI in CF children.

2- METHOD AND MATERIALS

2-1. Study design and participants

The present study is a before/after clinical trial and follow-up, without control group and blinding, where case and control are from the same group. Each case is its own control. Forty-four patients with cystic fibrosis who referred to Mofid children's Hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran between March 2020 and March 2021, were enrolled.

2-1-1. Inclusion and exclusion criteria

Inclusion criteria encompassed patients with cystic fibrosis over 6 years. Cystic fibrosis patients under 6 years of age, those in need of hospitalization, patients with acute exacerbations and attacks, patients with underlying diseases such as allergic bronchopulmonary aspergillosis, heart failure, and tuberculosis, patients with other acute illnesses occurring during treatment, and those who were allergic to any of the components of the CHS were excluded from this study. All patients participating in the study had cystic fibrosis, diagnosed by a pediatric pulmonologist.

2-2. Procedure

A checklist was designed to collect the demographic and clinical characteristics of the patients; it included age, gender, weight, height, BMI, and pulmonary symptoms. Also, the cystic fibrosis questionnaire-revised (CFQ-R) was used to determine the Severity of pulmonary symptoms and CFQ-R were filled for each patient. Results of physical examinations and complete patient history were recorded by a pediatric pulmonologist at the beginning and end of the study (after 12 weeks). All patients received their standard treatment. The Compound Honey Syrup® (Niak pharmaceutical company, Tehran, Iran) was also, simultaneously, prescribed at 5-10 cc dose twice daily according to the weight of children (weight over 30 kg, 10 cc; and under 30 kg, 5 cc). The syrup was first mixed with 100 cc of warm boiled water (both doses were mixed in 100 cc of water) and was administered for twice a day 30 minutes after the meal. The patients were told to take the missed dose if there were 8 hours or more between the missed and the next doses. The time interval between consumption of CHS and other therapeutic drugs was considered at least 2 hours. Mixed honey syrup is a popular drink in Traditional Persian medicine (TPM) that has been used for asthma and respiratory diseases for many years. In our study, compound honey syrup was prepared according to TPM medicinal documented manuscripts, but with minor changes (16, 20).

Essential explanations were given to the patients about the time and how to take the medicine by the researcher. In the second and fourth weeks after the first visit, the patients were followed by the researcher by phone (to inform about possible complications), and in the sixth week, the patients were again referred to the pulmonary clinic of Mofid Children's Hospital for examination by a pulmonologist in terms of symptoms, assessment and control of side effects drug, and re-prescription of medications.

After that, in the eighth and tenth weeks, the patients were followed up by the researcher over the phone (to inform about the medication consumption, and possible complications) and finally, in the twelfth week, the patients were visited by a pulmonologist, and BMI and pulmonary symptoms were measured again, and the CFQ-R questionnaires were also completed. Then, the patients were compared before and after taking the syrup, in terms of BMI and pulmonary symptoms.

2-3. Data analysis

The statistical analyses were performed by SPSS software Version 22 (IBM, Chicago, USA). The variables were described in terms of mean±SD and frequency (percentage). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to test for the normality of data distribution. Quantitative variables were compared by the use of paired-samples t-test or Wilcoxon test as appropriate. Chi-square test was used to compare the qualitative data between the groups. P-values less than 0.05 were considered statistically significant.

3- RESULTS

This study is a clinical trial, without control group and blinding. The participants consist of 44 cystic fibrosis patients aging over 6 years. The patients were selected according to the inclusion and exclusion criteria and followed up for three months. The mean age was 9 years with standard deviation of 4.17. Out of these 44 subjects, 26 (59.1%) were males and 18 (40.9 %) were females. Six cases had a history of cystic fibrosis in their family. Consanguineous marriage was observed in 34.1 % of the patients. Also, the age of diagnosis and starting the symptoms were evaluated based on the documentation and previous reference records. More details are provided in **Table 1**.

Table-1: Descriptive Characteristics of the study participants

Variables	Mean ± Standard deviation / Frequency (%)
Sex (Male, Female)	26:18 (59.1%, 40.9%)
Age (years)	9.36 ± 4.17
Age of diagnosis (months)	31.47 ± 45.88
Age of onset of the symptoms (months)	9.40 ± 19.34
Consanguinity (n %)	15 (34.1%)
Family history of cystic fibrosis (n %)	6 (13.6%)

According to the paired sample t-test, the efficacy of compound honey syrup was evaluated before and after the intervention. The weight difference was estimated as -1.08 which shows lower weight before the intervention and the significant increase after the intervention. The secondary outcome was evaluating the lung symptoms. Based on the, the increase in the mean score of the questionnaire indicated a decrease in pulmonary symptoms. So, as presented in **Table 2**, after the intervention, a decrease in all symptoms was observed. All the comparisons about the symptoms show significant clinical improvements.

4- DISCUSSION

The current study aimed at evaluating the effects of CHS on pulmonary symptoms and BMI in CF children. The results of our study showed that CHS is able to increase all scores in the CFQ-R questionnaire after 12 weeks of intervention, meaning that this compound was able to significantly reduce daily cough, wheezing, difficulty breathing, and night-time cough in children with CF.

Table-2: Growth indicators and pulmonary symptoms before and after the intervention

Variables	Before	After	P-value
Weight (kg)	29.17 ± 14.07	30.26 ± 14.03	< 0.001

Body mass index (kg/m2)	16.58 ± 3.75	16.99 ± 3.71	< 0.001
Pulmonary Symptoms			
Daily cough	2.70 ± 0.95	3.13 ± 0.63	< 0.001
Cough with phlegm	2.59 ± 0.87	3.00±0.88	0.003
Wheezing	3.13 ± 0.70	3.50 ± 0.54	< 0.001
Difficulty in breathing	3.18 ± 0.89	3.54 ± 0.58	0.002
Night cough	3.13 ± 0.73	3.56±0.75	0.004

Similar to our findings, the results of a study conducted by Sadr et al. evaluating the efficacy and safety of this Iranian multi-herb formulation (CHS) in the treatment of mild to moderate asthmatic patients, indicated that CHS group had significantly lower night as well as morning symptoms, activity limitation, shortness of breath, wheeze, and short-acting bronchodilator use compared to the control group after the treatment period (16).

Paul et al. reported that honey may be a better treatment than dextromethorphan, for cough and sleep problems associated with childhood upper respiratory tract infection. In their study, honey improved night coughs and respiratory symptoms (21). According to reports, the sweet taste of honey causes the secretion of saliva, and may even cause the secretion of mucus in the airways. It can reduce inflammation in the larynx and throat and subsequently improve coughs (22, 23).

Other components including ginger (24), saffron (25), cardamom (26), and galangal have shown the same properties which make CHS a suitable therapeutic option in the treatment of respiratory symptoms in CF patients (27).

Podlogar et al. pointed out that the active ingredients of ginger extract called 6-gingerol, 8-gingerol and 6-shogaol cause the smooth muscles of the human respiratory system to rest; and by changing calcium settings, it reduces the increase in respiratory sensitivities. The compounds in ginger reduce the secretion of Lipopolysaccharides-dependent interleukin-8, so it can be used as an anti-inflammatory medication in respiratory diseases (17). Also, Ahui et al. showed that the active substance 6-gingerol alone reduced eosinophilia, interleukin 4, interleukin 5, endotoxin levels in the lungs, and serum IgE levels in a mouse model of airway inflammation (28). Overall, ginger suppresses Th2-mediated immune responses and may play a role in the management of inflammatory diseases. The mechanism of ginger and its isolated active components, 6-gingerol, 8-gingerol, and 6-gingerol, relax Airway Smooth Muscle (ASM), and 8-gingerol reduces airway hyperresponsiveness rather by modulating (Ca2+)(24). Another significant compound used in CHS is cinnamon. Corren et al. noted that the consumption of cinnamon extract reduces the symptoms of nasal congestion, and also inhibits the secretion of prostaglandin D2, which is a type of inflammatory marker (29). Also, cinnamon extract inhibits the maturation of dendritic cells, and subsequently stops the proliferation of allergen-specific T cells and causes the production of Type 1 and 2 helper T cytokines (30). The anti-inflammatory properties of cinnamon are usually due to inhibition of nitric oxide, TNF-α, IL-1β and IL-6. However, it has been found that cinnamon has other effects, such as inhibiting the Mitogen-Activated Protein Kinase (MAPK) and nuclear factor-κβ (NF-κβ) signaling pathways (31).

The components of saffron include crocetin, picrocrocin, safranal and

kaempferol (32). Bronchodilatory effect of saffron is due to stimulation of beta-2 adrenergic receptors, H1 histamine receptors, and inhibition of muscarinic receptors (32).

On the other hand, in recent studies, the anti-inflammatory, antimicrobial and bronchodilatory properties of cardamom and galangal (other CHS components) have been mentioned (26, 33). Seo et al. reported that galangal improves the symptoms of inflammatory lung diseases by inhibiting the expression of Th1/th2 cytokines and reducing the production of IgE (33). A component of galangal, 1′-acetoxychavicol acetate (ACA) can reduce the eosinophilic infiltration and the IgE level in the lungs. In other words, the mechanism of galangal effect is that ACA can inhibit the expression of Th1/Th2 cytokines, IL-12α and interferon gamma (IFN-γ) (33). Moreover, the mechanism of efficacy of cardamom, as one of the constituents of CHS, is to create anti-inflammatory and bronchodilating effects. Cardamom also inhibits muscarinic receptors on airway smooth muscle by combining 1, 8 cineole (26). In our study, the effect of CHS on BMI was also measured in cystic fibrosis patients. It has been found that malnutrition plays a fundamental role in the progression of pulmonary symptoms of patients with CF, and thus leads to an improvement in nutritional status and prevents malnutrition, i.e., increasing BMI, has been a conventional target for improved health outcomes in CF. This has led to a decision by the CF Foundation that all individuals with CF should use the age-appropriate BMI method to assess weight and height (34). The results of our study showed that a 12-week treatment regimen with CHS is able to increase the BMI of children with CF in a significant manner. According to the literature, we could not attribute this effect of CHS on BMI to any of the mentioned components of this mixture; as all these ingredients have been shown to decrease the weight and obesity severity (35-37).

4-1. Strengths and limitations of the study

The strength of the study was that for the first time the effect of CHS was measured in CF patients. The main Limitations of the study include the small sample size and lack of spirometry measurement. Another limitation was the use of CHS with conventional therapy in CF patients, the effects of which may have influenced the study results.

It is suggested that longitudinal controlled trials with larger sample sizes and control groups should be conducted on other parameters related to the evaluation of CHS effectiveness on spirometry symptoms, quality of life in CF patients, and the expression of cystic fibrosis-related genes.

5- CONCLUSION

The current study showed that 12 weeks of treatment with CHS ameliorated the severity of symptoms, assessed by CFQ-R, in CF children. It also improved their nutritional status and BMI. Moreover, the results indicate that CHS can be a safe and effective complementary medicine for the treatment of CF children.

6- ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (Ethics code: IR.SBMU.MSP.REC.1398.877), and it was registered in the Iranian clinical trial system with the patented number of IRCT20200103045989N1. Written informed consent was obtained from each patient.

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