JoP Journal of Pharmacopuncture
Journal of Pharmacopuncture 2022;25(3):233-241
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2022.25.3.233
Original Article
Check for updates

The Effect of Glasthma Syrup in Asthma: a study protocol for a triple-blind randomized controlled trial

Ali Reza Derakhshan[1], Shahin Saeidinejat[2]*, Majid Khadem-Rezaiyan[3], Amir-Mohammad-Hashem Asnaashari[4], Majid Mirsadraee[5], Roshanak Salari[1], Farahzad Jabbari-Azad[6], Shima Jalali[7], Shabnam Jalali[7]

[1]School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Social Determinants of Health Research Center, Health School, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Community Medicine and Public Health, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Lung Disease Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[5]Department of Internal Medicine, Faculty of Medicine, Islamic Azad University-Mashhad Branch, Mashhad, Iran
[6]Department of Immunology and Allergy, Head of Allergy Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[7]Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran

Received January 24, 2022
Reviewed February 4, 2022
Accepted July 28, 2022

***Corresponding Author**
Shahin Saeidinejat
Social Determinants of Health Research center, Health School, Mashhad University of Medical Sciences, Shahid Fakoury Blvd, Mashhad 97165-91778, Iran
Tel: +98-915-5154-2384
E-mail: saeedish1@mums.ac.ir

Objectives: Asthma is a chronic disease, and the demand for herbal medicines in this field has increased in recent years. The new findings highlight the role of the gut-lung axis in the pathophysiology of asthma. Hence, this study will evaluate the safety and efficacy of Glasthma syrup, an herbal formula based on Persian medicine, in improving asthma and regulating intestinal permeability. The formula consists of five herbal ingredients that have anti-inflammatory effects on the respiratory tract, also known as gut tonics.
Methods: The study will be conducted as a placebo-controlled, triple-blind, randomized trial. It will consist of a 4-week intervention followed by a 4-week follow-up period. The target sample size is 20 patients with moderate asthma aged 18 to 60 years. Eligible participants will be randomly assigned to either the experimental group or the control group in equal numbers. Patients in the experimental group will take Glasthma syrup (7.5 mL, twice a day), while patients in the control group will take a matching placebo. Both groups will receive a 4-week combination of a long-acting beta2 agonist and a leukotriene modulator as standard of care. Inhaled corticosteroids can be used as rescue medication as needed.
Results: The primary outcomes are asthma symptom scale, lung function, and intestinal permeability. Secondary outcomes include quality of life, symptom recurrence rates, and blood tests. A safety assessment will also be conducted during the trial.
Conclusion: In this trial, the effects of Glasthma syrup in patients with moderate asthma will be examined. The study will also assess the effects of the formulation on the gut-lung axis by simultaneously monitoring the gut permeability index, asthma symptoms, and lung function.

Keywords: bronchial asthma, persian medicine, intestinal permeability, clinical trial

INTRODUCTION

In Persian medicine, the treatment of asthma with herbs has been mentioned in various formulas [1]. Despite the rich variety of medicinal preparations in Persian medicine, there has been limited research on their effectiveness and possible adverse effects [2-6]. Considering the increasing popularity of herbal and traditional remedies, it is necessary to evaluate the performance of these herbal therapeutic formulations and their side effects [7].

Asthma is a chronic disease, and multiple medications have been developed to reduce inflammation of the airways and con-

tract the smooth muscles of walls.

Common drugs for asthma contain, as active ingredients, medicinal plants mentioned in some traditional medicine recipes [8]. Physiologic effects such plants varies depending on the composition of each formulation.

This complexity is not fully understood, but empirical evidence suggests that they have a measurable effect on mucus accumulation, improve bronchial relaxation, and reduce airway inflammation [9].

According to Persian medical theory, the function of the gastrointestinal tract affects the incidence and severity of diseases of other organs and systems, such as the respiratory system. In recent years, several studies have confirmed the gut-lung axis theory [10-13].

Under the theory of the relationship between the gastrointestinal tract and the respiratory system, it seems that controlling nonspecific gastrointestinal malabsorption can greatly reduce the incidence and severity of asthma. In support of this theory, there are several formulations in the Persian medical literature that control respiratory symptoms using supplements that affect the gastrointestinal tract [14-17].

To test this theory, we designed an herbal formula comprising five herbal substances that have tonic effects on both the lungs and the gut: licorice root (Glycyrrhiza glabra), Echium amoenum flower, date fruit (Ziziphus jujuba), Cydonia oblonga fruit (papaya), and hazelnut.

Licorice root is the basis of this recipe. This herb improves gastrointestinal function and breathing, and it also has an anti-inflammatory effects [8].

Echium amoenum is used as a herbal tea for bronchitis, chronic coughs, asthma flare-up symptoms, and as a general tonic [17]. Some of its compounds (gamma-linoleic acid) has antioxidant effects [18-21].

Jujube fruit is a dietary supplement that contains high levels of bioactive compounds such as dietary fiber, minerals, and natural antioxidants. It induces a protective effect in IBD by improving intestinal barrier function [9].

Cydonia oblonga has anti-inflammatory and antioxidant properties [22]. It has been reported to show gastrointestinal benefits in gastroesophageal reflux disorder, gastritis, and colitis [23, 24].

Hazelnut was introduced specifically as a gut tonic for its antitussive properties [25], modulatory effects on the gut microbiom [26], and anti-inflammatory, antioxidant, and metabolic effects on the heart [27].

The aim of this study is to evaluate the efficacy and safety of this formulation (Glasthma syrup) on asthma symptoms, lung function test parameters, and intestinal permeability indices.

MATERIALS AND METHODS

1. Study registry

This is a single-center randomized triple-blind controlled trial. The trial was authorized at the Medical University of Mashhad, Iran (code: 991551), approved by the Iranian National Biomedical Research Ethics Committee, code IR.MUMS.REC.1400.076, and registered with the Iranian Clinical Trials Registry.

The goal of the trial is to analyze the effect of Glasthma syrup, compared with placebo, on respiratory symptoms, pulmonary function test results, and gut permeability index (lactulose/mannitol ratio) in patients with moderate asthma. This study complies with the Standard Protocol Item: Guidelines for Interventional Trials (SPIRIT) Recommendations (Table 1).

2. Trial procedure

The complete trial includes a screening assessment, a 1-week run-in period, a 4-week treatment period (weeks 1 to 4), and a 4-week follow-up period (weeks 5 to 8) (Fig. 1).

First, patients with asthma who met the inclusion criteria will be invited to participate in the study. They will be given the necessary explanations about the study conditions, and if they agree, after signing a written consent form, an asthma registry questionnaire will be completed [28]. The patients will have a complete blood count (CBC), liver and kidney function tests, total serum IgE test, pulmonary function test (PEF), urine analysis, creatinine clearance (ClCr), and a 5-hour urine L:M test.

After the baseline assessment, participants will be randomly assigned to receive Glasthma syrup or placebo syrup for 4 weeks. Symptom severity and quality of life will be self-assessed by participants and recorded weekly throughout the treatment period. Face-to-face blind assessments will be scheduled for the end of the fourth week. Patients in both groups will have virtual follow-up visits during the intervention and 4 weeks later to be informed on the medication use and possible side effects.

Assessments of symptoms and quality of life, as well as all blood, urine, and lung tests, will be repeated at the end of the 4-week intervention. After the intervention period, a 4-week

 https://doi.org/10.3831/KPI.2022.25.3.233

Table 1. Schedule of enrolment, interventions, and assessments

Time point	Study period								
	Allocation	Post Allocation				Close up			
	T0	T1	T2	T3	T4	T5	T6	T7	T8
Enrollment									
Eligibility screen	*								
Inform consent	*								
Medical history and physical examination	*								
Allocation	*								
Intervention Glasthma/control		*	*	*	*				
Assessment									
Baseline survey	*								
Asthma severity	*	*	*	*	*	*			
Quality of life	*	*	*	*	*	*			
Lung function	*					*			
L:M in urine	*					*			
Blood tests	*					*			
Rate of symptom relapse						*	*	*	*
Health resource utilization data	*	*	*	*	*				
Safety		*	*	*	*				
Follow up						*	*	*	
End line survey									*

follow-up period will follow. During these 4 weeks, patients will continue the standard treatment, with weekly recordings of symptom severity and quality of life scores, as well as the need for rescue medication.

Participants will be recruited by a pulmonologist and clinical allergist from the Respiratory Clinic at Ghaem Hospital in Mashhad. Classified online posters and advertisements will also be used to inform and engage patients. Inclusion criteria are a history of asthma over 6 months and an FEV1 of 60-80%.

Patients with one or more of the following conditions will be excluded: cognitive diseases, history of seizure disorder, use of oral or systemic corticosteroids, pregnancy or lactation, allergy to nuts, need for hospitalization for any reason, smoking, exacerbation of the disorder at the start of the study, high blood pressure or diabetes, and concurrent participation in other trials or participation in a trial in the previous month.

3. Interventions

Patients in the intervention group will be instructed to receive 7.5 mL of Glasthma syrup twice daily for 4 weeks in combination with an inhaled corticosteroid (fluticasone) and a long-acting inhaled beta-agonist (fumarate). The daily dose of Glasthma syrup contains aqueous extract of Cydonia oblonga (1.5 g), licorice root (Glycyrrhiza glabra, 0.7 g), jujube (Ziziphus jujuba, 0.7 g), Echium amoenum (1.2 g), and hazelnut (1.5 g). The formula for this syrup has been adapted from the recommendations of Persian medicine reference books and common medical evidence. Dosages for each ingredient were determined according to previous studies [8]. Aqueous extracts were immersed in a laboratory water bath at 50℃ for 6 hours. The drug has been tested for chemical and microbiological contamination in the Testa quality control laboratory. In addition, drug quality assessment was performed by measuring the polyphenol content of formulations in the Testa quality control laboratory. Participants in the control group will receive 7.5 mL of placebo syrup twice a day for 4 weeks with standard medications. Placebo syrup consists of a combination of carboxymethyl cellulose (CMC, 0.5%), Sativoside as the main sweetener (1%), and food coloring to obtain the color of Glasthma syrup.

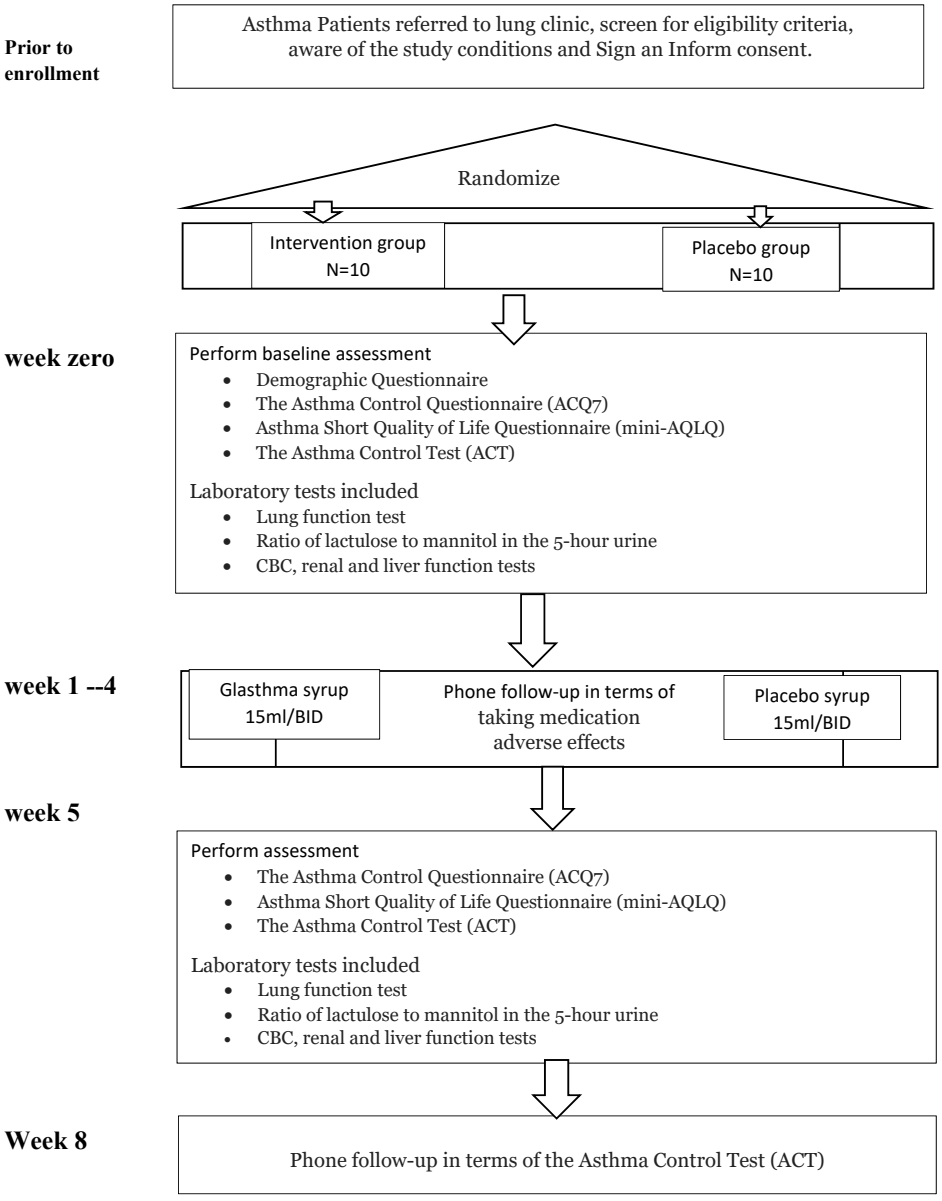

Figure 1. Flowchart of trial procedure.

4. Randomization, allocation concealment, and blinding

Eligible patients will be randomly allocated into the intervention group or the placebo group in a ratio of 1:1. Permuted block-randomization will be used for randomization. Each block has four numbers. Sequences generated via https://www.sealedenvelope.com will be provided to researchers in sealed, opaque, and sequentially numbered envelopes. Project researchers will open one of the envelopes as each patient arrives at the hospital, and the patient will be assigned to the group described in the envelope. Assignment data will be kept confidential until the trial ends and the assessment is complete. Patients, investigators, outcome assessors, and information analysts will be blinded to group assignments.

The randomization agenda and blind codes will be kept strictly confidential until the statistical evaluation is completed. Blind evaluation will be ensured by using a matching placebo syrup of the same color, shape, and taste as the intervention syrup. The quality of Glasthma syrup and matching placebo will be carefully controlled, checked, and verified by the researchers.

5. Sample size

The sample size used to evaluate the initial results needs to

 https://doi.org/10.3831/KPI.2022.25.3.233

be sufficient to achieve statistical and clinical significance. According to the L:M literature [29], a sample size of 5 patients was obtained: with an expected loss of 20%, 7 patients were selected. The sample size obtained based on FEV1 [30] and ACQ7 questionnaire [31] was also the same. Hence, a sample size of 7 participants in each group corresponds to a statistical power of 90%, ignoring 0.05 bilateral type I error, to detect a difference of 2.5 in this experiment with p-values less than 0.05 indicating statistical significance. We increased the sample size to 10 participants per group taking into account a 20% loss for follow-up and other potential losses related to non-compliance and quality control.

Researchers will attend a training session to prepare for their role. Each will be given a copy of the workflow and asked to commit to the protocol. The training will provide information on registration process and assessment of quality of life. PEF and blood tests and urinalysis will be performed by relevant specialists.

The data will be collected in a report file and entered into a pre-designed statistical software form. During the trial period, data will be entered and recorded twice by two different users, and any changes made on the data will be recorded and dated on the relevant forms. Two qualified people will check the quality of the data regularly. Data review and monitoring during the project will be performed by an independent supervisor other than the project sponsor or researcher. It is the responsibility of the Mashhad Medical University to monitor the data and the trial process and, if necessary, decide to terminate the study early.

RESULTS

1. Outcomes

Based on previous studies, the changes in patients' clinical symptoms and evaluation of lung function and intestinal permeability from the beginning to the end of the follow-up period were selected as the primary outcome of the research design.

The Asthma Control Questionnaire (ACQ) will also be used to assess the severity of the symptoms. The first five questions are about the symptoms of the disease. Question 6 examines the use of rescue drugs, and Question 7 examines the level of FEV1 in pre-bronchodilators. Each parameter is categorized from 0 (fully controlled) to 6 (fully uncontrolled). The minimum clinically significant difference is 0.5 [32].

Lung function test with HI-801 multifunction spirometer, change in forced expiratory volume per second (FEV1), ratio of forced vital capacity captured by forced expiratory volume per second (FEV1/FVC) before and after drug withdrawal in the intervention and placebo groups will be examined.

To determine gut permeability, we will measure the ratio of mannitol in the 5-hour urine at the beginning and end of the intervention. In this method, non-metabolized sugar molecules in the quantity of 5 grams of lactulose and 2 grams of mannitol in the form of sachet will be used and the degree of permeability or malabsorption of the intestine will be determined by the amount of secretion of these two sugars in 5-hour urine by standard LC-MS/MS (6410 LC/MS/MS triple quadrupole). The standard required amount is diluted with 10 mm ammonium acetate phase in HPLC grade water: ACN (80:20), SIL column of 25 cm, injection volume of 10 μL, flow rate of 0.6 mL/min. The negative status for lactulose is 341.2/161 or 341.2/101.1, while that for mannitol 181.1/101 or 181.1/89. The tests will be performed in a quality control laboratory.

As the secondary outcome, the patients' quality of life will be assessed using the Asthma Short Quality of Life Questionnaire (mini-AQLQ) at the beginning and end of the intervention [33]. This questionnaire comprising 15 questions will evaluate disease symptoms, environmental effects, patients' feelings, and limitations in patients' activity. For each question, the scores vary from 0 to 6; the lower the score, the lower the quality of life. The minimum clinically significant difference is 0.5 [34].

Laboratory tests to be performed include analysis of whole blood samples, total serum IgE levels, renal and liver function tests, urinalysis, and ClCr at the start and end of the intervention. In this study, patients will be excluded from the study if any disease is observed according to the test results at the start of admission. Changes in each dose are normally recorded to assess the efficacy or possible side effects of the drug.

In addition, other conditions, such as the need for hospitalization or emergency treatment and use of rescue medication, will also be recorded. If we notice symptoms of other diseases during the intervention, or if a patient requires an unforeseen medication, the patient will be excluded from the study, and the results will be recorded.

2. Safety assessment

Liver and kidney function tests will be performed using blood and urine samples at the beginning and end of the inter-

vention. During the intervention, researchers will also follow up with patients, and any signs, symptoms, and unexpected feelings will be recorded, reported, and linked to the experimental drug.

Results, severity, time of onset, duration, duration of treatment, and follow-up of side effects will be recorded in the report form. All side effects will be assessed to examine the causal impact of the intervention according to the criteria established by the Iranian National Biomedical Research Ethics Committee.

Participants will be excluded from the study if they experience intolerable side effects, acute or persistent organic disease, new-onset disease, a need to take non-asthma medication, or patient dissatisfaction during the study period. The patients' withdrawal from the plan will be recorded stating the reasons for discontinuing the drug and the final date of its use.

Deleted and terminated projects will be analyzed in the final report. Withdrawal of the patient without any reason is acceptable and will not interfere with the continuation of the daily treatment of the patient.

The researchers will explain the results of the clinical and laboratory tests to the patients. Participants will be provided with ongoing support throughout the study, including free registration, medical consultation, and follow-up.

3. Statistical analysis

Data analysis will be performed by independent statistical experts using IBM Statistics 16.0 software. Quantitative data will be expressed as mean and standard deviation, or median and quadratic range. Dual data, such as symptom recurrence, will be shown as 95% hazard ratios and confidence intervals. A p-value less than 0.05 will be considered to indicate a statistically significant difference.

Basic characteristics will be described using standard statistical analysis methods. Continuous variables will be analyzed using t-tests, while classified variables will be analyzed using chi-square tests. The main analysis will include the treatment intent and the subject of each protocol for initial results. The latter prospective approach will be used in an intention-to-treat analysis to assign missing data.

Results of quality of life scores, lung function tests, and blood and urine tests recorded at the start of the study will be compared with those recorded at the end of the intervention. Analysis of variance will be performed to compare the differences between the two groups in the levels changes from baseline to any time point, and paired t-tests will be used to compare pre-treatment and post-treatment data in the same group. Mixed effects from linear or logistic regression will be used to analyze factors that influence changes in outcomes by adjusting for baseline characteristics and other variables. Any causal relationship between the intervention and side effects will be considered.

DISCUSSION

The present protocol describes a placebo-controlled three-blind randomized clinical trial to examine the effects of an herbal formula on the intestinal-pulmonary axis by measuring intestinal permeability indices in addition to assessing the clinical signs of asthma and changes in lung function. In addition, a 4-week follow-up period following the 4-week treatment period will provide critical data on the rate of symptom recurrence in each group. To our knowledge, this is the first study to simultaneously measure the effects of herbal medicines on respiratory parameters and intestinal permeability.

CONCLUSION

In this protocol, the effects of drugs on the gastrointestinal and respiratory systems will be investigated. If the results demonstrate the drug's effectiveness on any system, the formula will be used in future clinical trials with larger samples.

ACKNOWLEDGEMENT

The researchers are particularly grateful to the staff in the hematology, biochemistry and spirometry labs for their help in getting the job done.

This study is a part of PhD thesis of Dr. Shahin Saeidinejat and supported by Mashhad University of Sciences.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

FUNDING

This high-priority trial has been approved by Mashhad University of Medical Sciences as the main project of Dr. Saeidina-

jat's doctoral dissertation. The project sponsor is not involved in the design, collection, analysis or interpretation of the data. Availability of data and materials.

TRIAL REGISTRATION

Iranian Clinical Trial Registry (https://www.irct.ir), IRCTID: IRCT20210309050643N2. Registered on 2021-07-19.

AVAILABILITY OF DATA AND MATERIALS

The data used and analyzed during the study will available at the request of the relevant author.

PUBLICATION POLICY

Our results will publish in reputable journals, regardless of positive or negative results.

RECRUITMENT

For this study began on December 23, 2021, under IRCT20210309050643N2 agreement. Final participants are expected to complete the 1-month follow-up evaluation on 23-04-2022.

ABBREVIATIONS

PM, Persian Medicine; FEV1, 1st second volume of forced exhalation; FVC, forced expiratory volume; PEF, expiratory flow peak; ACQ, Asthma Control Questionnaire; mini-AQLQ, Asthma Short Quality of Life Questionnaire; ACT, asthma control Test; AE, Adverse event.

AUTHORS' CONTRIBUTIONS

In this study, AD and SS conducted proposal design. The AA and MM have also reviewed and approved the recommendation. MK will statistically analyze the result of the project. RS has played an important role in identifying drug and placebo formulations and designing drug safety trends. The final version of this manuscript has been read and approved by all authors.

ETHICS COMMITTEE APPROVAL

The trial was approved by the Ethics Committee of Biomedical Research - Medical Sciences (IR.MUMS.REC.1400.076). In designing the consent form, the confidentiality of information, how to inform patients of the possible benefits and risks. The drafting of the protocol and any modifications will be carried out with the consent of the ethics committee. Informed consent will obtain from patients, and The patient's details will not mention in the results The authors declare that they have no competitive interests.

ORCID

Ali Reza Derakhshan, https://orcid.org/0000-0002- 3597-1312
Shahin Saeidinejat, https://orcid.org/0000-0002-1614-0855
Majid Khadem-Rezaiyan, https://orcid.org/0000-0003-2698-176X
Amir-Mohammad-Hashem Asnaashari, https://orcid.org/0000-0003- 2960-7132
Majid Mirsadraee, https://orcid.org/0000-0003-3420-9438
Roshanak Salari, https://orcid.org/0000-0003-4690-7823
Farahzad Jabbari-Azad, https://orcid.org/0000-0003-0673-4809
Shima Jalali, https://orcid.org/0000-0002-0696-2564
Shabnam Jalali, https://orcid.org/0000-0002-9093-0660

REFERENCES

1. Farahmand M, Khalili D, Ramezani Tehrani F, Amin G, Negarandeh R. Effectiveness of Echium amoenum on premenstrual syndrome: a randomized, double-blind, controlled trial. BMC Complement Med Ther. 2020;20(1):295.
2. Nejatbakhsh F, Karegar-Borzi H, Amin G, Eslaminejad A, Hosseini M, Bozorgi M, et al. Squill Oxymel, a traditional formulation from Drimia Maritima (L.) Stearn, as an add-on treatment in patients with moderate to severe persistent asthma: a pilot, triple-blind, randomized clinical trial. J Ethnopharmacol. 2017;196:186-92.
3. Hosseini SA, Zilaee M, Shoushtari MH, Ghasemi Dehcheshmeh M. An evaluation of the effect of saffron supplementation on the antibody titer to heat-shock protein (HSP) 70, hsCRP and spirometry test in patients with mild and moderate persistent allergic asthma: a triple-blind, randomized placebo-controlled trial. Respir Med. 2018;145:28-34.
4. Kaveh S, Kaveh N, Agin K, Sadr S, Choopani R, Rouzbahani AK. The effect of compound honey syrup on clinical manifestation of the adult asthma patients: a randomized, double-blinded,

placebo-controlled clinical trial. Trad Integr Med. 2022;7(2):195-202.
5. Emtiazy M, Oveidzadeh L, Habibi M, Molaeipour L, Talei D, Jafari Z, et al. Investigating the effectiveness of the *Trigonella foenum-graecum* L. (fenugreek) seeds in mild asthma: a randomized controlled trial. Allergy Asthma Clin Immunol. 2018;14:19.
6. Javadi B, Sahebkar A, Emami SA. Medicinal plants for the treatment of asthma: a traditional Persian medicine perspective. Curr Pharm Des. 2017;23(11):1623-32.
7. Tavakoli-Dastjerdi S, Tavakkoli-Kakhki M, Derakhshan AR, Teimouri A, Motavasselian M. Dietary modifications in fissure-in-ano: a qualitative study based on Persian medicine. Curr Nutr Food Sci. 2020;16(6):860-5.
8. Ghaemi H, Masoompour SM, Afsharypuor S, Mosaffa-Jahromi M, Pasalar M, Ahmadi F, et al. The effectiveness of a traditional Persian medicine preparation in the treatment of chronic cough: a randomized, double-blinded, placebo-controlled clinical trial. Complement Ther Med. 2020;49:102324.
9. Yue Y, Wu S, Li Z, Li J, Li X, Xiang J, et al. Wild jujube polysaccharides protect against experimental inflammatory bowel disease by enabling enhanced intestinal barrier function. Food Funct. 2015;6(8):2568-77.
10. Vaughan A, Frazer ZA, Hansbro PM, Yang IA. COPD and the gut-lung axis: the therapeutic potential of fibre. J Thorac Dis. 2019;11Suppl 17:S2173-80.
11. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. Mucosal Immunol. 2019;12(4):843-50.
12. Enaud R, Prevel R, Ciarlo E, Beaufils F, Wieërs G, Guery B, et al. The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Front Cell Infect Microbiol. 2020;10:9.
13. Marsland BJ, Trompette A, Gollwitzer ES. The gut-lung axis in respiratory disease. Ann Am Thorac Soc. 2015;12 Suppl 2:S150-6.
14. Jorjani E. [Treasure of Khwarazm Shah]. Tehran: Entesharat-e Bonyade Farhang-e Iran; 1976. Persian.
15. Aghili SMH. [Aghili's treatments]. Tehran: Research Institute for Islamic and Complimentary Medicine; 2008. Persian.
16. Jorjani SE. [Khofi Alaii (Hidden book of Alaii)]. Velayati A, Najmabedi M, editor. 2nd ed. Tehran: Ettela'at Press; 1990. Persian.
17. Mirsadraee M, Moghaddam SK, Saeidi P. Effect of borago extract on moderate persistent asthma, a phase two randomized, double blind placebo-controlled clinical trial. Eur Respir J. 2016;48 Suppl 60:PA4116.
18. Jin J, Boersch M, Nagarajan A, Davey AK, Zunk M. Antioxidant properties and reported ethnomedicinal use of the genus *Echium* (Boraginaceae). Antioxidants (Basel). 2020;9(8):722.
19. Anushiravani M, Manteghi AA, Taghipur A, Eslami M. Comparing effectiveness of a combined herbal drug based on Echium amoenum with citalopram in the treatment of major depressive disorder. Curr Drug Discov Technol. 2019;16(2):232-8.
20. Nelson JL, DeMichele SJ, Pacht ER, Wennberg AK. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants on antioxidant status in patients with acute respiratory distress syndrome. JPEN J Parenter Enteral Nutr. 2003;27(2):98-104.
21. Mirsadraee M, Khashkhashi Moghaddam S, Saeedi P, Ghaffari S. Effect of Borago officinalis extract on moderate persistent asthma: a phase two randomized, double blind, placebo-controlled clinical trial. Tanaffos. 2016;15(3):168-74.
22. Baars EW, Jong MC, Boers I, Nierop AF, Savelkoul HF. A comparative in vitro study of the effects of separate and combined products of Citrus e fructibus and Cydonia e fructibus on immunological parameters of seasonal allergic rhinitis. Mediators Inflamm. 2012;2012:109829.
23. Shakeri A, Hashempur MH, Mojibian M, Aliasl F, Bioos S, Nejatbakhsh F. A comparative study of ranitidine and quince (Cydonia oblonga mill) sauce on gastroesophageal reflux disease (GERD) in pregnancy: a randomised, open-label, active-controlled clinical trial. J Obstet Gynaecol. 2018;38(7):899-905.
24. Naeimi M, Kianifar H, Memariani Z, Kamalinejad M, Bijani A, Saghebi R, et al. Comparison of the efficacy of ranitidine and quince syrup on gastroesophageal reflux disease in children. Complement Ther Med. 2019;45:215-21.
25. Aghili MH. [Khulasah al-Hikmah]. Tehran: Research Institute for Islamic and Complementary Medicine; 2008. Persian.
26. Gargari G, Deon V, Taverniti V, Gardana C, Denina M, Riso P, et al. Evidence of dysbiosis in the intestinal microbial ecosystem of children and adolescents with primary hyperlipidemia and the potential role of regular hazelnut intake. FEMS Microbiol Ecol. 2018;94(5):fiy045.
27. de Souza RGM, Schincaglia RM, Pimentel GD, Mota JF. Nuts and human health outcomes: a systematic review. Nutrients. 2017;9(12):1311.
28. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, et al. International severe asthma registry (ISAR): protocol for a global registry. BMC Med Res Methodol. 2020;20(1):212.
29. Rabbani GH, Teka T, Saha SK, Zaman B, Majid N, Khatun M, et al. Green banana and pectin improve small intestinal permeability and reduce fluid loss in Bangladeshi children with persistent diarrhea. Dig Dis Sci. 2004;49(3):475-84.
30. Zhang HP, Wang L, Wang Z, Xu XR, Zhou XM, Liu G, et al. Chinese herbal medicine formula for acute asthma: a multi-center, randomized, double-blind, proof-of-concept trial. Respir Med. 2018;140:42-9.
31. Urata Y, Yoshida S, Irie Y, Tanigawa T, Amayasu H, Nakabayashi

M, et al. Treatment of asthma patients with herbal medicine TJ-96: a randomized controlled trial. Respir Med. 2002;96(6):469-74.
32. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902-7.
33. Grammatopoulou E, Skordilis E, Koutsouki D, Baltopoulos G. An 18-item standardized Asthma Quality of Life Questionnaire-AQLQ(S). Qual Life Res. 2008;17(2):323-32.
34. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the mini asthma quality of life questionnaire. Eur Respir J. 1999;14(1):32-8.