

## Effects of *Ziziphus jujuba* on the Prevention of Drug Induced Liver Enzyme Disorders in Pulmonary Tuberculosis Patients: Protocol for Randomized controlled trial

Seyedeh Zahra Maddahi<sup>1, 2</sup> , Assie Jokar<sup>3, 4</sup> , Nasser Behnampur<sup>5</sup> , Mohammad Kamalinejad<sup>6</sup> , Moloud Fakhri<sup>4</sup> 

<sup>1</sup>Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

<sup>2</sup>Antimicrobial Resistance Research Center, Mazandaran University of Medical Sciences, Sari, Iran

<sup>3</sup>Persian Medicine Department, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

<sup>4</sup>Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

<sup>5</sup>Department of Biostatistics, Health Management and Social Development Research Center, Golestan University of Medical Sciences, Gorgan, Iran

<sup>6</sup>School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

### Article Info

#### Article type:

Research Article

#### Article history:

Received: Dec. 8, 2021

Revised: Jun. 25, 2022

Accepted: Aug. 20, 2022

Published online: Feb. 16, 2023

#### ✉Correspondence to:

Dr. Moloud Fakhri, Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran.

Tel: +98 1133244893

Fax: +98 1133244894

Email: mmfir@yahoo.com

Dr. Assie Jokar, Persian Medicine Department, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

Tel: +98 9116399024

Fax: +98 -

Email: a.jokar@mazums.ac.ir

### ABSTRACT

Liver damage is the most common complication of anti-tuberculosis drugs, but there is currently no standard prevention for it. The main purpose of this study is to determine the effectiveness of *Ziziphus jujuba* (*Z. jujuba*) syrup on the prevention of liver enzyme disorder in TB patients.

This study is a protocol for randomized controlled trial. 48 patients will be included in the study who will be randomly assigned to one of the two groups of *Z. jujuba* syrup or placebo syrup based on the block randomization. Liver enzyme tests are measured at the beginning of the study, as well as days 14 and 28 of the study, which will be the primary outcome. The standard Visual Analog Scales questionnaire will be completed on days 0, 14, and 28 to assess cough, anorexia, and nausea in patients. The standard SF-36 quality of life questionnaire will be completed on days 0 and 28 of the study, which will be evaluated as the secondary outcome of the study.

The hypothesis of the study is that the incidence rate of liver enzyme disorder will be lower in patients treated with *Z. jujuba*, compared to those who received the placebo.

**Keywords:** Tuberculosis, *Ziziphus jujuba*, Liver enzyme disorder, Protocol study, Clinical trial

**How to cite this article:** Maddahi SZ, Jokar A, Behnampur N, Kamalinejad M, Fakhri M. Effects of *Ziziphus jujuba* on the Prevention of Drug Induced Liver Enzyme Disorders in Pulmonary Tuberculosis Patients: Protocol for Randomized controlled trial. J Bas Res Med Sci. 2022; 10(4):1-11.



© The Author(s).

Publisher: Ilam University of Medical Sciences

**Trial Registration:** The protocol of this study was registered in the Iranian Clinical Trials Registration Center (registration code IRCT20181107041586N1) on 2019-08-10.

**Protocol Version:** This paper is the first version of the protocol.

## Introduction

Pulmonary tuberculosis (TB) is an infectious disease caused by *Mycobacterium TB* (1). This disease is the leading cause of death from a single infectious agent disease and is ranked tenth in the list of the global burden of disease (2). Among the relatively noticeable side effects of the medications of this disease, liver injury is the most common and serious complication (3), which has various incidence rates in different parts of the world (4-7). The incidence rate of this disease in Iran has been reported to be 4.9-27.7% in different regions, which is also high (3, 8, 9).

Currently, our knowledge of the mechanism of hepatotoxicity caused by anti-tuberculosis medication is insufficient (10). The liver, as the most important metabolizer of anti-tuberculosis drugs, plays a key role in cleansing the toxins of such drugs. More than 50% of cases of acute liver failure are due to drug-induced liver intoxication, and this problem accounts for about 10% of liver transplants (11, 12).

Patients with tuberculosis who experience symptomatic hepatitis (anorexia, dark urine, nausea, and abdominal pain) or a 5-6-fold increase in liver enzymes, even without clinical symptoms, need to change their treatment protocol and often stop all medications. This can be costly for the patient and society, and increase the risk of transmission to others, drug resistance, and even death of the patients (1, 13).

Given that in recent years the WHO has emphasized the use of native plants in each land, it can be very helpful to use traditional Persian medicine resources to find an effective medicine for this disorder (14). *Ziziphus jujuba* (*Z. jujuba*) is one of the medicinal plants that has been used in ancient Iranian sources for the treatment of liver diseases, as well as chronic coughs, anorexia, and digestive problems (which are complications of TB) (15). This plant has many flavonoid and polyphenolic

compounds and antioxidant effects (16). Various studies on the effects of *Ziziphus* plant families have shown that they have hepatoprotective effects and can reduce the liver enzymes in mice exposed to toxins and drugs, which appear to be due to the above-mentioned antioxidant properties (16, 17).

Based on the literature review in Persian and English sources and databases, no clinical trial has been conducted on this issue, and the previous studies had been performed on animals. The present study aimed to investigate the effectiveness of jujube syrup on the prevention of elevated liver enzymes in TB patients and compare the obtained results with those of the placebo group in the form of phase III clinical trial. The secondary goal is to investigate the effectiveness of *Ziziphus Vulgaris* syrup on the quality of life as well as the amount of cough, anorexia, and nausea in these patients using Visual analog scales (VAS).

## Materials and Methods

This protocol is reported according to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT2013) (18). The main purpose of this study is to determine the effectiveness of jujube syrup on the prevention of liver enzyme disorder in TB patients. The secondary goal is to investigate the effectiveness of jujube syrup on the quality of life as well as the amount of cough, anorexia, and nausea in these patients using VAS.

## Participants

The inclusion criteria consisted of 1) willingness to participate in the study, 2) age range of 18-68 years, 3) recent diagnosis of pulmonary TB by an infectious disease specialist or a physician in the health centers, 4) liver test results of less than three times the maximum normal range, 5) no history of liver and kidney failure, and 6) no pregnancy and lactation.

On the other hand, the patients who discontinued the study or experienced severe drug side effects in the course of the study, and those who were misdiagnosed with TB and consumed less than half of the medicine for any reason were excluded from the study. No clinical trial has been performed on the hepatoprotective effect of the liver and the previous studies were conducted on animals. Therefore, a pilot study with a sample size of 7 cases in each group was performed and the mean and standard deviation of both ALT and AST variables were used to determine the sample size. Finally, the maximum sample was used for the conduction of the study. By the application of these values in the sample size formula for two independent and parallel groups, the sample size of each group was calculated at 24 subjects:

$$\alpha = 0.05, \beta = 0.20$$

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (SD_1^2 + SD_2^2)}{(\mu_1 - \mu_2)^2}$$

### Study Design

The present study is a multicentral, double-blind, randomized, controlled, and superiority trial with parallel groups with an allocation ratio of 1: 1. This exploratory phase III clinical trial was registered in IRCT (registration code: IRCT20181107041586N1) on 2019-08-10. In general, 48 patients will be entered in this study. The sample selection process will be continued for 9 months to obtain enough samples. The sample size will be divided into two groups. Since Golestan is one of the two provinces with the highest incidence and prevalence rate of tuberculosis in Iran, the patients will be selected from five health centers in Golestan province located in Gorgan, Aliabad, Azadshahr, Ramian, and Gonbad cities (19). Eligible patients who had recently been diagnosed with pulmonary tuberculosis will be identified based on the TB register system. The study flowchart is presented in Figure 1.

### Randomization and Allocation Concealment

Treatment allocation will happen when participants meet the inclusion criteria and fill out the informed written consent form. Simultaneous sampling was not possible due to the type of disease. Therefore, the patients were divided into two groups of 24 (intervention and placebo) through the block randomization method. Since the number of cases in each group is equal (allocation ratio of 1: 1) the best way is to create block sizes of four. With the random selection of the block, the number of each patient and the type of intervention for them is determined using closed envelopes. It should be noted that all the medicines prepared by the Faculty of Pharmacy were numbered and coded using randomization software.

### Blinding

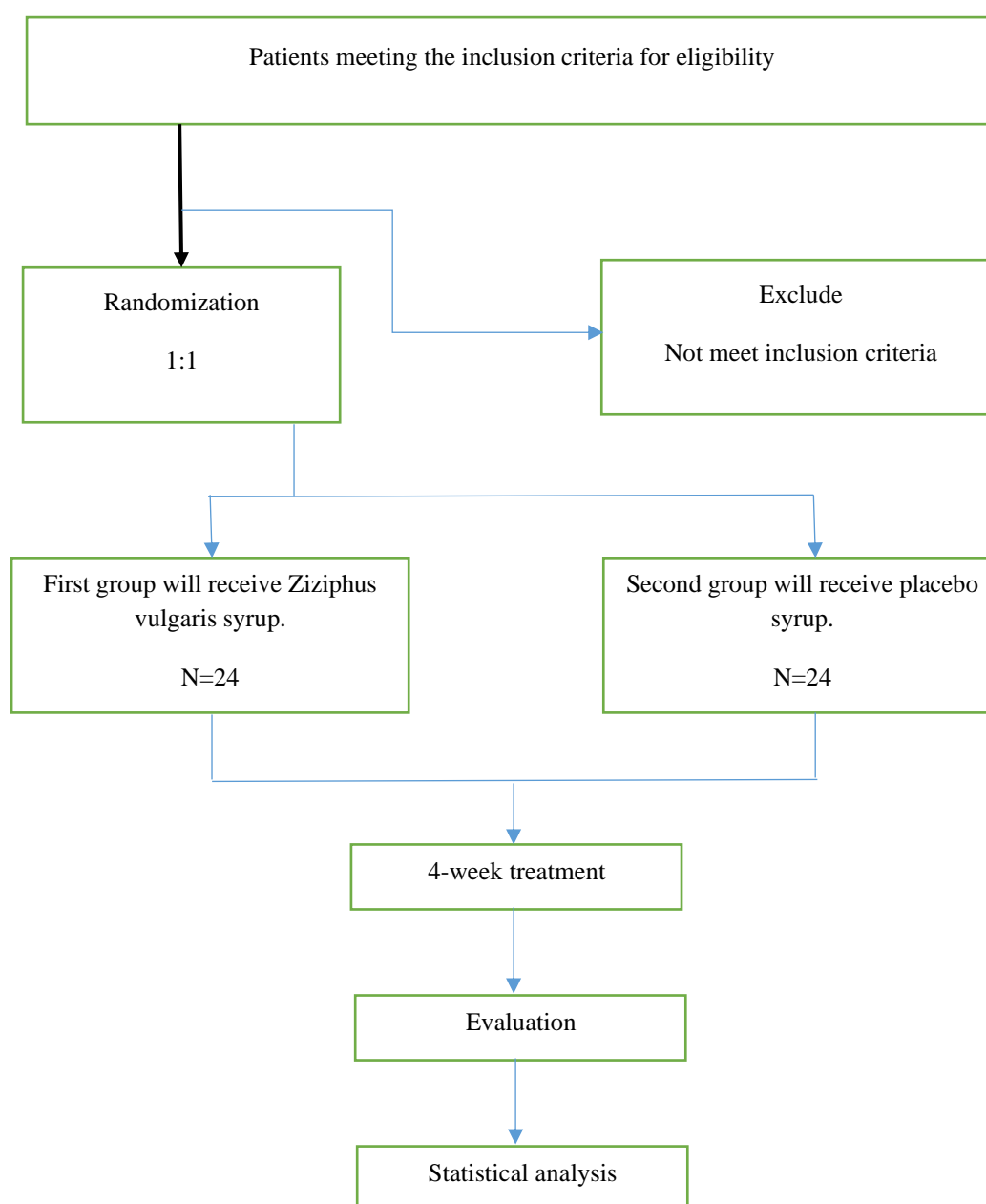
To make the study blind, after randomization and allocation of individuals to two groups, the medicines of the intervention and placebo groups were placed in a box and coded by a statistician who is not involved in the trial process. Therefore, patients, researchers, TB experts, DOTs agents, and laboratory staff will not know which patient receives what type of treatment. After finding each eligible new patient, the statistician will announce the code to the researcher and the researcher will continue the project without knowing the identity of the patient. Moreover, *Z. jujuba* and placebo syrups are similar in appearance (inside bottles with matte glass and the same shape and size) and concentration which will remain unknown to the project managers and participants until the end of the data analysis (double-blind).

### Interventions

In both groups, patients will receive their routine anti-tuberculosis medications based on the WHO directly observed therapy

short-course (DOTS) Standard plan and the National TB Guideline on a daily basis under the direct supervision of primary health workers or TB experts in the rural health centers (21). These executives are under the direct supervision of the person in charge of TB patients in each city and at a higher level the person in charge of TB

patients in the province. During the first two months of treatment, the patients were visited by the TB doctor of the city every two weeks so that in case of a problem, they were referred to an infectious disease specialist.



**Figure 1.** The diagram showing the study implementation method and its steps.

The intervention method is shown in Figure 1. The eligible participants were equally divided into the intervention and placebo groups based on block randomization (block size of four). Demographic

characteristics, including gender, age, occupation, and pre-intervention variables, were investigated by the researcher and recorded in the demographic form.

Eligible patients will first receive an oral explanation of the purpose of the study, its importance and benefits, the general procedure, and the treatment duration. If they are willing to participate, written informed consent were obtained from them. Afterward, the demographic characteristic and medical history forms were completed for the patients. During the 4-week treatment period in both groups treated with jujube syrup or placebo, daily consumption of DOTS anti-tuberculosis drugs (according to the national guideline of TB) was prescribed by primary health workers or experts in the health centers (21). Moreover, at the beginning and end of the treatment, as well as the end of the second week, blood samples for liver tests were taken from the patients.

The standard SF-36 (Short Form Health Survey Questionnaire) quality of life questionnaire, the validity, and reliability of which had been confirmed in Iran, were completed with the help of the project manager before the intervention and at the end of the fourth week of the treatment (22). The VAS were completed before the intervention and at the end of weeks 2 and 4 of the study for all the patients. In addition to being under the day-to-day care of the medical staff, participants were evaluated by the researcher on a weekly basis for the incidence and severity of drug side effects or any other problem.

The syrup (medicine and placebo) was given to the cases in a dose of 5 ccs twice a day (20 min after breakfast and dinner). Jujube and placebo syrups are quite similar regarding the appearance of the bottle (shape, color, and size) and the concentration of the drug, and will remain unknown to the researchers and participants until the end of the data analysis (double-blind). In addition to the provision of oral explanations to patients, they were provided with all the necessary information about the dosage, treatment duration, and usage in written form. To homogenize all the subjects and create similar behavior in them, an instruction manual was prepared

in written form, and also the necessary training was given to them. Furthermore, they were recommended to contact the researcher if they had any questions or problems.

In case of liver enzymes elevation to five times more than the normal level, or three times more than the normal level with clinical symptoms, such as nausea, anorexia, right upper quadrant pain, and jaundice, the patient were referred to an infectious disease specialist, and they were told to stop the medication for a few days to lower the level of enzymes. Moreover, the patients were told not to use the syrup until the specialist allows them to start taking anti-tuberculosis drugs. The syrup container was inspected by a DOTs agent at the end of the study. If the patient did not consume at least half of the syrup, s/he were excluded from the study. The assessments which should be made at each visit are shown in Table 2.

#### Standardization and Method of Preparation of the Syrup


Jujube fruit with the scientific name of *Z. jujuba* Mill (syn: *Ziziphus Vulgaris* Lamarck) from the Rhamnaceae family is ready for the preparation of the medicine after it is washed and dried. First, based on the concentration, 100 gr of dried *Z. jujuba* without kernels (pulp) should be put in 500 ccs of distilled water and boil it on the flame for 10 min. Afterward, it must be left to cool, and thereafter the contents of the container should be thoroughly mixed and filtered using a suitable filter. Subsequently, its water must be evaporated using the bain-marie method to obtain a dry extract. In this way, 15 gr of dry extract is obtained from 100 gr of dried *Ziziphus Vulgaris*. The resulting extract is prepared as a simple syrup USP with a sugar concentration of 66.7%, which finally results in a 10% syrup. To prepare the placebo syrup, we use the simple syrup USP method to prepare 66.7% syrup. The necessary microbiological tests and



standardizations were performed by the Faculty of Pharmacy of the University of Medical Sciences. Moreover, the total

phenolic and flavonoid compounds of the extract were determined there.

**Table 2.** The assessments which were made at each visit (Participant timeline).

	Allocation	Enrollment	Time			
Visit	Visit 1	Visit 2				
Time point	Day 0	Day 1	After 1 week	After 2 weeks	After 3 weeks	After 4 weeks
Enrollment and evaluation						
Eligibility screen						
Demographic	*					
ALT, AST, ALP	*			*		*
Visual analog scales	*			*		*
Short Form Health Survey Questionnaire	*					*
Randomization and allocation	*					
Drug distribution		*				
Intervention Drug or placebo						

The horizontal line indicates the length of time the participants have been surveyed.

## Outcomes

**Primary Outcomes:** Before the intervention and at the end of weeks 2 and 4 of the procedure, blood samples were taken from all participants for liver tests (ALT, AST, and ALP). For this purpose, 2ml of blood samples were taken from the patients in the health centers of the mentioned cities. They were sent to the health center of the province located in Gorgan city using the cold chain as soon as possible after the separation of serum so that all samples can be studied in the same laboratory with the same kits. The tests were performed by the BS-480 (Minray) autoanalyzer (manufactured by Pars Azmoun, Iran).

**Secondary Outcomes:** The standard SF-36 quality of life questionnaire was completed by the researcher before the intervention and at the end of the 4-week treatment. The validity and reliability of this questionnaire have been confirmed in Iran (22). Moreover, the VAS for the three variables of cough, anorexia, and nausea were completed before the intervention and at the end of weeks 2 and 4 of the study for all patients.

## Safety Assessment

No specific side effects have been caused by *Z. jujuba* on the studied patients. However, during the 4 weeks of the treatment, patients were visited daily by primary healthcare workers who were DOTS agents. They were asked to inform the researcher of any complications or physical and mental problems (related and unrelated) in the patients, within at most 24 hours. The researcher will also notify the executor, sponsor, and ethics committee if necessary. In addition, the researcher will call the patients on a weekly basis to become aware of their problems. Any participant who obtains at least one of the exclusion criteria at any stage of the research were excluded from the study.

## Quality Control

To ensure the quality of this study, a proper framework was considered before the beginning of the trial. Moreover, weekly monitoring was performed by the executor through telephone, and daily face-to-face monitoring will also be performed by the primary health workers during the

implementation of DOTS and any possible problems or complications (related or unrelated) were reported to the researcher. Furthermore, the completion and conformity of the forms and clinical trial procedures were investigated, such as medication compliance and withdrawal of participants.

### Ethical Considerations and Recruitment

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences on 2019.5.18 (ethics code: ID IR.MAZUMS.REC.1398.5326) and has the institutional review board approval. Moreover, it has been approved in IRCT (registration code: IRCT20181107041586N1).

The following were observed in this research:

- The 37 codes of ethics in research (Helsinki Statement, 2013 edition) were observed in this research (20).
- Participation in this study were voluntary and the patients were informed that they could leave the study at any time without affecting the treatment process.
- Written informed consent was obtained from all the patients without any coercion, threats, bribery, or seduction.
- The patients were assured that their personal information is kept confidential and would not be included in the research results.
- All the personal information of the patients is stored on a computer that has a password that is only available to the researcher and no one else has access to it.
- Any revision of the study protocol was reported to the ethics committee.

The Vice-Chancellor for Health Affairs of the University of Medical Sciences was informed the person who was in charge of TB patients in the five selected cities (Gorgan, Aliabad, Ramian, Azadshahr, and Gonbad) about the research, invite them to cooperate, and introduce the researcher to them, in a letter. The person in charge of TB patients in each city had the phone number of the researcher to inform him about any

newly diagnosed and eligible TB patients. In addition to correspondence with colleagues at the health care centers and the multicenter nature of the project, for the better cooperation of the patients, the transportation expenses of the patients were paid by the researcher. The DOT executives will also receive a sum for the daily follow-up on the patients. According to the predictions, the patient selection process will continue for 9 months, or whenever the sample size is completed. The present study abides by ethics and data protection laws. The collected data were kept confidential, according to the ethical principles stated in the declaration of Helsinki (20).

### Data Collection and Management

All source documents, including informed consent forms, questionnaires, and test results, were collected in accordance with standard operating procedures. In order to improve the quality of the data, all forms and questionnaires were completed by the researcher, and all the participants' tests were transferred to the Central Laboratory of the Health Center of the province (Gorgan) where the final evaluations were carried out by the same laboratory scientist and kit. The experiments were evaluated by the BS480 (Mindray) autoanalyzer (manufactured by Pars Azmoun, Iran).

The standard SF-36 quality of life questionnaire, which includes 36 items and its validity and reliability have been confirmed in Iran, were completed and collected by the researcher. The VAS for cough, anorexia, and nausea will also be completed 3 times at two-week intervals. To keep the participants in the study and prevent attrition, the researcher will pay for their transportation expenses. The researcher guarantees that the questionnaires and forms will remain anonymous and that all the collected data during the trial were kept confidential. The final clinical trial data were available to all authors. Moreover, the results were sent to one of the selected journals for publication.

### Data Processing and Statistical Analysis

The results of quantitative traits were described by calculating the mean and standard deviation while the results of qualitative traits were described using relative frequency tables and graphs. The normality of the distribution of quantitative traits in the two groups were examined using the Shapiro-Wilk test. If the normality of the data is confirmed, the homogeneity of the variance-covariance matrix was examined using Mauchly's Test of Sphericity.

After the approval of Mauchly's Test of Sphericity, the repeated measures ANOVA were used to evaluate the effect of the drug, the effect of the time, and the mutual effects of the drug and time. Otherwise, epsilon methods were used, such as Greenhouse-Geisser. If the normality of the data is not confirmed, equivalent nonparametric tests were used. Moreover, if the values of the studied traits are not homogenized before the intervention, repeated measures of ANCOVA analysis were employed. The intention-to-treat method will also be used if necessary and if treatment is not followed. The collected data were analyzed in SPSS (version 18) and R software. A  $p$ -value  $<0.05$  was considered statistically significant.

### Discussion

Hepatotoxicity is the most serious and common complication in TB patients which is caused by anti-tuberculosis drugs. Currently, there is no cure for it and if the patient becomes ill, the medication is stopped or changed, each of which has its own problems.

Given this situation, the best measure that can be considered is the use of medicinal plants which have been used for several thousand years to prevent this complication. A medicine that is consumed during the first few weeks of taking anti-TB drugs, when the risk of liver toxicity is increased and, can protect the liver and

prevent liver damage will have a positive effect on the treatment of these patients.

In recent years, similar studies have been conducted on other plants. In this regard, a study was conducted on the effects of garlic tablets and ginger capsules on liver toxicity in TB patients which did not reveal a significant difference between the two groups (23, 24).

According to the review of related literature, the present study is the first clinical trial to investigate the effect of *Z. jujuba* on the prevention of elevated liver enzymes caused by anti-tuberculosis drugs. However, this study had previously been performed on animals (16, 17). One study conducted by Ebrahimi et al., was performed to determine the effect of *Ziziphus Vulgaris* extracts on mice liver. They showed that *Ziziphus Vulgaris* fruit extract has shielding effects against toxins on liver cells (25). Another study by Amin et al was performed to examine the effects of the water extract of one type of *Zizyphus* on carbon tetrachloride (CCl<sub>4</sub>)-induced hepatic fibrosis, which showed *ZZizyphus Spina-Christi* significantly impede the progression of hepatic fibrosis (26).

It is hoped that the present study will lead to the development of a drug that can prevent liver toxicity in TB patients, and thereby take a significant step towards helping to treat these patients and minimizing the side effects of their treatment.

The strength of this study is its rigorous design, which is a randomized, double-blind, multi-central, parallel-group, placebo-controlled, superiority, and exploratory clinical trial. In addition, for the entire protocol, the spirit 2013 checklist has been completed and were attached.

Moreover, it seems that the form of the drug, which is syrup, will have a positive effect on its reception by the patients, considering that all TB drugs are in the form of tablets and capsules.

This study will reveal whether jujube syrup has the ability to prevent elevated liver enzymes while taking anti-tuberculosis



drugs, and more importantly, whether it can prevent drug-induced hepatotoxicity (DIH) and its widespread side effects. These questions were answered after the study is finished.

## Conclusion

The hypothesis of the study is that the incidence rate of liver enzyme disorder is lower in patients treated with jujube syrup, compared to those who received the placebo.

## Trial Status

This study is the first version of the protocol. Sampling began on November 9, 2019, and is expected to end on May 20, 2020. Only 18 patients were studied at the time of the submission of the article. Therefore, the sampling was not completed yet.

## References

1. Jameson JL. Harrison's principles of internal medicine: McGraw-Hill Education; 2018.
2. Azarkar Z, Sharifzadeh G, Ebrahimzadeh A, Olumi S. Time to Sputum Smear Conversion in Smear-Positive Pulmonary Tuberculosis Patients and Factors for Delayed Conversion. *Iran J Med Sci*. 2016 Jan;41(1):44-7.
3. Sharifzadeh M, Rasoulinejad M, Valipour F, Nouraie M, Vaziri S. Evaluation of patient-related factors associated with causality, preventability, predictability and severity of hepatotoxicity during antituberculosis [correction of antituberculosis] treatment. *Pharmacol Res*. 2005 Apr;51(4):353-8. doi: 10.1016/j.phrs.2004.10.009.
4. Mehta S. Malnutrition and drugs: clinical implications. *Dev Pharmacol Ther*. 1990;15(3-4):159-65. doi: 10.1159/000457640.
5. Parthasarathy R, Sarma GR, Janardhanam B, Ramachandran P,

## Acknowledgments

The authors would like to thank all the staff of the health centers and the laboratory scientist of the laboratories of Gorgan, Ramian, Azadshahr, Aliabad, and Gonbad cities, all the experts of the urban centers and the primary health workers of the rural health centers who cooperated with the researchers to achieve the best possible results. Moreover, the authors appreciate the help of all TB patients and their family members who participated in this study and will participate in the future.

It should be noted that this project was funded by Mazandaran University of Medical Sciences.

## Conflict of Interest

The authors declare that they are no conflicts of interest.

- Santha T, Sivasubramanian S, et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*. 1986;67:99-108. doi: 10.1016/0041-3879(86)90003-6.
6. Purohit S, Gupta P, Sharma T, Gupta D, Chawla M. Rifampicin and hepatic toxicity. *Indian J Tuberc*. 1983; 30:107-9.
7. Taneja DP, Kaur D. Study on hepatotoxicity and other side-effects of antituberculosis drugs. *J Indian Med Assoc*. 1990 Oct;88(10):278-80.
8. GhasemiBarghi R, HajAghaMohammadi A, Samimi R. Drug-induced hepatitis (Abundance and outcome during course of tuberculosis treatment): Seven-year Study on 324 patients with positive sputum in Iran. *Govaresh*. 2011; 16:134-8.
9. Sharifi-Mood B, Kouhpayeh H-R, Salehi M. Incidence of hepatotoxicity

- due to antitubercular medicine and assessment of risk factors. *Iran J Med Sci.* 2006; 6:44-7.
10. Nandi S. Adjuvant Phytotherapy against Antitubercular Drug Induced Hepatotoxicity. *J Bioanal Biomed.* 2016;8:e147. doi: 10.4172/1948-593X.1000e14.
  11. Chang C, Schiano T. Drug hepatotoxicity. *Aliment Pharmacol Ther.* 2007; 25:1135-51. doi: 10.1111/j.1365-2036.2007.03307.x.
  12. Fontana RJ. Acute liver failure including acetaminophen overdose. *Med Clin North Am.* 2008; 92:761-94. doi: 10.1016/j.mcna.2008.03.005.
  13. Tostmann A, Boeree MJ, Aarnoutse RE, De Lange WC, Van Der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol.* 2008; 23:192-202. doi: 10.1111/j.1440-1746.2007.05207.x.
  14. Sodhi CP, Rana SV, Mehta SK, Vaiphei K, Attari S, Mehta S. Study of oxidative-stress in isoniazid-rifampicin induced hepatic injury in young rats. *Drug Chem Toxicol.* 1997 Aug;20(3):255-69. doi: 10.3109/01480549709003881.
  15. Aghili Khorasani M. Makhzan-ol-Adviyah [Storehouse of Medicaments]. Tehran: Tehran University of Medical Sciences; 2009. P: 618-9.
  16. Liu G, Liu X, Zhang Y, Zhang F, Wei T, Yang M, et al. Hepatoprotective effects of polysaccharides extracted from *Zizyphus jujube* cv. Huanghetanzao. *Int J Biol Macromol.* 2015 May; 76:169-75. doi: 10.1016/j.ijbiomac.2015.01.061.
  17. Ebrahimi S, Ashkani ES, Emami Y, Riazifar S. Hepatoprotective Effect of *Zizyphus vulgaris* on Carbon Tetrachloride (CCl<sub>4</sub>) Induced Liver Damage in Rats as Animal Model. *Galen Med J.* 2013; 2(3):88-94. doi:10.31661/gmj.v2i3.95.
  18. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* 2013 Feb 5;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583.
  19. Metanat M, Sharifi-Mood B, Alavi-Naini R, Aminianfar M. The epidemiology of tuberculosis in recent years: Reviewing the status in south-eastern Iran. *Zahedan J Res Med Sci.* 2012;13(9):e93704.
  20. Muthuswamy V. The new 2013 seventh version of the Declaration of Helsinki--more old wine in a new bottle? *Indian J Med Ethics.* 2014 Jan-Mar;11(1):2-4. doi: 10.20529/IJME.2014.001.
  21. Nasehi M, Mirhaghani L. National tuberculosis control guide. Tehran: Andishmand Publisher. 2009:5-21; 2nd edition; Center of Infectious Disease Control, Ministry of Health and Medical Education.
  22. Montazeri A, Goshtasebi A, Vahdaninia M, Gandek B. The Short Form Health Survey (SF-36): translation and validation study of the Iranian version. *Qual Life Res.* 2005 Apr;14(3):875-82. doi: 10.1007/s11136-004-1014-5.
  23. Emrani Z, Shojaei E, Khalili H. Ginger for Prevention of Antituberculosis-induced Gastrointestinal Adverse Reactions Including Hepatotoxicity: A Randomized Pilot Clinical Trial. *Phytother Res.* 2016 Jun;30(6):1003-9. doi: 10.1002/ptr.5607.
  24. Tabarsi P, Fahimi F, Heidarzadeh N, Haghgoo R, Kazempour M, Masjedi M, et al. The Effect of Garcin® in Preventing AntiTB-Induced Hepatitis in Newly Diagnosed Tuberculosis Patients. *Iran J Pharm Res.* 2014 Winter;13(Suppl):169-76.
  25. Ebrahimi S, Sadeghi H, Pourmahmoudi A, Askariyan S, Askari S. Protective Effect of *Zizyphus Vulgaris* Extract, on Liver Toxicity in Laboratory Rats. *Armaghanj* 2011; 16 (2) :172-180.
  26. Amin A, Mahmoud-Ghoneim D. *Zizyphus spina-christi* protects against

carbon tetrachloride-induced liver  
fibrosis in rats. Food Chem Toxicol.

2009 Aug;47(8):2111-9.  
10.1016/j.fct.2009.05.038.

doi: