Cost-effectiveness of Traditional Persian Medicine-Based Diet on Non-Alcoholic Fatty Liver Disease

Marita Mohammadshahi¹, Nafiseh Hosseini Yekta², Mahshid Chaichi-Raghimi³, Mohammadreza Mobinizadeh¹, Zeinab Fakoorfard¹, Parisa Aboee¹, Alireza Olyaeemanesh¹, Zahra Gharib-Naseri4

Received 2023 December 15; Accepted 2024 January 22.

Abstract

Background: In the context of Persian traditional medicine, there are several therapeutic strategies for managing diseases, ranging from lifestyle changes to herbal remedies.

Objectives: Given the application of Persian traditional medicine in the management of chronic diseases, the burden of chronic illnesses, and the public's recourse to traditional medicine specialists, this study aimed to assess the cost-effectiveness of traditional medicine dietary regimens for the treatment of non-alcoholic fatty liver disease from the perspective of the payer.

Methods: In this study, we investigated the cost-effectiveness of providing nutrition counseling for lifestyle modification (changes in the aforementioned Setteh-e-Zarurieah) by a traditional medicine specialist compared to receiving counseling from a nutritionist for nonalcoholic fatty liver disease from the payer's perspective. The outcomes measured were changes in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes, body mass index (BMI), and the grade of fatty liver. Cost and effectiveness data were entered into Excel software, and the ICER ratio was calculated.

Results: The results indicated that the dietary regimen prescribed by Persian traditional medicine when compared to the nutritionist's recommended diet, resulted in a lower decrease in AST and ALT enzymes but led to a greater decrease in BMI (mean change = 0.42) and a significant change in the grade of fatty liver (OR = 9.75). Since the costs of tests, ultrasounds, and visits were equal in both groups, the cost difference was zero. In the first scenario, where traditional medicine is considered an alternative therapy and liver enzymes are the primary focus, providing nutritional counseling services by Persian traditional medicine may not be cost-effective. However, if we consider the grade of fatty liver and BMI as the primary variables, providing nutritional counseling services by Persian traditional medicine may be cost-effective.

Conclusions: Based on the available evidence, the treatment of fatty liver using Persian traditional medicine can be considered an effective and cost-effective complementary (or alternative) intervention. Considering the long-term costs imposed by the health system and insurance organizations, it is predicted that adding visits to Persian traditional medicine specialists may reduce overall healthcare system

Keywords: Traditional Persian Medicine; Non-Alcoholic Fatty Liver; Cost-Effectiveness

1. Background

Fatty liver is a chronic liver disorder characterized by the accumulation of lipids in hepatocytes, usually resulting from fat accumulation in the liver exceeding 5% of its weight, primarily in the perivenular and periportal areas. Fatty liver disease encompasses a spectrum of liver conditions, starting as the accumulation of fat in liver cells, which can progress to chronic and irreversible cirrhosis, leading to the destruction of liver cells. Primary nonalcoholic fatty liver disease is often associated with features of metabolic syndrome, including impaired glucose tol-



¹Iran's National Institute for Health Research, Tehran, Iran
²Department of Traditional Medicine, School of Traditional Medicine. Shahid Beheshti University of Medical Sciences, Tehran, Iran. Traditional Medicine & Matria Medica Research Center, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran Persian Medicine Office, Ministry of Health, Treatment, and Medical Education, Tehran, Iran

⁴Department of Pharmacoeconomics and Pharmaceutical Management, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^{*} Corresponding Author: Alireza Olyaeemanesh, Iran's National Institute for Health Research, Tehran, Iran. Email: arolyaee@gmail.com

erance (IGT), central obesity, hypertension, hypertriglyceridemia, and low HDL. The prevalence of this condition increases with the severity and combination of metabolic syndrome features (1, 2).

While numerous studies have explored the contextual factors contributing to nonalcoholic fatty liver disease, the exact pathogenesis of this multifactorial disease remains unclear. According to research, several factors have been identified as risk factors for this condition, including insulin resistance, oxidative stress, diabetes, blood lipid abnormalities, obesity, and metabolic syndrome (3-5).

Recent studies have reported a prevalence of non-al-coholic fatty liver disease (NAFLD) in Iran at 38.07% over the past 20 years. Various studies have investigated the prevalence of NAFLD in different segments of the Iranian population. In one study, the prevalence of NAFLD in Iran ranged from 2.9% to 7.1% in the general population. This range includes a 2.9% prevalence reported in Rogha et al.'s study and a 43.8% prevalence reported in Amirkalali et al.'s study among adults in northern Iran. The higher rate observed in some studies may be attributed to the elevated prevalence of metabolic syndrome in the Iranian population (6, 7).

In managing NAFLD, various treatment methods are employed; however, determining the most effective treatment method remains a work in progress, with limited research conducted in this area. According to available information, the primary approach involves non-pharmacological treatments, including exercise and dietary modifications for weight loss, discontinuation of potentially harmful medications, and management of diabetes and lipid profiles in patients. If patients do not respond adequately to these measures, pharmaceutical treatments are considered.

Traditional medicine offers another approach to managing NAFLD through dietary control. Traditional treatments focus on addressing the liver's temperament, prescribing warm-natured spices and herbs, both orally and occasionally topically, for individuals with a cold liver temperament. There is an emphasis on consuming a diet rich in warm-natured foods. In cases of a wet liver temperament, warm medications, and spices are recommended, in addition to exercise, dietary adjustments, and detoxification to eliminate excess phlegm. When addressing intrahepatic duct obstruction, diuretics are typically prescribed for obstructions on the convex part of the liver, while laxatives are recommended for obstructions on the concave part of the liver (8, 9).

2. Objectives

Considering the significance of NAFLD and the potential therapeutic benefits of traditional medicine, the objective of this study was to evaluate the cost-effectiveness of traditional medicine dietary regimens for the treatment of NAFLD, with a focus on the payer's perspective.

3. Methods

This research is a cost-effectiveness study that leveraged data from clinical trials to assess the safety and effectiveness of the technology involving lifestyle modification based on the Setteh-e-Zarurieah. The primary aim was to investigate the cost-effectiveness of Persian traditional medicine counseling compared to the absence of counseling in improving liver indicators among patients with NAFLD within the healthcare system of the Islamic Republic of Iran. The study's target population comprised adult individuals diagnosed with NAFLD in Iran. The analysis adopted the payer's perspective, incorporating direct medical costs into its evaluation.

The economic evaluation technique employed in this study was based on a comprehensive review of clinical and economic evidence related to this technology as applied in Iran, along with an assessment of its cost based on domestic prices. To accomplish this, the initial stage involved gathering relevant clinical outcome documents through necessary searches. Subsequently, domestic costing was utilized to analyze the costs associated with implementing this technology in comparison to the control group. Finally, considering the type of scientific evidence available for this technology, a cost-effectiveness assessment technique was applied to compare the use of lifestyle modification counseling against non-counseling in terms of improving fatty liver indicators in individuals with NAFLD within the healthcare system of the Islamic Republic of Iran.

Given the nature of the intervention, which involves the impact of specialized Persian traditional medicine counseling on the efficacy of NAFLD treatment, the study's timeline was synchronized with the clinical trial, extending until the point when treatment outcomes related to fatty liver improvement were achieved.

To assess the cost-effectiveness of the services, an incremental four-quadrant cost-effectiveness plane was utilized. In this plane, the vertical axis represents the difference in the cost of each service, while the horizontal axis depicts the difference in levels of clinical effectiveness. The result of the following ratio can be positioned in each quadrant of this plane, indicating different scenarios of the cost-effectiveness of the technology compared to the reference method. This ratio is derived from the following equation:

$$ICER = \frac{\Delta Cost}{\Delta Outcome}$$

Where ICER represents the incremental cost-effectiveness ratio, Δ Cost is calculated as the difference between C2 (the total cost of the service under investigation) and C1(the total cost of the standard method), and Δ Outcome is calculated as the difference between E2 (the clinical effectiveness of the service under investigation) and E1 (the clinical effectiveness of the standard method)

3.1. Extraction of Clinical Outcomes

To extract clinical outcomes using lifestyle modification counseling compared to no counseling, a systematic review was conducted by collecting relevant studies from reputable databases such as PubMed (Medline), Web of Sciences (ISI), and Scopus. The search was performed using the keywords "traditional (Persian) medicine" and "Nonalcoholic Fatty Liver Disease" up to November 2021. The inclusion criteria were published articles in English and Persian that utilized lifestyle modification counseling as an intervention compared to no counseling as a comparative arm in improving liver function indicators in individuals with NAFLD. The exclusion criteria included unpublished articles, conference and seminar abstracts, biochemical studies, non-clinical studies, and studies conducted on animals. After removing duplicate studies, the titles and abstracts of the remaining studies were reviewed. Finally, the required data were extracted after reading the full texts of the selected articles.

hospitalization, rehabilitation, and expenses associated with managing side effects. Since this study focused on the perspective of the payer, among the various types of costs, direct medical costs were utilized in the cost analysis.

4. Results

Based on the search, a total of 94 articles were identified. After removing duplicates, 81 studies remained. Subsequently, two independent reviewers evaluated their titles, abstracts, and full texts, resulting in the selection of 10 eligible studies. Finally, one randomized clinical trial met the inclusion criteria for further examination (Figure 1).

In health economics, costs are typically divided into

three categories: direct costs, indirect costs, and intan-

gible costs. Direct medical costs refer to expenses directly

associated with the treatment of a specific illness. This

category includes costs related to medication, treatment,

3.2. Cost Analysis

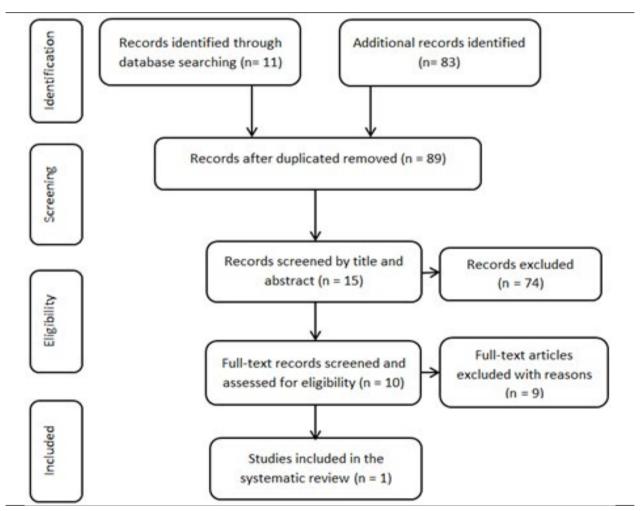


Figure 1. Flowchart of study selection based on PRISMA standard.

Three registered clinical trials investigated the effects of

dietary regimens based on Persian traditional medicine

in the treatment of NAFLD. The results from one of these trials were published. In this clinical trial, the effects of the dietary regimen and nutritional style (one of the six essential factors in the doctrine of essential basics according to traditional Persian medicine) on liver enzymes, fatty liver grade, and body mass index in patients with non-alcoholic fatty liver disease were examined.

In this randomized clinical trial, patients were assigned to either a dietary regimen based on traditional Persian medicine as the intervention group or a low-fat, lowcalorie diet as the control group, using a two-armed design with an active control group. The primary outcome under investigation was changes in aspartate aminotransferase (AST) and alanine aminotransferase levels, while secondary outcomes included changes in liver fat content (assessed through liver tissue inflammation using ultrasound) and changes in the patient's body mass index. All outcomes were assessed at baseline, 6 weeks, and 3 months after treatment. The results are presented in Table 1.

Outcome and Time	Intervention	Control	P-Value
Aspartate aminotransferase, U/L			
Baseline	37.72 ± 13.19	52.61 ± 29.59	0.143
6 weeks	28.94 ± 7.64	39.22 ± 15.99	0.021
12 weeks	24.22 ± 6.29	27.39 ± 7.20	0.169
P-value	< 0.001	< 0.001	
Alanine aminotransferase, U/L			
Baseline	37.56 ± 10.83	62.67 ± 52.07	0.252
6 weeks	44.28 ± 24.37	44.28 ± 24.37	0.013
12 weeks	28.56 ± 7.75	28.56 ± 7.75	0.133
P-value	< 0.001	< 0.001	
Body mass index, kg/m2			
Baseline	25.97 ± 1.28	24.38 ± 2.55	0.013
6 weeks	25.48 ± 1.24	23.97 ± 2.31	0.006
12 weeks	24.97 ± 1.27	23.70 ± 2.19	0.037
P-value	< 0.001	< 0.001	
Fatty liver grade			
Baseline	1.44 ± 0.51	1.61 ± 0.50	0.317
6 weeks	1.22 ± 0.42	1.56 ± 0.51	0.040
12 weeks	0.50 ± 0.51	1.22 ± 0.54	0.003
P-value	< 0.001	< 0.001	

^a Values are expressed as mean ± standard deviation.

Based on the clinical trial conducted for the treatment of patients with NAFLD using counseling provided by Persian traditional medicine specialists regarding lifestyle changes, patients should be visited by a traditional medicine specialist once a month during the treatment to assess their health status and liver function. Blood tests should also be conducted once a month to monitor liver factors. In terms of diagnostic costs, since the number of tests and ultrasounds performed for both groups was the same, they were excluded from the analysis.

4.1. Direct Medical Costs (Treatment)

4.1.1. Physician Visit Cost

Based on the tariff approved by the Cabinet on May 14, 2021, the cost of a physician's visit, including general practitioners, specialists, and PHD-degree specialists

(such as medical doctors with a specialization in traditional Persian medicine), was set at 219,400 Rials for non-electronic prescriptions (with a 20% private and 80% government distribution) and 353,600 Rials for electronic prescription programs. According to the study design, a patient was visited at baseline, in the sixth week, and in the third month.

4.2. Direct Medical Costs (Diagnostic)

- Blood tests to measure ALT and AST levels are conducted at baseline, during the sixth week, and in the third month
- To assess the fatty liver grade or the degree of liver inflammation, ultrasound imaging is used at baseline, during the sixth week, and in the 3rd month.

Based on the data obtained from the clinical trial and the existing discussions regarding traditional medicine, the services in this field can be considered as alternative services. Therefore, only the cost of visiting a traditional medicine doctor, which is equal to the cost of visiting a nutritionist, was included in the cost-effectiveness calculations. Additionally, based on the tariff for specialist physicians provided in both electronic and non-electronic formats in the 1400 tariff book, costs were considered separately in two scenarios. Accordingly, two general scenarios were defined for investigating cost-effectiveness as follows:

1- Considering the counseling service provided by Persian traditional medicine specialists regarding lifestyle changes as alternative medicine and taking into account the tariff for specialist physicians (including traditional medicine and nutrition specialists) based on non-electronic health visits (three physician visits during the treatment period).

2- Considering the counseling service provided by Persian traditional medicine specialists regarding lifestyle changes as alternative medicine and taking into account the tariff for specialist physicians (including traditional medicine and nutrition specialists) based on electronic health visits (three physician visits during the treatment period).

4.3. Costs for the Intervention and Control Groups

If an electronic prescription is implemented:

 $219\ 400 \times 3 = 658\ 200$

If an electronic prescription is not implemented:

 $353\,600 \times 3 = 1\,060\,800$

The results of cost-effectiveness assessment in different scenarios and for various clinical outcomes are presented in Tables 2 and 3:

Table 2. Effectiveness and Costs Based on Each Variable in Different Scenarios						
Strategy and Clinical Variable	E 1	E2	C1 (IRR)	C2 (IRR)		
First scenario						
Aspartate aminotransferase, U/L	-13.50	-25.22	658200	658200		
Alanine aminotransferase, U/L	-12.89	-34.11	658200	658200		
Body mass index, kg/m2	-1.00	-0.58	658200	658200		
Liver grade, OR	1.95	11.7	658200	658200		
Second scenario						
Aspartate aminotransferase, U/L	-13.50	-25.22	1060800	1060800		
Alanine aminotransferase, U/L	-12.89	-34.11	1060800	1060800		
Body mass index, kg/m2	-1.00	-0.58	1060800	1060800		
Liver grande, OR	1.95	11.7	1060800	1060800		

Table 3. Cost-Effectiveness Assessment Resu	ılts		
Strategy and Clinical Variable	Incremental Effective- ness	Incremental Cost	Incremental Cost-Effective- ness
First scenario			
Aspartate aminotransferase, U/L	11.72	0	0
Alanine aminotransferase, U/L	21.22	0	0
Body mass index, kg.m2	-0.42	0	0
Liver grade, OR	9.75	0	0
Second scenario			
Aspartate aminotransferase, U/L	11.72	0	0
Alanine aminotransferase, U/L	21.22	0	0
Body mass index, kg.m2	-0.42	0	0
Liver grade, OR	9.75	0	0

5. Discussion

As shown in Table 3, in terms of effectiveness, the diet prescribed by Persian traditional medicine specialists for lifestyle modification led to a lesser reduction in AST and ALT compared to the low-fat, low-calorie diet provided by nutrition specialists, indicating lower effective-

ness. However, in terms of reducing the body mass index (BMI), it led to a greater reduction, approximately 0.42. A significant difference was observed in the impact of the traditional medicine-based diet on fatty liver grade, with a considerable number of patients transitioning from

a higher grade to a lower grade in the traditional medicine group. The odds ratio, compared to the baseline, increased by 9.75 in this regard

Regarding the costs, since the number of tests and ultrasounds performed was the same for both groups, these were eliminated from the cost calculations. Only the cost of physician visits was considered, which, due to the identical amount for visits by traditional medicine and nutrition specialists, resulted in zero cost. Based on this, in scenarios one and two, where traditional medicine services were considered as an alternative medicine and liver enzymes were taken as the primary variable, the provision of nutritional counseling services from the perspective of traditional medicine would not be cost-effective. However, if fatty liver grade and body mass index are considered effectiveness variables, providing nutritional counseling services from the perspective of traditional medicine can be cost-effective.

Similar to the results of our study, Peng et al. conducted systematic reviews that showed the Chinese herb Danshen for the treatment of nonalcoholic fatty liver disease led to a significant decrease in the levels of ALT and AST (10). Liang et al. conducted a systematic review to assess the efficacy and safety of traditional Chinese medicines for NAFLD, and their results also showed that in about 50 trials, the test group (traditional medicine) was more effective than the control group (usual care) (11). Regarding the Iranian traditional medicine (ITM) diet, Gorji et al. (2017) in their study stated that treatment processes in ITM for NAFLD involve instructions for preserving or restoring health, including six essential principles (Settehe-Zarourieh). Additionally, a proper food regimen is recommended to patients, including some abstinence and using beneficial foods (hepatoprotective in NAFLD) (12).

In general, considering the level of available evidence, Persian traditional medicine can be used as an effective and cost-effective complementary (or alternative) intervention for the treatment of NAFLD. Regarding the costs incurred by the healthcare system and insurance organizations, it is anticipated that adding visits to traditional medicine specialists will lead to long-term cost savings in the healthcare system.

5.1. Study Limitations

Considering that the results of this study are based on a single clinical trial with relatively good quality but a small sample size and short-term follow-ups, there is a need for larger clinical trials with longer follow-up periods to achieve more robust effectiveness and cost-effectiveness results.

Authors' Contribution:

It was not declared by the authors.

Conflict of Interests:

The authors declared that they have no competing in-

Data Reproducibility:

It was not declared by the authors.

Funding/Support:

This research was funded by the Tehran University of Medical Sciences and the Ministry of Health and Medical Education.

References

- Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;346(16):1221-31. [PubMed ID:11961152]. https://doi. org/10.1056/NEJMra011775.
- 2. Huang TD, Behary J, Zekry A. Non-alcoholic fatty liver disease: a review of epidemiology, risk factors, diagnosis and management. *Intern Med J.* 2020;**50**(9):1038-47. [PubMed ID:31760676]. https://doi.org/10.1111/imj.14709.
- Suomela E, Oikonen M, Virtanen J, Parkkola R, Jokinen E, Laitinen T, et al. Prevalence and determinants of fatty liver in normal-weight and overweight young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med.* 2015;47(1):40-6. [PubMed ID:25333756]. https://doi.org/10.3109/07853890.2014.966752.
- Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-57. [PubMed ID:28714183]. https://doi.org/10.1002/hep.29367.
- Petta S, Di Marco V, Camma C, Butera G, Cabibi D, Craxi A. Reliability of liver stiffness measurement in non-alcoholic fatty liver disease: the effects of body mass index. *Aliment Pharmacol Ther.* 2011;33(12):1350-60. [PubMed ID:21517924]. https://doi.org/10.1111/j.1365-2036.2011.04668.x.
- Rogha M, Najafi N, Azari A, Kaji M, Pourmoghaddas Z, Rajabi F, et al. Non-alcoholic Steatohepatitis in a Sample of Iranian Adult Population: Age is a Risk Factor. *Int J Prev Med.* 2011;2(1):24-7. eng. [PubMed ID:21448401]. [PubMed Central ID:PMC3063465].
- Amirkalali B, Poustchi H, Keyvani H, Khansari MR, Ajdarkosh H, Maadi M, et al. Prevalence of Non-Alcoholic Fatty Liver Disease and Its Predictors in North of Iran. *Iran J Public Health*. 2014;43(9):1275-83. eng. [PubMed ID:26175982]. [PubMed Central ID:PMC4500430].
- 8. Afsharipour M. [Non-alcoholic fatty liver disease and its complications from the perspective of Iranian traditional medicine and popular medicine]. *Hist of Med.* 2020;**44**(12):98-111. Persian.
- Yao H, Qiao Y-J, Zhao Y-L, Tao X-F, Xu L-N, Yin L-H, et al. Herbal medicines and nonalcoholic fatty liver disease. World J Gastroenterol. 2016;22(30):6890. https://doi.org/10.3748/wjg.v22.i30.6890.
- Peng H, He Y, Zheng G, Zhang W, Yao Z, Xie W. Meta-analysis of traditional herbal medicine in the treatment of nonalcoholic fatty liver disease. *Cell Mol Biol (Noisy-le-grand)*. 2016;62(4):88-95. eng. [PubMed ID:27188741].
- Liang Z, Chen X, Shi J, Hu H, Xue Y, Ung COL. Efficacy and safety of traditional Chinese medicines for non-alcoholic fatty liver disease: a systematic literature review of randomized controlled trials. Chin Med. 2021;16(1):9. [PubMed ID:33430929]. [PubMed Central ID:PMC7802307]. https://doi.org/10.1186/s13020-020-00422-x.
- Gorji Z, Choopani R, Ghamarchehreh ME, Hekmatdoost A, Dehghan S. The recommended iranian traditional medicine (persian medicine) diet in non-alcoholic fatty liver disease. *Indo Am J Pharm Sci.* 2017;4(12):4551-62.