Review Article

Effect of Medicinal Plants and Natural Products on Liver Enzymes in Non-alcoholic Fatty Liver Patients in Iran: A Systematic Review and Meta-Analysis

Moloud Fakhri[1,2], Hafez Fakheri[3], Mohammad Azadbakht[1,4], Mahmood Moosazadeh[5], Seyde Sedighe Yousefi[1,6]

[1]Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, [2]School of Medicine, Mazandaran University of Medical Sciences, [3]Gut and Liver Research Center, Non-communicable Disease Institute, Mazandaran University of Medical Sciences, [4]Department of Pharmacognosy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, [5]Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute, Mazandaran University of Medical Sciences, [6]Department of Persian Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

Abstract

Background: Nonalcoholic fatty liver is the most common chronic liver disease. Regarding the side effects of synthetic medicines and the variety of natural products in Iran climate, the present study aimed to investigate the effect of medicinal plants and natural products on liver enzymes in patients with non-alcoholic fatty liver disease in Iran using meta-analysis. **Methods:** To extract the intended studies, internal and external databases, including SID, Magiran, IranDoc, PubMed, Scopus, Web of Science, Embase, Cochrane, and Clinical Trial Registration System of Clinical trial.gov, the ISRCTN system, as well as Clinical Trial Registration System affiliated to the World Health Organization were searched. The obtained data were analyzed in STATA.14 software. A *P* value less than 0.05 was considered statistically significant. **Results:** A total of 44 rstudies were reviewed with a sample size of 1298 participant; they were published in the period from 2009 to 2018, silymarin had the highest effect on the reduction of AST (SMD = -2.68), cinnamon excreted the most profound effect on ALT (SMD = -2.69). In addition, cinnamon had the highest effect on gamma-glutamyl transferase (GGT) (SMD:-3.17), and curcumin had the highest effect on alkaline phosphatase (ALP) (SMD = -1.88). In the lipid profile, the effect of medicinal herbs and natural products on lowering total cholesterol and LDL was statistically significant. In the glycemic profile, the effect of medicinal plants and natural products on the reduction of fasting blood sugar, insulin, and hemoglobin A1c levels was statistically significant. **Conclusions:** As evidenced by the obtained results, the highest effect of using natural products was observed in the reduction of GGT, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, respectively; nonetheless, the effect of natural products on ALP reduction was not statistically significant.

Keywords: *Biological products, herbal medicine, Iran, medicinal, non-alcoholic fatty liver disease, plants, therapeutics*

Background

Today, nonalcoholic fatty liver disease (NAFLD1) is the most common chronic hepatic disease. There are various laboratory methods for investigating this disease that measure circulating levels of enzymes, namely aspartate aminotransferase (AST2) and alanine aminotransferase (ALT3), as important blood indicators to assess liver health. Based on the findings of previous studies, high levels of these liver enzymes are not associated with NAFLD.[1] In NAFLD, ALT levels are higher than AST, and it is only in advanced stages of fatty liver and cirrhosis that the predominance of AST over ALT is seen.[2-4]

In total, 20%–40% of people in the world suffer from NAFLD, whereas its prevalence rate in Asia is around 5%–30%.[5] In a meta-analytic study that examined the prevalence of nonalcoholic fatty liver disease and its related factors in Iran in 2016, we saw that in 23 studies with a sample number of 25,865 people, the total prevalence of NAFLD in Iran was estimated at 33.9% (95% CI 26.4%–41.5%). This means that about one-third of the population of Iran suffers from some degree of non-alcoholic fatty liver disease, which is very worrying.[6] Risk factors of NAFLD include high-fat and -protein diet, male gender, metabolic syndrome symptoms, consumption of food before bed, and sedentary lifestyle.[7,8] Various types of anti-NAFLD medications are currently

1 Non-alcoholic fatty liver disease
2 Aspartate aminotransferase
3 Alanine aminotransferase

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Address for correspondence:
Dr. Moloud Fakhri, Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran. School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
E-mail: mmfir@yahoo.com
Dr. Seyde Sedighe Yousefi, Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran. Department of Persian Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
E-mail: s.yousefi@mazums.ac.ir

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under clinical development. In addition, metformin, statin, and bananas, rice, applesauce, and toast (BRAT) diet are currently being tested as NAFLD treatments in clinical trials. However, these drugs have negative side effects, such as the increased risk of infection and osteoporosis.[9-11] As many existing medications are directly or indirectly derived from plants, and recently there has been an interest in herbal and alternative medicines, the researchers have focused on traditional herbal medicines.[12-16] It should be noted that about 80% of the world population relies heavily on complementary and alternative medicine, especially herbal medications for their primary health care.[17-19] Iranians also use herbal medicines to treat some of the common diseases.[20-22] In a similar vein, Maryam Nikkhajuvi conducted a study to evaluate the efficacy of herbal medicines used in the treatment of NAFLD in clinical trials. She indicated that only a few herbs had side effects; nonetheless, the safety of each herbal product can be determined after careful evaluation and long-term follow-up.[23]

It is estimated that by 2030, nonalcoholic fatty liver disease with an obesity epidemic will be one of the leading causes of liver disease and mortality.[24] Considering the relatively high prevalence of nonalcoholic fatty liver disease in Iran and its individual and social complications, and also considering that a large number of studies have been conducted to investigate the effect of different natural products on this disease, in order to combine the results of previous studies and presenting general and accurate results on the effect of each of the natural products on nonalcoholic fatty liver in Iran, the present study was performed by systematic review and meta-analysis. To be able to compare the effect of different natural products and introduce the most effective natural product in reducing the level of liver enzymes.

Methods

Study protocol

The present study used systematic review and meta-analysis methods and aimed to investigate the effect of herbal medicine on the improvement of hepatic steatosis in patients with NAFLD in Iran. This meta-analysis was performed on several clinical trial studies. This study made use of the Preferred Reporting Items for Systematic reviews and Meta-Analyzes (PRISMA)4 Protocol,[25] which is used for systematic review and meta-analysis studies. We posted the protocol for this study on the PROSPERO site (ID: CRD42020153698, Date: 28.04.2020). Moreover, the protocol for this study was recorded at Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences (ID: IR.MAZUMS.REC.1398.6337, Date: 07.12.2019).

Statistical population

Participants in the selected studies were NAFLD patients with no limitations regarding age, gender, race, and type of herbal medicine.

Studied results

Primary results: Eligible trials should have at least one assessment of the serum level of liver enzymes, namely ALT, AST, gamma-glutamyl transferase (GGT5), and alkaline phosphatase (ALP) as the primary result.

Secondary results: Level of blood glucose, blood lipids, bilirubin, alkaline phosphatase, bodyweight loss, body size reduction, body mass index (BMI), and increased physical activity should be mentioned as secondary results.

Search strategy

In this systematic review, electronic databases such as PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar were searched without any limitations regarding date and language. Given that all eligible studies were conducted in Iran, bibliographic databases of Iran, namely SID[26] and Magiran[23] were also evaluated through electronic search. The search was performed using valid and standard keywords, namely " Biological Products**,** Plants, Medicinal, Herbal medicine, therapeutics, Non-alcoholic Fatty Liver Disease, Iran " as well as their Latin and Mesh equivalents (updated to 2019 September 3). Moreover, their combinations were also searched in English databases using conjunctions (AND, OR). Furthermore, the IranDoc research institute was used in order to search for informal sources, theses, research reports, and conference or seminar papers.[27]

Moreover, clinical trial registration systems such as ClinicalTrials.gov,[28] ISRCTN (BioMed Central publisher)[29], and World Health Organization[30] were also searched to find the articles that might have been rejected before publication. Furthermore, the references and bibliographies of all the primary studies that were included at the end of the PRISMA flowchart were also searched manually. For example, the search strategy on the Pabmad site is listed in the appendix.

Inclusion and exclusion criteria

PICO elements include: (population: NAFLD patients, intervention: natural products, comparison: the group that did not use natural products or used placebo, and outcomes: liver enzymes, namely ALT, AST, GGT, and ALP).

Inclusion criteria: Based on the inclusion criteria, the selected primary studies were 1) randomized or nonrandomized clinical trials, 2) with or without blinding, 3) performed on NAFLD patients, 4) with the intervention of natural product, 5) quasi-experimental study, 6) with intervention groups receiving natural products, 7) with

4 Preferred reporting items for systematic review and meta-analysis

5 Gamma-glutamyl transferase

the comparison or control group receiving placebo or no intervention, and 8) with at least one result regarding the serum levels of liver enzymes (i.e., ALT, AST, GGT, and ALP).

Exclusion criteria: On the other hand, the excluded studies were 1) conducted on nonrandomized sample size, 2) case studies, 3) lacking the required information, 4) below the standard based on the quality evaluation checklist of the clinical trials of the Cochrane library, 5) performed on statistical populations other than Iranians, 6) focused on the effects of natural and chemical medicines simultaneously, 7) conducted on alcoholic hepatic steatosis, and 8) not available in full text.

Qualitative evaluation of the studies

After the selection of the primary studies, two authors evaluated them using the evaluation checklist of the Cochrane library, independently. This checklist has 7 different items, each of which evaluates one important aspect of bias in clinical trials. Moreover, each item in the checklist is scored as high risk of bias, low risk of bias, and unknown. After the evaluation of all the studies, first, the inconsistencies between the evaluation results of the two authors were detected and resolved so that they reached a unanimous decision. The results of the qualitative evaluation of the studies are presented.

Data collection

Two researchers extracted the required data from the studies, independently, in order to minimize bias and error in data collection. The researchers entered the extracted data into a form that included the name of the researcher, study title, study population, type of the natural product, duration of use, and the mean values of the liver enzyme scores before and after using natural products. Moreover, a third researcher examined the collected data by the two previous researchers to resolve any possible contradictions.

If the required data was not reported in one of the primary studies, the corresponding author was contacted for the provision of that data. However, if the corresponding authors did not respond to the email, they were conducted three more times at three different time points (with a minimum of 5-day interval).

Statistical analysis

Given the quantitative nature of the primary results in these studies, the effect size of the intervention was calculated. Therefore, it is possible to calculate the intragroup mean difference index (mean difference of serum levels of ALP, AST, ALT, and GGT before and after the intervention) in the intervention group. The standardized mean difference (SMD) index (Formula 1), which is a classical effect size index, indicates the strength of the relationship between the intervention and the studied outcome. Usually, if the SMD is close to zero, it indicates the weakness of the relationship, whereas if it is close to one and even higher, it shows a strong relationship.[16] If the SMD confidence interval crosses zero, then the relationship is not statistically significant and vice versa.

Formula 1:

$$SMD = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation of outcome among participants}}$$

The selected studies were combined regarding their sample size, mean, and standard deviation. Furthermore, the Q Cochrane test and I^2 index were used to evaluate the heterogeneity of the studies. There are three categories regarding the I2 index (I^2 index below *25*% is low heterogeneity, between 25% and 75% is average *h*eterogeneity, and 75% or above is high heterogeneity).[31] The fixed and random effects models are frequently used for low and high heterogeneities, respectively. Therefore, for the purposes of the study, the random-effects model was used in the present research. Data analysis was performed in STATA software (version 14). Furthermore, a P value < 0.05 was considered statistically significant.

Results

Study selection process

Initially, 947 articles were selected by searching the above-mentioned databases. A number of 352 duplicate studies were excluded after examining the title of the studies. The abstracts of the remaining 595 articles were reviewed out of which 517 articles were ruled out based on the exclusion criteria. Out of the remaining 78 articles, 34 more papers were eliminated due to incomplete information or inaccessibility of their full texts. Finally, the remaining 44 articles entered the qualitative evaluation phase, and all of them were found to be of good quality and were entered into the meta-analysis process [Figure 1].

The data of studies that entered the systematic review and meta-analysis process after the qualitative evaluation stage are presented in Table 1.

In 44 investigated studies with a sample size of 1298 participants, the mean age of patients ranged from 11 to 66 years, and they were published from 2009 to 2018. In these studies, the standardized effect size of natural products on liver enzymes was as follows: aspartate aminotransferase (AST):-1.07 (CI 95%: -1.35 to -0.80), alanine aminotransferase (ALT): -0.98 (CI 95%: -1.21 to -0.74), Gamma-glutamyl transferase (GGT): -1.28 (CI 95%: -2.10 to -0.46), and alkaline phosphatase (ALP): -0.52 (CI 95%: - 1.37 to 0.34) [Table 2].

Medicinal herbs and natural products also affect the lipid profile. In the investigation of lipid profile, it was found that the standardized effect size of medicinal plants and natural

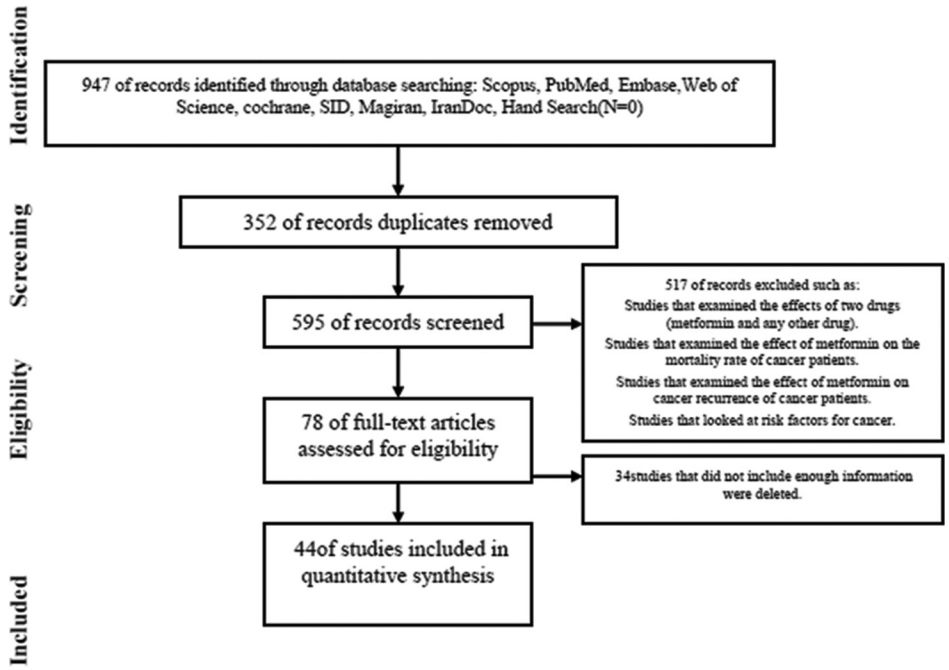

Figure 1: A flowchart of studies into the process of systematic review and meta-analysis

products on total cholesterol, high-density lipoproteins (HDL), low-density lipoprotein (LDL), and triglyceride was as follows: total cholesterol: -0.43 (CI95%: -0.69 to -0.18), HDL: 0.08 (CI95%: -0.22 to 0.38), LDL:-0.34 (CI95%: - 0.53 to -0.15), and triglyceride:-0.21 (CI95%: -0.42 to 0.01) [Table 2].

Regarding the effect of medicinal herbs and natural products on glycemic profile, the standard effect size of medicinal herbs and natural products on fasting blood sugar (FBS) was -0.35 (CI95%: -0.53 to -0.17), insulin: -1.10 (CI95%: -1.89 to - 0.30), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR): -0.30 (CI95%: -0.75 to 0.16), hemoglobin A1c (HbA1C): -1.99 (CI95%: -3.53 to -0.45), and high-sensitivity C-reactive protein (hs-CRP): -0.08 (CI95%: -0.26 to 0.10) [Table 2].

In this meta-analysis, the standardized effect size of medicinal plants and natural products on total bilirubin in patients with nonalcoholic fatty liver was -0.22 (CI95%: -0.50 to 0.06), direct bilirubin: -0.8 (CI95%: -0.30 to 0.15), liver fibrosis: -1.89 (CI95%: -3.83 to 0.04), and liver steatosis: -1.20 (CI95%: -2.20 to -0.21). Nevertheless, weight loss, size reduction, and intense physical activity are also effective in the reduction of liver fat in patients with nonalcoholic fatty liver [Table 2].

In Table 3, we examine the effects of using natural products on the liver enzymes of patients with nonalcoholic fatty liver and compare some subgroups, including the length of natural product use, type of natural product, and mean age of patients.

Regarding the length of natural product use, in the AST group, the lowest and highest effects were observed within 4 and 12 weeks of natural product use, respectively. In this subgroup, the reduction of fatty liver was not statistically significant only in patients who had used natural products for the reduction of nonalcoholic fatty liver for 16 weeks.

Regarding the type of natural products, it can be concluded that curcumin was the least effective with -0.44, whereas the most effective one was silymarin with -2.68. Moreover, the effect of natural products, such as caper, Faseed, ginger, ***Crocus sativus*** *L*., genistein, artichoke, pomegranate juice, and (mixture of *Melissa officinalis L*., *Cinnamomum zeylanicum,* and *Urtica dioica*) were not statistically significant.

Furthermore, when we separated the patients based on their mean age, it was found that the effect of natural products on the reduction of nonalcoholic fatty liver was not statistically significant in the age groups of 50–59 and 60–69 years. In the other age groups, the least impact was detected in two groups of 20–29 and 30–39 years (SMD: -0.79), whereas the highest impact was observed in the age group of 10–19 years (SMD: -9.74; Table 3). In the investigation of ALT enzyme, the effect of natural products on the reduction of fatty liver was not statistically significant in two groups who used natural products for 4 and 16 weeks. Moreover, among the other groups, the minimum and maximum effects were observed in groups who used natural products for 8 and 10 weeks, respectively.

In our evaluation of different types of natural products, it was found that curcumin was the least

Table 1: Specifications of articles which entered into the meta-analysis process

Author	Year of publication	Type of study	City of study	Type of natural products	Duration of natural products (week)	Dose	Age mean (year)	Method	Sample size
Ekhlasi, G[32]	2013	Clinical trial	Tehran	Orange Juice	12	250 ml	39.18	Sonography & blood test	32
Zamani, N[33]	2018	Clinical trial	Shiraz	Zataria multiflora	12	700 mg	36.8	Sonography & blood test	45
Khavasi, N[34]	2017	Randomized clinical trial	Zanjan	Caper	12	40-50 gr	40.32	blood test	22
Askari, F[35]	2013	Clinical trial	Tehran	Cinnamon	12	1.5 gr	39.5	Sonography	23
Yari, Z[36]	2015	Randomized clinical trial	Tehran	Faxseed	12	30 gr	45.04	blood test	24
Hasani, A[37]	2016	Clinical trial	Bardaskan	Chicory	8	200 ml	46.3	blood test	10
Rahimlu, M[38]	2016	Randomized clinical trial	Tehran	Ginger	12	2 gr	45.5	Sonography & blood test	23
Milajerdi, AR[39]	2016	Randomized clinical trial	Natanz	Crocus Satious L.	8	30 mg	54.57	blood test	18
Fathi, M[40]	2016	Clinical trial	Mashhad	Green Tea	8	6 gr	36.5	blood test	10
Esmaeilzadeh-Toluei, MR[41]	2017	Clinical trial	Mazandaran	Ginger	10	1 gr	50.5	blood test	12
Beheshti Namdar, A[42]	2014	Randomized clinical trial	Mashhad	Faxseed Oil	8	1 gr	38.7	Sonography & blood test	30
Moradi-Kelardeh, B[43]	2016	Clinical trial	Tehran	Curcumin	12	80 mg as Nanomicelle	66.72	Sonography & blood test	11
Sheybani Asl, Z[44]	2014	Clinical trial	Zahedan	Cinnamon & Cichorium intybus L.	4	2.5 g chicory and half a gram of cinnamon twice a day	43.55	blood test	25
Rahmani, S[45]	2016	a Randomized placebo-controlled trial	Isfahan	Curcumin	8	500 mg 70mg Curcumin	46.37	Sonography & blood test	40
Panahi, Y[46]	2017	a Randomized controlled trial	Tehran	Curcumin	8	1000 mg	44.98	Sonography & blood test	44
Ebrahimi-Mameghani, M[47]	2017	Randomized clinical trial	Tabriz	Chlorella Vulagaris	8	1200 mg	37	Sonography & blood test	29
Faghihzadeh, F[48]	2014	Randomized clinical trial	Isfahan	Resveratrol	12	500 mg	44.04	Sonography & blood test	25
Famouri, F[49]	2017	Clinical trial	Shahrekord	Silymarin	12	5 mg/Kg/Day	11.8	Sonography	20
Amanat, S[50]	2018	Randomized clinical trial	Shiraz	Genistein	8	250 mg	44.2	blood test	46
Haji agha mohammadi, AA[51]	2012	Randomized clinical trial	Qazvin	Licorice Root Extract	8	2 gr	39.9	Sonography & blood test	33
Panahi, Y[52]	2012	Randomized clinical trial	Tehran	Chlorella Vulagaris	12	1200 mg	51	Sonography & blood test	33
Pezeshki, A[53]	2016	Randomized clinical trial	Isfahan	Green Tea	12	500 mg	20-50	Sonography & blood test	35
Hashemi, SJ[54]	2009	randomized Control trial	Ahvaz	Silymarin	24	280 mg	39.28	blood test	50
Ahmadian, M[55]	2013	Clinical trial	Arak	Pomegranate pills	6	225 mg of dried pomegranate extract	20.46	Sonography & blood test	50
Talebi Pour, B[56]	---	Clinical trial	Zanjan	Chlorella Vulagaris	8	Chlorella supplements made by Algomed Company 3 times a day	35	Sonography & blood test	30
Talebi Pour, B[56]	---	Clinical trial	Zanjan	Artichoke	8	Artichoke Supplement	38	Sonography & blood test	30

Contd...

Table 1: Contd...

Author	Year of publication	Type of study	City of study	Type of natural products	Duration of natural products (week)	Dose	Age mean (year)	Method	Sample size
						from Algomed Company 2 times a day			
Aliashrafi, S[57]	2011-2012	Clinical trial	Tabriz	Chlorella Vulagaris	8	4 tablets of 300 mg daily Chlorella made by Algomed	37		29
Taghvaei, T[58]	2009-2010	Clinical trial	Sari	Silymarin	24	Silymarin tablets 140 mg twice daily	42.9	Sonography & blood test	21
Iranikhah, A[59]	---	Clinical trial	Qom	Silymarin	12	Silymarin Tablets 140 mg 3 times daily	11.73	Sonography & blood test	20
Hajagha mohammadi, AA[60]	---	randomized clinical trial	Qazvin	Silymarin	8	Silymarin 140 mg daily	40.3	Sonography	25
Hajiagha mohammadi, AA[61]	---	randomized clinical trial	Qazvin	Silymarin	8	Silymarin 140 mg daily	33.5	Sonography	22
Anushirvania, A[62]	2016-2017	Randomized, Double-Blind, Placebo-Controlled Clinical Trial	Shiraz	Silymarin	12	Silymarin 140 mg daily	47	Sonography	30
Saadati, S[63]	---	randomized placebo controlled clinical trial	Tehran	Curcumin	12	1500 mg	46.19	blood test	27
Saadati, S[64]	---	randomized placebo controlled clinical trial	Tehran	Curcumin	12	1500 mg	46.19	blood test	27
Mirhafez, SR[65]	---	Randomized, Double-Blind, Placebo-Controlled Clinical Trial	Neyshabur	Curcumin	8	250 mg equivalent to 50 mg pure curcumin	44.8	blood test	32
Jazayeri-Tehrani, SAR[66]	---	Randomized, Double-Blind, Placebo-Controlled Clinical Trial	Tehran	Nano-Curcumin	12	80 mg	41.8	Sonography & blood test	42
Ekhlasi, G[67]	2011	Clinical trial	Tehran	Pomegranate Juice	16	250 ml	39.27	Sonography & blood test	33
Khavasi, N[68]	2016	A Randomized, Double-blind, Clinical Trial	Zanjan	Caper	12	40-50 gr	40.32	blood test	22
Tabatabaee, SM[69]	---	A Randomized, Double-blind, Clinical Trial	Tehran	Green Tea	12	550 mg	41	Sonography, Biopsy, Fibroscan	21
Malekirad, AA[70]	2011	before-after clinical trial	Shiraz	Mixture of Melissa officinalis L., Cinnamomum zeylanicum and Urtica dioica	4	(1.5, 0.5 and 0.25 g/100 mL) twice daily	42.43	blood test	35
Solhi, H[71]	---	randomized clinical trial	Arak	Silymarin	8	210 mg	43.6	Sonography	33
Rangboo, V[72]	---	A Randomized, Double-blind, Clinical Trial	Qazvin	Artichoke (Cynara scolymus)	8	6 pills daily 2700 mg of plant extract	47.27	Sonography	30

Contd...

Table 1: Contd...

Author	Year of publication	Type of study	City of study	Type of natural products	Duration of natural products (week)	Dose	Age mean (year)	Method	Sample size
Masoodi, M[73]	---	A Randomized, Double-blind, Clinical Trial	Hormozgan	Silymarin	12	140 mg/q12h	48.42	Sonography & blood test	50
Panahi, Y[74]	---	A pilot double□blind randomized controlled trial	Tehran	artichoke leaf	8	600 mg/day	45.2	Sonography & blood test	49

effective (SMD: -0.35), whereas cinnamon was the most effective (SMD: -2.69). It is worth noting that the effects of natural products, such as orange juice, caper, ginger, ***Crocus sativus*** *L.*, cinnamon and *Cichorium intybus* L., genistein, pomegranate juice, and (mixture of *Melissa officinalis L.*, *Cinnamomum zeylanicum* and *Urtica dioica*), were not statistically significant.

Regarding the age group of patients, it can be concluded that the effect of natural products on the reduction of fatty liver in patients with the mean age of 50–59 and 60–69 years was not statistically significant. On the contrary, the minimum and maximum effects were observed in the age groups of 20–29 years (SMD: -0.73) and 10–19 years (SMD: -1.81), respectively [Table 3]. In the case of GGT, the patients who had used natural products for 8 weeks demonstrated no statistically significant change in the level of fat in their livers. The minimum effect of natural product use was detected within 10 weeks, whereas the maximum effect was observed within 12 weeks.

In an analysis of the type of natural product, it was revealed that the minimum effect was obtained by the use of Faseed (SMD: -0.60), whereas cinnamon was found to be the most effective (SMD: -3.17). In addition, the effects of such products as *Zataria multiflora*, ginger, and flaxseed oil were not statistically significant. Regarding the age of the patients, it was reported that the mean age of the patients was 30–39 years. The effect of using natural products on the reduction of the amount of fat in the liver was not statistically significant; however, the lowest and highest effects were reported in the age groups of 50–59 and 40–49 years, respectively [Table 3].

In the case of ALP, the effect of natural products on the fatty liver was not statistically significant in patients who had used them for 8 weeks. In an analysis which was conducted based on the type of natural products, the least effect was observed by the use of *Chlorella vulgaris* with -0.54, whereas the highest effect was detected by the use of curcumin with -1.88. Nevertheless, the effects of *Crocus sativus L.* and artichoke leaf were not statistically significant. In addition, no statistically significant relationship was found between ALP and different age groups [Table 3].

As it is widely known, exercise has a great impact on the treatment of patients with nonalcoholic fatty liver. Therefore, we evaluated the studies which examined the impact of exercise on patient recovery [Table 4]. As illustrated by the results of this table, the effect of aerobic exercise on the reduction of AST level was -0.03 (CI95%: - 2.25-2.19), ALT: -1.08 (CI95%: -1.80 to -0.35), GGT: -0.58 (CI95%: -1.39 to 0.24); nonetheless, it does not have any effect on the reduction of ALP levels (SMD = 0) [Table 4]. However, these results changed with the simultaneous use of aerobic exercise and natural products as follows: the effect of aerobic exercise and

Table 2: Standardized effect size of natural products on patients with non-alcoholic fatty liver disease in Iran

Subgroups	SMD	Low limit	Upper limit	*P*	I^2 (%)	Significance
Liver enzymes						
AST (IU/L)	-1.07	-1.35	-0.80	<0.0001	89.6	Yes
ALT (IU/L)	-0.98	-1.21	-0.74	<0.0001	86.5	Yes
GGT (IU/L)	-1.28	-2.10	-0.46	<0.0001	92.9	Yes
ALP (IU/L)	-0.52	-1.37	0.34	<0.0001	91.2	No
Lipid profile						
Cholesterol total	-0.43	-0.69	-0.18	<0.0001	77.4	Yes
HDL	0.08	-0.22	0.38	<0.0001	82.8	No
LDL	-0.34	-0.53	-0.15	0.001	58.4	Yes
TG	-0.21	-0.42	0.01	<0.0001	69	No
Glycemic profile						
FBS (mg/dL)	-0.35	-0.53	-0.17	0.003	54.1	Yes
Insulin (μIU/mL)	-1.10	-1.89	-0.30	<0.0001	95.5	Yes
HOMA-IR	-0.30	-0.75	0.16	<0.0001	85.4	No
HbA1C	-1.99	-3.53	-0.45	<0.0001	95.2	Yes
hs-CRP	-0.08	-0.26	0.10	0.249	21.1	No
Size reduction						
Waist Circumference (cm)	-0.31	-0.51	-0.11	0.009	54.8	Yes
Hip Circumference (cm)	-0.24	-0.46	-0.02	0.790	0	Yes
Waist to hip ratio	-0.78	-1.05	-0.51	0.043	51.8	Yes
Weight loss						
Weight (kg)	-0.21	-0.31	-0.10	0.918	0	Yes
BMI (kg/m^2)	-0.21	-0.38	-0.04	<0.0001	67	Yes
Liver disease						
liver fibrosis	-1.89	-3.83	0.04	<0.0001	95.6	No
liver steatosis	-1.20	-2.20	-0.21	<0.0001	92.2	Yes
Bilirubin						
Total bilirubin	-0.22	-0.50	0.06	0.203	34.9	No
Direct bilirubin	-0.08	-0.30	0.15	0.925	0	No
Intense physical activity	-0.15	-0.39	0.08	0.543	0	No

natural products on the reduction of AST levels was obtained at -1.55 (CI95%: - 2.85 to -0.24), ALT: -2.03 (CI95%: - 3.70 to -0.36), GGT: -0.43 (CI95%: - 1.24 to 0.38), and ALP: -0.04 (CI95%: - 0.84 to 0.76).

As indicated, aerobic exercise is effective in the reduction of liver enzyme levels. However, with the exception of GGT in the case of other enzymes, this effect is strengthened if aerobic exercises are accompanied by natural product use [Table 4].

Discussion

In 44 reviewed studies with a sample size of 1298 participants, the standardized effect size of natural products on the reduction of liver enzymes was as follows: AST: -1.07 (CI 95%: - 1.35 to -0.80), ALT: -0.98 (CI 95%: -1.21 to -0.74), GGT: -1.28 (CI 95%: -2.10 to -0.46) which was statistically significant. However, the effect of natural products on the reduction of ALP: -0.52 (CI 95%: - 1.37 to 0.34) was not statistically significant

In the investigation of lipid profile, it was found that the standardized effect size of medicinal plants and natural products on the reduction of total cholesterol and LDL was statistically significant; nonetheless, this relationship was not statistically significant in the case of triglycerides and HDL. In the glycemic profile, the effect of medicinal plants and natural products on FBS, insulin, and hemoglobin A1C was statistically significant, whereas the effect of natural products and medicinal plants on HOMA-IR and hs-CRP was not statistically significant.

Furthermore, the effect of natural products on the reduction of serum bilirubin direct and total bilirubin levels was not statistically significant. Regarding the effect of medicinal herbs and natural products on waist circumference, hip circumference, waist-to-hip ratio, weight, body weight index, and the intensity of physical activity in patients with nonalcoholic fatty liver, these relationships were statistically significant [Table 2]. The most effective natural product on the reduction of AST level was silymarin, whereas cinnamon had the greatest effect on the reduction of ALT and GGT levels. In addition, curcumin was the most effective natural product in the reduction of ALP levels.

Table 3: Standardized effect size of natural products on liver enzymes in patients with nonalcoholic fatty liver

Subgroups	SMD	Low limit	Upper limit
AST			
Duration of natural products (Week)			
4	-0.39	-0.76	-0.03
6	-0.79	-1.20	-0.39
8	-0.85	-1.23	-0.47
10	-0.68	-1.51	-0.47
12	-1.58	-2.13	-1.03
16	-0.44	-0.93	0.05
24	-0.72	-1.42	-0.03
Type of natural products			
Orange juice	-0.33	-0.82	0.17
Zataria multiflora	-1.01	-1.45	-0.57
Caper	-2.66	-6.09	0.77
Cinnamon	-2.05	-2.77	-1.33
Faseed	-0.69	-1.28	0.11
Chicory	-0.97	-1.91	-0.04
Ginger	-3.26	-8.36	1.85
Crocus satius L.	0.13	-0.53	0.78
Green Tea	-0.60	-0.95	-0.25
Flaxseed Oil	-1.25	-1.80	-0.69
Curcumin	-0.44	-0.66	-0.21
Cinnamon& Cichorium intybus L.	-0.58	-1.15	-0.01
Chlorella Vulagaris	-0.59	-0.85	-0.34
Resveratoral	-0.97	-1.55	-0.38
Silymarin	-2.68	-3.89	-1.47
Genistein	-0.09	-0.50	0.32
Pomegranate pills	-0.79	-1.20	-0.39
Artichoke	0.35	-0.16	0.86
Nano-curcumin	-1.01	-1.47	-0.56
Pomegranate Juice	-0.44	-0.93	0.05
Mixture of Melissa officinalis L., Cinnamomum zeylanicum and Urtica dioica	-0.27	-0.74	0.21
Artichoke (Cynara scolymud)	-1.89	-2.50	-1.28
Artichoke leaf	-0.70	-1.11	-0.29
Age group (year)			
10-19	-9.74	-12.02	-7.46
20-29	-0.79	-1.20	-0.39
30-39	-0.79	-1.12	-0.45
40-49	-1.27	-1.69	-0.85
50-59	-0.26	-0.66	0.14
60-69	-0.08	-0.91	0.76
ALT			
Time (Week)			
4	-0.36	-0.73	0.00
6	-0.73	-1.13	-0.32
8	-0.79	-1.11	-0.46
10	-1.45	-2.35	-0.54
12	-1.32	-1.79	-0.86
16	-0.44	-0.92	0.05
24	-0.96	-1.56	-0.36
Type of natural products			
Orange juice	-0.30	-0.80	0.19
Zataria multiflora	-1.10	-1.54	-0.66
Caper	-2.43	-5.24	0.37
Cinnamon	-2.69	-3.49	-1.88

Contd...

Table 3: Contd...

Subgroups	SMD	Low limit	Upper limit
Faseed	-0.86	-1.45	-0.26
Chicory	-1.00	-1.93	-0.06
Ginger	-5.73	-14.23	2.78
Crocus satius L.	-0.09	-0.75	0.56
Green Tea	-0.51	-0.86	-0.16
Faxseed Oil	-1.03	-1.57	-0.49
Curcumin	-0.35	-0.56	-0.14
Cinnamon& Cichorium intybus L.	-0.50	-1.06	0.06
Chlorella Vulagaris	-0.42	-0.70	-0.14
Resveratoral	-0.82	-1.40	-0.24
Silymarin	-1.64	-2.33	-0.94
Genistein	-0.18	-0.59	0.23
Pomegranante pills	-0.73	-1.13	-0.32
Artichoke	-1.25	-1.81	-0.70
Nano-curumin	-0.95	-1.40	-0.49
Pomegranante Juice	-0.44	-0.92	0.05
Mixture of Melissa officinalis L., Cinnamomum zeylanicum and Urtica dioica	-0.27	-0.74	0.20
Artichoke (Cynara scolymud)	-1.49	-2.06	-0.91
Artichoke leaf	-0.75	-1.15	-0.34
Age group (year)			
10-19	-1.81	-2.55	-1.07
20-29	-0.73	-1.13	-0.32
30-39	-0.86	-1.18	-0.54
40-49	-1.17	-1.57	-0.78
50-59	-0.49	-1.19	0.22
60-69	-0.24	-1.08	0.60
GGT			
Time (Week)			
8	0.05	-0.46	0.56
10	-1.29	-2.17	-0.40
12	-1.53	-2.59	-0.48
Type of natural products			
Zataria multiflora	-0.38	-0.79	0.04
Cinnamon	-3.17	-4.05	-2.29
Faseed	-0.60	-1.17	-0.02
Ginger	-3.12	-6.77	0.52
Faxseed Oil	0.05	-0.46	0.56
Resveratoral	-0.65	-1.22	-0.08
Age group (year)			
30-39	-1.11	-2.57	0.35
40-49	-1.46	-2.86	-0.06
50-59	-1.29	-2.17	-0.40
ALP			
Time (Week)			
8	-0.10	-0.57	0.37
12	-1.88	-2.46	-1.30
Type of natural products			
Crocus satius L.	0.29	-0.36	0.95
Chlorella Vulagaris	-0.54	-0.98	-0.09
Curcumin	-1.88	-2.46	-1.30
Artichoke leaf	-0.05	-0.35	0.44
Age group (year)			
40-49	-0.23	-0.81	0.34
50-59	-0.80	-2.93	1.33

Table 4: Evaluation of the effects of aerobic exercise on the reduction of liver enzyme levels

References	Natural products	Sample size	Aerobic Exercise					Aerobic Exercise + Natural products				
			Liver enzyme	Before		After		Sample size	Before		After	
				Mean	SD	Mean	SD		Mean	SD	Mean	SD
Hasani, A[37]	Chicory	10	AST	38.5	2	31.7	2.1	10	37.8	1.8	28	2.1
			ALT	50.56	3.6	43.3	3.4		58.9	2.3	40.5	2.2
Fathi, M[75]	Green Tea	10	AST	4.5	2.17	11.7	1.33	10	13.9	3.24	12.8	3.04
			ALT	17.8	4.66	15.9	4.01		19	4.13	16.8	4.13
Esmaelzadeh, MR[41]	Ginger	12	AST	17.27	3.62	12.82	4.8	11	16.18	4.42	12.18	5.25
			ALT	22.81	11.99	8.54	10.17		25.72	20.44	12.54	15.73
			GGT	28.96	14.02	22.32	9.88		38.26	26.13	28.53	13.95
Moradi-Kelardeh, B[43]	Curcumin	12	AST	27.16	5.44	23.16	4.51	11	27.22	2.66	23.54	2.81
			ALT	26.91	5.21	24.29	4.88		28.54	3.08	24.95	3.57
			ALP	365.25	84.61	364.66	86.05		320.09	81.99	317.27	81.75

It is noteworthy that out of 44 reviewed articles, only three studies, which were conducted by Zahra Yari,[36] Mehran Rahimlou,[38] and Forouzan Faghihizadeh[48] pointed to the use of fibro scans. Nevertheless, other studies did not provide any information on the diagnosis or treatment of this disease. This may be due to the difficulty and cost of the procedures, or the patients' reluctance to undergo these methods. Some related published review articles will be discussed and assessed in the following section. Nonetheless, no meta-analysis has so far been conducted on the effect of medicinal plants and natural products on the reduction of liver enzymes in nonalcoholic fatty liver patients. Moreover, previous studies yielded challenging and contradictory results. Therefore, the present study was performed on Iranian patients using meta-analysis for the first time.

In 2018, Mohammad Bagherinia highlighted the beneficial role of medicinal plants in the treatment of NAFLD, especially as a complement to a healthy lifestyle. All of the natural products described in the present study seemingly have oxidative benefits, cellular inflammation, and insulin resistance which always remain as "optimum movement" for the pathogenesis of NAFLD.[76] Mohammad Hossein Farzyai (2018) reported that curcumin can be effective in a variety of oxidative-related liver disorders. This potential is related to the effects of curcumin on liver toxicity, nonalcoholic steatohepatitis, alcoholic liver disease, liver fibrosis, cirrhosis, as well as liver injury. Experimental evidence suggests that curcumin exerts its prophylactic and therapeutic effect against oxidative-related liver disease through various cellular signaling pathways.[77] In 2018, Fariborz Mansour-Ghanaei *et al*.[78] conducted a study to investigate the effect of curcumin/turmeric supplementation on liver enzymes in patients with NAFLD. The results of the above studies are consistent with the results of the current meta-analysis because in the present meta-analysis, curcumin was revealed to be effective in reducing serum levels of ALT, AST, and ALP enzymes, and this relationship is statistically significant.

In a study in 2015, Tahmineh Akbarzadeh investigated a wide range of herbs that are commonly used in Iranian traditional medicine and have been identified as liver tonics with numerous effects on liver protection measures. It is worthy to mention that all of these herbs have displayed protection *in vitro* and *in vivo* conditions. Among the different plants reported in the mentioned study, the tubers (*Agrimonia eupatoria*), chicory (C. *intybus*), pomegranate (P. *granatum*), cinnamon (C. *zeylanicum*), saffron (C. *sativus*), roses (R) Damascena, and B. vulgaris are recommended in Persian medical literature.[79] The results of the mentioned study are inconsistent with our meta-analysis as in the current study, the effective use of hydroalcoholic extract of saffron was not statistically significant in the reduction of AST, ALT, and ALP levels. In addition, in our study, the use of cinnamon and chicory mixture was statistically significant in the reduction of AST level; nonetheless, it was not significant in reducing ALT levels. Along the same lines, Mohammad Taqi Moradi (2016) conducted a review study to report on the plants used in the treatment of liver diseases in traditional and ethnobotanical culture in different regions of Iran. He reported 27 medicinal plants from 19 families which were specifically used for the treatment of liver diseases. This reflects the richness of traditional Iranian medicine which has long considered the use of natural resources for the treatment of various diseases, including liver disease. Most of the plants included in this study belong to the Asteraceae family which contain phenolic compounds and have significant antioxidant effects. Phenolic compounds, such as flavonoids, can protect cells against glutathione depletion by enhancing the ability of antioxidant enzymes (such as glutathione peroxidase). These compounds with antioxidant properties can counteract the free radicals in the environment, thereby preventing their harmful effects. Flavonoids, as antioxidants, modify free radicals and antioxidants for liver protection.[80]

Camila Ribeiro de Avelar (2017) performed a study to evaluate the effect of silymarin on serum ALT, AST, and gamma-glutamyl terpeptidase (γGT) in patients with liver

disease. He suggested that the results of this meta-analysis, without clinical relevance, reduced serum levels of ALT and AST in patients with nonalcoholic fatty liver disease.[81] Along the same lines, in 2017, Sheng Zhong *et al*.[82] carried out a study to evaluate the therapeutic effect of silymarin on nonalcoholic fatty liver disease using meta-analysis. The results of this study showed that silymarin has a positive effect on reducing transaminases levels in patients with NAFLD Which was consistent with the result of our meta-analysis. Because in our meta-analysis, silymarin consumption had a significant effect on reducing the levels of AST and ALT enzymes.

In the same direction, the results of a study carried out by Xueru Yin *et al*. (2015)[83] indicated that green tea consumption reduced the risk of liver disease. Another study performed by Xi Jin (2008) which assessed the effect of green tea consumption on liver disease suggested that green tea consumption reduces the risk of liver disease.[84] In the present meta-analysis, green tea was demonstrated to have a positive effect on the reduction of serum levels of AST and ALT, and this effect was statistically significant.

In a study conducted by Ke-Qing Shi (2012), a systematic review and meta-analysis was performed on RCTs to evaluate the efficacy and safety of traditional Chinese medicine (TCM) in the treatment of NAFLD. This study indicated that TCM was effective in the treatment of NAFLD[30] which is in agreement with the results of the present study. Because in our meta-analysis, the effect of using many natural products in reducing the level of liver enzymes has been significantly positive.

Study limitations

Due to the lack of uniform distribution of studies in different regions of Iran, we could not present the effect of natural products on liver enzymes by regions of Iran (north, south, west, east and center) and see if the areas with richer vegetation with more herbal remedies were more successful in treating nonalcoholic fatty liver?

Lack of uniform distribution of studies on different liver enzymes: In other words, in all studies, the effect of natural products on all liver enzymes was not evaluated. Most studies focused on ALT and AST enzymes and fewer studies on GGT and ALP enzymes. Information such as diagnostics methods or treatment methods was not mentioned in most of the articles, so we cannot comment on different diagnostic methods or treatments methods and compare them with each other.

The severity of liver inflammation was not indicated in the reviewed studies; accordingly, we were not able to compare nonalcoholic fatty liver disease at three mild, moderate, and severe levels.

No information was available on the duration of the disease. Therefore, we do not know whether the reason for the insignificant effect of consuming natural products in reducing the level of liver enzymes was a long period of disease or not?

Furthermore, such issues as stress and anxiety in patients, the use of herbal or chemical medications, alcohol use, and hepatitis were not addressed in the investigated studies. Nevertheless, each of these issues is a risk factor for elevated liver enzymes. And the reason for the increase in the level of liver enzymes in the subjects could be the existence of one of these risk factors and has nothing to do with the development of nonalcoholic fatty liver disease. Given the limitations of the present study, it is recommended that a clinical trial be conducted to eliminate these limitations.

Conclusions

In 44 reviewed studies with a sample size of 1298 participants, patients had nonalcoholic Steatohepatitis (NASH) only in four studies,[58,71-73] and in other studies, the patients were inflicted with NAFLD. In these studies, the standardized effect size of natural products on the reduction of AST, ALT, GGT levels was statistically significant. Moreover, it was found that natural products had the highest effect on the reduction of GGT, AST, and ALT levels, respectively.

However, the effect of natural products on the reduction of ALP level was not statistically significant. Furthermore, the use of herbal medicines and natural products had a significant effect on weight loss and size reduction in patients with nonalcoholic fatty liver. As mentioned above, silymarin had the highest effect on AST (SMD = -2.68), cinnamon demonstrated the highest effect on ALT (SMD: -2.69), and the highest effect on GGT was related to the use of cinnamon (SMD: -3.17), and curcumin had the highest effect on ALP (SMD = -1.88). With regards to the lipid profile, the effect of medicinal herbs and natural products on lowering total cholesterol and LDL levels was statistically significant. Moreover, with regards to the glycemic profile, the effect of medicinal plants and natural products on the reduction of FBS, insulin, and HbA1C levels was statistically significant and had the greatest effect on the reduction of HbA1C levels.

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Ethics approval and consent to participate

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Consent to publish

All authors have agreed to publish the article.

Availability of data and materials

Primary data for neither humans nor animals were collected for this research work.

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Conflicts of interest

There are no conflicts of interest.

Search strategy in PubMed:

((((Herbal medicine[All Fields]) OR (Natural Products[All Fields] OR Biological Drugs[All Fields] OR Biologic Products[All Fields] OR Biologic Pharmaceuticals[All Fields])) AND (Nonalcoholic Fatty Liver[All Fields] OR NAFLD[All Fields] OR Nonalcoholic Steatohepatitis[All Fields])) AND Iran[Affiliation].

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References

1. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221-31.
2. Obika M, Noguchi H. Diagnosis and evaluation of nonalcoholic fatty liver disease. Exp Diabetes Res 2012;2012:145754.
3. Abenavoli L, Milic N, Di Renzo L, Preveden T, Medić-Stojanoska M, De Lorenzo A. Metabolic aspects of adult patients with nonalcoholic fatty liver disease. World J Gastroenterol 2016;22:7006-16.
4. Dyson J, Anstee Q, McPherson S. Non-alcoholic fatty liver disease: A practical approach to diagnosis and staging. Frontline Gastroenterol 2014;5:211-8.
5. Iloon Kashkooli R, Najafi S, Sharif F, Hamedi A, Hoseini Asl M, Najafi Kalyani M, *et al*. The effect of berberis vulgaris extract on transaminase activities in non-alcoholic Fatty liver disease. Hepat Mon 2015;15:e25067.
6. Moghaddasifar I, Lankarani KB, Moosazadeh M, Afshari M, Ghaemi A, Aliramezany M, *et al*. Prevalence of non-alcoholic fatty liver disease and its related factors in Iran. Int J Organ Transplant Med 2016;7:149-60.
7. Lankarani K, Ghaffarpasand F, Mahmoodi M, Lotfi M, Zamiri N, Heydari S, *et al*. Non alcoholic fatty liver disease in southern Iran: A population based study. Hepat Mon 2013;13:e9248.
8. Gu C-l, Zhang Y-k, Fu Y-x, Yang S-f, Li X-q. Effect of Tiaozhi Yanggan Decoction in treating patients with non-alcoholic fatty liver. Chin J Integr Med 2007;13:275-9.
9. Ford R, Fullerton M, Pinkosky S, Day E, Scott J, Oakhill J, *et al*. Metformin and salicylate synergistically activate liver AMPK, inhibit lipogenesis and improve insulin sensitivity. Biochem J 2015;468:125-32.
10. Choi Y, Yanagawa Y, Kim S, Park T. Involvement of SIRT1-AMPK signaling in the protective action of indole-3-carbinol against hepatic steatosis in mice fed a high-fat diet. J Nutr Biochem 2013;24:1393-400.
11. Yan F, Wang Q, Xu C, Cao M, Zhou X, Wang T, *et al*. Peroxisome proliferator-activated receptor α activation induces hepatic steatosis, suggesting an adverse effect. PLoS One 2014;9:e99245.
12. Bahmani M, Rafieian-Kopaei M, Hassanzadazar H, Saki K, Karamati S, Delfan B. A review on most important herbal and synthetic antihelmintic drugs. Asian Pac J Trop Med 2014;7:29-33.
13. Bahmani M, Rafieian-Kopaei M, Jeloudari M, Eftekhari Z, Delfan B, Zargaran A, *et al*. A review of the health effects and uses of drugs of plant licorice (Glycyrrhiza glabra L.) in Iran. Asian Pac J Trop Dis 2014;4:847-9.
14. Rafieian-Kopaei M. *In vitro* evaluation of antioxidant properties of ten Iranian medicinal plants. Iran Red Crescent Med J 2014;16:e10264.
15. Rafieian-Kopaei M, Baradaran A, Rafieian M. Plants antioxidants: From laboratory to clinic. J Nephropathol 2013;2:152-3.
16. Sedighi M, Rafieian-kopaei M, Noori-Ahmadabadi M. Kelussia odoratissima Mozaffarian inhibits ileum contractions through voltage dependent and beta adrenergic receptors. Life Sci 2012;9:1033–8.
17. Farnsworth N, Akerele O, Bingel A, Soejarto D, Guo Z. Medicinal plants in therapy. Bull World Health Organ 1985;63:965-81.
18. Bai R, Paull K, Herald C, Malspeis L, Pettit G, Hamel E. Halichondrin B and homohalichondrin B, marine natural products binding in the vinca domain of tubulin. Discovery of tubulin-based mechanism of action by analysis of differential cytotoxicity data. J Biol Chem 1991;266:15882-9.
19. Newman D, Cragg G, Snader K. The influence of natural products upon drug discovery. Nat Prod Rep 2000;17:215-34.
20. Madihi Y, Merrikhi A, Baradaran A, Ghobadi S, Shahinfard N, Ansari R, *et al*. Bioactive components and the effect of hydroalcoholic extract of Vaccinium myrtillus on postprandial atherosclerosis risk factors in rabbits. Pak J Med Sci 2013;29:384–9.
21. Hasanpour Z, Nasri H, Rafieian-Kopaei M, Ahmadi A, Baradaran A, Nasri P, *et al*. Paradoxical effects of atorvastatin on renal tubular cells an experimental investigation. Iran J Kidney Dis 2015;9:215-20.
22. Rabiei Z, Rafieian-Kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of Zizyphus jujube extract on memory and learning impairment induced by bilateral electric lesions of the nucleus Basalis of Meynert in rat. Neurochem Res 2014;39:353-60.
23. Nikkhajoei M, Choopani R, Tansaz M, Heydarirad G, Hashem-Dabaghian F, Sahranavard S, *et al*. Herbal medicines used in treatment of nonalcoholic fatty liver disease: A mini-review. Galen Med J 2016;5:107-13.
24. Fleischman MW, Budoff M, Ifran Zeb DL, Foster T. NAFLD prevalence differs among hispanic subgroups: The multi-ethnic study of atherosclerosis. World J Gastroenterol 2014;20:4987-93.
25. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
26. Shi K, Fan Y, Liu W, Li L, Chen Y, Zheng M. Traditional Chinese medicines benefit to nonalcoholic fatty liver disease: A systematic review and meta-analysis. Mol Biol Rep 2012;39:9715–22.
27. Iran Institute of Information Technology. Available from: http://www.irandoc.ac.ir/.
28. Available from: https://clinicaltrials.gov/.
29. Available from: https://www.isrctn.com/.

30. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjw2a32BRBXEiwAUcugiF8TCQCLeaSWC3Eb3G2D_oiUqQ2DPPfMDBZxVef-WFglTD1lQvUHaRoCB5UQAvD_BwE.
31. Higgins JP, Thompson SG. quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
32. Ekhlasi G, Shidfar F, Agah S, Merat S, Hosseini A. Does daily intake of orange juice along with weight loss diet affect serum lipoprotein profiles in patients with nonalcoholic fatty liver disease. Iranian J Endocrinol Metab 2014;15:435-42.
33. Zamani N, Shams M, Nimrouzi M, Zarshenas M, Foroughi A, Abarghooei E, *et al*. The effects of Zataria multiflora Boiss. (Shirazi thyme) on nonalcoholic fatty liver disease and insulin resistance: A randomized double-blind placebocontrolled clinical trial. Complement Ther Med 2018;41:118-23.
34. Khavasi N, Hosein Somi M, Khadem E, Faramarz iE, Ayati M, Fazljou S, *et al*. Effect of daily caper fruit pickle consumption on disease regression in patients with non-alcoholic fatty liver disease: A double-blinded randomized clinical trial. Adv Pharm Bull 2017;7:645-50.
35. Askari F, Abadi A, Rashidkhani B, Ghafari S, Jalali M, Hekmatdoost A. Effect of cinnamon on lipid profile, liver enzymes, insulin resistance and hs -CRP inflammatory factor in patients with nonalcoholic fatty liver disease. J Res Dev Nurs Midw 2013;10:47-55.
36. Yari Z, Rahimlu M, Poustchi H, Ebrahimi Daryani N, Hekmatdoost A. Effect of faxseed supplementation on liver enzymes, hepatic fibrosis and steatosis in nonalcoholic fatty liver disease: A randomized-controlled clinical trial. Iranian journal of nutrition sciences & food technology 2016;10:1-12.
37. Hasani A, Ansari R, Mazani A. Effect of 8 weeks of aerobic training and using chicory extractive supplementation on serum levels of ALT and AST enzymes in women with fatty liver. The Iranian Journal of Obstetrics, Gynecology and Infertility 2016;19:1-8.
38. Rahimlou M, Yari Z, Hekmatdoost A, Alavian M, Keshavarz A. Effect of ginger supplementation on liver enzymes, hepatic fibrosis and steatosis in nonalcoholic fatty liver disease: A double blind randomized-controlled clinical trial. Iran J Nutr Sci Food Technol 2016;11:1-8.
39. Milajerdi A, Jazayeri A, Jazayeri S, Hashemzadeh N, Shirzadi E, Derakhshan Z, *et al*. The effect of hydro-alcoholic extract of saffron stigma (crocus sativus l.) on metabolic control parameters, liver enzymes, and renal function parameters in type 2 diabetic patients. Journal of Medicinal Plants 2016;15:142-51.
40. Fathei M, Khairabadi S, Ramezani F, Hejazi K. The effects of eight weeks aerobic training, green tea supplementation and compound of them on serum liver enzymes and apolipoproteins in inactive overweight women. MJMS 2016;59:114-23.
41. Esmaelzadeh Toloee M, Faramarzi M, Noroozian P. Effect of aerobic training with ginger supplementation on some liver enzymes (AST, ALT, GGT) and resistance to insulin in obese women with type 2 diabetes. Medical J Mashhad University of Medical Sciences 2017;60:636-47.
42. Beheshti Namdar A, Bahari A, Vosughinia H, Saadatnia H, Esmaeelzade A, Ganji A, *et al*. Comparing the effect of flaxseed oil with vitamin E on non-invasive markers of liver in patients with nonalcoholic fatty liver disease. Medical J Mashhad University of Medical Sciences 2015;57:890-7.
43. Moradi-Kelardeh B, Azarbayjani M, Peeri M, Matinhomaee H. Effect of curcumin supplementation and resistance training in patients with nonalcoholic fatty liver disease. Journal of Medicinal Plants 2016;4:161-72.
44. Sheybani Asl Z, Malekirad A, Abdollahi M, Bakhshipour A, Dastjerdi H, Mostafalou S, *et al*. Effects of the mixture of cichorium intybus L. and cinnamomum zeylanicum on hepatic enzymes activity and biochemical parameters in patients with nonalcoholic fatty liver disease. Health 2014;6:1212-7.
45. Rahmani S, Asgary S, Askari G, Keshvari M, Hatamipour M, Feizi A, *et al*. Treatment of non-alcoholic fatty liver disease with curcumin: A randomized placebo-controlled trial. Phytother Res 2016;30:1540–8.
46. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendía L, Sahebkar A. Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: A randomized controlled trial. Drug Res (Stuttg) 2017;67:244-51.
47. Ebrahimi-Mameghani M, Sadeghi Z, Farhangi M, Vaghef-Mehrabany E, Aliashrafi S. Glucose homeostasis, insulin resistance and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: Beneficial effects of supplementation with microalgae Chlorella vulgaris: A double-blind placebo-controlled randomized clinical trial. Clin Nutr 2017;36:1001-6.
48. Faghihzadeh F, Adibi P, Rafiei R, Hekmatdoost A. Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease. Nutr Res 2014;34:837-43.
49. Famouri F, Salehi M, Rostampour N, Hashemi E, Shahsanaee A. The effect of silymarin on non-alcoholic fatty liver disease of children. J Herbmed Pharmacol 2017;6:16-20.
50. Amanat S, Eftekhari M, Bagheri Lankarani K, Fararouei M. Effect of genistein supplementation on insulin sensitivity, insulin resistance, and beta cells function index in patients with non-alcoholic fatty liver disease: A randomized, controlled trial. Iran J Nutr Sci Food Technol 2018;13:1-10.
51. Hajiaghamohammadi A, Ziaee A, Samimi R. The efficacy of licorice root extract in decreasing transaminase activities in non-alcoholic fatty liver disease: A randomized controlled clinical trial. Phytother Res 2012;26:1381-4.
52. Panahi Y, Ghamarchehreh M, Beiraghdar F, Zare R, Jalalian H, Sahebkar A. Investigation of the effects of Chlorella vulgaris supplementation in patients with non-alcoholic fatty liver disease: A randomized clinical trial. Hepatogastroenterol 2012;59:2099-103.
53. Pezeshki A, Safi S, Feizi A, Askari G, Karami F. The effect of green tea extract supplementation on liver enzymes in patients with nonalcoholic fatty liver disease. Int J Prev Med 2016;7:28.
54. Hashemi S, Hajiani E, Heydari S. A Placebo-controlled trial of silymarin in patients with nonalcoholic fatty liver disease. Hepat Mon 2009;9:265-70.
55. Ahmadian M. PhD Thesis pills on nonalcoholic fatty liver [persian] 2013.
56. Talebi Pour B, Jameshorani M, Salmani R. The effect of Chlorella Vulgaris vs. Artichoke on patients with non-alcoholic fatty liver disease (NAFLD): A randomized clinical trial. J Adv Med Biomed Res 2015;23:36-44.
57. Aliashrafi S, Ebrahimi Mameghani M, Kakaie F, Javadzadeh Y, Asghari Jafarabadi M. The effect of microalgae chlorella vulgaris supplementation on inflammatory factors in non-alcoholic fatty liver disease (NAFLD): A double-blind randomized clinical trial [persian]. J Mazand Univ Med Sci 2014;24:113-21.
58. Taghvaei T, Bahar A, Hosseini V, Maleki I, Kasrai M. Efficacy of silymarin on treatment of nonalcoholic steatohepatitis [persian]. J Mazand Univ Med Sci 2013;23:164-71.
59. Iranikhah A, Shapouri J, Heydari A, Aghaali M, Hajian H. Effects of silymarin on nonalcoholic fatty liver disease in children: A crossover clinical trial [persian]. J Mazandaran Univ Med Sci 2016;26:119-26.

60. Hajaghamohammadi A, Ziaee A, Rafiei R. The efficacy of silymarin in decreasing transaminase activities in non-alcoholic fatty liver disease: A randomized controlled clinical trial. Hepat Mon 2008;8:191-5.
61. Hajiaghamohammadi A, Ziaee A, Oveisi S, Masroor H. Effects of metformin, pioglitazone, and silymarin treatment on non-alcoholic fatty liver disease: A randomized controlled pilot study. Hepat Mon 2012;12:e6099.
62. Anushiravania A, Haddadib N, Pourfarmanbarb M, Mohammadkarimic V. Treatment options for nonalcoholic fatty liver disease: A double-blinded randomized placebo-controlled trial. Eur J Gastroenterol Hepatol 2019;31:613–7.
63. Saadati S, Sadeghi A, Mansour A, Yari Z, Poustchi H, Hedayati M, *et al*. Curcumin and inflammation in nonalcoholic fatty liver disease: A randomized, placebo controlled clinical trial. BMC Gastroenterol 2019;19:133.
64. Saadati S, Hatami B, Yari Z, Shahrbaf M, Eghtesad S, Mansour A, *et al*. The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease. Eur J Clin Nutr 2019;73:441-9.
65. Mirhafez S, Rezaei Farimani A, Dehhabe M, Bidkhori M, Hariri M, Nobakht Motlagh Ghouchani B, *et al*. Effect of phytosomal curcumin on circulating levels of adiponectin and leptin in patients with non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled clinical trial. J Gastrointestin Liver Dis 2019;28:183-9.
66. Jazayeri-Tehrani S, Rezayat S, Mansouri S, Qorbani M, Alavian S, Daneshi-Maskooni M, *et al*. Nano-curcumin improves glucose indices, lipids, inflammation, and Nesfatin in overweight and obese patients with nonalcoholic fatty liver disease (NAFLD): A double-blind randomized placebocontrolled clinical trial. Nutr Metab 2019;16:8.
67. Ekhlasi G, Shidfar S, Agah S, Merat S, Agha Fatemeh Hosseini K. Effect of pomegranate juice intake on lipid profile in patients with nonalcoholic fatty liver disease. Razi J Med Sci 2013;20:31-9.
68. Khavasi N, Somi M, Khadem E, Ayati M, Torbati M, Fazljou S. Daily consumption of the capparis spinosa reduces some atherogenic indices in patients with non-alcoholic fatty liver disease: A randomized, double-blind, clinical trial. Iran Red Crescent Med J 2018;20:e63446.
69. Tabatabaee S, Alavian S, Ghalichi L, Miryounesi S, Mousavizadeh K, Jazayeri S, *et al*. Green tea in non-alcoholic fatty liver disease: A double blind randomized clinical trial. Hepat Mon 2017;17:e14993.
70. Malekirad A, Vaezi G, Abdollahi M. Effects of mixture of melissa officinalis L., cinnamomum zeylanicum and Urtica dioica on hepatic enzymes activity in patients with nonalcoholic fatty liver disease. Int J Pharmacol 2012;8:204-8.
71. Solhi H, Ghahremani R, Kazemifar A, Hoseini-Yazdi Z. Silymarin in treatment of non-alcoholic steatohepatitis: A randomized clinical trial. Caspian J Intern Med 2014;5:9-12.
72. Rangboo V, Noroozi M, Zavoshy R, Rezadoost S, Mohammadpoorasl A. The effect of artichoke leaf extract on alanine aminotransferase and aspartate aminotransferase in the patients with nonalcoholic steatohepatitis. Int J Hepatol 2016;2016:4030476.
73. Masoodi M, Rezadoost A, Panahian M, Vojdanian M. Effects of silymarin on reducing liver aminotransferases in patients with nonalcoholic fatty liver diseases. Govaresh 2013;18:181-5.
74. Panahi Y, Kianpour P, Mohtashami R, Atkin S, Butler A, Jafari R, *et al*. Efficacy of artichoke leaf extract in non-alcoholic fatty liver disease: A pilot double-blind randomized controlled trial. Phytother Res 2018;32:1382-7.
75. Fathi M, Khairabadi S, Ramezani F, Hejazi K. The effects of eight weeks aerobic training, green tea supplementation and compound of them on serum liver enzymes and apolipoproteins in inactive overweight women. Medical J Mashhad University of Medical Sciences 2016;59:114-23.
76. Hasanpour AD. Influence of yoga and aerobics exercise on fatigue, pain and psychosocial status in patients with multiple sclerosis: A randomized trial. J Sports Med Phys Fitness 2016;56:1417-22.
77. Farzaei M, Zobeiri M, Parvizi F, El-Senduny F, Marmouzi I, Coy-Barrera E, *et al*. Curcumin in liver diseases: A systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients 2018;10:855.
78. Mansour-Ghanaei F, Pourmasoumi M, Hadi A, Joukar F. Efficacy of curcumin/turmeric on liver enzymes in patients with non-alcoholic fatty liver disease: Asystematic review of randomized controlled trials. Integr Med Res 2019;8:57-61.
79. Akbarzadeh T, Sabourian R, Saeedi M, Rezaeizadeh H, Khanavi M, Ardekani M. Liver tonics: Review of plants used in Iranian traditional medicine. Asian Pac J Trop Biomed 2015;5:170-81.
80. Moradi M, Asadi-Samani M, Bahmani M, Shahrani M. Medicinal plants used for liver disorders based on the Ethnobotanical documents of Iran: A Review. Int J Pharmtech Res 2016;9:407-15.
81. de Avelar C, Pereira E, de Farias Costa P, de Jesus R, de Oliveira L. Effect of silymarin on biochemical indicators in patients with liver disease: Systematic review with meta-analysis. World J Gastroenterol 2017;23:5004-17.
82. Zhong S, Fan Y, Yan Q, Fan X, Wu B, Han Y, *et al*. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease: A meta-analysis (PRISMA) of randomized control trials. Medicine 2017;96:e9061.
83. Yin X, Yang J, Li T, Song L, Han T, Yang M, *et al*. The effect of green tea intake on risk of liver disease: A meta analysis. Int J Clin Exp Med 2015;8:8339-46.
84. Jin X, Zheng R, Li Y. Green tea consumptionand liver disease: A systematic review. Liver Int 2008;28:990-6.