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

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 rsutudes 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. 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. In total, 20%–40% of people in the world suffer from NAFLD, whereas its prevalence rate in Asia is around 5%–30%. 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. Risk factors of NAFLD include high-fat and -protein diet, male gender, metabolic syndrome symptoms, consumption of food before bed, and sedentary lifestyle. Various types of anti-NAFLD medications are currently on the market, but the outcomes are not always good. In nonalcoholic fatty liver patients in Iran, a systematic review and meta-analysis. Int J Prev Med 2022;13:87.

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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. 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. 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. Iranians also use herbal medicines to treat some of the common diseases. In a similar vein, Maryam Nikkhajouvi 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.

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. 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-Analyses (PRISMA) Protocol, 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, body weight 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 and Magiran 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.

Moreover, clinical trial registration systems such as ClinicalTrials.gov, ISRCTN (BioMed Central publisher), and World Health Organization 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 **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 I^2 index (I^2 index below 25% is low heterogeneity, between 25% and 75% is average heterogeneity, 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...
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
| 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] | 2015 | 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 | Fasseed 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 |
| Faghizadeh, 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 Chlorella supplements made by Algomed Company 3 times a day | 20.46 | Sonography & blood test | 50 |
| Talebi Pour, B[56] | --- | Clinical trial | Zanjan | Chlorella Vulagaris | 8 | | 35 | Sonography & blood test | 30 |
| Talebi Pour, B[57] | --- | Clinical trial | Zanjan | Artichoke | 8 | | 38 | Sonography & blood test | 30 |

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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 |
|---------------------------------|---------------------|----------------------------------------|---------------|--------------------------|-------------------------------------|----------------------------------------------------------------------|----------------|---------------------------------|-------------|
| Fakhri, et al.                  | 2012               | Clinical trial                         | Tehran        | Silymarin                | 12                                  | Silymarin 140 mg 3 times daily                                      | 11.73           | Sonography & blood test         | 20          |
| Aliashrafi, S[57]               | 2011-2012           | Clinical trial                         | Tabriz        | Chlorella Vulagaris      | 8                                   | 4 tablets of 300 mg daily Chlorella made by Algomed                  | 37             | 29                             |
| Taghvaci, T[58]                 | 2009-2010           | Clinical trial                         | Sari          | Silymarin                | 24                                  | Silymarin tablets 140 mg twice daily                                | 42.9           | 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          |
| Tabatabaei, SM[69]              | ---                 | A Randomized, Double-blind, Clinical Trial | Tehran   | Green Tea              | 12                                  | 550 mg                                                               | 41             | Sonography, Biopsy, Fibrosc an | 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          |

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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
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.

| Subgroups                      | SMD   | Low limit | Upper limit | P     | I (%) | 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/m²)                    | -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           |
Table 3: Standardized effect size of natural products on liver enzymes in patients with nonalcoholic fatty liver

| Subgroups | AST | SMD | Low limit | Upper limit |
|-----------|-----|-----|-----------|-------------|
| Duration of natural products (Week) | AST | SMD | Low limit | Upper limit |
| 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 | AST | SMD | Low limit | Upper limit |
| 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 |
| Resveratral | -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) | AST | SMD | Low limit | Upper limit |
| 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 | AST | SMD | Low limit | Upper limit |
| Time (Week) | ALT | SMD | Low limit | Upper limit |
| 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 | ALT | SMD | Low limit | Upper limit |
| 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       |
| Resveratral                                                               | -0.82 | -1.40     | -0.24       |
| Silymarin                                                                  | -1.64 | -2.33     | -0.94       |
| Genistein                                                                  | -0.18 | -0.59     | 0.23        |
| Pomegranate pills                                                         | -0.73 | -1.13     | -0.32       |
| Artichoke                                                                 | -1.25 | -1.81     | -0.70       |
| Nano-curumin                                                              | -0.95 | -1.40     | -0.49       |
| Pomegranate 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        |
| Resveratral                                                               | -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 | Liver enzyme | Aerobic Exercise | Aerobic Exercise + Natural products |
|------------|-----------------|-------------|--------------|------------------|-------------------------------------|
|            |                 |             | Before | After | Before | After | Before | After |
| 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[35] | 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 our 44 reviewed articles, only three studies, which were conducted by Zahra Yari,[36] Mehran Rahimlou,[38] and Forouzan Faghihzadeh[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 non-alcoholic 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, non-alcoholic 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 ALT, AST, 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 transpeptidase (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.\cite{81} Along the same lines, in 2017, Sheng Zhong et al.\cite{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)\cite{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.\cite{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\cite{85} 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\cite{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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