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Effect of an Herbal Product on the Serum Level of Liver Enzymes in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blinded, Placebo-Controlled Trial

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. There is no definitive treatment for this, and prevention and treatment via diet and weight loss have been recommended.
Objectives: This study aimed to investigate the effect of *Dava Al-Balgham*, as one of the traditional medicine products, in patients with NAFLD.
Methods: The study was a randomized, double-blinded, placebo-controlled trial performed among 76 patients with NAFLD in a university-affiliated hospital, Qom, Iran, in 2017. The individuals were assigned into two groups of intervention (receiving *Dava Al-Balgham*; n = 37) and placebo (n = 39), using the randomized block allocation method. Both groups maintained the same diet and lifestyle. In the intervention group, two tablets of *Dava Al-Balgham* (a combination of *Nigella sativa*, *Zataria multiflora*, *Pistacia lentiscus*, and *Trachyspermum ammi*) were consumed with each meal for three months. In the other group, placebo tablets were used in the same manner. Pre- and post-intervention weight, waist circumference, and liver enzyme levels were measured. Chi-square, *t*-test, and analysis of covariance were used for comparing the two groups.
Results: The levels of liver enzymes, weight, and waist circumference decreased in both groups. The mean reduction in alanine transaminase (ALT) in the intervention group was 22.80, while it was 1.59 in the placebo group (P = 0.008). The mean weight loss in the intervention and placebo groups was 2.69 kg and 0.9 kg, respectively (P = 0.003). Moreover, the mean reduction in waist circumference in the intervention and placebo groups was 3.43 cm and 0.33 cm, respectively (P = 0.001).
Conclusions: *Dava Al-Balgham* tablets with the weight loss and hypolipidemic effect of its components can be used to help the prevention and treatment of NAFLD.

Keywords: Alanine Transaminase, Ammi, Apiaceae, *Dava Al-Balgham*, Lamiaceae, *Nigella sativa*, Non-alcoholic Fatty Liver Disease, Persian Medicine, Pistacia, Waist Circumference, Weight Loss

1. Background

Non-alcoholic fatty liver disease (NAFLD) includes a wide range of liver disorders such as simple steatosis, non-alcoholic steatohepatitis, and liver fibrosis (1) that can lead to cirrhosis, liver failure, and hepatocellular carcinoma (2). The overall prevalence of NAFLD is about 20% (3); it is 20% - 35% in western countries, 19% - 32% in Asia (4), and 33.95% in Iran (5). Most cases of NAFLD are asymptomatic and identified in laboratory findings and ultrasonography. So far, no definitive treatment has been suggested for NAFLD (6, 7) and treatments have mainly focused on eliminating risk factors such as metabolic syndrome, insulin resistance, obesity, and inactivity. The main recommendations for this disease are diet, weight loss, and exercise (8).

The World Health Organization (WHO) has promoted its traditional medicine strategy (9) and accepted various alternative treatments for diseases, such as herbal therapy, homeopathy, and traditional medicine (10). Persian medicine (PM) emphasizes disease prevention through lifestyle improvement and believes that the liver and its proper function are essential. According to the PM, each

part of the body has a certain temperament, and human health depends on its balance; thus, any defect in this balance can lead to diseases. Moreover, some diseases can be treated via the modification of body temperaments (11). From the perspective of Persian medicine, the liver is a vital organ in the body, and its typical temperament is warm and wet (11, 12). Many factors, such as poor nutrition, poor digestion, lack of physical activity, can induce liver distemperament, especially towards coldness and excessive wetness (11, 13). Liver distemperament can cause some diseases from mild to severe and chronic liver disease. A cold distemperament of liver in more advanced stages can result in chronic and irreversible diseases such as ascites (13).

In the Persian Medicine, there is no specific disease called fatty liver disease (FLD), but the signs and symptoms of liver diseases, especially their end stages, simulate NAFLD and its advanced stages, especially cirrhosis (14). *Dava al-Balagham* (DAB) is a herbal product, including a mix of *Nigella sativa, Zataria multiflora, Pistacia lentiscus*, and *Trachyspermum ammi,* which is used in the treatment of cold and wet distemperment of the body (15, 16). In the PM, *Nigella sativa, Zataria multiflora, Pistacia lentiscus,* and *Trachyspermum ammi* have been mentioned to improve food digestion and flatulence and strengthen the stomach and liver (10, 17). Therefore, this compound appears to be effective in the treatment of fatty liver.

2. Objectives

This study aimed to investigate the effect of *Dava Al-Balgham* on liver enzymes in patients with NAFLD.

3. Methods

3.1. Study Design and Settings

This randomized, double-blinded clinical trial was conducted on patients with NAFLD referring to Shahid Beheshti Hospital a governmental and referral Hospital affiliated to Qom University of Medical Sciences, Qom, Iran, in 2017. The subjects were evaluated for the inclusion and exclusion criteria for the recruitment to the trial by a gastroenterologist. This clinic is a health camp that offers free health check-ups and given healthy life education. During the educations, the patients were informed about these trials and the opportunity to participate in the trial offered to eligible patients.

The inclusion criteria consisted of a NAFLD diagnosis via ultrasonography, elevated liver enzymes (Aspartate aminotransferase (AST) > 35 and alanine aminotransferase (ALT) > 45), and the age between 18 and 65 years. The exclusion criteria were as follows: cirrhosis, hepatitis, Wilson's disease, hemochromatosis, vascular diseases of the liver, liver mass, allergy, gastrointestinal surgery, heart or renal failure, alcohol consumption $\geq$ 20 mL/day, ALT $\geq$ 120, total parental nutrition, the use of hepatotoxic drugs over the past six months, pregnancy, lactation, and any uncontrolled illnesses.

This study was registered at the Iranian Registry of Clinical Trials (IRCT2017073135415N1). In addition, the participants signed written informed consent forms, and the Research Council and Ethics Committee of Qom University of Medical Sciences approved the protocol of the study (code of ethics: IR.MUQ.REC.1396.44).

3.2. Randomization

The random allocation of patients to the groups was based on the block method. The size of each block was considered four; thus, there were six blocks of four consisting of AABB, ABAB, BBAA, BABA, ABBA, and BAAB. Each block was selected randomly using dice throwing. Each participant was assigned a code, and neither the patients nor the researchers were aware of the code assigned to any given patient. Then the participants were referred to the Beheshti Hospital's laboratory for the initial lab tests, so there were used the same laboratory calibrated equipment.

3.3. Outcome Measures

The tests included liver enzymes such as ALT and AST, and alkaline phosphatase (ALP) (18), blood urea, creatinine that were performed before and after the study in the laboratory of the Beheshti Hospital in Qom, Iran.

The patients were contacted every two weeks, and questions were asked about possible side effects; also, urea and creatinine tests and coagulation tests were performed to investigate the possible side effects of drug use.

3.4. Intervention

DAB tablets were obtained from the pharmacy of the traditional medicine clinic and used as the tested drug, which was a pre-made tablet, manufactured by the pharmaceutical company Niak, Gorgan, Iran, and its batch number was 96023. The drug constituted a combination of 105 mg *Nigella sativa*, 105 mg *Zataria multiflora*, 105 mg *Pistacia lentiscus*, and 105 mg *Trachyspermum ammi*. For the control group, completely similar pills to the DAB tablets were manufactured by that company as a placebo. The placebo tablets have the same shape, size, color, and weight to the DAB. The placebo tablets contained 500 mg cellulose. The participants took two tablets (1,000 mg per dose and 3,000 mg per day) of DAB or placebo after each meal for three months. In addition, both groups received the dietary and lifestyle guidelines for NAFLD based on current medical

recommendations so that the patients were not deprived of the main treatment of NAFLD during the study. The recommendations included avoiding high-sugar and high-fat foods, consuming more vegetables, whole grains, steamed foods, and doing regular exercise. Since both groups received the same recommendations, these recommendations are not confusing. At the end of the study, the subjects were re-examined for weight, waist circumference, and laboratory tests.

3.5. The Sample Size

The sample size required for the study, regarding the account of the results of Emtiazi study, and according to the following formula, was in each group, at least 35 patients. The minimum sample size in this study was 45 individuals per group (totally 90 cases).

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2} \quad (1)$$

Prior to the onset of the study, the participants signed written informed consent forms, and then their anthropometric characteristics such as height, weight, and waist circumference were recorded.

3.6. Statistical Analysis

Data were analyzed using the IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA). The cases with Low Corporation were excluded. The missing data in entered subjects was minimum. The chi-square test was used to compare the qualitative variables between the two groups. The *t*-test was run to compare the quantitative variables between the two groups, and the analysis of covariance (ANCOVA) was used to determine the effect of the intervention on the two groups. Per protocol method used for analysis. P values of less than 0.05 were considered statistically significant.

4. Results

In this study, 98 patients enrolled, and 18 subjects who had not met the inclusion criteria were excluded. In total, 80 patients recruited and randomized in the two groups (Figure 1). Three individuals were excluded from the intervention group for reasons such as starting another medication, travel, and constipation, and one individual left the placebo group to start another medication. Eventually, 37 individuals in the intervention group and 39 individuals in the placebo group completed the study and were assessed after three months. The analyses showed that the two groups were homogeneous in terms of age and other baseline variables (Table 1). There were 25 females in the intervention and 27 in the control group. (P = 0.48). Mean age of the participants in the intervention and placebo groups was 41 and 39.5, respectively (P = 0.49).

Table 1. The Baseline Measurements and Comparisons Between the Two Study Groups

Variables	Placebo, Mean ± SD	*Dava Al-Balgham*, Mean ± SD	P Value
Age, y	41.10 ± 10.05	39.49 ± 10.09	0.49
Height, cm	166.64 ± 8.47	172.09 ± 9.89	0.013
Weight, kg	81.85 ± 12.83	86.80 ± 15.91	0.143
BMI, kg/m^2	29.44 ± 3.84	4.16 ± 29.21	0.809
Waist circumference, cm	105.18 ± 6.31	5.33 ± 104.54	0.643
ALT, units/L	84.31 ± 21.41	74.54 ± 27.92	0.000
AST, units/L	43.31 ± 22.55	44.20 ± 19.42	0.711
ALP, units/L	182.32 ± 50.04	182.00 ± 59.42	0.557
Urea, mg/dL	26.85 ± 4.74	33.09 ± 7.39	0.020

The analysis of the results before and after the study reflected that weight, waist circumference, and liver enzymes decreased in both groups. However, the values of weight, waist circumference, and ALT in the intervention group was significantly lower than the placebo group (P = 0.003, P = 0.001, and P = 0.008), respectively (Table 2). Weight (84.11 ± 15; P < 0.001), waist circumference (101.11 ± 7.03; P < 0.001), ALT enzyme (51.74 ± 20.83; P < 0.001), and AST enzyme (35.11 ± 18.65; P = 0.023, while these values in the placebo group just showed a significant reduction in the level of AST enzyme with a mean value of 31.23 ± 16.42 (P = 0.001) (Table 3).

Table 2. The Changes in Weight, Waist Circumference, and Laboratory Findings in the Two Groups

Variables	Placebo, Mean ± SD	*Dava Al-Balgham*, Mean ± SD	P Value
Weight change, kg	2.41 ± 0.897	2.52 ± 2.69	0.003
Waist circumference change, cm	2.48 ± 0.33	4.81 ± 3.43	0.001
ALT, units/L	37.92 ± 1.59	28.30 ± 22.80	0.008
AST, units/L	21.16 ± 12.08	22.56 ± 9.09	0.558
ALP, units/L	45.07 ± 3.11	35.74 ± 10.33	0.522
Urea change, mg/dL	3.84 ± -1.46	7.54 ± 1.91	0.172

The levels of urea and creatinine were also evaluated before and after the study to detect the possible side effects of the tested intervention. The analysis showed that

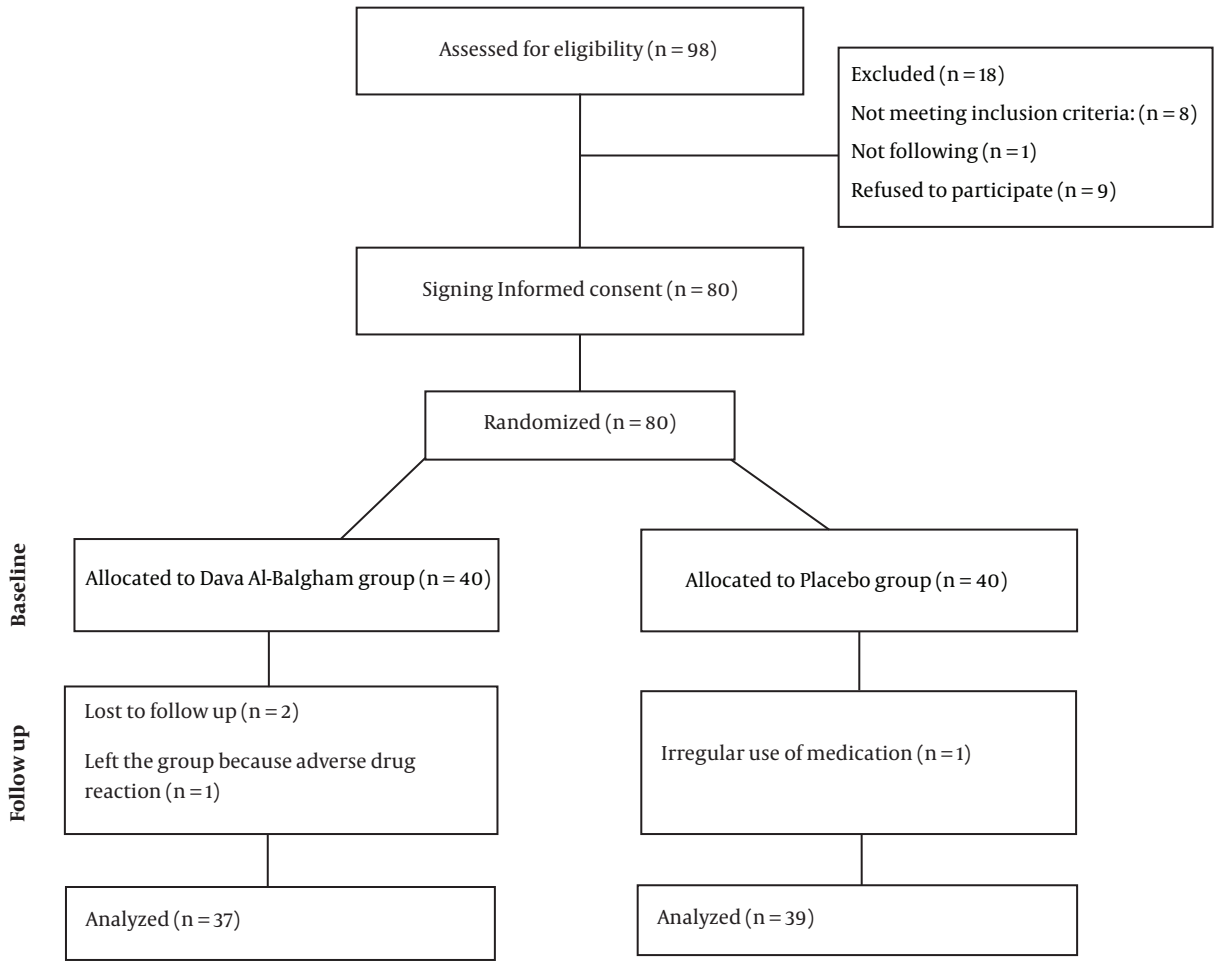

Figure 1. The CONSORT diagram showing the flow of the participants in each stage of the randomized trial

participation in the study did not show any adverse effects on these factors (Table 2). The ANCOVA test showed that the type of intervention was the only factor affecting the change in ALT (P-0.045), weight (P = 0.032), and waist circumference (P = 0.002), and gender and body mass index (BMI) status did not have significant effects on changes in ALT, weight, and waist circumference. During the study, one participant in the intervention group, who had a history of constipation, withdrew from the study because of exacerbation of his constipation.

5. Discussion

The current study investigated the effect of *Dava al-Balgham* on NAFLD treatment. The mean ALT enzyme in the intervention group was significantly lower than placebo (P = 0.008). Since the level of liver enzymes is effective in some of the well-known diagnostic panels of liver fibrosis, these decreases are valuable (19). The mean weight loss and waist circumference reduction significantly decreased in the intervention group. Weight loss is one of the primary and effective treatments in the fatty liver that reduces liver enzymes and improves the liver tissue (20, 21).

Dava Al-Balgham efficacy in hyperlipidemic patients was assessed in another clinical study and found that this drug decreased low-density lipoproteins (LDL) and cholesterol serum levels (22). Therefore, *Dava Al-Balgham* reduces lipid profile, which is an important factor in improving fatty liver.

The combination of *Nigella sativa, Zataria multiflora, Pistacia lentiscus*, and *Trachyspermum ammi* with Orlistat among overweight patients was assessed. The group receiving herbal combination showed more reductions in BMI (14). The result of this study was similar to our research

Table 3. Comparison of the Changes in Variables in Each Group Before and After the Intervention

Group/Variable	Before, Mean ± SD	After, Mean ± SD	P Value
Placebo			
Weight, kg	81.85 ± 12.83	80.12 ± 95.87	0.026
Waist circumference, cm	105.18 ± 6.31	6.68 ± 104.85	0.407
ALT, units/L	53.26 ± 21.41	38.56 ± 51.67	0.795
AST, units/L	43.31 ± 22.55	16.42 ± 31.23	0.001
ALP, units/L	182.32 ± 50.04	48.75 ± 179.21	0.718
Urea, mg/dL	26.85 ± 4.74	6.27 ± 28.31	0.195
Dava Al-Balgham			
Weight, kg	86.80 ± 15.91	84.11 ± 15.00	> 0.001
Waist circumference, cm	104.54 ± 5.33	101.11 ± 7.03	> 0.001
ALT, units/L	74.54 ± 27.92	51.74 ± 20.83	> 0.001
AST, units/L	44.20 ± 19.42	18.65 ± 35.11	0.023
ALP, units/L	182.00 ± 182.00	50.23 ± 171.67	0.170
Urea, mg/dL	33.09 ± 7.39	4.98 ± 31.18	0.421

and both showed the efficacy of the combination of these plants for weight loss.

Nigella sativa has anti-inflammatory, antioxidant, and hepatoprotective effects and helps control the progression of NAFLD (23) and significantly reduced the level of blood lipids and weight (24). *Nigella sativa* decreased ALT, AST, and BMI and improved ultrasonography of the liver (25). In another double-blinded clinical study, the effect of *Nigella sativa* on functional dyspepsia was examined and noted that the severity of functional dyspepsia significantly reduced (26). Therefore, *Nigella sativa* improves digestion, decreases lipids, ALT, AST, and weight; therefore, it is effective on fatty liver treatment.

Zataria multiflora decreased blood cholesterol (27) and could reduce liver enzymes and hepatoprotective, hypolipidemic, and antioxidant effects on the damaged liver (28). The anti-inflammatory, antihyperlipidemic, and antioxidant effects of the drug were proven in another study (29). Based on these studies, this plant is used for the treatment of fatty liver.

Pistacia lentiscus reduced inflammatory factors (30) and significantly decreased gastrointestinal symptoms, BMI, fasting blood sugar, and HbA1c (31). This plant has hepatoprotective effects by decreasing serum total cholesterol, LDL, and lipoprotein (32). The hepatoprotective effect of the *Pistacia lentiscus* extract was examined in rats. The results confirmed the hepatoprotective effects of *Pistacia lentiscus* by reducing the levels of AST, ALT, bilirubin, and ALP (33). Therefore, this plant is also one of the best remedies for treating and improving fatty liver.

Trachyspermum ammi has hepatoprotective properties (34), including antihyperlipidaemic (35) antioxidant and healing effects of indigestion symptoms and gastric infections (36-38).

According to the studies, each of these herbs has a hepatoprotective effect and reduces lipids profile. On the other hand, *Nigella sativa* and *Pistacia lentiscus* cause weight loss too. Therefore, the combination of these plants is effective with three mechanisms, including weight loss and decrease of lipid profile and liver enzymes to improve fatty liver.

5.1. Limitations

The present study was done in a three month period, while it is preferred to observe the changes in the ultrasonographic pattern and elasticity of the liver, six months after the intervention. However, conducting studies with a larger sample size, and more extended duration, with evaluation of the liver tissue changes could be considered.

5.2. Conclusions

According to previous studies that proved the antioxidant, hepatoprotective, antihyperlipidemic, anti-inflammatory, and digestive effects of the herbs that make up the DAB, this drug can be an alternative drug to prevent and treat NAFLD. In addition, according to the viewpoints of Persian Medicine, the proper function of the liver depends on the balance of its temperament and receiving well-digested foods from the stomach. The *Dava al-Balagham* has gastrointestinal effects such as reducing bloating and indirectly helps to improve liver function by improving digestion. Therefore, the DAB tablets could be used in the treatment of NAFLD, especially in the presence of obesity and gastrointestinal problems.

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Footnotes

Authors' Contribution: Study concept and design: Fatemeh Tooiserkany; acquisition of data: Ahmad Hormati; drafting of the manuscript: Fatemeh Aliasl; critical revision of the manuscript for important intellectual content:

Fatemeh Tooiserkany; administrative, technical, and material support: Ahmad Hormati; study supervision: Ahmad Hormati.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: This study was registered at the Iranian Registry of Clinical Trials (IRCT2017073135415N1). In addition, the participants signed informed consent forms, and the Research Council and Ethics Committee of Qom University of Medical Sciences approved the protocol of the study (code of ethics: IR.MUQ.REC.1396.44).

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