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The Effect of Ellagic Acid Supplementation on Inflammatory Markers and Adiponectin Levels in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Double-Blind Clinical Trial

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ABSTRACT

Background: The progression and pathogenesis of non-alcoholic fatty liver disease (NAFLD) are intimately connected to elevated oxidative stress and chronic inflammatory responses. With the antioxidant qualities of Ellagic acid (EA), this study aims to assay the impact of EA on inflammatory markers and adiponectin hormone in individuals with NAFLD. **Methods:** In a double-blind, controlled clinical trial, 44 people meeting the study criteria were randomly assigned to consume 180 mg of EA per day (EAG, n=22) or placebo (PG, n=22) over an 8-week period. Measurements of anthropometric indices, food intake, physical activity levels, inflammatory markers, and adiponectin were taken at both the beginning and conclusion of the trial. The results were evaluated with the help of SPSS software. **Results**. No meaningful statistical variations were noticed between the EA and placebo groups regarding anthropometric variables, dietary intake, or physical activity levels before and after the intervention (P>0.05). After receiving the supplement, the average changes of inflammatory agents, interleukin 6 (IL-6) (from 8.69±3.07 to 5.11±1.24 mg/dl, P=0.04), and tumor necrosis factor-alpha (TNF-α) (from 15.09±3.52 to 10.61±2.44 pg/ml, P=0.037), at the start and end of the study, were significantly reduced (P<0.05). In addition, a notable increase in the level of adiponectin was noted in the EAG group (P<0.05). **Conclusions.** In light of the outcomes, EA can be utilized as an effective therapeutic intervention to ameliorate complications derived from NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to the presence of fat in more than 5% of liver cells without any history of alcohol consumption or other liver conditions (Yin *et al.*, 2023). It is currently the leading cause of liver-related deaths globally and is predicted to become the primary reason for liver transplantation by 2030 (Hassanipour *et al.*, 2023). Studies estimate that NAFLD affects about 25% of the world's population (Henry *et al.*, 2022).

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The pathological conditions that occur in the vital organ of the body, the liver, are very similar to the biochemical manifestations of metabolic syndrome, such as dyslipidemia, or clinical symptoms, such as hypertension. It seems that the missing and less-noticed link in these symptoms is insulin resistance (Barghchi *et al.*, 2023). The underlying molecular and cellular mechanisms of NAFLD are not yet fully understood, and no medications have been officially approved for its treatment. As a result, basic and permanent methods such as changes in nutrition, sleep, and physical activity, which are collectively called lifestyle changes in the right direction are recommended approaches to manage the disease (Raza *et al.*, 2021).

One of the core and main known causes in the pathogenesis of this disease is inflammation. Recent research has shown that NAFLD is associated with widespread secretion and upregulation of proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α), Interleukin 6 (IL-6), and Interleukin-1 beta (IL-1β) (Katsarou *et al.*, 2020). The rise in the number of proinflammatory cytokines is related to the overproduction of reactive oxygen species (ROS), insulin resistance, liver inflammation, and fibrosis, which can lead to apoptosis (Ziolkowska *et al.*, 2021). Adiponectin is the most prevalent adipokine released by adipose tissue cells, which plays its anti-inflammatory function by interfering with the actions of nuclear factor kappa B (NF-kB), and reducing concentrations of inflammatory cytokines such as C-reactive protein (CRP), IL-6, and TNF-α. These properties make it a protective factor against liver diseases (Shabalala *et al.*, 2020). According to the results of the research, an elevation in the serum levels of inflammatory indicators and a reduction in adiponectin levels have been reported in patients with NAFLD. It seems that changes in the serum level of these factors cause a pro-inflammatory state, leading to several metabolic disorders in these patients (Ghorbanian and Egtesadi, 2022).

Given the roles of inflammation and oxidative stress in the development of NAFLD, research has shown that a diet high in polyphenols may be beneficial for the management and prevention of this issue (Abenavoli *et al.*, 2021). Ellagic acid (EA) is a naturally occurring polyphenol present in diverse fruits, such as raspberries, grapes, pomegranates, and nuts (Sharifi-Rad *et al.*, 2022). The results of scientific studies have shown that EA exerts its protective effects against metabolic syndrome diseases by eliminating oxygen-free radicals, regulating antioxidant enzymes, and improving inflammatory conditions (A LTamimi and Alshammari, 2022). So, the findings reflect that the anti-inflammatory effects of EA are induced by regulating cytokine expression, specifically TNF-α, IL-1β, and IL-6, as well as suppressing NF-KB and cyclooxygenase-2 (Cox-2) (Bhattacharjee *et al.*, 2021).

The study by Mirzaei *et al*. suggested that EA supplementation enhanced intestinal function and overall well-being for individuals experiencing irritable bowel syndrome (IBS) by regulating inflammatory factors and oxidative stress. In their study, EA was linked to a decrease in levels of IL-6 and CRP (Mirzaie and Bastani, 2022). Also, another study by Michicotl-Meneses pointed to a notable reduction in inflammatory marker levels (IL-1β, IL-6, and TNF-α), and an increase in adiponectin levels within the fat tissue of overweight mice due to the consumption of pomegranate juice (Michicotl-Meneses *et al.*, 2021). Considering the properties and potential of EA as a useful substance in the remedy of chronic inflammatory disease, the clinical evidence specifically investigating the effects of purified EA supplementation, rather than EA-rich foods on NAFLD remains limited. Therefore, this research sought to assess its impact on inflammatory markers and adiponectin serum levels in patients with NAFLD.

Materials and Methods

Study design and participants

This clinical trial was implemented as a randomized, double-blind, placebo-controlled study involving 44 patients aged 18-55 with NAFLD, who presented it to the gastroenterology

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department of Velayat Hospital, affiliated with Qazvin University of Medical Sciences. The patients were chosen based on the clinical consultant's opinion, using the liver ultrasound method while ruling out other liver diseases, which is a widely used procedure followed in the medical assessment of NAFLD.

Participants with a body mass index (BMI) below 30 kg/m^2 and moderate physical activity of both genders were enrolled in this study. The research excluded patients with acute illnesses such as cardiovascular, renal, and pulmonary diseases, cancer, diabetes, hepatitis B and C, Wilson's disease, and hemochromatosis, or any other liver disorders. Additionally, individuals who were pregnant or lactating, as well as those who had taken dietary supplements within the previous three months, were also not eligible. Participants were excluded from the study if they had made changes to their medication, physical activity, dietary habits, or lifestyle during the study period, consumed alcohol, had any history of allergies, used drugs that affect the liver, expressed dissatisfaction with the study, or reported any side effects from the supplement.

Randomization and blinding

This study aimed to examine the impact of 180 mg daily intake of EA for 8 weeks on inflammatory factors and adiponectin levels in patients with NAFLD. Appropriate questionnaires and tools were used to collect information on demographic and clinical features (medical history and medications), along with anthropometric measurements such as weight, height, and BMI. Weight and height measurements were taken for each individual utilizing a Seca scale (Seca, Hamburg, Germany) (with a precision of 0.1 kg) and a tape measure (with 0.1 cm accuracy), respectively. Additionally, the BMI was determined by taking the body weight in kilograms and dividing it by the square of the height in meters. (Weir and Jan, 2023). After matching people based on age, weight, and sex, they were randomly distributed to Ellagic acid (EAG, n=22) and placebo groups (PG, n=22) using randomized block methods. The randomization process was performed using a computer-generated random number sequence for block randomization. The allocation was conducted by an independent research assistant not involved in participant recruitment or outcome assessment. Each participant was given either a daily ellagic acid capsule (180 mg) or a placebo capsule made with wheat flour for a period of two months. It is worth noting that the appropriate dose selected for ellagic acid supplement was obtained from Ghadimi M (Ghadimi *et al.*, 2021). The placebo capsules were then made to look exactly like the supplement capsules in terms of shape, color, and size. In this study, both the participants, the investigator, and the expert physician were unaware who received supplements or a placebo. To ensure that the researcher remained oblivious to the contents of the capsules, they were categorized in two groups, A and B, by an individual who was not part of the study. The supplement was produced by the Supplement Spot company, while the placebo was created by the School of Pharmacy at Tabriz University of Medical Sciences. To manage for confounding variables like physical activity and diet, participants filled out a 3-day dietary recall questionnaire both at the beginning and conclusion of the study, while those engaged in moderate physical activity were recruited. Participants' dietary intake was assessed through the Nutritionist IV software (San Bruno, CA), which had been adapted to reflect the composition of Iranian foods. In order to assess the physical activity levels of the participants, the International Physical Activity Questionnaire (IPAQ) was employed. Existing guidelines were used to convert data from IPAQ into metabolic equivalent minutes per week (Wolin *et al.*, 2008). To prevent any samples from being lost, patients received weekly phone calls to ensure they were properly consuming their supplements. Capsule intake was monitored by counting the remaining EA capsules at the conclusion of the study, and participants with less than 10% consumption were excluded.

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Laboratory methods

Following a fasting period of 8-12 hours, venous blood specimens were obtained from the participants at the start and conclusion of the research, with 10 ml taken each time. The serum was separated, and the levels of inflammatory factors and adiponectin were measured in the plasma employing a specific kit and the ELISA technique. The collected samples were promptly preserved at -80 ℃ for subsequent laboratory examinations. Levels of inflammation-related factors, such as IL-6 and TNF-α, were also quantified by ELISA kits (Koma Biotech Inc., Korea) and (DIAsource Co, Belgium), respectively. Serum adiponectin concentration was measured using the ELISA kit of Mercodia, Sweden.

Sample size calculation

The triglyceride (TG) factor level was utilized to establish the sample size prior to and following the administration of the EA supplement in the study by Ghadimi (Ghadimi *et al.*, 2021). Based on the mean and standard deviation values of TG before and after the supplementation, which were 159.9±13.04 and 141.57±10.75 mg/dl, respectively, the calculated sample size for each group was determined to be 15. Considering the possibility of dropouts, a total of 22 participants were included in every group.

$$N= [(Z_{1-\alpha/2} + Z_{1-\beta})^2 (SD_1^2+SD_2^2)] /\Delta^2$$

Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of Qazvin University of Medical Sciences (Ethics code: IR.QUMS.REC.1400.362) (December 13, 2021), and the procedure adhered to the ethical principles outlined in the Declaration of Helsinki. Also, the trial was registered with the Iranian Registry of Clinical Trials website (IRCT20141025019669N21). It should be noted that all participants provided written informed consent before enrollment.

Data analysis

The statistical evaluations were performed utilizing SPSS version 20. Data were expressed as mean ± SD, and the distribution normality was assessed with the Kolmogorov-Smirnov test. The paired t-test statistical method was employed to compare mean variables within the same group, while the independent sample t-test method was utilized for comparing variables between two groups. The threshold for statistical significance was set at $p<0.05$ in this research.

Results

The study initially invited 55 patients to participate. However, 10 patients were excluded due to ineligibility or reluctance to engage (n=1). As a result, the study comprised 44 participants, with 22 receiving EA and 22 receiving a placebo. Subsequently, only 42 participants completed the study, and two individuals exited the placebo group due to personal matters (**Figure 1**). According to the study, the level of patient compliance was 95.45%. The study did not reveal any reported side effects. The general baseline profile of participants is displayed in **Table 1**. No meaningful statistical variations were detected in the individual characteristics between the two groups. Furthermore, there was no notable variation in the amount of physical activity. The participants' mean age in the EAG was 42.08±6.11 years, whereas in the PG, it was 39.13±5.31 years ($P>0.05$). As presented in **Table 1**, there were no notable differences in anthropometric measurements between the two groups at the start of the study. The mean and standard deviation of height (162.04±7.07 vs. 160.28±8.5 cm), weight (76.5±6.9 vs. 74.49±8.12 kg), and BMI (29.13±0.13 vs. 28.9±0.11 kg/m^2) were reported for the EAG and PO, respectively.

The amount of food consumed is provided in **Table 2**. As illustrated, at the beginning and end of the study, there were no significant differences observed in energy intake, macronutrient, and micronutrient levels ($P>0.05$).

The impact of EA on inflammatory factors and adiponectin has been demonstrated in **Table 3**. At the conclusion of the study, EA lowered the levels of TNF-α and IL-6 remarkably ($P<0.05$). Moreover, the level of adiponectin in the EA group displayed a substantial increase in contrast to the

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placebo group (P<0.05). Nevertheless, no meaningful alterations were noted in the placebo group at the end of the research (P>0.05, **Table 3**).

Table 1. The comparison of baseline characteristics of the participants.

Variable	Placebo (n=20)	Ellagic acid (n=22)	P-value[a]
Age (y)	39.13±5.31[c]	42.08±6.11	0.41
Height (cm)	160.28±8.5	162.04±7.07	0.70
Weight (kg)			
Before	74.49±8.12	76.5±6.9	0.55
After	74.13±8	76.14±6.5	0.61
P-value[b]	0.69	0.702	
Body mass index (kg/m²)			
Before	28.9±0.11	29.13±0.13	0.20
After	28.85±0.11	29.01±0.11	0.21
P-value[b]	0.31	0.32	
Physical activity (met-h/week)			
Before	30.14±3.63	28.18±4.57	0.14
After	30.29±3.47	28.33±4.6	0.14
P-value[b]	0.39	0.35	

[a]: Independent samples t-test; [b]: Paired samples t-test; [c]: Mean±.SD.

Discussion

In light of the limited number of clinical studies, most of which had examined foods containing EA on various diseases, including liver diseases and hepatic damage caused by chemicals and toxins, this study aimed to evaluate the effects of EA supplementation on inflammatory markers and adiponectin in patients with NAFLD. The present study indicated that taking 180 mg of EA for a duration of 8 weeks markedly decreased levels of TNF-α and IL-6.

Studies have indicated that oxidative stress is the main factor responsible for inflammation in NAFLD. So, the increase of ROS is linked to the generation of pro-inflammatory mediators, and lipid peroxidation, which ultimately leads to fibrogenesis, cirrhosis, and hepatic carcinoma (Dallio and Sangineto, 2021). In NAFLD, ROS regulates the activation of the NF-KB pathway, an important regulator of inflammation, by elevating the expression of TNF-α. In addition to its direct pro-inflammatory effects, TNF-α can also neutralize the function of adiponectin. As such, this pro-inflammatory cytokine is crucial in the pathophysiology of NAFLD by inducing insulin resistance and inflammation (Hong *et al.*, 2021).

Table 2. The comparison of the dietary intake at the baseline and the end of the study in patients with NAFLD.

Variables	Placebo (n=20)	Ellagic acid (n=22)	P-value[a]
Energy (kcal)			
Before	2503.29±361.01	2611.66±400.19	0.61
After	2477.55±387.11	2588.47±301.14	0.52
P-value[b]	0.58	0.48	
Protein (g)			
Before	86.23±18.55[c]	88.03±22.16	0.37
After	86.88±19.41	89.12±22.19	0.29
P-value	0.69	0.69	
Carbohydrate(g)			
Before	311.29±52.01	327.82±55.39	0.60
After	308.55±49.26	324.2±50.11	0.59
P-value	0.63	0.69	
Fat (g)			
Before	101.25±11.09	112.39±17.28	0.55
After	98.24±10.5	109.71±9.5	0.41
P-value	0.51	0.60	
Saturated fatty acids (g)			
Before	39.14±8.50	43.18±11.29	0.12
After	37.55±5.19	42.34±4.66	0.10
P-value	0.19	0.22	
Monounsaturated fatty acid (g)			
Before	25.43±11.01	32.87±9.63	0.09
After	23.39±9.51	30.83±10.13	0.08
P-value	0.12	0.29	
Polyunsaturated fatty acid (g)			
Before	36.29±11.08	33.44±14.50	0.21
After	35.22±10.09	33.31±9.42	0.22
P-value	0.23	0.20	
Fiber (g)			
Before	8.11±2.50	8.88±2.01	0.10
After	8.09±1.94	8.53±1.33	0.10
P-value	0.10	0.11	
Vitamin C (mg)			
Before	60.12±17.5	63.02±14.66	0.21
After	60.19±13.89	62.77±16.19	0.28
P-value	0.60	0.54	
Vitamin E (IU)			
Before	14.49±3.19	15.10±4.44	0.26
After	13.27±3.50	14.26±4.20	0.29
P-value	0.25	0.28	
Selenium (µg)			
Before	118.11±35.00	123.50±37.14	0.42
After	119.55±39.22	122.39±38.19	0.41
P-value	0.36	0.48	

[a]: Independent samples t-test; [b]: Paired samples t-test; [c]: Mean±.SD.

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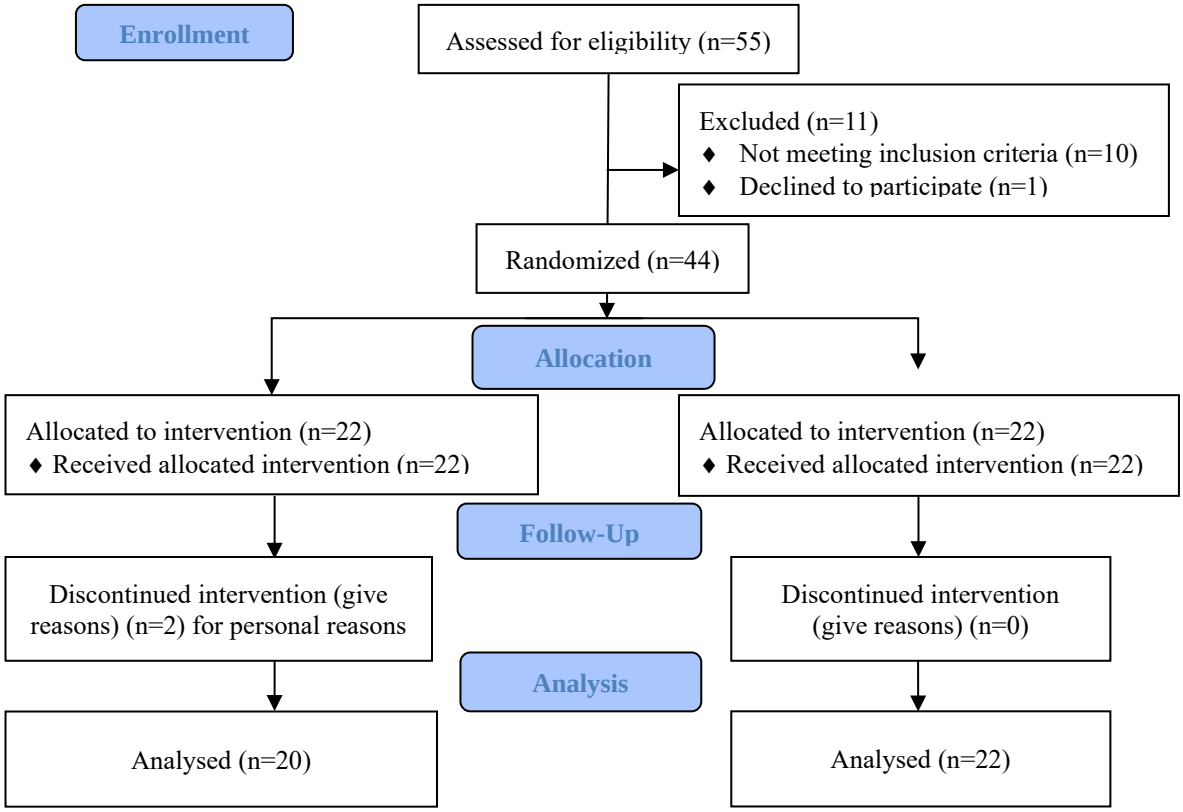

Figure 1. Consort flow diagram for the trial.

Chen *et al.*'s study revealed that in NAFLD, increased TNF-α levels activate NLR family CARD domain-containing protein 4 (NLRC4), leading to exacerbated inflammation and disease progression through the production of Interleukin-18 (IL-18) and IL-1β (Chen and Ma, 2019). Besides, adipose-derived IL6 has been found to influence hepatic IR by activating the suppressor of cytokine signaling 3 (SoCS3). This subsequently leads to elevated levels of Sterol regulatory element-binding protein-1 (SREBP-1) and De novo lipogenesis (DNL), leading to steatosis and hepatic fat accumulation (Duarte *et al.*, 2015). Aligned with the findings, a research study by Ghadimi *et al*. found that giving 180 mg of EA to patients with type 2 diabetes for a period of 8 weeks resulted in a significant reduction of inflammatory indicators like CRP, TNF-α, and IL-6. In their study, EA improved inflammatory conditions in patients through its antioxidant effects and ROS inhibition (Ghadimi *et al.*, 2021). Moreover, a study conducted by Aslan *et al*. in 2020 reported that EA improved brain damage caused by Carbon tetrachloride (CCL4) in rats by reducing TNF-α, NF-KB, and Cox-2. (Aslan *et al.*, 2020). Abnormal expression and increased activity of the Cox-2, which is produced by pro-inflammatory cytokines, can result in the progression of pathological conditions like inflammation. This suppression of Cox-2, a key enzyme in the inflammatory cascade, could be a pivotal mechanism through which EA alleviates inflammation and ameliorates complications in NAFLD (Hu *et al.*, 2019). However, the mentioned study found that EA was able to induce anti-inflammatory effects by inhibiting Cox-2.

Pomegranate and its metabolites can positively affect NAFLD by inhibiting inflammation-causing elements, including Peroxisome proliferator-activated receptors (PPARs), NF-KB, and Cox-2 suppression, and also inhibiting the phosphorylation of mitogen-activated protein kinases (MAPKs) (Zamanian *et al.*, 2023). According to Jafarirad *et al*.'s research in 2023, it

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was discovered that patients with NAFLD who consumed 450 mg of pomegranate extract (containing 40% EA) per day for a duration of 12 weeks experienced a significant decrease in IL-6 levels (Jafarirad *et al.*, 2023). In contrast to the results mentioned, a study by Sohrab discovered no noteworthy alteration in the plasma concentration of TNF-α in diabetic patients after daily intake of 250 ml of pomegranate juice for 12 weeks. The small amount of EA in pomegranate juice and the short length of the study may have caused the observed results (Sohrab *et al.*, 2014).

Table 3. Changes in baseline to endpoint measures for inflammatory biomarkers and adiponectin in two groups.

Variables	Placebo (n=20)	Ellagic acid (n=22)	P-value[a]
TNF-a (pg/ml)			
Before	14.82±2.11[c]	15.09±3.52	0.34
After	14.50±3.19	10.61±2.44	0.04
P-value[b]	0.35	0.03	
IL-6 (mg/dl)			
Before	8.14±2.60	8.69±3.07	0.22
After	8.76±2.45	5.11±1.24	0.03
P-value	0.21	0.04	
Adiponectin (mg/ml)			
Before	7.30±1.59	7.76±2.61	0.29
After	7.42±1.74	8.69±2.52	0.03
P-value	0.32	0.03	

[a]: Independent samples t-test; [b]: Paired samples t-test; [c]: Mean±.SD; **IL-6:** *Interleukin 6;* **TNF-α**: *Tumor necrosis factor-alpha.*

It is widely supported by evidence that adiponectin can play a protective role in NAFLD, which appears to enhance insulin sensitivity in the liver by reducing gluconeogenesis, inhibiting lipogenesis, and activating fatty acid oxidation through the effect on PPAR-α and Adenosine monophosphate-activated protein kinase (AMPK) (Daneshi-Maskooni *et al.*, 2017). In the research carried out by Mantovani *et al.*, low plasma adiponectin levels were strongly linked to the occurrence and intensity of NAFLD in individuals with type 2 diabetes. This highlights the potential contribution of adiponectin, likely through its role in enhancing insulin sensitivity and promoting fatty acid oxidation in the liver, in the advancement and development of NAFLD (Mantovani *et al.*, 2022).

Based on the present research, it was found that, following an eight-week intervention, there was a notable rise in adiponectin levels in the group that received EA in contrast to the placebo. An investigation carried out by Abdi et al. indicated that taking 150 ml of pomegranate fruit extract, along with three sessions of aerobic exercise per week (for six weeks), and both interventions together can effectively decrease serum adiponectin concentrations and IR in women diagnosed with type 2 diabetes (Abdi and Aohajer iravani, 2018). Contrary to the findings obtained from the current study, Yoshimura *et al.*'s study in 2013, which examined the effects of EA on serum adipocytokine levels and liver function in obese rats with type 2 diabetes, showed that administering 0.1% EA over a period of 68 days did not change the serum level of adiponectin substantially (Yoshimura *et al.*, 2013). In addition, in a study by Wang, neither high nor low doses of EA failed to affect adiponectin levels in DIO (obesity caused by a high-fat diet) rats, which was consistent with the work from Yoshimura *et.al* (Wang *et al.*, 2019). It's potentially the case that the short study duration contributed to the lack of positive outcomes of the mentioned research. This study has several strengths. It is the first to investigate the impact of EA supplementation on inflammatory markers and adiponectin levels in individuals with NAFLD. Additionally, the research was designed as a randomized clinical trial with parallel groups, employing a double-blind approach. Key factors such as body weight, physical activity, and diet were carefully controlled throughout the study. However, there are some limitations to consider. These include a limited budget, a small sample size, and a relatively short duration of the intervention. To obtain more conclusive results, future studies should involve larger sample sizes, longer intervention periods, and a range of supplement dosages.

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Conclusions

In conclusion, the study found that daily supplementation with 180 mg of EA for 8 weeks significantly reduced inflammatory markers in individuals with NAFLD, while also leading to a marked increase in adiponectin levels. Targeting inflammatory pathways in the treatment of NAFLD could be an effective therapeutic approach, given the central role of inflammation in the progression of the disease. Therefore, the results of this study suggest that EA may be a promising adjunctive treatment for these patients. However, further research is required to provide additional evidence.

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Conflicts of interest

The authors declared no conflicts of interest.

Authors' contributions

Rashidi Nooshabadi M, Khadem Haghighian H and Farzam SA were involved in methodology. Formal analysis and investigation were done by Mighani S, Rashidi Nooshabadi M, and Khadem Haghighian H. Writing the original draft preparation was carried out by Khadem Haghighian H and Mighani S. Writing the review and editing was conducted by Khadem Haghighian H. Funding acquisition was by Khadem Haghighian H. Resources were collected by Rashidi Nooshabadi M and Mighani S; Supervision was carried out by Khadem Haghighian H. All authors aproved the manuscript for publishing.

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