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RESEARCH ARTICLE

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Efficacy of artichoke leaf extract in non-alcoholic fatty liver disease: A pilot double-blind randomized controlled trial

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Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide and is potentially treatable, though there are few therapeutic agents available. Artichoke leaf extract (ALE) has shown potential as a hepatoprotective agent. This study sought to determine if ALE had therapeutic utility in patients with established NAFLD. In this randomized double-blind placebo-controlled parallel-group trial, 100 subjects with ultrasound-diagnosed NAFLD were randomized to either ALE 600 mg daily or placebo for a 2-month period. NAFLD response was assessed by liver ultrasound and serological markers including the aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and AST to platelet ratio index (APRI) score. Ninety patients completed the study (49 ALE and 41 placebo) with no side effects reported. ALE treatment compared with placebo: Doppler sonography showed increased hepatic vein flow ($p < .001$), reduced portal vein diameter ($p < .001$) and liver size ($p < .001$), reduction in serum ALT ($p < .001$) and AST ($p < .001$) levels, improvement in AST/ALT ratio and APRI scores ($p < .01$), and reduction in total bilirubin. ALE supplementation reduced total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and triglyceride concentrations ($p = .01$). This study has shown beneficial effects of ALE supplementation on both ultrasound liver parameters and liver serum parameters (ALT, AST, APRI ratio, and total bilirubin) in patients with NAFLD.

KEYWORDS

artichoke leaf extract (ALE), non-alcoholic fatty liver disease (NAFLD), phytochemical

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, and its incidence continues to rise (Krawczyk, Bonfrate, & Portincasa, 2010). This trajectory has been related to a dramatic change in dietary habits, notably an increase in consumption of fat and simple carbohydrates. NAFLD is associated with metabolic syndrome and thus with obesity, insulin resistance, impaired glucose tolerance, and dyslipidemia (Clark, 2006). Furthermore, patients with NAFLD are at risk for progression to cirrhosis and hepatocellular carcinoma. Hepatic steatosis develops due to anomalous lipid handling by the liver that sensitizes it to injury and inflammation. Subsequent increased hepatocyte injury characterizes non-alcoholic steatohepatitis, a condition associated with a mixed acute and chronic lobular inflammation, hepatocellular ballooning, and peri-sinusoidal fibrosis (Harrison, Torgerson, & Hayashi, 2003).

The progression of NAFLD is potentially reversible, and therefore, its identification is important (Vassilatou et al., 2010). Treatment of patients with NAFLD hinges upon weight loss via dietary modification (towards a diet low in carbohydrates and saturated fat) together with increasing physical activity. Weight loss alone may be inadequate to reverse disease. Additionally, a paucity of approved therapeutic agents

is available, and none reliably achieve disease reversal (Rotman & Sanyal, 2017). Several studies, however, have purported beneficial effects through dietary modifications of macronutrients and micronutrients (Clark, 2006) and the use of phytochemicals (Baghernya, Nobili, Blesso, & Sahebkar, 2017; Panahi et al., 2012; Panahi et al., 2016, 2017; Rahmani et al., 2016; Sahebkar, 2011; Zabihi, Pirro, Johnston, & Sahebkar, 2017).

Artichokes, widely consumed as part of a traditional Mediterranean diet (Rondanelli et al., 2016), yield one such macronutrient, artichoke leaf extract (ALE). In both pre-clinical and clinical studies, ALE has shown potential as a lipid lowering and hepatoprotective agent (Rondanelli et al., 2013). Beneficial effects of ALE stem largely from their component antioxidants, namely, mono-caffeoylquinic acid and dicaffeoylquinic acid (cynarin and chlorogenic acid), caffeic acid, and the volatile sesquiterpine and flavonoids (including the glycosides luteolin-7-beta-rutinoside, luteolin-7-beta-glucoside, and luteolin-4-beta-D-glucoside; Ben Salem et al., 2015). ALE's mechanism of action effecting lipid lowering likely results from luteolin's interaction with hydroxy-methyl-glutaryl-coenzyme A reductase, liver sterol regulatory element-binding proteins, and acetyl-CoA C-acetyltransferase (Gebhardt, 2002), as well as potentially lowering cholesterol through increased fecal excretion of bile salts (Qiang, Lee, Ye, Wu, & Hendrich, 2012).

We recently performed a systematic review and meta-analysis of the literature on the beneficial lipid-lowering effects of artichoke extracts. From this, we concluded that, in patients with mild to moderate hypercholesterolemia, supplementation with artichoke extract resulted in significant reduction in both total and low-density lipoprotein cholesterol (LDL-C) and triglycerides but without affecting plasma levels of high-density lipoprotein cholesterol (HDL-C). Moreover, the cholesterol-lowering effect appeared to relate directly to the baseline LDL-C level rather than to dose or duration of treatment (Sahebkar et al., 2017).

Given its lipid lowering and hepatoprotective effects, in the current randomized controlled study, we sought to determine the efficacy of ALE as a treatment for NAFLD.

2 | MATERIALS AND METHODS

2.1 | Subjects

Subjects were selected from those adults aged 18 years or above referred to the Gastroenterology and Hepatology Clinic of the Baqiyatallah Hospital (Tehran, Iran) with a diagnosis of hepatic steatosis (grades 1–3) based on liver ultrasonography; liver biopsies were not undertaken as there was no clinical indication to do so. Exclusion criteria included pregnancy or breastfeeding, alcoholic fatty liver disease, smoking, biliary diseases (e.g., gallstone), consumption of hypoglycemic, hypolipidemic, and anti-inflammatory medications as well as any drug known to affect hepatic function, and the presence of hepatitis, coronary, renal, pulmonary, and thyroid diseases. Lifestyle modification in the form of dietary advice was given to all patients.

This was a double-blind study, and subjects were randomized to receive either ALE (600 mg/day in three divided doses every 8 hr; n = 50) or matched placebo (n = 50) group. Randomization was performed by alternative assignment of participants to matched and blinded drug and placebo blisters. ALE was administered as tablets containing 200-mg dried ALE standardized to contain 2-mg cynarine as the active ingredient (Cynarol®, Niak Pharmaceuticals, Gorgan, Iran).

The study protocol was approved by the institutional Ethics Committee, and written informed consent was obtained from participants. The clinical trial protocol has been registered under the Iranian Registry of Clinical Trials ID: IRCT2015122125641N1.

2.2 | Anthropometric measurements

Anthropometric indices and blood pressure were measured at baseline and at the end of the study as previously reported (Panahi et al., 2017).

2.3 | Blood sampling and biochemical measurements

Fasting blood samples were taken at baseline and after 8 weeks of supplementation. Blood samples were centrifuged for 10 min at a speed of 2,000 rpm to separate the serum and stored at −80 °C until assayed. Measurement at baseline and at the end of the trial at 8 weeks was undertaken for glucose, insulin, glycated hemoglobin, fasting lipids (total cholesterol, LDL-C, HDL-C, and triglycerides), liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase), total and direct bilirubin, and uric acid, using routine enzymatic assays with commercial kits (Pars Azmoon, Tehran, Iran). AST to platelet ratio index score (APRI) was calculated according to a formula previously described (Wai et al., 2003). AST to ALT ratio was also calculated at baseline and at the study end.

2.4 | Liver Doppler sonography

Liver sonography was performed after 8–12-hr fast using a Mindray DC-8 diagnostic ultrasound system (convex 3.5–5.0 MHz) at baseline and at study end. Ultrasound assessments were performed by the same radiologist blinded to the type of allocation and with the same instrument. Assessments were performed in the supine position as described previously (Panahi et al., 2017). Hepatic steatosis was scored as 0 (no fat accumulation), 1 (mildly elevated echogenicity with normal appearance of diaphragm and intrahepatic vessel borders), 2 (moderately elevated echogenicity with slightly impaired appearance of the diaphragm and intrahepatic vessel borders), and 3 (severely elevated echogenicity with markedly impaired appearance of the diaphragm, intrahepatic vessel borders, and the posterior portion of the right hepatic lobe).

The portal vein was evaluated in a sagittal oblique view demonstrating the vessel's longest axis. The antegrade hepatopetal flow throughout the entire cardiac cycle was considered as the portal vein flow. The length of the liver on the sagittal view in the mid-clavicular line was considered as liver size and was measured in the left posterior oblique position.

2.5 | Statistical analysis

This was a pilot study given that there were no appropriate studies on which to base a formal power analysis. Power and sample size for pilot studies has been reviewed by Birkett and Day (1994) who concluded that a minimum of 20 *df* was required to estimate effect size and variability. Hence, it was planned to recruit 50 participants per group allowing for a 20% dropout rate and covariate adjustment.

Statistical analyses were performed using the SPSS software version 11.5 (SPSS Inc., Chicago, Illinois, USA). Magnitude of changes in each parameter during the trial was calculated and compared between the groups using independent samples *t*-test (for normally distributed data) or Mann–Whitney *U* test (for non-normally distributed data). Categorical variables were compared using Fisher's exact test and difference in proportions of ordinal variables using non-parametric tests. A *p* value of <.05 was considered as statistically significant in all analyses. All analyses were performed per protocol.

3 | RESULTS

3.1 | Baseline characteristics

Eighty-one subjects completed the study. There were nine dropouts in the ALE group and one in the placebo group, and all were due to the perceived lack of benefit of the preparation (Figure 1). There were no adverse events throughout the trial. Baseline characteristics of the study population are summarized in Table 1.

3.2 | Anthropometric indices and blood pressure

Supplementation with ALE was associated with a significant reduction in body mass index ($p = .001$) and waist circumference ($p = .009$) compared with placebo. Diastolic blood pressure did not differ between

TABLE 1 Comparison of baseline and demographic characteristics between the study groups

	ALE	Placebo	*p* value
N	49	40	—
Female (%)	24 (49%)	15 (37.5%)	.293
Age (years)	45.2 ± 11.8	47.1 ± 10.5	.409
BMI (kg/m^2)	29.4 ± 4.1	28.9 ± 3.5	.572
Waist circumference (cm)	103.4 ± 9.6	101.3 ± 11.5	.352
SBP (cmHg)	11.7 ± 1.2	12.3 ± 1.1	.011
DBP (cmHg)	7.6 ± 0.8	8.0 ± 0.5	.012
Total bilirubin (mg/dl)	0.9 ± 0.4	0.8 ± 0.2	.033
Direct bilirubin (mg/dl)	0.4 ± 0.2	0.4 ± 0.1	.781
ALT (U/L)	52.5 ± 39.9	37.4 ± 25.1	.042
AST (U/L)	38.0 ± 20.8	27.6 ± 10.2	.003
ALP (U/L)	199.7 ± 52.1	169.6 ± 40.1	.003
Glucose	104.1 ± 24.7	105.6 ± 23.4	.830
Insulin (μU/ml)	12.2 ± 6.1	10.5 ± 3.1	.111
HbA1c (%)	6.0 ± 0.9	6.0 ± 0.9	.914
Total cholesterol (mg/dl)	217.0 ± 38.2	188.4 ± 38.6	.001
LDL-C (mg/dl)	141 ± 38.7	116.2 ± 39.0	.004
HDL-C (mg/dl)	46.9 ± 13.7	47.3 ± 11.0	.879
Triglycerides (mg/dl)	180.3 ± 64.4	148.7 ± 67.0	.026
Non-HDL-C (mg/dl)	170.1 ± 39.8	141.1 ± 36.8	.001
Uric acid (mg/dl)	5.9 ± 0.8	5.4 ± 0.7	.004
AST/ALT	0.9 ± 0.3	0.9 ± 0.3	.818
APRI score	0.4 ± 0.4	0.3 ± 0.1	.040
Hepatic vein flow velocity (cm/s)	16.1 ± 3.9	17.5 ± 3.5	.080
Portal vein diameter (mm)	11.3 ± 0.8	10.6 ± 2.0	.027

Note. Values are expressed as mean ± *SD* or number (%).

ALE = artichoke leaf extract; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

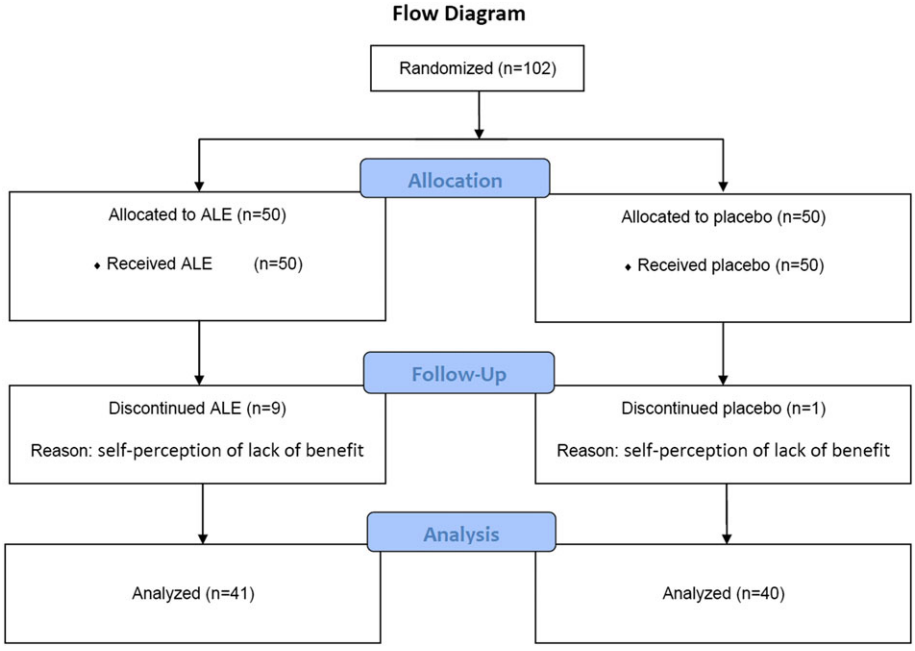

FIGURE 1 Flow diagram of study. ALE = artichoke leaf extract [Colour figure can be viewed at wileyonlinelibrary.com]

groups (p = .069), though systolic blood pressure was elevated by ALE compared with placebo (p = .046).

3.3 | Liver Doppler sonography

Between-group comparisons of the liver ultrasonographic findings revealed a significant improvement in NAFLD severity in the ALE versus placebo group (p < .001; Table 2). Within group comparison for the ALE supplementation, ultrasonographic findings for NAFLD were improved in 81.6% of subjects, whereas the remaining 18.4% remained unchanged from baseline. Within-group comparison of the placebo arm showed an improvement in NAFLD severity of 5.0%, 67.5% were unchanged, and in 27.5% of subjects, the NAFLD disease severity was worse. The number of subjects with improved NAFLD severity was significantly higher in the ALE versus placebo group (p < .001; Table 2).

Findings of Doppler sonography indicated an increase in hepatic vein flow (p < .001) accompanied by reduction of portal vein diameter (p < .001) and liver size (p < .001) following treatment with ALE compared with the placebo group (Table 3).

3.4 | Liver enzymes, bilirubin, and uric acid

Between-group comparisons revealed a significant reduction in serum ALT (p < .001) and AST (p < .001) levels after treatment with ALE versus placebo. Serum alkaline phosphatase was found to be reduced with ALE, but this reduction did not reach statistical significance when compared with placebo (p = .082). With respect to bilirubin levels, a significant reduction in total (p = .002) but not direct bilirubin (p = .802) was observed in the ALE versus placebo group. There was also a significant reduction in serum uric acid levels following ALE supplementation versus placebo (p < .001). At baseline, there were no differences in the AST/ALT ratio and the APRI score. However, at the end of 8-week ALE treatment, there was a significant improvement in both the AST/ALT ratio and the APRI scores versus placebo (p < .01).

3.5 | Lipid profile and glycemic factors

Between-group comparisons revealed a significant effect of ALE compared with placebo in reducing serum concentrations of total cholesterol (p < .001), LDL-C (p < .001), non-HDL-C (p < .001), triglycerides (p < .001), and HDL-C concentrations (p = .011).

Supplementation with ALE was not found to cause any significant alteration in glycemic indices including glucose (p = .915), insulin (p = .517), and glycated hemoglobin (p = .282).

TABLE 2 Comparison of NAFLD severity between the study groups

	ALE	Placebo	p value
Improved	40 (81.6%)	2 (5.0%)	p < .001
Unchanged	9 (18.4%)	27 (67.5%)	
Worsened	0 (0%)	11 (27.5%)	

Note. Values are expressed as number (%).

ALE = artichoke leaf extract; NAFLD = non-alcoholic fatty liver disease.

TABLE 3 Comparison of changes in biochemical indices between the study groups

	ALE (n = 49)	Placebo (n = 40)	p value
BMI (kg/m^2)	−1.1 ± 1.2	−0.1 ± 1.4	.001
Waist circumference (cm)	−1.8 ± 2.2	−0.1 ± 3.5	.009
SBP (cmHg)	0.2 ± 0.9	−0.1 ± 1.0	.046
DBP (cmHg)	0.2 ± 0.9	−0.1 ± 0.7	.069
Total bilirubin (mg/dl)	−0.2 ± 0.2	−0.1 ± 0.1	.002
Direct bilirubin (mg/dl)	−0.004 ± 0.1	0.002 ± 0.1	.802
ALT (U/L)	−20.0 ± 27.6	4.5 ± 7.6	<.001
AST (U/L)	−11.2 ± 11.7	3.8 ± 6.5	<.001
ALP (U/L)	−4.6 ± 23.6	2.5 ± 14.0	.082
Glucose (mg/dl)	−4.3 ± 20.6	−6.6 ± 17.8	.915
Insulin (μU/ml)	−0.7 ± 5.9	−0.1 ± 1.8	.517
HbA1c (%)	0.1 ± 1.9	−0.3 ± 0.6	.282
Total cholesterol (mg/dl)	−46.0 ± 44.9	16.3 ± 47.6	<.001
LDL-C (mg/dl)	−36.5 ± 29.6	17.0 ± 21.9	<.001
HDL-C (mg/dl)	−4.7 ± 7.5	−1.0 ± 5.2	.011
Triglycerides (mg/dl)	−51.2 ± 41.2	5.2 ± 25.1	<.001
Non-HDL-C (mg/dl)	−41.3 ± 43.4	17.3 ± 47.9	<.001
Uric acid (mg/dl)	−0.7 ± 0.5	0.3 ± 0.3	<.001
AST/ALT	0.08 ± 0.2	−0.03 ± 0.2	.010
APRI score	−0.012 ± 0.2	0.04 ± 0.1	<.001
Liver size (mm)	−5.1 ± 6.0	1.7 ± 23.7	<.001
Hepatic vein flow velocity (cm/s)	3.5 ± 3.1	−2.3 ± 2.9	<.001
Portal vein diameter (mm)	−0.3 ± 0.9	1.0 ± 1.5	<.001

Note. Values are expressed as mean ± *SD* or number (%).

ALE = artichoke leaf extract; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

3.6 | Safety

ALE was safe and well tolerated in this trial, and there were no reports of any adverse events during the course of the trial.

4 | DISCUSSION

This pilot study has shown that 2 months of treatment with ALE increased hepatic vein flow and reduced portal vein diameter and liver size in comparison with placebo. These findings were accompanied by a reduction of both AST and ALT as well as traditional liver markers. Emerging data suggest that ALT has a role as a predictor of mortality independent of liver disease and is an indicator of general health (Kim et al., 2008). The AST/ALT ratio and the APRI ratio were shown to be improved by ALE supplementation suggesting an improvement in hepatic function in these NAFLD subjects. The APRI ratio has been shown to have good sensitivity and specificity relating to disease activity in hepatitis C patients and to correlate with the degree of fibrosis (Borsoi Viana, Takei, Collarile Yamaguti, Guz, & Strauss, 2009); additionally, the APRI

ratio has been reported as predictive of patients with NAFLD at increased risk of liver-related complications (Angulo et al., 2013). Non-invasive tests for liver disease, as used in this study, have been shown to consistently detect unrecognized liver disease in the general population (Harris, Harman, Card, Aithal, & Guha, 2017).

It is unclear if the improvement in NAFLD parameters was due to a direct or indirect effect of ALE therapy. In animal studies, a direct molecular effect through multiple pathways has been suggested following a Jerusalem artichoke preparation that improved the gene expression of malic enzyme 1, associated with fatty acid synthesis; decorin, related to fibrosis; and cytochrome P450, family 1, subfamily a, polypeptide 2; and nicotinamide phosphoribosyltransferase, associated with inflammation (Chang et al., 2014). Hepatic steatosis develops due to anomalous lipid handling by the liver that sensitizes it to injury and inflammation. We have recently reported as a systematic review and meta-analysis (Sahebkar et al., 2017) the beneficial effects of ALE on LDL-C and triglycerides that were also reflected in the current study. The direct effect of ALE on lipid parameters possibly affects the hepatic indices, as accumulation of triglycerides in hepatocytes is the main culprit in the development of hepatic steatosis, and hypertriglyceridemia is a frequent phenotype in patients with NAFLD (Chatrath, Vuppalanchi, & Chalasani, 2012). Besides correction of hypertriglyceridemia, reduction of LDL-C after ALE supplementation is an important finding, as LDL-C is a causal risk factor for atherosclerotic cardiovascular disease (Ference et al., 2017), and cardiovascular diseases is the main cause of mortality in patients with NAFLD (Chatrath et al., 2012). In spite of positive effects on LDL-C and triglycerides, we observed a significant reducing effect of ALE on serum HDL-C concentrations. However, the observed reduction was mild, and it should be noticed that the causal association between pharmacological modulation of HDL-C levels and cardiovascular risk is uncertain (Zakiev, Feng, Sukhorukov, & Kontush, 2017). Finally, ALE may exert an indirect effect on the improvement in NAFLD indices, as the body mass index fell in those receiving ALE supplementation, and weight loss is a recognized therapy for NAFLD (Clark, 2006).

The gold standard test for diagnosing NAFLD and staging advanced disease is the liver biopsy, but this diagnostic approach is limited by sampling error, cost, and related morbidity and mortality. The American Association for the Study of Liver Diseases (Chalasani et al., 2012) recommends non-invasive serum markers for screening liver dysfunction, especially those with metabolic risk factors, and recommends liver biopsy only be considered in those patients with raised serum markers.

Limitations of our study include that a liver biopsy was not undertaken; although this might have added weight to our findings, clinically, the biopsy was not warranted. This was a pilot study, and the findings need to be confirmed with a larger randomized definitive study that can be powered on the results presented here.

In conclusion, this study has shown the beneficial effects of ALE supplementation on both ultrasound liver parameters and liver serum parameters of ALT, AST, and total bilirubin in patients with an ultrasound diagnosis of NAFLD.

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CONFLICT OF INTEREST

The authors have no competing interest to declare.

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