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Original Research

Artichoke leaf extract reduces steatosis and decreases liver size in prebariatric patients: A randomized placebo-controlled pilot trial—The "SteatoChoke-Study"

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KEYWORDS
Steatosis;
Artichoke;
Obesity;
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MASLD;
FibroScan

BACKGROUND/OBJECTIVES: The increasing incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) poses a major healthcare challenge. This condition is particularly prevalent in patients with obesity. Artichoke leaf extract (ALE) has known hepatoprotective, antioxidant, and lipid-lowering properties. While ALE has been studied for its impact on liver metabolism, its specific effectiveness in individuals with obesity and MASLD remains unclear. This study investigates the effectiveness of ALE in reducing liver steatosis in patients scheduled for bariatric surgery. To our knowledge, this is the first study to examine ALE's "antisteatotic" efficacy in this clinical context.

METHODS: Forty participating bariatric surgery candidates received either ALE or a placebo for 6 weeks before measurements. Steatosis was quantified using FibroScan (controlled attenuation parameter, CAP), and liver size was assessed via ultrasound. Secondary outcomes included serum laboratory parameters and body composition, measured through bioelectrical impedance analysis.

RESULTS: ALE intake significantly reduced CAP values and liver lobe diameters compared to placebo, indicating decreased steatosis and liver volume. Improvements were already evident after 3 weeks. In female participants, total and low-density lipoprotein cholesterol levels improved. However, transaminase levels—particularly aspartate aminotransferase—increased in the ALE group. Body composition improved, with reductions in fat mass percentage.

CONCLUSIONS: ALE effectively reduces liver steatosis and size and improves body composition in patients with obesity and MASLD. Unlike prior studies, we observed a significant transaminase increase, suggesting a distinct hepatic response in individuals with obesity. Further research is needed to evaluate ALE's metabolic and hepatic effects specifically in this population beyond the prebariatric setting.

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Introduction

The escalating prevalence of obesity and its associated comorbidities, notably metabolic dysfunction-associated steatotic liver disease (MASLD), poses a significant challenge to global health systems. The prevalence of MASLD and metabolic dysfunction-associated steatohepatitis (MASH) among candidates for bariatric surgery ranges up to 90%.[1-7] MASH, particularly, as a progression of MASLD is linked with advancement through fibrosis to cirrhosis and increased mortality rates in general but also after bariatric surgery.[8]

While metabolic surgery is able to induce remission of initially present steatosis in the postoperative course, it is advisable for several reasons to reduce the degree of steatosis prior to the procedure. This could not only favorably influence the long-term postoperative outcome but also enhance operability and reduce perioperative risk. An enlarged and fatty liver poses dual challenges during laparoscopic bariatric procedures. Firstly, the enlarged left liver lobe complicates access to the gastroesophageal junction. Secondly, the soft, fatty liver tissue is more susceptible to bleeding during surgical manipulation. Consequently, an enlarged and fatty liver is the leading cause for either aborting the procedure or converting from laparoscopic to open approach, accounting for about half of such conversions.[9]

Presently, it is recommended that patients planned for bariatric surgery undergo a preoperative low-calorie diet, which varies across countries and institutions, to reduce liver volume and facilitate surgery.[10-19]

Fintelmann et al. already demonstrated in 1996 the effectiveness of artichoke leaf extract (ALE) in influencing various aspects of liver metabolism, especially in terms of antioxidant, hepatoprotective, and lipid-lowering properties.[20] In their 2018 randomized controlled trial, Panahi et al.[21] demonstrated that supplementation with ALE extract reduced hepatic steatosis, decreased liver size, and lowered serum transaminase levels.

This study aims to investigate the efficacy of ALE in mitigating liver steatosis specifically in patients with obesity scheduled for bariatric surgery, in contrast to previous studies[20,21] that included normal-weight to overweight participants. To the best of our knowledge, we are the first to investigate the effectiveness of ALE regarding its "antisteatotic" efficacy in a clinical prebariatric setting.

Materials and methods

This prospective, randomized, placebo-controlled, single-blind, monocentric intervention study was approved by the local ethics committee (Reference No.: 305/21) and is registered in the German Clinical Trials Register (Reference No: DRKS00024706, Date of registration: April 29, 2024).

The study included a total of 40 patients scheduled for bariatric surgery. It was conducted between 2022 and 2023 in our bariatric competence center. The study was conducted in compliance with the Declaration of Helsinki and the ethical guidelines of each institution.

Throughout the manuscript, the terms 'male' and 'female' refer to biological sex as recorded in the medical files. Gender identity was not assessed. The cohort comprised 16 male and 24 female patients, all of whom provided written informed consent to participate. Sample size estimation was based on the anticipated group difference in controlled attenuation parameter (CAP) values between baseline (TP0) and the first postintervention timepoint (TP1). In the absence of prior data on the effect of ALE on CAP values, a reduction of 12 to 15 dB/m was assumed in the intervention group. For the control group, no substantial improvement was expected (0-3 dB/m). Based on these assumptions, a mean difference of 14 dB/m with a SD of 15 dB/m in both groups was used for calculation. Using PASS 2019 software (Power Analysis and Sample Size Software, Version 19.3, NCSS, LLC) and a 2-sided independent samples *t*-test (equal variances), a sample size of 20 participants per group was required to achieve 80.75% power at a significance level of $\alpha = 0.05$. This calculation was intended to ensure sufficient power to detect an effect at the primary postintervention timepoint. The actual data analysis, however, was conducted using linear mixed models (LMM) to appropriately account for repeated measurements and time-by-group interactions across multiple timepoints.

A stratified randomization was conducted by a study nurse, who was not involved in the study. The division was carried out using a web-based randomizer (www.randomizer.at) in a 1:1 ratio, with biological sex as stratification factor. Study participants were allocated into 2 distinct groups: the control group ($n = 20$) received a placebo for 6 weeks, and the Artichoke group ($n = 20$) was administered ALE over the same period. Following the initial 3-week phase, both groups underwent a "liver reduction diet" for an additional 3 weeks prior to their bariatric surgery (Fig. 1).

All included participants were evaluated by FibroScan, blood screening, liver sonography and bioelectrical impedance analysis (BIA) measurements at 3 different timepoints (TP0-TP2).

This study was conducted in accordance with the Declaration of Helsinki, ensuring ethical standards and patient safety throughout the research process.

Exclusion criteria were as follows:

1. Patients with a history of infectious liver disease (hepatitis).
2. Patients with other liver diseases such as metabolic storage disorders or autoimmune disease.
3. Alcohol consumption >30 g/d for men, >20 g/d for women.
4. Age <18 years or >65 years.
5. No informed consent available.
6. Consumption of hepatotoxic medication.
7. Body mass index (BMI) <35 kg/m^2.
8. Known allergy to artichokes and/or other thistle-like plants.

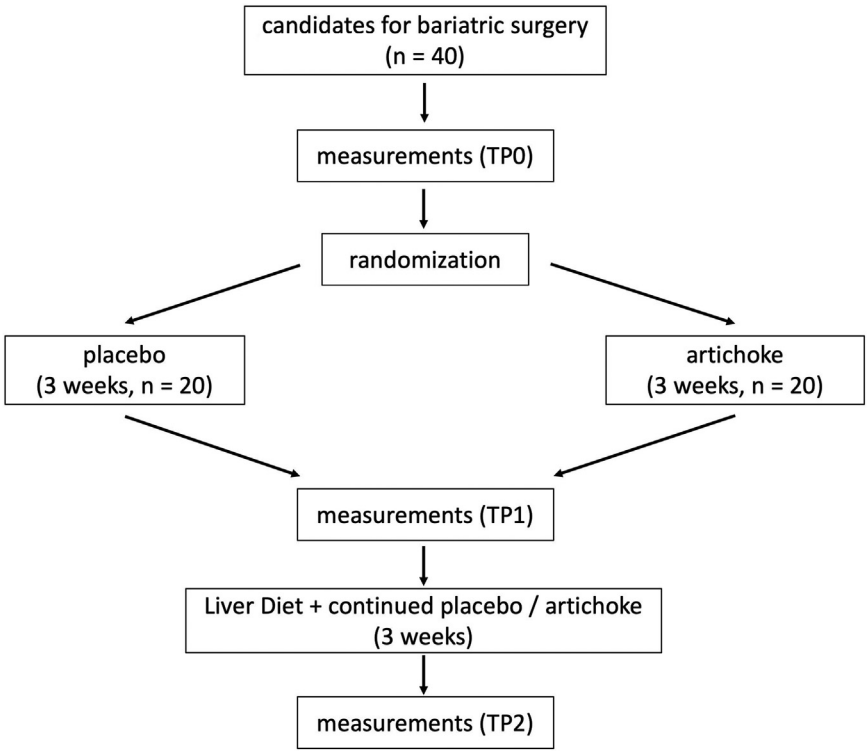

Figure 1. Study design. A total of 40 patients scheduled for bariatric surgery were enrolled and randomized 1:1 into 2 groups: the artichoke group ($n = 20$), receiving 2600 mg/d of artichoke leaf extract (ALE, standardized to 2.5% cynarine), and the placebo group ($n = 20$), receiving an inert, identically encapsulated compound. Both interventions were taken for 3 weeks. Following this phase, all participants continued their assigned treatment and simultaneously underwent a standardized 3-week liver reduction diet. Outcome measurements were performed at 3 timepoints: TP0 = baseline (prior to intervention), TP1 = after 3 weeks of ALE/placebo, and TP2 = after an additional 3 weeks of liver diet and continued intervention.

9. Pacemaker.
10. Concurrent medication intake of anticoagulant drugs of the coumarin type (phenprocoumon, warfarin).
11. Lack of patient compliance.
12. Cholecystolithiasis.

Outcome measures

The primary outcome focused on the impact of ALE on changes in the grade of steatosis, as measured by the CAP value, across the different timepoints, as well as on the change of liver size measured by liver sonography. The secondary outcomes involved assessing the changes in serum levels of various parameters and the BIA data.

Intervention and diet

The ALE (Vegavero Organic, Vanatari International GmbH), containing 2.5% cynarine as the active compound known for its hepatoprotective effects,[20] was administered to participants in the artichoke group in the form of 4 capsules per day ([2-0-2] equivalent to a daily dose of 2600 mg of ALE). The ALE used in this study (Vegavero Organic, Vanatari International GmbH) was a certified organic dry extract standardized to contain 2.5% cynarine (measured as total polyphenols, expressed as cynarine). According to the certificate of analysis (COA), the extract contained 2.9% cynarine and was compliant with European Pharmacopoeia (EP) specifications regarding identity, purity, and microbial and heavy metal limits. The extract was derived from fresh Cynara scolymus L. leaves and manufactured under controlled conditions in France (organic control code: DE-ÖKO-006). Identification tests confirmed the presence of chlorogenic acid and luteolin-7-glucoside as secondary active constituents. Residual pesticides were not permitted, and heavy metal levels remained below accepted thresholds (Pb < 3.0 mg/kg, Cd < 1.0 mg/kg, Hg < 0.1 mg/kg). Microbiological safety was confirmed with total plate count < 1000 cfu/g and absence of *Salmonella, E. coli*, and *Staphylococcus aureus*.

The manufacturing process adhered to organic standards and good manufacturing practices, including multiple filtration, extraction, concentration, and drying steps (Supplementary Fig S1).

For 42 ± 5 days, but no more than 47 days, the ALE (1 capsule = 650 mg) was taken twice daily (2-0-2) with the main meals along with a glass of water. The placebo provided to the control group was matched in appearance but contained no active ingredients.

Following the initial 3-week supplementation phase, all participants underwent a standardized preoperative "liver reduction diet" for an additional 3 weeks, in accordance with

the institutional protocol for bariatric surgery preparation. Participants received detailed dietary instructions from a trained nutritionist. The daily regimen consisted of 2 protein shakes (≥80% protein content) consumed at breakfast and dinner. The main meal at lunchtime included a raw vegetable or salad component, 180 g of lean meat or fish, and 200 g of cooked vegetables. Simple and complex carbohydrates were strictly avoided throughout the dietary phase. The intended macronutrient composition was approximately 35% to 45% protein, 30% to 40% fat, and 20% to 30% carbohydrates. The total daily caloric intake was limited to a maximum of 1100 kcal, representing a substantial caloric deficit relative to estimated maintenance needs in this patient population.

Measurements and data collection

The evaluation of each participant encompassed a comprehensive assessment regimen, including blood screening, ultrasound measurements of liver size, and FibroScan assessments with determination of CAP values to evaluate steatosis. Additionally, BIA was used to assess changes in body composition. Importantly, all measurements were conducted at 3 distinct timepoints to monitor changes over time. The collected data from these evaluations were stored in a Microsoft Excel file for subsequent analysis.

FibroScan

CAP measurements were performed with FibroScan touch 502 (Echosens). All measurements were performed by a single operator. The examination was standardized and performed on the right lobe of the liver through the intercostal space, using the XL probe. Measurements were performed on 3 different timepoints (TP0-TP2). Ten successful acquisitions per TP were performed for all patients as per the manufacturer's instructions.

Liver sonography

The sonographic determination of liver size (parenchymal thickness) for both the left and right liver lobes was carried out using standardized measurement points or anatomical "landmarks" (Fig. 2). The right liver lobe was visualized through a transthoracic approach according to the "plane of Y0,"[22] searching for the Y-shaped bifurcation of the posterior and anterior branches of the right portal vein while simultaneously depicting the gallbladder in longitudinal section. A measurement line orthogonal to the sector probe (Hitachi, Ltd) was drawn from the peripheral liver capsule through the legs of the "Y" to the central liver capsule. This distance was used as the parenchymal thickness for the right liver lobe. The left liver lobe was visualized along with the abdominal aorta subcostally in the epigastric region in a longitudinal section. Again, a measurement line from the superficial to the central liver capsule orthogonal to the sector probe was drawn, and the length was determined.

Bioelectrical impedance analysis

The BIA was performed using the Seca BCA01A according to the manufacturer's specifications (Seca, software: seca analytics 115) at each time point. The data were digitally stored for further processing.

Measurement timepoints

Measurements were performed at 3 critical timepoints across the study period:

1. TP0: before the administration of either placebo or artichoke extract.
2. TP1: after the completion of the 3-week placebo or artichoke extract administration and just before starting the liver diet.
3. TP2: after completing the 3-week liver diet, immediately prior to surgery.

Data analysis

Statistical analyses were conducted using IBM SPSS Statistics (Version 29.0) and RStudio (Version 2025.05.1+513). Continuous variables were tested for normal distribution and log-transformed where necessary to meet model assumptions. Model-based group means were back-transformed to the original scale to improve interpretability. Group comparisons over time were performed using repeated-measures analysis of variance (ANOVA) or linear mixed-effects models (LMMs) with fixed effects for timepoint, group, and their interaction (Group × Timepoint), and a random intercept for subjects. Degrees of freedom were estimated using the Satterthwaite approximation for LMMs and the Greenhouse–Geisser correction for ANOVA models where appropriate.

Within-group comparisons across timepoints were conducted using separate LMMs within each treatment arm, including a fixed effect for timepoint and a random intercept for subject. The contrasts (TP0-TP1, TP0-TP2, TP1-TP2) were defined a priori. Where applicable, *P*-values were adjusted for multiple testing using the Bonferroni method. For binary outcomes (eg, pathological laboratory values), generalized linear mixed models (GLMMs) with a logit link and a random intercept for subjects were used.

All reported *P*-values are 2-tailed, and *P*-values $<.05$ were considered statistically significant. Effect sizes (η^2G) are reported only for statistically significant results to facilitate interpretation of findings with potential clinical relevance.

Results

Baseline characteristics of participants

Forty subjects completed the study. There were no adverse events throughout the trial. Table 1 summarizes the descrip-

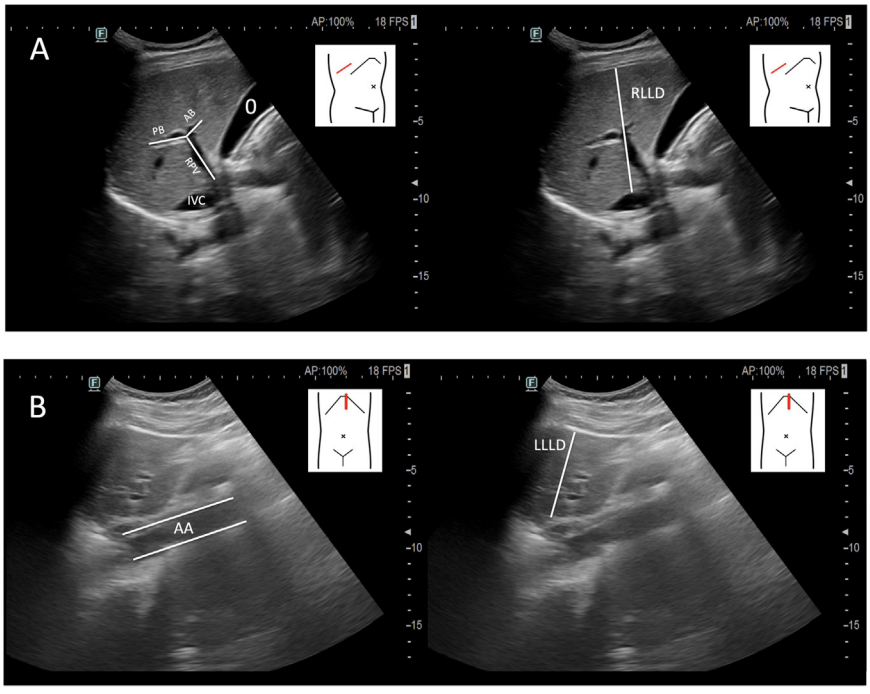

Figure 2. Ultrasound-based measurement of liver lobe diameters. Diameters were recorded in millimeters at each timepoint (TP0-TP2) for quantification of liver size changes during the intervention. (A) Right liver lobe: The "plane of Y0" is used as a standardized anatomical reference. The bifurcation of the posterior branch (PB) and anterior branch (AB) of the right portal vein (RPV) forms the characteristic Y-shape; the gallbladder is marked as "0." The inferior vena cava (IVC) is visualized as an additional landmark. The right liver lobe diameter (RLLD) was measured from the peripheral to the central liver capsule, placed orthogonally to the ultrasound probe and through the bifurcation of the portal vein. (B) Left liver lobe: The abdominal aorta (AA) was used as the anatomical reference in a subcostal longitudinal section. The left liver lobe diameter (LLLD) was measured at the point of maximum parenchymal thickness, again orthogonal to the probe.

Table 1. Baseline characteristics of the study participants (before initiation of intervention).

Characteristics	Artichoke group	Placebo group
N	20	20
Mean age (y)	43.0 ± 9.21	45.65 ± 11.54
Gender (f/m)	(12/8)	(12/8)
Mean BMI (kg/m^2)	48.76 ± 4.30	50.36 ± 6.31
Number of comorbidities	3.55 ± 1.47	4.15 ± 1.27

Data are presented as mean ± SD or absolute counts. The *Artichoke group* received 2600 mg/d of artichoke leaf extract (ALE, standardized to 2.5% cynarine) during the intervention phase. The *Placebo group* received a visually identical placebo.
Abbreviations: BMI, body mass index; f/m, female/male.

tive characteristics of the study participants. Baseline characteristics were comparable between groups.

Primary outcomes

CAP: A repeated-measures ANOVA revealed a significant group × time interaction, F (1.82, 69.21) = 3.94, P = .027, η^2G = 0.034 (small effect), indicating differential changes in hepatic steatosis severity between groups over time. Bonferroni-adjusted post-hoc comparisons showed no significant difference between groups at TP0 (P = .186), but significantly lower CAP values in the Artichoke group at TP1 (Δ = 27.8 dB/m, 95% CI [1.3, 54.3], P = .040) and TP2 (Δ = 46.9 dB/m, 95% CI [24.2, 69.6], P = .0002) compared to Placebo (Fig. 3).

Within-group analyses indicated no significant changes over time in the Placebo group. In contrast, the Artichoke group showed a marked reduction in CAP from TP0 to TP1 (Δ = 31.7 dB/m, 95% CI [14.4, 49.0], P = .0001) and from TP0 to TP2 (Δ = 52.9 dB/m, 95% CI [30.1, 75.6], P < .0001). The numerical decrease from TP1 to TP2 did not reach statistical significance (Δ = 21.1 dB/m, 95% CI [−0.8, 43.1], P = .062).

Left liver lobe diameter: The analysis of the left liver lobe diameter revealed a significant reduction over time in the Artichoke group, which was not observed in the Placebo group (Fig. 4). The repeated-measures ANOVA revealed a significant group × time interaction, F (1.55, 51.22) = 6.53, P = .006, η^2G = 0.019 (small effect). Post-hoc comparisons showed no significant difference between groups at TP0 (Δ = 4.17 mm, 95% CI [−7.70, 16.0], P = .480). At TP1, a nonsignificant difference was observed (Δ = 10.33 mm, 95% CI [−1.33, 22.0], P = .081), whereas at TP2, the Artichoke group had significantly smaller diameters compared to Placebo (Δ = 15.40 mm, 95% CI [3.60, 27.2], P = .012).

Within-group comparisons indicated that in the Artichoke group, the left lobe diameter was significantly reduced from TP0 to TP1 (Δ = −7.47 mm, 95% CI [−12.18, −2.76], P

$< .001$) and from TP0 to TP2 ($\Delta = -9.74$ mm, 95% CI [−16.31, −3.16], $P < .001$), with no significant change between TP1 and TP2 ($\Delta = -2.26$ mm, 95% CI [−6.64, 2.12], $P = .10$). No significant changes were observed within the Placebo group across time points ($P > .22$).

Right liver lobe diameter: The repeated-measures ANOVA also revealed a significant group × time interaction, F (1.83, 62.19) = 6.67, $P = .003$, $\eta^2G = 0.039$ (small effect). Post-hoc tests showed no significant between-group differences at TP0 ($\Delta = -5.62$ mm, 95% CI [−18.16, 6.92], $P = .369$) or TP2 ($\Delta = 3.00$ mm, 95% CI [−8.13, 14.13], $P = .588$), but a significant difference at TP1 $\Delta = 10.38$ mm, 95% CI [0.24, 20.52], $P = .045$), with smaller diameters in the Artichoke group.

Within groups, the Artichoke group showed significant reductions from TP0 to TP1 ($\Delta = -13.00$ mm, 95% CI [−19.70, −6.30], $P < .001$) and from TP0 to TP2 ($\Delta = -11.74$ mm, 95% CI [−20.36, −3.11], $P = .002$), with no change from TP1 to TP2 ($\Delta = 1.26$ mm, 95% CI [−6.04, 8.57], $P = .63$). No significant changes occurred within the Placebo group (TP1-TP0: $\Delta = 3.00$ mm, 95% CI [−4.08, 10.08], $P = .881$; TP2-TP0: $\Delta = -3.12$ mm, 95% CI [−12.24, 6.00], $P = 1.000$; TP2-TP1: $\Delta = -6.12$ mm, 95% CI [−13.84, 1.60], $P = .162$).

Secondary outcomes

The overall analysis of various blood values from TP0 to TP2 is summarized in Table 2. A significant group × time interaction emerged only for aspartate aminotransferase (AST) levels (F [2, 76] = 3.52, $P = .035$), indicating differential changes between the Artichoke and Placebo groups over time. Bonferroni-adjusted post-hoc comparisons showed no significant group differences at TP0 ($\Delta = 0.48$ U/L, 95% CI [−3.85, 4.81], $P = .765$) or TP1 ($\Delta = -0.24$ U/L, 95% CI [−4.33, 3.85], $P = .901$), but significantly higher AST levels in the Artichoke group at TP2 ($\Delta = 3.73$ U/L, 95% CI [0.64, 6.82], $P = .019$) (Fig. 5A).

For alanine aminotransferase (ALT), a trend-level group × time interaction was detected F (2, 76) = 2.55, $P = .086$, $\eta^2G = 0.014$, and no significant between-group differences were observed at any timepoint (TP0: $\Delta = 0.06$ U/L, 95% CI [−3.65, 3.77], $P = .974$; TP1: $\Delta = -1.56$ U/L, 95% CI [−4.92, 1.80], $P = .352$; TP2: $\Delta = 1.58$ U/L, 95% CI [−1.58, 4.74], $P = .318$).

Within the Artichoke group, ALT values showed a numerical but nonsignificant increase from TP1 to TP2 ($\Delta = 2.94$ U/L, 95% CI [−0.02, 5.90], $P = .053$). When analyzing the proportion of pathological ALT values, a sig-

Table 2. Laboratory values in both study groups.

	TP0		TP1		TP2		*P* (T×G)
	Placebo	Artichoke	Placebo	Artichoke	Placebo	Artichoke	
Cholesterol [mg/dL]	191.70 ± 7.84	193.70 ± 9.95	201.78 ± 7.46	186.95 ± 6.85	169.94 ± 6.13	168.47 ± 8.47	.564
HbA1c [%]	6.22 ± 0.26	6.08 ± 0.32	6.29 ± 0.28	6.09 ± 0.35	5.92 ± 0.16	7.06 ± 1.58	.981
Triglycerides [mg/dL]	147.75 ± 10.45	162.55 ± 13.97	143.56 ± 8.30	163.16 ± 29.51	114.28 ± 6.21	131.79 ± 19.37	.961
ALT [U/L]	34.70 ± 4.29	39.50 ± 4.76	41.72 ± 5.73	39.95 ± 4.26	41.33 ± 5.26	50.16 ± 3.45	.086
AST [U/L]	27.85 ± 1.69	29.65 ± 2.35	32.33 ± 2.71	31.63 ± 2.59	28.33 ± 1.99	34.84 ± 2.23	**.035**
AP [U/L]	89.05 ± 5.88	85.00 ± 3.82	93.17 ± 6.74	82.32 ± 3.75	78.06 ± 5.10	73.47 ± 3.11	.221
γGT [U/L]	47.55 ± 7.58	53.50 ± 12.36	55.00 ± 9.75	46.42 ± 6.94	33.50 ± 4.51	37.16 ± 6.52	.520
LDL-cholesterol [mg/dL]	121.90 ± 6.62	122.15 ± 7.98	129.67 ± 6.14	117.74 ± 5.89	106.94 ± 5.26	101.32 ± 7.76	.370
Leucocytes [1000/µL]	8.22 ± 0.55	8.96 ± 0.43	7.57 ± 0.76	8.52 ± 0.40	7.46 ± 0.59	7.71 ± 0.47	.630
CRP [mg/L]	10.93 ± 1.99	9.89 ± 2.33	17.25 ± 5.19	11.77 ± 2.32	8.84 ± 1.83	7.42 ± 1.67	.884
IL-6 [pg/mL]	7.72 ± 1.52	5.00 ± 0.65	7.83 ± 1.74	5.95 ± 0.78	4.11 ± 0.64	4.15 ± 0.53	.189
HDL-cholesterol [mg/dL]	48.35 ± 2.45	48.95 ± 3.58	48.44 ± 2.52	49.16 ± 3.80	43.39 ± 1.73	44.16 ± 2.82	.881
Non-HDL-cholesterol [mg/dL]	143.35 ± 6.95	144.75 ± 9.04	138.00 ± 12.32	130.90 ± 9.17	113.85 ± 10.25	118.00 ± 10.27	.894
Thrombocytes [1000/µL]	292.85 ± 19.47	286.00 ± 15.95	298.56 ± 18.64	295.47 ± 13.77	286.89 ± 17.39	281.79 ± 12.67	.744
DeRitis	0.92 ± 0.07	0.83 ± 0.05	0.90 ± 0.08	0.85 ± 0.04	0.79 ± 0.07	0.73 ± 0.04	.842
APRI	0.11 ± 0.01	0.11 ± 0.01	0.12 ± 0.02	0.11 ± 0.01	0.11 ± 0.01	0.13 ± 0.01	.062

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; CRP, C-reactive protein; DeRitis, AST/ALT ratio; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IL-6, interleukin-6; LDL, low-density lipoprotein; TP, time point; γGT, gamma-glutamyltransferase.

Data are presented as mean ± SEM. The *Artichoke group* ($n = 20$) received 2600 mg/d of artichoke leaf extract (standardized to 2.5% cynarine) for 3 weeks; the *Placebo group* ($n = 20$) received visually identical capsules without active ingredients. Time points: TP0 = baseline, TP1 = after 3 weeks of intervention, TP2 = after an additional 3 weeks of "liver diet" with continued artichoke/placebo (total intervention duration: 6 weeks). Statistical analysis was performed using linear mixed-effects models (LMMs) with timepoint, group, and their interaction (Group × Timepoint [T×G]) as fixed effects and subject as a random intercept. Variables were log-transformed when necessary to meet model assumptions. Model-based group means were back-transformed to the original scale for interpretability. A subgroup analysis by sex is included in the supplementary material (Tables S1 & S2). A *P*-value <.05 was considered statistically significant.

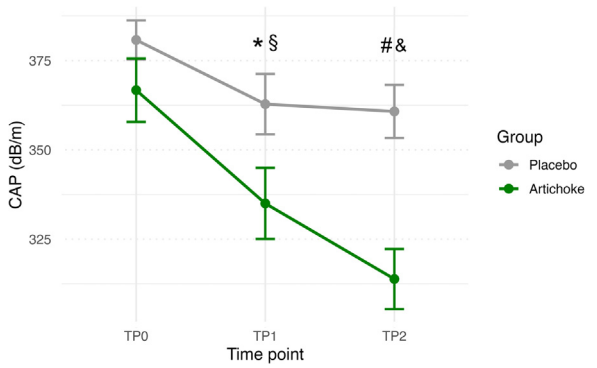

Figure 3. Change in controlled attenuation parameter (CAP) over time in both study groups. Data represent means ± SEM. The *Artichoke group* ($n = 20$) received 2600 mg/d of artichoke leaf extract (2.5% cynarine) for 3 weeks; the *Placebo group* ($n = 20$) received visually matched capsules without active ingredients. TP0 = baseline (prior to intervention), TP1 = after 3 weeks of artichoke/placebo, TP2 = after an additional 3 weeks of "liver diet" with continued artichoke/placebo (total intervention duration: 6 weeks). Statistical analysis was performed using repeated-measures analysis of variance with group and time as factors, followed by Bonferroni-adjusted post-hoc pairwise comparisons. $^{*}P < .05$: between-group difference at the respective time point. $\#P < .001$: between-group difference at the respective time point. $\S P = .001$: within-group change from TP0 to TP1 in the Artichoke group. $\&P < .0001$: within-group change from TP0 to TP2 in the Artichoke group.

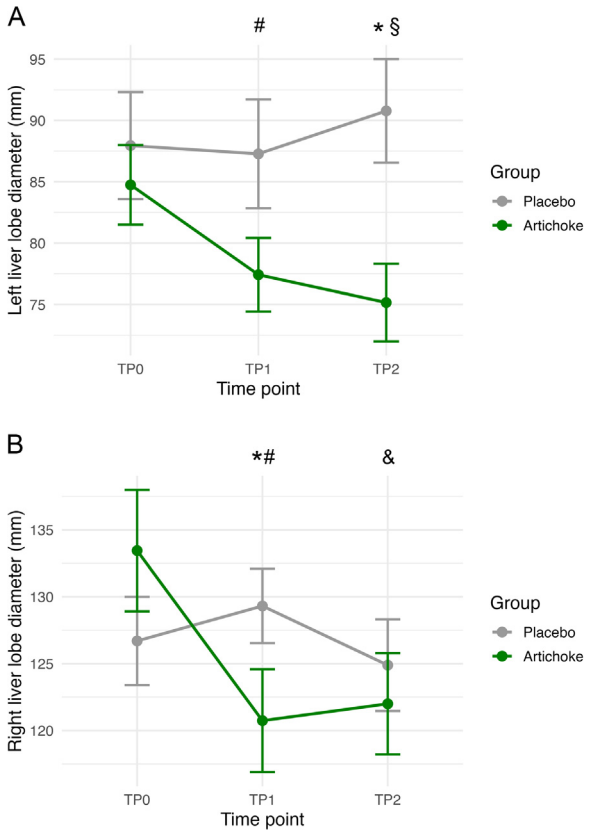

Figure 4. Changes in liver lobe diameter over time in both study groups. Values represent group means ± SEM. The *Artichoke group* ($n = 20$) received 2600 mg/d of artichoke leaf extract (standardized to 2.5% cynarine) for 3 weeks; the *Placebo group* ($n = 20$) received visually identical capsules without active ingredients. Time points: TP0 = baseline, TP1 = after 3 weeks of intervention, TP2 = after an additional 3 weeks of "liver diet" with continued artichoke/placebo (total intervention duration: 6 weeks). Statistical analysis was performed using repeated-measures analysis of variance with group and time as factors, followed by Bonferroni-adjusted pairwise post-hoc comparisons. To further explore the interaction effects, within-group changes in liver lobe diameters over time were analyzed using linear mixed-effects models. (A) Left liver lobe diameter. $^{*}P < .05$: between-group difference at the respective time point. $\#P < .001$: within-group change from TP0 to TP1 in the Artichoke group. $\S P < .001$: within-group change from TP0 to TP2 in the Artichoke group. (B) Right liver lobe diameter. $^{*}P < .05$: between-group difference at the respective time point. $\#P < .001$: within-group change from TP0 to TP1 in the Artichoke group. $\&P < .05$: within-group change from TP0 to TP2 in the Artichoke group.

nificant increase was observed from TP1 to TP2 in the Artichoke group (odds ratio [OR] = 4.17, 95% CI [1.06, 19.1], $P = .049$), but not in the Placebo group (OR = 0.64, 95% CI [0.17, 2.37], $P = .506$) (Fig. 5B). A similar pattern was seen from TP0 to TP2 (Artichoke: OR = 4.58, 95% CI [1.18, 20.8], $P = .035$; Placebo: OR = 2.40, 95% CI [0.62, 10.1], $P = .212$). No significant changes occurred from TP0 to TP1 in either group (Artichoke: OR = 1.10, $P = .882$; Placebo: OR = 3.75, $P = .060$).

Between TP0 and TP1, biological sex-specific patterns were observed for low-density lipoprotein (LDL) and total cholesterol levels (see Supplementary Material). In female participants, a significant interaction was found for LDL cholesterol ($\beta = -15.12$ mg/dL, 95% CI [−29.15, −1.09], $P = .039$), reflecting an increase under placebo (+6.82 ± 15.22 mg/dL; 95% CI [−3.45, 17.11], $P = .181$) and a decrease under artichoke (−8.29 ± 16.95 mg/dL; 95% CI [−18.73, 2.15], $P = .115$). For total cholesterol, the interaction indicated a numerical but nonsignificant decrease ($\beta = -17.42$ mg/dL, 95% CI [−35.51, 0.67], $P = .057$), with an increase under placebo (+7.64 ± 19.78 mg/dL, 95% CI [−5.49, 20.39], $P = .242$) and a decrease under artichoke (−9.98 ± 20.92 mg/dL, 95% CI [−22.81, 2.86], $P = .120$). In male participants, no significant interaction effects were detected, and mean changes were small in both groups.

BIA revealed selective group differences in body composition changes over time (Table 3). A significant group × time interaction was observed for mass percentage (FM%; F [2, 67.26] = 3.67, $P = .031$) and skeletal muscle mass of the left arm (SMM arm left; F [2, 67.11] = 3.94, $P = .025$). Numerical but nonsignificant interaction effects were observed for absolute fat mass (FM; F [2, 67.05] = 2.63, $P = .060$) and fat mass index (FMI; F [2, 67.07] = 2.53, $P = .068$). For all other parameters, including body weight, BMI, fat-free mass (FFM), phase angle, and visceral adipose tissue (VAT), no significant group × time interactions were found ($P > .05$).

For FM%, post-hoc comparisons indicated an increase from TP0 to TP1 in the Placebo group (+1.31%, 95% CI

Table 3. Bioelectrical impedance analysis (BIA) data.

	TP0		TP1		TP2		Global
	Placebo	Artichoke	Placebo	Artichoke	Placebo	Artichoke	*P* (T×G)
Weight [kg]	147.26 ± 5.07	142.84 ± 4.40	147.47 ± 4.98	142.35 ± 4.44	143.82 ± 4.68	136.72 ± 4.29	.896
BMI [kg/m²]	50.35 ± 1.41	48.76 ± .96	50.22 ± 1.43	48.81 ± .93	48.92 ± 1.31	45.30 ± 1.70	.337
FM [kg]	72.22 ± 3.26	71.65 ± 1.59	75.09 ± 3.27	70.99 ± 1.57	70.21 ± 3.21	67.72 ± 1.49	.060
FM [%]	48.97 ± 1.31	50.58 ± 1.04	50.52 ± 1.22	50.87 ± 1.11	48.37 ± 1.39	50.18 ± 1.05	.031
FMI [kg/m²]	24.76 ± 1.08	24.66 ± 0.71	25.56 ± 1.10	24.71 ± 0.73	23.82 ± 1.07	23.39 ± 0.63	.068
FFM [kg]	75.04 ± 3.10	71.19 ± 3.45	73.15 ± 2.77	69.82 ± 3.50	74.33 ± 2.74	68.48 ± 3.42	.064
FFM [%]	51.03 ± 1.31	49.56 ± 1.07	49.48 ± 1.22	49.13 ± 1.11	51.61 ± 1.39	49.82 ± 1.05	.075
FFMI [kg/m²]	25.60 ± 0.83	24.11 ± 0.71	24.74 ± 0.72	23.89 ± 0.72	25.09 ± 0.71	23.28 ± 0.71	.056
SMM total [kg]	37.60 ± 1.72	35.75 ± 1.87	36.86 ± 1.58	34.95 ± 1.90	37.27 ± 1.50	34.21 ± 1.90	.231
SMM torso [kg]	15.87 ± 0.70	15.81 ± 0.90	15.84 ± 0.70	15.36 ± 0.87	15.89 ± 0.64	15.01 ± 0.95	.685
SMM leg left [kg]	8.87 ± 0.45	7.92 ± 0.35	8.60 ± 0.42	7.76 ± 0.37	8.66 ± 0.42	7.62 ± 0.36	.321
SMM leg right [kg]	8.84 ± 0.44	8.14 ± 0.43	8.58 ± 0.40	8.11 ± 0.52	8.67 ± 0.42	7.87 ± 0.42	.187
SMM arm left [kg]	1.97 ± 0.11	1.88 ± 0.13	1.85 ± 0.10	1.82 ± 0.13	1.97 ± 0.10	1.82 ± 0.14	.025
SMM arm right [kg]	2.06 ± 0.12	2.00 ± 0.14	1.98 ± 0.10	1.91 ± 0.13	2.06 ± 0.10	1.91 ± 0.14	.381
TBW [L]	56.22 ± 2.22	53.35 ± 2.49	54.86 ± 1.99	52.28 ± 2.53	55.52 ± 1.94	51.17 ± 2.48	.103
TBW [%]	38.03 ± 0.91	36.83 ± 0.70	36.89 ± 0.85	36.58 ± 0.75	38.32 ± 0.95	37.03 ± 0.72	.053
ECW [L]	25.61 ± 0.90	24.09 ± 1.02	24.86 ± 0.80	23.63 ± 1.03	24.99 ± 0.79	23.04 ± 0.97	.104
ECW [%]	17.33 ± 0.33	16.68 ± 0.25	16.72 ± 0.28	16.58 ± 0.28	17.24 ± 0.32	16.73 ± 0.25	.082
ECW/TBW [%]	45.74 ± 0.43	45.38 ± 0.38	45.52 ± 0.56	45.40 ± 0.42	45.16 ± 0.45	45.30 ± 0.49	.654
Xc [Ohm]	38.16 ± 1.53	43.19 ± 1.84	41.38 ± 2.05	44.31 ± 1.79	40.89 ± 1.62	44.83 ± 1.73	.289
phase angle [°]	5.09 ± 0.17	5.22 ± 0.13	5.22 ± 0.22	5.28 ± 0.14	5.29 ± 0.18	5.26 ± 0.15	.480
R [Ohm]	431.82 ± 15.14	473.60 ± 18.55	455.63 ± 14.17	481.84 ± 19.40	444.08 ± 15.46	489.01 ± 19.24	.138
REV [kcal/d]	2391.10 ± 83.07	2348.35 ± 76.68	2409.17 ± 82.83	2317.33 ± 74.74	2386.19 ± 77.55	2272.11 ± 76.98	.723
GEV [kcal/d]	3166.85 ± 200.58	3288.30 ± 108.88	3304.53 ± 124.42	3035.82 ± 193.49	3328.44 ± 112.64	3170.16 ± 111.96	.228
VAT [L]	9.14 ± 1.01	9.95 ± 1.10	9.24 ± 1.02	9.68 ± 1.02	9.93 ± 0.97	9.65 ± 1.06	.726

Abbreviations: BMI, body mass index; ECW, extracellular water; ECW/TBW, ratio of extracellular to total body water; FFM, fat-free mass; FFMI, fat-free mass index (FFM/height²); FM, fat mass; FMI, fat mass index (FM/height²); GEV, total energy expenditure; phase angle, cellular health indicator derived from impedance; R, resistance; REV, resting energy expenditure; SMM, skeletal muscle mass; TBW, total body water; VAT, visceral adipose tissue; Xc, reactance.

Localizations such as *arm left, torso*, or *leg right* refer to the anatomical regions where muscle mass was assessed.

Data are presented as mean ± SEM. The *Artichoke group* ($n = 20$) received 2600 mg/d of artichoke leaf extract (standardized to 2.5% cynarine) for 3 weeks; the *Placebo group* ($n = 20$) received visually identical capsules without active ingredients. Time points: TP0 = baseline, TP1 = after 3 weeks of intervention, TP2 = after an additional 3 weeks of "liver diet" with continued artichoke/placebo (total intervention duration: 6 weeks). Statistical analysis was performed using linear mixed-effects models (LMMs) with timepoint, group, and their interaction (Group × Timepoint [T×G]) as fixed effects and subject as a random intercept. Variables were log-transformed when necessary to meet model assumptions; corresponding estimates were back-transformed to the original scale for interpretability. Detailed pairwise changes for each time interval (TP0-TP1, TP1-TP2, TP0-TP2), including post-hoc *P*-values for between-group differences in change, are provided in Supplementary Table S3. A subgroup analysis by sex is included in the supplementary material (Tables S4 and S5). A *P*-value <.05 was considered statistically significant.

[0.60, 2.03], $P = .030$) and no change in the Artichoke group (−0.06%, 95% CI [−0.76, 0.67], $P = .970$). From TP1 to TP2, no further significant within-group changes occurred ($P > .37$).

For SMM arm left, the Artichoke group showed a decrease from TP1 to TP2 (−0.054 kg, 95% CI [−0.090, −0.018], $P = .025$), while the Placebo group exhibited a slight numerical increase (+0.024 kg, 95% CI [−0.015, 0.064], $P = .219$), resulting in the significant interaction.

For FM and FMI, numerical interaction effects were driven by an increase from TP0 to TP1 in the Placebo group (+1.31 kg, 95% CI [0.45, 2.18], $P = .007$; and +0.44 kg/m², 95% CI [0.16, 0.73], $P = .004$, respectively) and a concurrent decrease in the Artichoke group (−0.69 kg, 95% CI [−1.56, 0.18], $P = .116$; and −0.22 kg/m², 95% CI [−0.51, 0.07], $P = .130$, respectively). From TP1 to TP2, both groups lost fat mass (Placebo: 4.26 kg, 95% CI [−5.73, −2.83], $P < .001$; Artichoke: 3.77 kg, 95% CI [−5.08, −2.43], $P < .001$; Placebo FMI: 1.43 kg/m², 95% CI [−1.93, −0.94], $P < .001$; Artichoke FMI: 1.32 kg/m², 95% CI [−1.77, −0.87], $P < .001$) with no significant between-group differences ($P = 1.000$).

Discussion

The hepatoprotective effect of ALE was initially described in 1966 and 1968 in a rat model by Maros et al.[23,24]

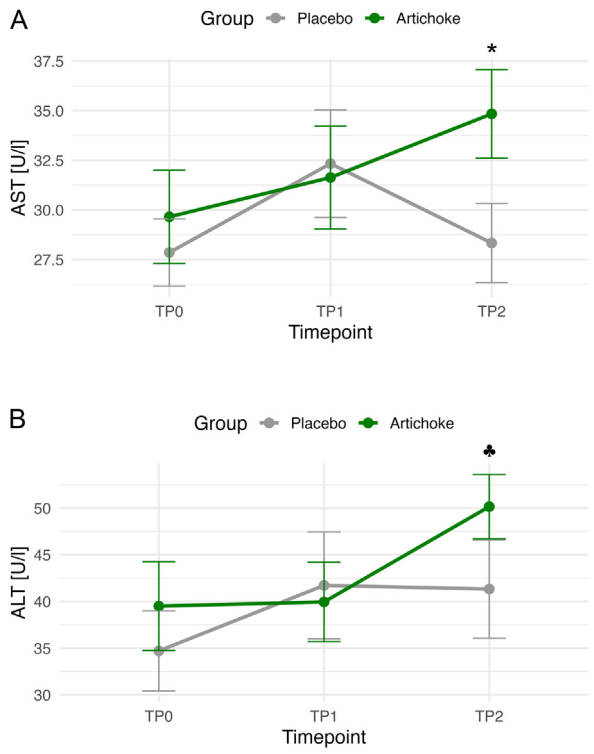

Figure 5. Changes in transaminase levels over time in both study groups. Values represent group means ± SEM. The *Artichoke group* ($n = 20$) received 2600 mg/d of artichoke leaf extract (standardized to 2.5% cynarine) for 3 weeks; the *Placebo group* ($n = 20$) received visually identical capsules without active ingredients. Time points: TP0 = baseline, TP1 = after 3 weeks of intervention, TP2 = after an additional 3 weeks of "liver diet" with continued artichoke/placebo (total intervention duration: 6 weeks). Statistical analysis was performed using linear mixed-effects models (LMMs) with timepoint, group, and their interaction (Group × Timepoint [T×G]) as fixed effects and subject as a random intercept. Variables were log-transformed to meet model assumptions. Model-based group means were back-transformed to the original scale for interpretability. Bonferroni-adjusted post-hoc tests were applied for TP-specific group comparisons. A P-value <.05 was considered statistically significant. (A) AST (aspartate aminotransferase). $^*P < .05$: between-group difference at the respective time point. (B) ALT (alanine aminotransferase). ♣$P < .05$: within-group change of pathological values (Artichoke: TP0 to TP2).

This finding was corroborated by subsequent research that further elucidated ALE's lipid-lowering efficacy.[25,26] In 1996, Fintelmann et al. highlighted ALE's beneficial impact on liver metabolism, specifically noting that, beyond its lipid-lowering and antioxidant properties, ALE also inhibits cholesterol biosynthesis and significantly reduces serum triglyceride levels.[20]

Panahi et al. further demonstrated that ALE has a positive effect on MASLD in individuals without obesity and is capable of reducing the extent of steatosis, using echogenicity as a criterion through qualitative ultrasound findings.[21] In their subsequent 2018 trial, they further showed that an 8-week intake of ALE not only reduces transaminases, improves the DeRitis quotient and the AST-to-platelet-ratio index (APRI), but also lowers serum bilirubin, LDL, non-high-density lipoprotein, and triglyceride levels. In a meta-analysis,[27] the available randomized controlled trials on the effect of artichoke supplementation on liver enzymes were analyzed, and a total of 7 studies were included. Overall, this meta-analysis demonstrated that artichoke supplementation lowers ALT and AST levels in individuals without obesity. The average BMI in these studies ranged between 24.5 and 30 kg/m^2.

Given the marked escalation in obesity and MASLD incidence to epidemic proportions, and the fact that up to 95% of individuals scheduled for bariatric-metabolic surgery present with hepatic steatosis, we aimed to investigate the effects of ALE in this population.

In this study, ALE supplementation for 6 weeks reduced hepatic steatosis and liver volume, as measured quantitatively by FibroScan and standardized liver sonography. From TP1 to TP2, when both groups received a standardized liver reduction diet, the ALE group continued to decrease in CAP values and liver size, suggesting an additive or synergistic effect beyond diet alone. Owing to the also demonstrated significant reduction in CAP values within the Artichoke group, we interpret these findings as a reduction in liver volume due to the decrease in steatosis. It should be noted that even within the Artichoke group, the average CAP value remained above 280 dB/m during the study period, corresponding to third-grade steatosis. However, we believe that longer consumption of ALE could have further reduced the level of steatosis, as a further decline in average CAP values by TP2 within the Artichoke group and stagnation within the control group were observed. This pattern suggests that the steatosis-lowering effect of ALE may not have reached its full potential within the initial 6-week intervention period. This assumption is supported by previous studies showing time-dependent improvements in hepatic steatosis with prolonged ALE intake. For instance, Panahi et al.[21] conducted an 8-week trial in nonobese, nonalcoholic fatty liver disease patients and reported significant reductions in hepatic steatosis (qualitatively assessed via ultrasound), along with improvements in liver size (−5.1 ± 6.0 mm), liver enzymes, lipid profile, and insulin resistance. These findings highlight the cumulative metabolic effects of extended ALE supplementation. Notably, our study demonstrates a comparable steatosis-lowering effect already after only 3 weeks of ALE intake in individuals with obesity, using the more precise CAP measurement.

In contrast to Panahi et al.[21] and Amini et al.,[27] we did not observe reductions in the De Ritis ratio, APRI, bilirubin, triglycerides, or serum transaminases. Instead, we found a statistically significant increase in AST in the ALE group, with ALT showing a nonsignificant upward trend. The proportion of pathological ALT values increased significantly within the ALE group between TP1 and TP2. The clinical significance of these mild transaminase elevations is uncertain but may reflect transient oxidative stress during hepatic lipid mobilization and processing of fatty acids and cholesterol. In patients with advanced steatosis and obe-

sity, rapid beta-oxidation—particularly via peroxisomes—can increase hydrogen peroxide and reactive oxygen species (ROS) production, potentially exceeding antioxidant capacity and causing transient hepatocellular stress.[28] Although ALE has demonstrated antioxidant properties in previous studies,[29,30] it is plausible that, in this population, the initial metabolic shift temporarily overwhelmed these defenses. This remains speculative, as we did not assess oxidative stress biomarkers (eg, malondialdehye [MDA], glutathione [GSH/GSSG], 8-hydroxy-2'-deoxyguanosine [8-OHdG]), and should be examined in future work. The differing results could also be explained by the fact that our study population was exclusively composed of individuals with third-degree steatosis and third-degree obesity, whereas Panahi et al.[21] included patients with steatosis ranging from first to third degree, primarily focusing on subjects without obesity.

The observed reductions in total cholesterol and LDL cholesterol among female participants align with earlier studies in nonobese populations. No effect was detected in male participants, likely due to limited statistical power; given the small subgroup size and post-hoc nature of this analysis, these results should be considered exploratory.

In line with the morphological changes of the liver in terms of volume reduction as well as (sex-specific) changes in the serum lipid profile in the Artichoke group, a change in body composition was observed during the BIA measurements. Apparently, the described effects of ALE are not limited to the liver alone but act systemically, thereby also influencing body composition. BIA changes, including a significant reduction in fat mass percentage and trends toward lower absolute fat mass and fat mass index, were detected early (TP0-TP1) in the ALE group, preceding the later rise in transaminases (TP1-TP2). The delayed rise in AST and ALT may reflect a transient phase of hepatocellular stress, potentially triggered by increased hepatic fatty acid influx and intrahepatic lipid mobilization. In insulin-resistant states, such as MASLD, this influx is predominantly driven by enhanced peripheral adipose tissue lipolysis rather than by de novo lipogenesis within hepatocytes[31] providing an extrahepatic source of free fatty acids that can promote lipotoxic stress. This pattern suggests that peripheral effects—potentially mediated through adipose tissue—may be temporally decoupled from hepatic metabolic adjustments. Preclinical studies support this interpretation, demonstrating that ALE-derived metabolites protect adipocytes against lipotoxic stress, reduce hypertrophy, and modulate adipose-tissue–derived cytokines.[32,33]

Taken together, these findings support a model in which hepatic stress and systemic metabolic improvements may occur concurrently but follow distinct and possibly tissue-specific kinetics. In our population with severe obesity and MASLD, early reductions in fat mass may thus reflect peripheral anti-inflammatory and lipolytic effects of ALE, while hepatocellular stress, as indicated by delayed increases in transaminases, may represent a secondary response to altered hepatic lipid turnover or detoxification demands.

Our cohort represents a specific and clinically relevant population—patients with morbid obesity and high-grade steatosis awaiting bariatric surgery. In this context, liver volume plays a crucial role: an enlarged liver, particularly an enlarged left lobe, can obstruct access to the underlying stomach, especially in the hiatus region. Moreover, steatotic liver tissue is softer and more fragile, making it more susceptible to intraoperative injury during retraction.[34] The observed reductions in liver volume and inflammatory markers are therefore not only statistically relevant but may also directly translate into improved surgical conditions. Notably, the magnitude of liver volume reduction—in the centimeter range—may be clinically meaningful, as bariatric procedures are performed almost exclusively laparoscopically under substantial optical magnification, where even small dimensional changes can markedly improve intraoperative visualization and exposure of the operative field.

From a clinical standpoint, ALE presents an appealing adjunctive option in the management of MASLD: it is over-the-counter, inexpensive, well tolerated, and easy to integrate into preoperative care pathways. Especially in high-risk patients undergoing bariatric surgery, the noninvasive nature of ALE may facilitate implementation and patient adherence. Although this trial was conducted in a specific prebariatric population (patients with obesity prior to metabolic surgery), the observed metabolic and inflammatory improvements may hold relevance for broader MASLD/MASH populations beyond surgical candidates. However, the currently available evidence on the efficacy of ALE—particularly in patients with obesity and MASLD—is still insufficient to justify its inclusion in clinical practice guidelines. Rather, our findings, alongside prior exploratory studies, should be regarded as a rationale for conducting larger randomized controlled trials with extended intervention and follow-up durations to determine long-term efficacy and safety.

Limitations: Our study's limitations include its single-center design, the relatively small sample size, and the absence of long-term follow-up data to assess the durability of the observed effects. The sample size calculation was powered for changes in CAP, but not for multiple secondary endpoints such as laboratory or body composition parameters. Consequently, the statistical power for these outcomes is limited, increasing the risk of type I error and chance findings. Although significant effects were observed after 42 days, future studies with larger, more diverse cohorts and extended follow-ups are necessary to validate our findings and explore the long-term efficacy, safety, and durability, as well as potential variations in response based on these variables.

As with most plant-based nutraceuticals, batch-to-batch variability of the ALE preparation cannot be entirely ruled out. Furthermore, the presence and potential activity of polyphenols beyond the primary marker compound were not comprehensively quantified. This limitation must be acknowledged. While further standardization and detailed phytochemical profiling are desirable, it should also be considered whether future studies might instead employ

pharmaceutical-grade preparations as investigational products to ensure defined composition and reproducibility.

Although FibroScan diagnostics provide quantitative values, like sonography, they are dependent on the examiner and thus potentially error-prone. To minimize this source of error as much as possible, all measurements were conducted by one examiner using a standardized technique. We are planning a follow-up study in which magnetic resonance imaging (MRI)-based diagnostics will be used to quantify hepatic steatosis, thereby eliminating operator dependency. In this upcoming trial, the duration of ALE supplementation will also be extended to evaluate longer-term effects.

The observed changes in body composition—particularly in fat mass percentage and regional skeletal muscle mass—suggest systemic effects of ALE beyond hepatic metabolism. However, the use of BIA introduces potential variability due to its sensitivity to hydration status. While BIA is a practical and noninvasive tool, its precision is limited in severely obese individuals compared to imaging modalities such as dual-energy X-ray absorptiometry (DEXA) or MRI. The results should therefore be interpreted with appropriate caution.

Conclusions

In conclusion, our findings suggest that ALE may contribute to reducing liver steatosis and size, as well as improving body composition and lipid profile in patients with obesity. Given the complexity of managing patients with obesity and MASLD/MASH, the integration of ALE into clinical care protocols could offer a novel, noninvasive strategy to improve patients' risk profile, preoperative conditions, and patient safety. Further research is warranted to expand upon these findings and to establish guidelines for ALE in this clinical context.

CRediT authorship contribution statement

Sebastian Holländer: Writing – original draft, Formal analysis, Conceptualization. **Evelyn Marth:** Investigation, Formal analysis, Conceptualization. **Philipp Robert Scherber:** Formal analysis. **Antonios Spiliotis:** Formal analysis. **Ammar Al-Ali:** Writing – review & editing. **Gereon Gäbelein:** Writing – review & editing. **Matthias Glanemann:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the local Ethics Committee (Ethikkommission der Ärztekammer des Saarlandes, Reference No.: 305/21).

Informed consent statement

Written informed consent was obtained from all subjects involved in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2025.10.063.

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