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Effect of nano-curcumin supplementation on liver fibrosis in patients with NAFLD-associated fibrosis: a double-blind randomized controlled trial

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Hepatic fibrosis, resulting from chronic liver injury, can lead to cirrhosis and liver failure. Curcumin shows anti-fibrotic potential but has low bioavailability. This 16-week double-blind, randomized, placebo-controlled trial evaluated the effects of 80 mg/day nano-curcumin on liver fibrosis, steatosis, liver function test, and anthropometric parameters in 55 adults (30–70 years) with stage ≥ F2 NAFLD-induced fibrosis. Primary outcomes were liver fibrosis and steatosis assessed by FibroScan and FIB-4. Secondary outcomes included changes in liver function tests and anthropometric parameters including body composition. Both groups improved in fibrosis and steatosis, with no significant differences were found between them. The FIB-4 index decreased significantly in the nano-curcumin group ($p = 0.022$), but between-group differences were not significant ($p = 0.135$). ALT and AST significantly decreased in the nano-curcumin group ($p < 0.001$ and $p = 0.004$), with significant group differences ($p < 0.05$). GGT reduction was significant between groups after adjustment ($p = 0.043$), and LDH levels also decreased significantly in the nano-curcumin group ($p < 0.001$), with a significant between-group difference ($p = 0.016$). No statistically significant between-group differences were observed in anthropometric parameters. Nano-curcumin improved liver enzymes but showed no significant effect on fibrosis or steatosis compared to placebo. Further research is needed to confirm long-term benefits. *Trial registration* Iranian Registry of Clinical Trials IRCT20210427051098N2 (Available from: https://irct.behdasht.gov.ir).

Keywords Liver fibrosis, Nano-curcumin, Liver enzymes, Fibrosis, Steatosis, Liver function test, Antioxidant therapy

Abbreviations

ACC	Acetyl-CoA carboxylase
Akt	Protein kinase B
ALB	Albumin
ALP	Alkaline phosphatase

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ALT	Alanine aminotransferase
APRI	AST to platelet ratio index
AST	Aspartate aminotransferase
BARD	Body mass index, AST/ALT Ratio, diabetes
BF	Body fat
BMI	Body mass index
BMR	Basal metabolic rate
ChREBP	Carbohydrate-responsive element-binding protein
D-Bil	Direct bilirubin
FAS	Fatty acid synthase
FIB-4	Fibrosis-4 index
GGT	Gamma-glutamyl transferase
GPx	Glutathione peroxidase
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment for insulin resistance
HSC	Hepatic stellate cell
IL-6	Interleukin-6
LBM	Lean body mass
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NFS	NAFLD fibrosis score
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PI3K	Phosphoinositide 3-kinase
PI3K/Akt	Phosphoinositide 3-kinase/protein kinase B (Akt)
PLT	Platelets
PPAR-γ	Peroxisome proliferator-activated receptor gamma
SOD	Superoxide dismutase
SREBP-1c	Sterol regulatory element-binding protein 1c
T2DM	Type 2 diabetes mellitus
T-Bil	Total bilirubin
TC	Total cholesterol
TG	Triglycerides
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
WC	Waist circumference

Hepatic fibrosis represents a critical pathological response to chronic liver injury, characterized by excessive extracellular matrix (ECM) deposition and progressive scarring[1]. This condition arises from a wide range of etiologies, including viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and autoimmune disorders[2,3]. NAFLD, linked to obesity, type 2 diabetes, and metabolic syndrome, progresses from simple fat accumulation to more severe stages like Non-Alcoholic Steatohepatitis (NASH (, fibrosis, and cirrhosis. While weight loss is key for treatment, it is often difficult to achieve and maintain, increasing the need for alternative therapies to slow or reverse fibrosis progression[4–6]. Left untreated, fibrosis can advance to cirrhosis, leading to severe complications such as portal hypertension, hepatocellular carcinoma (HCC), and liver failure[7]. Cirrhosis alone accounts for approximately 1 million deaths annually worldwide, underscoring the urgent need for effective therapeutic strategies to manage liver fibrosis[8].

Central to the pathophysiology of liver fibrosis is the activation of hepatic stellate cells (HSCs), which transform into myofibroblast-like cells under the influence of chronic liver injury[2]. These cells are major drivers of ECM production, contributing to fibrotic scar formation. Targeting HSC activation and downstream fibrotic processes has therefore become a primary focus in developing antifibrotic therapies[9,10].

Despite significant advances, liver fibrosis remains challenging to diagnose and manage. Liver biopsy, though considered the gold standard for fibrosis staging, is invasive and associated with potential complications[11]. Non-invasive diagnostic modalities, such as transient elastography and serological markers, have shown promise, yet there remains a pressing need for safe, effective, and widely accessible therapeutic interventions[12,13].

Curcumin, a natural polyphenol derived from the rhizome of *Curcuma longa* (turmeric), has garnered significant attention due to its broad-spectrum therapeutic properties, including anti-inflammatory, antioxidant, and antifibrotic effects[14,15]. These benefits have been demonstrated in various preclinical models of chronic liver disease, with curcumin showing potential in modulating hepatic stellate cell (HSC) activation, reducing oxidative stress, and inhibiting pro-fibrogenic pathways. However, its clinical application has been limited by poor bioavailability, rapid metabolism, and limited systemic absorption[16–18].

Recent advancements in nanotechnology have led to the development of nanocurcumin formulations. Encapsulation in nanosized carriers such as liposomes, polymeric nanoparticles, and nanocrystals enhances curcumin's solubility, stability, and bioavailability, allowing for more effective systemic delivery and therapeutic outcomes[19,20]. Nanocurcumin has been proposed as a potentially beneficial approach for the prevention and management of liver fibrosis[21,22]. Despite this, most research in this area has focused on conventional curcumin rather than nanocurcumin, and clinical studies investigating curcumin's effects on liver fibrosis have

predominantly been conducted in animal models. To the best of our knowledge, there are currently no published clinical trials exploring the therapeutic effects of nanocurcumin in patients with liver fibrosis[21,23–27].

This study aims to address this gap by investigating the effects of nano-curcumin supplementation on liver fibrosis, steatosis, Liver Function Tests, and the Fibrosis-4 index (FIB-4) in individuals with liver fibrosis caused by non-alcoholic fatty liver disease. By evaluating its impact on fibrotic markers and liver function, this research seeks to clarify the potential role of nano-curcumin in managing liver fibrosis. Ultimately, the goal is to generate supportive evidence for its potential integration as an adjunctive therapeutic option in clinical settings.

Materials and methods

Study design

This randomized, double-blind, placebo-controlled trial was conducted at the Gastroenterology and Liver Clinic of Shariati Hospital, Tehran, Iran. The study design and methodology followed the SPIRIT 2013 guidelines to ensure rigor and transparency in reporting clinical trials[28]. The trial was registered in the Iranian Registry of Clinical Trials (IRCT20210427051098N2). The reporting of this study adheres to the CONSORT 2025 (Consolidated Standards of Reporting Trials) guidelines (Supplementary)[29]. The study protocol was approved by the institutional review board and research ethics committee of Shahid Sadoughi University of Medical Sciences (approval ID: IR.SSU.SPH.REC.1401.157) on January 29, 2023, and all procedures were performed in accordance with relevant guidelines and regulations.

Participants

Participants included in this study were adults aged between 30 and 70 years who met the eligibility criteria. Eligible individuals were those previously diagnosed with liver fibrosis at stage F2 or higher, all of whom had fibrosis attributed to NAFLD[30], and had been referred to the Gastroenterology Clinic at Shariati Hospital, affiliated with Tehran University of Medical Sciences (TUMS). Specifically, patients with liver fibrosis stages F2, F3, F2–F3, and F3–F4 were included, while individuals with cirrhosis (stage F4) were excluded.

Exclusion criteria comprised a variety of conditions and circumstances: individuals with a history of alcohol addiction or substance abuse, those with chronic or acute liver diseases (such as hepatitis B or C, biliary or autoimmune liver disorders, and inherited metabolic liver diseases like hemochromatosis or Wilson's disease) were excluded. Pregnant or lactating women, individuals taking hepatotoxic, anti-inflammatory, corticosteroid, or hormonal medications, and patients with severe comorbidities (e.g., active cancer, advanced lung, or kidney disease) were also not eligible.

Additional exclusions applied to participants on active weight-loss regimens, those who had recently changed medications, individuals using interfering supplements, or those undergoing warfarin therapy due to bleeding risks. Furthermore, individuals who were unwilling to participate, unable to comply with the study protocol, or who experienced gastrointestinal side effects from nanocurcumin supplementation were excluded from the study.

Intervention

This randomized study involved two groups: one that received nanocurcumin and another that received a placebo. Participants assigned to the intervention group took one 40 mg capsule of nanocurcumin twice daily[31], while those in the placebo group received identical-looking capsules that lacked the active ingredient. The daily dose of 80 mg nanocurcumin (40 mg twice daily) was selected based on previous clinical trials demonstrating both safety and efficacy in patients with NAFLD and related patient populations[31–33]. Both types of capsules were manufactured by Exir Nano Sina (ENS) Company in Iran, with maltodextrin used as the placebo filler. The capsules were identical in appearance, color, and scent to preserve the blinding of the study.

Participants were provided with a sufficient number of capsules at the beginning of the study and at the end of weeks 4, 8, and 12. The intervention period lasted 16 weeks, and capsule distribution was planned accordingly. They were instructed to take the capsules with a main meal and cold water. Although conventional curcumin has been associated with gastrointestinal side effects such as nausea, vomiting, and diarrhea, these symptoms are less frequently observed with the nanomicellar form used in this trial. All participants, regardless of group assignment, also received dietary and physical activity guidance to complement standard care.

Outcome measures and data collection procedures

Liver fibrosis and steatosis assessment

The primary outcomes of this study included changes in liver fibrosis and steatosis, both measured at baseline and after 16 weeks using Fibroscans 502 instrument (EchoSense, 5 MHz), a medical device based on transient elastography[34,35]. All assessments were conducted by the same experienced gastroenterologist to ensure consistency. During the procedure, participants lay on their backs with their right hand raised above their head while the probe was applied to the right intercostal area.

Liver stiffness, a marker of fibrosis, was reported in kilopascals (kPa) and interpreted using the METAVIR scoring system:

F0: No fibrosis.
F1: Mild fibrosis, liver structure intact.
F2: Portal fibrosis with occasional septa.
F3: Multiple septa, no cirrhosis.
F4: Established cirrhosis, severe liver damage[36].

Additionally, the FIB-4 index was calculated as a non-invasive, serum-based method to assess liver fibrosis[37]. The FIB-4 index was determined using the following formula:

$$\mathrm{FIB}-4=\frac{(\mathrm{Age}\ [\mathrm{years}]\times\ \mathrm{AST}\ [\mathrm{U/L}])}{(\mathrm{Platelet\ count}\ [10^9/\mathrm{L}]\times\sqrt{\mathrm{ALT}}\ [\mathrm{U/L}])}$$

This index provides an estimate of liver scarring and has been validated across different patient populations.

To evaluate steatosis (fat accumulation in the liver), the Controlled Attenuation Parameter (CAP) test was employed, with results expressed in decibels per meter (dB/m), ranging from 100 to 400. This non-invasive technique provided reliable data on both fibrosis and fat buildup using ultrasound technology, thereby eliminating the need for liver biopsy in assessing disease progression[38].

Assessment of liver function test

To evaluate liver function, several biochemical parameters were measured at both baseline and at the conclusion of the intervention, including serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (T-Bil), direct bilirubin (D-Bil), gamma-glutamyl transferase (GGT), albumin (ALB), and platelet count (PLT). All measurements were performed using standardized laboratory techniques to ensure consistency and reliability. Specifically, serum parameters were assessed using enzyme colorimetric methods on the Cobas c 311 analyzer (Roche Diagnostics GmbH, Germany), and platelet count was determined with an automated hematology analyzer (Sysmex, Japan).

Anthropometric measurements

Participants' anthropometric data were collected under standardized conditions[39]. Height was measured to the nearest 0.5 cm while subjects stood upright without shoes. Body weight was recorded with an accuracy of 100 g using a digital scale, with participants wearing minimal clothing and no footwear. Waist circumference (WC) was measured to the nearest 0.5 cm at the midpoint between the lowest rib and the iliac crest using a flexible tape measure. Body Mass Index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Body composition parameters, including body fat percentage (%BF), lean body mass (LBM), and basal metabolic rate (BMR), were assessed using the BC 418 MA Segmental Body Composition Analyzer (Tanita Corp., Tokyo, Japan)[40,41], a validated bioelectrical impedance analysis device.

Dietary intake assessment

To assess dietary intake, a 24-h dietary recall[42,43] was collected on three non-consecutive days at both the beginning and end of the study (including four weekdays and two weekend days). All reported food items were converted into gram weights using standard reference booklets, and the average intake was calculated based on six total dietary recalls per participant.

Physical activity assessment

Physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ) short form, administered at baseline[44]. Physical activity data were analyzed according to validated guidelines, which converted reported activity durations into metabolic equivalent task hours per day (MET-h/day), enabling comparison across individuals.

Lifestyle guidance and control of confounding factors

Both intervention and control groups received general lifestyle guidance regarding diet and physical activity. However, no specific dietary or exercise regimens were prescribed that could independently affect outcomes related to fibrosis, steatosis, liver function tests, or metabolic health.

Adherence monitoring and tolerability

Participant adherence and tolerability were tracked through daily diaries in which capsule consumption and any adverse effects were recorded. In addition, biweekly phone follow-ups were conducted, and capsule counts were performed during monthly study visits to further verify compliance.

Sample size calculation

The required sample size was estimated based on the primary outcome of the study—liver fibrosis—using G*Power software (version 3.1.9.2). Drawing on findings from a previous study[45], an effect size of 0.9 was assumed. With a Type I error (α) set at 5%, statistical power ($1-\beta$) of 80%, and an anticipated attrition rate of 10%, the total sample size was determined to be 50 participants (25 in each group). However, to account for potential dropouts and ensure sufficient power, 55 participants were ultimately recruited and randomized into the study.

Randomization and blinding

Participants were randomly assigned to either the intervention or control group using a block balanced randomization method to ensure equal allocation. Both groups received oral supplements manufactured by Exir Nano Sina (ENS) Company, Iran. The supplements were identical in appearance—including size, color, shape, and packaging—to maintain effective blinding. To uphold the double-blind design, an independent third party, not involved in the research process, labeled the supplement containers as "A" or "B," thus concealing group allocation from both participants and study investigators.

Statistical analysis

All statistical analyses were conducted using SPSS software (version 24). The Chi-square test was applied to assess differences in categorical variables between the two groups. For continuous variables, normality was evaluated using appropriate tests. Normally distributed continuous data were analyzed using independent samples t-tests for between-group comparisons and paired t-tests for within-group changes. If any continuous variable had not met normality assumptions, the Mann–Whitney U test would have been used for between-group comparisons and the Wilcoxon signed-rank test for within-group changes. For between-group comparisons and to evaluate treatment effects, Generalized Linear Models (GLM) were employed, with adjustments based on baseline values, and further adjustments for age, sex, diabetes status, calorie intake changes, and BMI variations when applicable. A p-value less than 0.05 was considered statistically significant.

Results

Participant recruitment and randomization

As illustrated in Fig. 1, a total of 1,048 patients were screened for eligibility in this clinical trial. Of these, 645 individuals were excluded due to not meeting the inclusion criteria, and 348 declined to participate. Ultimately, 55 eligible patients were randomly assigned to one of two groups: 27 patients in the nano-curcumin group and 28 in the placebo group. Throughout the study period, no participants withdrew from the trial, and all enrolled individuals were included in the final analysis. Given that adverse effects are generally reduced in nanomicellar formulations, in the present study, only a single case of transient itching was reported in the nanocurcumin group, limited to the initial days of administration, and it did not result in study discontinuation.

Baseline characteristics of patients

As shown in Table 1, the two groups (nanocurcumin and placebo) were comparable at baseline, with no statistically significant differences observed in demographic or clinical characteristics. This indicates that the randomization was successful and the groups were well-matched before the intervention.

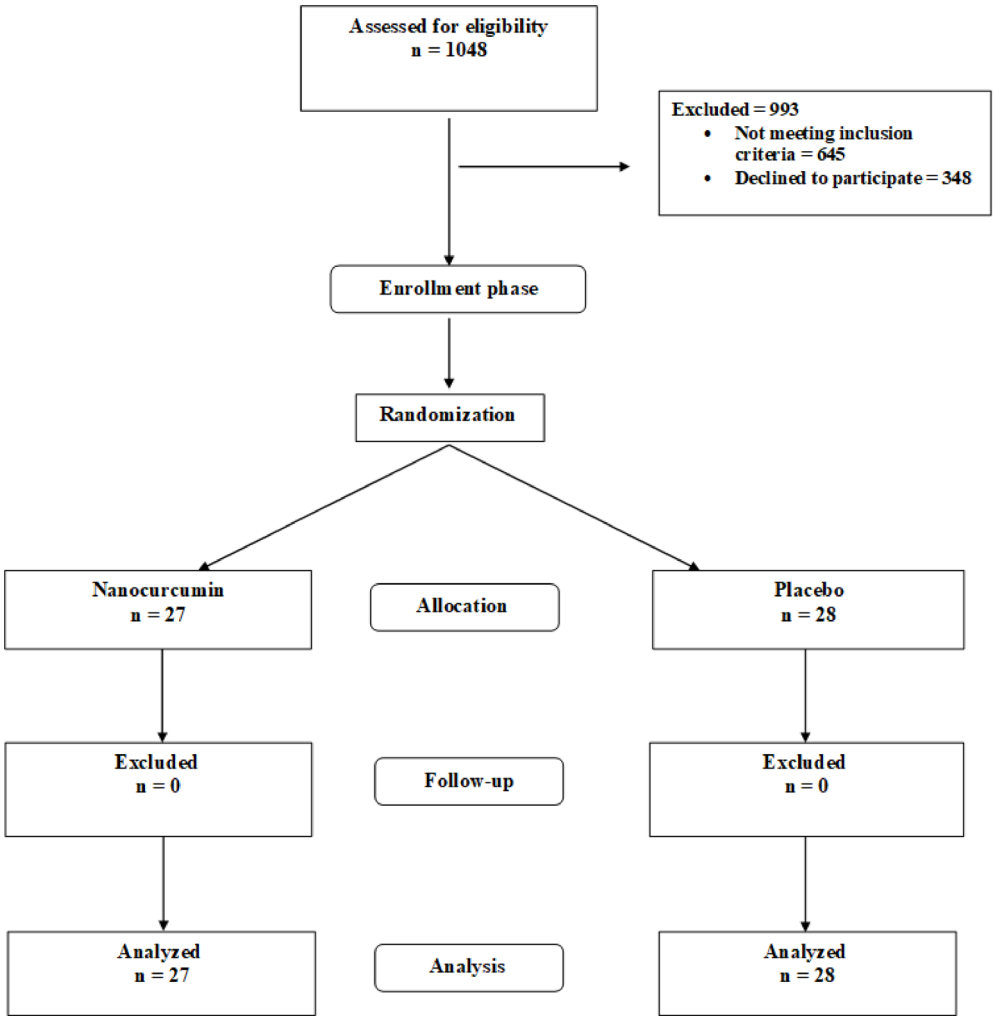

Fig. 1. CONSORT diagram.

Variable	Placebo (n = 28)	Nano-curcumin (n = 27)	*P* value
Age (years)	53.85 ± 10.48†	50.48 ± 12.07†	0.27
Gender (Male, %)	12 (42.9%)	16 (59.3%)	0.22
Height (cm)	164.62 ± 11.65†	169.12 ± 10.01†	0.13
Diabetes (%)	11 (39.3%)	11 (40.7%)	0.91
Physical activity (MET-hr/day)	29.66 ± 2.93†	31.17 ± 3.25†	0.07
Creatinine (mg/dl)	0.85 ± 0.14†	0.89 ± 0.20†	0.42

Table 1. Baseline characteristics of patients. Qualitative data were analyzed using the Pearson Chi-Square test, while quantitative data were analyzed using the Independent Sample t-test. †Mean ± Standard Deviation.

Variable	Placebo (n = 28)				Nano-curcumin (n = 27)						
	Baseline	After 16 weeks	Change	*P* value†	Baseline	After 16 weeks	Change	*P* value†	*P* value¥	*P* value*	*P* value**
Energy (kcal)	1507.56 ± 570.70	1533.70 ± 561.72	26.14 ± 435.31	0.753	1663.79 ± 649.63	1733.80 ± 698.24	56.38 ± 429.65	0.509	0.48	0.541	0.574
Carbohydrates (%)	57.81 ± 8.04	57.95 ± 7.54	0.14 ± 8.99	0.935	57.11 ± 7.21	55.86 ± 7.35	− 1.40 ± 9.47	0.455	0.73	0.309	0.149
Protein (%)	16.83 ± 3.79	16.24 ± 3.16	− 0.58 ± 4.40	0.490	16.90 ± 3.95	16.26 ± 4.10	− 0.51 ± 4.82	0.590	0.94	0.978	0.663
Fat (%)	28.93 ± 5.20	29.17 ± 5.60	0.24 ± 6.13	0.837	29.45 ± 5.56	31.01 ± 6.25	1.58 ± 8.02	0.323	0.72	0.266	0.160
Cholesterol (mg/d)	190.26 ± 70.58	193.49 ± 78.65	3.22 ± 65.37	0.796	212.95 ± 80.48	219.32 ± 74.06	5.39 ± 47.34	0.566	0.271	0.541	0.538
SFA (g/d)	15.13 ± 6.26	15.49 ± 6.47	0.36 ± 4.93	0.696	16.85 ± 7.09	17.90 ± 6.15	0.93 ± 4.79	0.331	0.344	0.326	0.346
MUFA (g/d)	9.27 ± 3.83	9.49 ± 3.96	0.22 ± 3.02	0.650	10.32 ± 4.34	10.97 ± 3.77	0.57 ± 2.93	0.340	0.354	0.434	0.333
PUFA- w6 (g/d)	6.86 ± 2.84	7.03 ± 2.93	0.16 ± 2.23	0.412	7.64 ± 3.21	8.12 ± 2.79	0.42 ± 2.17	0.319	0.482	0.356	0.397
PUFA- w3(g/d)	3.20 ± 1.32	3.28 ± 1.37	0.07 ± 1.04	0.368	3.56 ± 1.50	3.79 ± 1.30	0.19 ± 1.01	0.529	0.441	0.562	0.511
Vitamin E (mg/d)	19.52 ± 8.08	19.99 ± 8.35	0.47 ± 6.36	0.475	21.74 ± 9.15	23.10 ± 7.93	1.20 ± 6.18	0.223	0.398	0.382	0.345
Vitamin C (mg/d)	109.26 ± 44.43	110.59 ± 40.13	1.33 ± 33.71	0.835	118.78 ± 49.92	123.62 ± 59.07	3.59 ± 44.82	0.686	0.458	0.591	0.506
Zinc (mg/d)	12.35 ± 4.46	12.46 ± 5.44	0.11 ± 5.24	0.909	13.89 ± 5.63	13. 83 ± 5.90	− 0.08 ± 4.24	0.923	0.265	0.797	0.964
Selenium (µg/d)	74.12 ± 26.81	74.80 ± 33.66	0.68 ± 31.48	0.811	83.37 ± 33.78	83.02 ± 35.41	− 0.48 ± 25.46	0.823	0.165	0.597	0.564
Beta-carotene (µg/d)	1809.07 ± 684.84	1840.44 ± 674.07	31.36 ± 522.37	0.753	1996.55 ± 779.56	2080.57 ± 837.89	67.66 ± 515.58	0.509	0.347	0.541	0.574
Lycopene (µg/d)	2110.58 ± 798.99	2147.18 ± 786.41	36.59 ± 609.43	0.653	2329.31 ± 909.48	2427.33 ± 977.54	78.94 ± 601.51	0.411	0.255	0.430	0.460

Table 2. Daily energy intake, macronutrients, fatty acids, cholesterol, micronutrients, and antioxidants before and after intervention. ¥The Independent Samples t-test was used to compare baseline values between the two groups. *Generalized Linear Models: Adjusted comparisons based on baseline values of the assessed parameter. **Generalized Linear Models: Adjusted comparisons based on baseline values of the assessed parameter, age, sex, diabetes status, calorie intake changes, and body mass index changes. †Paired t-test.

Energy intake, macronutrients, and anthropometric parameters

At the beginning of the study, there were no significant differences in energy and macronutrient intake between the nanocurcumin and placebo groups (all $P > 0.05$). The mean energy intake was 1663.79 ± 649.63 kcal in the nanocurcumin group and 1507.56 ± 570.70 kcal in the placebo group ($P = 0.48$). The percentage of carbohydrate, protein, and fat intake also did not differ significantly between the two groups (Table 2). These findings indicate that the nutritional status of participants was similar in both groups before the intervention.

According to the results presented in Table 2, after the intervention, no significant differences were observed in energy and macronutrient intake between the nanocurcumin and placebo groups (all $P > 0.05$). The mean energy intake was 1733.80 ± 698.24 kcal in the nanocurcumin group and 1533.70 ± 561.72 kcal in the placebo group, with changes from baseline not reaching statistical significance ($P = 0.541$). Similarly, the percentage of carbohydrate, protein, and fat intake did not differ significantly between the groups (all $P > 0.05$). Furthermore, after adjusting for baseline values, age, sex, diabetes status, caloric intake changes, and body mass index, no significant differences were detected (all $P > 0.05$).

Furthermore, as shown in Table 2, no significant differences were observed between the nano-curcumin and placebo groups in the intake of cholesterol, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids omega-6 (PUFA-ω6), polyunsaturated fatty acids omega-3 (PUFA-ω3), vitamin E (α-tocopherol), vitamin C (ascorbic acid), zinc, selenium, beta-carotene, and lycopene at baseline or after 16 weeks of intervention (all $P > 0.05$). These results indicate that fatty acid composition, cholesterol, and micronutrient intake, including vitamins, carotenoids, and minerals, remained similar between groups throughout the study period.

According to the results presented in Table 3, at baseline, there were no significant differences in anthropometric indices, body composition, and basal metabolic rate between the nanocurcumin and placebo groups (all $P > 0.05$). The mean weight was 88.33 ± 20.37 kg in the nanocurcumin group and 90.51 ± 20.09 kg in the placebo

Variable	Placebo (n = 28)				Nano-curcumin (n = 27)						
	Baseline	After 16 weeks	Change	*P* value†	Baseline	After 16 weeks	Change	*P* value†	*P* value¥	*P* value*	*P* value**
Weight (kg)	90.51 ± 20.09	86.03 ± 19.33	− 3.03 ± 4.62	**0.002**	88.33 ± 20.37	85.83 ± 19.00	− 2.49 ± 3.76	**0.002**	0.69	0.645	0.609
Body mass index (kg/m^2)	33.30 ± 6.13	31.50 ± 5.50	− 1.15 ± 1.66	**0.001**	30.60 ± 4.96	29.52 ± 4.57	− 0.80 ± 1.26	**0.004**	0.07	0.553	0.554
Waist circumference (cm)	114.16 ± 13.14	110.64 ± 13.17	− 3.51 ± 3.59	**≤ 0.001**	109.24 ± 13.29	105.61 ± 13.37	− 3.62 ± 3.83	**≤ 0.001**	0.17	0.861	0.869
Lean body mass (g)	56.82 ± 12.51	55.77 ± 12.27	− 0.75 ± 3.74	0.302	57.85 ± 13.02	57.20 ± 12.93	0.01 ± 2.21	0.965	0.76	0.328	0.395
Body fat percentage (%)	36.82 ± 7.17	34.77 ± 6.58	− 1.57 ± 1.88	**≤ 0.001**	34.22 ± 5.45	32.23 ± 6.42	− 1.87 ± 2.15	**≤ 0.001**	0.13	0.562	0.583
Basal metabolic rate (kcal)	1347.07 ± 292.89	1312.22 ± 259.12	− 33.00 ± 102.17	0.105	1398.55 ± 276.23	1376.76 ± 275.17	− 8.30 ± 33.84	0.222	0.51	0.136	0.246

Table 3. Anthropometric parameters before and after intervention. Bold values indicate the represent statistically significant measurements, highlighting the effects of nano-curcuminsupplementation on liver fibrosis and associated biochemical and anthropometric outcomes. ¥The Independent Samples t-test was used to compare baseline values between the two groups. *Generalized Linear Models: Adjusted comparisons based on baseline values of the assessed parameter. **Generalized Linear Models: Adjusted comparisons based on baseline values of the assessed parameter, age, sex, diabetes status, calorie intake changes, and body mass index changes. †Paired t-test.

group ($P = 0.69$). Similarly, body mass index (BMI) was comparable between the groups (30.60 ± 4.96 kg/m^2 in the nanocurcumin group vs. 33.30 ± 6.13 kg/m^2 in the placebo group, $P = 0.07$).

Regarding body composition, no significant differences were observed between the groups in body fat percentage and lean body mass. The percentage of body fat was 34.22 ± 5.45% in the nanocurcumin group and 36.82 ± 7.17% in the placebo group ($P = 0.13$). Furthermore, the mean basal metabolic rate (BMR) was reported as 1398.55 ± 276.23 kcal in the nanocurcumin group and 1347.07 ± 292.89 kcal in the placebo group, with no statistically significant difference ($P = 0.51$).

According to the results presented in Table 3, after the intervention, significant changes in some anthropometric indices and body composition were observed in both the nanocurcumin and placebo groups compared to baseline. Weight, BMI, WC, and body fat percentage significantly decreased in both groups (all $P < 0.05$). No significant changes were observed in lean body mass or BMR in either group (all $P > 0.05$).

In the between-group comparison, none of the mentioned variables showed significant differences (all $P > 0.05$). Additionally, after adjusting for baseline values, age, sex, diabetes status, changes in caloric intake, and BMI, no significant differences were detected (all $P > 0.05$).

Liver fibrosis, steatosis, fibrosis-4 index, and liver function tests

At baseline, there were no significant differences in liver fibrosis, hepatic steatosis, and fibrosis-4 index between the nanocurcumin and placebo groups (Table 4). The mean liver fibrosis score was 10.50 ± 2.66 kPa in the nanocurcumin group and 10.08 ± 1.62 kPa in the placebo group ($P = 0.92$). The mean hepatic steatosis score was 327.96 ± 49.30 dB/m in the nanocurcumin group and 341.96 ± 41.77 dB/m in the placebo group ($P = 0.38$). Additionally, there was no significant difference in the FIB-4 between the two groups ($P = 0.504$).

As shown in Table 4, baseline comparisons of liver function markers revealed that the mean ALT level was higher in the nanocurcumin group (46.00 ± 28.19 U/L) than in the placebo group (31.42 ± 14.17 U/L), with the difference reaching statistical significance ($P = 0.04$). Similarly, AST levels were higher in the nanocurcumin group (38.44 ± 23.38 U/L) compared to the placebo group (27.21 ± 10.07 U/L), with a *P*-value approaching significance ($P = 0.05$). A statistically significant difference was also observed in baseline albumin levels ($P = 0.008$). No other significant differences were noted between the groups in terms of GGT ($P = 0.59$), ALP ($P = 0.29$), LDH ($P = 0.10$), total bilirubin ($P = 0.25$), direct bilirubin ($P = 0.38$), or platelet count ($P = 0.82$).

According to the results in Table 4, after the intervention, liver fibrosis decreased in both groups, but there was no significant difference between them. The mean change in fibrosis was − 1.64 ± 1.83 kPa in the nanocurcumin group and − 1.41 ± 1.71 kPa in the placebo group ($P = 0.798$). Similarly, hepatic steatosis decreased in both groups (− 42.03 ± 38.26 dB/m in the nanocurcumin group and − 44.64 ± 41.34 dB/m in the placebo group), but the between-group difference was not significant ($P = 0.745$). However, within-group comparisons revealed significant reductions in both fibrosis and steatosis in both groups ($P < 0.001$).

Regarding the FIB-4, the mean change was − 0.17 ± 0.36 in the nanocurcumin group and − 0.01 ± 0.38 in the placebo group, with no significant between-group difference ($P = 0.135$). However, within-group analysis showed a significant reduction in FIB-4 in the nanocurcumin group ($P = 0.022$), while no significant change was observed in the placebo group ($P = 0.870$).

For ALT, the mean change was − 19.59 ± 16.89 U/L in the nanocurcumin group and − 0.14 ± 11.45 U/L in the placebo group, with a significant between-group difference ($P < 0.001$). Within-group analysis showed a significant reduction in ALT in the nanocurcumin group ($P < 0.001$), but no significant change in the placebo group ($P = 0.948$). Similarly, the mean AST reduction was − 15.03 ± 16.31 U/L in the nanocurcumin group and − 0.92 ± 11.64 U/L in the placebo group, with a significant between-group difference ($P = 0.004$). Within-group

Variable	Placebo (n = 28)				Nano-curcumin (n = 27)						
	Baseline	After 16 weeks	Change	*P* value†	Baseline	After 16 weeks	Change	*P* value†	*P* value¥	*P* value*	*P* value**
Liver fibrosis (kPa)	10.08 ± 1.62	8.67 ± 1.96	− 1.41 ± 1.71	**≤ 0.001**	10.50 ± 2.66	8.85 ± 2.49	− 1.64 ± 1.83	**≤ 0.001**	0.92	0.798	0.913
Hepatic steatosis (dB/m)	341.96 ± 41.77	297.32 ± 46.39	− 4.64 ± 41.34	**≤ 0.001**	327.96 ± 49.30	285.92 ± 42.47	− 4.03 ± 3.26	**≤ 0.001**	0.38	0.745	0.230
Fibrosis-4 index	1.17 ± 0.63	1.16 ± 0.66	− 0.01 ± 0.38	0.870	1.29 ± 0.62	1.11 ± 0.66	− 0.17 ± 0.36	**0.022**	0.50	0.135	0.309
ALT (U/L)	31.42 ± 14.17	31.28 ± 16.20	− 0.14 ± 11.45	0.948	46.00 ± 28.19	26.40 ± 15.60	− 19.59 ± 16.89	**≤ 0.001**	**0.04**	**≤ 0.001**	**≤ 0.001**
AST (U/L)	27.21 ± 10.07	26.28 ± 12.10	− 0.92 ± 11.64	0.676	38.44 ± 23.38	23.40 ± 11.20	− 15.03 ± 16.31	**≤ 0.001**	0.05	**0.004**	**0.010**
ALP (U/L)	92.53 ± 38.26	86.96 ± 41.30	− 5.57 ± 20.37	0.159	79.03 ± 18.40	79.81 ± 21.45	− 0.77 ± 14.54	0.783	0.29	0.262	0.161
GGT (U/L)	61.46 ± 6.45	53.17 ± 51.47	− 8.28 ± 47.81	0.367	59.77 ± 5.54	35.19 ± 16.53	− 15.65 ± 18.00	**≤ 0.001**	0.59	0.084	**0.043**
LDH (U/L)	198.96 ± 49.66	190.67 ± 54.99	− 8.28 ± 20.37	0.065	180.62 ± 33.59	158.53 ± 25.29	− 20.61 ± 23.83	**≤ 0.001**	0.10	**0.016**	**0.025**
Albumin (g/dl)	4.57 ± 0.25	4.55 ± 0.26	− 0.02 ± 0.21	0.547	4.79 ± 0.31	4.71 ± 0.25	− 0.08 ± 0.20	0.054	**0.008**	0.666	0.976
Platelets (1000/ML)	266.07 ± 123.75	269.57 ± 154.03	3.50 ± 65.66	0.780	238.18 ± 63.11	225.81 ± 51.22	− 12.37 ± 33.32	0.065	0.82	0.295	0.337
Total bilirubin (mg/dL)	0.58 ± 0.26	0.56 ± 0.24	− 0.01 ± 0.16	0.642	0.64 ± 0.30	0.65 ± 0.35	0.00 ± 0.18	0.885	0.25	0.522	0.718
Direct bilirubin (mg/dL)	0.21 ± 0.09	0.20 ± 0.09	− 0.01 ± 0.05	0.243	0.23 ± 0.09	0.23 ± 0.10	− 0.006 ± 0.04	0.525	0.38	0.499	0.340

Table 4. Liver fibrosis, steatosis, fibrosis-4 index, and liver function tests before and after intervention. Bold values indicate the represent statistically significant measurements, highlighting the effects of nano-curcuminsupplementation on liver fibrosis and associated biochemical and anthropometric outcomes. ¥The Independent Samples t-test was used to compare baseline values between the two groups. *Generalized Linear Models: Adjusted comparisons based on baseline values of the assessed parameter. **Generalized Linear Models: Adjusted comparisons based on baseline values of the assessed parameter, age, sex, diabetes status, calorie intake changes, and body mass index changes. †Paired t-test. Abbreviations: ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase), GGT (Gamma-Glutamyl Transferase), LDH (Lactate Dehydrogenase).

analysis indicated a significant decrease in AST in the nanocurcumin group ($P < 0.001$), but not in the placebo group ($P = 0.676$).

For GGT, the mean change was − 15.65 ± 18.00 U/L in the nanocurcumin group and − 8.28 ± 47.81 U/L in the placebo group, with no significant between-group difference ($P = 0.084$). However, after adjusting for baseline values, age, sex, diabetes, caloric intake changes, and BMI, the between-group difference became significant ($P = 0.043$). Additionally, within-group analysis showed a significant reduction in GGT in the nanocurcumin group ($P < 0.001$), whereas no significant change was observed in the placebo group ($P = 0.367$).

The mean change in ALP levels was − 0.77 ± 14.54 U/L in the nanocurcumin group and − 5.57 ± 20.37 U/L in the placebo group, with no significant difference between groups in the crude analysis ($P = 0.262$). After adjustment for baseline values, age, sex, diabetes status, calorie intake changes, and BMI, the difference remained non-significant ($P = 0.161$). Additionally, within-group changes were not statistically significant in either the nanocurcumin ($P = 0.783$) or placebo group ($P = 0.159$).

Albumin levels showed a mean change of − 0.08 ± 0.20 g/dL in the nanocurcumin group and − 0.02 ± 0.21 g/dL in the placebo group. Between-group differences were not significant after adjustment ($P = 0.666$ unadjusted; $P = 0.976$ adjusted). Within-group reductions did not reach statistical significance in either group ($P = 0.054$ for nanocurcumin, $P = 0.547$ for placebo).

For LDH, the mean change was − 20.61 ± 23.83 U/L in the nanocurcumin group and − 8.28 ± 22.83 U/L in the placebo group, with a significant between-group difference ($P = 0.016$). Within-group analysis showed a significant reduction in LDH in the nanocurcumin group ($P < 0.001$), whereas no significant change was observed in the placebo group ($P = 0.065$).

The mean change in platelet count was − 12.37 ± 33.32 (× 1000/μL) in the nanocurcumin group and + 3.50 ± 65.66 in the placebo group, with no statistically significant between-group differences before ($P = 0.295$) or after adjustment ($P = 0.337$). Within-group changes were not significant in either group ($P = 0.065$ for nanocurcumin, $P = 0.780$ for placebo).

Total bilirubin levels showed minimal change in both groups (0.00 ± 0.18 mg/dL for nanocurcumin vs. − 0.01 ± 0.16 mg/dL for placebo), with no significant between-group differences ($P = 0.522$ unadjusted, $P = 0.718$ adjusted). Within-group changes were not significant in either arm ($P = 0.885$ for nanocurcumin, $P = 0.642$ for placebo).

Direct bilirubin levels slightly decreased in both groups (− 0.006 ± 0.04 mg/dL for nanocurcumin and − 0.01 ± 0.05 mg/dL for placebo), with no significant between-group differences in unadjusted ($P = 0.499$) or adjusted ($P = 0.340$) analyses. Within-group changes were also not significant ($P = 0.525$ for nanocurcumin, $P = 0.243$ for placebo).

Discussion

The present study aimed to investigate the effects of nanocurcumin supplementation on fibrosis, steatosis, liver function indices, and anthropometric Parameters in patients with liver fibrosis due to NAFLD. It is worth noting that while the updated nomenclature "MASLD" (Metabolic dysfunction-associated steatotic liver disease) has recently been proposed to replace "NAFLD", the traditional term is used throughout this manuscript to

ensure consistency with the cited literature and maintain clarity for readers. The findings demonstrated that nanocurcumin supplementation significantly reduced serum levels of liver enzymes (ALT, AST, LDH, and GGT) compared to the placebo group. Additionally, a reduction in liver fibrosis and steatosis scores was observed following nanocurcumin intake; however, these changes did not reach statistical significance when compared to the placebo group.

With respect to liver fibrosis and steatosis, reductions in fibrosis, steatosis, and FIB-4 were observed in the nanocurcumin group; however, these changes did not reach statistical significance in the between-group comparisons. Recently, several studies have investigated the effects of curcumin supplementation on liver fibrosis and steatosis. Saadati et al. (2018) evaluated the effects of 1500 mg of curcumin for 12 weeks in patients with NAFLD. Fibrosis was assessed using non-invasive indices including FibroScan, FIB-4, Aspartate Aminotransferase to Platelet Ratio Index (APRI), NAFLD Fibrosis Score (NFS), and Body mass index, AST/ALT ratio, Diabetes (BARD). The results showed a significant reduction in fibrosis as measured by FibroScan, FIB-4, and APRI in the curcumin group, while no significant changes were observed with NFS and BARD. These findings highlight that curcumin has potential to improve fibrosis, yet the sensitivity of the assessment tools strongly influences the observed outcomes[46]. Our findings, which also showed within-group improvements but non-significant between-group effects, are partly consistent with this study and suggest that although nanocurcumin may exert biological effects, detecting robust clinical changes may require larger sample sizes or longer interventions.

In another study by Safari et al., NAFLD patients received phytosomal curcumin (250 mg/day) for 12 weeks. According to FibroScan data, the reduction in both liver fibrosis and steatosis was significantly greater in the curcumin group compared to the placebo group[47]. Additionally, Mirhafez et al. (2021) reported that supplementation with 250 mg/day of curcumin phytosome for 8 weeks led to a significant reduction in hepatic steatosis grade in patients with non-alcoholic fatty liver disease[48]. Compared to these studies, our trial did not demonstrate significant between-group differences. This discrepancy could be due to the more advanced disease stage of our participants (F2–F3 fibrosis) relative to the generally milder NAFLD cases included in Safari and Mirhafez, as advanced fibrosis is typically less responsive to short-term nutritional interventions.

In our study, fibrosis was assessed using FibroScan and the FIB-4. Although significant reductions were observed from baseline within the nanocurcumin group, the between-group differences were not statistically significant. This pattern indicates that nanocurcumin may help stabilize or slightly improve fibrosis markers, but the magnitude of benefit is insufficient to reach statistical superiority in moderate-to-advanced disease stages. Notably, Saadati et al. employed a broader panel of indices, including BARD and NFS, in addition to FibroScan[46]. While FibroScan is considered the most accurate and standard method for assessing liver fibrosis, composite indices such as BARD and NFS are often used due to cost and accessibility constraints. Hence, the use of FibroScan and FIB-4 in our study enhances the reliability of the fibrosis assessment. Taken together, the alignment of our within-group improvements with Saadati et al. suggests a real, though modest, biological effect of nanocurcumin on fibrosis progression.

Furthermore, in a clinical trial by Hellmann et al. (2021), lecithin-formulated curcumin (200 mg twice daily) for 6 weeks had no significant effect on hepatic fat content in obese individuals with mild steatosis, as measured by magnetic resonance spectroscopy[49]. In contrast, Selmanovic et al. (2021) observed that 400 mg/day of curcumin significantly improved ultrasound morphological characteristics of the liver in patients with metabolic syndrome, indicating a potential role in hepatic fat reduction[50]. Moreover, Devara et al. (2021) demonstrated that intravenous administration of curcumin nanosuspensions significantly enhanced liver protection and drug bioavailability in rats with liver fibrosis[51]. Together with our results, these mixed findings underscore that curcumin's clinical efficacy is highly context-dependent, influenced by disease severity, delivery system, and treatment duration.

The differences from previous studies may be explained by discrepancies in disease stage, curcumin formulation, assessment methods, and overall study design. First, differences in the stage of liver disease among study populations are likely to play a key role. For example, while studies such as Safari et al. and Mirhafez et al. included patients with early-stage NAFLD (steatosis grades 1–3), our study exclusively enrolled participants with FibroScan-confirmed liver fibrosis (F2–F3), representing a more advanced disease stage. This likely accounts for the less pronounced between-group effects in our study, as advanced fibrosis is known to respond more slowly to dietary and phytochemical interventions. Second, formulation-specific differences in curcumin bioavailability may contribute to variability in treatment efficacy. While we used a nano-formulated curcumin, which has enhanced absorption over conventional forms, some prior studies employed phytosomal or lecithin-based curcumin, which may differ in their pharmacokinetic profiles and tissue distribution. Although nanocurcumin is expected to have superior bioavailability, this advantage may not fully overcome the diminished therapeutic responsiveness seen in advanced liver disease. Third, heterogeneity in assessment methods for fibrosis and steatosis may influence study findings. While we utilized FibroScan and FIB-4, considered accurate and non-invasive tools, other studies incorporated additional indices such as APRI, NFS, and BARD. This methodological diversity complicates direct comparisons and may partly explain why some studies observed larger treatment effects. Additionally, variations in study design, sample size, adherence to intervention, and concurrent lifestyle modifications may also contribute to inconsistent findings across trials.

Regarding liver function tests, nanocurcumin supplementation significantly reduced liver enzyme levels, including ALT, AST, LDH, and GGT, compared to the placebo group. However, changes in other liver function markers such as albumin, ALP, total bilirubin, and direct bilirubin were not statistically significant between the groups. Previous studies have also reported the beneficial effects of curcumin on liver enzymes through various mechanisms. In a double-blind clinical trial, Rahmani et al. investigated the effects of 500 mg of curcumin administered for two months in 80 patients with NAFLD. Their findings showed a significant decrease in ALT and AST levels in the curcumin group[52]. This result parallels our finding of reduced ALT and AST, although

our study additionally demonstrated reductions in LDH and GGT, suggesting that nanocurcumin might exert broader effects on hepatocellular injury markers. Similarly, Saadati et al. administered 1500 mg of curcumin for 12 weeks to patients with NAFLD and observed a significant reduction in ALT levels in the curcumin group, although changes in AST, GGT, ALP, and other markers were not statistically significant between the groups[53]. This partial response aligns with our observation that ALT is the most consistently improved enzyme, while other markers show variable responsiveness across studies. Moreover, a clinical trial conducted by Hellmann et al. (2021) found that six weeks of lecithin-formulated curcumin (200 mg twice daily) supplementation led to a reduction in GGT levels among obese individuals with mild steatosis. This finding is consistent with our significant reduction in GGT and suggests that curcumin, regardless of formulation, may particularly benefit cholestatic or oxidative stress–related pathways reflected by GGT. In another study by Mirhafez et al., 250 mg of phytosomal curcumin was given for 8 weeks to patients with NAFLD, resulting in a significant decrease in AST levels, with no significant changes in other liver enzymes[48]. Together, these findings highlight that while curcumin consistently lowers at least one aminotransferase (ALT or AST) across studies, our trial extends this evidence by showing concurrent improvements in multiple hepatocellular enzymes with nanocurcumin. Taken together, our results are broadly consistent with these trials, particularly regarding improvements in ALT, AST, and GGT, which strengthens the evidence that curcumin can ameliorate hepatic injury markers. However, the more pronounced enzyme reductions observed in our study compared to some earlier reports may reflect the use of a nano-formulated curcumin with superior bioavailability and potentially greater systemic effects. In contrast, the lack of effect on albumin, ALP, and bilirubin highlights that nanocurcumin primarily improves hepatocellular injury and oxidative stress markers rather than synthetic or excretory functions, which are usually preserved until later stages of liver disease.

Curcumin, a bioactive polyphenolic compound, exerts its anti-fibrotic effects through modulation of multiple signaling pathways. These mechanisms include attenuation of inflammation, inhibition of oxidative stress, regulation of apoptosis, and suppression of fibrogenic pathways such as transforming growth factor-beta (TGF-β), Wnt, Hedgehog, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[54]. The TGF-β/Smad pathway is a key regulator in hepatic fibrogenesis, promoting the activation of HSCs and extracellular matrix deposition. Curcumin reduces the expression and release of TGF-β and inhibits the nuclear translocation of Smad transcription factors, thereby preventing matrix accumulation and liver scarring[55–57].

The Wnt/β-catenin pathway also plays a critical role in HSC proliferation and survival. Curcumin suppresses β-catenin stability and nuclear translocation, downregulating pro-fibrogenic gene expression and consequently reducing collagen production and improving liver architecture[58–60]. The Hedgehog pathway, associated with chronic inflammation and HSC survival, is another contributor to fibrogenesis. Curcumin reduces Hedgehog ligand production and inhibits downstream signaling mediators such as GLI transcription factors, thus attenuating pathway activation and fibrotic progression[61].

The NF-κB pathway, which regulates chronic inflammation, promotes HSC activation through increased expression of inflammatory cytokines like Tumor Necrosis Factor-alpha (TNF-α) and interleukin-6 (IL-6). Curcumin limits chronic inflammation and fibrosis progression by inhibiting NF-κB nuclear translocation and suppressing cytokine production[62,63]. In addition, curcumin mitigates oxidative damage to hepatocytes by reducing oxidative stress and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), thereby slowing the fibrogenic process[64].

Additionally, curcumin inhibits lipogenesis pathways such as sterol regulatory element-binding protein 1c (SREBP-1c) and peroxisome proliferator-activated receptor gamma (PPAR-γ), thereby preventing lipid accumulation in hepatocytes. The reduction in hepatic steatosis can alleviate inflammation and cellular damage, contributing to lower ALT and AST levels[65,66]. Insulin resistance also plays a major role in liver injury and elevated liver enzymes. Curcumin improves insulin sensitivity and suppresses inflammatory pathways associated with insulin resistance, thus enhancing liver metabolism and further reducing ALT and AST levels[67,68]. These mechanistic pathways provide biological plausibility for the clinical outcomes observed in our trial, where improvements in ALT, AST, LDH, and GGT likely reflect curcumin's combined effects on hepatocellular injury, inflammation, and lipid metabolism[54,64].

Although no significant between-group differences were observed in albumin levels, this marker remains a critical indicator of hepatic synthetic function, and its stability may reflect preserved liver function during the study period[69]. Albumin levels tend to decline in more advanced liver disease and cirrhosis[70]; however, our study population included patients with fibrosis stages below cirrhosis (F2–F3), which may explain the absence of notable changes. This interpretation aligns with prior evidence showing that curcumin's effects are more pronounced on injury and inflammation markers than on synthetic function, which usually remains intact until later disease stages.

Similarly, platelet count, which did not significantly change during the study, is an established indirect marker of liver fibrosis and portal hypertension[71]. Decreased platelet counts are often associated with progression to advanced fibrosis due to splenic sequestration and reduced thrombopoietin production by the liver[72]. Since our population had moderate fibrosis (F2–F3), stability of platelet counts is expected and indicates no short-term worsening or reversal of fibrosis during the intervention. The absence of change in platelet count in our study, together with a lack of comparable clinical trial evidence, underscores the need for future research to determine whether curcumin can influence hematologic markers of fibrosis progression.

In addition, total and direct bilirubin, which are indicators of hepatic excretory function, also showed no significant changes[73]. This may be expected in patients without decompensated liver disease. Although no interventional trials to date have evaluated curcumin's effect on bilirubin metabolism, the preservation of bilirubin levels in our study further supports the notion that participants had relatively compensated liver function at baseline. Therefore, our findings collectively indicate that while nanocurcumin exerts measurable improvements in hepatocellular enzymes, its influence on synthetic and excretory markers is limited in

patients with moderate fibrosis. This pattern of response reinforces curcumin's role as an adjunctive therapy for hepatocellular protection rather than a direct modifier of advanced liver function.

In relation to anthropometric parameters, significant within-group reductions in body weight, BMI, WC, and body fat percentage were observed In both the nanocurcumin and placebo groups following the intervention. However, no statistically significant differences were found between the two groups. Various studies have investigated the effects of curcumin on anthropometric parameters. For instance, Rahmani et al. reported that daily supplementation with 500 mg of curcumin for two months in 80 patients with NAFLD significantly reduced weight and BMI in the intervention group, while no notable changes were observed in the placebo group[52]. This finding appears stronger than our results, possibly because their study did not emphasize lifestyle modifications in the placebo group, while in our trial both groups received structured recommendations that may have minimized between-group contrasts. Similarly, Saadati et al. investigated the impact of 1500 mg of curcumin over 12 weeks in NAFLD patients and found significant reductions in weight, waist circumference, and BMI in both intervention and placebo groups, with no significant difference between groups[53]. This outcome is in line with our observations and further supports the idea that lifestyle or placebo effects can produce comparable anthropometric improvements. In another study by Panahi et al. (2017), 87 patients with NAFLD received either 1000 mg/day of phytosomal curcumin (in two divided doses) or a placebo for 8 weeks. Significant reductions were observed in anthropometric indices, including BMI and WC, in both groups[74]. These findings also resemble our data and suggest that improvements in anthropometric measures are not necessarily attributable to curcumin alone but may largely reflect concurrent lifestyle advice or natural disease fluctuations.

The absence of significant between-group differences in our study may be attributed to the fact that both groups received similar recommendations for healthy lifestyle practices aimed at liver health. The implementation of comparable dietary and physical activity guidance across both groups may have masked any independent effects of curcumin on anthropometric outcomes. In this respect, our findings agree more closely with Saadati et al. and Panahi et al., and diverge from Rahmani et al., highlighting how variations in study design, particularly the degree of lifestyle counseling, can shape the observed outcomes.

A key factor influencing the outcomes could be differences in curcumin dosage and formulation. Some previous studies employed higher doses (500–1500 mg/day), potentially yielding more pronounced effects on body composition. Nevertheless, our study used a nano-formulated curcumin with enhanced bioavailability compared to conventional curcumin. Moreover, some studies have utilized phytosomal curcumin, a distinct formulation. Since absorption and efficacy differ among nano-, phytosomal, and liposomal curcumin, observed effects in prior studies may be due to differences in formulation rather than dose alone. Thus, while Rahmani et al. reported group-specific benefits with conventional curcumin at 500 mg/day, our trial with nano-curcumin at a lower dose did not show superiority over placebo, indicating that formulation advantages may not fully compensate for dose differences or disease severity. Additionally, earlier studies primarily included patients with NAFLD without advanced fibrosis, whereas our trial focused on individuals with liver fibrosis secondary to NAFLD. The greater disease severity in our participants may have attenuated their responsiveness to the intervention.

Hepatic and visceral lipogenesis is a major mechanism contributing to fat accumulation in NAFLD, regulated by transcription factors such as SREBP-1c and carbohydrate-responsive element-binding protein (ChREBP). Curcumin has been shown to downregulate these factors, thereby inhibiting key enzymes like acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), which reduces fatty acid synthesis and fat accumulation in the liver and visceral tissue[67,68]. Furthermore, curcumin can upregulate PPAR-γ activity, enhancing fatty acid oxidation and reducing peripheral fat storage[65,75].

Insulin resistance is another central factor in NAFLD-induced fibrosis pathogenesis. In insulin-resistant states, cells fail to respond adequately to insulin, promoting lipogenesis, reducing fatty acid oxidation, and leading to increased fat storage. Curcumin improves insulin signaling by activating the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway and enhancing insulin receptor expression, thereby facilitating glucose uptake[76,77]. It also reduces TNF-α and IL-6-mediated inflammation, thereby ameliorating insulin resistance and lipid metabolism[78]. Although these mechanisms suggest curcumin could positively affect anthropometric indices, our trial demonstrates that in patients with more advanced disease and under lifestyle management, these theoretical benefits may not translate into clinically significant between-group differences. Therefore, further well-designed trials are warranted to clarify the clinical relevance of these metabolic effects.

Strengths and limitations

One of the strengths of the present study was the appropriate intervention duration (16 weeks), which allowed for the evaluation of more sustained effects of nano-curcumin supplementation. Moreover, the use of standardized methods to assess liver function enhanced the accuracy and credibility of the findings. Another notable strength was the control of potential confounding variables, such as changes in caloric intake and BMI, which enabled a more accurate interpretation of the results. Additionally, this study employed a nanomicellar formulation of curcumin, known for its markedly improved bioavailability and absorption compared to conventional curcumin. To the best of our knowledge, this is the first clinical trial to specifically examine the effects of nanocurcumin supplementation in patients with confirmed liver fibrosis, rather than merely assessing liver fat or early NAFLD stages. This makes the study novel in both target population and formulation.

Despite these strengths, the study had some limitations. First, key molecular pathways associated with liver fibrosis were not assessed. A more comprehensive evaluation of fibrogenic signaling pathways, such as TGF-β, Wnt, Hedgehog, and NF-κB, could have provided a better understanding of the potential mechanisms underlying the observed effects of nano-curcumin. Secondly, while the study was designed as a randomized, double-blind trial, the relatively small sample size may have limited the statistical power to detect minor but potentially clinically meaningful differences between the groups.

Research implications and recommendations

The findings of this study may inform the development of therapeutic interventions aimed at improving liver function in patients with fibrosis resulting from NAFLD. Given the observed improvements in hepatic enzymes following nano-curcumin supplementation, this compound may serve as a complementary approach alongside lifestyle modifications and standard treatments. However, the absence of statistically significant effects on liver fibrosis and steatosis in this study highlights the need for further investigations with larger sample sizes, longer intervention durations, or alternative dosing strategies to more comprehensively evaluate the potential of nano-curcumin, particularly in patients with advanced fibrosis.

Future research should explore the potential impact of higher doses and longer intervention periods to determine whether extended exposure to nano-curcumin could yield more pronounced benefits on liver fibrosis and steatosis. Moreover, given the inherently low bioavailability of curcumin, the use of optimized delivery systems—such as nano-curcumin, phytosomes, liposomes, or other advanced technologies—has garnered attention for enhancing solubility and absorption. Although this study employed nano-curcumin to improve bioavailability and efficacy, comparative studies examining nano-curcumin alongside other advanced formulations like phytosomes or liposomes could further clarify differences in effectiveness and bioavailability among these compounds.

Additionally, larger and multicenter clinical trials are warranted to enhance the generalizability of the findings and to provide stronger evidence regarding the clinical efficacy of nano-curcumin. Future studies should not only focus on liver enzyme regulation but also further investigate liver fibrosis and steatosis, particularly in human populations with advanced liver involvement. While molecular and cellular mechanisms—such as modulation of gene expression and key signaling pathways—have been demonstrated in preclinical and animal studies, validating these mechanisms in human subjects remains crucial. Moreover, comparative trials assessing nano-curcumin against other well-known anti-inflammatory and antioxidant agents, such as silymarin, resveratrol, or vitamin E, could help clarify its relative therapeutic value in managing NAFLD-related liver fibrosis.

Conclusion

The results of this study demonstrated that 16 weeks of nano-curcumin supplementation had beneficial effects on certain indicators of liver function, particularly hepatic enzyme levels. However, no significant differences were observed between the nano-curcumin and placebo groups in other aspects of the disease, including liver fibrosis and steatosis. These findings suggest that while nano-curcumin may contribute to improved liver function, further research is required to establish its definitive role in the treatment of liver fibrosis.

Data availability

The datasets from this study are available from the corresponding author upon reasonable request.

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Author contributions

H.G: Writing—original draft, Writing—review & editing, Investigation, data collection, Methodology, Data curation, Conceptualization, Formal analysis. SS.KH, H.MKH, AA.S, H.P, A.M, AP.HT, and MR.J: Writing—review & editing, Supervision, Conceptualization, Methodology, Investigation. SJ: Methodology, Formal analysis, Data curation, Writing—review & editing. All authors read and approved the final manuscript. SSKH supervised the study.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was designed as a parallel-group, randomized, double-blind, placebo-controlled clinical trial (registration ID: IRCT20210427051098N2). It received ethical approval from the Institutional Review Board and the Research Ethics Committee of Shahid Sadoughi University of Medical Sciences (SSUMS), Yazd, Iran, on January 29, 2023 (approval ID: IR.SSU.SPH.REC.1401.157). All participants were informed about the study's aims, procedures, potential risks, and benefits, and each provided written informed consent prior to enrollment.

Consent for publication

Not applicable.

Additional information

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