

Original Research Article

The effect of curcumin-piperine supplementation on liver transient elastography and biochemical indices in patients with non-alcoholic fatty liver disease: A randomized controlled trial

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Abstract

Objective: Non-alcoholic fatty liver disease (NAFLD), characterized by an excessive buildup of triglycerides in hepatocytes, currently lacks an approved pharmacological treatment. This study investigated the therapeutic potential of a curcumin-piperine supplement, leveraging curcumin's established antioxidant, anti-inflammatory, anti-steatotic, and anti-fibrotic properties, with piperine enhancing its bioavailability. The objective was to assess its impact on cardiometabolic markers, liver function, and the progression of hepatic steatosis and fibrosis.

Materials and Methods: Sixty NAFLD patients were enrolled in a randomized, 12-week, placebo-controlled study. Participants were randomly assigned to a treatment group receiving a daily oral supplement of 500 mg curcumin and 5 mg piperine, or a control group receiving a placebo. Measurements of anthropometrics, biochemical indices, and hepatic steatosis and fibrosis via FibroScan were taken at baseline and study end.

Results: Anthropometric indices, and hepatic fibrosis decreased significantly within groups but not between groups for curcumin-piperine supplementation compared to placebo ($p < 0.05$). There were no significant differences between curcumin-piperine supplementation and placebo in total cholesterol, LDL-C (low-density lipoprotein, cholesterol), HDL-C (high-density lipoprotein, cholesterol), ALT (alanine transaminase), AST (aspartate transaminase), FBS (fasting blood sugar) and hepatic steatosis after 12 weeks.

Conclusions: Curcumin-piperine supplementation showed no significant impact on hepatic or biochemical markers linked to NAFLD when compared to placebo, suggesting it may not be a beneficial adjunct therapy.

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Introduction

Non-alcoholic fatty liver disease (NAFLD), the most prevalent chronic liver disease, is characterized by the buildup of fat, particularly triglycerides, in over 5-10% of hepatocytes (Simeone *et al.* 2017). Obesity and type 2 diabetes are major causes of NAFLD and the increase in their prevalence reflects in the increased prevalence of NAFLD which has been estimated in Iran, for example, to be 25.24% and 33.9% in 2017 and 2018, respectively (Castera 2018; Rabiee *et al.* 2017). The pathogenesis of NAFLD is complex and not entirely understood. However, it is fundamentally regarded as a metabolic condition influenced by a convergence of factors including insulin resistance, endocrine dysregulation, dietary habits, and genetic susceptibility (Carr *et al.* 2016; Cobbina and Akhlaghi 2017). Untreated NAFLD poses a significant risk for the development of advanced liver pathologies, such as non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis, and ultimately, hepatocellular carcinoma (Carr *et al.* 2016; Mikolasevic *et al.* 2016). There is increasing evidence that the effects of NAFLD are not confined the liver but are also associated with various chronic conditions, most notably cardiovascular disease, type 2 diabetes, and chronic kidney disease (Mikolasevic *et al.* 2016).

The gold standard for diagnosing NAFLD is, at present, a liver biopsy with histological grading of steatosis and fibrosis, but the invasive nature of a liver biopsy has led to a greater focus on non-invasive alternative tests (Tsai and Lee 2018). These noninvasive methods include fibroscan, ultrasound, computerized tomography (CT) scan, magnetic resonance imaging (MRI), and examination of liver enzyme levels such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Jazayeri-Tehrani *et al.* 2017). Transient elastography, or fibroscan, is a new technology for diagnosing liver fibrosis based on liver

stiffness measurement (LSM) using ultrasound and low-frequency elastic waves (Guo *et al.* 2017; Saadati *et al.* 2019a), which has the advantages of a low sampling error as well as high sensitivity and specificity for diagnosing NAFLD and cirrhosis (Carvalho-Furtado *et al.* 2019; Guo *et al.* 2017; Saadati *et al.* 2019a).

In the absence of approved pharmacological treatments for NAFLD, management of the disease relies on lifestyle modifications which include weight loss, healthy diet, and regular physical activity (Kwak and Kim 2018). Recently, complementary medicine has been considered a possible approach in the treatment of chronic diseases such as NAFLD (Perumpail *et al.* 2018). Overall, many different herbal remedies and dietary supplements have shown promise and are being explored as potential treatments for NAFLD. Some of these are dietary factors including spices, beverages or foods, including resveratrol, milk thistle, coffee, green tea and turmeric and whilst no toxic effects have been observed, there is still little clinical evidence of their efficacy in the treatment of NAFLD, and further clinical studies are needed (Perumpail *et al.* 2018). As the principal polyphenol in turmeric, curcumin has been investigated to as a potential therapeutic agent for NAFLD. This is attributed to its multifaceted properties which include acting as an antioxidant and possessing anti-inflammatory, anti-coagulant, anti-steatotic, and anti-fibrotic effects (Ahmadi *et al.* 2022; Amel Zabihi *et al.* 2017; Hewlings and Kalman 2017; Kahkhaie *et al.* 2019; Keihanian *et al.* 2018; Mohammadi *et al.* 2019; Mokhtari-Zaer *et al.* 2018; Sahebkar 2014). These properties of curcumin have led to its use to treat illnesses such as diabetes, metabolic syndrome, obesity, traumatic brain injury, coronavirus disease 2019 (COVID-19) and respiratory diseases (Askari *et al.* 2022; Heidari *et al.* 2023; Panahi *et al.* 2016; Panahi *et al.* 2015; Panahi *et al.* 2017a). The efficacy of curcumin has been well-

established in preclinical and animal models of NAFLD. However, its clinical application in human subjects is currently restricted due to a paucity of robust clinical evidence (Amel Zabihi et al. 2017). Previous clinical studies have used different forms and doses of curcumin such as phytosomal curcumin, nanocurcumin, phospholipidated curcumin, curcumin-standardized turmeric extract, and curcumin-piperine combination. The results have been contradictory for NAFLD disease severity, and hepatic enzyme and lipid profile changes, indicating the need for more studies (Cicero et al. 2020; Jazayeri-Tehrani et al. 2019; Mirhafez et al. 2021; Panahi et al. 2017c; Panahi et al. 2018; Panahi et al. 2019; Rahmani et al. 2016). Despite its significant therapeutic potential, the clinical application of curcumin is hindered by its low aqueous solubility, poor oral absorption, and rapid metabolism (Gera et al. 2017). When curcumin is consumed alone and at a dose of 2 g, serum levels are very low or undetectable; however, its co-administration with piperine (a natural alkaloid from pepper) can increase its bioavailability (Shoba et al. 1998) and efficacy by inhibiting its glucuronidation in the liver and intestine (Heidari et al. 2023; Mohseni et al. 2021; Monroy et al. 2013; Shoba et al. 1998). As a result, the use of piperine in combination with curcumin can improve the pharmacokinetic characteristics and efficacy of oral curcumin supplement (Heidari et al. 2023; Mirzaei et al. 2017).

Despite the growing interest in curcumin therapeutic potential for NAFLD, a notable research gap exists in the literature. Few studies have utilized a validated FibroScan method to accurately assess the impact of curcumin on hepatic fibrosis. Moreover, prior investigations have typically employed high-dose curcumin supplements with inherently limited bioavailability, which may confound results (Saadati et al. 2019a; Saadati et al. 2018; Saadati et al. 2019b).

Therefore, the absence of a clinical trial investigating the effect of curcumin-piperine supplementation on liver steatosis and fibrosis using a valid fibroscan method in patients with NAFLD, prompted us to undertake this study and explore the effects of curcumin-piperine co-administration on cardiometabolic factors, steatosis and hepatic fibrosis in NAFLD patients.

Materials and Methods

Study design and participants

We performed a double-blind randomized clinical trial involving patients with NAFLD. The study was carried out at clinics associated with Isfahan University of Medical Sciences and took place from July 2020 to May 2021. The study protocol received approval from the Ethics Committee of Isfahan University of Medical Sciences (ethics code: IR.MUI.RESEARCH.REC.1398.462). The protocol was also officially registered on the Iran Registry of Clinical Trials (IRCT) website (<https://en.irct.ir/trial/43732>; IRCT registration number: IRCT20121216011763N42). All participants provided written informed consent prior to the trial. The study was conducted in accordance with the Declaration of Helsinki and its reporting follows the CONSORT guidelines for clinical trials.

All patients with NAFLD referred to the affiliated clinic of Isfahan University of Medical Sciences (Imam Musa Sadr Clinic) were screened for eligibility. Inclusion criteria were willingness to give informed consent, age 18 to 65 years, and NAFLD diagnosed by ultrasound. Participants were excluded from the study if they had a history of pregnancy, lactation, heart, lung, or kidney diseases, hepatitis, cirrhosis, biliary or immune system disorders, hypertension, hypothyroidism, or Cushing's syndrome. Additionally, individuals with a history of weight loss or bariatric surgery within the past year were excluded. The use of certain medications and supplements

also served as an exclusion criterion, including lipid- and glucose-reducing drugs, vitamin E, vitamin D, ursodeoxycholic acid, phenytoin, tamoxifen, lithium, corticosteroids, methotrexate, and any other therapeutic supplements for NAFLD.

Stratified permuted block randomization method, using block size 4 based on gender and age was used for randomization (by a random number generator

(<https://www.sealedenvelope.com/simple-randomiser/v1/lists>)). The randomization numbers were determined by an independent statistician. Allocation concealment was conducted by keeping randomization numbers within sequentially numbered sealed opaque envelopes that were opened consecutively when the patient was admitted. A trained nutritionist carried out the tasks of both patient enrollment and group assignment. Eligible individuals were randomly assigned to either of two groups of curcumin-piperine (500 mg curcumin plus 5mg piperine; n=30) (Sami Labs Ltd., Bangalore, India) or placebo (505 mg microcrystalline cellulose; n=30) (1:1).

Intervention

The combination of curcumin and piperine at a dosage of 500+5 mg/day has been widely utilized in clinical practice and has demonstrated both safety and efficacy in previous clinical trials (Askari *et al.* 2023; Askari *et al.* 2022; Boshagh *et al.* 2023; Mirhafez *et al.* 2021; Panahi *et al.* 2017b; Sharifi *et al.* 2023). While higher doses of curcumin have been found to be safe (Chainani-Wu 2003; Hsu and Cheng 2007), we chose to administer a dose of 505 mg/day, as previous studies employing curcumin-piperine at this dosage have shown promising effects on various biochemical and clinical parameters in diverse populations (Boshagh *et al.* 2023; Heidari *et al.* 2023; Mirhafez *et al.* 2021; Panahi *et al.* 2019; Saberi-Karimian *et al.* 2020; Sharifi *et al.* 2023). Therefore, for our

study, we employed the dose of 505 mg/day for a duration of 12 weeks. Patients in both the intervention and placebo groups were administered one capsule daily containing 500 mg of curcuminoids plus 5 mg piperine or one placebo capsule containing 505 mg microcrystalline cellulose after breakfast and the same diet and exercise recommendations were given to both groups (Panahi *et al.* 2019). To maintain the integrity of the double-blind design, the capsule manufacturer (Sami Labs Limited, Bangalore, India) labeled the capsules as A and B. The active and placebo capsules were similar in weight, size, color, aroma, and shape and were distributed in similar containers. To help retention and compliance, patients were contacted by phone or text message every week and were reminded to take the capsules. Participant compliance was measured monthly by counting the capsules left in their bottles. A minimum compliance rate of 90% was required for a participant to continue in the study (Grymonpre *et al.* 1998).

To control for the potential confounding effects of dietary intake and physical activity, a detailed assessment was performed throughout the study by completing a food diary and a physical activity diary. Participants were instructed to complete a three-day food diary (two weekdays and one weekend day) at three distinct time points: baseline, week six, and at the conclusion of the study. The nutritional data, including food intake, daily energy, and total caloric consumption, was calculated from these records using the Nutritionist 4 (N4) software. Additionally, physical activity levels were quantified by having subjects complete a three-day physical activity questionnaire, from which we derived Metabolic Equivalents (METs) per hour per day (MET.h.d).

Clinical and para-clinical assessment

Anthropometric indices including height, weight, waist circumference, and BMI (body mass index) were measured at the beginning of the study and 12 weeks

after the intervention. Body weight was measured with a digital scale with an accuracy of 0.1 kg in the morning on an empty stomach without shoes and with minimal clothing. Height was measured with an accuracy 0.1 cm by an inelastic meter. BMI was calculated by dividing weight (kg) by height squared (cm). Waist circumference was also measured with an accuracy of 0.1 cm in the standing position.

Blood samples were taken after 10-12 hr of fasting, at the beginning and end of the study to determine the lipid profile, blood glucose, and liver enzymes. Fasting blood glucose (FBG), liver enzymes, triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were determined using enzymatic methods. Serum liver enzyme levels (ALT and AST) were determined using the enzymatic photometric method (IFCC).

The non-invasive fibroscan method was used to evaluate hepatic fibrosis and steatosis. Fibroscan was performed by a physician who was unaware of the objectives of the study. Due to the potential increase in liver stiffness from postprandial blood flow, patients had to fast for two hours prior to the fibroscan procedure (Arena et al. 2013; Wilder and Patel 2014). The fibroscan was performed in the supine position, and a probe was placed on the skin in the hepatic area and was performed without patient discomfort (Kemp and Roberts 2013). A Touch Echosense 502 device (serial number: sin F 60759, Ref: 1907-100-000) from France was used to perform the FibroScan measurements in this trial. FibroScan-derived scores were used to assess the degree of fibrosis, with specific cutoff points defining the severity. Minimal fibrosis was designated by scores between 4.7 and 5.0 kPa, moderate fibrosis by scores of 5.0 to 9.4 kPa, and severe fibrosis or cirrhosis was diagnosed at scores of 9.5 kPa or above.

Statistical analysis

The sample size was calculated taking into account $\alpha = 0.05$, a power of 80%, and a standardized effect size equal to $\Delta = 0.8$ based on the index of fibroscan controlled attenuation parameter (CAP) score (Saadati et al. 2019a), which required 26 patients in each group and to account for dropouts, 30 patients in each group were to be recruited.

The analysis was based on the per-protocol method, so participants who fully complied with the intervention were included in the analysis. To assess the normal distribution of variables, the skewness test and q-q plot were used. Logarithmic transformation was used to normalize non-normal variables (skewed to the right). In the present study, data is described for quantitative variables as mean \pm standard deviation (SD) and for qualitative variables as a number.

Baseline characteristics were compared between the two groups using an independent samples t-test for quantitative data and a Pearson's Chi-square test for qualitative data. Changes over time within each group were analyzed with paired samples t-tests, and the analysis between groups was performed using analysis of covariance (ANCOVA).

All statistical analyses were conducted using SPSS software version 22 (SPSS Inc., Chicago, IL), and a p-value of less than 0.05 ($p < 0.05$) was considered statistically significant.

Results

A total of 60 patients with NAFLD were initially enrolled in the study. Fifty-nine patients successfully completed the 12-week intervention (n=30 in the curcumin-piperine group and n=29 in the placebo group). One patient was withdrawn from the study due to personal reasons, and his data were excluded from the final analysis (Figure 1).

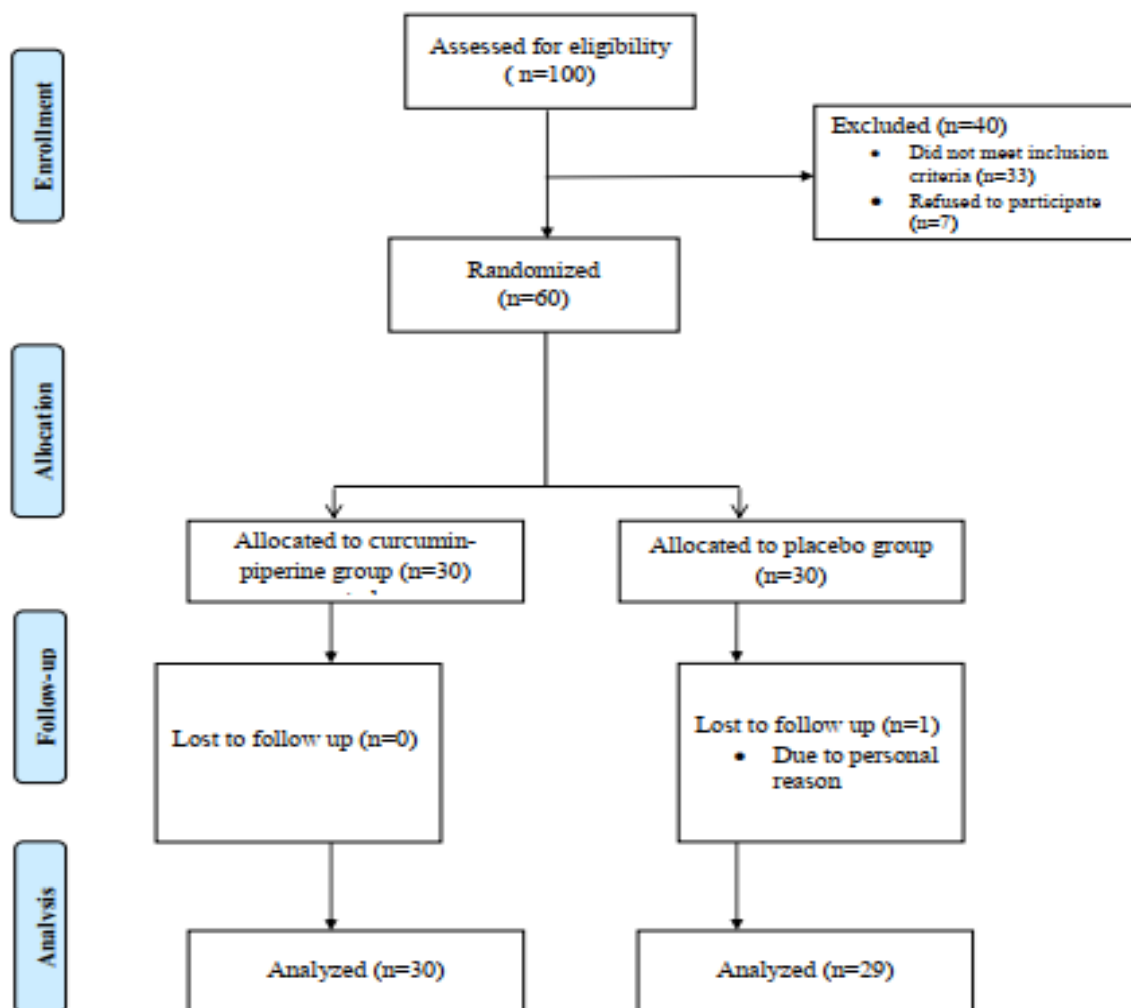


Figure 1. Flow diagram of the trial.

No adverse events or side effects were reported by participants in either the curcumin-piperine or placebo groups during the 12-week study. Furthermore, a comparison of baseline data revealed no significant differences between the groups for any of the measured parameters, confirming successful randomization (Table 1).

As reported in Table 2, mean energy intake, carbohydrate, protein, fat, cholesterol, fiber, vitamins E, C, and D, and selenium during the study in the two groups consuming curcumin-piperine and placebo did not differ significantly between the two groups. However, the mean intake of fructose in the intervention group was higher ($p=0.02$). The physical activity between the two groups did not differ significantly during the study period.

After 12 weeks of intervention, anthropometric indices including weight and BMI decreased significantly within groups for both curcumin-piperine (-1.63%, -1.66%) and placebo (-1.56%, -1.35%) ($p<0.05$), but waist circumference (WC) was reduced significantly only within the intervention group (-2.32%) ($p=0.01$). None of the reported changes showed a significant difference between the two groups (Table 3)

After 12 weeks, within-group analysis for the curcumin-piperine arm showed a significant increase in total cholesterol (TC) (6.59%) and LDL-C levels (14.48%) ($p<0.05$), but between-group analysis showed no significant difference compared to placebo group. No significant difference was seen for either within or between the

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two groups for ALT, AST, TG, LDL-C or HDL-C (Table 4).

As shown in Table 5, after 12 weeks, the within-group analysis for the curcumin-piperine group showed that the fibrosis score was significantly reduced (-9.41%, p

= 0.04), but there was no significant difference between the intervention and placebo groups. Hepatic steatosis (steatosis score and percent steatosis) did not differ significantly within or between the intervention and placebo groups.

Table 1. Clinical and biochemical characteristics of study participants at baseline between the Curcumin-piperine and placebo groups

Variables	Curcumin-piperine group (n=30)	Placebo group (n=29)	p-value	
Age (years)	46.06±8.27	48.83±8.66	0.211	
Male (n)	19	12	0.071	
Female (n)	11	18		
Weight (kg)	87.26±12.79	82.69±13.81	0.240	
WC (cm)	102.37±7.94	101.30±8.35	0.614	
BMI (kg/m ²)	30.55±2.57	29.53±2.76	0.655	
FBG (mg/dl)	104.20±50.09	104.80±33.47	0.957	
TC (mg/dl)	196.10±29.69	186.20±46.66	0.332	
TG (mg/dl)	192.93±76.24	217.46±127.09	0.369	
HDL-C (mg/dl)	46.66±10.92	43.43±10.56	0.249	
LDL-C (mg/dl)	110.84±23.31	99.27±35.44	0.141	
ALT (U/L)	39.16±23.12	43.96±56.93	0.670	
AST (U/L)	35.73±15.44	33.16±14.50	0.510	
Fibrosis score (kPa)	5.95±1.94	5.81±1.57	0.761	
Steatosis score (dB/m)	311.23±33.96	304.90±42.43	0.526	
Steatosis percent (%)	68.46±18.79	61.93±26.32	0.824	
Smoking (n)	Yes	5	3	0.706
	No	25	27	

WC, waist circumference; BMI, body mass index; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine transaminase; AST, aspartate transaminase. Quantitative variables are reported as mean ± standard deviation and p-values obtained from independent sample t-tests. Qualitative variables are reported as numbers and p-values obtained from the Chi-square test.

Table 2. The mean of dietary intakes and physical activity in curcumin-piperine and placebo groups

Nutrients	Curcumin-piperine group(n=30)	Placebo group (n=29)	p-value
Energy (kcal/d)	1886.47±556.73	1817.85±480.85	0.611
Carbohydrate (g/d)	269.76±82.50	255.86±73.02	0.492
Protein (g/d)	80.55±23.62	76.61±22.28	0.509
Fat (g/d)	60.40±21.62	59.46±16.83	0.851
Cholesterol (mg/d)	219.19±103.76	220.99±116.48	0.950
Dietary fiber (g/d)	33.78±12.79	33.47±12.12	0.648
Fructose	18.71±6.90	14.20±7.66	0.020
Vitamin E (mg/d)	19.99±12.06	20.51±11.95	0.867
Vitamin C (mg/d)	107.15±50.83	88.61±43.36	0.134
Vitamin D (µg/d)	0.61±0.78	0.50±0.49	0.515
Selenium (mg/d)	0.12±0.05	0.12±0.04	0.856
Physical activity (MET.h.d)	34.60±6.69	35.59±4.50	0.507

MET.h.d; metabolic equivalent hours per day. p-values obtained from independent sample t-test.

Table 3. Anthropometric indices and their changes in the curcumin-piperine and placebo groups at baseline and after 12 weeks

Variables	Curcumin-piperine group (n=30)				Placebo group (n=29)				p-value ^b	p-value ^c
	Before intervention	After intervention	Change (percentage change)	p-value ^a	Before intervention	After intervention	Change (percentage change)	p-value ^a		
Weight (kg)	87.26±12.79	85.83±12.75	-1.43±2.29 (-1.63%)	0.002	82.69±13.81	81.40±13.65	-1.29±2.27 (-1.56%)	0.005	0.950	0.779
BMI (kg/m ²)	30.55±2.57	30.04±2.58	-0.51±0.78 (-1.66%)	0.001	29.53±2.76	29.13±3.11	-0.24±1.90 (-1.35%)	0.005	0.617	0.937
WC (cm)	102.37±7.94	99.99±8.28	-2.38±4.71 (-2.32%)	0.010	101.30±8.35	100.34±8.27	-0.68±3.81 (-0.94%)	0.170	0.236	0.547

BMI, body mass index; WC, waist circumference. Values are mean±standard deviation. a Obtained from paired sample t-test. b Obtained from ANCOVA (adjusted for baseline values). c Obtained from ANCOVA (adjusted for baseline values and mean of fructose).

Table 4. Biochemical parameters in the curcumin-piperine and placebo groups at baseline and after 12 weeks

Variables	Curcumin-piperine group (n=30)				Placebo group (n=29)				p-value ^b	p-value ^c
	Before intervention	After intervention	Change (percentage change)	p-value ^a	Before intervention	After intervention	Change (percentage change)	p-value ^a		
FBG (mg/dl)	104.20±50.09	103.70±28.96	-0.5±32.37 (-0.47%)	0.933	104.80±33.47	105.68±27.76	0.89±23.75 (0.83%)	0.840	0.730	0.910
TC (mg/dl)	196.10±29.69	209.03±42.18	12.93±33.16 (6.59%)	0.041	186.20±46.66	190.41±48.46	3.41±16.11 (2.26%)	0.264	0.152	0.069
TG (mg/dl)	192.93±76.24	178.60±71.99	-14.33±87.43 (-7.42%)	0.377	217.46±127.09	199.89±98.78	-19.89±72.34 (-8.07%)	0.150	0.696	0.631
HDL-C (mg/dl)	46.66±10.92	46.53±11.41	-0.13±7.56 (-0.27%)	0.924	43.43±10.56	43.37±11.75	-0.034±8.05 (-0.13%)	0.819	0.707	0.311
LDL-C (mg/dl)	110.84±23.31	126.90±39.74	16.05±33.27 (14.48%)	0.013	99.27±35.44	106.82±37.56	7.51±18.03 (7.60%)	0.033	0.193	0.114
ALT (U/L)	39.16±23.12	34.40±18.80	-4.76±14.87 (-12.15%)	0.090	43.96±56.93	30.79±16.61	-13.75±60.03 (-29.95%)	0.227	0.373	0.298
AST (U/L)	35.73±15.44	34.90±10.36	-0.83±11.75 (-2.32%)	0.701	33.16±14.50	37.65±13.90	4.41±16.23 (13.54%)	0.154	0.193	0.252

FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine transaminase; AST, aspartate transaminase. Values are mean±standard deviation. a Obtained from paired sample T test. b Obtained from ANCOVA (adjusted for baseline values). c Obtained from ANCOVA (adjusted for baseline values and mean of fructose intake).

Table 5. Hepatic steatosis and fibrosis and their changes in the curcumin-piperine and placebo groups at baseline and after 12 weeks

Variables	Curcumin-piperine group (n=30)				Placebo group (n=29)				p-value ^b	p-value ^c
	Before intervention	After intervention	Change (percentage change)	p-value ^a	Before intervention	After intervention	Change (percentage change)	p-value ^a		
Fibrosis score (kPa)	5.95±1.94	5.39±1.30	-0.56±1.43 (-9.41%)	0.041	5.81±1.57	5.64±1.39	-0.2±0.96 (-2.92%)	0.256	0.215	0.324
Steatosis score (dB/m)	311.23±33.96	305.06±39.87	-6.61±31.00 (-1.98%)	0.285	304.90±42.43	302.27±44.35	-4.68±44.74 (-0.86%)	0.577	0.982	0.851
Steatosis percent (%)	68.46±18.79	64.83±21.12	-3.63±17.57 (-5.30%)	0.267	61.93±26.32	61.03±24.69	-2.41±24.69 (-1.45%)	0.636	0.813	0.921

Values are mean±standard deviation. a Obtained from paired sample T test. b Obtained from ANCOVA (adjusted for baseline values). c Obtained from ANCOVA (adjusted for baseline values and mean of fructose intake)

Discussion

The 12-week study in NAFLD patients demonstrated that participants in the intervention group experienced statistically significant reductions in weight (-1.63%), waist circumference (-2.32%), BMI (-1.66%), and hepatic fibrosis (-9.41%). However, it is important to note that while the changes in weight and anthropometric indices were statistically significant, their clinical significance may be limited. Furthermore, a comparison between the intervention and control groups revealed no statistically significant differences for these measures, nor for other biochemical markers, including FBG, TC, TG, LDL-C, HDL-C, ALT, AST, and hepatic steatosis.

With respect to hepatic enzymes, in a recent meta-analysis study by Vajdi et al. in 2024, it was found that curcumin supplementation was able to significantly reduce ALT and AST levels, but no such effects were observed in the case of curcumin-piperine supplementation (Vajdi et al. 2024) that the findings of Vajdi et al. study confirm the results of the present study. Regarding the lipid profile, total cholesterol levels increased in both the curcumin-piperine and placebo groups (6.59% vs. 2.26%, respectively); however, this increase reached statistical significance only in the intervention group. LDL-C levels showed a significant rise in both groups (14.48% in the curcumin-piperine group vs. 7.60% in the placebo group), yet the between-group comparison revealed no significant difference, suggesting that the curcumin-piperine supplementation was not more effective than placebo. In other human and animal studies, curcumin supplementation was reported to improve the lipid profile, liver enzymes and FBG (fasting blood glucose) in patients with NAFLD and other metabolic diseases (Alwi et al. 2008; Jazayeri-Tehrani et al. 2019; Mirhafez et al. 2021; Rahmani et al. 2016; Saadati et al. 2019a; Soliman 2005; Yuan et al. 2019). A meta-analysis by Khalili et al. in 2022, showed that curcumin supplementation significantly reduced

AST, TC, TG, and FBG levels but had no significant effect on improving BMI, HDL-C, LDL-C, or ALT (Khalili and Nammi 2022). On the other hand, in contrast to the present study, in the meta-analysis by Hosseini et al., it was found that curcumin-piperine supplementation significantly reduced TC and LDL-C in people with metabolic syndrome (Hosseini et al. 2023). The increased levels of TC and LDL-C in present study may have been contributed to by the significantly higher fructose intake in the intervention group compared with the placebo group (Table 2) (Schaefer et al. 2009; Zhang et al. 2013). Higher fructose intake can lead to increased liver fat, VLDL-C, TG, apo B100 (the main LDL apoprotein), and CRP (C-reactive protein) with negative effects on hepatic metabolism. Possible mechanisms of the effect of fructose on lipid profile include its inhibitory effect on LDL receptors, hyperglycemia and decreased insulin sensitivity (Jameel et al. 2014; Schaefer et al. 2009; Stanhope et al. 2011). However, this finding does not negate the conclusion that the curcumin-piperine preparation was ineffective in comparison to placebo in modifying NAFLD parameters.

The 12-week supplementation with curcumin-piperine significantly reduced weight (-1.63%), waist circumference (-2.32%), and BMI (-1.66%) within group, while no significant difference was observed compared with the placebo group. Based on the provision of identical dietary and physical activity recommendations to both groups, as well as the monitoring of food intake and physical activity at the beginning, middle, and end of the study, it is noteworthy that there was no significant difference in weight loss or BMI between the two groups, as indicated in Table 2. Consequently, the weight loss observed in both groups could be attributed to individuals' increased awareness of their illness, resulting in improved dietary choices and enhanced physical activity compared to their previous habits. However, it is also plausible that the weight

loss experienced by participants in both groups, regardless of the reason, contributed to the lack of statistical significance in the current study. Therefore, further research is warranted in this field to gain a deeper understanding. Previous studies have reported an improvement of anthropometric indices with curcumin-piperine supplementation (Hariri and Haghghatdoost 2018; Jazayeri-Tehrani et al. 2019; Panahi et al. 2017c), whilst other studies have not shown any effect (Hariri and Haghghatdoost 2018; Saadati et al. 2019a; Safari et al. 2021). This highlights the need to undertake robust, blinded studies with an appropriate placebo as in this study, to circumvent potentially misleading results. The mechanism of action by which curcumin has been proposed to affect anthropometric indices is the inhibition of adipocyte activity, fat mass, and lipogenesis (Jazayeri-Tehrani et al. 2019; Jin et al. 2018; Zhang et al. 2013), whilst increasing lipolysis, energy consumption, brown adipose tissue activity and probiotic-like activities (Jazayeri-Tehrani et al. 2019; Jin et al. 2018; Zhang et al. 2013).

After 12 weeks of curcumin-piperine supplementation hepatic fibrosis reduced within the intervention group (-9.41%), but did not differ significantly compared to placebo. A reduction in hepatic fibrosis should have been reflected in a decrease in hepatic steatosis that was not seen, and further supports that curcumin-piperine may be ineffective adjunct treatment for NAFLD. Few studies have studied the effect of curcumin supplementation on hepatic steatosis and fibrosis measured by the precision and specificity of the fibroscan method. Studies conducted in 2018 and 2019 by Saadati et al. using the fibroscan showed that daily supplementation with 1500 mg of curcumin alone for 12 weeks could lead to a significant reduction in liver fibrosis and steatosis (Saadati et al. 2019a; Saadati et al. 2018; Saadati et al. 2019b), though curcumin supplementation did not add

value to the effect of diet (Saadati et al. 2018), in accord with the study here. Other studies have reported positive effects of curcumin supplementation using ultrasound to evaluate liver status (Jazayeri-Tehrani et al. 2019; Panahi et al. 2017c; Rahmani et al. 2016). Insulin resistance and consequent hyperglycemia are among the important pathophysiological mechanisms of NAFLD (Carr et al. 2016). Increasing the level of available glucose leads to increased non-enzymatic glycosylation and formation of advanced glycosylation end products (AGEs). Subsequent, binding of AGEs to their cellular receptors leads to the induction of different signal pathways, production of proinflammatory mediators, and increased oxidative stress and cell growth (Ramasamy et al. 2009; Stefanska 2012). AGEs also cause liver fibrosis by increasing cell proliferation and activating liver stellate cells. Evidence from *in vivo* and *in vitro* studies has shown that curcumin prevents hepatic fibrosis due to hyperglycemia and hypercholesterolemia *via* inhibiting the activation of liver stellate cells (Kang et al. 2002; Kang and Chen 2009; Stefanska 2012; Tang and Chen 2010), and it can prevent the progression of liver damage and fibrosis in obese mice by reducing the size of adipocytes, the number of macrophages and mast cells, and the replacement of collagen in adipose tissue (Jekal et al. 2015; Saadati et al. 2018). However, it would appear that the positive effects of curcumin *in vitro* and in animal models may not translate in humans. One important reason that other studies may have found an effect of curcumin on NAFLD parameters is that of the dose of the preparation. A systematic review reported that beneficial effects of curcumin supplementation on disease severity were observed only in clinical studies administering doses of 1000 mg or higher (Mansour-Ghanaei et al. 2019); however, when curcumin is consumed alone and at a dose of 2 g, serum levels are very low or undetectable suggesting that if curcumin is having an effect it is perhaps not a direct

systemic effect but rather indirect and peripheral effect, possibly through the microbiome (Scazzocchio et al. 2020).

The strengths of the study included that it was a robust design with an appropriate placebo and is one of the very few studies to investigate the effect of curcumin supplementation on NAFLD using the fibroscan method. Limitations of this study include that no assessment of oxidative stress or inflammatory factors was undertaken, and it was not possible to measure the progression of NAFL to NASH with the fibroscan. A dose of 500 mg curcumin may have been too low in comparison to other studies but this was offset by enhancing its bioavailability with piperine. The impact of undertaking the study during the COVID-19 pandemic and the resultant social stresses on individuals during this period might have impacted the study results.

Compared to placebo, curcumin-piperine supplementation did not affect any of the hepatic or biochemical markers associated with NAFLD and would not appear to be an effective adjunct therapy. Further robust studies are needed to confirm this finding given the controversy of the reported effects of curcumin in NAFLD.

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Conflicts of interest

The authors report no conflicts of interest in the course of conducting this research or in the preparation of this manuscript.

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Ethical Considerations

The study protocol received approval from the Ethics Committee of Isfahan University of Medical Sciences (ethics code:

IR.MUI.RESEARCH.REC.1398.462). The protocol was also officially registered on the Iran Registry of Clinical Trials (IRCT) website (<https://en.irct.ir/trial/43732>; IRCT registration number: IRCT20121216011763N42).

All participants provided written informed consent prior to the trial. The study was conducted in accordance with the Declaration of Helsinki and its reporting follows the CONSORT guidelines for clinical trials.

Code of Ethics

IR.MUI.RESEARCH.REC.1398.462

Authors' Contributions

The authors' accountabilities were as follows: Study design: Gh.A, A.S, M.B, S.R; Data gathering: S.R, Z.Kh, A.E; Statistical analysis: Z.H; Drafting the manuscript: S.R; Critically revised the manuscript: Gh.A, M.B, A.S, T.S. All authors have read and approved the final manuscript before submission.

Availability of data and materials

The datasets generated during the current study are available via the corresponding author (Gh.A) on reasonable request.

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