

Efficacy of curcumin plus piperine co-supplementation in moderate-to-high hepatic steatosis: a double-blind, randomized, placebo-controlled clinical trial

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CITATION

Sharifi, Shima; Bagherniya, Mohammad; Khoram, Ziba; Varzaneh, Amrollah Ebrahimi; Atkin, Stephen; Jamialahmadi, Tannaz; et al. (2023). Efficacy of curcumin plus piperine co-supplementation in moderate-to-high hepatic steatosis: a double-blind, randomized, placebo-controlled clinical trial. Royal College of Surgeons in Ireland. Journal contribution. <https://hdl.handle.net/10779/rcsi.22226068.v1>

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[10779/rcsi.22226068.v1](https://hdl.handle.net/10779/rcsi.22226068.v1)

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Efficacy of Curcuminoids plus Piperine Co-supplementation in Moderate-to-high Hepatic Steatosis: A Double-Blind Randomized Placebo-Controlled Clinical Trial

Abstract

Background & Aim: Non-alcoholic Fatty Liver Disease (NAFLD) is a global health problem that can progress to steatohepatitis and cirrhosis. Insulin resistance, dyslipidemia, obesity and inflammation, that are common risk factors for NAFLD, are reported to be improved by curcumin; therefore, the aim of this study was to determine the effect of curcumin+piperine on these risk factors, hepatic steatosis and fibrosis in NAFLD patients with moderate-to-high hepatic steatosis.

Methods: Patients diagnosed with moderate-to-high NAFLD by liver sonography were randomized to either curcumin+piperine (500 mg/day curcumin plus 5 mg/day piperine) for 12-weeks (n=30) or placebo groups (n=30). Liver fibroscan, anthropometric measurements, dietary intake, physical activity, blood pressure, lipid profile, hs-CRP, fasting blood glucose (FBG) and liver enzymes were assessed at baseline and after 12 weeks of follow-up. Intention-to-treat analysis was undertaken.

Results: Curcumin+piperine decreased waist circumference (WC) ($p=0.026$), systolic blood pressure ($p=0.001$), total cholesterol (TC) ($p=0.004$), low density lipoprotein-cholesterol (LDL-C) ($p=0.006$), FBG ($p=0.002$), alanine transaminase (ALT) ($p=0.007$) and aspartate (transaminase) AST ($p=0.012$) compared with placebo. However, fibroscan measurement did not differ between curcumin+piperine and placebo ($p>0.05$).

Conclusion: Fibroscan measurement as a marker of NAFLD improvement did not differ after 12 weeks of curcumin+piperine; however, curcumin+piperine may be considered as adjunct therapy to improve anthropometric measures, blood pressure, lipid profile, blood glucose and liver function in NAFLD patients.

IRCT registration number: RCT20121216011763N47

Keywords: Non-alcoholic Fatty Liver Disease, Fatty Liver, Curcumin, Piperine, Controlled Clinical Trial

1. Introduction

Non-alcoholic hepatic steatosis is defined as the presence of a single vacuole of fat in the hepatocyte without inflammation (steatosis) and lobular inflammation excluding alcohol consumption (1). The pathogenesis of Non-alcoholic Fatty Liver Disease (NAFLD) include elevated levels of free fatty acid (FFAs) delivery to the liver, increased synthesis of FAs in the liver and decreased oxidation of FFA, together with the synthesis of very-low-density lipoprotein (VLDL) (2, 3). Other causes include medications, metabolic abnormalities, nutritional status, Wilson disease and celiac sprue (2, 3). Worldwide prevalence rate of NAFLD is estimated to be 25.24% with the highest rate in the Middle East (4). White and Hispanic populations are more susceptible to NAFLD compared with African Americans (5). Patients with obesity, diabetes mellitus, polycystic ovary disease and metabolic syndrome are also at the risk of hepatic steatosis (6). The progression of hepatic steatosis is a slow process and characterized by chronic inflammation, degeneration, scarring and fibrosis of hepatic cells. As fibrosis develops, cirrhosis develops following which the liver cells become damaged irreversibly (7).

Lifestyle modification focusing on a healthy diet and regular physical activity with weight reduction is the first line treatment of hepatic steatosis. Currently there is no approved pharmacological treatment for hepatic steatosis (8); therefore, finding new compounds to improve liver status for patients with hepatic steatosis is of therapeutic importance. Medicinal plants have been shown to have therapeutic benefit in differing disease states and have been used for centuries in different traditional medicine systems (9). The turmeric plant (*Curcuma longa* L.) has been used for hundreds of years as a food spice in Asian countries, as well as for its medicinal properties (10).

Curcumin is the main polyphenol compound of turmeric that has several pharmacological effects including antioxidant and anti-inflammatory, immunomodulatory, anti-Alzheimer, anti-tumor, anti-ischemic, anti-hyperlipidemic, analgesic and hypouricemic activities (11-14). There are several studies reporting that curcumin can modulate the expression of genes and the activity of enzymes involved in lipid metabolism, resulting in reduced plasma concentrations of cholesterol and triglycerides, and increased high density lipoprotein-cholesterol (HDL-C) levels (15). The low bioavailability of curcumin can be enhanced with the coadministration with piperine (16), an alkaloid compound extracted from the seeds of *Piper nigrum*.

Several clinical trials report that curcumin may have a promising role in improvement of NAFLD (17, 18). Nevertheless, to the best of our knowledge, there is no study to investigate the effect of curcumin+piperine supplementation on hepatic steatosis, assessed by using the fibroscan as a more reliable method its diagnosis. Biopsy is the gold standard method for the diagnosis of NAFLD; however, it is invasive with a recognized morbidity and mortality. The fibroscan is a reliable and non-invasive method that can replace biopsy in the diagnosis and for patient follow-up (19). Given the previous reports on the potential beneficial effects of curcumin, we hypothesized that the enhanced bioavailability of curcumin+piperine may show utility in improving liver function in patients with moderate-to-high hepatic steatosis patients staged by the fibroscan.

2. Material and Methods

2.1 Study design and participants

This was an interventional, parallel randomized, double blind, placebo controlled clinical trial in adult patients (18-65 years) with moderate-to-high hepatic steatosis referred to the Isfahan

Endocrine & Metabolism Research Center (IEMRC), Isfahan, Iran from September 2020 to May 2021. The inclusion criteria were males and females aged 18-65 years with moderate-to-high hepatic steatosis, diagnosed by a gastroenterologist based on the findings of fibroscan sonography. Exclusion criteria included individuals with a history of alcohol use, other chronic diseases, malignancies, consumption of antioxidant supplements, metformin, corticosteroids, urodeoxycholic acid, lithium, tamoxifen, phenytoin, methotrexate, a history of bariatric surgery or weight loss of more than 5% of their body weight in the preceding 12 months and pregnancy. All participants give written informed consent. Demographic characteristics, family history of NAFLD, smoking and medication history were collected from all patients. Primary outcomes of the study were fibroscan results, liver function tests, FBS, lipid profile, blood pressure, hs-CRP, and anthropometric measures. Dietary factors and physical activity were secondary outcomes of our study.

The Ethics Committee of National Institute for Medical Research Development (NIMAD) approved the protocol of this study (ethics code: IR.NIMAD.REC.1398.306) and the study was undertaken in accord with the Declaration of Helsinki standards and guidelines. Our approved and registered study protocol can be found at IRCT.ir (No. IRCT20121216011763N47).

2.2 Sample size

Based on a 10-unit difference in the mean fibroscan controlled attenuation parameter (CAP) score with a power of 80% ($\beta = 20\%$) and $\alpha=0.05$, a sample size of 25 for each group was calculated. Thirty moderate-to-high NAFLD patients in each curcumin+piperine and placebo groups were recruited to account for a 20% drop-out rate.

2.3 Randomization, intervention and blinding

NAFLD patients were equally assigned to either curcumin+piperine or placebo groups using block randomization. Stratification of blocks were based on gender and body mass index (BMI). Therefore, four blocks were generated by Random Allocation Software (RAS) (20) and identified by the letters A, B, C, and D.

Participants in the intervention and placebo groups received one capsule daily of 500 mg curcumin plus 5 mg piperine or an identical capsule containing maltodextrin (Sami Labs Limited (Bangalore, India)), for a duration of 12-weeks. According to the US Food and Drug Administration (FDA), curcuminoid is “Generally Recognized as Safe” (GRAS) (21). Capsules were placed in the packages and then labeled according to the generated blocks. Each participant received the capsules based on the order code assigned for them. To confirm the compliance of individuals with the intervention, capsule counting in each package was undertaken (consuming at least 90% of the capsules during the study period) and weekly phone interviews were performed.

2.4 Liver fibroscan

As a non-invasive method, fibroscan (Echosens, France) was used to assess the amount of hepatic steatosis and fibrosis before and after the intervention. The fibroscan was conducted by an expert who was blinded to the intervention. Lying supine, an ultrasound-like probe was placed over the liver area in the right mid-axillary line. At least 2 hours of fasting was observed before the procedure. The fibroscan score was reported as kilopascal units, ranging from 2.4 to 75.4 kPa (22). Histopathological stage of fibrosis (Metavir score) was defined as follows: F0, normal; F1, portal fibrosis without septa; F2, portal fibrosis few fibrotic septa; F3, portal fibrosis with numerous

septa; F4, cirrhosis. There is a significant correlation between the fibroscan score and Metavir stage. Fibroscan cut-offs of F1, F2, F3, and F4 stages are 4.95, 6.25, 10.1, and 17.15 kPa, respectively (23). Controlled Attenuation Parameter (CAP) measures hepatic steatosis (fat content of liver) independently from the presence of fibrosis. CAP was also measured by fibroscan. Steatosis stages were categorized based on steatosis percent as follows: S0, < 5%; S1, 5%-33%; S2, 34%-66%; and S3, $\geq 67\%$ (24).

2.5 Anthropometric and blood pressure measurements

Before and after the intervention, weight and height of participants were measured respectively with the accuracy of 0.1 kg and 0.1 cm, respectively using the calibrated scales (Seca, Hamburg, Germany) in the standing position with light clothes and no shoes and then BMI was calculated as weight (kg) divided by height (m) squared. A tape measure was used to measure waist circumference to the nearest 1 mm at a point midway between the costal margin and the iliac crest. Systolic and diastolic blood pressures were measured in the seated position on the right upper arm, resting at chest height using a calibrated mercury sphygmomanometer (Riester; Diplomat) in the morning before and after the trial with a precision of 3 mmHg. Two minutes after the first measurement, the second measurement was performed, and the mean of these measurements was reported as the final blood pressure.

2.6 Assessment of dietary intake and physical activity

To assess the dietary status of patients, a three-day food record was filled at the beginning and end of the study. Using the data from these records, dietary and calorie intakes were calculated according to the Iranian updated Nutritionist IV software (San Bruno, CA, USA).

The participants' physical activity was reported as metabolic equivalents (MET) per minutes per week (METs, min/week) (25) before and after the trial by completing an international physical activity questionnaire in its short form (IPAQ-SF) (26).

2.7 Biochemical measures

Fasting samples of venous blood were taken before and after the trial and the collected samples were centrifuged to separate the serum following which they were kept at -80 °C until batch analysis. Enzymatic methods using the Pars Azmun kits (Iran, Karaj) were used to measure serum triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and high sensitivity C-reactive protein (hs-CRP).

2.8 Statistical analysis

The intention-to-treat (ITT) analysis was performed. Kurtosis, skewness and their corresponding z values, and standard deviation (SD) were calculated to assess the normality as described previously (27). Frequency (percentage), mean \pm SD, and geometric mean (95% CI) were expressed in the cases of categorical, normally- and non-normally distributed numerical data, respectively. The between and within-group mean differences were compared by using the independent and paired sample t-tests, respectively. In the cases of non-normal quantitative data, Mann-Whitney-U and Wilcoxon signed-ranks tests were used, respectively. The qualitative variables were compared implementing Fisher's exact test. To extract the effect sizes with the baseline and confounding adjustments analysis of covariance (ANCOVA) was used. In the cases of non-normally distributed data, quantile regression was used. The appropriate graphs were generated using Graph Pad Prism version 9.0 (La Jolla, CA, USA). p-value of less than 0.05 was

considered to be statistically significant. All analyzes were conducted performing STATA version 16.0 software (College Station, TX, USA).

3. Results

3.1 Baseline characteristics, dietary factors, and physical activity

A total of 72 patients were initially assessed to be included in the current study, of whom 60 patients fulfilled the inclusion and exclusion criteria. The CONSORT flowchart is illustrated in **Figure 1**. There were no significant differences between the curcumin+piperine and placebo groups in terms of gender, age, family history of NAFLD, education status, and smoking (**Table 1**).

There were no significant differences between the two groups at the baseline in terms of energy, protein, carbohydrate, cholesterol, saturated fat, PUFA, fiber intakes, and physical activity as shown in **Table 2**. However, MUFA and total fat intakes were significantly higher in the placebo group (P -value=0.013 and P -value=0.034, respectively). There were significant decreases within the curcumin+piperine group after 12-weeks in terms of energy, protein, carbohydrate, total fat, saturated fat, and MUFA, but no difference in other variables (**Table 2**).

3.2 Metavir scores, steatosis stages, steatosis percent, and fibroscan results

Curcumin+ piperine supplementation had no effect on the Metavir score or steatosis stage within and between the groups (**Table 3**). There was no difference within and between groups in changes in the fibroscan patient score (Mean differences \pm SE: -0.8 ± 0.14 in the intervention group and -

0.32 ± 0.24 in the placebo group) and steatosis percent (Mean differences ± SE: -11.53 ± 4.13 in the intervention group and -2.67 ± 3.51 in the placebo group) (p -values >0.05) (**Figure 2 A and B**).

3.3 Anthropometric, biochemical, and blood pressure measures

Weight, BMI, and WC significantly decreased in the curcumin+ piperine group after 12-week of intervention. Moreover, following adjustment of baseline values significant decreases in weight, BMI, and WC were shown for the curcumin+ piperine group compared to placebo (p -values=0.011, 0.017, and 0.003, respectively) (**Table 4**). However, only WC was significantly reduced following age, gender, changes in physical activity and calorie intake adjustment (p -value=0.026).

Systolic blood pressure in the curcumin+ piperine group was significantly decreased after 12-week of supplementation and this decrease was also significant after baseline values and confounding adjustments in comparison with the placebo group (p -values= 0.023, 0.003, and 0.001, respectively). Mean change of diastolic blood pressure did not differ between and within the groups (**Table 4**).

There was a significant decrease in TG, TC, and LDL after 12-week of curcumin+ piperine intervention within and between the groups compared with the placebo group (p -value <0.05). However, serum HDL-C did not differ within and between groups (p -values=0.288 and 0.544, respectively) (**Table 4**).

FBG was decreased after 12-week within the curcumin+ piperine group. ANCOVA tests with adjustment of baseline values and confounding variables showed a decrease in FBG for curcumin+ piperine supplementation compared to placebo (p -values<0.001 and 0.002, respectively) (**Table 4**).

Paired-t test showed that curcumin+pipерine after 12-week of supplementation significantly improved liver function (p -value=0.039 for ALT and p -value=0.006 for AST), conversely serum ALT in the placebo group significantly increased after 12-weeks of trial duration (P -value= 0.011). ANCOVA tests showed the beneficial effect of curcumin+ pipерine on liver function after baseline values and confounding adjustment, in comparison with the placebo group (P -value <0.05) (**Table 4**).

Within group serum hs-CRP significantly decreased for both curcumin+ pipерine, and placebo groups (p -values <0.001 and =0.007, respectively), but did not differ between groups. (**Table 4**).

3.4 Side effects

Curcumin+pipерine had no side effects in any patient during the study.

4. Discussion

This clinical trial investigated the hepatoprotective effects of curcumin + piperine compared to placebo in 60 patients with moderate-to-high NAFLD patients and showed that 500 mg/day curcumin plus 5 mg/day piperine supplementation for a 12-week duration was not effective in alleviating Metavir score, steatosis stage and percent, nor the fibroscan patient score. Fibroscan as a reliable method of assessment was used for the first time to evaluate the hepatoprotective effects of curcumin supplementation. Anthropometric measures, systolic blood pressure, TG, TC, LDL-C, FBG, and liver function were significantly improved by curcumin+piperine after 12 weeks.

To increase the accuracy of the results, all possible confounders were assessed. Groups were well matched for age, gender, family history of NAFLD, education level, smoking and baseline values of studied markers.

This is the first study to evaluate the effect of curcumin+piperine supplementation on hepatic fibrosis and steatosis assessed by fibroscan. In accord with our results, Saadati et al. reported that curcumin had no significant effect on hepatic fibrosis and steatosis (28). The strength of our study as compared with this previous study was adjustment of the confounders by the ANCOVA test. However, with this adjustment curcumin+piperine supplementation did not show any significant effect on the fibroscan results. Although, they administered curcumin in a high dosage (1500 mg/day) compared with our study, we added piperine to increase the bioavailability of curcumin. A major difference between these two studies was the study population; Saadati et al. included NAFLD patients in the initial stages whilst moderate-to-high NAFLD patients were investigated in our study. Additional studies with a focus on patients with non-alcoholic steatohepatitis (NASH) would be warranted to determine if curcumin+piperine had a beneficial effect on NAFLD/NASH patients. It is of interest that the liver function markers of ALT and AST were improved over the

12 week period in this study suggesting that the study was too short a duration to see the effects with the fibroscan and longer studies would be necessary.

The anti-obesity effects of curcumin+piperine were possibly due to its effects on decreasing energy intake. Curcumin can induce glucagon-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY) secretion, as the appetite-related hormones, resulting in suppression of appetite (29). Other possible anti-obesity mechanisms of curcumin are down-regulation of Janus Kinase (JNK) (30), reduction of cortisol in adipocytes (31), inhibition of adipocyte differentiation through suppression of transcription factor Peroxisome Proliferator-Activated Receptor- γ (PPAR- γ), and enhancement of monophosphate-activated protein kinase and consequently lipolysis (32, 33). JNK is one of the main mediators of metabolic disturbances such as insulin resistance and inflammation in many tissues (34). Elevated levels of cortisol in adipocytes induces central obesity (35). Different trials have examined the anti-obesity effects of curcumin, in which the pooled results in a meta-analysis showed that curcumin significantly decreased weight and BMI (36).

Isolated systolic blood pressure is more common in NAFLD patients (11.6%) than isolated diastolic blood pressure (5%) (37), as seen in our patients. Therefore, the significant effect of curcumin on decreasing systolic blood pressure, but not diastolic blood pressure, seen in our patients might be related to this fact. The main anti-hypertension mechanism of action of curcumin is its improving effect on nitric oxide bioavailability that contributes to vasodilation (38). Moreover, curcumin can lead to downregulation of adhesion molecules involved in endothelial dysfunction (39).

The anti-hyperlipidemic effect of curcumin has been reported before and several studies have confirmed this effect in different health conditions (40-42). Jarhahzadeh et al. reported that turmeric could reduce TG and LDL-C but not TC levels in NAFLD patients (43). In contrast,

Saadati et al. showed that curcumin supplementation decreased only serum cholesterol as compared with placebo group (28). Results similar to our findings on the lipid profile were reported by Panahi et al. with 200 mg/day curcumin administration for a 8-week duration on NAFLD patients (44). Pooled-analysis on nine RCTs revealed that curcumin supplementation reduces TC, LDL-C but not TG and HDL-C in NAFLD patients (17). However, curcumin had lowering effects on TG in some demographic subgroups suggesting potential ethnic differences. Interaction of curcumin with some targets including PPAR- α , PPAR- γ , lipoprotein lipase, and cholesteryl ester transfer protein (CETP) contribute to its anti-hyperlipidemic functions. Curcumin acts as the natural agonist of PPAR- γ ; through which suppresses the gene expression of LDL-C receptor (45, 46).

The beneficial effect of curcumin on FBG level in NAFLD patients has been previously shown (11, 47), as well in a meta-analysis of nine studies (17). However, a study by Chashmniam et al. with low dosage and short duration of curcumin reported a controversial improvement in NAFLD patients (48). Ghorbani et al. has reported on the mechanistic evidence for the anti-hyperglycemic effects of curcumin. The main suggested mechanisms are inhibitory effects of curcumin on hepatic gluconeogenesis and the hyperglycemia-induced inflammatory state, as well as its up-regulatory effects on PPAR that can contribute to a decrease in insulin resistance and AMPK, which is associated with a decrease in hepatic gluconeogenesis and glycogenolysis. In addition there are stimulatory effects on glucose uptake by up-regulation of glucose transporters, and increased insulin sensitivity by regulation of insulin receptors and mediators involved in insulin signaling (49).

Mean hs-CRP in our patients was in the low-normal range (50). Therefore, the slight decrease in both groups, which resulted in a statistically significant result, is likely not clinically significant.

Saadati et al. also reported that curcumin had no significant effect on the hs-CRP level despite decreases in both curcumin and placebo groups (18). The main anti-inflammatory mechanism of action of curcumin is related to its inhibitory effects on nuclear factor Kappa-B (NF- κ B) as the main regulator of inflammatory cytokines (18).

A meta-analysis by Mansour-Ghanaei et al. pooling four RCTs reported a significant decrease in AST level in an 8-week duration of supplementation (51). In accord with two studies by Panahi et al. with 1000 mg/day for 8-week (52) and Rahmani et al. with 500 mg/day for 8-week of curcumin (53) reported its beneficial effects on liver functions. Navekar et al. who administered turmeric for 12-week did not report any significant result (54). Also, non-significant effects of curcumin on liver enzymes in Moradi-Kelardeh et al. study might be related to their low administered dosage (80 mg/day) (55). The beneficial effect of curcumin on liver enzymes may be related to its anti-oxidant and anti-inflammatory natures (56).

In addition to increasing the bioavailability of curcumin, the biological effects of piperine cannot be ignored. These actions include anti-hyperglycemic, anti-oxidant, anti-diarrheal, antibacterial, and anti-parasitic activities (57). There are several molecular targets of piperine including PPAR- γ , NF- κ B, AMPK, JNK, and inflammatory cytokines (58). Therefore, synergistic effects of piperine and curcumin on NAFLD can be considered in the future studies, perhaps comparing directly with curcumin alone.

The present study has some limitations. First, some dietary factors were statistically different at the baseline between two groups including total fat and MUFAs. However, adjusting the dietary intakes with ANCOVA minimized their effects on final results. Second, some data were non-normally distributed and their analysis were performed with non-parametric tests, which have less statistical power than parametric tests. In addition, the improvement in liver function may suggest

that a longer duration of the study would be needed in order to see changes in the fibroscan measurement. However, our study had some strengths. First, this is the first study to investigate the effect of curcumin+piperine on hepatic steatosis by fibroscan as a more reliable method of assessment. Second, the possible effects of confounders were minimized with appropriate statistical tests.

5. Conclusion:

Fibroscan measurement as a marker of NAFLD improvement did not differ after 12 weeks of curcumin+piperine; however, curcumin+piperine may be considered as adjunct therapy to improve anthropometric measures, blood pressure, lipid profile, blood glucose and liver function in NAFLD patients.

Acknowledgment:

The authors would like to thank National Institute for Medical Research Development (NIMAD) and Isfahan Endocrine & Metabolism Research Center (IEMRC) for supporting this study.

Funding:

This research was funded by National Institute for Medical Research Development (NIMAD) (grant number: 987596).

Authors Contribution:

S. S. and G. A. designed the study, collected and analyzed the data, and prepared the manuscript. M. B., Z. K., S.L.A and A. E. V. collected the data and critically revised the manuscript. A. S. designed the study and edited the manuscript.

Conflict of Interest:

The authors declare no conflict of interest.

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Table 1: Baseline characteristics of subjects in the Curcumin+Piperine and Placebo groups

Characteristics	Curcumin+Piperine (n=30)	Placebo (n=30)	P-value
Age (years)*	43±9.72	47.5±13.31	0.140
Sex (n/%)			0.430
Male	20 (67)	16 (53)	
Female	10 (33)	14 (47)	
Family History of NAFLD (n/%)			1.000
Yes	13 (43)	12 (40)	
No	17 (57)	18 (60)	
Education (n/%)			0.875
Under diploma	15 (50)	16 (53)	
Undergraduate	12 (40)	10 (33)	
Graduate	3 (10)	4 (14)	
Smoking (n/%)			0.333
Yes	8 (27)	4 (13)	
No	22 (73)	26 (87)	

* Value is presented as mean ± SD

P values are for comparison of variable between zinc and placebo groups (all analyzed by Fisher's exact two-sided test except age that was analyzed by t-independent test).

Table 2. Dietary factors and physical activity in the Curcumin+Piperine and Placebo groups

	Curcumin+Piperine (n=30)			Placebo group (n=30)			<i>P</i> -value		
Variable	Baseline	Week 12	Mean Change	Baseline	Week 12	Mean change	<i>P</i> ¹	<i>P</i> ²	<i>P</i> ³
Energy (Kcal/d)	2474 ± 215.73	2240.19 ± 312.64	-233.82	2571.13 ± 324.87	2538.7 ± 321.35	-32.43	0.179	0.001	0.001
<i>P</i> ⁴	<0.001		(-324.33, -143.32)	0.344		(-101.43, 36.57)			
Protein (g/d)	83.01 ± 9.77	76.81 ± 11.49	-6.2	83.9 ± 12.31	82.95 ± 11.64	-0.95	0.758	0.044	0.127
<i>P</i> ⁴	0.010		(-10.81, -1.59)	0.711		(-6.13, 4.23)			
Carbohydrate (g/d)	372.43 ± 41.74	334.19 ± 60.85	-38.23	378.79 ± 59.25	377.64 ± 56.53	-1.15	0.632	0.006	0.004
<i>P</i> ⁴	<0.001		(-57.91, -18.54)	0.887		(-17.54, 15.24)			
Total Fat (g/d)	72.47 ± 10.39	66.23 ± 10.21	-6.24	80.04 ± 16.05	77.37 ± 15.72	-2.67	0.034	0.002	0.297
<i>P</i> ⁴	0.003		(-10.11, -2.36)	0.351		(-8.43, 3.09)			
Cholesterol (mg/d)	280.45 ± 105.62	274.75 ± 136.69	-5.7	330.86 ± 161.9	244.07 ± 86.62	-86.79	0.159	0.304	0.085
<i>P</i> ⁴	0.855		(-68.84, 57.43)	0.017		(-157.22, -16.35)			
Saturated Fat (g/d)	23.22 ± 3.63	21.52 ± 4.4	-1.7	24.99 ± 5.51	24.93 ± 5.03	-0.05	0.149	0.007	0.267
<i>P</i> ⁴	0.062		(-3.49, 0.09)	0.967		(-2.47, 2.37)			
MUFAs (g/d)	23.67 ± 3.99	21.93 ± 3.16	-1.74	27.68 ± 7.42	26.56 ± 6.44	-1.12	0.013	0.001	0.690
<i>P</i> ⁴	0.004		(-2.9, -0.59)	0.450		(-4.1, 1.87)			
PUFAs (g/d)	18.19 ± 4	16.3 ± 3.29	-1.88	19.48 ± 4.57	17.09 ± 4.56	-2.38	0.249	0.445	0.669
<i>P</i> ⁴	0.005		(-3.15, -0.61)	0.022		(-4.4, -0.36)			
Fiber (g/d)	12.68 ± 2.71	13.66 ± 2.24	0.98	13.09 ± 2.29	12.72 ± 4.96	-0.38	0.524	0.349	0.282
<i>P</i> ⁴	0.102		(-0.21, 2.17)	0.735		(-2.63, 1.88)			

Physical activity ^b	707.62 ± 308.65	678.83 ± 276.21	-28.79	901.85 ± 503.03	841.57 ± 483.72	-60.28	0.078	0.116	0.514
(METs, min/week)			(-83.43, 25.84)	0.141		(-141.69, 21.12)			
<i>P</i> ⁴	0.290								

^a Mean ± SD and Mean Change (95 % CI) are presented for normally distributed data

Mean change for the 12-week period

*P*¹: p-values for comparison of variables between two groups by independent t-test at baseline

*P*²: p-values for comparison of variables between two groups by independent t-test at week 12

*P*³: p-values for comparison of mean change of variables between two groups by independent t-test

*P*⁴: p-values for comparison of variables within groups by paired t-test

Table 3: Metavir scores and steatosis stages in the Curcumin+Piperine and Placebo groups

Variable	Curcumin+Piperine (n=30)		Placebo group (n=30)		Percent Changes (%)	
	Before	Week 12	Before	Week 12	Intervention	Placebo
Metavir Score (n/%)						
F0	13 (43.3)	21 (70)	13 (43.3)	16 (53.3)	26.7	10
F2	3 (10)	1 (3.3)	3 (10)	2 (6.7)	-7.7	-3.3
F3	1 (3.3)	0 (0)	0 (0)	0 (0)	-3.3	0
F0F1	13 (43.3)	8 (26.7)	13 (43.3)	12 (40)	-16.6	-3.3
F3F4	0 (0)	0 (0)	1 (3.3)	0 (0)	0	-3.3
P-values	0.146 ^a		0.791 ^a		1.000 ^b	0.274 ^c
Steatosis Stage (n/%)						
S0	0 (0)	1 (3.3)	0 (0)	0 (0)	3.3	0
S1	0 (0)	4 (13.3)	0 (0)	0 (0)	13.3	0
S2	8 (26.7)	8 (26.7)	8 (26.7)	8 (26.7)	0	0
S3	22 (73.3)	17 (56.7)	22 (73.3)	22 (73.3)	-16.6	0
P-values	0.065 ^a		1.000 ^a		1.000 ^b	0.127 ^c
Number (%) and Percent Change are presented for data. Percent change for the 12-week period. ^a p-values for comparison of variables within groups by Sign test. ^b p-values for comparison of variables between two groups by Fisher’s exact test at baseline. ^c Effect of intervention on variables based on changes (positive change, no change, and negative change) in each group by Fisher’s exact test.						

Table 4. Anthropometric parameters, biochemical measures, and blood pressure in the Curcumin+Piperine and Placebo groups

Variable	Curcumin+Piperine (n=30)	Placebo group (n=30)	Mean Difference (95% CI), <i>P</i>
Weight (kg)			
Baseline	83.27 ± 10.83	84.23 ± 14.58	-0.97 (-7.61, 5.67), 0.772 ^b
Week 12	81.23 ± 70.73	84.07 ± 15.19	-2.83 (-9.64, 3.98), 0.011 ^c , 0.125 ^d
Mean Change (95% CI), <i>P</i> ^a	-2.03 (-3.21, -0.85), 0.001	-0.17 (-0.99, 0.66), 0.682	
BMI (kg/m ²)			
Baseline	29.46 ± 3.34	29.36 ± 4.29	0.1 (-1.89, 2.09), 0.921 ^b
Week 12	28.77 ± 3.61	29.28 ± 4.39	-0.51 (-2.58, 1.57), 0.017 ^c , 0.141 ^d
Mean Change (95% CI), <i>P</i> ^a	-0.69 (-1.1, -0.28), 0.002	-0.08 (-0.37, 0.21), 0.569	
WC (cm)			
Baseline	101.37 ± 8.93	105 ± 11.9	-3.63 (-9.08, 1.81), 0.187 ^b
Week 12	99.13 ± 9	104.9 ± 11.65	-5.77 (-11.14, -0.39), 0.003 ^c , 0.026 ^d
Mean Change (95% CI), <i>P</i> ^a	-2.23 (-3.61, -0.85), 0.002	-0.1 (-0.68, 0.48), 0.728	
SBP (mmHg)			
Baseline	12.13 ± 0.43	12.43 ± 0.9	-0.3 (-0.66, 0.64), 0.107 ^b
Week 12	11.97 ± 0.32	12.53 ± 0.82	-0.57 (-0.89, -0.24), 0.003 ^c , 0.001 ^d
Mean Change (95% CI), <i>P</i> ^a	-0.17 (-0.31, -0.02), 0.023	1.00 (-0.17, 0.37), 0.448	
DBP (mmHg)			
Baseline	8 ± 0.37	8.03 ± 0.32	-0.03 (-0.21, 0.15), 0.711 ^b
Week 12	7.97 ± 0.41	7.97 ± 0.41	0.00 (-0.21, 0.21), 0.963 ^c , 0.389 ^d
Mean Change (95% CI), <i>P</i> ^a	-0.03 (-0.22, 0.15), 0.712	-0.07 (-0.26, 0.13), 0.489	
Serum TG (mg/dl)			
Baseline	152.11 ± 63.02	167.15 ± 71.56	-15.04 (-49.89, 19.81), 0.391 ^b

Week 12	124.07 ± 44.3	169.77 ± 81.45	-45.7 (-79.8, -11.6), 0.01 ^c , 0.072 ^d
Mean Change (95% CI), <i>P</i> ^a	-28.04 (-43.57, -12.52), 0.001	2.61 (-25.76, 30.99), 0.852	
Serum TC (mg/dl)			
Baseline	186 ± 46.41	188.58 ± 40.48	-2.58 (-25.09, 19.92), 0.819 ^b
Week 12	164.4 ± 37.08	186.7 ± 46.95	-22.3 (-44.16, -0.44), 0.009 ^c , 0.004 ^d
Mean Change (95% CI), <i>P</i> ^a	-21.6 (-33.66, -9.55), 0.001	-1.88 (-13.54, 9.77), 0.743	
Serum LDL (mg/dl)			
Baseline	117.54 ± 49.05	108.33 ± 29.46	9.22 (-11.7, 30.13), 0.381 ^b
Week 12	103.31 ± 29.2	108.48 ± 36.96	-15.18 (-32.39, 2.04), 0.013 ^c , 0.006 ^d
Mean Change (95% CI), <i>P</i> ^a	-14.24 (-28, -0.47), 0.043	10.16 (-3.5, 23.82), 0.139	
Serum HDL (mg/dl)			
Baseline	35.15 ± 12.06	36.84 ± 10.61	-1.69 (-7.56, 4.18), 0.567 ^b
Week 12	38.03 ± 9.44	39.78 ± 9.09	-1.75 (-6.54, 3.04), 0.544 ^c , 0.51 ^d
Mean Change (95% CI), <i>P</i> ^a	2.88 (-2.57, 8.33), 0.288	2.95 (-1.18, 7.07), 0.155	
Serum FBG (mg/dl)			
Baseline	88.13 ± 17.23	93.1 ± 19.12	-4.97 (-14.37, 4.44), 0.295 ^b
Week 12	76.98 ± 12	91.47 ± 15.1	-14.48 (-21.53, -7.43), <0.001 ^c , 0.002 ^d
Mean Change (95% CI), <i>P</i> ^a	-11.15 (-16.16, -6.14), <0.001	-1.63 (-8.41, 5.14), 0.626	
Serum ALT (U/L)			
Baseline	29.36 ± 10.56	24.52 ± 7.67	4.84 (0.06, 9.62), 0.047 ^b
Week 12	24.32 ± 8.74	31.24 ± 16.56	-6.93 (-13.82, -0.04), 0.007 ^c , 0.007 ^d
Mean Change (95% CI), <i>P</i> ^a	-5.04 (-9.81, -0.28), 0.039	6.73 (1.67, 11.79), 0.011	
Serum AST (U/L)			
Baseline	28.62 ± 9.48	26.18 ± 8.08	2.44 (-2.11, 6.99), 0.288 ^b
Week 12	24.32 ± 6.39	26.53 ± 7.2	-2.22 (-5.74, 1.3), 0.023 ^c , 0.012 ^d
Mean Change (95% CI), <i>P</i> ^a	-4.3 (-7.28, -1.31), 0.006	0.35 (-2.02, 2.73), 0.762	
Serum hs-CRP (mg/l)			
Baseline	0.11 (0.05, 0.24)	0.08 (0.04, 0.16)	0.03 (27), 0.505 ^b
Week 12	0.03 (0.02, 0.04)	0.03 (0.02, 0.06)	0 (0), 1.000 ^c , 0.995 ^d

Mean Change (%), P^a	-0.08 (-73), <0.001	-0.05 (-62.5), 0.007
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Abbreviations: BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FBG: fasting blood glucose; ALT: alanine transaminase; AST: aspartate transaminase; hs-CRP: high-sensitivity C-reactive protein.

Mean \pm SD and Mean Difference (95 % CI) between the groups are presented for data except hs-CRP that is presented as Geometric Mean (95% CI) and Mean Difference of geometric means (Percent Change).

Mean Changes are presented within the groups for data except hs-CRP that is presented as Mean Change of geometric means (Percent Change) for the 12-week period.

^a p-values for comparison of variables within groups by paired t-test for normally distributed variables and Wilcoxon signed-ranks test for hs-CRP.

^b p-values for comparison of variables between two groups by independent t-test for normally distributed variables and Mann-Whitney-U-test for hs-CRP at baseline.

^c ANCOVA test, adjusted for baseline values (Model 1) for normally distributed variables and Quantile regression for hs-CRP.

^d ANCOVA test, adjusted for baseline values, age, sex, changes in physical activity and calorie intake (Model 2) for normally distributed variables and Quantile Regression for hs-CRP.