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RESEARCH ARTICLE

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Curcuminoids plus piperine improve nonalcoholic fatty liver disease: A clinical trial

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) as a prevalent hepatic disease is associated with an increased risk of morbidity and mortality related to the liver and cardiovascular disease (CVD). Lifestyle modification and good metabolic control is the first line of treatment, but not always efficacious in reversing NAFLD pathogenesis. Curcumin is a dietary phytochemical with hepatoprotective activities, though its low bioavailability is considered as a major challenge for clinical applications. Therefore, in this study, in order to improve the bioavailability of curcumin, it was coadministered with piperine and we investigated the effects of this bioavailability-enhanced curcumin on serum hepatic enzymes, lipid profile, and glycemic indices in patients with NAFLD.

Methods: In this randomized controlled parallel-group trial, 70 subjects with ultrasound-determined NAFLD were randomized to either 500 mg curcuminoids coadministered with 5 mg piperine daily or placebo for 12 weeks. NAFLD severity (on the basis of sonography) and hepatic function was assessed at baseline and at the study end.

Results: Seventy subjects completed the study. Supplementation with curcuminoids plus piperine significantly reduced the hematocrit ($P = 0.027$), erythrocyte sedimentation rate ($P = 0.048$) and the serum concentrations of alanine aminotransferase ($P = 0.035$), aspartate aminotransferase ($P = 0.042$), alkaline phosphatase ($P = 0.004$), cholesterol ($P < 0.016$), low-density lipoprotein cholesterol ($P < 0.017$), Iron ($P = 0.026$), and Hemoglobin ($P = 0.025$) and increased total iron-binding capacity ($P = 0.003$). However, except albumin, changes in other parameters were not statistically different between groups. In addition, administration of curcuminoids plus piperine significantly improved NAFLD severity ($P < 0.001$), which was statistically different compared with the placebo group ($P = 0.022$). Also, the percentage of improved patients was marginally higher in the curcuminoids plus piperine group when compared with the placebo group ($P = 0.058$).

Conclusion: This study suggested beneficial effects of combined curcuminoids and piperine supplementation on disease severity in patients with NAFLD.

KEYWORDS
curcumin, hepatic enzymes, lipid profile, NAFLD severity, nonalcoholic fatty liver disease (NAFLD)

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), with the worldwide prevalence of 6%-33% in general population,[1,2] is the most common and under-diagnosed hepatic disease,[3] which include a broad spectrum of disorders like simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis and, eventually, cirrhosis.[1,3-6] It has been reported that the prevalence of NAFLD rise to 50% in patients with dyslipidemia and to 90% in diabetic patients.[2] The association between NAFLD and metabolic syndrome and thus with obesity, insulin resistance, impaired glucose tolerance, dyslipidemia, and ultimately, increased risk of morbidity and mortality related to the liver and cardiovascular disease (CVD), have been reported by several studies.[1,3,5-9] Pathogenesis of NAFLD is complex and is incompletely understood but it has been reported that it is a reversible condition.[4,10] However, there are no efficient and accessible FDA-approved pharmacological treatments for NAFLD.[1] Therefore, good metabolic control through dietary modification and increased physical activity is always the first line of recommended treatment but it is not often fully efficacious in reversing the diseases especially at advanced stages.[6,8,11] Hence, novel treatments to control or slow the progression of NAFLD are urgently needed. It has been reported that nutraceuticals have some benefits in reducing hepatic fat, transaminase levels, inflammation and oxidative burden in NAFLD.[6] Curcumin, a yellow pigment of *Curcuma longa L.* (turmeric), with proven lipid-lowering, antioxidant, anti-inflammatory, insulin-sensitizing, and anti-fibrotic properties, exhibits hepatoprotective activity and is a typical herbal compound that may be efficacious in NAFLD treatment.[1,6,10,12-20] Nevertheless, the low bioavailability of this phytochemical poses a potential challenge against the attainment of maximum therapeutic benefit.[21] Therefore, in this study, in order to improve the bioavailability of curcumin, it was coadministered with piperine and we investigated the effect of this bioavailability-enhanced curcumin on serum hepatic enzyme, lipid profile, glycemic indices, and disease severity in patients with NAFLD.

2 | MATERIALS AND METHODS

2.1 | Subjects

The study population comprised of adults referring to the Baqiyatallah Hospital (Tehran, Iran) with NAFLD diagnosed on the basis of hepatic sonography. Exclusion criteria were pregnancy or breastfeeding, viral or autoimmune hepatitis, hemochromatosis, Wilson's disease, hepatic cirrhosis, fatty liver disease because of alcohol consumption and history of cardiovascular, renal, thyroid or neoplastic diseases, alcohol or opium abuse, consumption of hypoglycemic, hypolipidemic and corticosteroid medications as well as any drug known to affect hepatic function. All patients received dietary and lifestyle advises before the start of the trial.

Eligible subjects were randomly allocated to the curcumin (500 mg/day) (n = 35) or control (n = 35) group. The patients were advised to take curcumin capsules (C3 Complex, Sami Labs Ltd, Bangalore, India) after meal for 12 weeks. Curcuminoids and placebo capsules were matched in shape, size, and color, and the color of the placebo was matched to that of curcuminoid powder. To enhance the oral bioavailability of curcuminoids, 5 mg piperine (Bioperine; Sami Labs Ltd) was added to each 500 mg curcuminoid capsule. C3 Complex preparation that was used in the present study contains the three major curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin in patented ratio.

The study was approved by the institutional Ethics committee and informed consent was obtained from participants. This trial was registered at the UMIN Clinical Trials Registry under Trial No. UMIN000033774.

2.2 | Blood sampling and biochemical measurements

Fasted blood samples were collected from the drawn from a cubital vein at baseline and after 12 weeks of supplementation. Blood samples were centrifuged for 10 minutes at a speed of 2000–1500 rpm to separate the serum. Serum samples were kept at −70°C until analyses. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and direct bilirubin, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and glucose were measured at baseline and at the end of study using routine enzymatic assays with commercial kits (Pars Azmoon, Tehran, Iran).

2.3 | Liver Doppler sonography

Hepatic fat content and the severity of hepatic steatosis was evaluated as described previously.[10]

2.4 | Statistical analysis

Statistical analyses were performed using the SPSS software version 11.5 (SPSS Inc, Chicago, Illinois). The study population size was estimated at the significance level of 95%, with a power of 80% and an effect size of 0.7 for AST and ALT. The data were expressed as mean ± SD or number (%). Within-group

comparisons were performed using paired samples t test or Wilcoxon signed-ranks test. Between-group comparisons were performed using independent samples t test or the Mann-Whitney U test. Categorical variables were compared using Fisher's Exact test. A P value of <0.05 was considered statistically significant in all analyses.

3 | RESULTS

3.1 | Baseline characteristics and patient disposition

A total of 70 subjects (35 in each group) completed this study. The mean age was 46.63 ± 2.21 years in curcuminoids + piperine and 47.51 ± 2.45 years in placebo groups. Except LDH ($P = 0.014$) that showed significant baseline difference between the study groups, there were no other significant differences between curcuminoids + piperine versus placebo groups in the cases of gender, age, biochemical factors, lipid profiles, glycemic indices, severity of NAFLD and hematological parameters. Baseline characteristics of the study population are summarized in Table 1.

3.2 | Effect of curcuminoids + piperine on biochemical parameters

Administration of curcuminoids + piperine significantly reduced the serum concentrations of ALT

TABLE 1 Baseline comparisons between the study groups

		Curcuminoids (N = 35)	Placebo (N = 35)	*P* value
Age, y		46.63 ± 2.21	47.51 ± 2.45	0.789
Sex	Female	15 (42.9%)	16 (45.7%)	0.810
	Male	20 (57.1%)	19 (55.7%)	
ALT, U/L		50.23 ± 4.60	38.88 ± 4.27	0.075
AST, U/L		34.26 ± 3.63	31.82 ± 2.36	0.578
ALK, U/L		198 [169.25-221.25][a]	174 [143.5-218][a]	0.186
BIL, mg/dL		0.9 [0.6-1.1][a]	0.7 [0.6-0.975][a]	0.229
ALB, g/dL		4.52 ± 0.09	4.30 ± 0.07	0.050
TG, mg/dL		152 [112.5-192.5][a]	123 [94.5-179.75][a]	0.065
TC, mg/dL		196 ± 6.84	180.44 ± 5.68	0.083
LDL-C, mg/dL		113.12 ± 6.22	104.99 ± 5.38	0.326
HDL-C, mg/dL		46.09 ± 2.43	44.29 ± 1.97	0.564
TIBC, μg/dL		341.85 ± 8.70	338.09 ± 7.31	0.743
Fe, μg/dL		106.40 ± 6.73	92.64 ± 6.12	0.138
Ferritin, μg/L		103.83 ± 9.49	100.96 ± 10.53	0.841
LDH, U/L		359.21 ± 13.74	310.27 ± 13.46	0.014*
FPG, mg/dL		101.97 ± 2.96	103.85 ± 4.66	0.739
HbA1c, %		5.52 ± 0.11	5.52 ± 0.09	0.975
BUN, mg/dL		13.57 ± 0.77	13.65 ± 0.86	0.951
Cr, mg/dL		1.06 ± 0.03	1.06 ± 0.03	0.988
TSH, mIU/L		1.655 [1.305-2.635][a]	1.81 [1.22-2.34][a]	0.711
WBC, 10^9/L		7.46 ± 0.32	7.42 ± 0.36	0.942
RBC, 10^9/L		5.28 ± 0.08	5.14 ± 0.10	0.301
Hb, g/dL		15.26 ± 0.26	14.88 ± 0.28	0.321
HCT, %		45.18 ± 0.68	44.22 ± 0.73	0.340
Plt, 10^9/L		247.27 ± 13.64	235.90 ± 12.78	0.545
ESR, mm/hr		9.65 ± 1.01	10.22 ± 0.81	0.660

Abbreviations: ALB, albumin; ALK, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BIL, bilirubin; BUN, blood urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; FBS, fasting plasma glucose; Hb, hemoglobin; HbA1c, glycated hemoglobin; HCT, hematocrit; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Plt, platelet; RBC, red blood cell; TC, total cholesterol; TG, triglyceride; TIBC, total iron-binding capacity; TSH, thyroid-stimulating hormone; UA, uric acid; WBC, white blood cell.

Note. Values are expressed as mean ± SEM, mean ± * = StatisticallySEM, * = Statistically significant, a = Valuesa = Values which expressed as Median [IQR].

($P = 0.035$), AST ($P = 0.042$), and ALP ($P = 0.004$), however, the reduction in levels of bilirubin, BUN, creatinine, and increases in the levels of ALB and LDH was not statistically significant ($P > 0.05$). In the placebo group except for ALB and LDH concentrations ($P < 0.001$), which were significantly increased, the levels of other biochemical parameters were not statistically altered **(**Table 2**)**. The elevation of ALB level in the placebo group was higher than curcuminoids + piperine ($P = 0.002$). However, changes in serum levels of other biochemical parameters were not statistically different between groups ($P > 0.05$**;** Table 3**)**.

3.3 | Effect of curcuminoids + piperine on lipid profiles and glycemic indices

Curcuminoids + piperine administration significantly reduced the serum concentrations of cholesterol ($P < 0.016$) and LDL-C ($P < 0.017$). However, reduction in TG and FPG levels and a slight increase in HDL-C and HbA1c levels were not statistically significant ($P > 0.05$). In placebo group, the cholesterol ($P = 0.035$) and LDL-C ($P = 0.000$) concentrations were significantly decreased, though, TG, HDL-C, FPG, and HbA1c levels showed nonsignificant elevation ($P > 0.05$**;** Table 2**)**. Our results demonstrated although the TG, cholesterol and FPG levels were lower in curcuminoids + piperine group

TABLE 2 Pretrial vs post-trial comparisons in each group

	Curcuminoids (N = 35)			Placebo (N = 35)		
	Before	**After**	***P* value**	**Before**	**After**	***P* value**
ALT, U/L	45 [26-68][a]	29 [24-36][a]	0.035*	29.5 [19-54.5][a]	28 [23-43][a]	0.831
AST, U/L	34.26 ± 3.63	24.78 ± 2.10	0.042*	31.82 ± 2.36	26.14 ± 2.03	0.100
ALP, U/L	198 [169.25-221.25][a]	153.5 [133.5-195.25][a]	0.004*	194.39 ± 17.12	188.91 ± 12.31	0.993
BIL, mg/dL	0.9 [0.6-1.1][a]	0.8 [0.625-1][a]	0.421	0.84 ± 0.07	0.82 ± 0.03	0.795
ALB, g/dL	4.52 ± 0.09	4.57 ± 0.06	0.661	4.30 ± 0.07	4.74 ± 0.05	0.000*
TG, mg/dL	152 [112.5-192.5][a]	148.5 [99.25-182][a]	0.232	123 [94.5-179.75][a]	155 [121-169][a]	0.245
TC, mg/dL	196 ± 6.84	170.84 ± 6.95	0.016*	180.44 ± 5.68	160.8 ± 5.96	0.035*
LDL-C, mg/dL	113.12 ± 6.22	92.1 ± 5.90	0.017*	104.99 ± 5.38	75.62 ± 4.19	0.000*
HDL-C, mg/dL	46.09 ± 2.43	46.27 ± 1.57	0.863	44.29 ± 1.97	47.63 ± 1.76	0.273
TIBC, μg/dL	341.85 ± 8.70	377.52 ± 5.40	0.003*	338.09 ± 7.31	377.14 ± 4.78	0.000*
Fe, μg/dL	106.40 ± 6.73	84 ± 3.25	0.026*	92.64 ± 6.12	81.46 ± 3.18	0.106
Ferritin, μg/L	103.83 ± 9.49	95.39 ± 7.51	0.346	100.96 ± 10.53	91.93 ± 4.66	0.468
LDH, U/L	359.21 ± 13.74	378.45 ± 7.27	0.204	310.27 ± 13.46	363.56 ± 8.25	0.000*
FPG, mg/dL	101.97 ± 2.96	97.22 ± 2.92	0.105	96.5 [89.75-117][a]	102 [98.5-106][a]	0.175
HbA1c, %	5.52 ± 0.11	5.66 ± 0.07	0.595	5.52 ± 0.09	5.59 ± 0.06	0.644
BUN, mg/dL	13.57 ± 0.77	13 ± 0.46	0.583	13 [10-16.5][a]	12 [11-12.5][a]	0.105
Cr, mg/dL	1.06 ± 0.03	1.03 ± 0.03	0.539	1.06 ± 0.03	1.07 ± 0.02	0.472
TSH, mIU/L	2.15 ± 0.21	2.15 ± 0.19	0.886	1.81 [1.22-2.34][a]	2.01 [1.47-2.96][a]	0.136
WBC, 10^9/L	7.46 ± 0.32	6.77 ± 0.19	0.355	7.45 [6.03-8.18][a]	6.15 [5.69-7.30][a]	0.019*
RBC, 10^9/L	5.28 ± 0.08	5 ± 0.11	0.110	5 [4.66-5.57][a]	4.9 [4.50-5.20][a]	0.080
Hb, g/dL	15.26 ± 0.26	14.57 ± 0.28	0.025*	14.88 ± 0.28	14.13 ± 0.18	0.019*
HCT, %	45.18 ± 0.68	43.58 ± 0.81	0.027*	44.22 ± 0.73	44.18 ± 0.59	0.803
Plt, 10^9/L	247.27 ± 13.64	258.3 ± 10.88	0.342	235.90 ± 12.78	255.66 ± 8.55	0.155
ESR, mm/hr	9 [5-13][a]	5 [3-6.5][a]	0.048*	11 [7-12.75][a]	5 [3-6][a]	0.000*
NAFLD severity	2 [1-2][a]	1 [0.75-1.25][a]	0.000*	1 [1-2][a]	1 [1-2][a]	0.478

Abbreviations: ALB, albumin; ALK, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BIL, bilirubin; BUN, blood urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; FBS, fasting plasma glucose; Hb, hemoglobin; HbA1c, glycated hemoglobin; HCT, hematocrit; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; Plt, platelet; RBC, red blood cell; TC, total cholesterol; TG, triglyceride; TIBC, total iron-binding capacity; TSH, thyroid-stimulating hormone; UA, uric acid; WBC, white blood cell.

Note. Values are expressed as mean ± SEM, * = Statistically significant, a = Values which expressed as Median [IQR].

TABLE 3 Comparison of changes in the evaluated parameters between the study groups

	Mean change		
	Curcuminoids (N = 35)	**Placebo (N = 35)**	***P* value**
ALT, U/L	−12.63 ± 5.05	−1.27 ± 6.19	0.163
AST, U/L	−9.44 ± 4.45	−5.68 ± 3.35	0.499
ALK, U/L	−44.69 ± 17.68	−0.21 ± 22.86	0.130
BIL, mg/dL	0 [(−0.3)–0.125][a]	0.1 [(−0.2) −0.275][a]	0.372
ALB, g/dL	0.05 ± 0.11	0.48 ± 0.08	0.002*
TG, mg/dL	−10.59 ± 15.18	19.44 ± 18.67	0.227
TC, mg/dL	−23.86 ± 9.32	−19.21 ± 8.71	0.717
LDL-C, mg/dL	−18.96 ± 7.50	−31.12 ± 6.45	0.221
HDL-C, mg/dL	0.45 ± 2.58	2.97 ± 2.66	0.503
TIBC, μg/dL	29.86 ± 9.34	37.72 ± 9.48	0.558
Fe, μg/dL	−22.10 ± 9.18	−11.79 ± 7.09	0.375
Ferritin, μg/L	−9.47 ± 9.85	−9 ± 12.24	0.977
LDH, U/L	20.16 ± 15.45	58.10 ± 13.46	0.063
FPG, mg/dL	−5.29 ± 3.15	1.31 ± 4.83	0.272
HBA1c, %	0.07 ± 0.13	0.05 ± 0.10	0.894
BUN, mg/dL	−0.58 ± 1.05	−1.95 ± 0.98	0.348
Cr, mg/dL	−0.02 ± 0.04	0.02 ± 0.03	0.346
TSH, mIU/L	−0.04 ± 0.25	0.31 ± 0.37	0.448
WBC, 10^9/L	−0.30 ± 0.31	−0.92 ± 0.38	0.218
RBC, 10^9/L	−0.16 ± 0.10	−0.41 ± 0.17	0.226
Hb, g/dL	−0.59 ± 0.25	−0.71 ± 0.29	0.754
HCT, %	−1.85 ± 0.79	−0.23 ± 0.91	0.191
Plt, 10^9/L	12.46 ± 12.86	21.23 ± 14.57	0.659
ESR, mm/hr	−2.68 ± 1.19	−5.25 ± 0.89	0.083
NAFLD severity	(−1)[(−1)–0][a]	0 [(−1)–0][a]	0.022*

Abbreviations: ALB, albumin; ALK, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BIL, bilirubin; BUN, blood urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; Hb, hemoglobin; HbA1c, glycated hemoglobin; HCT, hematocrit; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; Plt, platelet; RBC, red blood cell; TC, total cholesterol; TG, triglyceride; TIBC, total iron-binding capacity; TSH, thyroid-stimulating hormone; UA, uric acid; WBC, white blood cell.

Note. Values are expressed as mean ± SEM, * = Statistically significant, a = Values which expressed as median [IQR].

when compared with placebo, but, these changes were not statistically significant. In addition, placebo-mediated increasing in HDL-C and decreasing in LDL-C levels were not statistically significant compared with changes in curcuminoids + piperine group ($P > 0.05$; Table 3).

3.4 | Effect of curcuminoids + piperine on severity of NAFLD

Administration of curcuminoids + piperine significantly reduced NAFLD severity ($P < 0.001$; Table 2), which was statistically different ($P = 0.022$) compared with placebo group (Table 3), that showed no changes from baseline (Table 2). In addition, the percentage of patients showing improvement was higher in the curcuminoids + piperine group when compared with the placebo group, however, it was not statistically significant ($P = 0.058$; Table 4).

3.5 | Effect of curcuminoids + piperine on hematological parameters

The changes in hematological parameters are within the normal range and suggest that curcuminoids treatment did not have any adverse effect on the hematological parameters.

Administration of curcuminoids + piperine could significantly decrease the HCT ($P = 0.027$), ESR ($P = 0.048$), levels of Fe ($P = 0.026$), and Hb ($P = 0.025$) and increased TIBC ($P = 0.003$), though, reduction in the level of ferritin, WBC and RBC count and increasing in the platelet count were not statistically significant ($P > 0.05$). Also, a significant increase in TIBC ($P < 0.001$) and decrease in WBC count ($P = 0.019$), ESR ($P < 0.001$), and Hb level ($P = 0.019$) were observed in the placebo group (Table 2). However, changes in CBC, Fe, ferritin, ESR and TIBC were not statistically different between the groups ($P > 0.05$; Table 3).

4 | DISCUSSION

Natural polyphenols like curcumin have the potential to alleviate NAFLD.[1,5,10,22] The present trial also demonstrated that dietary supplement of curcuminoids + piperine could significantly reduce the serum concentrations of ALT, AST, and ALP and disease severity in patients with NAFLD and improve their condition. Consistent with our results, Rahmani et al[22] also demonstrated that in patients with NAFLD bioavailability-enhanced curcumin could significantly decrease the serum levels of AST and ALT compared with the placebo group. Curcumin treatment could reduce AST and ALP levels in a rat model of NAFLD when compared with the untreated

TABLE 4 Comparison of NAFLD severity between the study groups

		Curcuminoids			Placebo				
		Before	After	Improved	Before	After	Improved	*P* value	*P* value baseline
NAFLD severity	Grade 0	3 (8.6%)	8 (23.5%)	18 (52.9%)	6 (17.1%)	6 (17.1%)	11 (31.4%)	0.058	0.274
	Grade 1	10 (28.6%)	18 (52.9%)		15 (42.9%)	19 (54.3%)			
	Grade 2	21 (60%)	8 (23.5%)		13 (37.1%)	8 (22.9%)			
	Grade 3	1 (2.9%)	0 (0%)		1 (2.9%)	2 (5.7%)			

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

control,[1] and, in comparison to lovastatin therapy.[12] Hypoalbuminemia and hyperbilirubinemia are other abnormalities that are found in cirrhotic-stage of NAFLD patients.[8] In the present study subjects, the albumin and bilirubin levels were within the normal range and curcuminoids + piperine treatment maintained their levels within the normal range. Although the placebo group showed an increase in albumin, which was statistically significant, they were still within the normal range.

Curcumin supplementation has been shown to reduce serum LDL-C, non-HDL-C, total cholesterol and TGs, and increase HDL-C levels in patients with metabolic syndrome, and also, it was shown to be effective on amending of metabolic attributes of NAFLD especially those related to lipid and glucose metabolism.[5] As shown by Yan et al,[23] curcumin through inhibition of hepatic lipogenesis and promoting bile acids metabolism could diminish the hepatic steatosis and reversed the abnormalities of serum lipid in mice the NAFLD model. It has also been shown that curcumin treatment could reduce TG and LDL-C levels even more than lovastatin therapy in the rat NAFLD model.[12] In addition, Rahmani et al,[22] also demonstrated that in patients with NAFLD bioavailability-enhanced curcumin could significantly decrease the serum levels of total cholesterol, LDL-C, TGs, glucose, and glycated hemoglobin compared with the placebo group. In agreement with these reports, our results also indicated that curcuminoids + piperine administration could significantly decrease the serum concentrations of cholesterol and LDL-C in patients with NAFLD. While, the reduction in TG slight increase in HDL-C and HbA1c levels were not statistically significant in this group. It is noteworthy that the TG levels were increased in the placebo group, although the increase was not significant.

In addition to abnormal liver enzymes and lipid profile in patients with NAFLD, they could be identified via hepatic steatosis (grades 1-3) on the basis of liver sonography.[5,24] Curcumin has been reported have a therapeutic advantage in protecting against liver steatosis and fibrosis.[24] As shown by Cunningham et al,[1] curcumin reduced hepatic steatosis in female Wistar rats, and so, mitigated the development of NAFLD progression. In Corroboration, our results also revealed that the administration of curcuminoids + piperine significantly improved NAFLD severity, which was also significantly better than the placebo group. Treatment with curcuminoids + piperine could improve the condition of 52.9% patients as compared to 31.4% in placebo. Curcumin is thought to act by the activation of AMPK and inhibition of SREBP-1 and thereby reduce hepatic fat accumulation in high-fat/cholesterol diet (HFD)-induced obese mice and protect against the development of hepatic steatosis.[25] Another mechanism for curcumin action is through inhibition of SREBP-2 and LDLR gene expression, and also, inducing of SREBP-1c expression that both mediated by activation of PPARγ, could reinstate lipid storage capacity of hepatic stellate cells and protect against liver steatosis and fibrosis.[24,26,27] Also, it has been demonstrated that increasing in the hepatic protein of SREBP-1c was more in curcumin therapy when compared with lovastatin therapy in rats with NAFLD. Our results indicated that the percentage of patients with improvement in NAFLD was significantly higher in the curcuminoids + piperine group when compared with the placebo group.

NAFLD has been reported to be associated with increased WBC count.[28] Angulo et al[8] observed that elevated serum ferritin levels, increased transferrin saturation, and hepatic iron overload may increase the severity of liver disease, which can further lower the number of platelets and may imply the presence of advanced disease with cirrhosis in NAFLD, thus, we evaluated the effects of curcuminoids + piperine on hematological parameters in NAFLD patients too. The subjects in our study were those with moderate NASH and their hematological parameters were in the normal levels. Administration of curcuminoids + piperine resulted in a decrease the HCT, ESR, levels of Fe and Hb and increased TIBC, albeit within the normal range whereas the level of ferritin, WBC, and RBC platelets count were within the reference range for these markers.

In conclusion, findings of the present trial suggest a hepatoprotective effect of curcuminoids + piperine supplementation which reduced the disease severity in patients with NAFLD and improved their condition. While no pharmacological therapy has yet been approved for NAFLD, curcuminoids and piperine combined supplementation may provide a safe, and viable treatment for patients and curtail the progression of NAFLD

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CONFLICT OF INTERESTS

Muhammed Majeed is the founder of Sabinsa Corp. and Sami Labs Ltd.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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