Curcumin and Piperine Combination for the Treatment of Patients with Non-alcoholic Fatty Liver Disease: A Double-Blind Randomized Placebo-Controlled Trial

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Abstract

Background: Experimental and clinical studies have revealed that curcumin may be an effective therapy for non-alcoholic fatty liver disease (NAFLD). Hence, the aim of this study was to assess the effect of curcumin plus piperine administration on NAFLD.

Methods: Adults 18–65 years-old diagnosed with NAFLD by liver sonography were randomly allocated to curcumin (500 mg/day) or placebo groups for 2 months. All participants received both dietary and exercise advice. Anthropometric and biochemical measurements as well as hepatic ultrasound were performed at baseline and final conditions.

Results: Seventy-nine participants were recruited and randomly allocated into the curcumin (n = 39) or placebo (n = 40) groups. There were no significant differences between placebo and curcumin groups for demographic

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and clinical characteristics and NAFLD grade at baseline. After the treatment period, the curcumin group exhibited lower alkaline phosphatase (−16.2 ± 22.8 versus −6.0 ± 22.5 mg/dL, $p = 0.04$) concentrations and severity of NAFLD compared with the placebo group ($p = 0.04$).

Conclusion: Results of this clinical trial suggest that short-term treatment with curcumin plus piperine administration improves NAFLD severity.

Keywords

Curcumin · Piperine · Fatty liver disease · Steatosis · Clinical trial

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most frequent liver diseases which has been rapidly increasing in its incidence owing to different contributors such as obesity, sedentary lifestyles, and high-fat diets. The prevalence of NAFLD is 80–90% in obese adults, 30–50% in diabetic patients, 90% in hyperlipidemia, 3–10% in children, and 40–70% in obese children [1]. NAFLD comprises different hepatic disorders including simple steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma [2]. The interaction of genes, hormones, nutrition, insulin resistance, lipotoxicity, and hepatic inflammation is involved in the complex pathophysiology of NAFLD [3]. Because there is no well-established pharmacological management for NAFLD, effective therapies are needed in order to treat this chronic liver disease.

Curcumin is a natural compound obtained from turmeric, a member of the Zingiberaceae family [4]. Owing to the biological effects of curcumin such as antioxidant, anti-inflammatory, immunoregulatory, hepatoprotective, antidiabetic, lipid-lowering, and anti-tumor effects [5–13], this nutraceutical has emerged as a promising therapeutic option for NAFLD. Even recent meta-analyses have revealed a favorable impact of curcumin supplementation on NAFLD [14–16]. However, low bioavailability and rapid biotransformation of this polyphenol have resulted in a limited application and controversial findings. In this regard, it has been demonstrated that piperine, an extract from black pepper, may improve the bioavailability and pharmacokinetics of curcumin in both animals and humans [17]. Therefore, the aim of this study was to assess the effect of curcumin plus piperine administration on NAFLD.

2 Method

2.1 Trial Design

This was a 2-month, double-blind, placebo-controlled, parallel-group trial with an allocation ratio of 1:1 for the two groups. It was performed in the Northeastern region of Iran, in Neyshabur City. The study was registered and certified by the Iranian Registry of Clinical Trials (IRCT registration number: IRCT2015052322381N1; http://www.irct.ir), the Institutional Review Board and the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.fm.REC.1395.303). Before any procedures were initiated, all patients enrolled in this clinical trial signed an informed consent document.

2.2 Randomization

The participants were distributed using a balanced block randomization technique into two groups designated for treatment with either curcumin or placebo. This was achieved through two steps, First, two letters were arranged and typed on two pieces of paper labeled "A" for "curcumin" and "B" for "placebo". The possible quad blocks were AABB, ABAB, ABBA, BBAA, BABA, and BAAB. Second, the number was selected randomly through a random number table. The randomization procedure was concealed to make sure the allocation sequence was

executed without the researcher having knowledge over which patient was in which group. In this way, the treatments were placed in boxes that were labeled with a serial number from 1 to 80 for all subjects in the two groups. Apart from the trial leader, the contents of each box were not known to the trial operators.

2.3 Study Population

All adults aged 18–60 who met the NAFLD criteria based on ultrasound evaluation and laboratory results were eligible for the study. A normal liver was determined if the liver parenchyma echogenicity was equal to or slightly higher than that of the renal parenchyma and NAFLD was determined on the basis of more liver echogenicity than that of the renal parenchyma due to fatty infiltration [18]. Patients were recruited from January 2017 to August 2017 at Bahman Hospital (Neyshabur, Iran). The conditions for inclusion were as follows: age between 18–65 years and ultrasound diagnosis of fatty liver. Exclusion criteria were pregnancy and/or lactation for women, the presence of acute or chronic liver disorders such as viral (hepatitis B and C) and autoimmune hepatitis, usage of anti-inflammatory drugs such as corticosteroids and liver enzyme inducer drugs, the presence of alcoholic liver disease, or metabolic liver disorders including Wilson's disease and hemochromatosis, Budd–Chiari syndrome, as well as other medical disorders such as hyper/hypothyroidism, cardiovascular diseases, and cancer. This procedure resulted in 80 patients with NAFLD being selected and 8 were excluded from the study.

2.4 Intervention

A combination of curcumin and piperine was used for intervention in this trial. Piperine is extracted from black pepper, which has been clinically proven to naturally enhance absorption of pharmaceuticals including the curcuminoids. In the treatment group, subjects received curcumin–piperine capsules [Curcumin C3 complex™ (500 mg) plus Bioperine™ (5 mg) patented extract obtained from black pepper fruits (*Piper nigrum*) standardized to a minimum of 95% piperine] or placebo capsules once daily. The capsules were consumed by the patients for two months as directed. In order to better follow-up medication use by the patients, the treatment bottles were allocated to the subjects at the beginning and at the end of the first month of intervention period and any remaining capsules were counted.

2.5 Assessment of Outcomes

The ultrasound examination and the biochemical and anthropometric measurements were the primary and secondary outcome measures, respectively.

2.6 Biochemical and Anthropometric Measurement

To measure biochemical and laboratory variables, venous blood samples were taken from each patient after an overnight fasting period at points before and after the intervention on days 0 and day 60. Blood samples were centrifuged at 1000 × g for 10 min for preparation of serum. Biochemical and laboratory measurements including fasting blood glucose (FBG), lipid profiles, and liver function tests were conducted immediately using serum aliquots in the BT-2000 Auto Analyzer machine (Biotechnica, Rome, Italy), using Pars Azmoon kits (Pars Azmoon Inc., Tehran, Iran).

Anthropometrics and body mass were analyzed by the InBody 770 device (model: BPM040S12FXX, Seoul, South Korea) with an accuracy of 0.1 kg. All patients were shoeless with thin clothes during the tests, according to the manufacturer's recommended procedure. Body weight, fat mass, body mass index (BMI), waist:hip ratio (WHR), and other anthropometric measurements were again carried out by each device using standard protocols. Additionally, a

digital stadiometer (Model BSM 370, Seoul, South Korea) was used to measure height with an accuracy to the nearest 0.1 cm [19].

In addition to the intervention, all patients were advised based on the National Institutes of Health and the North American Association for the study of obesity to have an energy-balanced diet according to the clinical guidelines for identifying, assessing, and managing overweight and obesity in adults. According to the guideline, the diet should consist of carbohydrate (52–53% of the total energy value), fiber (20–30 g/day), total fat (≤30% of the total energy value, one-thirds saturated and two-thirds unsaturated), cholesterol (<300 mg/dL), and protein (15–18% of the total energy value). All patients were also advised to exercise for a minimum of 30 min, three times per week.

2.7 Statistical Analysis

For assessing the normality of variables the Kolmogorov–Smirnov test was used. Normal and non-normal distribution variables (parametric and non-parametric) were shown as the mean ± standard deviation (SD) and median (interquartile range (IQR), respectively. The independent T-test and the Mann–Whitney U test were performed for comparing characteristics of patients between groups of curcumin and placebo, for normal and non-normal distribution variables, respectively. The dependent t-test and the Wilcoxon signed-rank test were used to compare two related samples (before and after) for parametric and non-parametric variables, respectively. Additionally, categorical data such as sex and smoking were analyzed using chi-square and Fisher's exact test.

3 Results

Eighty-five patients with NAFLD were eligible for the study and 6 of these were excluded because they did not meet the inclusion criteria (Fig. 1). Thus, 79 participants were randomly allocated into the curcumin (n = 39) or placebo (n = 40) groups. During the follow-up period, there were 9 dropouts due to the side effects of curcumin or because the intervention was abandoned due to forgetful consumption of drug, travel, or inaccessibility in the follow-up period. Thus, the dropout rate was approximately 11%.

3.1 Characteristics of the Study Participants

Demographic and clinical characteristics of the study population are shown in Table 1. There were no significant differences between the placebo and curcumin groups for age, sex, smoking and drug consumption, history of diseases, anthropometric measurements, systolic blood pressure (SBP), diastolic blood pressure (DBP), and NAFLD grade at baseline.

3.2 Comparison of NAFLD Criteria Within Groups

Table 2 shows anthropometric, biochemical, and sonographic data before and after the intervention period. Regarding the anthropometric data, body fat mass, BMI, hip circumference, and waist circumference were significantly reduced in both treatment groups. In addition, weight and waist–hip ratio were significantly reduced in the placebo group but not affected in the curcumin group. According to the biochemical parameters, only HDL-C and ALP showed a significant decrease after the intervention in the placebo and curcumin groups, respectively. The comparison of liver sonography data within the groups revealed that the grade of NAFLD was significantly decreased after consumption of curcumin (P = 0.004) but no significant change was observed in the placebo group (P = 0.796).

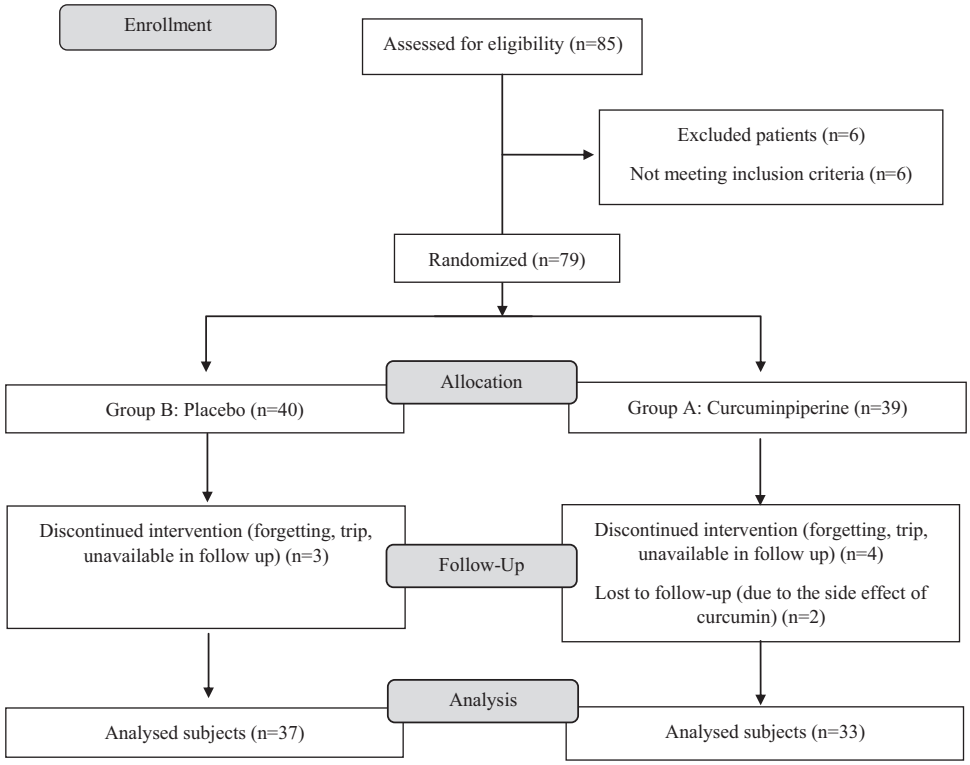

Fig. 1 Flow diagram of study population

3.3 Comparison of NAFLD Criteria Between Groups

Table 3 shows the comparison of anthropometric, biochemical, and NAFLD ultrasound data between the curcumin and placebo groups after the 2-month intervention period. Only ALP and NAFLD grade showed significant changes between the study groups. The curcumin group exhibited lower ALP concentrations and severity of the NAFLD compared with placebo group. There were no significant differences for any of the other variables.

4 Discussion and Future Perspectives

Results of this randomized placebo-controlled trial suggest that curcumin piperine supplementation exerts a hepatoprotective effect in patients with NAFLD. In agreement with our findings, a previous study reported a positive effect of curcuminoids plus piperine administration on NAFLD [20]. In this context, it has been described that curcumin therapy prevents hepatic steatosis by improving intestinal barrier function and reducing hepatic inflammation through down-regulation of toll-like receptor 4 (TLR4), tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [21]. Further, curcumin supplementation may protect against NAFLD by decreasing hepatic lipid accumulation and oxidative stress through modulation of fatty acid uptake [22]. Also, curcumin treatment improves histological changes of NAFLD including fibrosis and intrahepatic accumulation of CD4+ cells [23]. It has been suggested that curcumin may regulate endogenous and exogenous metabolism in NAFLD via the nuclear factor erythroid 2-related factor 2/farne-

Table 1 Baseline characteristics of patients in curcumin and placebo groups

Characteristics		NAFLD patients		
		Placebo (n = 37)	Curcumin (n = 33)	P-value[a]
Age, years		43.1 ± 11.6	45.6 ± 11.0	0.328
Male (%)		60	53.8	0.581
Smoker (%)		17.5	2.6	0.057
Ex-smoker (%)		60	65.8	0.718
Drug intake (%)		2.7	0	0.425
History of diabetes		15	17.9	0.724
History of hypertension		12.5	15.4	0.545
History of heart disease		12.5	2.6	0.096
History of myocardial infarction		2.5	0	0.368
History of kidney disease		27.5	12.8	0.105
History of liver disease		15	20.5	0.263
History of hyperlipidemia		37.5	30.8	0.473
History of weight loss		22.5	25.6	0.849
Height (cm)		165.7 ± 10.9	164.2 ± 10.1	0.529
Weight (kg)		80.0 ± 11.9	83.1 ± 10.6	0.243
BMI (kg/m^2)		29.2 ± 4.2	30.9 ± 4.3	0.093
SBP (mmHg)		112.5 ± 14.7	118.8 ± 18.8	0.104
DBP (mmHg)		79.9 ± 10.2	84.5 ± 12.0	0.077
NAFLD grade (%)	(1)	47.5	43.6	0.745
	(2)	47.5	46.2	
	(3)	5	10.3	

The continuous and categorical variables were described respectively, as mean ± SD and percentage

NAFLD nonalcoholic fatty liver disease, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

[a]The continuous and categorical variables were evaluated using the independent Student's t-test and chi-square/Fisher's exact test, respectively

soid X receptor/liver x receptor (Nrf2/FXR/LXRα) pathway [24]. In addition, curcumin might reverse hepatic steatosis by suppressing the expression of CD36 and peroxisome proliferator-activated receptor-gamma (PPAR-γ) via activation of the cAMP response element-binding protein [25]. In this line, curcumin attenuates fatty liver through the decrease in DNA methylation levels, increased PPAR-α mRNA and protein expression, and reduced hepatic lipid accumulation [26]. Additionally, curcumin mitigates hepatic steatosis by regulating hepatic lipid metabolism via 5′ AMP-activated protein kinase (AMPK) activation [27]. Thus, the aforementioned molecular mechanisms of curcumin could explain its beneficial effects on NAFLD.

On the other hand, a recent clinical trial found a significant improvement in lipid profile and hepatic enzymes after curcumin treatment in patients with NAFLD [28], which contrasts with our results. This inconsistency may be related to the short treatment period of our study, which might have been insufficient to induce significant changes in biochemical parameters. Nonetheless, it is noteworthy that the positive effects of curcumin are often found using doses greater than 1500 mg/day [29], while we only administered 500 mg/day. This could also explain the lack of effect of curcumin administration on anthropometric and biochemical parameters.

Although there were significant differences between the study groups at baseline, it is

Table 2 Comparison of important characteristics affecting the NAFLD within groups, before and after intervention

Characteristics		Placebo (n = 37)			Curcumin (n = 33)		
		Before	After	P-value	Before	After	P-value
Weight (kg)		80.0±11.9	76.4±11.0	0.021	83.1±10.9	82.0±10.4	0.106
BMI (kg/m^2)		29.2±4.2	28.6±3.8	0.023	30.9±4.4	30.2±4.7	0.001
HC (cm)		103.1±5.4	101.6±5.0	0.002	105.4±5.7	104.5±5.7	0.001
AC (cm)		99.5±11.1	97.0±9.7	0.001	102.0±9.6	100.5±10.0	0.002
WHR		0.9±0.1	0.9±0.1	0.040	0.9±0.1	0.9±0.1	0.074
Body fat mass		28.3±9.5	26.8±7.9	0.009	32.1±10.2	30.5±10.4	0.001
TG (mg/dL)		135.5(108.0-166.0)	130.5(100.0-177.7)	0.678	111.0(91.0-160.0)	121.5(93.2-171.7)	0.712
TC (mg/ dL)		194.0±36.2	188.7±36.0	0.304	185.5±41.7	180.8±33.8	0.510
HDL-C (mg/ dL)		45.6±10.6	43.5±8.9	0.033	43.8±9.8	42.9±10.7	0.381
LDL-C (mg/ dL)		105.6±25.2	107.5±32.1	0.696	99.4±23.6	104.1±27.0	0.304
AST (mg/ dL)		25.5±9.6	28.8±9.7	0.139	24.3±8.5	27.4±9.7	0.096
ALP (mg/ dL)		185.8±51.1	181.3±48.0	0.116	202.9±57.2	186.6±50.2	0.001
ALT (mg/ dL)		40.2±28.1	38.9±17.6	0.753	32.3±20.6	32.6±18.6	0.930
FBG (mg/ dL)		107.8±43.9	107.1±46.5	0.810	95.1±15.3	93.2±16.7	0.351
SBP (mmHg)		112.5±14.7	116.6±15.3	0.194	120.1±20.2	119.8±22.8	0.906
DBP (mmHg)		79.9±10.2	83.0±9.7	0.157	85.7±13.3	83.0±11.1	0.357
NAFLD grade (%)	(0)	0	5.4	0.796*	0	12.1	0.004*
	(1)	47.5	40.5		43.6	45.5	
	(2)	47.5	45.9		46.2	42.4	
	(3)	5	8.1		10.3	0	

Respectively, dependent Student's t and Wilcoxon tests were performed to compare normal and non-normal variables
Significant values are shaded in gray
For normal and non-normal distribution variables, values are expressed as mean ± SD and median (interquartile range (IQR), respectively
NAFLD nonalcoholic fatty liver disease, *BMI* body mass index, *HC* measured circumference of hip, *AC* measured circumference of abdomen, *WHR* waist–hip ratio, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FBG* fasting blood glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase
*Wilcoxon signed ranks test

important to note that those individuals in the curcumin intervention group were heavier in terms of weight, BMI, waist circumference, and body fat mass, which could explain the lack of effect of curcumin on anthropometric measurements. According to the biochemical parameters, lipids and hepatic enzymes were within the normal ranges in the curcumin group and, therefore, significant changes after the treatment period may not have been expected to occur.

There were a number of limitations in this study that should be taken into account. First, due to the short treatment duration of the present clinical trial, the long-term efficacy of curcumin plus piperine administration could not be evaluated. Second, NAFLD severity was only assessed by hepatic ultrasound, although this method has shown a high sensitivity, specificity, and accuracy for the diagnosis of fatty liver [29].

In conclusion, the results of this clinical trial suggest that short-term administration with curcumin plus piperine diminishes NAFLD severity. Although curcumin might be considered as a therapeutic option for the treatment of NAFLD, further clinical trials are mandatory to confirm the potential beneficial effects of this nutraceutical in both prevention and treatment of NAFLD. Such trials should explore different dosages and treatment periods.

Conflict of Interest None.

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Table 3 Changes of anthropometric, biochemical, and NAFLD ultrasound grading between groups of curcumin placebo

		Placebo (n = 37)	Curcumin (n = 33)	P-value
Weight (kg)		-1.9±4.3	-1.0±3.8	0.403
BMI (kg/m^2)		-0.3±0.9	-1.6±2.1	0.205
Body fat mass		-1.0±2.1	-1.6±2.1	0.317
WHR		-0.01±0.02	-0.01±0.02	0.877
AC (cm)		-1.8±2.4	-1.5±2.8	0.722
HC (cm)		-0.9±1.4	-0.8±1.4	0.835
TC (mg/ dL)		-5.7±40.0	-4.7±42.8	0.913
HDL-C (mg/ dL)		-2.7±7.7	-0.9±6.2	0.264
LDL-C (mg/ dL)		2.0±30.5	4.6±26.9	0.685
TG (mg/dl)		-0.5(-22.5-28.2)	-1.0(-22.7-31.2)	0.996
SBP (mmHg)		3.5±13.0	-0.3±12.8	0.306
DBP (mmHg)		4.0±13.5	-2.7±14.8	0.100
FBG (mg/ dL)		-1.0±26.8	-1.9±12.3	0.856
ALT (mg/ dL)		-1.3±25.5	0.2±16.9	0.759
AST (mg/ dL)		2.5±10.5	3.0±9.2	0.863
ALP (mg/ dL)		-6.0±22.5	-16.2±22.8	0.044
NAFLD grade (%)	(-2)	0	9.1	0.048*
	(-1)	18.9	21.2	
	(0)	67.6	69.7	
	(1)	10.8	0	
	(2)	2.7	0	

Independent Student's t and Mann–Whitney U tests were performed to compare normal and non-normal distribution variables, respectively. Values are expressed as mean ± SD and median (interquartile range (IQR)) for normal and non-normal distribution variables, respectively

Significant values are shaded in gray

BMI body mass index, *HC* measured circumference of hip, *AC* measured circumference of abdomen, *WHR* waist–hip ratio, *FBG* fasting blood glucose, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglycerides, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *NAFLD* nonalcoholic fatty liver disease

*Mann–Whitney U test

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