3 The Effect of Curcumin Phytosome on the Treatment of Patients with Non-alcoholic Fatty Liver Disease: A Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a global health problem with increasing prevalence among overweight and obese patients. It is strongly associated with conditions of insulin resistance including type 2 diabetes mellitus (T2DM) and obesity. It has detrimental consequences ranged from simple steatosis to irreversible hepatic fibrosis and cirrhosis. Curcumin is a dietary polyphenol with potential effect in improving NAFLD. Therefore, the aim of this trial was to examine the effect of curcumin supplementation on various aspects of NAFLD. In this trial, a total number of 80 patients were randomised to receive either curcumin at 250 mg daily or placebo for 2 months. Lipid profiles, hepatic enzymes, anthropometric indices and hepatic fat mass were assessed at the baseline and the end of the trial, and compared within the groups. The

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grade of hepatic steatosis, and serum aspartate aminotransferase (AST) levels were significantly reduced in the curcumin group ($p = 0.015$ and $p = 0.007$, respectively) compared to the placebo. There was also a significant reduction in high density lipoprotein (HDL) levels and anthropometric indices in both groups with no significant differences between the two groups. Low dose phospholipid curcumin supplementation each day for 2 months showed significant reduction in hepatic steatosis and enzymes in patients with NAFLD compared to placebo. Further studies of longer duration and higher dosages are needed to assess its effect on other parameters of NAFLD including cardiovascular risk.

Keywords

NAFLD · Non-alcoholic fatty liver disease · Curcumin · Phytosome · Turmeric · NASH

3.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a global health problem with increasing prevalence worldwide in parallel with obesity. It is a condition of excess hepatic fat accumulation in non-alcoholic subjects [1], associated with conditions of insulin resistance such as type 2 diabetes mellitus (T2DM) and obesity. Therefore, it is regarded as a hepatic manifestation of metabolic syndrome [2]. NAFLD has a wide spectrum of manifestations from simple steatosis with benign hepatic features to non-alcoholic steatohepatitis (NASH) and irreversible hepatic fibrosis [3]. NASH is a necroinflammatory process of the hepatic cells with a tendency to progress to liver cirrhosis and hepatocellular carcinoma [4]. The pathophysiology of NAFLD is associated with metabolic diseases such as insulin resistance and obesity [5]. It was initially hypothesised that the hepatic triglyceride accumulation is mediated by inflammatory reactions (cytokine/adipokines, oxidative stress and mitochondrial dysfunction) as the main driver for the underlying pathogenesis of steatohepatitis and fibrosis [6]. However, more recent hypotheses have proposed that the pathophysiology of NAFLD is driven by a combination of genetic, epigenetic, environmental and nutritional factors, as well as by obesity, hormone secretion from adipose tissue and insulin resistance [7].

Despite the recent advances in understanding of the pathological mechanism of NAFLD, effective therapeutic options are still limited. Currently, treatment options are primarily focused on improving metabolic parameters such as body weight, physical activity, insulin sensitivity, as well as lipid profiles and glycaemic control. Thus, insulin sensitising agents (e.g., metformin or pioglitazone), lipid lowering compounds (e.g. statins), weight loss medications (e.g., orlistat or sibutramine) and even bariatric surgery have been introduced as potential means for managing NAFLD [8]. There are also numerous new and emerging potential NASH therapeutic approaches including anti-oxidants such as vitamin C, vitamin E and anti-inflammatory agents [9, 10]. However, the challenge still remains to gain approval of these as a treatment approach in NAFLD patients. Within the past few years, curcumin popularity as a potential therapeutic option for treatment of NAFLD has increased. Traditionally, curcumin is in common use in Asian cooking, but also used as household triage for various diseases [11]. Its safety and therapeutic activities, including anti-inflammatory and antioxidant properties, have been reported in several previous studies [12–21]. It has been shown that curcumin prevents liver fibrosis and subsequent liver cirrhosis through its anti-inflammatory effects and suppression of the hepatic satellite cell (HSC) activity [22]. Furthermore, short term supplementation with curcumin has been demonstrated to improve anthropometric measures, hepatic enzymes and liver fat mass, as assessed by ultrasonography [23].

Given the limited number of clinical studies investigating the potential therapeutic effects of curcumin supplementation on various metabolic parameters in patients with NAFLD, we aimed to examine the therapeutic effect of low dose phospholipid curcumin on lipid profiles, hepatic enzymes and hepatic fat mass in patients with NAFLD in a randomised controlled clinical

study. Previous studies have shown that this curcumin formulation drives higher systemic levels of curcumin compared to the non-formulated version, thereby increasing its bioavailability [24, 25].

3.2 Methods

3.2.1 Trial Design

This study was an 8-week, double-blind, placebo-controlled, parallel-group conducted in Neyshabur City in the northeast of Iran. The allocation ratio was 1:1 for two groups. The study was approved by the Institutional Review Board and the Ethical Committee of Neyshabur University of Medical Sciences (Code: IR.NUMS.REC.1394.18). Also, the study was registered in the Iranian Registry of Clinical Trials (http://www.irct.ir; IRCT registration number: IRCT2015052322381N1). All participants who were recruited signed a consent form before any trial-related procedures occurs.

3.2.2 Participants

Eligible patients were all adults aged 18 to 65 years who met the eligibility criteria for NAFLD according to ultrasound examination and laboratory results. NAFLD was defined based on higher echogenicity of the liver compared with that of the renal parenchyma due to fatty infiltration. A normal liver was defined if the echogenicity of the liver parenchyma was equal to or only slightly higher than that of the renal parenchyma [26]. Eighty patients with NAFLD were

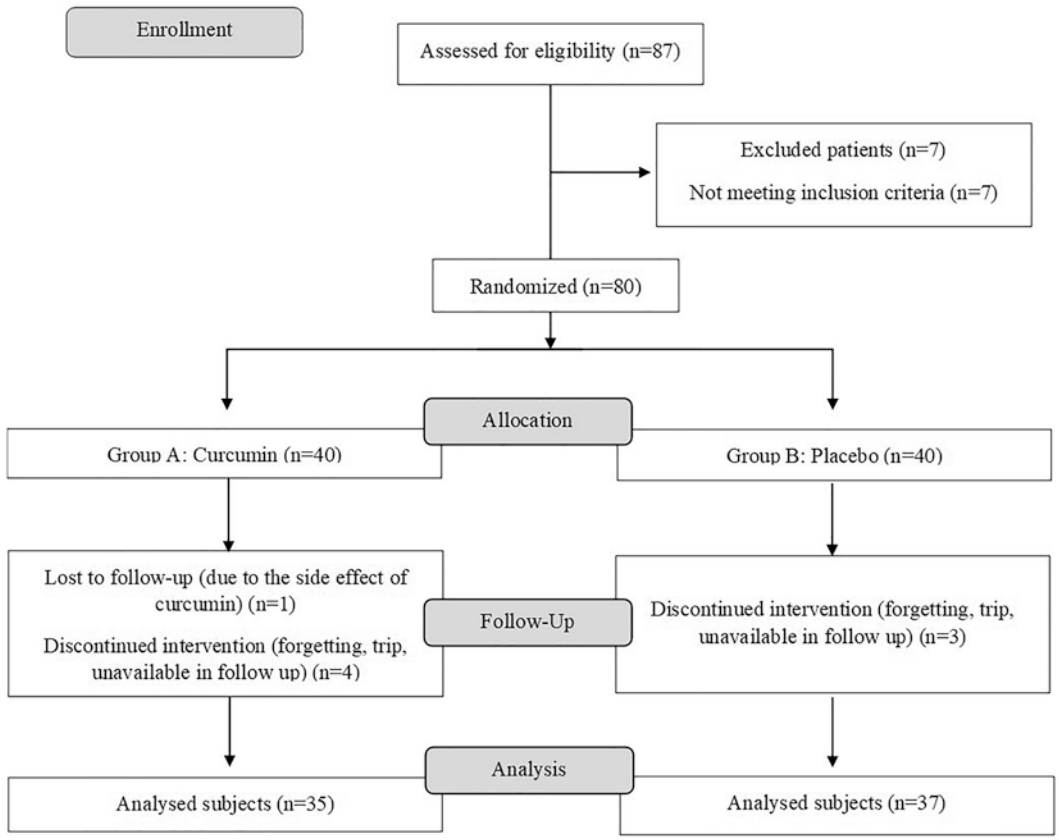

Fig. 3.1 Flow diagram of study participation

recruited for the study and 8 of these dropped out (Fig. 3.1). Referred patients of the 22 Bahman Hospital (Neyshabur, Iran) from January 2017 to August 2017 were recruited. The exclusion criteria included females with pregnancy/lactation, the presence of alcoholic liver disease, severe heart or lung disease, or the taking of anti-inflammatory drugs such as corticosteroids and liver enzyme inducer drugs, acute or chronic liver disorders such as viral and autoimmune hepatitis, metabolic liver disorders including hemochromatosis and Wilson's disease, Budd–Chiari syndrome, or other medical disorders such as hyper/hypothyroidism, alpha-1 antitrypsin deficiency, celiac disease or cancer.

3.2.3 Randomization

The subjects were randomly allocated to the curcumin or control group using a balanced block randomization technique. Accordingly, two letters were prepared and written on two sheets of paper with "A" for "curcumin" and "B" for "control." The following quad blocks were possible: AABB, ABAB, ABBA, BBAA, BABA and BAAB. After this, the number was selected randomly using a table of random numbers. To ensure that implementation of the random allocation sequence occured without the knowledge of which patient will receive which treatment, the entire randomization process was concealed. To achieve this, the drugs had already been put in envelopes labelled a serial number from 1 to 80 and no one knew the nature of the envelopes apart from the coordinator of the trial.

3.2.4 Intervention

The patients in the treatment group received capsules of phospholipidated curcumin (250 mg/day, Meriva curcumin phytosome; Indena SpA, Milan, Italy). Each capsule was composed of 250 mg curcumin phytosome powder, which was equivalent to 50 mg/day pure curcuminoids. The control group received matched placebo capsules at the same dose. The drug consumption route was oral for a period of 2 months. To keep track of the medication, the bottles of the drug were given to the subjects at the beginning and in the middle (after 1 month) of the interventions period.

3.2.5 Assessment of Outcomes

The primary and secondary outcomes were ultrasound examination and the anthropometric and clinical measurements, respectively.

3.2.5.1 Biochemical and Anthropometric Measurement

Venous blood samples were taken from each patient after an overnight fasting period before and after the intervention on days 0 and 60. This was carried out since the levels of biochemical measurements can be influenced by food intake and diurnal rhythms. For separation of serum, blood samples were centrifuged at 1000 x g for 10 min. Biochemical and lab measurements such as lipid variables, fasting blood glucose (FBG) and liver function tests were performed immediately after serum preparation via the BT-2000 Auto Analyzer machine (Biotechnica; Rome, Italy) using Pars Azmoon kits (Pars Azmoon Inc., Tehran, Iran).

Bodyweight and body mass were measured using the BPM040S12FXX 770 device (In Body; Seoul, South Korea), with an accuracy of 0.1 kg. According to the protocol of the device, all patients were barefoot with lightweight clothing during the measurements. Body mass index (BMI; kg/m^2) and other anthropometric measurements were calculated using the device. Body height was measured by a BSM 370 digital stadiometer (InBody), with accuracy to the nearest 0.1 cm.

Due to the difference in the diet of patients and its possible impact on outcomes, the subjects reported a favourable response to the diet. All

patients were asked to have an energy balanced diet according to the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults from the National Institutes of Health and the North American Association for the study of obesity. According to the guideline, the recommended diet consists of ≤30% fat (one-third saturated and two-thirds unsaturated fatty acids), 52–53% carbohydrates, 20–30 g/day fibre, < 300 mg/dL cholesterol and 15–18% protein (all percentages related to the total energy value). Also, all patients were advised to exercise three times each week for at least 30 min.

3.2.5.2 Statistics Analysis

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

3.3 Results

Out of 87 patients recruited with NAFLD, 7 subjects did not meet the inclusion criteria (Fig. 3.1). Thus, 80 patients were randomly allocated to the two groups (curcumin and control). After enrolment of all patients, 8 were lost during the follow up period due to curcumin side effects, discontinuation or forgetfulness regarding the intervention, or unavailability for other reasons.

3.3.1 Characteristics of Patients

The demographics and medical history of the patients with NAFLD are shown in Table 3.1. As can be seen, there was no significant difference between the curcumin and placebo groups apart for history of hypertension.

3.3.2 Anthropometric, Biochemical and Sonography Analyses

Anthropometric, biochemical and sonography data before and after intervention are given in Table 3.2. This showed that high-density lipoprotein cholesterol (HDL-C) was significantly increased in the placebo group, while this was decreased in the curcumin group ($p < 0.05$). Also, aspartate aminotransferase (AST) levels and NAFLD grade (based on sonography) were significantly decreased after the curcumin treatment ($p < 0.05$). However, there were no significant differences in these parameters in the placebo group. No other variables showed significant differences due to treatment.

3.3.3 Comparison of the Changes of Anthropometric, Biochemical and Sonography Data of Patients with NAFLD Between the Curcumin and Placebo Groups

The changes of anthropometric, biochemical and-sonography data before and after intervention are represented in Table 3.3. The changes in each variable were obtained through data differences before and after the intervention. As can be seen in Table 3.3, AST and NAFLD grade were decreased significantly following treatment in the curcumin group compared to the effects on these same parameters in the placebo group ($p < 0.05$). The comparison of changes of other variables such as anthropometric, blood pressure and other biochem-

Table 3.1 Characteristics of demographic, medical history, biochemical, anthropometric and sonography of all patients with NAFLD at baseline

Characteristics		NAFLD patients		
		Placebo (n = 37)	Curcumin (n = 35)	P-value[a]
Age (year)		43.1 ± 11.6	45.0 ± 11.1	0.459
Sex (male)		60	55	0.821
Smoker		17.5	7.9	0.312
Ex-smoker		60	67.6	0.163
Taking medication		2.7	2.8	0.996
History of hypertension		12.5	36.8	0.021
History of diabetes		15	13.2	0.815
History of hyperlipidemia		37.5	52.6	0.277
History of heart disease		12.5	10.5	0.730
History of weight loss		22.5	23.7	0.514
History of kidney disease		27.5	18.4	0.424
History of liver disease		15	10.5	0.738
Weight (kg)		80.0 ± 11.9	85.3 ± 18.6	0.152
BMI (kg/m^2)		29.2 ± 4.2	30.8 ± 5.1	0.153
Body fat mass		28.3 ± 9.5	33.0 ± 11.6	0.064
HC (cm)		103.1 ± 5.4	105.4 ± 8.1	0.168
AC (cm)		99.5 ± 11.1	104.9 ± 12.9	0.060
WHR		0.9 ± 0.1	0.9 ± 0.1	0.043
NC (cm)		39.2 ± 2.8	39.9 ± 3.4	0.358
FBG (mg/dL)		107.8 ± 43.9	103.1 ± 46.3	0.645
TC (mg/ dL)		194.0 ± 36.2	202.8 ± 37.2	0.289
TG (mg/ dL)		135.5(108.0–166.0)	132.0(114.5–180.0)	0.446
HDL-C (mg/ dL)		45.6 ± 10.6	44.8 ± 9.6	0.731
LDL-C (mg/ dL)		105.6 ± 25.2	111.2 ± 29.5	0.369
SBP (mm hg)		112.5 ± 14.7	117.3 ± 14.1	0.150
DBP (mm hg)		79.9 ± 10.2	84.1 ± 14.3	0.141
NAFLD grade	(1)	47.5	30	0.266
	(2)	47.5	62.5	
	(3)	5	7.5	

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

[a]The continuous and categorical variables were analysed using independent student t test and chi square/ Fisher's exact, respectively

BMI body mass index, *HC* measured circumference of hip, *NC* measured circumference of neck, *AC* measured circumference of abdomen, *WHR* waist-hip ratio, *FBG* fasting blood glucose, *TC* total Cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NAFLD* non-alcoholic fatty liver disease

ical data were not significantly different between the curcumin and placebo groups ($p > 0.05$).

3.4 Discussion

The present clinical study investigated the significant impact of low dose phospholipid curcumin supplementation on biochemical markers of NAFLD. In addition to abnormal liver enzymes and lipid profile, the sonographic features of hepatic steatosis (grades 1–3) were improved by the treatment. Consistent with current research findings, Rahmani et al. also showed the reduction of serum levels of AST and ALT as well as hepatic fat mass using bioavailability-enhanced curcumin in patients with NAFLD compared to the placebo group. The therapeutic properties of curcumin in improving liver steatosis and fibrosis have been previously reported [27, 28].

Table 3.2 Comparison of anthropometric, biochemical and sonography data of patients with NAFLD within groups

		Placebo (n = 37)			Curcumin (n = 35)		
Characteristics		Before	After	P-value	Before	After	P-value
Weight (kg)		80.0 ± 11.9	76.4 ± 11.0	0.021	85.3 ± 18.6	79.1 ± 12.1	0.102
BMI (kg/m2)		29.2 ± 4.2	28.6 ± 3.8	0.023	30.8 ± 5.1	29.1 ± 3.8	0.005
Body fat mass		28.3 ± 9.5	26.8 ± 7.9	0.009	33.0 ± 11.6	28.8 ± 7.7	0.001
HC (cm)		103.1 ± 5.4	101.6 ± 5.0	0.002	105.4 ± 8.1	102.5 ± 5.9	0.004
AC (cm)		99.5 ± 11.1	97.0 ± 9.7	0.001	104.9 ± 12.9	100.0 ± 9.1	0.001
WHR		0.9 ± 0.1	0.9 ± 0.1	0.040	0.9 ± 0.1	0.9 ± 0.1	0.002
NC (cm)		39.2 ± 2.8	38.5 ± 2.5	0.070	39.9 ± 3.4	38.8 ± 2.4	0.158
FBG (mg/dl)		107.8 ± 43.9	107.1 ± 46.5	0.810	103.1 ± 46.3	95.2 ± 12.7	0.413
TC (mg/dl)		194.0 ± 36.2	188.7 ± 36.0	0.304	202.8 ± 37.2	199.4 ± 44.5	0.466
TG (mg/dl)		135.5(108.0–166.0)	130.5(100.0–177.7)	0.678	132.0(114.5–180.0)	161.0(113.5–211.0)	0.301
HDL-C (mg/dl)		45.6 ± 10.6	43.5 ± 8.9	0.033	44.8 ± 9.6	42.3 ± 7.8	0.022
LDL-C (mg/dl)		105.6 ± 25.2	107.5 ± 32.1	0.696	111.2 ± 29.5	118.0 ± 34.4	0.232
SBP (mmHg)		112.5 ± 14.7	116.6 ± 15.3	0.194	117.3 ± 14.1	115.7 ± 13.4	0.823
DBP (mmHg)		79.9 ± 10.2	83.0 ± 9.7	0.157	84.1 ± 14.3	81.1 ± 8.6	0.671
AST (mg/dl)		25.5 ± 9.6	28.8 ± 9.7	0.139	32.1 ± 17.4	26.9 ± 8.5	0.028
ALT (mg/dl)		40.2 ± 28.1	38.9 ± 17.6	0.753	46.2 ± 33.3	41.6 ± 23.4	0.171
ALP (mg/dl)		185.8 ± 51.1	181.3 ± 48.0	0.116	200.0 ± 69.2	194.3 ± 67.8	0.147
NAFLD grade, %	(0)	0	5.4	0.796[a]	0	11.4	0.001[a]
	(1)	47.5	40.5		30	45.7	
	(2)	47.5	45.9		62.5	40	
	(3)	5	8.1		7.5	2.9	

Dependent student t and Wilcoxon test were performed for comparing normal and non-normal variables before and after intervention, respectively
Values are expressed as mean ± SD and median (interquartile range (IQR)) for normal and non-normal distribution variables, respectively
BMI body mass index, *HC* measured circumference of hip, *NC* measured circumference of neck, *AC* measured circumference of abdomen, *WHR* waist-hip ratio, *FBG* fasting blood glucose, *TC* total Cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *NAFLD* non-alcoholic fatty liver disease
[a]Ordinary data was analysed by Wilcoxon test

Table 3.3 Changes of anthropometric, biochemical and sonography data of patients with NAFLD between groups

		Placebo (n = 37)	Curcumin (n = 35)	P-value
Weight (kg)		−1.9 ± 4.3	−0.8 ± 2.6	0.260
BMI (kg/m^2)		−0.3 ± 0.9	−0.6 ± 1.1	0.338
Body fat mass		−1.0 ± 2.1	−1.8 ± 2.7	0.240
HC (cm)		−0.9 ± 1.4	−0.7 ± 1.2	0.670
AC (cm)		−1.8 ± 2.4	−1.7 ± 2.1	0.944
WHR		−0.01 ± 0.02	−0.01 ± 0.01	0.746
NC (cm)		−0.3 ± 0.9	−0.1 ± 0.6	0.451
FBG (mg/dL)		−1.0 ± 26.8	−6.1 ± 45.0	0.554
TC (mg/ dL)		−5.7 ± 40.0	−4.8 ± 40.0	0.914
TG (mg/ dL)		−0.5(−22.5–28.2)	8.0(−28.0–55.5)	0.707
HDL-C (mg/dL)		−2.7 ± 7.7	−3.0 ± 7.7	0.861
LDL-C (mg/dL)		2.0 ± 30.5	5.5 ± 27.0	0.603
SBP (mmHg)		3.5 ± 13.0	−0.5 ± 11.0	0.264
DBP (mmHg)		4.0 ± 13.5	−1.2 ± 13.0	0.179
AST (mg/ dL)		2.5 ± 10.5	−5.5 ± 14.5	0.007
ALT (mg/ dL)		−1.3 ± 25.5	−5.7 ± 25.0	0.449
ALP (mg/ dL)		−6.0 ± 22.5	−8.5 ± 35.0	0.701
NAFLD grade, %	(−2)	0	2.9	0.015[a]
	(−1)	18.9	48.6	
	(0)	67.6	45.7	
	(1)	10.8	2.9	
	(2)	2.7	0	

Independent student t and Mann Whitney U test were performed for comparing 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

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

[a]Mann Whitney U test was performed

The current findings are consistent with those of a previous trial with a high bioavailability curcumin-phosphatidylcholine complex that was administered at a higher dose (1000 mg/day) [23]. Most of the previous studies which used higher doses of curcumin used concentrations ranging from 500 mg to 1000 mg per day [29, 30], as a means of maximizing therapeutic effects. However, in this trial we managed to demonstrate the efficacy of curcumin in improving metabolic parameters at an even lower dose (250 mg per day for 8 weeks). Similar results were reported in previous animal studies where curcumin consumption dosages ranged from 50 mg to 200 mg a day, and these demonstrated significant improvement in insulin resistance, hepatic fat levels and it attenuated liver injury [21, 32].

These results can be explained by hormetic effect of curcumin. For example, low-dose curcumin administration could have antioxidant characteristics and high dose may induce autophagy and apoptosis. The observed biphasic dose–response potential of curcumin on cells showed the stronger effect of low dose administration than at higher dosages [33].

Curcumin modulates some metabolic risk factors such as inflammation, along with lipid, glycemic and oxidative pathways in NAFLD [34]. Regarding these positive effects and the lack of approved medications for NAFLD, it would be valuable to investigate the hepatoprotective effect of phospholipid-curcumin in NAFLD patients. Thus, curcumin may be able to slow down the initiation of the "first hit" in development of hepatic steatosis as well as significantly reduce the pro-inflammatory cytokines triggering the "second hit" of NAFLD pathogenesis [23].

Lifestyle changes through increasing the adherence to a well-established diet and optimal physical activity are considered as an initial step in the prevention and treatment of NAFLD [35, 36]. In this trial, all participants were instructed to follow energy balanced diets according to the current clinical guidelines for management of overweight and obesity. This is the likely reason why we did not find significant differences in terms of weight reduction and glycaemic control between the groups. The enhancement of physical performance and physiological fatigue reduction following curcumin supplementation might contribute to BMI reduction and other indices of NAFLD [37].

This study has several strengths. These include the balanced block randomisation design, rigorous inclusion and exclusion criteria, a lengthy (8 week) follow up period, and the direct comparison of curcumin and placebo effects. Moreover, we used phospholipid-curcumin which has optimal bioavailability unlike the natural form of curcumin used in previous studies which has a lower bioavailability [38].

There are also limitations of this trial that should be considered in interpretation of the results. First, we used ultrasonography to assess hepatic steatosis instead of other modalities such as elastography or histopathology. In addition, it was a single centre trial which could jeopardise its generalizability.

3.5 Conclusions and Future Perspectives

In conclusion, the findings of the present trial suggest a hepatoprotective effect of low dose phospholipid-curcumin supplementation associated with disease severity alterations in patients with NAFLD. While no pharmacological therapy has yet been approved for NAFLD, supplementation with curcumin may provide a safe and viable approach for patients and suppress the progression of NAFLD. However, further trials over longer durations and which assess various dosages of curcumin and its effects on the metabolic parameters in patients with NAFLD are needed.

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Conflict of Interests None.

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