Plant Archives Vol. 20, Supplement 2, 2020 pp. 3640-3647 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

TURMERIC SUPPLEMENTATION IN NONALCOHOLIC FATTY LIVER DISEASE: A RANDOMIZED DOUBLE BLIND CONTROLLED TRIAL

Durdana Husain[1], Maryam Jarahzadeh[2]*, Pezhman Alavinejad[3], Afshin Rezazadeh[4] and Mohammad Haghighizadeh[5]

[1]Department of Nutrition, Faculty of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Department of Nutrition, School of Paramedicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Department of Infectious Diseases of the Digestive System, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Department of Radiology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Department of Statistics and Epidemiology, School of Hygiene, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Corresponding author: maryam.jarahzadeh@gmail.com

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease that affects a high proportion of the world's population, and is tightly associated with obesity and metabolic syndrome. Turmeric is a perennial plant belonging to the Zingiberaceae family, and several studies have shown that turmeric has antioxidant, anti-inflammatory and hypolipidaemic effects. The aim of this study was to evaluate the effects of turmeric on liver enzymes, lipid profiles and malondialdehyde (MDA) in patients with NAFLD. This double-blind placebo-controlled trial was conducted on 64 NAFLD patients. All the subjects were randomly assigned to two groups, receivingeither turmeric (2 g) or placebo capsules for 8 weeks. Changes in liver enzymes, lipid profiles, and MDA were measured before and after the study in order to evaluate the effectiveness of turmeric on NAFLD patients. At the end of the study, the group who received turmeric showed a significant reduction in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and gamma-glutamyltranspeptidase [GGT]) compared to the placebo group ($p < 0.05$). In addition, the triglycerides, LDL and MDA concentration decreased, whereas HDL increased significantly within the turmeric group as compared to baseline. Nonetheless, there was no significant change in the placebo group. Furthermore, there were no significant changes in the level of cholesterol and VLDL, as well as in grades of NAFLD in both the groups. This study suggested that taking 2g turmeric daily was effective in improving NAFLD characteristics.

Keywords: Nonalcoholic fatty liver, turmeric, enzymes, malondialdehyde, lipid profile, liver echogenicity.

Introduction

Liver injury is very common worldwide (AlGhamdi, 2019; Shateri *et al.*, 2019; Albalawi *et al.*, 2019). Nonalcoholic fatty liver disease (NAFLD) refers to a wide spectrum of liver disorders ranging from the accumulation of large vacuoles of triglyceride with inflammation (steatosis) to nonalcoholic steatohepatitis(NASH), fibrosis and cirrhosis (Musso *et al.*, 2010; Puri and Sanyal, 2012).

NAFLD is now recognized as the most common liver dysfunction and increases in prevalence in parallel with epidemics of obesity and type II diabetes (Petta *et al.*, 2009). In the northern and southern United States, Australia, New Zealand, Middle East and Europe, estimates of NAFLD prevalence rate vary between 10 to 24 % (Lankarani *et al.*, 2013). The prevalence of NAFLD in Iranian adult general population has been reported as high as 21.5% to 31.5% (Sohrabpour *et al.*, 2010; Lankarani *et al.*, 2013). The most important causes of the non-alcoholic fatty liver are obesity, hyperglycemia, type II diabetes and hyperlipidemia (Pagano *et al.*, 2002; Farrell *et al.*, 2008). Researches have shown that high-fat diet leads to liver steatosis (Assy *et al.*, 2000). Triglycerides and cholesterol are important biological lipids but high consumption of these lipids through diet can lead to hypertriglyceridemia and hypercholesterolemia (Hokanson, 2002; Kametani *et al.*, 2002). Esterification of free fatty acid (FFA) and glycerol in the hepatocytes forms triglycerides and accumulation of triglycerides in the liver leads to NAFLD. Free fatty acids arise in the liver in three different ways: lipolysis (the hydrolysis of FFA and glycerol from triglyceride) within adipose tissue, dietary sources, and de novo lipogenesis (Postic and Girard, 2008).

Etiology of nonalcoholic fatty liver diseases is not well known. The "multiple hit" hypothesis considers multiple insults acting together on genetically predisposed subjects to induce NAFLD and provides a more accurate explanation of NAFLD pathogenesis. Such hits include insulin resistance, hormones secreted from the adipose tissue, nutritional factors, gut microbiota and genetic and epigenetic factors (Buzzetti *et al.*, 2016). Oxidative stress leads to peroxidation cell membrane lipid in the liver. Products of oxidation are harmful, and this combination can lead to an inflammatory response in liver cells and eventually, can cause fibrosis and apoptosis (Edmison and McCullough, 2007; Younossi, 2008).

It is difficult to treat NAFLD and find an ideal treatments for it, although the changes in life style behavior like physical activity, dietary habits as well as bariatric surgery can be used to reduce liver fat but it is difficult to achieve these life style changes and maintaining them. On the other hand, there are some drugs which can be used for the treatment of NAFLD. Most of these drugs have weight loss effect and some patients are unable to tolerate the side effects of these chemical drugs (Puri and Sanyal, 2002). So nutraceutical agents may be beneficial in treatment of NAFLD.

Considering the role of oxidative stress in the pathogenesis of the disease and low levels of antioxidants in these patients, use of antioxidants has attracted the attention

of researchers (Sunilson *et al.*, 2008). Several plant-derived natural products have the potential to be hepatoprotective and therefore, can be used to treat acute and chronic liver diseases (Tandon *et al.*, 2008; Zeashan *et al.*, 2008; Varatharajan and Promwichit, 2009; Adaramoye *et al.*, 2010).

The hepatoprotective activity of turmeric (Curcuma longa) or its constituent is reported in the literature (Deshpande *et al.*, 1998; Miyakoshi *et al.*, 2004; Bao *et al.*, 2010; Černý *et al.*, 2011; El-Shahat *et al.*, 2012). Turmeric, a dried powder derived from the rhizome of Curcuma longa Linn, is an herb that has been used as a dietary spice and in traditional medicine for centuries (Bjelakovic *et al.*, 2007; Aggarwal *et al.*, 2013). Curcuminoids, a mixture of curcumindiferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin, are vital constituents of turmeric (Ahmed and Gilani, 2014). The most active and nontoxic component of turmeric is curcumin, composing2–5% of turmeric (Gupta *et al.*, 2013). It is an antioxidantand anti-inflammatory (Sharma, 1976; ABE *et al.*, 1999; Hsu and Cheng, 2007). Lee et al. (2010) showed that administration of turmeric on carbon tetrachloride (CCl4)-induced hepatotoxicity in rats reduced aspartate aminotransferase (AST) and alanine aminotransferase (ALT)of the serum, and caused the hepatic malondialdehyde levels to decrease significantly. In a recent study by Moghadam et al., it was found that turmeric extract against liver toxicity and oxidative stress induced by methotrexate decreased malondialdehyde(MDA) and serum levels of liver aminotransferase in the liver of rats (Moghadam *et al.*, 2015). In another study by Elahi et al., it was shown that turmeric powder reduced the accumulation of lipids in serum in rats fed with high-fat diet (Elahi, 2012). Kim et al. also observed that the serum AST, ALT and gamma-glutamyltranspeptidase (GGT) levels were significantly reduced in subjects with elevated ALT levels who received turmeric powder (Kim *et al.*, 2013). Because there is no universal treatment for NAFLD (Lirussi *et al.*, 2007) and due to the antioxidant and anti-inflammatory properties of turmeric (Menon and Sudheer, 2007), we considered that oral turmeric may be effective in managing NAFLD and preventing its progression. Therefore, we designed this clinical trial to investigate the impact of oral turmeric on liver enzymes, lipid profile, and MDA, as well as the grades of echogenicity and hepatic steatosis among patients with NAFLD.

Materials and Methods

Study Design

This study was designed as a randomized, double-blind, placebo-controlled clinical trial. Patients with NAFLD were selected from the gastroenterology clinic of Jundishapur University of Medical Sciences, Ahvaz, Iran. Subjects with any history of a chronic liver disease (other than NAFLD), renal failure, or gastrointestinal diseases, or those currently consuming vitamin supplements or anticoagulation medicines were excluded. In all the patients, NAFLD diagnosis was confirmed by elevation of liver enzymes, the absence of alcohol consumption and an ultrasonography scan of the liver (Lirussi *et al.*, 2007; Puri and Sanyal, 2012). None of the NAFLD subjects were taking weight-lowering agents, oral medications for diabetes mellitus, or hepatotoxic medications. At the time of initiation of research 76 patients was registered at the clinic. The subjects were briefed about the objectives of the study and their cooperation was sought with written consent. Statistically, a sample size of 32 subjects in both intervention and control group were sufficient. Considering attrition rate of about 10 percent, a total of 72patients were enrolled for the study. They were randomly assigned to either the intervention or the control group.

Overall, 64 patients were completed the study. Daily 2g turmeric and placebo (wheat flour) capsules were prescribed for the intervention and control group, respectively and they were encapsulated by the School of Traditional Medicine of Tehran University of Medical Sciences. The intervention period was 2 months. The subjects were advised to use turmeric after main meals to enhance absorption in the small intestine due to the presence of dietary fat (Carter, 2008; Mehta *et al.*, 2012).

The turmeric dosage and study duration were selected according to previous reports (Bhowmik *et al.*, 2009; Adab *et al.*, 2013). We called the participants once a week to remind them of the supplements and they were asked to report any adverse effects. The medicine history, demographic data and diet habits of each patient were recorded by using a self-administered questionnaire at the beginning of the study. Physical activity was recorded by IPAQ-short version. To evaluate dietary intake, including energy, fat, protein, and carbohydrate, 24-hour dietary recalls for three days (2 working days and a holiday) were obtained from all the subjects at pre and post intervention. In the 24 hour dietary recall method, the interviewer asks the subjects to recall the exact food intake during the previous twenty four hour period or the previous day and it was recorded by participants. Quantities of food consumed are estimated in household measures and then converted into grams. Nutrient intake of the subjects was analyzed by using modified Nutritionist IV software (version 3.5.2, First Data Bank; Hearst Corp, San Bruno, CA).

Anthropometric Assessments

To measure height and weight of the participants, a measuring tape and digital scale were used. Accordingly, height was recorded with an accuracy of 0.1cm while the participants were in standing and an upright position without shoes, and weight was measured with minimal clothing and without shoes, with a precision of 0.1 kg.

Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Waist circumference (WC) was measured by using a non-stretchable tape applied horizontally mid-way between the lowest hip margin and the iliac crest., and hip circumference (HC) was taken at the point yielding the maximum circumference over the buttocks, without any pressure on the surface. These measurements were recorded with a precision of 0.1 cm.

Waist circumference is a convenient and simple measure which is unrelated to height, correlates closely with BMI. The ratio of waist to hip circumference (WHR) is an approximate index of intra-abdominal fat mass and total body fat. There is an increased risk of metabolic complications for man with the waist circumference≥102cm, and women with waist circumference >88cm (Tsigos *et al.*, 2008).

Biochemical Analysis

Blood samples from all the patients were obtained before and after the 8-week intervention. From each participant, a 10 ml blood sample was obtained in the fasting condition and poured into evacuated tubes. Also, serum was prepared after centrifugation (3000 rpm, 4°C, and 15 minutes) by a trained examiner, and then stored frozen (-70°C) until analysis. To control hormone variation, blood samples were not collected from women during their menstrual period. Hematological factors including ALT, AST andGGTwere determined by an automated biochemical analyzer (Hitachi-7180E, Tokyo, Japan) with a Pars Azmoon reagent kit (Tehran, Iran). The MDA was determined by turbid metric immunoassay (LDN Co., Germany).

Ultrasonography scans of the liver were performed with a 3.5/5 MHz probe at entry and at the end of the study period by a single expert radiologist blinded to the treatment method of the patients (General Electric LOGIQ 400 CL). The grade of hepatic echogenicity was measured for each patient and then the degree of steatosis was categorized using the following scale: 0 (normal), 1 (mild), 2 (moderate), 3 (severe).

Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL) version 18 for Windows. First, the normal distribution of all the variables was checked with the Kolmogorov-Smirnov test. To compare qualitative variables confounding smoking and sex between two groups Chi Square test is used. We compared the means of the variables of each group by using independent sample t-tests for both the groups. The end values of each variable were also compared with the baseline values using paired sample t-tests. Differences with p values < 0.05 were considered as significant. For the comparison of mean of confounding quantitative variables like anthropometric and dietary in each group variance analysis for the repeated measured data is used.

Other quantitative variables in this study measured by Paired t test, and Wilcoxon and Mann-Whitney test was used for variable which were not normal distribution.

Ethics Statements

This study was designed as a randomized, double-blind, placebo-controlled clinical trial. The trial was approved by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (IR.Ajums.rec.1394.104). This study was also registered at IRCT.ir (IRCT 2015092924262N1). Written informed consent was signed by all the participants.

Results and Discussion

Characteristics of the patients

Sixty-four patients were included in the study and randomly assigned into 2 groups—turmeric (n = 32) or placebo (n = 32). The number and percentage of females in the intervention group and the control group were 13 (40.6%) and 13 (40.6%), respectively. Patient screening, enrollment, and retention by the treatment group are shown in Figure 1. There were no significant difference in age, sex, smoking, physical activity, body weight, energy intake, liver measurement, lipid profile, and glycemic status between the two groups at baseline (Table 1). We found a significant decrease in the weight, waist, and WHR within the both groups; however, no significant differences were observed between the 2 groups in terms of these variables (Table 2). At the end of the intervention, the percentages of NAFLD grades in the turmeric-treated group were not markedly reduced (p = 0.271) compared to the control group, but intra group differences in the turmeric-treated group showed a significant reduction in the percentages of NAFLD grades (p = 0.020, Table 3). At the end of the 8-wk treatment period, a significant improvement in liver enzymes was seen within and between both the groups. Compared with the placebo group, patients taking turmeric capsules had a significant decrease in the following liver enzymes: ALT (P < 0.043), AST (P < 0.044), and GGT (P< 0.046) (Table 4). As shown in Table 5, after the 8-week intervention, triglycerides (P = .041), LDL (P = .035), HDL (P = .049) and MDA (P = .005) changed significantly within the turmeric group as compared to baseline. But there was no significant change in blood cholesterol (p= .196) and VLDL level (P = .417).

Table 1: Baseline characteristics of participants enrolled.

Variables	Turmeric group (n = 32)	Placebo group (n = 32)	P value[1]
Age (years)	44.12 ± 8.35[2]	38.56 ± 10.43	0.22
Sex(M/F)	19/13	19/13	1.000[α]
Smoking			1.000[β]
Yes	3(9.38%)	2(6.25%)	
No	29(90.62%)	30(93.75%)	
Physical activity			0.491[α]
Inactive	26(81.25%)	28(87.5%)	
Minimally active	6(18.75%)	4(12.5%)	
Height (cm)	167.8 ± 11.6	167.6 ± 9.15	0.948
Body weight (kg)	82.9 ± 14.3	85.1 ± 18.5	0.572
WC (cm)	104.7 ± 10.7	105.6 ± 15.0	0.768
HC(cm)	110.5 ± 9.1	110.6 ± 10.1	0.979
WHR	0.94 ± 0.04	0.95 ± 0.06	0.679
BMI (kg/m2)	29.5 ± 4.9	30.1 ± 5.10	0.613
SBP (mmHg)	129 ±16	124 ± 16	0.346
DBP (mmHg)	81 ± 8	81 ± 9	0.769
Energy (kcal/day)	2199.0 ± 62.5	2059.9 ± 62.0	0.375

Protein (g/day)	91.5 ± 40.8	76.1 ± 24.1	0.072
Fat (g/day)	70.3 ± 32.6	62.4 ± 29.1	0.310
Carbohydrate (g/day)	312.1 ± 11.7	305.5 ± 10.4	0.812

Abbreviation: M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC = waist circumference, HC = hip circumference, WHR = waist-to-hip ratio, BMI = body mass index.
1= Analyzed by Independent t-test, 2= Values are presented as mean ± SD. α=Analyzed by Pearson χ2, β=Analyzed by Fisher's exact-test.

Table 2: Effects of Turmeric on Anthropometric Characteristics in Patients with NAFLD.

Variables	**Turmeric group (n = 32)**	**Placebo group (n = 32)**	**P 1**
Body weight (kg)			
pre intervention	82.9 ± 14.3	85.1 ± 18.4	0.572
post intervention	81.3±13.6	83.5 ±17.1	0. 571
P2	0.001	0.021	
WC (cm)			
pre intervention	104.7 ± 10.7	105.6 ± 15.0	0.768
post intervention	101.7 ±10.6	102.6 ± 11.7	0.752
P2	0.001	0.018	
HC(cm)			
pre intervention	110.5 ± 9.1	110.6 ± 10.1	0.979
post intervention	108.4 ± 8.8	109.8 ± 10.0	0.562
P2	0.001	0.161	
WHR			
pre intervention	94 ± 0.04	95 ± 0.06	0.679
post intervention	93 ± 0.04	93 ± 0.04	0.755
P2	0.024	0.035	
BMI (kg/m2)			
pre intervention	29.5 ± 4.9	30.1 ± 5.1	0.613
post intervention	28.9 ± 4.6	29.7 ± 4.6	0.544
P2	0.001	0.071	

NAFLD = nonalcoholic fatty liver disease, WC = waist circumference, WHR = waist-to-hip ratio, BMI = body mass index.
Data are expressed as mean ± SD. P1 resulted from independent sample t tests and P2 resulted from paired sample t test.

Table 3: Effects of Turmeric on NAFLD Degree in Patients with NAFLD.

NAFLD degree	**Turmeric n =32**	**Placebo n=32**	**P1**
pre intervention			
Normal	0	0	
Mild	24(75%)	23(71.9%)	0.787
Moderate	7(21.9%)	8(25%)	
Severe	1(3.1%)	1(3.1%)	
post intervention			
Normal	2(6.25%)	1(3.1%)	
Mild	26(81.2%)	24(75 %)	0.271
Moderate	4(12.5%)	7(21.9%)	
Severe	0	0	
P2	0.020	0.102	

NAFLD = nonalcoholic fatty liver disease.
Data are expressed as n (%). P1 resulted from Mann-Whitney U test between the 2 groups and P2 resulted from Wilcoxon test within each group.

Table 4: Effects of Turmeric on Serum Levels of Liver Enzymes in Patients with NAFLD.

Variables	**Turmeric n=32**	**Placebo n =32**	**P1**
FBS			.
pre intervention	105.16 ± 12.85	100.70 ± 12.62	0.167
post intervention	101.08 ± 10.51	97 ± 10.94	0.134
P2	0.060	0.002	
ALT (U/L)			
pre intervention	39.56 ± 22.41	35.42 ± 18.51	0.424
post intervention	30.51 ± 12.61	39.50 ± 21.15	0.043
P2	0.038	0.307	
AST (U/L)			
pre intervention	26.81 ± 10.54	27.29 ± 11.53	0.861
post intervention	21.19 ± 5.67	25.26 ± 9.66	0.044

P2	0.021	0.303	
GGT(U/L)			
pre intervention	33.81 ± 17.50	32.91 ± 20.26	0.767
post intervention	25.62 ± 9.88	31.59 ± 16.70	0.046
P2	0.000	0.562	
AST/ALT ratio			
pre intervention	0.744 ± 0.23	0.829 ± 0.23	0.146
post intervention	0.773 ± 0.21	0.763 ± 0.05	0.887
P2	0.449	0.198	

NAFLD =nonalcoholic fatty liver disease, FBS= fasting blood sugar, AST = aspartate aminotransferase, ALT= alanine aminotransferase, GGT= gammaglutamyltranspeptidase, LDL= low-density lipoprotein, HDL= high-density lipoprotein, MDA= Malondialdehyde.
Data are expressed as mean ± SD. P1 resulted from independent sample t tests and P2 resulted from paired sample t tests.

Table 5: Effects of Turmeric on Lipid profile and Malondialdehyde in Patients with NAFLD.

Variables	Turmeric n=32	Placebo n =32	P1
Triglycerides (mmol/L)			
pre intervention	164.34± 80.12	176.44 ± 91.96	0.577
post intervention	141.78 ± 65.57	155.62 ± 85.35	0.470
P2	0.043	0.188	
Cholesterol (mmol/L)			
pre intervention	195.88 ± 35.38	194.50 ± 34.29	0.875
post intervention	186.50 ± 36.49	182.62±29.36	0.641
P2	0.196	0.143	
LDL (mmol/L)			
pre intervention	121.93 ± 28.77	116.52 ± 27.11	0.442
post intervention	108.40 ± 26.83	104.60 ± 22.99	0.545
P2	0.035	0.052	
HDL (mmol/L)			
pre intervention	40.28 ± 6.66	42.45 ± 10.17	0.316
post intervention	42.34 ± 4.13	44.59 ±7.17	0.129
P2	0.049	0.247	
VLDL(mmol/L)			
pre intervention	32.86 ± 16.02	35.28 ± 18.39	0.577
post intervention	28.35 ± 13.11	31.12 ± 17.07	0.470
P2	0.043	0.188	
Cholesterol/HDL ratio			
pre intervention	5.03 ± 1.37	4.71 ± .0.97	0.294
post intervention	4.45 ± 1.00	4.16 ± 0.80	0.211
P2	0.021	0.012	
LDL/HDL ratio			
pre intervention	3.12 ± 0.94	2.81 ± 0.72	0.155
post intervention	2.57 ± 0.66	2.38 ± 0.59	0.235
P2	0.003	0.005	
MDA(mmol/L)			
pre intervention	0.278 ± 0.14	0.237 ± 0.13	0.241
post intervention	0.167 ± 0.10	0.189 ± 0.13	0.487
P2	0.001	0.191	

The present study was a randomized, double-blind clinical trial reveal that administration of turmeric (2 g/day) for 8 weeks had beneficial effects on serum levels of some parameters of lipid profile, hepatic enzymes, MDA, and degree of steatosis in patients with NAFLD. The results of our study show that the 2g turmeric consumption significantly reduced serum TG and LDL-c, and increased serum HDL-c level. However, it had no effect on TC and VLDL levels. Decreasein serum TG is probably due to multiple induction pathways of fatty acid catabolism (e. g., fatty acid β-oxidation and TG hydrolysis**)**.

Metabolites of curcuminoid serve as ligands that are likely to activate PPAR-α (peroxisome proliferator activated receptor alpha). The transcription of genes encoding in the beta-oxidation pathway in the liver is regulated by PPAR-α. Therefore, PPAR-α plays a central role in the control of lipid homeostasis. On the other hand fatty acid synthetase (FAS) is a key enzyme in 'de novo' fatty acid and TG synthesis, which is regulated by SREBP (sterol regulatory element binding protein).

Curcumin could decrease lipid synthesis through activating AMPK (adenosine mono phosphate activated protein kinase), which further inhibits protein expression in SREBP-1 and leads to the reduction of the transcription activity of FAS (Schoonjans *et al.*, 1996).

Concerning the effects of turmeric or curcuminon serum levels of lipid profile, hepatic enzymes, MDA, and degree of steatosis in patients with NAFLD and other diseased conditions, several studies on experimental animals and human subjects were done and shown improvement in

liver function but not all (Schoonjans *et al.*, 1996; Miyakoshi *et al.*, 2004; Bhowmik *et al.*, 2009; Bao *et al.*, 2010; Lee *et al.*, 2010; Pakfetrat *et al.*, 2015).

A study conducted by Adab et al. on patients with type II diabetes showed significant decreases in TG and LDL-c, but no significant effect on TC and HDL-c after 8 week consumption of 2.1g turmeric powder daily (Adab *et al.*, 2013).

Curcumin leads to lower plasma LDL-c via reduction of CE (cholestryl ester) transfer from HDL and/or enhanced clearance of plasma LDL-c which can be mediated by hepatic CD36 and SRB1 (scavenger receptor class B member 1) under condition of LDLR deficiency. Curcumin-induced reduction of CE transfer between lipoproteins due to CETP (cholestryl ester transfer protein) inhibition results in decreasing LDL-c with simultaneous increase of HDL-c concentration. In addition, the SRB1 in the liver could increase the flux of reverse cholesterol transport (Schoonjans *et al.*, 1996). A study conducted by Kim et al. found that 12 weeks of fermented turmeric powder (FTP) supplementation at a dosage of 3g/day had no effect on serum levels of TG, total cholesterol, LDL-c and HDL-c in patients with mild to moderate elevated ALT levels (Kim *et al.*, 2012).

Abnormal liver enzyme levels (ALT, AST, and GGT) are used to presumptive diagnosis of NAFLD and their increase in blood indicates liver dysfunction (Puri and Sanyal, 2012). It is proposed that reduction in ALT and AST levels reflects improvement in hepatic function. Therefore, data from the current trial, showing a reduction of ALT and AST levels, suggest that turmeric may improve hepatic function while study conducted by Pakfitrat et al. could not find any significant change in the liver enzyme in end-stage renal disease patients (Pakfetrat *et al.*, 2015). Furthermore, Chuengsamarn et al. also could not find any significant differences in AST and ALT between the curcumin-treated and placebo-treated groups in patients with diabetes (Chuengsamarn *et al.*, 2014). In another study, Salama et al. showed that supplementation with Curcuma longa rhizome ethanolic extract (CLRE) in a rat model of induced liver cirrhosis over 8 weeks liver biochemistry (ALT, AST, and GGT) was significantly lower in the Curcumalonga-treated groups compared with controls (Salama *et al.*, 2013).

We estimated the liver oxidative stress by measuring the oxidative stress marker MDA. The current study showed that turmeric supplementation for 8 weeks resulted in a significant decrease in the MDA as compared to baseline within the group receiving turmeric. In order to compare our findings with others, we find that studies conducted by Moghadam *et al.* (2015), Pakfetrat *et al.* (2015), Acar *et al.* (2012) and Hemeida *et al.* (2008) regarding reduction of MDA by supplementation with turmeric or curcumin were consistence with ours.

Liver ultrasonography, being safe, inexpensive, widely available and well tolerated, is the first-line imaging technique used to diagnose NAFLD both in the clinical and epidemiological setting (Lee and Park, 2014). Thus, we assessed the degree of steatosis in patients with use of this technique, and the current study showed that consumption of turmeric for 8 weeks resulted in a significant decrease in the degree of steatosis within the groups receiving turmeric, as compared to baseline. According to the study of Elahi et al., a higher degree of steatosis which was developed in rats fed with high-fat emulsion for 6 weeks, and administration of turmeric powder resulted in the prevention of hepatic fatty deposition in hepatocytes (Elahi, 2012).

Several limitations existed in our study. Firstly, due to ethical considerations, we could not use liver biopsy which is a more accurate diagnostic tool. Secondly, follow-up duration was not long enough to consider the effects of turmeric on the hepatic system. Thirdly, we could not exactly evaluate the loyalty of the participants to the treatments; however, we controlled this problem, by repeated follow-up visits and counting the capsules.

Conclusion

The results of this randomized double blind placebo controlled clinical trial suggest that 2g of turmeric supplementation for 8 weeks could improve NAFLD characteristics and be administered as a good adjuvant therapeutic with hypolipidemic and antioxidant properties for this disease. Although this study verifies our hypothesis, further evidence from randomized controlled trial with larger numbers of subjects, for a longer period of time and with histologic endpoints are required.

Acknowledgments

We sincerely thank all patients who participated in this study; this study would not be possible without their cooperation. We also thank Miss Meerlohi from Department of Laboratory Sciences, School of Para Medicine, Ahvaz JundishapurUniversity of Medical Sciences, Ahvaz, Iran, for cooperation in measuring biochemical factors.

References

Abe, Y., S. Hashimoto and T. Horie (1999) Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. Pharmacol. Res., 39(1): 41-7.

Acar, A., E. Akil, H. Alp, O. Evliyaoglu, E. Kibrisli, A. Inal, et al. (2012) Oxidative damage is ameliorated by curcumin treatment in brain and sciatic nerve of diabetic rats. Int. J. Neurosci., 122(7): 367-72.

Adab, Z., S. Eghtesadi, M. Vafa, I. Heydari, A. Shojaei, H. Haqqani, et al. (2013) Effect of turmeric on body measurement indices, glycemic condition, and lipid profile in hyperlipidemic patients with type 2 diabetes. Iranian Journal of Nutrition Sciences & Food Technology, 8(3): 217-27.

Adaramoye, O., A. Odunewu and E. Farombi (2010) Hepatoprotective effect of Curcuma longa L. in D-galactosamine induced liver injury in mice: evidence of antioxidant activity. Afr J Med Med Sci., 39: 27-34.

Aggarwal, B.B., W. Yuan, S. Li and S.C. Gupta (2013) Curcumin‐free turmeric exhibits anti‐inflammatory and anticancer activities: Identification of novel components of turmeric. Mol Nutr Food Res., 57(9): 1529-42.

Ahmed, T. and A.H. Gilani (2014) Therapeutic potential of turmeric in Alzheimer's disease: curcumin or curcuminoids? Phytother Res., 28(4): 517-525.

Albalawi, A.M., A.S. Albalawi, H.S.T. Albalawi, S.K. Almuhawwis, M.A. Alswilem and F.M. Aldakhil (2019) Evaluation of Recent Updates Regarding Acetaminophen-Induced Acute Liver Failure. Arch. Pharma. Pract., 10(3): 56-60.

AlGhamdi, S.A. (2019) Drug-Induced Fatty Liver. Int. J. Pharm. Res. Allied Sci., 8(4): 82-90.

Assy, N., K. Kaita, D. Mymin, C. Levy, B. Rosser and G. Minuk (2000) Fatty infiltration of liver in hyperlipidemic patients. Dig Dis Sci., 45(10): 1929-34.

Bao, W., K. Li, S. Rong, P. Yao, L. Hao, C. Ying, et al. (2010) Curcumin alleviates ethanol-induced hepatocytes oxidative damage involving heme oxygenase-1 induction. J. Ethnopharmacol., 128(2): 549-53.

Bhowmik, D., K. Kumar, M. Chandira and B. Jayakar (2009) Turmeric: a herbal and traditional medicine. Arch. Appl. Sci. Res., 1(2): 86-108.

Bjelakovic, G., D. Nikolova, L.L. Gluud, R.G. Simonetti and C. Gluud (2007) Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. Jama, 297(8): 842-57.

Buzzetti, E., M. Pinzani and E.A. Tsochatzis (2016) The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism, 65(8): 1038-48.

Carter, A. (2008) Curry Compound Fights Cancer in the Clinic. JNCI J. Natl. Cancer Inst., 100(9): 616-617.

Černý, D., N. Lekić, K. Váňová, L. Muchová, A. Hořínek, E. Kmoníčková, et al. (2011) Hepatoprotective effect of curcumin in lipopolysaccharide/-galactosamine model of liver injury in rats: relationship to HO-1/CO antioxidant system. Fitoterapia, 82(5): 786-91.

Chuengsamarn, S., S. Rattanamongkolgul, B. Phonrat, R. Tungtrongchitr and S. Jirawatnotai (2014) Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. J Nutr Biochem., 25(2): 144-50

Deshpande, U., S. Gadre, A. Raste, D. Pillai, S. Bhide and A. Samuel (1998) Protective effect of turmeric (Curcuma longa L.) extract on carbon tetrachloride-induced liver damage in rats. Indian J Exp Biol., 36(6): 573-577.

Edmison, J. and A.J. McCullough (2007) Pathogenesis of non-alcoholic steatohepatitis: human data. Clin Liver Dis., 11(1): 75-104.

Elahi, R.K. (2012) Preventive effects of turmeric (Curcuma longa Linn.) powder on hepatic steatosis in the rats fed with high fat diet. Life Sci J., 9(4): 5462-5468.

El-Shahat, M., S. El-Abd, M. Alkafafy and G. El-Khatib (2012) Potential chemoprevention of diethylnitrosamine-induced hepatocarcinogenesis in rats: Myrrh (Commiphora molmol) vs. turmeric (Curcuma longa). Acta Histochem., 114(5): 421-428.

Farrell, G.C., J. George, Pd.M. Hall and A.J. McCullough (2008) Fatty liver disease: NASH and related disorders: John Wiley & Sons.

Gupta, S.C., B. Sung, J.H. Kim, S. Prasad, S. Li and B.B. Aggarwal (2013) Multitargeting by turmeric, the golden spice: From kitchen to clinic. Mol Nutr Food Res., 57(9): 1510.

Hemeida, R. and O. Mohafez (2008) Curcumin attenuates methotraxate-induced hepatic oxidative damage in rats. J. Egypt. Natl. Cancer. Inst., 20(2): 141-148.

Hokanson, J.E. (2002) Hypertriglyceridemia and risk of coronary heart disease. Curr. Cardiol. Rep., 4(6): 488-93.

Hsu, C.H. and A.L. Cheng (2007) Clinical studies with curcumin. Adv. Exp. Med. Biol., 595: 471-80.

Kametani, T., H. Koshida, T. Nagaoka and H. Miyakoshi (2002) Hypertriglyceridemia is an independent risk factor for development of impaired fasting glucose and diabetes mellitus: a 9-year longitudinal study in Japanese. Intern. Med., 41(7): 516-21.

Kim, S.-W., K.-C. Ha, E.-K. Choi, S.-Y. Jung, M.-G. Kim, D.-Y. Kwon, et al. (2013) The effectiveness of fermented turmeric powder in subjects with elevated alanine transaminase levels: a randomised controlled study. BMC Complement Altern Med., 13(1): 58.

Kim, Y.-J., Y.-H. You and W.-J. Jun (2012) Hepatoprotective activity of fermented Curcuma longa L. on galactosamine-intoxicated rats. J Korean Soc Food Sci Nutr., 41(6): 790-795.

Lankarani, K.B., F. Ghaffarpasand, M. Mahmoodi, M. Lotfi, N. Zamiri, S.T. Heydari, et al. (2013) Non alcoholic fatty liver disease in southern Iran: a population based study. Hepat Mon., 13(5): e9248.

Lee, H.-S., L. Li, H.-K. Kim, D. Bilehal, W. Li, D.-S. Lee, et al. (2010) The protective effects of Curcuma longa Linn. Extract on carbon tetrachloride-induced hepatotoxicity in rats via upregulation of Nrf2. J. Microbiol. Biotech., 20(9): 1331-1338.

Lee, S.S. and S.H. Park (2014) Radiologic evaluation of nonalcoholic fatty liver disease. World J. Gastroenterol., 20(23): 7392–7402.

Lirussi, F., L. Azzalini, S. Orando, R. Orlando and F. Angelico (2007) Antioxidant supplements for non-alcoholic fatty liver disease and/or steatohepatitis. Cochrane Database Syst. Rev., 1: CD004996.

Mehta, A., G. Kaur and Chintamaneni (2012). Piperine and Quercetin Enhances Antioxidant and Hepatoprotectiveeffet of Curcumin in Paracetamol Induced oxidative stress. Int. J. Pharmacology, 8(2): 101-107.

Menon, V.P. and A.R. Sudheer (2007) Antioxidant and anti-inflammatory properties of curcumin. Adv. Exp. Med. Biol., 595: 105-25.

Miyakoshi, M., Y. Yamaguchi, R. Takagaki, K. Mizutani, T. Kambara, T. Ikeda, et al. (2004) Hepatoprotective effect of sesquiterpenes in turmeric. Biofactors, 21(1–4): 167-70.

Moghadam, A.R., S. Tutunchi, A. Namvaran-Abbas-Abad, M. Yazdi, F. Bonyadi, D. Mohajeri, et al. (2015) Pre-administration of turmeric prevents methotrexate-induced liver toxicity and oxidative stress. BMC Complement Altern Med., 15(1): 246.

Musso, G., R. Gambino and M Cassader (2010) Non-alcoholic fatty l iver disease from pathogenesis to management: an update. Obes Rev., 11(6): 430-445.

Pagano, G., G. Pacini, G. Musso, R. Gambino, F. Mecca, N. Depetris, et al. (2002) Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology, 35(2): 367-372.

Pakfetrat, M., M. Akmali, L. Malekmakan, M. Dabaghimanesh and M. Khorsand (2015) Role of turmeric in oxidative modulation in end-stage renal disease patients. Hemodial Int., 19(1): 124-131.

Petta, S., C. Muratore and A. Craxi (2009) Non-alcoholic fatty liver disease pathogenesis: the present and the future. Dig Liver Dis., 41(9): 615-625.

Postic, C. and J. Girard (2008) Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance:

lessons from genetically engineered mice. J Clin Invest., 118(3): 829.

Puri, P. and A.J. Sanyal (2012) Nonalcoholic fatty liver disease: definitions, risk factors, and workup. Clin Liver Dis., 1(4): 99-103.

Salama, S.M., M.A. Abdulla, A.S. AlRashdi, S. Ismail, S.S. Alkiyumi and S. Golbabapour (2013) Hepatoprotective effect of ethanolic extract of Curcuma longa on thioacetamide induced liver cirrhosis in rats. BMC Complement. Altern. Med., 13(1): 56.

Schoonjans, K., B. Staels and J. Auwerx (1996) Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. J. Lipid. Res., 37(5): 907-25.

Sharma, O. (1976) Antioxidant activity of curcumin and related compounds. Biochem. Pharmacol., 25(15): 1811-1812.

Shateri, K., S. Vousoghian, S. Oshnoei and A. Mohammadi (2019) Association of osteoporosis with non-alcoholic fatty liver disease in adults. J. Adv. Pharm. Edu. Res., 9(S2): 51-57.

Sohrabpour, A.A., H. Rezvan, S. Amini-Kafiabad, M. Dayhim, S. Merat and A. Pourshams (2010) Prevalence of nonalcoholic steatohepatitis in Iran: a population based study. Middle East J Dig Dis., 2(1): 14.

Sunilson, J., P. Jayaraj, M.S. Mohan, A. Kumari and R. Varatharajan (2008) Antioxidant and hepatoprotective effect of the roots of Hibiscus esculentus Linn. Int. J. Green Pharm., 2(4): 200.

Tandon, V.R., V. Khajuria, B. Kapoor, D. Kour and S. Gupta (2008) Hepatoprotective activity of Vitex negundo leaf extract against anti-tubercular drugs induced hepatotoxicity. Fitoterapia, 79(7): 533-538.

Tsigos, C., V. Hainer, A. Basdevant, N. Finer, M. Fried, et al. (2008) Management of obesityin adults: European clinical practice guidelines. Obes. Facts, 1(2): 106–116.

Varatharajan, R. and P. Promwichit (2009) Hepatoprotective activity of Coccinia grandis leaves against carbon tetrachloride induced hepatic injury in rats. Int. J. Pharmacol., 5(3): 222-227.

Younossi, Z. (2008) Review article: current management of non‐alcoholic fatty liver disease and non‐alcoholic steatohepatitis. Alimentary Pharmacology & Therapeutics, 28(1): 2-12.

Zeashan, H., G. Amresh, S. Singh and C.V. Rao (2008) Hepatoprotective activity of Amaranthus spinosus in experimental animals. Food Chem Toxicol, 46(11): 3417-3421.