Prev. Nutr. Food Sci. 2022;27(1):37-44
https://doi.org/10.3746/pnf.2022.27.1.37
ISSN 2287-8602

Effect of Turmeric Supplementation on Blood Pressure and Serum Levels of Sirtuin 1 and Adiponectin in Patients with Nonalcoholic Fatty Liver Disease: A Double-Blind, Randomized, Placebo-Controlled Trial

Ali Kalhori[1], Maryam Rafraf[2], Roya Navekar[2], Aida Ghaffari[3], and Mohammad Asghari Jafarabadi[4]

[1]Department of Nutrition, Science and Research Branch, Islamic Azad University, Tehran 1477893855, Iran
[2]Nutrition Research Center, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz 51666-14711, Iran
[3]Department of Nutrition Science, Islamic Azad University-Sarab Branch, Sarab, Iran
[4]Department of Statistics and Epidemiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan 4513956111, Iran

ABSTRACT: Nonalcoholic fatty liver disease (NAFLD) is commonly associated with obesity. This randomized, double-blind, placebo-controlled trial aimed to evaluate the effects of turmeric on serum adiponectin and sirtuin 1 (SIRT1) levels, blood pressure, and body mass index (BMI) in patients with NAFLD. A total of 46 eligible patients with NAFLD (BMI, 25.0～39.9 kg/m^2) were randomly allocated to turmeric and placebo groups using block randomization. The turmeric group (n=23) was administered 3,000 mg/d turmeric powder in six 500-mg capsules for 12 weeks, whereas the placebo group (n=23) was administered six placebo capsules/d for 12 weeks. Body weight, BMI, serum SIRT1 and adiponectin levels, and systolic and diastolic blood pressures were measured at baseline and 12 weeks after intervention. Serum SIRT1 levels increased significantly in the turmeric group compared with the placebo group. Additionally, participants in the turmeric group exhibited lower weight, BMI, and systolic blood pressure after 12 weeks of intervention compared with the baseline. Turmeric effectively improved SIRT1 levels in patients with NAFLD compared with the placebo. The efficacy of turmeric might increase with long-term use at higher doses.

Keywords: curcuminoids, nonalcoholic fatty liver disease, turmeric

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent liver diseases, affecting approximately 25% of the global population, with the highest prevalence reported in the Middle East and South America (Younossi et al., 2016). The prevalence of NAFLD is higher among individuals with obesity, affecting 57.5% to 74.0% of these individuals (Bedossa, 2017). The pathophysiology of NAFLD includes excessive hepatic fat accumulation in the absence of alcohol abuse; this accumulation may lead to pure steatosis, which is not accompanied by severe necroinflammatory injury, or to a complex pattern with inflammation, hepatocyte injury, apoptosis, and nonalcoholic steatohepatitis (NASH) in extreme cases (Bedossa, 2017). Previous studies suggest a bidirectional association between NAFLD and the components of metabolic syndrome, including obesity, type 2 diabetes mellitus, hypertension, and dyslipidemia. These components can predict the presence of steatohepatitis in patients with NAFLD, thereby increasing the risk of progressive liver disease (VanWagner and Rinella, 2016).

Although earlier studies suggested that the primary underlying pathogenesis of steatohepatitis and fibrosis included inflammatory processes involving cytokines, adipokines, oxidative stress, and mitochondrial dysfunction, which mediated hepatic triglyceride accumulation, recent studies suggest that the combination of genetic, epigenetic, environmental, and nutritional factors; obesity; adipose tissue; hormone secretion; and insulin resistance might contribute to NAFLD (Buzzetti et al., 2016).

As one of the most critical energy sources, adipose tissue plays a vital role in the production and secretion of adipokines with pro- and anti-inflammatory properties.

Received 5 November 2021; Revised 14 November 2021; Accepted 15 December 2021; Published online 31 March 2022

Correspondence to Roya Navekar, E-mail: Roya.nave@gmail.com
Author information: Ali Kalhori (Student), Maryam Rafraf (Professor), Roya Navekar (Graduate Student), Aida Ghaffari (Professor), Mohammad Asghari Jafarabadi (Professor)

As a critical adipokine, adiponectin is involved in NAFLD pathology by affecting insulin resistance (Ishtiaq et al., 2019). Changes in fat mass may lead to a decline in adipokine production, thereby decreasing adiponectin levels. Based on the association between adipose tissue and liver, impeding adipokine production can impact liver metabolism and hepatic insulin sensitivity (Stern et al., 2016). Studies in humans have also shown that adiponectin levels are significantly lower in patients with NAFLD than in healthy controls (Ebrahimi et al., 2018).

Liver functions as a significant metabolic regulator of glucose and lipid hemostasis depend on metabolic enzymes. Among these regulators, sirtuin 1 (SIRT1), a member of the nicotine adenine dinucleotide (NAD^+)-dependent enzyme family, has garnered extensive attention owing to its biological roles in glucose and lipid metabolism (Ye et al., 2017). Evidence suggests that SIRT1 is involved in several metabolic pathways, namely β-oxidation, oxidative stress, inflammation, insulin secretion, and sensitivity (Kosgei et al., 2020). In addition, SIRT1 facilitates fatty acid β-oxidation through peroxisome proliferator-activated receptor-γ coactivator 1-α and inhibits *de novo* lipogenesis; thus, alterations in pathways involving SIRT1 can potentially lead to metabolic disorders, including NAFLD (Stacchiotti et al., 2019).

Despite the knowledge regarding the pathological mechanisms underlying NAFLD, available treatments that effectively prevent the progression of NAFLD to more severe stages, notably NASH, are limited. Currently, first-line treatments focus on the modification of metabolic parameters, including insulin sensitivity, physical activity, body weight, lipid profile, and glycemic control (Lam and Younossi, 2010). Studies evaluating different therapeutic approaches, such as antioxidants, anti-inflammatory agents, and iron supplementation, have not yet established their efficacy (Yang et al., 2019), and safe and effective treatments for NAFLD are an area of great interest.

Turmeric is the powdered rhizome of *Curcuma longa*, a member of the Zingiberaceae family (Maheshwari et al., 2006). Curcuminoids, the core components of turmeric extract, are considered safe compounds for human consumption, demonstrating many beneficial effects against several diseases. Curcuminoids have already been shown to play a role in increasing adiponectin and SIRT1 levels, improving insulin resistance, and reducing tumor necrosis factor-α, interleukin (IL)-6, and IL-1β levels (Ganjali et al., 2017). Curcuminoids have also been proposed to act as protective agents (antioxidants) against hypertension (Kukongviriyapan et al., 2016). Moreover, in an *in vivo* rat model study, curcumin supplementation was reported to improve anthropometric measures and hepatic enzyme levels (Kyung et al., 2018). Panahi et al. (2017) demonstrated that curcumin supplementation exerted protective effects against liver fibrosis and cirrhosis.

Due to the paucity of clinical studies investigating the potential efficacy of turmeric in patients with NAFLD, we conducted a randomized, double-blind, placebo-controlled trial to evaluate the therapeutic effect of turmeric on body weight, body mass index (BMI), serum levels of SIRT1 and adiponectin, and blood pressure in patients with NAFLD.

MATERIALS AND METHODS

Participants

Patients with NAFLD aged 20 to 60 years were recruited from those referred to the Sheikh-ol-Raees Clinic in Tabriz, Iran. NAFLD diagnosis was based on ultrasound liver examination (SonoAce X6 Samsung Medison Ultrasound, Samsung Medison, Seoul, Korea) performed by a gastroenterologist. For further diagnostic validation, eligible patients were evaluated by a physician. The inclusion criteria were the diagnosis of NAFLD based on the observation of steatosis in liver ultrasound, age range of 20 to 50 years in females and 20 to 60 years in males, and BMI of 25 to 39.9 kg/m^2. According to the guidelines of the American Gastroenterological Association, the extent of macrovesicular steatosis was used to determine the grade of hepatic steatosis as follows: grade 0, absence of macrovesicular steatosis; grade 1, up to 33% macrovesicular steatosis; grade 2, 33% to 66% macrovesicular steatosis; and grade 3, >66% macrovesicular steatosis (Sanyal, 2002). The exclusion criteria were as follows: alcohol consumption; pregnancy; lactation; menopause; following a specific diet; anemia; being an athlete; history of cardiovascular or gastrointestinal disease or diabetes; liver transplantation; other acute or chronic hepatic diseases (e.g., hepatitis B and C infection or other liver infections); biliary disease; gall bladder or kidney stones; autoimmune disease; cancer; hereditary disorders affecting liver function (e.g., hemochromatosis and Wilson's disease); and use of hepatotoxic drugs, oral contraceptives, or vitamin supplements at the time of trial enrollment or 1 month before any trial-related procedures.

Trial design

This study was designed as a 12-week randomized, double-blind, placebo-controlled trial with a parallel group. The sample size was calculated considering a type I error (α) of 5% and a power of 90% with a 2-tailed test, based on the change in serum adiponectin levels in a pilot study of eight patients before trial initiation. Therefore, the estimated sample size was a minimum of 16 participants per group. A drop-out rate of 30% was estimated; therefore, the final sample size was 23 participants per group. A total of 46 individuals who met the inclusion criteria

and agreed to participate in the trial were recruited. The participants were randomly assigned to receive either turmeric capsules (n=23) or matched placebo capsules (n=23) for 12 weeks (Fig. 1). Four participants were lost to follow-up and subsequently dropped out from the trial.

The trial was approved by the Institutional Review Board, and part of the study results were previously published (Navekar et al., 2017). The Ethical Committee of Tabriz University of Medical Sciences approved the trial protocol (approval no. TBZMED.REC.1394.436). The trial was also registered with the Iranian Registry of Clinical Trials website (registration no. IRCT201406183664N12). The written informed consent was obtained from the participants prior to any trial related procedure.

***Randomization*:** The participants were randomly allocated to the turmeric or the placebo group using block randomization. To avoid selection bias, randomization with a block size of four was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). To ensure the implementation of the random allocation sequence, a coordinator was assigned and the capsules were subsequently put in envelopes labeled with a serial number ranging from 1 to 46. Only the trial coordinator was aware of the nature of the envelopes based on the serial number allocated to each participant.

***Blood sampling and clinical and anthropometric measurements*:** Blood samples were collected after overnight fasting at baseline and the end of the trial. Serum samples were allowed to clot for approximately 10 min before centrifugation at 470 *g* for approximately 10 min at 4°C. The samples were aliquoted and frozen at −70°C until further analyses. Fasting serum levels of SIRT1 and adiponectin were measured at baseline and the end of the trial using enzyme-linked immunosorbent assay kits (Eastbiopharm, Hangzhou, China) and Mediagnost (Tübingen, Germany), respectively.

Anthropometric indices and blood pressure were measured and evaluated at baseline and the end of the trial. All participants completed a general questionnaire to collect general information and the background status of the patients such as their age, name, any related disorders. Information on dietary intake was obtained using a 3-day dietary record at the beginning and the end of weeks 6 and 12 of the trial period, and data were analyzed using the Nutrition 4 software (First Databank, San Bruno, CA, USA). Body weight was measured after overnight fasting, with the participants dressed in light clothing, using a Seca scale (Seca, Hamburg, Germany; ±0.5 kg accuracy). Under the same conditions, height was measured using a mounted tape (±0.5 cm), with the participants being barefoot during the measurement. BMI was calculated using the following formula: BMI=weight (kg)/height^2 (m^2). Participants were asked to rest for 15 min before the measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP), which was performed twice using a handheld sphygmomanometer (Honsun HS-20A, Spirit Medical Co., Ltd., Taipei, Taiwan), and the average of the two measurements was recorded.

***Intervention*:** *C. longa* L. rhizomes were purchased and subsequently approved by the Herbarium of the Botany Department, Faculty of Pharmacy, Tabriz University of Medical Sciences, Iran, for further preparation. Briefly, the rhizomes were washed and dried at room temperature and subsequently crushed using a powder mixer. The obtained powder was filled in 500-mg capsules. To maintain comparability between the two groups, capsules of the same size and color, which contained starch, were prepared as placebo treatment. The turmeric group received 3,000 mg/d turmeric, in the form of six 500-mg capsules/d, for 12 weeks, with two capsules ingested before each main meal. The placebo group received six placebo capsules/d for 12 weeks. To record subject compliance, all participants in both groups were interviewed by phone call once a week throughout the trial.

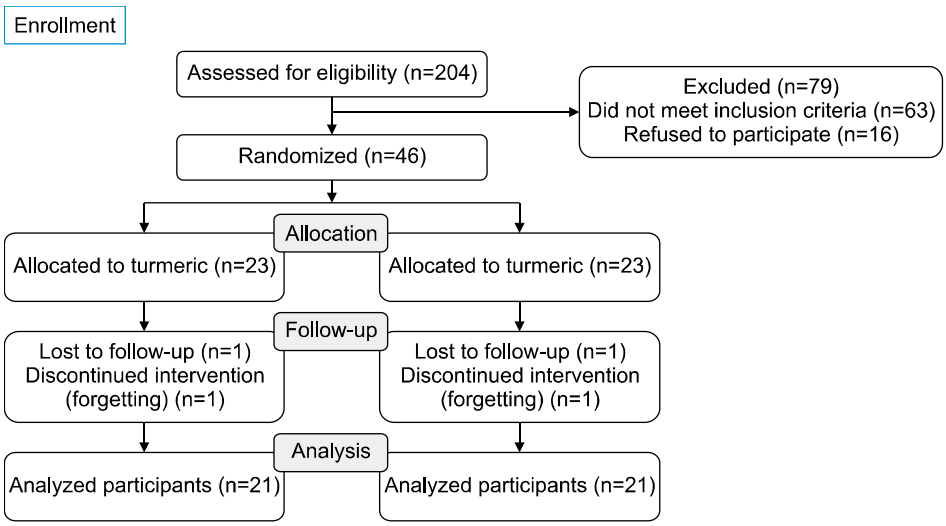

Fig. 1. Study flowchart of patient enrollment.

Statistical analysis

All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). The normal distribution of continuous variables was determined using Shapiro-Wilk test. Data were expressed as mean±standard deviation and median (minimum value~maximum value) for normally and non-normally distributed data, respectively. Within-group comparisons were performed using paired-samples *t*-test for normally distributed data or Wilcoxon's signed-rank test for non-normally distributed data. Between-group comparisons were performed using independent-samples *t*-test for normally distributed data or Mann-Whitney U-test for non-normally distributed data. One-way repeated-measures analysis of variance was used to examine the trend of dietary intake changes at baseline and weeks 6 and 12 in each group. Analysis of covariance was performed to eliminate the effect of confounding factors at baseline or during the trial. Comparisons of categorical variables between the two groups were performed using the χ^2 test. A *P*-value of <0.05 was considered to indicate statistical significance. The following formula was used to determine the percentage of change in variables: % change=[(after values −before values) / before values]×100.

RESULTS

A total of 42 participants, including 21 participants in each group, completed the trial. The drop-out rate due to follow-up loss did not significantly differ between the study groups (8.7% in both groups). Throughout the trial, none of the participants reported significant side effects, indicating the potential safety of the capsule contents. The baseline parameters of the study groups are summarized in Table 1. At baseline, there were no significant differences in age, sex, weight, height, DBP, SBP, SIRT1, and adiponectin levels, and BMI between the two groups.

Table 1. Characteristics of the study groups at baseline

Characteristic	Placebo (n=21)	Turmeric (n=21)	*P*-value
Sex (male/female)	8/13	10/11	0.53
Age (yr)	40.38±9.26	42.09±7.23	0.51
Weight (kg)	87.40±15.08	85.26±16.47	0.66
Height (cm)	162.80±9.60	163.23±8.08	0.88
BMI (kg/m^2)	32.92±4.81	31.81±4.58	0.45
SBP (cmHg)	11.57±0.93	11.54±0.93	0.95
DBP (cmHg)	7.50±1.10	7.88±0.96	0.94
SIRT1 (ng/dL)	11.2 (5.2~22.2)	10.6 (4.90~58.5)	0.93
Adiponectin (ng/dL)	427.09±213.61	425.09±182.71	0.97

Data are presented as number only, mean±SD, or median (range).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SIRT1, sirtuin 1.

Effect of turmeric supplementation on anthropometric characteristics

The within-group comparisons revealed significant reductions in BMI and weight in the turmeric group, but not in the placebo group, at the end of the trial compared with the baseline values (Table 2). However, the between-group comparisons did not reveal significant weight and BMI changes between the two groups (*P*>0.05).

Effect of turmeric on blood pressure

Supplementation with turmeric was associated with a significant decrease in SBP (*P*=0.01) but not DBP (*P*=0.07) in the turmeric group based on the within-group comparisons (Table 2). No significant differences were noted in SBP and DBP in the placebo group at the end of the trial compared with the baseline (Table 2).

Effect of turmeric supplementation on SIRT1 and adiponectin levels

The serum SIRT1 levels were significantly higher at the end of the trial compared with the baseline in the turmeric group (*P*=0.01), whereas a similar difference in SIRT1 levels was not observed in the placebo group (*P*=0.92; Table 2). The between-group comparison revealed that compared with the placebo, the consumption of turmeric led to a significant increase in serum SIRT1 levels (Ta-

Table 2. Within-group comparisons of biochemical and anthropometric data of the participants

Characteristic	Placebo (n=21)			Turmeric (n=21)		
	Baseline	After	*P*-value	Baseline	After	*P*-value
Weight (kg)	87.40±15.08	87.04±15.01	0.43	85.26±16.47	84.49±16.76	0.04
BMI (kg/m^2)	32.92±4.81	32.81±4.94	0.48	31.81±4.58	31.52±4.73	0.04
SBP (cmHg)	11.57±0.93	11.40±1.50	0.35	11.54±0.93	11.11±0.83	0.01
DBP (cmHg)	7.50±1.10	7.61±1.17	0.14	7.88±0.96	7.38±0.66	0.07
SIRT1 (ng/dL)	11.2 (5.2~22.2)	11.2 (8.8~20.6)	0.92	10.6 (4.9~58.5)	14 (8.6~56.9)	0.01
Adiponectin (ng/dL)	427.09±213.61	490.95±266.25	0.34	425.09±182.71	532.57±272.67	0.05

Data are presented as mean±SD or median (range).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SIRT1, sirtuin 1.

Table 3. Comparison of changes between the study groups

Difference	Placebo (n=21)	Turmeric (n=21)	*P*-value
Weight (kg)	−0.36±2.03	−0.77±1.58	0.47
BMI (kg/m^2)	−11.00±0.71	−0.29±0.59	0.38
SBP (cmHg)	−0.17±0.80	−0.43±0.73	0.27
DBP (cmHg)	−0.24±0.72	−0.50±1.21	0.40
SIRT1 (ng/dL)	0.10 (5.00～7.60)	3.20 (9.30～9.10)	0.04
Adiponectin (ng/dL)	63.86±301.86	107.48±235.45	0.60

Data are presented as mean±SD or median (range).
BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure; SIRT1, sirtuin 1.

ble 3). The serum adiponectin levels also exhibited a slight increase at the end of the trial compared with the baseline in the turmeric group (P=0.05), but a significant change was not observed in the placebo group (P=0.34; Table 2). Moreover, the change in serum adiponectin levels at the end of the trial was not significantly different between the two groups (P=0.60; Table 3).

Dietary intake assessment

The within-group comparison of the daily dietary intakes of patients with NAFLD throughout the trial revealed that there were no significant differences in the consumption of the four main macronutrients during the trial period (Table 4).

DISCUSSION

In the present study, we found that the daily macronutrient intakes based on the 3-day dietary records did not significantly change within the treatment groups during the trial period. Therefore, the findings of our clinical trial are not attributable to changes in dietary patterns related to the intervention. To the best of our knowledge, this is the first study investigating the association between serum SIRT1 levels and turmeric supplementation. Our analyses suggest the potential efficacy of turmeric in improving SIRT1 levels in patients with NAFLD.

SIRT1 has been demonstrated to play important roles in a variety of processes, including energy homeostasis and liver function, and exerts protective effects in obesity and metabolic disorders (Nguyen et al., 2020). Low serum levels of SIRT1 have been linked to the elevation of peroxisome proliferator-activated receptor-γ coactivator 1-α and the acetylation of nuclear factor κB, leading to inflammation in patients with type 2 diabetes mellitus (Kitada et al., 2011). SIRT1 expression and activity decline with weight gain, which is likely associated with the dysregulation of the NAD$^+$/SIRT pathway expression in obese patients, which can lead to other conditions, such as inflammation, insulin resistance, impaired insulin homeostasis, and liver steatosis (Jukarainen et al., 2016).

Table 4. Within-group comparisons of daily dietary intakes of patients with nonalcoholic fatty liver disease throughout the trial

Variable	Placebo (n=21)				Turmeric (n=21)			
	Before	Week 6	Week 12	*P*-value	Before	Week 6	Week 12	*P*-value
Energy (kcal/d)	2,409.90±759.99	2,349.90±696.09	2,304.00±666.24	0.59	2,507.20±598.74	2,500.00±22.08	2,490.10±581.17	0.35
Carbohydrates (g/d)	388.44±135.50	381.50±124.15	380.39±101.86	0.96	412.68±110.56	418.52±113.24	414.33±116.37	0.84
Protein (g/d)	84.10±29.38	84.19±29.88	86.39±29.97	0.47	87.07±29.60	86.92±28.56	85.08±28.90	0.72
Fat (g/d)	50.80±16.59	52.19±12.10	55.02±27.97	0.40	48.93±17.01	51.30±19.90	56.35±22.03	0.16

Data are presented as mean±SD.

Concerning its role in downregulating sterol response element-binding protein 1c, a key activator of *de novo* lipogenesis in the liver, SIRT1 triggers β-oxidation in hepatocytes, thereby limiting weight gain and preventing obesity (Liou et al., 2019). Colak et al. (2014) also demonstrated that the activation of SIRT1 improves NAFLD.

Conversely, the downregulation of SIRT1 can augment fatty liver and inflammation, given that lower SIRT1 levels have been reported in obese patients with NAFLD (Mariani et al., 2015). Another study also revealed that *SIRT1* mRNA levels in visceral and subcutaneous adipose tissues were reduced in obese women compared with normal-weight women (Song et al., 2013). Liu et al. (2019) showed that the lack of SIRT1 activity can lead to liver steatosis in animal models. Therefore, SIRT1 should be considered a potential therapeutic target of NAFLD.

Most of the previous studies investigating the efficacy of curcuminoids used curcumin extract. In contrast, we aimed to investigate the efficacy of turmeric, which includes a combination of different compounds and can be used in regions where curcumin extract may not be available, given that turmeric is a commonly used spice for culinary purposes. Supplementation with 3,000 mg/d turmeric was not associated with any side effects based on the weekly interviews of the study participants throughout the trial. In addition, previous clinical trials investigated the efficacy of up to 1,500 mg/d curcumin extract, which contains more curcuminoids than turmeric (Nelson et al., 2017).

Several functional pharmacological properties have been attributed to turmeric, which is composed of a wide variety of compounds, including bioactive nonvolatile curcuminoids (curcumin, dimethoxycurcumin, and bisdemethoxycurcumin) and mixtures of volatile oils (mono- and sesquiterpenoids) (Lobo et al., 2009). Although phenolic compounds are considered to be responsible for antioxidant properties, recent studies have revealed that volatile compounds might also exert antioxidant effects. In most studies, the biological functions of volatile compounds (mono- and sesquiterpenoids) have not been well established (Mimica-Dukić et al., 2016).

Curcumin, as a component of turmeric, has been suggested to increase the level and activity of adenosine monophosphate-activated protein kinase, which can activate nicotinamide phosphoribosyltransferase (NAMPT). NAMPT produces NAD^+, which helps in the activation of SIRT1, an NAD^+-dependent enzyme (Zendedel et al., 2018). Yang et al. (2013) demonstrated that curcumin increased SIRT1 levels and decreased mitochondrial oxidative stress in rat cardiomyocytes. In addition, curcumin can activate peroxisome proliferator-activated receptor (*PPARγ*) gene expression. Although its role has not been fully established, PPARγ might be involved in the translocation of hepatic triglycerides and free fatty acids to adipose tissue, thereby ameliorating hepatic fat accumulation (Skat-Rørdam et al., 2019).

In the present study, we found a significant decrease in SBP in the turmeric group at the end of the trial compared with the baseline, although there was no significant difference in SBP between the two groups. Curcumin was previously reported to prevent hypertension through its antioxidant and chelating properties (Bhullar et al., 2013). Curcumin contains a phenolic ring that neutralizes oxidant molecules such as OH and $O_2^{\bullet}$ and reacts with di-ketone groups when they are combined with $OH^{\bullet}$ and H_2O_2; therefore, curcumin can suppress the adverse effect of oxidative stress on the sympathetic system and can subsequently control blood pressure (Kukongviriyapan et al., 2016). Moreover, SIRT1 inhibits the expression of angiotensin II receptor type I in vascular smooth muscle cells and prevents vasoconstriction and hypertension (Jalali et al., 2020); this effect of SIRT1 might explain the reduction in SBP observed in the turmeric group, which exhibited a significant increase in SIRT1 levels. In agreement with our findings, Khajehdehi (2012) reported that SBP was reduced in patients with lupus nephritis who received turmeric supplementation.

However, the current study findings are inconsistent with the reports of several studies. Kukongviriyapan et al. (2016) reported that high-dose curcumin reduced DBP to a greater extent than SBP. Additionally, Chuengsamarn et al. (2014) reported that the daily consumption of 1.5 mg/d curcumin for 6 months did not lead to significant changes in SBP or DBP in patients with type 2 diabetes mellitus. Therefore, additional clinical studies should be conducted to elucidate the potential beneficial effects of turmeric on blood pressure.

Our results also suggest that turmeric supplementation might increase serum adiponectin levels, although the change in adiponectin levels was not statistically different between the placebo and turmeric groups. PPARγ has been proposed to exert an anti-inflammatory effect through forming a heterodimeric complex with the retinoid X receptor alpha transcription factor and controlling adiponectin gene expression. Mechanistically, this process activates PPARγ expression. Therefore, PPARγ-mediated upregulation of and increase in adiponectin levels should lead to an increase in its antifibrogenic and anti-inflammatory effects in the liver (Lim and Kwon, 2010). In a randomized controlled trial, 8 weeks of curcumin supplementation increased serum adiponectin levels in patients with metabolic syndrome (Panahi et al., 2017). In another study of patients with type 2 diabetes mellitus, 6 months of curcumin supplementation (1,500 mg/d) increased adiponectin levels by 152% (Chuengsamarn et al., 2014).

Meta-analyses reveal the beneficial impact of BMI reduction in patients with NAFLD. Although our between-

group comparison did not demonstrate a significant decrease in BMI in association with turmeric supplementation, we found a significant reduction in BMI following treatment in the turmeric group. Potential explanations are the duration and dosage of turmeric supplementation.

The present study has several limitations. First, the trial was designed as a single-dose study, and the correlation between the abovementioned variables and higher turmeric doses remains unclear. Second, the small sample size and relatively short follow-up duration are additional limitations. Third, only participants with grade 1 or 2 NAFLD were included in the study and the study findings might not be applicable to those with grade 3 NAFLD or NASH. Fourth, the bioavailability of curcumin from turmeric is lower than that from other forms of curcumin supplementation (Nelson et al., 2017).

In summary, this study showed that turmeric effectively improved SIRT1 levels in patients with NAFLD compared with the placebo group. The efficacy of turmeric may increase with the long-term use of higher doses. Based on the available data, turmeric can be considered a promising therapeutic option to control NAFLD. Future trials should assess the effect of turmeric on liver fibrosis.

ACKNOWLEDGEMENTS

The authors are grateful for the patients' cooperation who consented to participate in our study.

FUNDING

This work was supported by the Research Deputy of Tabriz University of Medical Sciences, Tabriz, Iran.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Concept and design: MR. Analysis and interpretation: AK. Data collection: RN. Writing the article: AK. Critical revision of the article: AG. Final approval of the article: all authors. Statistical analysis: MAJ. Obtained funding: RN. Overall responsibility: AK.

REFERENCES

Bedossa P. Pathology of non-alcoholic fatty liver disease. Liver Int. 2017. 37:85-89.

Bhullar KS, Jha A, Youssef D, Rupasinghe HP. Curcumin and its carbocyclic analogs: structure-activity in relation to antioxidant and selected biological properties. Molecules. 2013. 18:5389-5404.

Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016. 65:1038-1048.

Chuengsamarn S, Rattanamongkolgul S, Phonrat B, Tungtrongchitr R, Jirawatnotai S. Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. J Nutr Biochem. 2014. 25:144-150.

Colak Y, Yesil A, Mutlu HH, Caklili OT, Ulasoglu C, Senates E, et al. A potential treatment of non-alcoholic fatty liver disease with SIRT1 activators. J Gastrointestin Liver Dis. 2014. 23: 311-319.

Ebrahimi R, Zand S, Shanaki M. The association of serum level of CTRP1 with common bile duct diameter and other manifestations in patients with non-alcoholic fatty liver. Arch Med Lab Sci. 2018. 4:23-29.

Ganjali S, Blesso CN, Banach M, Pirro M, Majeed M, Sahebkar A. Effects of curcumin on HDL functionality. Pharmacol Res. 2017. 119:208-218.

Ishtiaq SM, Rashid H, Hussain Z, Arshad MI, Khan JA. Adiponectin and PPAR: a setup for intricate crosstalk between obesity and non-alcoholic fatty liver disease. Rev Endocr Metab Disord. 2019. 20:253-261.

Jukarainen S, Heinonen S, Rämö JT, Rinnankoski-Tuikka R, Rappou E, Tummers M, et al. Obesity is associated with low NAD^+/SIRT pathway expression in adipose tissue of BMI-discordant monozygotic twins. J Clin Endocrinol Metab. 2016. 101:275-283.

Jalali M, Mahmoodi M, Mosallanezhad Z, Jalali R, Imanieh MH, Moosavian SP. The effects of curcumin supplementation on liver function, metabolic profile and body composition in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2020. 48:102283. https://doi.org/10.1016/j.ctim.2019.102283

Khajehdehi P. Turmeric: reemerging of a neglected Asian traditional remedy. J Nephropathol. 2012. 1:17-22.

Kosgei VJ, Coelho D, Guéant-Rodriguez RM, Guéant JL. Sirt1-PPARS cross-talk in complex metabolic diseases and inherited disorders of the one carbon metabolism. Cells. 2020. 9:1882. https://doi.org/10.3390/cells9081882

Kukongviriyapan U, Apaijit K, Kukongviriyapan V. Oxidative stress and cardiovascular dysfunction associated with cadmium exposure: beneficial effects of curcumin and tetrahydrocurcumin. Tohoku J Exp Med. 2016. 239:25-38.

Kyung EJ, Kim HB, Hwang ES, Lee S, Choi BK, Kim JW, et al. Evaluation of hepatoprotective effect of curcumin on liver cirrhosis using a combination of biochemical analysis and magnetic resonance-based electrical conductivity imaging. Mediators Inflamm. 2018. 2018:5491797. https://doi.org/10.1155/2018/5491797

Kitada M, Takeda A, Nagai T, Ito H, Kanasaki K, Koya D. Dietary restriction ameliorates diabetic nephropathy through anti-inflammatory effects and regulation of the autophagy via restoration of Sirt1 in diabetic Wistar fatty (fa/fa) rats: a model of type 2 diabetes. Exp Diabetes Res. 2011. 2011:908185. https://doi.org/10.1155/2011/908185

Lim JH, Kwon TK. Curcumin inhibits phorbol myristate acetate (PMA)-induced MCP-1 expression by inhibiting ERK and NF-κB transcriptional activity. Food Chem Toxicol. 2010. 48:47-52.

Lobo R, Prabhu KS, Shirwaikar A, Shirwaikar A. *Curcuma zedoaria* Rosc. (white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties. J Pharm Pharmacol. 2009. 61:13-21.

Liu HW, Kao HH, Wu CH. Exercise training upregulates SIRT1 to attenuate inflammation and metabolic dysfunction in kidney and liver of diabetic db/db mice. Nutr Metab. 2019. 16:22. https://doi.org/10.1186/s12986-019-0349-4

Liou CJ, Lee YK, Ting NC, Chen YL, Shen SC, Wu SJ, et al. Protective effects of licochalcone A ameliorates obesity and nonalcoholic fatty liver disease via promotion of the Sirt-1/AMPK pathway in mice fed a high-fat diet. Cells. 2019. 8:447. https://doi.org/10.3390/cells8050447

Lam B, Younossi ZM. Treatment options for nonalcoholic fatty liver disease. Therap Adv Gastroenterol. 2010. 3:121-137.

Mimica-Dukić N, Orčić D, Lesjak M, Šibul F. Essential oils as powerful antioxidants: misconception or scientific fact?. In: Jeliazkov VD, Cantrell CL, editors. Medicinal and Aromatic Crops: Production, Phytochemistry, and Utilization. American Chemical Society, Washington, DC, USA. 2016. p 187-208.

Mariani S, Fiore D, Basciani S, Persichetti A, Contini S, Lubrano C, et al. Plasma levels of SIRT1 associate with non-alcoholic fatty liver disease in obese patients. Endocrine. 2015. 49:711-716.

Maheshwari RK, Singh AK, Gaddipati J, Srimal RC. Multiple biological activities of curcumin: a short review. Life Sci. 2006. 78: 2081-2087.

Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. J Med Chem. 2017. 60:1620-1637.

Navekar R, Rafraf M, Ghaffari A, Asghari-Jafarabadi M, Khoshbaten M. Turmeric supplementation improves serum glucose indices and leptin levels in patients with nonalcoholic fatty liver diseases. J Am Coll Nutr. 2017. 36:261-267.

Nguyen LT, Saad S, Chen H, Pollock CA. Parental SIRT1 overexpression attenuate metabolic disorders due to maternal high-fat feeding. Int J Mol Sci. 2020. 21:7342. https://doi.org/10.3390/ijms21197342

Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendía LE, Sahebkar A. Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: a randomized controlled trial. Drug Res. 2017. 67:244-251.

Sanyal AJ; American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. Gastroenterology. 2002. 123:1705-1725.

Stern JH, Rutkowski JM, Scherer PE. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell Metab. 2016. 23:770-784.

Stacchiotti A, Grossi I, García-Gómez R, Patel GA, Salvi A, Lavazza A, et al. Melatonin effects on non-alcoholic fatty liver disease are related to microRNA-34a-5p/Sirt1 axis and autophagy. Cells. 2019. 8:1053. https://doi.org/10.3390/cells8091053

Skat-Rørdam J, Højland Ipsen D, Lykkesfeldt J, Tveden-Nyborg P. A role of peroxisome proliferator-activated receptor γ in non-alcoholic fatty liver disease. Basic Clin Pharmacol Toxicol. 2019. 124:528-537.

Song YS, Lee SK, Jang YJ, Park HS, Kim JH, Lee YJ, et al. Association between low SIRT1 expression in visceral and subcutaneous adipose tissues and metabolic abnormalities in women with obesity and type 2 diabetes. Diabetes Res Clin Pract. 2013. 101:341-348.

VanWagner LB, Rinella ME. Extrahepatic manifestations of non-alcoholic fatty liver disease. Curr Hepatol Rep. 2016. 15:75-85.

Yang Y, Duan W, Lin Y, Yi W, Liang Z, Yan J, et al. SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia reperfusion injury. Free Radic Biol Med. 2013. 65:667-679.

Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016. 64:73-84.

Ye X, Li M, Hou T, Gao T, Zhu WG, Yang Y. Sirtuins in glucose and lipid metabolism. Oncotarget. 2017. 8:1845-1859.

Yang Z, Wu J, Li X, Xie D, Wang Y, Yang T. Association between dietary iron intake and the prevalence of nonalcoholic fatty liver disease: a cross-sectional study. Medicine. 2019. 98:e17613. https://doi.org/10.1097/MD.0000000000017613

Zendedel E, Butler AE, Atkin SL, Sahebkar A. Impact of curcumin on sirtuins: a review. J Cell Biochem. 2018. 119:10291-10300.