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RESEARCH PAPER

The nanocurcumin reduces appetite in obese patients with non-alcoholic fatty liver disease (nafld): a double-blind randomized placebo-controlled clinical trial

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ABSTRACT

Objective(s): Various beneficial effects of curcumin have been seen specially as anti-inflammator and antioxidant agent. However, until now no human studies have been done on curcumin's role in control of appetite. So, the present study was done to determine the effect of nanocurcumin on appetite in obese Non-Alcoholic Fatty Liver Disease (NAFLD) patients.

Materials and Methods: This study was done in the central hospital of Oil Company, Tehran. According to the eligiblity criteria, 84 NAFLD patients with obesity were enrolled. The patients were devided randomly to 2 equal groups (nanocurcumin and placebo, 80 mg/day with meals, follow-up monthly for 3 months). In addition, lifestyle advises were presented. The general questionnaire, appetite sensations (using visual analogue scales [VAS]), , weight and height at the beginning and the end of the study were recorded

Results: The mean age and body mass index (BMI) were 41.8(±5.6), 30.67(±2.14)and 42.5(±6.2)yrs and 30.75(±2.35)kg/m2 for nanocurcumin and placebo groups respectively. The baseline characteristics and dietary intakes were similar between patients, exception for energy, total fat, saturated fat, monounsaturated fatty acid, vitamins D, B1, B6, and folate (DFE). The appetite significantly reduced according to both unadjusted and adjusted analysis models.

Conclusion: This study was the first assess of nanocurcumin's role in control of appetite among obese NAFLD patients. Overall results showed the nanocurcumin supplementation reduced appetite significantly. However, determining the potential role of curcumin in managing of NAFLD- and obesity-related conditions need further study.

Keywords: *Appetite, Nanocurcumin, Non-Alcoholic Fatty Liver Disease (NAFLD), Obesity, Trial*

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INTRODUCTION

Recently herbal medicine has attracted the attention of many researchers. The pharmacological benefits of curcumin have been proven. Curcumin is a yellow flavor obtained from the Curcuma longa Linn's rhizome. Curcumin is a pleiotropic molecule which may modulate intracellular signaling pathways involving in regulation of cell growth, apoptosis, and inflammation. Curcumin can prevent and/or treat some ailments (such as diabetes, cancer, and autoimmune, metabolic,

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lung, liver, neurological, cardiovascular diseases) owing to its anti-oxidant, antiatherosclerotic, anti-inflammatory, antirheumatic, cardioprotective, lipid-modifying, and antidepressant impacts and a wonderful safety profile [1-4].

NAFLD is a popular chronic liver ailment and is connected with metabolic syndrome, obesity, dyslipidemia, diabetes, and cardiovascular ailments. NAFLD prevalence ranges from 6 % to 35 % in seniors making it a prominent public health problem. NAFLD happens when triglycerides (TGs) are accumulated, progressing to liver fibrosis, non-alcoholic steatohepatitis, liver cancer, and cirrhosis [5].

The major cause of NAFLD is over-eating and inactivity, inducing obesity, overweight, and type-2 diabetes. Nutritional problems in NAFLD have been detected, but eventual taste perturbations have not been adequately studied [6].

Particularly, overeating and obesity induce NAFLD. Nutritional disorders in NAFLD patients involve surplus energy, lipids, and carbohydrates intake, and lack of dietary adequate amount of vitamins, polyunsaturated fatty acids, and minerals. Although nutritional therapeutic methods are needed for treating NAFLD and prophylaxis. Continuous nutrition treatment is hard for the majority of patients due to their lifestyle and dietary habits, and because the treatment motivation is different among patients. In evaluation of dietary habits, those consumed insufficiently or excessively and also people with improper eating habits should be individually evaluated. Successful nutrition treatment needs patients' training, on the basis of examinations of individual nutrients, and continuing the therapy. Since the beginning and progress of NAFLD are correlated with lifestyle and dietary habits, nutritional treatment methods are needed for these patients and those at risk of NAFLD [7].

Appetite means the willing to eat, sometimes because of hunger. Appealing foods can excite appetite when there is no hunger. Appetite is present in all higher life-forms and regulates sufficient consumption of energy to satisfy metabolic requirements. It is controlled by an intense interplay between the adipose tissue, digestive tract, and the brain. Appetite is related to individuals' behavior. Appetitive and consumption behaviors are processes which include energy consumption, while all other behaviors influence the energy release. When stressed, levels of appetite might rise and augment intake of food. Declined appetite to eat is called anorexia, while polyphagia or hyperphagia increases eating. Impairment in regulation of appetite causes bulimia nervosa, anorexia nervosa, overeating, cachexia, and binge eating dysfunction. Regulating appetite (the appestat) has been investigated in the last decade. Regulating appetite is a complicated process including the many hormones, gastrointestinal tract, and the autonomic and central nervous systems [8]. The circulating gut hormones that control multiple pathways in the body stimulate appetite [9]. An excessive or limited appetite is not pathological necessarily. Unusual appetite is related to eating habits inducing malnutrition and associated conditions like obesity and its associated problems. Environmental and genetic parameters may control appetite; abnormalities in both can cause unusual appetite. Anorexia may have many reasons, but might be due to psychological (autoimmune, infectious, or malignant disease) or physical (stress, mental dysfunctions) factors. Similarly, hyperphagia may be caused by mental disorders (e.g., depression), hormonal imbalances, etc. Dyspepsia, or indigestion, may influence appetite. One of its signs is "overly full" feeling after beginning to eat. Taste and smell ("dysgeusia", bad taste) or the lack thereof can affect appetite [10]. Abnormal appetite can be associated with genetics on a chromosomal scale [11].

The intake of herbal drinks or spiced foods causes higher thermogenesis and sometimes higher satiety. Thus, these ingredients may be assumed functional agents that contribute to prevention of obesity and a positive energy balance. Some spices like ginger, red pepper, mustard, and tabasco sauce have attracted attention due to their potential influences on fat oxidation and thermogenesis. Their main influential ingredients are the capsaicinoid homologs and capsaicinoids (dihydrocapsaicin and capsaicin). Nevertheless, there is no scientific data on other spice compounds' function on neuropeptides associated with feeding regulation. The previous studies have broadly indicated the regulatory mechanisms of neuropeptides on food consumption using a goldfish model (Carassius auratus). For instance, orexin-A, neuropeptide Y, and acyl ghrelin stimulate orexigenic influences, while in this species α-melanocyte-stimulating hormone, corticotropin-releasing hormone

(CRH), and cholecystokinin prevent appetite. Assuming the tested spice compounds, curcumin can decrease cumulative food consumption. The decrease of appetite stimulated by curcumin therapy in goldfish may be mediated by the vagal afferent and then via the CRH/CRH receptor pathway [12].

The present study set to determine the influence of nanocurcumin on appetite and food consumption in patients with obesity and NAFLD.

METHODS

Study design

The present study was done as parallel part of a double-blind randomized clinical trial on obese patients [13]. Objectives were enrolled into two groups of nanocurcumin supplement and placebo administration. Gender, mean of age, height, the economic status, education, job, and marital status were compared between two groups before the intervention. Further, the weight average and appetite score were compared in patients receiving either placebo or following nanocurcumin supplementation before and after the intervention. These criteria were also compared between the individuals in each treatment groups.

Study inclusion criteria were age 25-50 years, Overweight/obesity (25≤BMI<35), NAFLD based on the ultrasonography diagnosis, andinformed consent and the exclusion criteria were a history of alcohol consumption during the last 12 months based on personal admission, regular intakes of nonsteroidal anti-inflammatory drugs, antibiotics, and corticosteroids during the last 6 months, misuses of narcotics, psychotropic medication, and smoking over the last 6 months, intakes of anti-secretory drugs causing acholoridy, amiodarone, valproate, prednisone, tamoxifen, perhexiline, and methotrexate, liver fat-inducing drugs, hormone drugs, statins, antihypertensives, and ursodeoxycholic acid (UDCA) usage during the last 6 months, intakes of supplements, such as probiotics, multivitamins/minerals, antioxidants, and omega-3 at least twice a week during the study or the last 3 months, diagnosis of pathological conditions affecting the liver, such as viral hepatitis, acute or chronic liver failure, cholestasis, liver transplantation, acute systemic disease, cystic fibrosis disease, muscular dystrophy, previous gastrointestinal surgery, neurological disorders, structural abnormalities of the gastrointestinal tract, diabetes, heart failure, thyroid disorders, kidney diseases, respiratory failure, psychological disorders, hereditary hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, autoimmune diseases, celiac disease, and any types of malignancy, rapid weight loss, Total Parenteral Nutrition (TPN), and protein malnutrition over the last 6 months, secondary causes of NAFLD such as drugs, surgical procedures, environmental toxins, conditions leading to physical disability, uncontrolled hypertension (>140/90 mmHg), breastfeeding, pregnancy, or a plan for pregnancy in the next 3 months, being a professional athlete or doing regular exercise, and taking no more than 10% of the prescription supplements [13, 14].

Subjects

The patients were referred to a major executor after being diagnosed by a radiologist if meeting the eligibility criteria at the central hospital of the polyclinic of National Iranian Oil Company (NIOC), Tehran, Iran. At the beginning, all the study details were clarified and an informed consent form was provided and a general questionnaire was filled by the interviewer. Moreover, the appetite sensations were measured using visual analogue scales [VAS] at the beginning and end of study after 12 hours of fasting. The appetite ratings were measured using 10 cm VAS booklets. Appetite was considered as hunger, satiety, fullness as described previously [15].

The necessary lifestyle changes, including a low-calorie diet (weight loss of 0.5-1 kg per week based on BMI during the trial) and increased physical activity (moderate intensity aerobic exercise about 30-45 min at least three times a week) were prescribed. Anthropometrics, including weight, height, and waist circumference were measured using a digital scale, stadiometer, and non-elastic tape, respectively. Weight measurement (without shoes and minimum clothing with an accuracy of 100 g), height measurement (in a standing position without shoes with heels stuck to the wall and head looking frontwards with an accuracy of 0.5 cm), and waist circumference was measured in the middle of the last rib and the iliac crest with an accuracy of 0.5 cm and minimal clothing. The other factors were also measured at the beginning and the end of the study [13]. Finally, the measurements were privately presented to the patients.

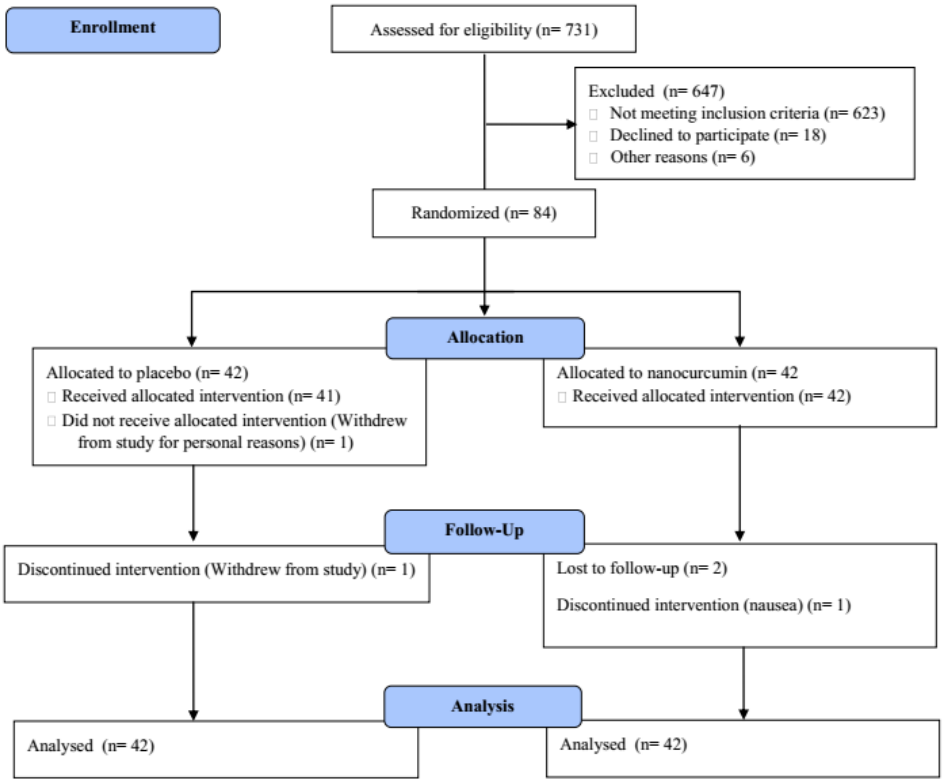

Fig 1. Consolidated Standards of Reporting Trials flow diagram of the study participants. NAFLD, nonalcoholic fatty liver disease

Sample size

A total of 84 samples with a confidence interval (CI) of 95%, power of 80%, and loss of 15% divided equally into two groups (42 patients in each group) by using the block randomization method as have been published previously [13].

Intervention and randomization

Age and gender distributions in both groups were controlled using a stratified randomization. The supplementation ratio was 1:1 for the groups. An assistant conducted the block randomization. The nanocurcumin and placebo intervention allotment was double blinded to the investigator and patients. The supplements where offered in A and B packages were blinded to the investigators and participants.

No side effects and toxicity caused by taking 210 mg of nanocurcumin have been reported [16]. The supplementation dose of Sinacurcumin was 80 mg/day (two 40-mg capsules per day according to company's order: one capsule with breakfast and another one with dinner). Sinacurcumin and placebo supplements were donated by Exir Nano Sina Company.

The supplements were distributed on a monthly basis, while any possible complications were recorded regarding the numbers of ingested capsules and given back packets. Also, the study progress was pursued by calling the subjects once a week.

Lifestyle changes

A low-calorie diet for about 0.5-1 kg weight loss per week was presented by a qualified dietician and increasing the physical activity was also recommended for changing the lifestyle.

The ultrasound test was done by only one radiologist after 12 h of fasting. The weight and height were measured using a non-elastic tape, digital scale, and stadiometer, respectively. Weight with minimal clothing without shoes (100 g accuracy), height in a standing position without shoes with heels sticking to the wall and head keeping flat and looking forward (0.5 cm accuracy), and waist circumference at the middle of the last rib and the iliac crest with minimal clothing were measured at the beginning and end of the study.

Table 1. The general characteristics and physical activity level of obese patients with NAFLD

Factors		Nanocurcumin (n=42) n(%) or Mean(SD)	Placebo (n=42) n(%) or Mean(SD)	P-value
Age (yrs)		41.8(5.6)	42.5(6.2)	0.2*
Gender	male	23(54.8)	23(54.8)	1.0**
	female	19(45.2)	19(45.2)	
Height (cm)		167.8(9.8)	167.7(9.0)	0.8*
Marriage status	single	5(11.9)	7(16.7)	0.5**
	married	37(88.1)	35(83.3)	
Job status	employee, free job/retired	31(73.8)	25(59.5)	0.1**
	housewife, unemployed	11(26.2)	17(40.5)	
Education level	up to associate degree	21(50)	20(47.6)	0.8**
	Bachelor and higher	21(50)	22(52.4)	
Economic level	Low (≤3 living items)	0(0)	0(0)	0.8**
	moderate (4-6 living items)	19(45.2)	18(42.9)	
	High (≥7 living items)	23(54.8)	24(57.1)	
Physical activity level (Baseline)	low (<600 MET-minutes/week)	31(73.8)	28(66.7)	0.4**
	Moderate (600 to < 1500 MET-minutes/week)	11(26.2)	14(33.3)	
	High (≥ 1500 MET-minutes/week)	0(0)	0(0)	
Physical activity level (After 3 months)	low (<600 MET-minutes/week)	27(64.3)	26(61.9)	0.8**
	Moderate (600 to < 1500 MET-minutes/week)	15(35.7)	16(38.1)	
	High (≥ 1500 MET-minutes/week)	0(0)	0(0)	

*Mann-Whitney; **Chi-square

The study was conducted at the central hospital of the National Iranian Oil Company (NIOC), Tehran, Iran.

The details of enrolments, interventions, and assessments were presented in previous trial protocol. Furthermore, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist was completed in an additional file. An assistant checked the trial progress regularly and independently [13].

Data analysis

The data entry, coding, security, and saving were checked in order to assure the accuracy of the data. The data normality was examined using a Kolmogorov-Smirnov test. Moreover, Chi-squre, Mann-Whitney, t-test, and two-way repeated measures-ANOVA (TWRM-ANOVA) statistical tests were applied. Also, data of all randomized participants were analyzed using intention to treat (ITT) analysis model. The confounders for adjusted analysis model were energy, total fat, saturated fat, monounsaturated fatty acid, vitamins D, B1, B6, and folate (DFE). CI (Confidence Interval) of 95% was considered in all the tests. The significance value was considered to be less than 0.05. Data analysis was done using $SPSS_{16}$ statistical software.

RESULTS

Characteristics of Patients

Based on Fig 1, 731 participants were assessed for eligibility of the study enrollment (medical history). 108 participants met the eligibility criteria, of whom 18 were declined and six could not enroll to the study. Finally, 84 patients were randomized. After randomization, in placebo group, one patient did not receive allocated intervention and withdrew from the study (due to personal reasons), thus out of 84 patients that completed the first visit (nanocurcumin n = 42; placebo n = 42), one of them was declined. Moreover, four patients lost the follow-up (for personal reasons and nausea; three patients in nanocurcumin group; one patient in placebo group). Finally, collected data of 84 patients was analyzed according to ITT analysis model.

The general characteristics and physical activity level of 84 obese NAFLD patients were presented in Table 1. As shown, the mean age and BMI of nanocurcumin and placebo groups were 41.8(±5.6) and 42.5(±6.2) yrs and 30.67(±2.14) and30.75(±2.35) kg/m^2, respectively, which there were not statistical different between placebo

Table 2. The baseline mean of weight, BMI, and appetite score in obese patients with NAFLD

Factors	Intervention	Mean(SD)	P-value
Weight (kg)	Nanocurcumin (n=42)	86.54(10.98)	0.9*
	Placebo (n=42)	86.70(11.15)	
BMI (kg/m2)	Nanocurcumin (n=42)	30.67(2.14)	0.9**
	Placebo (n=42)	30.75(2.35)	
Appetite (score)	Nanocurcumin (n=42)	6.81(1.48)	0.9*
	Placebo (n=42)	6.84(1.86)	

*t-test; **Mann-Whitney

and nanocurcumin groups (P>0.05). Furthermore, there weren't any significance difference in gender, education and physical activity level and also in marriage, job and economic status between two groups (P>0.05) (Table 1). The mean frequency of supplement compliance was 95.9±2.2 % and 97.9±1.4 % for nanocurcumin and placebo groups. Baseline characteristics were also similar between patients, exception in the dietary intake of vitamins D and B6 (P<0.05, Tables 1, 2, and3).

Changes in factors

The dietary intakes were almost similar between groups during study, exception for energy, total fat, saturated fat, monounsaturated fatty acid, vitamins D, B1, B6, and folate (DFE) (P<0.05, Table 3) that considered as confounders in final analysis model. Also there was a significant decrease in weight, BMI, and appetite score means in both groups.

As shown in table.4 the time-by-treatment interaction effect was statistically significant in decreasing appetite in both unadjusted and adjusted analysis models.

Safety

The patients reported no side effects associated with mentioned treatment during the study exception for nausea that was reported by one patient in nanocurcumin group.

DISCUSSION

Curcumin was assumed as a therapy for jaundice, an appetite suppressant, and a digestive agent. Assuming Indian and Chinese drugs, turmeric was employed as an anti-inflammatory medicine to cure gastric gas, colic, chest pains, toothaches, and menstrual problems. This spice could cure stomach and liver ailments, treat wounds, and lighten scars, and it was also used as a cosmetic. Although curcumin potential to protect food by its antioxidant mechanism, to make food colorful, and to make food tasty, make it popular, its health enhancing influences are less taken into consideration [17].

The present study evaluated the impact of curcumin in regulating appetite in obese NAFLD patients. The results showed that supplementation with nanocucumin could decrease appetite in NAFLD patients.

NAFLD is a common liver illness specified by surplus deposition of lipid in the hepatic tissue and subsequent inflammatory and oxidative injury. The anti-tumor, anti-inflammatory, antioxidant, lipid-modifying and also exciting the appetite properties of the polyphenolic compound, curcumin, are well known before [4, 18]. Panahi and colleagues showed that supplementation with phytosomal curcumin could reduce BMI (- 0.99 ± 1.25 vs. - 0.15 ± 1.31; p< 0.004) and waist circumference (- 1.74 ± 2.58 vs. - 0.23 ± 3.49; p< 0.03) in comparison with control group in NAFLD patients. Also their findings showed that the ultrasonographic results were improved in 75.0 % of patients in phytosomal curcumin treated group, whereas the improvement was observed only in 4.7 % (p< 0.001) of control group. They showed also a reducing in aspartate aminotransferase and alanine aminotransferase serum enzymes levels in the phytosomal curcumin treated group (p< 0.001) at the end of experiment whereas they were increased for control group at the same time (p< 0.001) [4].

Around 20 to 30 % of adults have some risk factors such as abdominal or central obesity, impaired glucose tolerance, insulin resistance (IR) and atherogenic dyslipidemia (elevated triglyceride level, decreased HDL-cholesterol and risen LDL cholesterol level), also so-called metabolic syndrome (MetS). Selmanovic and colleagues showed that women represented such risk factors more than men (65:35) meaningfully, which is associated with the reality that women suffered more from metabolic impairments compared with men. They also showed significant decreasing in weight, BMI, and waist circumference in individuals with MetS and prediabetes (PD) after consumption of curcumin supplement at the dose of 400 mg/day for one year, as well as the same shown for subjects with MetS and DM T2 [19].

Table 3. The dietary intakes in obese patients with NAFLD

Dietary intakes		Nanocurcumin (n=42) Mean(SD)	Placebo (n=42) Mean(SD)	P-value	
Energy (kcal)	Baseline	2473.2(470.5)	2338.6(496.3)	0.2*	0.001**
	1.5 Months	2089.9(412.9)	2267.0(468.4)	0.07	
	3 Months	2019.4(380.5)	2205.9(476.0)	0.05	
Protein (g)	Baseline	100.7(30.7)	97.1(32.7)	0.6	0.3
	1.5 Months	93.7(24.9)	93.8(31.8)	0.8	
	3 Months	84.1(28.7)	92.9(31.4)	0.2	
Protein (%)	Baseline	16.3(3.7)	16.5(4.1)	0.7	0.2
	1.5 Months	18.0(3.8)	16.4(3.9)	0.06	
	3 Months	16.6(4.8)	16.7(4.1)	0.8	
Carbohydrate (g)	Baseline	296.1(55.6)	280.5(81.9)	0.3	0.3
	1.5 Months	253.8(68.9)	252.3(58.9)	0.9	
	3 Months	256.2(47.8)	266.0(73.3)	0.3	
Carbohydrate (%)	Baseline	48.5(7.7) %	47.8(9.0) %	0.7	0.5
	1.5 Months	48.4(8.7) %	45.1(8.7) %	0.08	
	3 Months	51.2(7.4) %	48.1(8.0) %	0.07	
Fat total (g)	Baseline	103.1(32.8)	97.0(27.4)	0.3	0.001
	1.5 Months	82.3(22.5)	102.4(31.1)	0.001	
	3 Months	78.7(20.6)	90.4(24.6)	0.02	
Fat total (%)	Baseline	37.00(6.9) %	37.5(7.4) %	0.7	0.1
	1.5 Months	35.5(6.7) %	40.2(7.1) %	0.003	
	3 Months	34.8(4.9) %	37.0(6.6) %	0.09	
Cholesterol (mg)	Baseline	268.2(168.8)	282.3(178.7)	0.7	0.3
	1.5 Months	273.9(150.8)	271.3(153.1)	0.9	
	3 Months	198.3(126.8)	263.9(125.6)	0.01	
Saturated fat (g)	Baseline	27.03(11.4)	25.5(9.2)	0.7	0.03
	1.5 Months	22.5(7.2)	27.9(9.7)	0.005	
	3 Months	21.2(8.5)	25.6(9.8)	0.03	
Monounsaturated fatty acid (g)	Baseline	37.8(13.7)	36.1(9.8)	0.5	0.008
	1.5 Months	30.4(8.9)	36.7(11.6)	0.006	
	3 Months	28.5(8.2)	33.7(9.0)	0.008	
Polyunsaturated fatty acid (g)	Baseline	26.4(13.6)	25.0(11.6)	0.5	0.06
	1.5 Months	20.3(7.6)	26.6(15.3)	0.1	
	3 Months	20.2(6.8)	22.1(7.1)	0.4	
Vitamin A (RAE) (µg)	Baseline	316.8(210.7)	349.0(264.2)	0.6	0.6
	1.5 Months	366.9(287.1)	319.7(270.6)	0.2	
	3 Months	416.2(378.3)	407.0(344.8)	0.4	
Carotenoids (mg)	Baseline	8.0(6.9)	7.5(6.6)	0.7	0.8
	1.5 Months	8.5(6.7)	8.0(6.6)	0.7	
	3 Months	8.1(6.7)	8.7(7.7)	0.9	
Vitamin C (mg)	Baseline	97.0(84.4)	79.8(61.3)	0.4	0.9
	1.5 Months	83.8(61.0)	74.2(69.4)	0.1	
	3 Months	95.1(73.5)	85.7(71.8)	0.2	
Calcium (mg)	Baseline	1086.0(502.2)	1115.7(521.2)	0.7	0.1
	1.5 Months	1025.8(360.1)	910.2(473.1)	0.03	
	3 Months	897.8(408.9)	1076.8(475.1)	0.06	
Iron (mg)	Baseline	15.0(3.5)	14.8(5.0)	0.7	0.3
	1.5 Months	14.1(4.0)	13.7(3.1)	0.6	
	3 Months	13.1(3.1)	14.1(4.0)	0.1	
Vitamin D (µg)	Baseline	1.0(1.8)	1.9(2.1)	0.01	0.02
	1.5 Months	2.4(3.6)	1.1(1.6)	0.03	
	3 Months	2.1(3.5)	1.4(1.6)	0.9	
Vitamin E (mg)	Baseline	29.7(19.0)	28.7(13.1)	0.7	0.5
	1.5 Months	24.9(9.2)	27.0(14.6)	0.4	
	3 Months	23.7(8.6)	26.9(8.2)	0.1	
Vitamin B1 (mg)	Baseline	1.9(0.3)	1.7(0.5)	0.08	0.01
	1.5 Months	1.6(0.4)	1.5(0.4)	0.3	
	3 Months	1.5(0.3)	1.7(0.5)	0.06	
Vitamin B2 (mg)	Baseline	1.9(0.7)	2.0(0.8)	0.5	0.1
	1.5 Months	1.9(0.6)	1.8(0.6)	0.1	

	3 Months	1.7(0.7)	1.9(0.7)	0.1	
	Baseline	30.3(13.2)	27.8(12.9)	0.4	
Vitamin B3 (mg)	1.5 Months	25.7(10.2)	27.2(14.7)	0.8	0.4
	3 Months	24.2(10.6)	26.3(11.9)	0.4	
	Baseline	2.2(0.7)	1.9(0.6)	0.05	
Vitamin B6 (mg)	1.5 Months	1.8(0.5)	1.8(0.7)	0.5	0.02
	3 Months	1.7(0.6)	1.9(0.6)	0.1	
	Baseline	504.0(222.7)	443.6(181.5)	0.3	
Folate (DFE) (µg)	1.5 Months	425.7(155.8)	426.5(149.7)	0.7	0.04
	3 Months	413.0(126.7)	471.7(152.9)	0.05	
	Baseline	4.1(2.5)	4.4(2.5)	0.6	
Vitamin B12 (µg)	1.5 Months	5.1(2.8)	4.6(2.5)	0.5	0.6
	3 Months	4.3(3.0)	4.4(2.4)	0.9	
	Baseline	148.6(224.4)	134.9(287.3)	0.1	
Vitamin K (µg)	1.5 Months	142.6(279.7)	86.5(135.3)	0.5	0.8
	3 Months	192.2(366.3)	168.8(419.1)	0.6	
	Baseline	12.4(3.3)	12.7(3.7)	0.7	
Zinc (mg)	1.5 Months	12.6(4.0)	12.4(3.3)	0.7	0.7
	3 Months	11.5(3.7)	12.1(4.5)	0.6	
	Baseline	113.7(34.2)	119.9(54.1)	0.7	
Selenium (µg)	1.5 Months	120.4(58.1)	99.2(37.9)	0.09	0.2
	3 Months	112.0(57.7)	106.6(44.5)	0.6	
	Baseline	29.8(12.8)	31.0(16.1)	0.9	
Fiber total (g)	1.5 Months	30.1(16.5)	27.1(15.1)	0.5	0.09
	3 Months	24.5(9.5)	31.5(15.6)	0.03	

*Total of column: t-test or Mann-Whitney; **Total of column: Two way repeated measures-ANOVA (TWRM-ANOVA)

In randomized controlled research of Di Pierro, and colleagues (2015), the tolerability and efficiency of curcumin in overweight individuals affected from metabolic syndrome was investigated. Their results showd that curcumin raised weight loss from 1.88 to 4.91%, increased reduction percentage of body fat (from 0.70 to 8.43%), enhanced waistline decline (from 2.36 to 4.14%), enhanced hip circumference decrease from 0.74 to 2.51% and increased decline of BMI (from 2.10 to 6.43%) ($p< 0.01$ for all comparisons). Also their findings indicated that its tolerability was great for all treatments, and no dropout was observed [20].

Kang and coworkers (2011) studied the pharmacological effects of spice compounds including curcumin on regulating appetite by using a goldfish model (Carassius auratus), emphasizing on the effect of neuropeptides. Goldfish were intraperitoneally injected test solutions having every spice or vehicle (containing 10% dimethyl sulfoxide in saline), and the variations in food consumption were estimated every 15 min for 60 min. Curcumin could decrease cumulative food consumption and was thus selected for more studies. Anorexigenic action induced by curcumin decreased by intracerebroventricular injection of the corticotropin-releasing hormone (CRH) receptor antagonist α-helical. The expression levels of mRNA for CRH were assessed, which is a strong anorexigenic neuropeptide in goldfish, in the diencephalon at 1 h after being treated with curcumin, and it was found that it was increased. Thus, they deduced that, the decrease of appetite stimulated by curcumin therapy in goldfish was mediated by the vagal afferent and then via the CRH/CRH receptor pathway [12].

A meta-analysis study revealed a correlation between curcumin supplementation and a reduced leptin level. The researchers deduced that it could be the functional mechanism of curcumin effects [21].

On the other hand, in another study conducted by Ciftci (2010) the effectiveness of curcumin on TCDD (Tetrachlorodibenzo-p-dioxin), as a persistent environmental pollutant was investigated the result showed that curcumin inhibited the effect of TCDD on immune system and body weight gain. whereas TCDD caused significant reductions in the body weight gain, curcumin reversed this effect of TCDD [22].

Multiple researches revealed that polyphenols such as curcumin might be influential in prevention of small enhancements in weight throughout overfeeding. Howere, more investigations are needed prior accepting polyphenols' potential role in reduction of weight in overweight and obese subjects. In conclusion, although overall results support that polyphenol supplementation could be a complementary method in diet therapy, indeed, more treatments (12 months or more) are required to induce the impact of polyphenols on

Table 4. The changes of weight, BMI, and appetite score in obese patients with NAFLD

Factors	Intervention	Baseline Mean(SD)	3 Months Mean(SD)	P-value*	Mean Difference (CI 95 %)	P-value** Time	Treatment	Interaction
Weight (kg)	Nanocurcumin (n=42)	86.54(10.98)	83.89(10.74)	<0.001	-2.65 (-3.38, -1.91)	<0.001	0.8	0.3
	Placebo (n=42)	86.70(11.15)	84.39(11.04)	<0.001	-2.31 (-3.06, -1.55)	0.1	0.3	0.3
BMI (kg/m^2)$	Nanocurcumin (n=42)	30.67(2.14)	29.72(2.10)	<0.001	-0.95 (-1.09, -0.80)	<0.001	0.6	0.2
	Placebo (n=42)	30.75(2.35)	29.94(2.53)	<0.001	-0.81 (-0.97, -0.64)	0.03	0.9	0.3
Appetite (score)	Nanocurcumin (n=42)	6.81(1.48)	5.48(1.38)	<0.001	-1.33 (-1.42, -1.23)	<0.001	0.1	<0.001
	Placebo (n=42)	6.84(1.86)	6.55(1.81)	0.003	-0.29 (-0.41, -0.16)	0.007	0.2	0.002

$Cubically transformed; *Paired t-test; **two way repeated measures-ANOVA, top row: unadjusted; bottom row: adjusted for energy, fat total, saturated fat, monounsaturated fatty acid, vitamins D, B1, B6, and folate (DFE)

body weight [23].

The strengths of the present study were evaluation of appetite in obese NAFLD patients using a randomized double-blind design, regulation of possible confounders, utilizing the multiple eligibility standards, and employing curcumin nanoparticles form. The limitations were patients' unwillingness to participate in the study, choosing a single center, self-report on some standards like medicines and supplements consumption, and incapability to clarify potential intermediary mechanisms.

CONCLUSION

Our findings showed that three-month supplementation of obese NAFLD subjects with nanocurcumin could decrease appetite. Hence, it is crucial to investigate the capacity of curcumin in regulating NAFLD- and obesity-related aspects. Further trials particularly with focusing on intermediary mechanisms of curcumin involving in appetite regulation are required.

ABBREVIATIONS

NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, VAS: visual analogue scales, TPN: total parenteral nutrition, IPAQ: international physical activity questionnaire, TWRM-ANOVA: two way repeated measures-analysis of covariance, ITT: intention to treat, DFE: dietary folate equivalent, CI: confidence interval

DECLARATION

ETHICAL APPROVAL AND CONSENT

The ethical approval of this trial was conducted by the ethics committee of Tehran University of Medical Sciences (Ethical Code: IR.TUMS.REC.1395.2612). All the participants will complete an informed consent form (in Persian). Participation in and continuation of the supplementation is free and voluntary for the patients. In the trial, advice on the lifestyle modification will be presented to the patients free of charge. The health care services of the hospital will be provided without inconsistency. The side effects of the supplements had not been previously published. The patients' personal information will be kept confidential.

TRIAL REGISTRATION

The trial was registered at the Iranian Registry of Clinical Trials (IRCT) (IRCT2016071915536N3 and 27/12/2015).

COMPETING INTERESTS

There is no potential conflict of interests with respect to the research, authorship, and publication.

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AUTHORS' CONTRIBUTIONS

SAJT, MJHA, and SMR conceived and developed the idea for the study and revised the manuscript. SM, SMA, and MDM contributed to the data collection. MDM wrote numerous drafts on the study. MQ contributed to the statistical interpretations. Ultimately, all the authors read and approved the final manuscript.

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