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Nano-curcumin effects on nicotine dependence, depression, anxiety and metabolic parameters in smokers: A randomized double-blind clinical study

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ABSTRACT

Background: Smoking is clearly associated with metabolic profiles/abnormalities, psychological dysfunction, and symptoms of nicotine dependence. Nano-Curcumin (Nano-CUR) is a medicinal herb with antianxiety, antioxidant antidepressant-like effects, and anti-inflammatory properties. This RCT aimed to determine the therapeutic effects of Nano-CUR in smokers on clinical symptoms and metabolic parameters.

Methods: This trial was conducted on 70 participants with cigarette smoking. Smokers in two arms received soft gel capsules Nano-CUR 80 mg/daily for 3 months (n = 35) and placebo (n = 35), respectively. Primary outcomes (Nicotine dependence syndrome scale, depression, and anxiety beck score), and secondary outcomes (glycemic, lipid, stress oxidative, and inflammation profiles) were analyzed before and 3-months after the intervention in smokers.

Results: Nano-CUR supplementation significantly decreased nitric oxide, malondialdehyde, and C-reactive protein levels ($P < 0.05$), compared to the control. Furthermore, no significant effect change was shown in nicotine dependence syndrome, depression, anxiety, and other metabolic parameters ($p > 0.05$).

Conclusion: Nano-CUR intake may have favorable effects on C-reactive protein, malondialdehyde, and nitric oxide in subjects with cigarette smoking. More RCT are required to evaluate the effectiveness of Nano-CUR supplementations in smokers in order to reject or support these conclude.

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1. Introduction

Tobacco use is one of the health threats; killing millions of the population yearly throughout the world, and the current trend of death are continuing. In 2030, it is estimated within 80 % of deaths will be as to tobacco and smoking [1,2]. Cigarette smoking trends continue to increase in middle-income and low-income countries. The prevalence of cigarette smoking showed in Iran, Saudi Arabia, Pakistan, Qatar, and Jordan was 12 %, 20 %, 23 %, 25 %, and 30 %, respectively [1]. Also, tendency to cigarette smoking was various in different regions of Iran and had a bout of 7.9 % [2]. The prevalence of cigarette smoking has annually decreased by 1.6 % globally and has stagnated in recent years in Iran, which is despite its side effects, far less than the 5.8 % goal set by WHO [3,4]. Smoking has a relationship with several diseases (e.g., oral, throat, laryngeal, lung, esophageal, kidney, bladder, cervical, pancreatic, and liver cancers) [5]. Smoking is considered a risk factor for metabolic disorders due to its negative effects on abdominal obesity, glucose levels, lipid parameters and blood pressure [6]. Furthermore, smoking is a common risk agent for generating inflammation, and oxidative stress [7]. Exposure to cigarette smoking has been related to an enhanced risk of psychiatric illnesses (e.g., anxiety and depression) [8].

Alternative and Complementary medicines are becoming increasingly popular universally. Primarily herbal medicine is called phytotherapy. Curcumin (CUR) is a lipophilic material of a polyphenol nature. CUR is obtained from Curcuma longa L. and a plant from the ginger family, generally known as turmeric or saffron Indian. Turmeric powder, which is used as a spice, is obtained during the drying process and contains curcuminoids [9,10]. Given CUR'si antioxidant and anti-inflammatory properties, it has been hypothesized that CUR might be effective in the treatment of neuropsychiatric disturbance (e.g., depression and anxiety) [11]. In vivo and in vitro studies have shown that CUR can reduce cigarette smoke-induced inflammation by modulating the PPARγ–NF–κB pathway [12]. Recently, a meta-analysis by Shen et al. [13], indicated that CUR has beneficial effects on parameters of inflammation, lipid and glucose metabolism, and weight loss in subjects with polycystic ovary syndrome. Also, Shafabakhsh et al. showed in a study that CUR consumption (12 weeks) can improve sleep quality, total antioxidant, glutathione, malondialdehyde and PPAR-g gene expression. However, it had no effect on depression, anxiety and mRNA expression of IL-8, VEGF, TGF-b and IL-1 genes [14]. However, in a meta-analysis of ten RCTs comprising 523 patients in 2022, Emami et al. showed that CUR has no significant effect on anti-inflammatory markers [15]. Possible mechanisms of action of CUR could involve improving the apoptotic status of liver tissue, increasing polyunsaturated sphingomyelin expression, and inhibiting oxidative stress and inflammation [16,17].

The CUR effects on nicotine dependence syndrome, mental health, glycemic, and lipid indices, inflammatory, and oxidative stress markers of smokers have not been investigated. Therefore, This RCT aimed to examine whether the Nano-CUR improves the clinical symptoms and metabolic parameters in cigarette smoking. To our knowledge, this is the first RCT that examine Nano-CUR in smokers.

2. Material and methods

2.1. Participants

This is a clinical trial study. After receiving the approval of the Ethics Committee of Kashan University of Medical Sciences (IRCT20170420033551N12), 70 smokers referred to Golabchi Clinic (Kashan, Iran) between the ages of 17 and 50 were randomly selected. All clinical trial methods were performed by an addiction specialist, psychiatrist, psychologist, and pharmacologist, by the Helsinki declaration. This trial was designed with 80 % power, with 2- sided a = 0.05 (type I error), and type two errors (β) were 0.20. The sample size was calculated based on the therapeutic effects of CUR (on metabolic markers) in patients with T2 diabetes and CHD [14]. To detect a 0.36 mean difference in MDA levels between the 2 arms based on SDs observed in the trial study (0.6 and 0.3 in the CUR and placebo arms). The number of individuals needed to treat to detect this difference was 28/per arm. Due to the possibility of dropping out of participants, 35 participants were determined in each group. The inclusion criteria were smoking dependence (Fagerstrom test score more than 4), people looking to quit smoking, age of 17–50 years old, and complete informed consent. Exclusion criteria were taking anti-oxidant and anti-inflammatory supplement, report any side effects of therapy during the treatment period, history of metabolic disorders (e.g., diabetes, thyroid and hypertension), pregnant women, positive urine test for morphine, methamphetamine, and cannabis, use of psychiatric and neurological drugs such as benzodiazepines and antidepressants. All participants were given informed written consent before enrollment in this clinical trial (In participants were below 18 years of age, informed consent was obtained from a parental/guardian).

2.2. Study design

Demographic information of the participants was collected using a questionnaire. In this RCT, after randomization (balanced block randomization), subjects with cigarette smoking were assigned to receive either soft gel capsules of Nano-CUR (80 mg daily; n = 35) or placebo capsules (containing starch; n = 35) for 3 months. Nano-CUR and placebo were purchased from Exir Nano Sina (Tehran, Iran). Placebo and Nano-CUR capsules were similar in terms of shape, appearance and color. In this study, sampling was done by simple sampling method. The enrolled smokers were assigned to two arms using a balanced block randomization list with a 1:1 allocation, and block sizes of four was created (using Epi Info™ software). In addition, the allocation of drugs was done in labeled opaque bottles (A: treatment arm, and B: control arm). The subjects and researchers were blinded about the content (allocation and Randomization) until the final analyses.

2.3. Variable assessments

Primary outcomes: Nicotine Dependence Syndrome Scale, depression beck score, anxiety beck score.

Secondary outcomes: oxidative stress, glycemic index, lipid profile, and inflammation profiles. Evaluations were done at baseline and after the intervention (12 weeks).

2.4. Clinical assessment

Depression was evaluated by BDI questionnaire. Also, anxiety was evaluated using the BAI anxiety questionnaire. Nicotine dependence was investigated using Nicotine Dependence Syndrome Scale (NDSS) [18–20]. BDI and BAI are 21 and 20 question questionnaires respectively. Each question has a score between 0 and 4. Higher scores indicate higher levels of depression and anxiety. The validity and reliability of the Persian form of both questionnaires have been confirmed in previous studies [21,22]. NDSS is a multidimensional instrument to measure nicotine dependence. The NDSS includes scores for different aspects of dependency (Drive, Priority, Tolerance, Continuity, and Stereotypy) and an overall score of dependency [20]. Also, validation of the Persian version, and cultural adaptation have been proven in Iran [21,22].

2.5. Biochemical assessment

Metabolic and biochemical markers, including glycemic index (Insulin, FPG, and HOMA-IR), lipid profile (Total cholesterol (TC), Triglycerides (TG), LDL-C, VLDL-C, and HDL-C), inflammation (CRP and NO levels), and oxidation scale (TAC, GSH, and MDA concentrations) were performed at beginning and the end of the intervention period in all participants. At the beginning and end of the intervention, blood samples (10 ml) were taken from the participants for biochemical tests. In order to separate the plasma, the blood samples were centrifuged (1000 rpm for 20 min) and then the serum and plasma were stored at -80° c. At the end, the samples were analyzed in the laboratory of Metini Hospital (Kashan, Iran). Serum insulin concentration was measured by ELISA method. FPG concentration and lipid profile were measured using the commercial kit (Pars Azmoon, Tehran, Iran). Insulin resistance was assessed using the homeostasis assessment model [HOMA-IR, glucose (nmol/L) x insulin (microU/L)/22.5]. CRP levels in serum can be measured by quantitative and qualitative methods. Furthermore, Griess method, ferric reducing antioxidant power method, and Beutler et al. method were used for measuring total antioxidant capacity (TAC), glutathione (GSH), and Nitric oxide (NO) concentrations, respectively. Also, Malondialdehyde (MDA) levels measured by the thiobarbituric acid reactive substances spectrophotometric test with intra- and inter-assay CVs were less than 5 % [23–26].

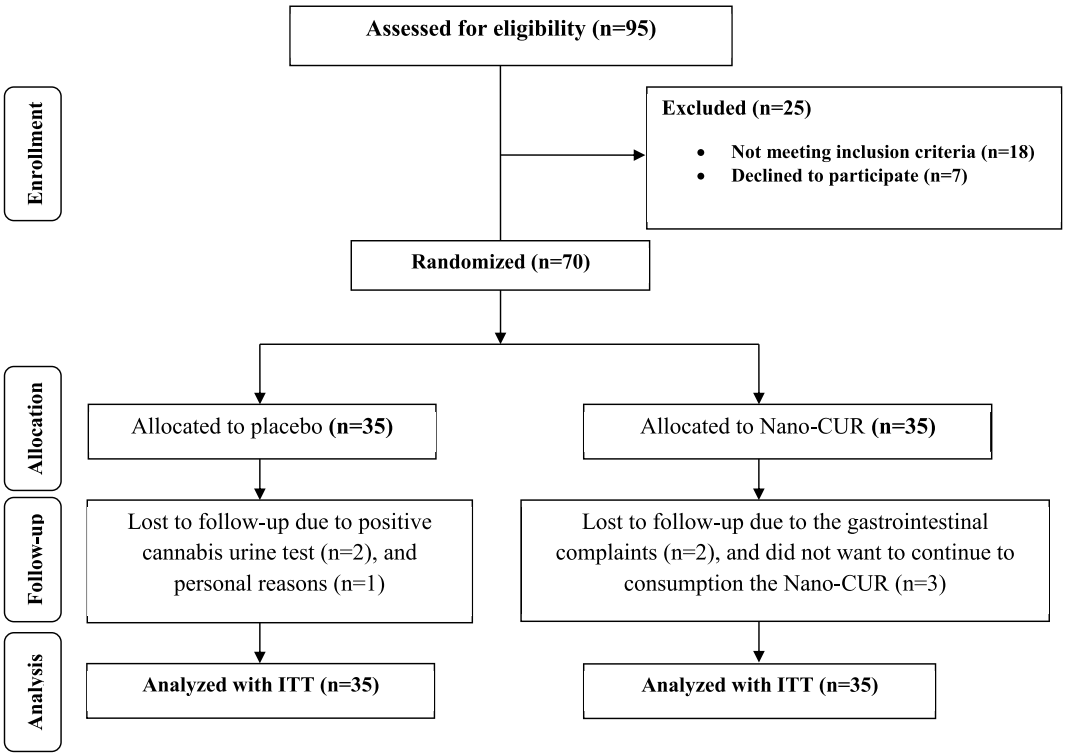

Fig. 1. Flow diagram of the randomized-controlled trial.

2.6. Statistical analysis

The Kolmogorov-Smirnov statistic was performed to assess the normality of data. Qualitative and quantitative data are presented as mean with standard deviation (SD), and the frequency distribution accordingly. Differences in demographic characteristics among the two intervention arms were evaluated by two-sample *t*-test and Chi-square test. Multiple linear regression models were applied to define the treatment intervention impacts on RCT outcomes after adjusting for baseline values of parameters. The analyses were performed according to the intention-to-treat (ITT) approach. Missing values were addressed according to the last-Observation-Carried-Forward technique. ITT protocol was performed according to all randomized individuals and all parameters. All analyses were done at an alpha level of 0.05.

3. Results

During recruitment, the eligible people were 70 participants and randomly assigned to either supplementation or control arms to receive Nano-CUR or placebo, respectively (35 subjects to each treatment arm). In the Nano-CUR arm, two participants voluntarily left the RCT because of increased gastrointestinal complaints (Subjects reported headaches and diarrhea 7 days after using Nano-CUR), and three participants voluntarily left the RCT because they did not want to continue to consumption the Nano-CUR (Individuals continued the intervention for 19 days, and to personal reasons did not want to continue intervention). In the placebo arm, two of the subjects discontinued RCT because of a positive urine test for cannabis, and one subject was excluded from the RCT because of personal reasons. Finally, the trial was analyzed based on the findings of 62 smokers [Nano-CUR (n = 30), and control (n = 32)]. The flow-chart CONSORT of the participants is shown in Fig. 1.

Noteworthy, the Nano-CUR caused no serious adverse events. Although, gastrointestinal side effects were reported in two smokers using Nano-CUR such as nausea and abdominal pain, which did lead to excluding two participants from the RCT.

Table 1 illustrated the baseline general characteristics of the enrolled subjects. There were no significant differences among the Nano-CUR and placebo arms in variables of baseline age, age at first cigarette smoking, duration of cigarette smoking, gender, education, status of marital, job, and Number of frequency cigarette smoking.

After the 12-week intervention, there were no significant changes in primary outcomes scores of BDI, BAI, and NDSS in the intervention arm compared with the placebo arm ($p > 0.05$) **(Table 2)**. In secondary outcomes, the changes in hs-CRP levels comparing the baseline with 12 weeks were different between the Nano-CUR and the placebo arms, which the Nano-CUR arm had decreased CRP levels but not the placebo arm (β −0.50 mg/L; 95 % CI, −0.85, −0.14; P = 0.006). Also, Nano-CUR supplementation significantly

Table 1
General characteristics of participants[a].

Variable	Nano-CUR (n = 35)	Placebo (n = 35)	P[b]	P[d]
Age (years)	33.05 ± 10.05	32.14 ± 9.55	0.84	0.69
Age at first cigarette smoking (y)	20.65 ± 3.71	21.91 ± 3.61	0.13	0.15
Duration of cigarette smoking (y)	11.34 ± 9.69	10.02 ± 8.38	0.65	0.54
Gender (%)				
Female	7 (20)	6 (17.1)	0.65[c]	0.75[e]
Male	28 (80)	29 (82.9)		
Education (%)				
Illiterate	1 (2.9)	2 (5.7)		
Elementary	9 (25.7)	8 (22.9)		
Intermediate	11 (31.4)	14 (40)	0.98[c]	0.86[e]
Diploma	5 (14.3)	3 (8.6)		
College education	9 (25.7)	8 (22.9)		
Status of marital (%)				
Single	14 (40)	17 (48.6)		
Married	15 (42.9)	16 (45.7)	0.18[c]	0.31[e]
Widow/Divorced	6 (17.1)	2 (5.7)		
Job (%)				
Unemployed	11 (31.4)	9 (25.7)		
Employed	7 (20)	6 (17.1)	0.97[c]	0.90[e]
Others	14 (40)	16 (45.7)		
Housewife	3 (8.6)	4 (11.4)		
Number of frequency cigarette smoking (days)				
One pack of cigarettes	17 (48.6)	19 (54.3)	0.54[c]	0.55[e]
Two packs of cigarettes	12 (34.3)	8 (22.9)		
Three packs of cigarettes	3 (8.6)	6 (17.1)		
More than three packs of cigarettes	3 (8.6)	2 (5.7)		

[a] Data are mean ±SDs and percentage.
[b] Obtained from independent *t*-test (Before ITT protocol).
[c] Obtained from Pearson Chi-square test (Before ITT protocol).
[d] Obtained from independent *t*-test (After ITT protocol).
[e] Obtained from Pearson Chi-square test (After ITT protocol).

improved NO and MDA levels (β −2.29 μmol/L; 95 % CI, −4.27, −0.31; P = 0.02 and β −0.51 μmol/L; 95 % CI, −0.94, −0.08; P = 0.01, respectively) compared with the placebo **(Table 3).** Moreover, the glycemic indices, lipid profiles, TAC, and GSH levels differed in the Nano-CUR arm compared with the placebo arm but none of these changes were statistically significant (p > 0.05) **(Table 3).**

4. Discussions

Our study is one of the first to explore the effects of Nano-CUR on clinical scales of nicotine and metabolic indicators among individuals who smoke. After daily supplementation of Nano-CUR for 12 weeks, we observed that it did not have any significant impact on nicotine dependence or mental health conditions like depression and anxiety. However, we did notice significant changes in MDA, NO, and hs-CRP levels among subjects who smoked cigarettes, while there were no significant changes in other metabolic indicators. According to reports, administering CUR at 1.2 g/day to over 100 participants for 18 months did not cause any safety concerns or adverse effects. Previous research studies have also found no significant toxicity associated with oral consumption of CUR [27–29]. However, during our own research, two individuals experienced gastrointestinal complaints and three patients expressed unwillingness to continue using the active medication. Data reporting the effects of Nano-CUR supplementation on the nicotine dependence syndrome scale in smokers are scarce. For example, in an animal study, curcuminoid administration was shown to improve nicotine dependence and relapse by inhibiting the activity of the enzyme acetylcholinesterase in the brain [30]. On the other hand, the impact of CUR on peripheral neuropathy relies on α7 nAChR receptors in the spinal cord, as it has both anti-inflammatory and antinociceptive properties [31]. The α7 nAChRs are responsible for the conditioned incentive motivation caused by exposure to nicotine-associated environmental cues [32]. It is possible that CUR did not reduce nicotine dependence by acting on α7 nAChR.

Participants who smoked cigarettes showed no significant changes in BDI and BAI scores compared to those who took the placebo. Tobacco use has been linked to psychopathological conditions like anxiety, depression, and attention-deficit/hyperactivity disorder [33–35]. CUR has indicated potential anxiolytic- or antidepressant-like activities in some studies and can reduce the severity of symptoms without significant adverse effects [36,37]. Esmaily et al. [38], found that 1g/day of CUR for 30 days has an anti-anxiety effect in obese individuals, but no impact on BDI scores. Another study showed that 80 mg of Nano-CUR (daily for 8 weeks) decreased anxiety and depression scores in diabetic patients with neuropathy, but no significant change in stress score [39]. In contrast to our study, Lopresti AL and Drummond PD reported that low-dose CUR extract (250 mg BID), high-dose CUR extract (500 mg BID), or combined low-dose CUR extract plus saffron (15 mg BID, for 12 weeks) is effective in reducing anxiety (STAI) and depressive (IDS) symptoms in major depressive disorder (MDD) patients [40]. However, CUR supplementation (1000 mg/day; twelve weeks) did not effectively change BDI and BAI scores in Type 2 diabetes mellitus patients with coronary heart disease [14]. A systematic review of the antidepressant effects of curcumin found that differing doses and routes of administration may have affected results and comparisons [41].

The present RCT suggested that intervention with the Nano-CUR supplement was associated with a significant reduction in serum MDA, NO, and hs-CRP concentrations in smokers. Consistent with our study, the findings of an updated meta-analysis of a number of RCTs indicated a reduction in hs-CRP levels with less than 2000 mg CUR per day in subjects with auto-inflammatory conditions. Hence, CUR seems to have beneficial effects on reducing CRP and hs-CRP concentrations in pro-inflammatory settings [42]. In addition, a review of some RCTs and preclinical studies show the beneficial effects of CUR-piperine in improving lipid profile, glycemic levels, and antioxidant indices in diabetes, improving the inflammatory levels caused by metabolic disturbance, reducing depression and oxidative stress in neurological disorders, COVID-19, improving asthma, and chronic respiratory diseases [43–46]. Moreover, Patients with metabolic syndrome showed an improvement in triglyceride and HOMA-β levels, but in an RCT by Bateni et al. [47], there were no differences in blood pressure, other biochemical factors (e.g., HbA1c, FBS, HOMA-IR), and other lipid variables following 12-weeks of 80 mg/day Nano-CUR supplementation between Nano-CUR and placebo arms [47]. CUR modulates the multiple molecular targets and cellular transduction pathways. For example, induction of the AGE gene receptor expression, synthesis of glutathione, PPARγ activity, NF-kB, Nrf2, STAT-3, IL-1β, TNF-α, adiponectin, leptin, and resistin, which may lead to its therapeutic role in metabolic

Table 2
Effect of Nano-CUR intake on depression, anxiety, and nicotine dependence scale.

Variables	Nano-CUR (n = 35)		Placebo (n = 35)		Difference in outcome measures between Nano-CUR and placebo treatment arms[a]		
	Week 0	Week 12	Week 0	Week 12	β (95 % CI)	P[b]	P[c]
BDI	24.45 ± 7.06	24.08 ± 6.59	22.22 ± 6.57	22.71 ± 6.31	−0.62 (−1.85, 0.59)	0.35	0.31
BAI	17.88 ± 6.46	17.74 ± 6.32	16.20 ± 6.75	16.48 ± 6.41	−0.28 (−1.42, 0.85)	0.67	0.61
NDSS	44.34 ± 7.51	44.31 ± 7.54	42.05 ± 8.95	42.37 ± 8.41	−0.07 (−1.45, 1.31)	0.84	0.91

Data are mean ±SDs.
BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; NDSS, Nicotine Dependence Syndrome Scale.
[a] "Outcome measures" refers to the change in values of measures of interest among week 0 and week 12. β [difference in the mean outcomes measures between intervention arms (Nano-CUR arm = 1 and placebo arm = 0)].
[b] Obtained from multiple regression models; adjusted for baseline values of each depression, anxiety, and nicotine dependence variables, age and duration of cigarette smoking) (Before ITT protocol).
[c] Obtained from multiple regression models; adjusted for baseline values of each depression, anxiety, and nicotine dependence variables, age and duration of cigarette smoking) (After ITT protocol).

Table 3
Effect of Nano-CUR supplementation on metabolic indicators levels.

Variables	Nano-CUR (n = 35)		Placebo (n = 35)		Difference in outcome measures between Nano-CUR and placebo treatment arms[a]		
	Week 0	Week 12	Week 0	Week 12	β (95 % CI)	P[b]	P[c]
FPG (mg/dL)	86.01 ± 9.61	85.74 ± 9.85	86.45 ± 12.00	86.76 ± 10.75	−0.65 (−1.86, 0.55)	0.29	0.28
Insulin (μIU/mL)	8.16 ± 2.63	7.86 ± 2.14	7.82 ± 1.88	7.86 ± 1.69	−0.25 (−0.72, 0.22)	0.28	0.29
HOMA-IR	1.73 ± 0.60	1.70 ± 0.50	1.71 ± 0.42	1.71 ± 0.37	−0.04 (−0.14, 0.06)	0.54	0.43
Triglycerides (mg/dL)	168.89 ± 35.43	168.52 ± 34.69	160.49 ± 36.33	161.15 ± 35.02	−0.57 (−3.11, 1.95)	0.84	0.65
VLDL-cholesterol (mg/dL)	35.23 ± 5.70	35.16 ± 5.54	32.87 ± 6.60	33.00 ± 6.29	−0.05 (−0.56, 0.44)	0.84	0.81
Total cholesterol (mg/dL)	187.49 ± 32.80	186.93 ± 31.69	185.98 ± 26.72	186.16 ± 24.53	−0.56 (−4.28, 3.15)	0.98	0.76
LDL-cholesterol (mg/dL)	113.16 ± 32.09	112.78 ± 31.15	112.52 ± 28.13	112.53 ± 25.99	−0.32 (−3.99, 3.33)	0.93	0.85
HDL-cholesterol (mg/dL)	38.81 ± 5.88	38.71 ± 5.48	40.46 ± 4.95	40.50 ± 5.07	−0.29 (−1.27, 0.67)	0.59	0.54
Hs-CRP (mg/L)	5.41 ± 1.34	4.93 ± 1.21	5.40 ± 1.53	5.44 ± 1.40	−0.50 (−0.85, −0.14)	0.009	0.006
NO (μmol/L)	44.15 ± 8.50	42.23 ± 7.23	45.28 ± 7.64	45.49 ± 8.06	−2.29 (−4.27, −0.31)	0.01	0.02
TAC (mmol/L)	714.72 ± 164.77	733.05 ± 185.14	709.71 ± 203.62	699.85 ± 187.54	28.27 (−14.29, 70.85)	0.19	0.18
GSH (μmol/L)	588.08 ± 69.12	572.89 ± 66.03	550.11 ± 75.67	549.32 ± 75.01	19.77 (−7.88, 47.43)	0.18	0.15
MDA (μmol/L)	3.89 ± 2.08	3.47 ± 1.53	3.86 ± 2.71	3.96 ± 2.34	−0.51 (−0.94, −0.08)	0.02	0.01

Data are mean ±SDs.
FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL-cholesterol, high density lipoprotein-cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-cholesterol, low density lipoprotein-cholesterol; NO, nitric oxide; VLDL-cholesterol, very low density lipoprotein-cholesterol; TAC, total antioxidant capacity; MDA, malondialdehyde.
[a] "Outcome measures" refers to the change in values of measures of interest between week 0 and week 12. β [difference in the mean outcomes measures between intervention arms (Nano-CUR arm = 1 and placebo arm = 0)].
[b] Obtained from multiple regression models; adjusted for baseline values of each biochemical variables, age and duration of cigarette smoking) (Before ITT protocol).
[c] Obtained from multiple regression models; adjusted for baseline values of each biochemical variables, age and duration of cigarette smoking) (After ITT protocol).

abnormalities [48–50]. Also, CUR products are natural anti-oxidants that exert their protective effects via the elevation of an anti-oxidant defense system and free radical scavenging. Furthermore, CUR ingestion might reduce oxidative damage via chelating the redoxactive metals, and inhibiting chain reactions producing metal ion-induced free radicals [51,52].

One limitation of the trial was that the smokers orally consumed Nano-CUR for a period of 3 months, hence long-term intervention outcome effects of the Nano-CUR are unknown. Also, budget limitations prevented from evaluation of more important primary outcomes including nicotine levels and urinary cotinine excretion. It appears that future investigations are required to assess the effects of the various doses of the complementary Nano-CUR on above mentioned outcomes in a larger population of smokers.

5. Conclusion

This trial showed that 12-weeks consumption of Nano-CUR might be effective in lowering the Malondialdehyde, Nitric oxide, C-reactive protein levels in smokers, but it not improves the nicotine dependence syndrome, anxiety, depression, and other metabolic indicators levels. This RCT is limited by the small sample size; hence, larger-term RCTs are required to confirm such results.

Ethics approval and consent to participate

The participants were educated about the purpose of the study, and All participants gave their signed written informed consent letters (In participants were below 18 years of age, informed consent was obtained from a parental/guardian). Ethical considerations were approved by the Kashan University of Medical Sciences research committee following the Declaration of Helsinki, with the ethical code: **IR.KAUMS.MEDNT.REC.1401.017**.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Peyman Mamsharifi: Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization. **Bahareh Farokhi:** Visualization, Validation, Software, Methodology, Investigation, Data curation, Conceptualization. **Raha Hajipoor-Taziani:** Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Data curation, Conceptualization. **Fatemeh Alemi:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pooya Hazegh:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Shaghayegh Masoumzadeh:** Writing – review & editing, Writing –

original draft, Methodology, Investigation, Data curation. **Leila Jafari:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis. **Amir Ghaderi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Somayeh Ghadami Dehkohneh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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