Curcumin nanomicelle versus curcumin improves lipid profile, stress oxidative factors and inflammatory markers in patients undergoing coronary elective angioplasty; A Randomized Clinical Trial

Bijan Helli
  Ahvaz Jondishapour University of Medical Sciences

Hadis Gerami
  Tehran University of Medical Sciences

Maria Kavianpour
  Tehran University of Medical Sciences

Habib Heybar
  Ahvaz Jondishapour University of Medical Sciences

Seyed Kianoosh Hosseini
  Tehran University of Medical Sciences

Hossein Khadem haghighian (✉ khademnut@yahoo.com)
  Qazvin University of Medical Sciences   https://orcid.org/0000-0002-7445-1846

Research

Abstract

Background: Curcumin exhibited antioxidant and anti-inflammatory effects. The aim of this study, assess and compare curcumin and nano- curcumin effects on lipid profile, oxidative stress index and inflammatory factors of heart patients.

Methods: This Randomized, Double-Blind, Placebo-Controlled Clinical Trial conducted on 90 patients undergoing coronary elective angioplasty. Patients were randomly divided into 3 groups. The first group received a 500 mg capsule of curcumin daily. The second group received an 80 mg capsule of nano-curcumin daily. The placebo group also received capsules similar to curcumin for 8 weeks. Lipid profile, stress oxidative factors and inflammatory markers measured in baseline and end of the investigation.

Results: At the end of study, statistically significant changes was seen in the total cholesterol (TC), triglyceride (TG) and low density lipoprotein (LDL) in the intervention groups to the control group (p<0.05). These changes in the nano-curcumin group were greater than the curcumin group. Curcumin and nano-curcumin supplementation also caused a statistically significant improvement in plasma levels of total antioxidant capacity (TAC), malondialdehyde (MDA), Superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), high-sensitivity C-reactive protein (hs-CRP), Interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) in comparison to the placebo (p<0.05).

Conclusion: Complementary therapy of cardiovascular patients with curcumin and nano-curcumin supplements, could improve lipid profile, stress oxidative index and, inflammatory factors. The effects of curcumin on nano formula may be better for cardiac patients due to high bioavailability. However, further investigation is suggested in this regard.

Introduction

One of the mainly factors resulted in death is the cardiovascular disease (CVD) in the world wide[1]. According to the World Health Organization (WHO) report prevalence of CVD increased, that projected combined death toll of 24 million by 2030[2]. Epidemiologic studies have reported the several risk factors for this category of diseases. In the pathophysiology of atherosclerosis, impaired plasma levels of lipoproteins including high cholesterol, high LDL cholesterol, high serum TG, low HDL cholesterol, and lipid metabolism disorders are more than other factors affecting atherosclerosis[3]. Also, increased inflammation and oxidative stress are considered to be major risk factors for atherosclerosis and cardiovascular disease. Among the main causes of cardiovascular disease, inflammation has a pivotal role in all steps atherothrombosis. Inflammatory cytokines, including IL-1, TNF-α, and CRP induce the expression of cellular adhesion molecules, which mediate adhesion of leukocytes to the vascular endothelium. CRP can also induce monocytes to express tissue factor, a glycoprotein that plays an important role in coagulation[4, 5].

Furthermore, Reactive Oxygen Species (ROS) at physiological levels are now known as a signaling molecules to regulate a wide range of actions in the cardiovascular system and to contribute to the

maintenance of cardiovascular homeostasis[6]. Many scientific investigations have to be done on the role, mechanism and sources of ROS in heart cells. Much studies are required to determine ROS inhibitors for clinical applications[7]. Decreasing in blood circulation to the heart and straitened arteries are the main features of the disease[8]. With the advancement of surgical techniques in last years, some techniques such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have been introduced for boosting in coronary heart disease (CHD) patients conditions. Nevertheless, on the reports of the several studies, reperfusion injury and microvascular blocking may occur after PCI. Also in subjects who experience new remedy such as stenting, resulted in no-reflow development. Endothelial layer integrity by eliminating risk factors associated with it by lipid lowering agents, free radical scavengers, and antioxidants can be effective in restoring endothelial function and reducing disease progression[9, 10].

Curcumin is a polyphenols compound separated from turmeric. It is found that curcumin has many pharmacological effects including antioxidant, anti-inflammation, eliminating free radicals, anti-tumor, lipid regulation and anti-coagulation[11]. Clinical trials showed no severe toxic or side effect. It is also reported that after application of curcumin in coronary heart disease, the lipid level is effectively controlled and the incidence of cardiovascular event is reduced[12]. Various methods are used to increase the availability of curcumin in tissue or plasma. The results show that the use of nano-carriers with curcumin increases the effectiveness of curcumin in preventing diseases and increases 22-fold access to curcumin, and this action and the use of curcumin in the nano formulation can be an important and reliable[13]. Curcumin nano-micelle which is a registered curcumin product (SinaCurcumin®) was prepared for oral use. Considering the fact that there is no study about nano-type turmeric effect in patients undergoing coronary angioplasty, we decided to study and compare curcumin and nano-curcumin effects on lipid profile, inflammatory factors and oxidative stress index of heart patients.

Methods

Patients

This study was conducted as a double-blind, placebo-controlled clinical trial. All patients completed a written informed consent form before entering the study. The study was done according to the Declaration of Helsinki and later revisions as a statement of ethical principles for medical research involving human subjects. One hundred Cardiac patients aged 40–80 years, undergoing coronary angioplasty and regularly refer to the cardiology clinic of Ahvaz Gholestan Hospital are enrolled by the specialty cardiologist of this project. The exclusion criteria of the study were patients with LDL below 70 (mg/dl), renal or hepatic dysfunction, heart problems in the last month, stomach ulcer, gallstones, inflammatory disease or uncontrolled autoimmune, breastfeeding or pregnant women, unexpected complications during the study, such as dizziness, heart attack, and intolerance to curcumin, and those who wanted to discontinue the study at any time. The study was registered in the Iranian Registry of Clinical Trials website by the IRCTID: IRCT20141025019669N6, and protocol had approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Design

All patients met the inclusion criteria were randomly divided into 3 groups: curcumin, nano- curcumin, and placebo groups. The first group received a 500 mg capsule of curcumin daily. The second group received an 80 mg capsule of nano- curcumin daily. The placebo group also received capsules similar to curcumin. The study lasted 60 days. Randomization number allocated for qualified subject that was formed by a computer software. Next a table of randomization was created by the method of random permuted blocks. Each qualified patient received a randomization number, which was determined by a computer generated schedule. Then a randomization table was generated by the method of random permuted blocks. The investigator and patients were blinded to the treatment condition. Nanomicelle formulation of curcumin is a novel formulation of curcumin in world that produced by Exir Nano Sina company. Patient's demographic data, including age, gender, medical history and medications intake were collected. Anthropometric indices including: height and weight were measured then body mass index (BMI) was calculated in kilograms per meters squared. In order to assess the diet of patients in terms of energy intake, macronutrients, types of fatty acids, some vitamins and minerals, 3 d food diary (2 weekdays and1 weekend) completed through face-to-face interviews and telephone calls. Dietary intakes were analyzed using Nutritionist 4 software (First Databank, Inc., Hearst Corporation) using the database from tables of content and nutritional value of Iranian food products. Lipid profile, stress oxidative factors and inflammatory markers measured in baseline and end of the investigation.

Laboratory Methods

At baseline and at the end of the investigation, after 12 hours of fasting, 10 cc of venous blood samples were collected and after serum isolation, they were kept at -80 ° C until assay. Blood samples without EDTA centrifuged (Beckman Avanti J-25, USA) at a rate of 3000 rpm for 10 minutes in order to separation of serum.

Total cholesterol levels were determined by the enzymatic spectrophotometric method using an auto-analyzer (Abbott, model Alcyon 300, USA) with Pars-Azmoon Kit (Tehran, Iran). Triglyceride and HDL were determined by the enzyme colorimetric method using an automatic analyzer (Abbott, Model Alcyon 300, and USA) with Pars-Azmoon Kit. LDL-C was calculated by Friedwald formula; LDL-C (mg/dl) = TC- (HDL-C + TG/5).

Serum MDA levels were measured by tiobarbituric acid method. Colorimetric method was used for analyzing serum TAC (Randox Laboratories Ltd, UK). This method has completely been explained by Khosrowbeygi et al[14]. Also glutathione peroxidase enzyme was measured by spectrophotometric and superoxide dismutase enzyme was performed with Randox lab, UK.

Turbidimetric immunoassay was used for measuring of hs-CRP levels (BioSystems Co, Barcelona, Spain). Also enzyme-linked immunosorbent assay (ELISA) (DIAsource Co, Belgium) was used for determining serum levels of TNF-α. The amount of IL-1β was measured by using the Bendermed quantitative

detection kit made in Austria, with precision of picograms per milliliter by ELISA method according to the manufacturer's instructions in the laboratory.

Sample size calculation

To determine the sample size, we used the MDA factor before and after the intervention, which was used in Yunes Panahi et al. study[15]. Thus, if the mean and standard deviation of the MDA before and after the supplementation was 19.84 ± 3.60 and 16 ± 2.88, for each group of 25 people was calculated. Considering the drop in participants during the study, 30 people were considered for each group.

$N= [(Z1-\alpha/2 + Z1-\beta)\ 2\ (SD12 + SD22)] / \Delta2\ Z1-\alpha/2 = 2.58,\ Z1-\beta = 1.64\ N = 25$

Statistical Analysis

SPSS software v.20 was utilized as a data analyst. Due to the normal distribution of variables, which were checked by Kolmogorov–Smirnov test. Also paired t-test is used to compare before and after supplementation in each group and one way ANOVA was applied to compare groups. The percentage change of each variable was also calculated by the formula $[(E-B)/ B* 100]$, where E is the end of treatment values and B is the baseline values. All data presented as mean ± SD and statistically signification was defined as $P < 0.05$.

Results

One hundred patients were qualified to participate in this study at the beginning. Ninety two patients completed the intervention. One patient from the curcumin group withdrew from the study because of personal reasons. One patient from the placebo group dropped out due to personal reasons. Their data were excluded from the final statistical analysis (Fig. 1)

Demographic and baseline characteristics

The patient's demographic and baseline characteristics are presented in Table 1. According to Table 1 there are no significant differences in terms of age, weight, body mass index (BMI), ejection fraction and Hemoglobin. Coronary risk factors for coronary artery disease were evenly distributed between the groups. The stented target vessels were similarly among the groups.

Table 1

Comparison of characteristics between groups in the baseline.

Variables		Curcumin Group N = 30	Nano micelle Group N = 30	placebo Group N = 30	P-value
Age (years, Mean ± SD)		55.27 ± 7.11	56.19 ± 6.9	54.06 ± 5.23	∗0.701
Weight (Kg, Mean ± SD)		73.07 ± 8.05	72.69 ± 7.02	73.31 ± 6.11	∗0.773
Body Mass Index (K g/m², Mean ± SD)		28.1 ± 2.4	27.81 ± 2.09	28.01 ± 1.93	∗0.801
Ejection fraction (%)		47.58 ± 6.9	48.23 ± 6.03	47.44 ± 5.54	∗∗0.501
Hemoglobin (g/dL)		13.74 ± 0.71	13.6 ± 0.62	13.7 ± 0.57	∗0.401
Risk factor	Hypertension (%)	12 (40)	13 (43.33)	11 (36.66)	∗∗0.42
	Smoking (%)	10 (33.33)	11 (36.66)	9 (30)	∗∗0.311
Coronary lesions	LAD (%)	8 (26.66)	7 (23.33)	8 (26.66)	∗∗0.634
	LCX (%)	6 (20)	5 (16.66)	7 (23.33)	∗∗0.723
	RCA (%)	5 (16.66)	4 (13.33)	5 (16.66)	∗∗0.819
*Based on statistical analyzes Independent samples t test					
** Based on statistical analyzes Chi-squared test					

Dietary intake of the subjects

The mean of energy and macronutrient intake at baseline of the study were summarized in Table 2. As shown there were no statistically significant difference between the groups in terms of average daily intake the energy, protein, fat, saturated fatty acids, unsaturated fatty acids and some micronutrients (P > 0.05).

Table 2

Average daily intake of calorie, carbohydrate, protein, fat, vitamin C, E and Se in the baseline.

Variables	Curcumin Group N = 30	Nano micelle Group N = 30	placebo Group N = 30	P-value
Energy (kcal)	1819 ± 221.13	1786 ± 186.7	1850 ± 201.47	0.511
Carbohydrate (g)	243.7 ± 45.19	239.4 ± 42.11	245.04 ± 43.31	0.601
Protein (g)	70.41 ± 11.57	69.73 ± 9.81	71.21 ± 10.03	0.724
Fat (g)	62.5 ± 7.27	60.6 ± 5.35	65.11 ± 7.49	0.501
PUFA(g)	20.1 ± 2.09	19.31 ± 2.25	21.07 ± 2.93	0.806
Vitamin C (mg)	67.11 ± 13.5	65.19 ± 17.01	69.12 ± 15.9	0.617
Vitamin E (IU)	8.07 ± 0.83	8.19 ± 0.54	8.76 ± 0.13	0.819
Selenium	117.01 ± 26.13	115.85 ± 23.19	119.03 ± 25.3	0.401
The data are expressed in mean ± SD.				

Lipid profile

There were no statistically significant differences in lipid profile between groups at baseline of the study (P > 0.05, Table 3). There were no significant changes in the placebo group in the lipid profile, but total cholesterol, triglyceride and LDL in the intervention groups after the completion of the study significantly decreased. According to Table 3, these changes in the nano-curcumin group were greater than the curcumin group. Also the HDL levels was increased in intervention groups, but these changes were not significant.

Table 3

Comparison of changes in levels of lipid profiles before and after intervention in study groups

Variables		Curcumin Group N = 30	Nano micelle Group N = 30	placebo Group N = 30	P1
TC (mg/dL)	Baseline	261.11 ± 48.51	255.07 ± 46.63	259.91 ± 50.02	0.709
	End	191.4 ± 37.11	172.13 ± 38.9	256.1 ± 43.83	0.001
	P2	0.04	0.01	0.713	
	Percentage Changes	-26.69	-32.51	-1.46	
TG (mg/dL)	Baseline	242.01 ± 73.19	247.9 ± 69.19	241.8 ± 63.9	0.84
	End	169.5 ± 50.04	147.13 ± 42.51	238.2 ± 55.27	0.001
	P2	0.039	0.01	0.638	
	Percentage Changes	-29.96	-40.64	-1.48	
HDL-c (mg/dL)	Baseline	40.04 ± 5.42	41.07 ± 4.73	41.34 ± 5.06	0.902
	End	44.13 ± 4.3	44.27 ± 5.01	40.17 ± 4.02	0.161
	P2	0.23	0.14	0.53	
	Percentage Changes	10.21	7.79	-2.83	
LDL-c (mg/dL)	Baseline	172.6 ± 28.51	164.01 ± 28.13	170.3 ± 30.11	0.806
	End	113.4 ± 30.3	98.21 ± 25.03	168.9 ± 24.1	0.001
	P2	0.037	0.001	0.611	
	Percentage Changes	-34.29	-40.11	-0.82	

P1: Comparing the mean of lipid profiles between groups (The statistical analyzes Anova)

P2: Comparing the mean of lipid profiles in each group at the baseline and end of the study (The statistical analyzes Paired samples t-test)

Antioxidant Indices

The mean of antioxidant indices are shown in groups before and after study in Table 4. In the intervention groups, the mean of TAC, SOD and GSH-Px were increased ($p \leq 0.05$) that were statistically significant,

but there was no significant change in placebo group. Plasma MDA was also affected by curcumin and nano-curcumin supplementation. This factor significantly decreased in the intervention groups (P < 0.05). As shown in Table 4, these changes in the nano-curcumin group were greater than the curcumin group.

Table 4

Comparison of changes in levels of antioxidant indices before and after intervention in study groups

Variables		Curcumin Group N = 30	Nano micelle Group N = 30	placebo Group N = 30	P1
TAC (mmol/L)	Baseline	0.91 ± 0.13	0.95 ± 0.61	0.89 ± 0.52	0.805
	End	1.48 ± 0.34	1.79 ± 0.29	0.91 ± 0.43	0.001
	P2	0.037	0.022	0.61	
	Percentage Changes	62.63	88.42	2.24	
SOD (U/mg Hb)	Baseline	1605.41 ± 221.07	1655.17 ± 262.4	1619.11 ± 246.5	0.713
	End	1803.1 ± 285.7	1983.03 ± 311.2	1609.17 ± 213.4	0.021
	P2	0.034	0.01	0.62	
	Percentage Changes	12.31	19.80	-0.61	
GSH-Px (U/g Hb)	Baseline	39.88 ± 7.13	38.43 ± 8.03	40.63 ± 9.17	0.823
	End	50.11 ± 9.19	57.13 ± 9.51	42.19 ± 8.51	0.001
	P2	0.041	0.029	0.51	
	Percentage Changes	25.65	48.65	3.83	
MDA	Baseline	1.19 ± 0.2	1.23 ± 0.41	1.17 ± 0.17	0.901
	End	0.84 ± 0.1	0.63 ± 0.13	1.1 ± 0.15	0.001
	P2	0.003	0.001	0.184	
	Percentage Changes	-29.41	-48.78	-5.98	
P1: Comparing the mean of antioxidant indices between groups (The statistical analyzes Anova)					
P2: Comparing the mean of antioxidant indices in each group at the baseline and end of the study (The statistical analyzes Paired samples t-test)					

Inflammatory factors

The effect of supplementations on inflammatory biomarkers in cardiovascular patients have been summarized in Table 5. After 8 week, inflammatory biomarkers levels were affected by curcumin and nano-curcumin. This factors significantly decreased in the intervention groups (P < 0.05). As shown in Table 5, these changes in the nano-curcumin group were greater than the curcumin group.

Table 5

Comparison of changes in levels of inflammatory factors before and after intervention in study groups

Variables		Curcumin Group N = 30	Nano micelle Group N = 30	placebo Group N = 30	P-value
Il- 1 b	Baseline	4.41 ± 1.23	4.51 ± 1.34	4.55 ± 1.07	0.792
	End	3.09 ± 0.93	2.49 ± 0.88	4.23 ± 1.1	0.001
	P1	0.031	0.02	0.56	
	Percentage Changes	-29.93	-44.78	-7.03	
TNF-a (pg/ml)	Baseline	19.61 ± 4.72	18.95 ± 4.09	19.11 ± 4.23	0.685
	End	16.01 ± 3.52	14.06 ± 3.27	19.02 ± 4.1	0.001
	P1	0.033	0.021	0.605	
	Percentage Changes	-18.35	-25.8	-0.47	
hs-CRP(ng/ml)	Baseline	2.42 ± 0.23	2.5 ± 0.4	2.51 ± 0.39	0.704
	End	1.39 ± 0.29	1.33 ± 0.18	2.49 ± 0.22	0.001
	P1	0.032	0.01	0.67	
	Percentage Changes	-42.56	-46.8	-0.79	
P1: Comparing the mean of inflammatory factors between groups (The statistical analyzes Anova)					
P2: Comparing the mean of inflammatory factors in each group at the baseline and end of the study (The statistical analyzes Paired samples t-test)					

Discussion

CVD are the main critical healthiness complication of the worldwide and their outcomes have been reported as an out of every three deaths in the United States[16]. While remarkable scientific attempts has

been straighten to identifying bimolecular functions regulating the beginning and developing of disease, much remains controversial[17]. One of the important and useful remedy option for subjects with acute coronary syndrome is the PCI that can be main way for improving in patients with coronary artery anomalies. However some complications such as myocardial injury due to PCI were reported that causing to impecunious prognosis[18]. According to the current investigations antioxidant and anti-inflammatory properties of polyphenols have been detected[19]. Turmeric has a main polyphenol ingredient called curcumin that is obtainable as an over-the-counter (OTC) supplement widespread of world[20]. This randomized, controlled trial assessed the effects of curcumin and nano-curcumin in the in patients undergoing coronary elective angioplasty. The results showed a significant effect of curcumin and nano-curcumin on lipoid profile, stress oxidative indices and inflammatory markers. Several studies have investigated the effect of curcumin oral intake in cardiovascular diseases and some of which are consistent with the present study and some contradict it. The results of some other studies indicate the anti-sclerotic property of curcumin[21, 22].

The results of Chuengsamarn S et al. study regarding the use of curcumin supplementation on coronary artery disease also showed a significant decrease in plasma TG concentration in the intervention group, which was consistent with the present study[23]. However, in a study by Baum L et al. in 2007, consumption 1 and 4 grams of curcumin daily for 6 months did not show any significant changes in lipid profiles[24]. In order to justify the results of this study, in addition to the low sample size, supplementation of curcumin has no effect in healthy subjects with normal lipid profile.

Also, results of Adibian et al. study showed that daily supplementation with 1500 mg curcumin for 10 weeks reduced serum concentration of triglyceride in the intervention group compared to the baseline. But the mean serum concentrations of total cholesterol, LDL-C, and HDL-C had no significant change at the end[25]. The cause of the no changes in serum levels of some of the lipid profile components in this study is that not all participants were hyperlipidemia. In addition, there is a low bioavailability of curcumin, which metabolism is fast in the body and its systematic elimination occurs[26]. Regarding the cholesterol-lowering mechanism by curcumin, a hypothesis has been clarified in animal studies, which is also an involving effect of curcumin on inhibition of dietary cholesterol absorption and consequent reduction of serum cholesterol[27]. For this fact, several mechanisms have been introduced. Stopping in micelle development, stimulating fecal excretion of total steroids and bile acids are examples of these mechanisms. Increasing of bile acids excretion resulted in more conversion of cholesterol to bile acids. This fact, cholesterol conversion bile acids, is the main pathway of cholesterol elimination and accounts for about 50% of daily cholesterol excretion[28].

The another possible mechanism of curcumin in improving dyslipidemia improves cholesterol catabolism by enhancing the activity of the cholesterol 7 hepatic hydroxylase enzyme, which inhibits the synthesis of cholesterol by inhibiting the HMGCOA reductase enzyme[29]. Enhancing of the expression of hepatic CYP7A1 gene by curcumin consumption, resulted in reducing the blood cholesterol levels and approved the hypocholesterolemic properties of curcumin[30]. Expression of AMP-activated protein kinase and

peroxisome proliferator-activated receptor boosted by curcumin that affected energy metabolism of subcutaneous adipocyte tissue in mice that treated with curcumin-supplemented high fat diet[31].

Interestingly, although curcumin shows antioxidant properties by supplying hydrogen radicals and scavenging free radicals, there are a growing number of evidences that it can act as pro-oxidant under certain condition by generating ROS[32]. Results of our study indicated that curcumin supplementation improved status of oxidative stress. In this study intake of curcumin and nano-curcumin increased the mean of TAC, SOD and GSH-Px, also plasma MDA significantly decreased in the intervention groups. Results of Banaeifar et al. study demonstrated that Eight weeks consumption of curcumin caused a significant increase on the level of SOD and GSH-Px enzymes in the rats[33]. Also the results of Quiles et al. showed that curcumin reduces oxidative stress and lipid peroxidation and attenuates aortic fatty streak development in rabbits that treated with atherogenicity diets[34]. According to the Alizadeh F and et al. scientific report, 10 weeks of curcumin nanomicelle supplementation resulted in a statistically significant improvement in plasma levels of TAC, MDA, CRP and TNF-α in comparison to the placebo in asthenoteratospermia patients[35].

Immoderate ROS generation has a main role in the beginning, developing and clinical outcomes in CVD. Although many studies have been done and considerable development and advances occurred in field of free radical biology and cardiovascular treatment, but main mechanisms of CVD and outcomes of pathophysiologically increased ROS in cardiovascular tissue not fully understood[7]. Nuclear factor kappa B (NF-κB) signaling pathway activated with ROS. NF-κB proteins are a subset of transcription factors that manage the expression of genes affiliated with inflammation. According the scientific results, ROS can control the activation and inhibition of NF-κB-signaling. Protecting versus over generation of free radicals in body can occur with superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX), as an anti-oxidant enzymes cooperatively with the nonenzymatic system such as glutathione and vitamins (A, C, and E)[5].

Anti-oxidant properties of curcumin have been greatly researched. This polyphenol can inhibit ROS degradation and also reduce inflammatory factors through down regulation of pro-inflammatory cytokines and transcription factors[29]. Scientific research has also paid great attention to the immunomodulatory role of curcumin. In this regard, activity of immune system cells such as T-cells, B-cells, macrophages, neutrophils, natural killer (NK) cells, and dendritic cells are regulated with curcumin. Also, curcumin, at low doses, may boost antibody responses. These molecular affirmations propose that its detailed beneficial effects could be because of direct anti-oxidative and anti-inflammatory properties, additionally in part to its capacity to control the immune systems[26, 20].

Curcumin inhibits the production of active oxygen species. It linked to thyroxin reductase and turns it to nicotine amide dinucleotide phosphate oxidase (NADPH oxidase) which prevents from ROS formation. Also it increases glutathione gene expression and through iron binding it can do its antioxidant role[36]. Results of this study indicated that inflammatory biomarkers levels were significantly decreased in the intervention groups. Curcumin has suppressive effect on production of the inflammatory cytokine TNF- α,

which in turn leads to inhibition of NF-KB being responsible for promoting intracellular inflammation. It down regulates various pro-inflammatory cytokine expressions such as TNF-α, interleukins (IL-1, IL-2, IL-6, IL-8, IL-12) and chemokines, most likely through inactivation of the nuclear transcription factor, nuclear factor (NF)-κB[37].

This randomized, controlled trial was the first study that studied and compared the effects of curcumin and nano-curcumin in the in patients undergoing coronary elective angioplasty. The results of this research have been statistically reported and discussed. Distinctly, to explain the clinical relevance of these data, more investigations with larger sample size, different doses and longer duration are required. Also, because of owing to budget limitations we were not able to measure other biomarkers such as ROS radicals and some important inflammatory factors.

Conclusions

In conclusion, the results of this study implied that 8 weeks of treatment with curcumin and nano curcumin had a beneficial effect in reducing the total cholesterol, triglyceride, and LDL cholesterol, CRP, TNFα and IL-1b, also improving the stress oxidative index in CVD patients. The polyphenolic component such as curcumin may be helpful for CVD patients.

Abbreviations

BMI:Body Mass Index, CABG:Coronary Artery Bypass Grafting, CHD:Coronary Heart Disease, CVD:Cardiovascular Disease, ELISA:Enzyme-Linked Immunosorbent Assay, GSH-Px:Glutathione Peroxidase, HDL:High density lipoprotein, Hs-CRP:High-sensitivity C-reactive protein, IL-1β:Interleukin 1 beta, LDL:low density lipoprotein, MDA:Malondialdehyde, PCI:Percutaneous Coronary Intervention, ROS:Reactive Oxygen Species, SOD:Superoxide Dismutase, TAC:Total antioxidant capacity, TC:Total Cholesterol, TG:Triglyceride, TNF-α:Tumor Necrosis Factor Alpha, WHO:World Health Organization

Declarations

Acknowledgments

Authors' contributions

Funding

Availability of data and material

The data analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

We confirm that any aspect of the work covered in this manuscript that has involved either human patient has been conducted with the ethical approval of all relevant bodies, in Ethical committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran by grant number of: NRC-9620. On the other hand, the protocol was registered in IRCT by number IRCT20141025019669N6 code. All the eligible and volunteered subjects had been written consent for supplementary care prior to research.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Association AD (2018) 9. Cardiovascular disease and risk management: standards of medical care in diabetes—2018. Diabetes care 41 (Supplement 1):S86-S104

2. Barengo NC, Antikainen R, Borodulin K, Harald K, Jousilahti P (2017) Leisure-time physical activity reduces total and cardiovascular mortality and cardiovascular disease incidence in older adults. Journal of the American Geriatrics Society 65 (3):504-510

3. Rovio SP, Pahkala K, Nevalainen J, Juonala M, Salo P, Kähönen M, Hutri-Kähönen N, Lehtimäki T, Jokinen E, Laitinen T (2017) Cardiovascular risk factors from childhood and midlife cognitive performance: the Young Finns Study. Journal of the American College of Cardiology 69 (18):2279-2289

4. Guinan EM, Doyle SL, O'Neill L, Dunne MR, Foley EK, O'Sullivan J, Reynolds JV, Hussey J (2017) Effects of a multimodal rehabilitation programme on inflammation and oxidative stress in oesophageal cancer survivors: the ReStOre feasibility study. Supportive Care in Cancer 25 (3):749-756

5. Ferguson KK, Meeker JD, McElrath TF, Mukherjee B, Cantonwine DE (2017) Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. American journal of obstetrics and gynecology 216 (5):527. e521-527. e529

6. Daiber A, Di Lisa F, Oelze M, Kröller-Schön S, Steven S, Schulz E, Münzel T (2017) Crosstalk of mitochondria with NADPH oxidase via reactive oxygen and nitrogen species signalling and its role for vascular function. British journal of pharmacology 174 (12):1670-1689

7. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F (2018) Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascular pharmacology 100:1-19

8. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, Cuthbertson DJ, Dobson R, Grozinsky-Glasberg S, Steeds RP (2017) Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. Journal of the American College of Cardiology 69 (10):1288-1304

9. Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, Trovik T, Eskola M, Romppanen H, Kellerth T (2016) Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. The Lancet 388 (10061):2743-2752

10. Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, Kandzari DE, Morice M-C, Lembo N, Brown III WM (2016) Everolimus-eluting stents or bypass surgery for left main coronary artery disease. New England Journal of Medicine 375 (23):2223-2235

11. Hill-Kapturczak N, Thamilselvan V, Liu F, Nick HS, Agarwal A (2018) Mechanism of heme oxygenase-1 gene induction by curcumin in human renal proximal tubule cells. American Journal of Physiology-Renal Physiology

12. Falke J, Parkkinen J, Vaahtera L, Hulsbergen-van de Kaa C, Oosterwijk E, Witjes J (2018) Curcumin as Treatment for Bladder Cancer: A Preclinical Study of Cyclodextrin-Curcumin Complex and BCG as Intravesical Treatment in an Orthotopic Bladder Cancer Rat Model. BioMed Research International 2018

13. Tsai Y-M, Jan W-C, Chien C-F, Lee W-C, Lin L-C, Tsai T-H (2011) Optimised nano-formulation on the bioavailability of hydrophobic polyphenol, curcumin, in freely-moving rats. Food chemistry 127 (3):918-925

14. Khosrowbeygi A, Zarghami N (2007) Levels of oxidative stress biomarkers in seminal plasma and their relationship with seminal parameters. BMC clinical pathology 7 (1):6

15. Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A (2015) Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. Clinical nutrition 34 (6):1101-1108

16. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM (2017) Evolocumab and clinical outcomes in patients with cardiovascular disease. New England Journal of Medicine 376 (18):1713-1722

17. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M (2016) Cardiovascular disease in Europe: epidemiological update 2016. European heart journal 37 (42):3232-3245

18. Wagner H, Terkelsen CJ, Friberg H, Harnek J, Kern K, Lassen JF, Olivecrona GK (2010) Cardiac arrest in the catheterisation laboratory: a 5-year experience of using mechanical chest compressions to facilitate PCI during prolonged resuscitation efforts. Resuscitation 81 (4):383-387

19. González-Sarrías A, Espín JC, Tomás-Barberán FA (2017) Non-extractable polyphenols produce gut microbiota metabolites that persist in circulation and show anti-inflammatory and free radical-scavenging effects. Trends in Food Science & Technology 69:281-288

20. Kocaadam B, Şanlier N (2017) Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Critical reviews in food science and nutrition 57 (13):2889-2895

21. Spoorthi B, Gautham S, More SS, Maiti AK (2018) Nutraceuticals: Potential therapeutic agents for the treatment and prevention of cardiovascular diseases. Journal of Pharmacy Research| Vol 12 (2):231

22. Bhatia VJ, Nair SS (2018) Nutraceuticals as Potential Chemopreventive Agents: A Review. The Natural Products Journal 8 (1):3-13

23. Chuengsamarn S, Rattanamongkolgul S, Phonrat B, Tungtrongchitr R, Jirawatnotai S (2014) Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. The Journal of nutritional biochemistry 25 (2):144-150

24. Baum L, Cheung SK, Mok VC, Lam LC, Leung VP, Hui E, Ng CC, Chow M, Ho PC, Lam S (2007) Curcumin effects on blood lipid profile in a 6-month human study. Pharmacological research 56 (6):509-514

25. Adibian M, Hodai H, Sohrab G Effect of curcumin supplementation on anthropometric measurements in patients with type 2 diabetes. In: World Congress on Clinical Trials in Diabetes, 2016. BioScientifica,

26. Siviero A, Gallo E, Maggini V, Gori L, Mugelli A, Firenzuoli F, Vannacci A (2015) Curcumin, a golden spice with a low bioavailability. Journal of Herbal Medicine 5 (2):57-70

27. Zingg JM, Hasan ST, Meydani M (2013) Molecular mechanisms of hypolipidemic effects of curcumin. Biofactors 39 (1):101-121

28. Srinivasan K (2013) Dietary spices as beneficial modulators of lipid profile in conditions of metabolic disorders and diseases. Food & function 4 (4):503-521

29. Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A (2018) Curcumin as a potential candidate for treating hyperlipidemia: a review of cellular and metabolic mechanisms. Journal of cellular physiology 233 (1):141-152

30. Manjunatha H, Srinivasan K (2007) Hypolipidemic and antioxidant effects of curcumin and capsaicin in high-fat-fed rats. Canadian journal of physiology and pharmacology 85 (6):588-596

31. Wang L, Yin Y, Hou G, Kang J, Wang Q (2018) Peroxisome Proliferator-Activated Receptor (PPARγ) Plays a Protective Role in Cigarette Smoking-Induced Inflammation via AMP-Activated Protein Kinase (AMPK) Signaling. Medical science monitor: international medical journal of experimental and clinical research 24:5168

32. Gómez-Estaca J, Balaguer M, López-Carballo G, Gavara R, Hernández-Muñoz P (2017) Improving antioxidant and antimicrobial properties of curcumin by means of encapsulation in gelatin through

electrohydrodynamic atomization. Food Hydrocolloids 70:313-320

33. Banaeifar A, Shahkandi H, Behbodi Tabrizi L (2016) Protective Effect of Curcumin Supplementation and 8 Weeks of Endurance Training on the Antioxidant Index of the Liver of Rats. Iranian Journal of Nutrition Sciences & Food Technology 11 (4):39-46

34. Quiles JL, Mesa MD, Ramírez-Tortosa CL, Aguilera CM, Battino M, Gil Á, Ramírez-Tortosa MC (2002) Curcuma longa extract supplementation reduces oxidative stress and attenuates aortic fatty streak development in rabbits. Arteriosclerosis, Thrombosis, and Vascular Biology 22 (7):1225-1231

35. Alizadeh F, Javadi M, Karami AA, Gholaminejad F, Kavianpour M, Haghighian HK (2018) Curcumin nanomicelle improves semen parameters, oxidative stress, inflammatory biomarkers, and reproductive hormones in infertile men: A randomized clinical trial. Phytotherapy Research 32 (3):514-521

36. Yin H, Guo Q, Li X, Tang T, Li C, Wang H, Sun Y, Feng Q, Ma C, Gao C (2018) Curcumin Suppresses IL-1β Secretion and Prevents Inflammation through Inhibition of the NLRP3 Inflammasome. The Journal of Immunology:ji1701495

37. Elburki M, Moore D, Terezakis N, Zhang Y, Lee HM, Johnson F, Golub L (2017) A novel chemically modified curcumin reduces inflammation-mediated connective tissue breakdown in a rat model of diabetes: periodontal and systemic effects. Journal of periodontal research 52 (2):186-200
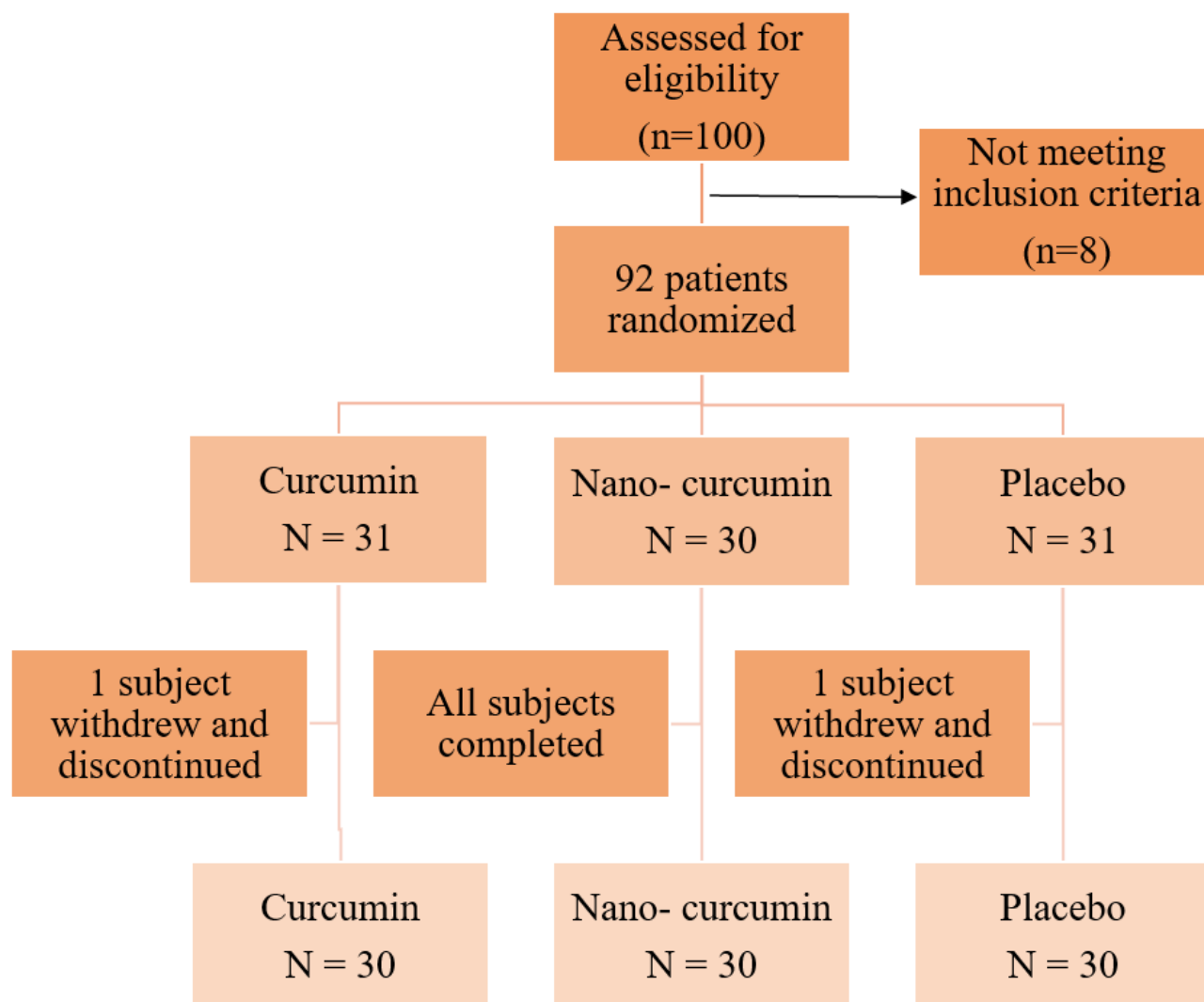
Figures

Figure 1

Flowchart of patients' enrolment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc