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Randomized control trials

Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis

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SUMMARY

Background: Oxidative stress and inflammation have been proposed as emerging components of metabolic syndrome (MetS). Curcuminoids are natural polyphenols with strong antioxidant and anti-inflammatory properties.

Objective: To study the effectiveness of supplementation with a bioavailable curcuminoid preparation on measures of oxidative stress and inflammation in patients with MetS. Our secondary aim was to perform a meta-analysis of data from all randomized controlled trials in order to estimate the effect size of curcuminoids on plasma C-reactive protein (CRP) concentrations.

Methods: In this randomized double-blind placebo-controlled trial, 117 subjects with MetS (according to the NCEP-ATPIII diagnostic criteria) were randomly assigned to curcuminoids (n = 59; drop-outs = 9) or placebo (n = 58; drop-outs = 8) for eight weeks. Curcuminoids were administered at a daily dose of 1 g, and were co-supplemented with piperine (10 mg/day) in order to boost oral bioavailability. Serum activities of superoxide dismutase (SOD) and concentrations of malondialdehyde (MDA) and CRP were measured at baseline and at study end. Regarding the importance of CRP as a risk marker and risk factor of cardiovascular disease, a random-effects meta-analysis of clinical trials was performed to estimate the overall impact of curcuminoid therapy on circulating concentrations of CRP. The robustness of estimated effect size was evaluated using leave-one-out sensitivity analysis.

Results: Supplementation with curcuminoid-piperine combination significantly improved serum SOD activities ($p < 0.001$) and reduced MDA ($p < 0.001$) and CRP ($p < 0.001$) concentrations compared with placebo. Quantitative data synthesis revealed a significant effect of curcuminoids vs. placebo in reducing circulating CRP concentrations (weighed mean difference: −2.20 mg/L; 95% confidence interval [CI]: −3.96, −0.44; $p = 0.01$). This effect was robust in sensitivity analysis.

Conclusions: Short-term supplementation with curcuminoid-piperine combination significantly improves oxidative and inflammatory status in patients with MetS. Curcuminoids could be regarded as natural, safe and effective CRP-lowering agents.

Abbreviations: ARE, antioxidant response element; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; FBS, fasting blood sugar; GRAS, generally recognized as safe; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; MDA, Malondialdehyde; MetS, metabolic syndrome; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; ROS, reactive oxygen species; SBP, systolic blood pressure; SOD, superoxide dismutase.

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1. Introduction

Metabolic syndrome (MetS) is a global health problem that arises as a consequence of the co-occurrence of several cardiometabolic risk factors including hyperglycemia, hypertension, abdominal obesity and dyslipidemia [1]. Accumulation of these risk factors significantly increases the risk of coronary heart disease (CHD) and its equivalents such as Type 2 diabetes [2]. Oxidative stress can be considered as a unifying feature of the seemingly discrete components of metabolic syndrome [3,4]. Accumulating evidence from experimental and clinical works indicate a strong association between metabolic syndrome and oxidative stress [3,4]. Numerous studies have shown overproduction of reactive oxygen species (ROS), elevated biomarkers of lipid peroxidation and protein oxidation, and depleted levels of both enzymatic and non-enzymatic antioxidants in patients with MetS [5–7]. What is more, there is evidence indicating that oxidative stress is not merely a risk marker of MetS but an active contributor to the early steps of the disease, owing to the pathologic role of ROS in insulin resistance, visceral adiposity, endothelial damage and lipoprotein metabolism [3,8]. Therefore, restoration of impaired redox state by antioxidant therapy has been proposed as a promising therapeutic strategy for patients with MetS. Inflammation is another pathomechanism that may serve as a mechanistic link among metabolic syndrome components. A low-grade inflammatory status commonly underlies MetS and is characterized by elevated levels of pro-inflammatory cytokines and C-reactive protein (CRP) in plasma [9,10]. Serum CRP concentrations have been repeatedly reported to be directly associated with several cardiovascular as well as metabolic diseases. Mounting evidence indicates that oxidative stress can activate NF-κB and trigger the release of pro-inflammatory cytokines and CRP [11]. On the other hand, leukocytes that are infiltrated in response to inflammation are a rich source of ROS. Therefore, inflammation and oxidative stress are highly inter-related and cross-promote each other in a vicious cycle, resulting in the progression of MetS to cardiometabolic outcomes [4]. Owing to the pivotal role of oxidative stress and inflammation in the pathogenesis of MetS, concomitant targeting of both these factors would be of paramount importance in the management of disease.

Curcuminoids are bioactive principles of the famous dietary spice, turmeric. Having a polyphenolic structure, curcuminoids have been extensively studied in different diseases including experimental models of metabolic and cardiovascular diseases [12]. Among the myriad of biological activities of curcuminoids [13–24], antioxidant [25–27] and anti-inflammatory [28,29] activities are of particular interest owing to the pivotal role of these parameters in the pathogenesis of MetS. Curcuminoids are known to inhibit several transcription factors (e.g. NF-κB) and enzymes (e.g. p38 MAPK and JNK) involved in inflammation, decrease expression and release of pro-inflammatory cytokines and acute phase reactants, scavenge ROS, reduce lipid peroxidation and up-regulate antioxidant enzymes [30–32]. In spite of these beneficial actions [33,34], no study has yet assessed the antioxidant and anti-inflammatory effects of curcuminoids in patients with MetS. The single evidence is our recent study, in which we showed a significant effect of supplementation with a bioavailability-enhanced preparation of curcuminoids in improving serum concentrations of lipoproteins in patients with MetS [35]. The present study aimed to extend our understanding of the benefits of curcuminoid therapy in MetS by measuring serum activities of superoxide dismutase (SOD; as a measure of systemic antioxidant capacity), malondialdehyde concentrations (MDA; as a measure of lipid peroxidation) and CRP (as a measure of systemic inflammation) as measures of systemic oxidative stress and inflammation. In addition, regarding the importance of CRP as a risk marker and risk factor of cardiovascular disease, a meta-analysis of randomized controlled trials was performed to estimate the effect size of curcuminoid therapy in changing circulating concentrations of this protein.

2. Materials and methods

2.1. Subjects

Participants were recruited from the Cardiology and Endocrinology Clinics of the Baqiyatallah Hospital (Tehran, Iran). Inclusion criteria were males and females who were not originally receiving lipid-lowering therapy, for whom a diagnosis of MetS was made according to the criteria defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines a follows: ≥3 of the following conditions: waist circumference ≥102 cm (male) or ≥88 cm (female), blood pressure ≥130/85 mmHg, triglycerides ≥1.7 mmol/L, HDL-C <1.03 mmol/L (males) or <1.29 mmol/L (females), fasting blood sugar (FBS) ≥6.1 mmol/L [36].

Exclusion criteria were pregnancy or breastfeeding, lack of compliance with the study medication (defined as not using the medication for >1 week), participation in a concomitant trial, hypersensitivity to the study medication, presence of malignancies and impossibility to give informed consent. The study protocol was given approval by the institutional Ethics Committee and written informed consent was obtained from participants.

2.2. Study design

This study was a phase III randomized double-blind placebo-controlled trial with a parallel-group design. After assessing for eligibility, subjects who met the inclusion criteria were randomly allocated to either curcuminoids (Curcumin C3 Complex®, Sami Labs LTD, Bangalore, India; n = 59) or matched placebo (n = 58) for a period of eight weeks. Curcuminoids were administered at a daily dose of 1 g (500 mg b.i.d.). In order to address the poor bioavailability problem of curcuminoids, 5 mg piperine (Bioperine®; Sami Labs LTD, Bangalore, India) was added to each 500 mg curcuminoid capsule [37]. C3 Complex® preparation that was used in the present study contains three major curcuminoids i.e. curcumin, demethoxycurcumin and bisdemethoxycurcumin in patented ratio.

2.3. Blood sampling

Overnight fasting blood samples were collected at baseline and at study end. The samples were allowed to clot for about 30 min and then centrifuged at 750 g for 10 min to obtain serum. Sera were aliquoted and frozen at −80 °C until measurements.

2.4. Measurements

Serum activities of SOD and concentrations of MDA were determined spectrophotometrically using routine methods. Serum high-sensitivity C-reactive protein (hs-CRP) was measured using an immunoturbidimetric assay with a commercial kit. Weight, height, and systolic and diastolic blood pressures were measured according to standard procedures [38]. To calculate BMI, weight (in kilograms) was divided by height (in squared meters [m^2]).

2.5. Statistical analysis

Statistical analyses were performed using the SPSS software version 11.5 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ± SD or number (%). Within-group comparisons were

performed using paired samples *t*-test or Wilcoxon signed-ranks test for normally and non-normally distributed data, respectively. Between-group comparisons were performed using independent samples *t*-test or Mann–Whitney U test for normally and non-normally distributed data, respectively. Comparison of categorical variables between the groups was performed using Chi-square test. Bivariate correlations between changes in serum levels of CRP, SOD and MDA were performed using Pearson's and Spearman's correlation coefficients for normally and non-normally distributed data, respectively. Univariate analysis of covariance (ANCOVA) using general linear model was used to adjust for the effect of potential confounders on the association between curcuminoid supplementation and changes in serum levels of CRP, MDA and SOD. Power calculations were performed using PS – Power and Sample Size Calculation software [39].

2.6. Meta-analysis

2.6.1. Search strategy

MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) and SCOPUS (http://www.scopus.com) databases were searched to find controlled clinical trials investigating the impact of supplementation with curcuminoids on circulating levels of CRP. The search terms were (curcumin OR curcuminoid OR curcuminoids) AND (C-reactive protein OR CRP OR hsCRP OR hs-CRP). No language restriction was used in the literature search. The last search was conducted on May 30, 2014. Retrieved articles were deemed appropriate for meta-analysis if they met all of the following criteria: (i) having a randomized controlled design in either parallel or cross-over form, (ii) administering purified or standardized preparations containing known amounts of curcumin or curcuminoids as monotherapy or as adjunctive therapy provided that appropriate control group is included, (iii) presenting sufficient data on the baseline and post-trial concentrations of CRP in both curcuminoids and control groups, and (iv) published in a peer-reviewed journal. Exclusion criteria were (i) non-clinical studies, (ii) using crude non-standardized *Curcuma* spp. extracts, and (iii) lack of an appropriate control group in the study design.

2.7. Quantitative data synthesis

Meta-analysis was conducted using the Cochrane Program Review Manager version 5.1 (Cochrane Collaboration, Oxford, UK) software. Circulating CRP concentrations were collated in mg/L. Standard deviations at one time point were calculated with the formula SD = SEM × square root *n* (SEM: standard error of the mean, *n*: number of participants). Standard deviations (SDs) of the mean difference were calculated using the formula: square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5 [40]. In case of reporting circulating CRP concentrations in median and interquartile range, the mean and SD were estimated using the recommendations of Hozo et al. [41].

For parallel and cross-over trials, net changes in measurements (change scores) were calculated as follows: (measure at end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at end of follow-up in the control group – measure at baseline in the control group). A random-effects model and the generic inverse variance method were used owing to the heterogeneity of studies in terms of design (parallel or cross-over), dosage and formulation of curcuminoids administered, and inter-study variations in the inclusion criteria (underlying disease, age, gender and anthropometric indices). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method [42,43]. Heterogeneity was assessed using Cochran Q test and I^2 index [42,43].

2.8. Meta-regression

To explore the association between changes in circulating CRP levels and administered doses of curcuminoids (as a potential moderator variable), a random-effects meta-regression was carried out using unrestricted maximum likelihood method. Meta-regression analysis was performed using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ).

2.9. Publication bias

The presence of potential publication bias was assessed using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation and Egger's weighted regression tests. Potentially missing studies were imputed using Duval & Tweedie "trim and fill" correction. Publication bias assessments assessments were performed using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ).

3. Results

One hundred and seventeen subjects met the inclusion criteria and were assigned to either curcuminoid-piperine combination ($n = 59$) or placebo ($n = 58$). One hundred subjects completed the trial. Drop-outs were comparable between the groups (nine subjects in the curcuminoids and eight subjects in the placebo group). The reason for drop-outs was loss to follow-up, which were also comparable between the groups.

Curcuminoid and placebo groups were comparable at baseline with respect to age, gender, smoking frequency, systolic blood pressure (SBP), diastolic blood pressure (DBP), hs-CRP and MDA ($p > 0.05$). However, BMI ($p = 0.002$) and serum levels of FBS ($p < 0.001$) and HbA1c ($p = 0.035$) concentrations were higher in the curcuminoid group. Serum SOD activity was significantly lower in the curcuminoid vs. placebo group ($p = 0.002$) (Table 1).

Supplementation with curcuminoids caused a significant reduction in serum levels of hs-CRP ($p < 0.001$), MDA ($p < 0.001$), glucose ($p < 0.001$), and HbA1c ($p = 0.048$), but increased SOD activities ($p < 0.001$). In the placebo group, serum SOD activities ($p = 0.001$) and glucose ($p = 0.011$) concentrations were increased, but no change occurred in hs-CRP, MDA and HbA1c levels ($p > 0.05$). SBP and DBP levels were reduced by the end of trial in curcuminoid ($p < 0.001$) and placebo ($p = 0.019$ for SBP and $p = 0.026$ for DBP)

Table 1
Baseline characteristics of study groups.

	Curcuminoids-piperine	Placebo	*p*-Value
Age	44.80 ± 8.67	43.46 ± 9.70	0.468
Female	23 (46%)	27 (54%)	0.424
Smoking	12 (24%)	8 (16%)	0.317
BMI (kg/m^2)	25.46 ± 2.46	22.80 ± 5.37	0.002
SBP (mmHg)	135.56 ± 13.16	135.70 ± 14.74	0.960
DBP (mmHg)	88.34 ± 7.81	88.72 ± 8.18	0.813
Hs-CRP (g/L)	6.52 ± 2.16	7.10 ± 1.80	0.148
SOD (IU/mL)	1.47 ± 0.31	1.70 ± 0.41	0.002
MDA (nmole/mL)	19.38 ± 3.08	19.56 ± 2.73	0.758
FBS (mg/dL)	155.46 ± 40.89	136.98 ± 52.40	<0.001
HbA1c (%)	6.69 ± 1.44	6.07 ± 1.33	0.035

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; SOD: superoxide dismutase; MDA: malondialdehyde; FBS: fasting blood glucose.

groups. The same pattern of changes was observed after separate analysis for each gender (Table 2).

When the magnitude of changes were compared between the groups, curcuminoids were found to improve serum levels of all three main efficacy measures including hs-CRP ($p < 0.001$), SOD ($p < 0.001$) and MDA ($p < 0.001$), plus a reduction of FBS ($p < 0.001$) compared with placebo. The statistical power calculated for the reductions in plasma hs-CRP, MDA and FBS were 100%, 100% and 95%, respectively, and 100% for the elevation of SOD activities. These improvements were observed in both male and female subgroups (Table 3).

Bivariate correlation analysis indicated a significant negative association between changes in serum activities of SOD and concentrations of MDA ($p = 0.004$, $r = -0.40$) in the curcuminoid group. No other significant correlation was observed in the curcuminoid nor in the placebo group ($p > 0.05$). As mentioned earlier, the groups were different at baseline with respect to BMI and FBS values. In order to check the effect of these potential confounders on the observed associations, univariate ANCOVA was performed. Changes in serum levels of each parameter, i.e. CRP, MDA and SOD were separately entered into the model as the dependent variable. Independent variables were assignment to treatment group (yes/no) and baseline BMI and FBS values. Based on the results, the impact of curcuminoid supplementation on all three parameters (SOD, MDA and CRP) remained statistically significant ($p < 0.001$) after adjustment for covariates (baseline BMI and FBS).

Table 3
Between-group comparison of changes in the evaluated parameters between the study groups.

	Curcuminoids-piperine	Placebo	*p*-Value
Total			
Hs-CRP (mg/L)	−2.12 ± 1.53	0.06 ± 1.60	<0.001
SOD (U/mL)	0.94 ± 0.48	0.27 ± 0.53	<0.001
MDA (nmole/mL)	−3.76 ± 2.43	0.60 ± 4.43	<0.001
SBP (mmHg)	−8.76 ± 16.42	−6.70 ± 18.12	0.553
DBP (mmHg)	−7.56 ± 9.11	−3.62 ± 11.19	0.056
FBS (mg/dL)	−25.74 ± 42.24	5.62 ± 31.32	<0.001
HbA1c (%)	−0.31 ± 1.08	−0.23 ± 1.34	0.624
Male			
Hs-CRP (mg/L)	−2.15 ± 1.26	−0.26 ± 1.32	<0.001
SOD (IU/mL)	1.09 ± 0.47	0.37 ± 0.47	<0.001
MDA (nmole/mL)	−4.04 ± 2.12	0.04 ± 4.75	0.001
SBP (mmHg)	−9.19 ± 17.88	−5.65 ± 15.62	0.464
DBP (mmHg)	−8.11 ± 9.68	−3.56 ± 11.91	0.143
FBS (mg/dL)	−30.22 ± 48.83	14.26 ± 29.74	<0.001
HbA1c (%)	−0.46 ± 1.17	0.28 ± 1.14	0.027
Female			
Hs-CRP (mg/L)	−2.09 ± 1.83	0.33 ± 1.78	<0.001
SOD (U/mL)	0.75 ± 0.44	0.19 ± 0.58	<0.001
MDA (nmole/mL)	−3.43 ± 2.76	1.07 ± 4.17	<0.001
SBP (mmHg)	−8.26 ± 14.89	−7.59 ± 20.26	0.896
DBP (mmHg)	−6.91 ± 8.55	−3.67 ± 10.76	0.249
FBS (mg/dL)	−20.48 ± 33.21	−1.74 ± 31.27	0.003
HbA1c (%)	−0.13 ± 0.97	−0.67 ± 1.37	0.122

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; SOD: superoxide dismutase; MDA: malondialdehyde; FBS: fasting blood glucose.

3.1. Meta-analysis

Apart from the present trial, eight studies met the inclusion criteria comprising an overall of 10 treatment arms; with 281 subjects receiving curcuminoid preparations and 281 subjects receiving placebo [12,15,27,44–48]. All studies were randomized placebo-controlled trials, and were conducted as double-blind apart from a single study that had a single-blind design [44]. Duration of supplementation in the included studied ranged between 2 and 12 weeks, and administered doses of curcuminoids ranged between 80 mg/day to 6 g/day.

Meta-analysis of included trials indicated a significant reduction of serum CRP concentrations following supplementation with curcuminoids (weighed mean difference: −2.20 mg/L; 95% confidence interval [CI]: −3.96 to −0.44; $p = 0.01$) (Fig. 1). The robustness of this effect size was checked using leave-one-out sensitivity analysis. This analysis showed that the CRP-lowering effect of

Table 2
Within-group comparison of changes in the evaluated parameters between the study groups.

	Curcuminoids-piperine			Placebo		
	Baseline	End-trial	*p*-Value	Baseline	End-trial	*p*-Value
Total						
Hs-CRP (mg/L)	6.52 ± 2.16	4.40 ± 1.74	<0.001	7.10 ± 1.80	7.16 ± 1.49	0.791
SOD (U/mL)	1.47 ± 0.31	2.41 ± 0.37	<0.001	1.70 ± 0.41	1.98 ± 0.29	0.001
MDA (nmole/mL)	19.38 ± 3.08	15.62 ± 2.59	<0.001	19.56 ± 2.73	20.16 ± 3.11	0.343
SBP (mmHg)	135.56 ± 13.16	126.80 ± 9.68	<0.001	135.70 ± 14.74	129.00 ± 7.95	0.019
DBP (mmHg)	88.34 ± 7.81	80.78 ± 5.02	<0.001	88.72 ± 8.18	85.10 ± 7.52	0.026
FBS (mg/dL)	155.46 ± 40.89	129.72 ± 9.81	<0.001	136.98 ± 52.40	142.60 ± 36.66	0.011
HbA1c (%)	6.69 ± 1.44	6.38 ± 1.23	0.048	6.07 ± 1.33	5.84 ± 1.00	0.249
Male						
Hs-CRP (mg/L)	6.41 ± 2.06	4.26 ± 1.68	<0.001	7.48 ± 1.97	7.22 ± 1.65	0.354
SOD (U/mL)	1.39 ± 0.30	2.48 ± 0.34	<0.001	1.66 ± 0.35	2.03 ± 0.29	0.001
MDA (nmole/mL)	19.33 ± 2.63	15.30 ± 2.33	<0.001	19.74 ± 3.00	19.78 ± 3.03	0.965
SBP (mmHg)	136.96 ± 13.41	127.78 ± 11.04	0.013	134.13 ± 12.49	128.48 ± 7.60	0.097
DBP (mmHg)	88.52 ± 9.49	80.41 ± 4.33	<0.001	89.87 ± 8.52	86.30 ± 7.86	0.165
FBS (mg/dL)	160.04 ± 47.17	129.81 ± 11.56	0.003	123.78 ± 30.01	138.04 ± 25.30	0.005
HbA1c (%)	6.83 ± 1.39	6.37 ± 1.28	0.050	5.67 ± 1.28	5.96 ± 1.02	0.246
Female						
Hs-CRP (mg/L)	6.65 ± 2.31	4.57 ± 1.83	<0.001	6.78 ± 1.60	7.11 ± 1.37	0.338
SOD (U/mL)	1.57 ± 0.30	2.32 ± 0.39	<0.001	1.74 ± 0.46	1.93 ± 0.28	0.100
MDA (nmole/mL)	19.43 ± 3.60	16.00 ± 2.88	<0.001	19.41 ± 2.52	20.48 ± 3.19	0.192
SBP (mmHg)	133.91 ± 12.96	125.65 ± 7.88	0.014	137.04 ± 16.54	129.44 ± 8.36	0.062
DBP (mmHg)	88.13 ± 5.42	81.22 ± 5.78	0.001	87.74 ± 7.91	84.07 ± 7.21	0.088
FBS (mg/dL)	150.09 ± 32.24	129.61 ± 7.50	0.002	148.22 ± 64.25	146.48 ± 44.24	0.308
HbA1c (%)	6.52 ± 1.50	6.39 ± 1.20	0.525	6.41 ± 1.30	5.74 ± 0.98	0.027

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; SOD: superoxide dismutase; MDA: malondialdehyde; FBS: fasting blood glucose.

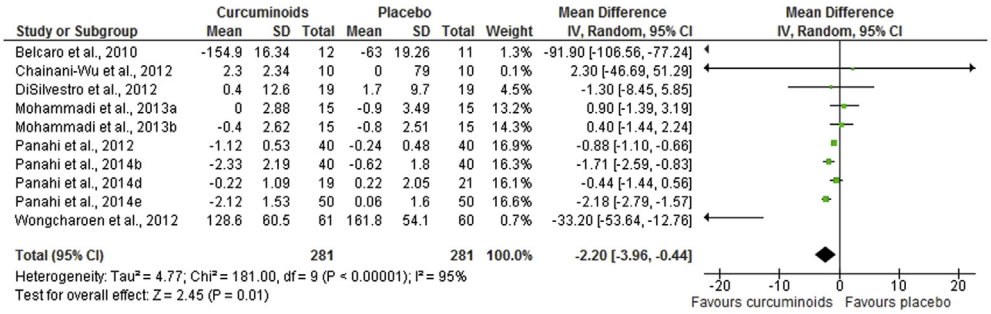

Fig. 1. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of curcuminoid supplementation on circulating C-reactive protein concentrations.

curcuminoids is robust and is not significantly influenced by elimination of any of the included studies (Table 4).

3.2. Meta-regression

Random-effect meta-regression did not indicate any association between the administered dose of curcuminoids and observed changes in circulating CRP concentrations (slope: −0.002; 95% CI: −0.007 to 0.011; Z = 0.42; tau^2; $p = 0.67$) (Fig. 2).

3.3. Publication bias

The begg's funnel plot for the effects of curcuminoids on circulating CRP concentrations was found to be asymmetric, suggestive of potential publication bias (Fig. 3). However, Begg's rank correlation test (Tau with continuity correction = −0.18, *z*-value = 0.72, one-tailed *p*-value = 0.24) and Egger's linear regression tests (intercept = −1.93, standard error = 1.92, 95% CI = −6.35 to 2.49, *t*-value = 1.01, df = 8, two-tailed $p = 0.34$) did not indicate significant publication bias. Also, trim and fill adjustment did not change the pooled effect size (Fig. 3).

4. Discussion

The present results clearly showed that eight-week supplementation with the bioavailability-optimized curcuminoid-piperine combination improves biomarkers of systemic antioxidant capacity (SOD), lipid peroxidation (MDA) and inflammation (CRP). These results confirm the findings of our original study [35] in which a significant improvement of all lipid profile indices including total and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides was observed. There is also clinical evidence indicating that supplementation with curcuminoids improves glucose homeostasis parameters and insulin resistance [49,50], and favorably modulates serum levels of adipokines such as adiponectin [49] and resistin [51].

Inflammation and oxidative stress have been proposed as emerging components of MetS [3,4,9,10], implying the potential utility of antioxidant and anti-inflammatory agents in the therapeutic armamentarium of MetS. Among the biomarkers of oxidative stress, measurement of SOD activity is of special importance owing to the association of the activity of this enzyme with a number of components and thus the severity of MetS. In this study, serum activities of SOD were increased by 48% following supplementation with curcuminoid-piperine combination [52]. In a previous cross-over study in obese individuals at a high risk of MetS, supplementation with curcuminoids (1000 mg/day for four weeks) in combination with piperine (10 mg/day) led to a significant reduction of serum pro-oxidant-antioxidant balance as a measure of systemic oxidative stress status [25]. The same dose of curcuminoid-piperine combination was reported to improve serum activities of SOD, glutathione peroxidase and catalase in subjects with chronic dermatologic complications due to sulfur mustard exposure, after four weeks of supplementation [26]. In another trial in patients with solid tumors, eight-week supplementation with a lecithinized curcuminoid preparation (Meriva®; 900 mg/day equivalent to 180 mg/day curcuminoids) was found to improve serum SOD activities plus other antioxidant indices including serum catalase activities and concentrations of reduced glutathione and thiobarbituric acid reactive species [27]. In a long-term study in β-thalassemia/Hb E patients, supplementation with curcuminoids (500 mg/day) for 12 months resulted in a significant improvement of red blood cell SOD, glutathione peroxidase, reduced glutathione and MDA content [53]. Several mechanisms contribute to the

Table 4
Results of leave-one-out sensitivity analysis.

	Curcuminoids (*n*)	Quantitative data synthesis					Heterogeneity analysis		
		Placebo (*n*)	Effect size	95% CI	*Z-value*	*p*-Value	*Q (df)*	*Tau²*	*I²*
Overall effect	281	281	−2.20	−3.96 to −0.44	2.45	0.01	181.00 (9)	4.77	95%
Leave-one-out sensitivity analysis									
Belcaro et al. [46].	269	270	−1.00	−1.81 to −0.20	2.45	0.01	33.45 (8)	0.71	76%
Panahi et al. [44].	241	241	−4.12	−6.97 to −1.27	2.83	0.005	172.64 (8)	11.73	95%
Wongcharoen et al. [12].	220	221	−1.93	−3.66 to −0.20	2.19	0.03	171.49 (8)	4.54	95%
Chinani-Wu et al. [45].	271	271	−2.21	−3.98 to −0.44	2.45	0.01	180.98 (8)	4.80	96%
Disilvestro et al. [43].	262	262	−2.25	−4.06 to −0.44	2.44	0.008	181.00 (8)	4.82	96%
Mohammadi et al. [15].	266	266	−2.70	−4.61 to −0.79	2.77	0.006	178.25 (8)	4.89	96%
Mohammadi et al. [15].	266	266	−2.69	−4.64 to −0.75	2.72	0.007	178.64 (8)	4.99	96%
Panahi et al. [27].	241	241	−2.65	−4.79 to −0.51	2.43	0.02	178.58 (8)	6.10	96%
Rahimnia et al. [47].	262	262	−2.80	−4.88 to −0.71	2.63	0.009	179.62 (8)	5.75	96%
Panahi et al., 2014[a]	231	231	−3.04	−5.45 to −0.63	2.47	0.01	165.97 (8)	8.00	95%

[a] Present study.

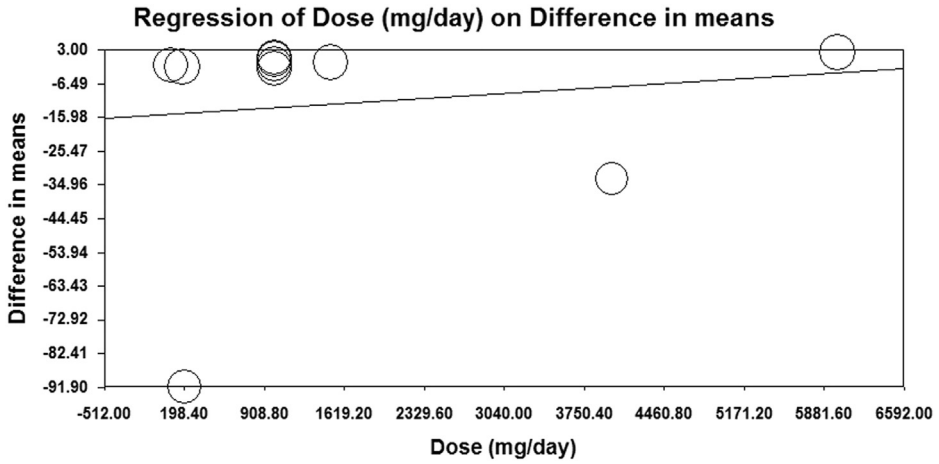

Fig. 2. Random-effect meta-regression analysis of the impact of administered dose on the C-reactive protein-lowering effect of curcuminoids.

antioxidant actions of curcuminoids including inhibition of ROS production, scavenging of free radicals by phenolic hydroxyl groups, inhibition of lipid peroxidation, and up-regulation of phase II antioxidant enzymes via activation of the nuclear factor erythroid 2 p45 (NF-E2)-related factor (nrf-2)-antioxidant response element (ARE) axis [54].

With respect to the impact of curcuminoids on plasma concentrations of CRP, there is conclusive evidence from the updated meta-analysis – performed in this study – to support the effectiveness of curcuminoids as CRP-lowering agents. CRP can contribute to atherothrombosis via several mechanisms including promotion of endothelial damage, thrombogenesis, complement activation and plaque remodeling [55]. The calculated size of the CRP-lowering effect of curcuminoids appears to be more realistic compared with the previous analysis [72], owing to the higher number of studies included. The calculated effect size is of clinical relevance, especially when taking into account the fact that both study groups had a CRP level of >6.0 mg/L at baseline. It has been reported that CRP levels >3.0 mg/L are a strong predictor of atherosclerotic CVD and a strong prognostic factor for MetS [56,57]. The effect size of calculated for the CRP-lowering effects of statins is fairly large for a natural product, particularly when taking into account the magnitude of CRP reduction by statins in meta-analyses [58–60]. Curcuminoids are strong down-regulators of NF-κB signaling pathway and significantly reduce synthesis of pro-inflammatory cytokines such as interleukin-6, interleukin-1β and tumor necrosis factor-α. These cytokines have been shown to regulate the expression of CRP in human hepatocytes [61]. Aside from down-regulation of the NF-κB pathway, curcuminoids can inhibit other master-regulators of inflammation including cyclo-oxygenases 1 [62] and 2 [63], 5-lipoxygenase [64], and inducible nitric oxide synthase [65].

A key determinant of the efficacy of curcuminoids in clinical practice is the formulation that is administered. Bioavailability of curcuminoids is limited by poor absorption, and rapid metabolism and elimination [66]. The alkaloid piperine is an active ingredient of Piper spp. and has been shown to overcome several pharmacokinetic drawbacks of curcuminoids. Piperine reduces the activity of glucuronidase enzymes both at the site of intestinal brush border and liver, resulting in improved absorption of curcuminoids. Increased intestinal perfusion and enterocyte permeability are additional mechanisms whereby piperine improves the bioavailability of curcuminoids [37,67]. A possible reason for lack of greater CRP-lowering effect in studies administering higher doses of

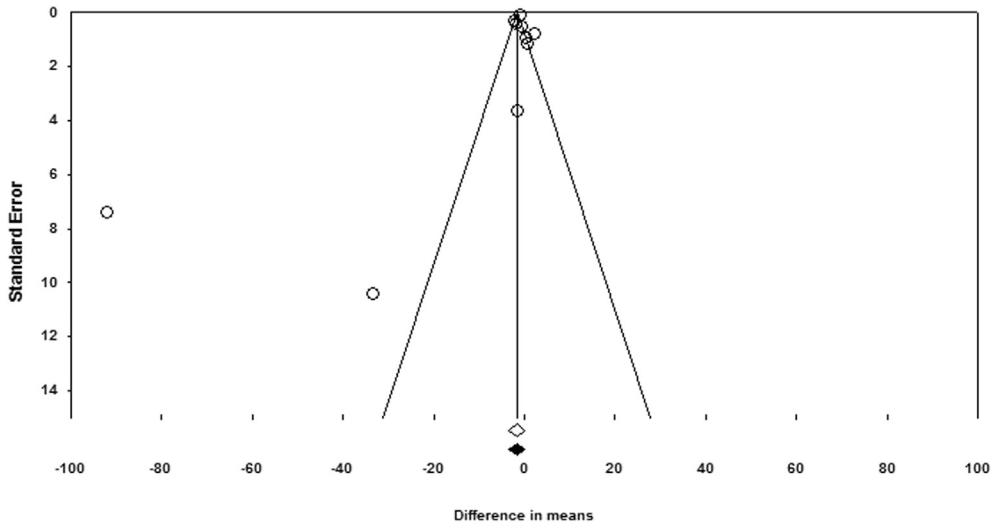

Fig. 3. Funnel plots detailing publication bias in the studies reporting the impact of curcuminoid supplementation on circulating C-reactive protein concentrations.

curcuminoids is using non-optimized preparations of curcuminoids [12,46], resulting in the non-significant dose–effect relationship in the meta-regression analysis.

The present study is subject to a number of potential limitations. The study had a pilot nature and the population size was determined according to the available resources. Nevertheless, our results were significant given the present number of participants, and power calculation showed that this study was sufficiently powered to demonstrate a significant change in the efficacy measures evaluated. The 14% drop-out rate in the present trial was due to the loss to follow-up of participants, who did not refer to the study clinic for blood sampling. This attrition rate of <20% is generally acceptable for an RCT, particularly when considering that the number of drop-outs in the study groups was similar. In our trial the older definition of NCEP-ATP III guidelines was used for the diagnosis of MetS. Since the major change in the updated NCEP-ATP III guidelines [68] pertains to the new threshold to define impaired fasting glucose (>100 mg/dL in the updated guideline versus >110 mg/dL in the older version), using the older version in the current trial is unlikely to cause inclusion of people without MetS into the study. Finally, anthropometric indices were not evaluated in the present study. Whilst clinical trials with curcuminoids have failed to show any significant change in anthropometric parameters [15,51,69,70], further research in subjects with MetS is still necessary to look if the observed antioxidant and anti-inflammatory effects of curcuminoids could be associated with a change in body weight and fat percentage.

In view of the existing evidence, curcuminoids could be suggested as an effective supplement to be used for the management of MetS. A particular advantage of curcuminoids is their safety. Curcuminoids have been approved by US FDA as "Generally Recognized As Safe" (GRAS), and their good tolerability and toxicity profile has been shown by several clinical trials, even at high doses between 4000–8000 mg/day [71]. However, future larger-scale studies are recommended to investigate the impact of curcuminoid supplementation on the metabolic, inflammatory and oxidative indices over a longer duration of follow-up, and also assess the potential protective effects of curcuminoids against development of cardiovascular events and diabetic complications. Finally, it remains to be tested if administration of curcuminoid-piperine at doses higher than that used in this study would result in better controlling of inflammation and oxidative stress in patients with MetS.

Author contributions

All authors contributed to the work presented in this paper. AS, YP and MM discussed core ideas. MSJ, NK and EN handled patient selection and recruitment. YP, MSH, NK and EN handled laboratory experiments. AS performed statistical analysis including meta-analysis. AS and MM prepared and edited the manuscript. All authors approved the manuscript for submission.

Conflict of interest

Muhammed Majeed is the CEO of Sabinsa Corporation and Sami Labs Ltd.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.12.019.

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