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REVIEW

Are Curcuminoids Effective C-Reactive Protein-Lowering Agents in Clinical Practice? Evidence from a Meta-Analysis

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Background: Inflammation plays a pivotal role in the pathogenesis of atherosclerosis and cardiovascular disease (CVD). In this context, C-reactive protein (CRP) has been identified as a strong predictor and independent risk factor of CVD. Curcuminoids are multifunctional natural product with promising cardioprotective and anti-inflammatory properties. Curcuminoids have been suggested to lower circulating levels of CRP, but clinical findings have not been consistent. Objectives: To pool the published results of clinical trials on the impact of supplementation with curcuminoids on circulating levels of CRP. Methods: PubMed/MEDLINE and SCOPUS databases were searched for clinical trials reporting circulating CRP changes in individuals receiving curcuminoids. Effect sizes with 95% confidence intervals (CI) were calculated using a random-effects model. Inter-study heterogeneity was assessed using Cochran's Q and I^2 tests. Sensitivity analyses were conducted using leave-one-out method. Results: Six trials comprising 172 subjects in the curcuminoids group and 170 subjects in the placebo group fulfilled the eligibility criteria and included in the meta-analysis. Compared with placebo, supplementation with curcuminoids was associated with a significant reduction in circulating CRP levels (weighed mean difference: −6.44 mg/L; 95% CI: −10.77 – −2.11; $p = 0.004$). This significant effect was maintained in subgroups of trials that used bioavailability-improved preparations of curcuminoids and had supplementation duration of ≥4 weeks, but not in the subgroups without these characteristics. Conclusions: Supplementation with curcuminoids may reduce circulating CRP levels. This effect appears to depend on the bioavailability of curcuminoids preparations and also duration of supplementation. Future well-designed and long-term trials are warranted to verify this effect of curcuminoids. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: curcumin; turmeric; *Curcuma longa* L; anti-inflammatory; coronary heart disease; atherosclerosis.

INTRODUCTION

Inflammation plays a fundamental role in the pathogenesis of atherosclerosis and cardiovascular disease (CVD) (Albert, 2007; Tousoulis *et al*., 2011). C-reactive protein (CRP) is a pentraxin-like protein composed of five identical subunits that is produced by hepatocytes and serves as an acute phase reactant (Urlimann *et al*., 1966; Gewurz *et al*., 1995). CRP is routinely used as a reliable biomarker of systemic inflammation in relation with different pathophysiologic states. However, it has only recently been unveiled that circulating levels of this protein could serve as an independent predictor of CVD outcomes in both primary and secondary prevention (Liuzzo *et al*., 1994; Morrow *et al*., 1998; Lindahl *et al*., 2000; Ridker *et al*., 1997, 2005; Clearfield, 2005). Moreover, circulating CRP levels are associated with the extent of myocardial ischemia and necrosis as well as progression and severity of atherosclerosis (Lagrand *et al*., 1999). Aside from its prognostic significance, emerging evidence suggests that CRP is actively implicated in the development of atherosclerosis (Lagrand *et al*., 1999; Yu and Rifai, 2000; Nakou *et al*., 2008). The mechanisms for the pathogenic effects of raised CRP concentrations are not completely understood but suggested to be activation of complement system (via classic pathway) and induction of foam cell formation (Nakou *et al*., 2008). It has been reported that CRP promotes local complement activation in the ischemic myocardium as well as in the atherosclerotic lesion (Kilgore *et al*., 1994). This activation triggers a cascade of events including neutrophil activation and degranulation and thrombogenesis, finally leading to endothelial dysfunction and myocardial damage (Yu and Rifai, 2000; Lagrand *et al*., 1999; Engler *et al*., 1983; Carson and Johnson, 1990). In addition, CRP has been illustrated to stimulate the aggregation of low-density lipoprotein (LDL) particles and opsonize their uptake by macrophages, thereby promoting foam cell formation (Fu and Borensztajn, 2002). Given the compelling evidence on the contribution of elevated CRP to the risk of CVD, reduction of circulating levels of this protein has emerged as a new therapeutic approach. Both preclinical and clinical investigations have provided interesting clues to the beneficial impact of CRP reduction on CVD risk (Montecucco and Mach, 2009; Joshi and Jacobson, 2010; Yu and Rifai, 2000).

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Curcuminoids are bioactive polyphenolic compounds from dried rhizomes of *Curcuma longa* L. (turmeric) that have a multitude of benefits for treating a wide variety of disorders (Shehzad *et al*., 2013; Ahuja *et al*., 2011; Epstein *et al*., 2010; Sahebkar *et al*., 2013; Mohammadi *et al*., 2013; Sahebkar, 2012a, 2012b; Panahi *et al*., 2012a, 2012b; Sahebkar, 2010). Turmeric is a medicinal plant reputed in several traditional systems of medicine. Medicinal application of turmeric dates back to thousands of years ago. It has been proposed that medicinal properties of turmeric are mainly exerted by curcuminoids (Strimpakos and Sharma, 2008.). Curcuminoids include three principal components namely curcumin (diferuloylmethane; 77%), demethoxycurcumin (also known as curcumin I; 17%) and bisdemethoxycurcumin (also known as curcumin II; 6%) (Anand *et al*., 2007). Curcuminoids possess significant anti-inflammatory effects due to their interaction with multiple inflammatory mediators at the gene and protein levels (Jurenka, 2009; Shehzad *et al*., 2010). Noteworthy, several lines of *in-vitro* and *in-vivo* evidence have illustrated the cardioprotective actions of curcuminoids (Kapakos *et al*., 2012; Wongcharoen and Phrommintikul, 2009; Srivastava and Mehta, 2009). These include attenuation of ischemia/reperfusion injury (Yeh *et al*., 2005), isoproterenol-induced myocardial infarction (Nirmala and Puvanakrishnan, 1996), attenuation of anthracyclin-associated cardiotoxicity (Swamy *et al*., 2012), hypolipidemic (Mohammadi *et al*., 2013) and anti-atherosclerotic activities (Coban *et al*., 2012), inhibition of lipid peroxidation and LDL oxidation (Chen *et al*., 2006; Sarvalkar *et al*., 2011), protection against development of cardiac hypertrophy (Li *et al*., 2008) and abdominal aortic aneurysm (Fan *et al*., 2012), and mitigation of endothelial dysfunction through blocking the migration and proliferation of vascular smooth muscle cells (Motterlini *et al*., 2000.). Another effect of curcuminoids that is important for cardiovascular health is reduction of CRP levels. The CRP-lowering effects of curcuminoids have been reported in several preclinical studies (Jomezadeh *et al*., 2012; Shin *et al*., 2011; Ashour *et al*., 2011; Devadasu *et al*., 2011). However, translational studies which have assessed the impact of curcuminoids supplementation on circulating levels of CRP as a surrogate marker of inflammation have yielded inconsistent results (Mohammadi *et al*., 2013; DiSilvestro *et al*., 2012; Panahi *et al*., 2012a, 2012b; Wongcharoen *et al*., 2012; Chainani-Wu *et al*., 2012; Belcaro *et al*., 2010) (Table 1). Hence, the present study set out to meta-analyse all clinical trials investigating changes in circulating CRP concentrations following curcuminoids supplementation in order to obtain a more conclusive result on this potentially promising effect of curcuminoids.

METHODS

Search strategy. A search strategy was applied to identify controlled clinical trials investigating the impact of supplementation with curcuminoids on circulating levels of CRP. The search followed the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement and was undertaken in two stages (Moher *et al*., 2009). MEDLINE

Table 1. Effect of curcuminoids on circulating CRP levels in animal studies.

Animal model	Intervention	Route of administration	Treatment duration	Outcome measure(s)	Finding on CRP
Male Wwistar rats	Curcumin 1%, 3% and 5% vs. hydrocortisone 1%	Intraperitoneal lavage	Single dose	Development of post-operative intra-abdominal adhesions.	Significant reductions with curcumin 3% and 5% but not curcumin 1% and hydrocortisone 1%
High-fat diet fed LDLR$^{-/-}$ mice	Curcumin (0.02% w/w in diet) vs. lovastatin (0.02% w/w in diet) vs. control diet	Oral	18 weeks	Development of atherosclerotic lesions in the aorta	Significant reduction of plasma CRP compared to the control diet; comparable efficacy statin
High-fat diet fed Male albino rats	Curcumin (300 mg/kg body weight/day) vs. *Ruta chalepensis* (40 mg/kg body weight/day) vs. control hypercholesterolemic diet	Oral gastric intubation	90 days	Changes in the biomarkers of liver function, oxidative damage and inflammation	Significant reduction of plasma CRP compared to both hypercholesterolemic control and *Ruta chalepensis* groups
Streptozocin-induced diabetic rats	Curcumin nanoparticles (100 mg/kg/day curcumin) vs. coenzyme Q10 nanoparticles vs. control	Oral gavage	15 days	Changes in the biomarkers of inflammation and lipid metabolism	Significant reduction of plasma CRP compared to diabetic rats.

CRP: C-reactive protein.

(http://www.ncbi.nlm.nih.gov/pubmed) and SCOPUS (http://www.scopus.com) databases were searched using the following search terms: (curcumin OR curcuminoid OR curcuminoids) AND (CRP OR hsCRP OR hs-CRP). The wild-card term '*' was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The last search was conducted on April 01, 2013. Retrieved papers were hand searched for additional eligible studies.

Study selection. Studies were considered eligible for inclusion into this review if they met all of the aforementioned criteria: (i) having a clinical case–control or case-cross-over design, (ii) intervention study using curcumin or curcuminoids as monotherapy or as adjunctive therapy provided that appropriate control group is included, (iii) providing adequate data on the baseline and post-trial concentrations of CRP in both curcuminoids and control groups, (iv) used purified or standardized preparations containing known amount of curcumin or curcuminoids for intervention, and (v) published in a peer-reviewed journal. Studies that: (i) were not of a clinical design, (ii) used crude non-standardized *Curcuma* spp. extracts, and (iii) did not include an appropriate control group, were excluded.

Data extraction. From eligible studies, the following data were extracted using a standard protocol: 1) first author's name; 2) publication year; 3) study location; 4) inclusion criteria; 5) number of participants in the case and control groups; 6) age, gender and body mass index (BMI) of study participants; 7) information regarding randomization, blinding and drop-outs (to be used for quality assessment), 8) prevalence of coronary artery disease, type 2 diabetes and dyslipidemia; and 9) baseline and post-trial concentrations of CRP or mean change during the course of trial. In case of incomplete data on the baseline and/or post-trial concentrations of CRP, the authors of the respective article were contacted.

Quality assessment of the retrieved studies. Eligible studies were methodologically and independently assessed for their quality by employing the Jadad score level-of-evidence rating for randomized controlled trials (Jadad *et al*., 1996). Jadad scale ranges from score 0 to 5, with higher scores indicative of better quality. The items for quality assessment in the Jadad scale include randomization, blinding, and description of withdrawals and dropouts. Using this scale, the overall quality of a trial could be classified as low (Jadad score of <3) or high (Jadad score of ≥ 3).

Quantitative data synthesis. Meta-analysis was conducted using the Cochrane Program Review Manager version 5.1 (Cochrane Collaboration, Oxford, UK). Circulating CRP concentrations were collated in mg/L. Standard deviations (SDs) at one time point were calculated with the formula SD = SEM × square root *n* (SEM: standard error of the mean, *n*: number of participants). 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 (Hiuge *et al*., 2007). In case of reporting circulating adiponectin concentrations in median and interquartile range, the mean and SD were estimated using the recommendations of Hozo *et al.* (Hozo *et al*., 2005).

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 to accommodate for the heterogeneity of studies in terms of design (parallel or cross-over), curcuminoids dosage and formulation, and nature of included populations (underlying disease, age, gender, and BMI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using one-study remove approach. Heterogeneity analysis was performed using the Cochran Q test and I^2 index. Power calculations were performed by using the PS: Power and Sample Size Calculation v3.0 (Vanderbilt University).

RESULTS

Flow of included studies

Systematic database search yielded 27 articles, excluding duplicates. The eligibility of these articles was screened using predefined criteria, and this led to the exclusion of 18 articles for not meeting the inclusion criteria. Full texts of the nine articles that were provisionally accepted were further evaluated, and three articles were excluded. The reasons for exclusion were using a non-purified and non-standardized curcuminoids preparation (Nieman *et al*., 2012), and not including an appropriate control group in the study (Holt *et al*., 2005; Slonim *et al*., 2009). Finally, six studies fulfilled the eligibility criteria and included for further review and meta-analysis (Mohammadi *et al*., 2013; DiSilvestro *et al*., 2012; Panahi *et al*., 2012a, 2012b; Wongcharoen *et al*., 2012; Chainani-Wu *et al*., 2012; Belcaro *et al*., 2010) (Fig. 1).

Characteristics of included studies

A total of 312 individuals were included across the six eligible studies, including 172 subjects in the curcuminoids arm and 170 in the placebo arm (participants of cross-over trials were treated as both case and control and received both curcuminoids and placebo, but at different periods). Retrieved articles were published between 2010 and 2013, from Iran (Mohammadi *et al*., 2013; Panahi *et al*., 2012a, 2012b), USA (DiSilvestro *et al*., 2012; Chainani-Wu *et al*., 2012), Thailand (Wongcharoen *et al*., 2012) and Italy (Belcaro *et al*., 2010). Five of the trials had a randomized design (Mohammadi *et al*., 2013; DiSilvestro *et al*., 2012; Panahi *et al*., 2012a, 2012b; Wongcharoen *et al*., 2012; Chainani-Wu *et al*., 2012) and used either blocked random sequence generation (Wongcharoen *et al*., 2012; Chainani-Wu *et al*., 2012), or alternative allocation of

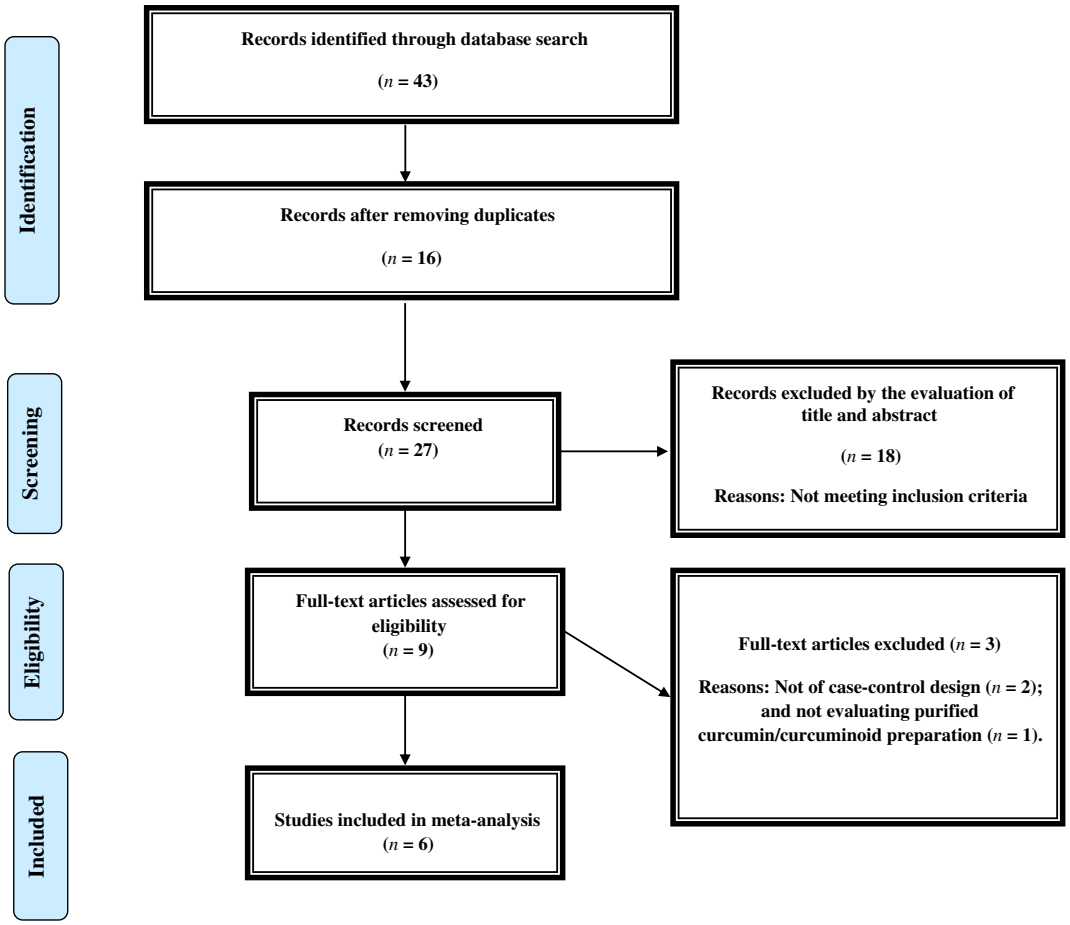

Figure 1. Flow diagram of the study selection process.

patients to curcuminoids or placebo (Mohammadi *et al.*, 2013; Panahi *et al.*, 2012a, 2012b). One trial did not provide any information regarding the randomization (Belcaro *et al.*, 2010). The treatment effects in the control group of all included trials were masked with placebo. One study had a cross-over design (Mohammadi *et al.*, 2013), while the remaining were parallel. Duration of trials ranged from 6 days (Wongcharoen *et al.*, 2012) to 3 months (Belcaro *et al.*, 2010). Curcuminoids dosage used was 80 mg/day (DiSilvestro *et al.*, 2012), 200 mg/day (Belcaro *et al.*, 2010), 1000 mg/day (Mohammadi *et al.*, 2013; Panahi *et al.*, 2012a, 2012b), 4000 mg/day (Wongcharoen *et al.*, 2012), and 6000 mg/day (Chainani-Wu *et al.*, 2012), though in different formulations in terms of bioavailability. The population size of studies ranged from 20 (Chainani-Wu *et al.*, 2012) to 121 (Wongcharoen *et al.*, 2012) subjects. Case and control groups were matched in their age in all included trials. With respect to gender, apart from one study that was exclusively conducted among men (Panahi *et al.*, 2012a, 2012b), other studies recruited subject from both genders, though females were predominant in trials by Mohammadi *et al.* (2013) and DiSilvestro *et al.* (2012). Included studies differed in terms of quality. Four trials were classified as high quality (Jadad score $\geq$3) (Mohammadi *et al.*, 2013; Panahi *et al.*, 2012a, 2012b; Wongcharoen *et al.*, 2012; Chainani-Wu *et al.*, 2012) while the remaining two were classified as low quality (Jadad score $<$3) (DiSilvestro *et al.*, 2012; Belcaro *et al.*, 2010). Baseline characteristics of included trials are summarized in Table 2.

CRP assay

Circulating CRP levels were assayed in plasma (DiSilvestro *et al.*, 2012; Wongcharoen *et al.*, 2012; Belcaro *et al.*, 2010) or serum samples (Mohammadi *et al.*, 2013; Panahi *et al.*, 2012a, 2012b; Chainani-Wu *et al.*, 2012). The analytical methods employed for CRP assay were ELISA (DiSilvestro *et al.*, 2012), laser nephelometry (Belcaro *et al.*, 2010) or immunoturbidimetry (Panahi *et al.*, 2012a, 2012b), whilst three studies did not provide assay details (Mohammadi *et al.*, 2013; Chainani-Wu *et al.*, 2012; Wongcharoen *et al.*, 2012).

Effect of curcuminoids on circulating CRP in individual studies

The mean percentage change in circulating CRP concentrations ranged between −36.0% (Belcaro *et al.*, 2010) and +29.8% (Chainani-Wu *et al.*, 2012) in the placebo group whilst the changes in the curcuminoids group ranged between −92.2% (Belcaro *et al.*, 2010) and +2.9% (DiSilvestro *et al.*, 2012). Comparison of the magnitude of changes in circulating CRP levels between curcuminoids and placebo group revealed a significant difference in three studies (Belcaro *et al.*, 2010; Wongcharoen *et al.*, 2012; Panahi *et al.*, 2012a, 2012b). The percentage changes by curcuminoids and placebo in the included studies are illustrated in Table 3.

Table 2. Demographic characteristics of the included studies.

Study		Mohammadi *et al*. (2013)[a]	Mohammadi *et al*. (2013)[b]	Panahi *et al*. (2012a, 2012b)	Chainani-Wu *et al*. (2012)	Wongcharoen *et al*. (2012)	DiSilvestro *et al*. (2012)	Belcaro *et al*. (2010)
Jadad score		4		4	5	3	1	0
Year		2013		2012	2012	2012	2012	2010
Location		Iran		Iran	UUSA	Thailand	USA	Italy
Design		Randomized double-blind placebo-controlled cross-over trial		Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized single-blind placebo-controlled parallel trial	Placebo-controlled Parallel trial
Duration of trial		30 days		4 weeks	2 weeks	6 days	4 weeks	3 months
Inclusion criteria		Obese individuals with dyslipidemia		Patients suffering from chronic complications due to sulfur mustard	Patients with oral lichen planus	Patients undergoing coronary artery bypass grafting	Healthy middle aged individuals	Patients with symptomatic osteoarthritis and elevated CRP
Curcuminoid preparation		C3 complex® (purified curcuminoids)		C3 complex® (purified curcuminoids)	C3 complex® (purified curcuminoids)	Purified curcuminoids	Longvida® (curcumin lapidated with vegetable-derived stearic acid destrin, soy lecithin and ascorbyl palmitate) containing 20% curcumin	Meriva® (complex of curcumin with phosphatidylcholine) containing 20% curcumin
Intervention		Curcumin (1000 mg/day) vs. placebo		Curcumin (1000 mg/day) vs. placebo	Curcumin (6000 mg/day) vs. placebo	Curcumin (4000 mg/day) vs. placebo	Curcumin (80 mg/day) vs. placebo	Curcumin (200 mg/day) vs. placebo
Participants	**Case**	15	15	40	10	61	19	12
	Control			40	10	60	19	11
Age (yrs)	**Case**	39.0 ± 9.0	37.9 ± 12.7	47.5 ± 10.7	60.8 ± 8.6	61.0 ± 9.1	47.0 ± 21.8	43.3 ± 5.1
	Control			48.3 ± 8.5	56.2 ± 11.7	61.1 ± 8.2	48.0 ± 26.2	44.2 ± 4.8
Male (%)	**Case**	10.5	25.0	100	20	55.7	10.5	33.3
	Control			100	50	58.3	10.5	45.5
Smoker (%)	**Case**	NS	NS	NS	NS	13.1	0	NS
	Control			NS	NS	6.7	0	NS
BMI (kg/m^2)	**Case**	33.4 ± 3.7	31.8 ± 3.4	NS	NS	24.1 ± 3.4	NS	NS
	Control			NS	NS	24.8 ± 4.8	NS	NS
CAD (%)	**Case**	0	0	NS	NS	100	0	0
	Control			NS	NS	100	0	0
Diabetes (%)	**Case**	0	0	NS	NS	37.7	0	0
	Control			NS	NS	50	0	0
Dyslipidemia (%)	**Case**	100	100	NS	NS	90.2	NS	NS
	Control					86.7	NS	NS

Values are expressed as mean ± SD. [a]Curcuminoids-placebo arm of the cross-over trial; [b]placebo-curcuminoids arm of the cross-over trial. CAD: coronary artery disease; CRP: C-reactive protein; NS: not stated.

Table 3. Effect of curcuminoids on circulating CRP in individual studies.

Study	Placebo group	Curcuminoids group	Power*	Treatment effect
Mohammadi *et al*. (2013)[a]	−11.1%	0%	11.0%	>0.05
Mohammadi *et al*. (2013)[b]	−5.6%	−9.4%	6.7%	
Panahi *et al*. (2012)	−9.5%	−43.4%	100%	<0.001
DiSilvestro *et al*. (2012)	+20%	+2.9%%	6.3%	>0.05
Wongcharoen *et al*. (2012)	NS	NS	88.3%	0.031
Chainani-Wu *et al*. (2012)	+29.1%	0%	81.6%	0.190
Belcaro *et al*. (2010)	−36.0%	−92.2%%	100%	<0.05

[a]Curcuminoids-placebo arm of the cross-over trial; [b]placebo-curcuminoids arm of the cross-over trial. CRP: C-reactive protein; NS: not stated.
*The meta-analysis had an overall 100% power to detect significant difference in circulating CRP levels between curcuminoids and placebo groups.

Quantitative data synthesis

Meta-analysis was carried out on change scores obtained from seven treatment arms in six included articles, comprising a total of 172 subjects in the curcuminoids group and 170 subjects in the placebo group. Random-effects analysis revealed a significant CRP lowering effects following supplementation with curcuminoids (weighed mean difference: −6.44 mg/L; 95% confidence interval (CI): −10.77 – −2.11; $p = 0.004$) (Fig. 2). Power analysis indicated that pooled population size has 100% power to detect the significant difference in circulating CRP levels between curcuminoids and placebo groups. Subgroup analyses were also performed to assess the individual effects of chronic (≥4 weeks) vs. acute (<4 weeks) supplementation, and bioavailability-improved vs. non-improved curcuminoids formulations. Significant treatment effects were observed in subgroups with longer duration of supplementation as well as those using bioavailability-improved curcuminoids preparations (both subgroups consisted of the same studies, weighed mean difference: −9.28 mg/L; 95% CI: −15.28 – −3.28; $p = 0.002$), but not in subgroups without the above mentioned characteristics (weighed mean difference: −13.93 mg/L; 95% CI: −48.59 – +20.73; $p = 0.43$) (Fig. 3).

Sensitivity analysis

The robustness of the observed effect size was tested using leave-one-out approach (Sahebkar, 2012a, 2012b). The statistically significant combined effect size for the impact of curcuminoids supplementation on CRP levels was found to be sensitive to the study of Belcaro *et al.* (Belcaro *et al*., 2010), whilst elimination of each of the other studies from the quantitative data synthesis did not influence the robustness of calculated combined effect size. In spite of applying a random-effects approach, the overall rate of heterogeneity was high, and all studies contributed to this heterogeneity (Table 4).

DISCUSSION

During the past decades, convergence of clinical findings has led to a paradigm shift in the understanding of atherosclerosis pathophysiology from a lipid-centric disease to a disease caused by both elevated lipid levels and a heightened state of inflammation (Ridker *et al*., 2008; Ross, 1999). Based on this revised view, prevention and treatment of CVD is best achieved through a dual-goal therapy, involving aggressive treatment for reducing both LDL-cholesterol and CRP (Ridker *et al*., 2008). Among different approaches that have been proposed for the purpose of CRP reduction (Joshi and Jacobson, 2010; Prasad, 2006; Montecucco and Mach, 2009; Sahebkar, 2011), statin therapy has been the most effective (Chan *et al*., 2004; Ghayour-Mobarhan *et al*., 2008; Joshi and Jacobson, 2010). Moreover, it has been suggested that combination therapy with statins and other types of hypolipidemic agents such as ezetimibe (Pearson *et al*., 2006; Kastelein *et al*., 2008), fenofibrate (Jones *et al*., 2009), and colesevelam (Bays *et al*., 2006) may yield greater reduction rates in circulating CRP levels, though findings have not been consistent (Goldberg *et al*., 2006, 2009; Taylor *et al*., 2004). However, not all patients are indicated for lipid-lowering therapy, and thus there is a need for specific CRP-lowering agents that can be used in all disorders with a strong inflammatory component. To this end, curcuminoids could be a promising candidate due to their well-established

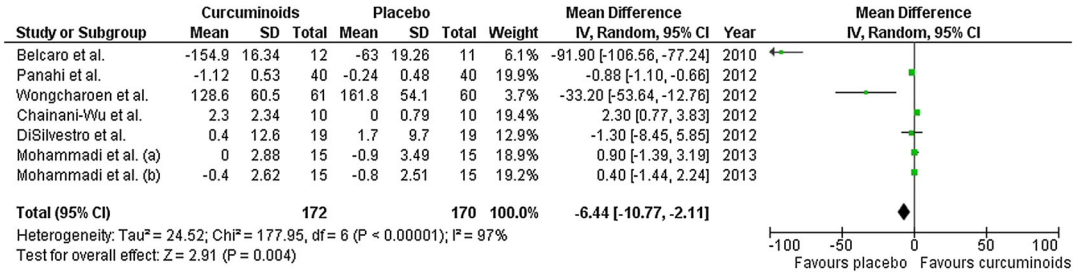

Figure 2. Net change in circulating C-reactive protein concentrations associated with curcuminoids supplementation. The overall effect size has been obtained using a random-effect model and weighted by inverse variance of each trial. Different arms of the included cross-over trial have been denoted as a (curcuminoids-placebo arm) and b (placebo-curcuminoids arm).

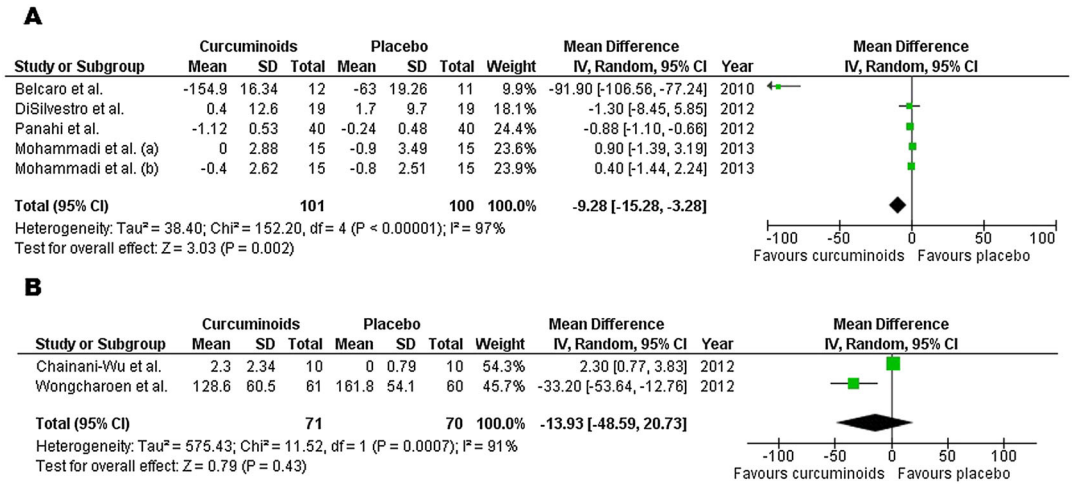

Figure 3. Net change in circulating C-reactive protein concentrations associated with curcuminoids supplementation in subgroups of trials that used bioavailability-improved preparations of curcuminoids, and had supplementation duration of ≥4 weeks (both subgroups consisted of the same studies) (A) vs. subgroups without these characteristics (B). The overall effect size has been obtained using a random-effect model and weighted by inverse variance of each trial. Different arms of the included cross-over trial have been denoted as a (curcuminoids-placebo arm) and b (placebo-curcuminoids arm).

Table 4. Leave-one-out sensitivity analysis and heterogeneity analysis of combined effect size for the impact of curcuminoids supplementation on circulating CRP concentrations.

		Quantitative data synthesis					Heterogeneity analysis			
	Curcuminoids group (*n*)	Placebo group (*n*)	Overall effect size	95% CI	*Z-value*	*p*-value	Tau^2	*Q*	*df (Q)*	I^2
Overall effect	172	170	−6.44	−10.77 – −2.11	2.91	0.004	24.52	177.95	6	97%
Mohammadi *et al*. (2013)[a]	157	155	−9.19	−14.46 – −3.93	3.42	0.0006	30.44	175.80	5	97%
Mohammadi *et al*. (2013)[b]	157	155	−9.87	−15.49 – −4.24	3.44	0.0006	35.44	176.27	5	97%
Panahi *et al*. (2012a, 2012b)	132	130	−12.92	−20.41 – −5.43	3.38	0.0007	69.21	168.36	5	97%
DiSilvestro *et al*. (2012)	153	151	−7.32	−12.02 – −2.63	3.06	0.002	25.18	177.93	5	97%
Wongcharoen *et al*. (2012)	111	110	−5.25	−9.57 – −0.94	2.38	0.02	23.35	168.31	5	97%
Chainani-Wu *et al*. (2012)	162	160	−10.97	−16.92 – −5.02	3.61	0.0003	40.45	161.81	5	97%
Belcaro *et al*. (2010)	160	159	0.20	−1.73 – 2.14	0.21	0.84	3.53	29.67	5	83%

[a]Curcuminoids-placebo arm of the cross-over trial;
[b]Placebo-curcuminoids arm of the cross-over trial. CRP: C-reactive protein; NS: not stated.

anti-inflammatory properties (Shehzad *et al*., 2013; Jurenka, 2009). The results of the present meta-analysis confirmed this hypothesis and indicated a significant effect of curcuminoids in reducing circulating CRP levels.

The impact of formulation on the biological activities of curcuminoids is an important issue that needs to be accurately taken into account. The major obstacle that hinders the promising *in-vitro* effects of curcuminoids to be translated in preclinical and clinical studies is the strikingly low bioavailability of these phytochemicals, which is itself due to the their low aqueous solubility, poor intestinal absorption, and rapid metabolism and elimination from the body (Strimpakos and Sharma, 2008). Pharmacokinetic studies have indicated extremely low serum concentrations following oral administration of curcuminoids. To overcome the problem of bioavailability, several approaches have been applied. These include, but are not limited to, coadministration of curcuminoids with adjuvants, and using liposomes, micelles, phospholipid complexes, polymeric nanoparticles, and structural analogues of curcuminoids (Shehzad *et al*., 2010; Anand *et al*., 2007). Among the six studies included in the current review, four used bioavailability-boosted preparations of curcuminoids (Mohammadi *et al*., 2013; Panahi *et al*., 2012a, 2012b; Belcaro *et al*., 2010; DiSilvestro *et al*., 2012). Mohammadi *et al*. (2013) and Panahi *et al*. (2012a, 2012b) coadministered curcuminoids with piperine, an alkaloid from Piperaceae family. Piperine is known to interfere with intestinal and hepatic glucoronidation of curcumin, thereby enhancing its absorption and reducing its metabolism and elimination (Shoba *et al*., 1998). Belcaro *et al*. (2010) used a commercial product of curcumin, Meriva®, which is a complex of curcumin with soybean phosphatidylcholine in a 1:2 weight ratio. This complexation has been shown to improve gastrointestinal absorption of curcumin, thereby yielding higher plasma levels and slower elimination kinetics (Cuomo *et al*., 2011; Marczylo *et al*., 2007). DiSilvestro *et al*. (2012) also used a lipidated form of curcumin, Longvida®, to improve its bioavailability. This product is a solid lipid matrix containing soybean phosphatidylcholine along with vegetable stearic acid dextrin, ascorbyl palmitate, and hydroxypropyl methylcellulose, which considerably improve the bioavailability

and kinetic profile of curcuminoids (Begum *et al*., 2008; Gota *et al*., 2010). Interestingly, this meta-analysis indicated a significant combined effect of curcuminoids in reducing CRP levels in the subgroup of studies that used improved formulations of curcuminoids, but not in the subgroup of studies in which curcuminoids were administered without any adjuvant or formulation improvement. This underlines the importance of increasing the bioavailability of curcuminoids as a prerequisite to get the maximal therapeutic efficacy.

The CRP-lowering effects of curcuminoids are most likely secondary to the anti-inflammatory properties of these phytochemicals. The mRNA transcription of CRP and other acute phase reactants in hepatocytes is mainly stimulated by interleukin-6 and, to a lesser extent, by other pro-inflammatory cytokines such as IL-1β and tumor necrosis factor-α (Mackiewicz *et al*., 1991). Production of these pro-inflammatory cytokines is controlled by nuclear factor kappa B (NF-κB) transcription signaling pathway. Curcumin is a well-known suppressor of the NF-κB pathway and has been shown to inhibit the activity of IκB kinase and AKT. These effects lead to the prevention of IκB phosphorylation and subsequent nuclear translocation of NF-κB (Shishodia *et al*., 2005). Aside from NF-κB, curcuminoids are also capable to blunt the expression and/or release of pro-inflammatory cytokines through interacting with other regulatory transcription factors, receptors and signaling pathways, e.g. Wnt/b-catenin, signal transducer and activators of transcription-3, nuclear factor erythroid-2-related factor-2 and peroxisome proliferator activated receptor-γ (Aggarwal, 2010; Epstein *et al*., 2010; Shehzad *et al*., 2011; Menon and Sudheer, 2007; Schaffer *et al*., 2011).

The current review was limited in a number of ways. First, the number of studies on the topic was few, and most of them had small population size. However, the meta-analysis was sufficiently powered to detect the significant effect of curcuminoids in the combined population. Second, the possibility of unpublished trials with negative results cannot be ruled out, which is a common limitation of meta-analysis studies. Third, duration of supplementation with curcuminoids in most of the trials was relatively short, and only two trials administered curcuminoids for ≥8 weeks. Fourth, eligible studies were heterogeneous in different ways, including curcuminoids dosage and bioavailability, and duration of supplementation. Besides, the inclusion criteria differed between the studies and only two trials were conducted among patients with high CVD risk. Fifth, changes in circulating CRP levels were not among the primary outcome measures of any of the included trials. Hence, future trials with an *a priory* goal to assess CRP changes following supplementation with curcuminoids are greatly recommended. Finally, it remains to be elucidated by prospective trials if addition of curcuminoids to statins, as the most widely prescribed drug class in CVD patient and currently the best known type of CRP-lowering agents, leads to a significantly greater reduction in CRP levels and incidence of primary and secondary CVD events.

CONCLUSION

The findings of this systematic review and meta-analysis indicate a possible benefit of supplementation with curcuminoids, particularly in the form of bioavailability-improved preparations, in reducing circulating concentrations of CRP. Whilst identification of factors influencing CRP-lowering effect of curcuminoids merits further investigation, it appears that bioavailability, dosage, and duration of supplementation are important determinants. Future well-designed and long-term trials are required to verify CRP reduction following curcuminoids supplementation and also the clinical significance of such an effect.

Conflict of Interest

The author has no competing interests to declare.

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