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Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The aim of the meta-analysis was to evaluate the efficacy of purified curcuminoids supplementation on plasma activities of superoxide dismutase (SOD), catalase and glutathione (GSH) and lipid peroxides as parameters of oxidative stress. Seven randomized controlled trials were finally selected for the meta-analysis. There was a significant increase of serum SOD activities after curcuminoids supplementation (weighted mean difference [WMD]: 1.15 U/mL, 95% confidence interval [CI]: 0.49–1.82, $p = 0.0007$). In a subgroup analysis, no significant effects was observed in the subset of studies administering curcuminoids for <6 weeks (WMD: 0.75 U/mL, 95%CI: –0.56–2.05, $p = 0.26$), but a significant increase of SOD activities was found with supplementation duration ≥6 weeks (WMD: 1.46 U/mL, 95%CI: 0.60–2.32, $p = 0.0009$). The curcuminoids significantly reduced serum lipid peroxides (WMD: –6.35 nmol/mL, 95%CI: –11.06 to –1.64, $p = 0.008$), increased GSH concentrations (WMD: 5.39 μg/mL, 95%CI: 1.17–9.60, $p = 0.01$), and catalase activity (WMD: 51.78 U/mL, 95%CI: 15.71–87.85, $p = 0.005$). This meta-analysis showed a significant effect of curcuminoids in elevating serum SOD and catalase activities, GSH concentrations, and reduction of serum lipid peroxides.

1. Introduction

Oxidative stress is a state of imbalance between the production of reactive oxygen intermediates and the capacity of biological antioxidant defense mechanisms in favor of the former (Davies, 1995). It has been shown that oxidative stress is implicated in the pathogenesis of over 100 human disorders (Davies, 1995; Kedziora-Kornatowska et al., 2010). Superoxide anion is a biologically important reactive oxygen intermediate, with known capacity to produce other toxic species (e.g. hydrogen peroxide, peroxynitrite and peroxynitrite

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Abbreviations: ARE, antioxidant response element; BMI, body mass index; CI, confidence interval; CMA, comprehensive meta-analysis; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; GSH, glutathione; LDL-C, low-density lipoprotein cholesterol; PLGA, polylactic-co-glycolic acid; PRISMA, preferred reporting items for systematic reviews and meta-analysis; SOD, superoxide dismutase; SDs, standard deviations; WMD, weighed mean difference

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degradation products) leading to oxidative stress (Fridovich, 1995). The best known physiological neutralizer of superoxide radicals is the enzyme superoxide dismutase (SOD), which converts superoxide to hydrogen peroxide, the latter being subsequently converted to H_2O through the action of glutathione peroxidase and catalase (Kowalski, Banach, Barylski, Irzmanski, & Pawlicki, 2008; Yilmaz, 2012). Some available studies have shown protective effects of exogenous SOD administration against a range of abnormalities, most importantly cancer and cardiovascular disease (CVD) (Carillon, Rouanet, Cristol, & Brion, 2013). Aside from direct chelating activity, exogenous administration of SOD has been shown to promote endogenous expression of antioxidant and anti-inflammatory elements (Nelson, Bose, Grunwald, Myhill, & McCord, 2006; Rosenfeld et al., 1996; Skarpanska-Stejnborn et al., 2011). It has been hypothesized that SOD administration can increase the nuclear-factor-E2-related factor (Nrf2)-antioxidant response element (ARE) interaction and down-regulate NF-κB expression (Carillon et al., 2013).

These positive effects have attracted increasing attention to the administration of SOD as a powerful antioxidant and anti-inflammatory drug for human diseases (Carillon et al., 2013; Davies, 1995; Rosenfeld et al., 1996). However, oral delivery of SOD like many other proteins is hampered by extremely low bioavailability which is the consequence of problems such as low intestinal permeability, lack of hydrophobicity and rapid hydrolysis by proteases in the gastrointestinal tract (Giri & Misra, 1984; Park, Kwon, & Park, 2011; Zidenberg-Cherr, Keen, Lonnerdal, & Hurley, 1983). On the other hand, parenteral routes of administration (e.g. subcutaneous, intravenous or intramuscular) are limited by the problem of low compliance. Moreover, even if SOD is safely delivered into the blood circulation, its half-life would be very short owing to rapid elimination and preferential accumulation in the renal tissue (Huber, Menander-Huber, Saifer, & Williams, 1980; Swart et al., 1999).

Aside from formulation development attempts to encapsulate SOD for oral delivery, a promising strategy to take advantage of beneficial effects of SOD is to use SOD mimetic agents with non-peptide structures (Marchiani, Rozzo, Fadda, Delogu, & Ruzza, 2014). One such agent is curcumin, a polyphenolic compound that is the pigment of the famous spice turmeric, and which has been extensively investigated with respect to its medicinal properties (Lin, 2007; Marchiani et al., 2014). Curcumin has a unique structure with phenolic hydroxyl- and methoxy-groups, which are responsible for radical scavenging activity, and a central methylenic moiety capable of H-atom donation and breaking chain oxidation reaction (Lin, 2007; Marchiani et al., 2014). This phytochemical possesses numerous pharmacological properties including protective effects against cancer (Panahi, Beiraghdar et al., 2014; Panahi, Saadat, Beiraghdar, & Sahebkar, 2014; Zlotogorski et al., 2013), inflammatory disorders (Panahi, Saadat et al., 2014; (Panahi, Sahebkar, Parvin, & Saadat, 2012; Sahebkar, 2014a; Sahebkar et al., 2013), depression and anxiety (Panahi, Badeli, Karami, & Sahebkar, 2014), atherogenic dyslipidemia (Mohammadi et al., 2013; Sahebkar, 2014b, 2014c), metabolic syndrome (Panahi, Khalili, Hosseini, Abbasinazari, & Sahebkar, 2014; Panahi, Saadat et al., 2014; Sahebkar, 2013b), Alzheimer's and Parkinson's diseases (Darvesh et al., 2012), some dermatologic disorders (Nguyen & Friedman, 2013; Panahi, Sahebkar, Amiri et al., 2012), osteoarthritis (Panahi, Rahimnia et al., 2014; Rahimnia, Panahi, Sharafi, Alishiri, & Sahebkar, 2014), and some pulmonary disorders (Panahi, Ghanei, Bashiri, Hajihashemi, & Sahebkar, 2014; Panahi, Ghanei, Hajhashemi, & Sahebkar, 2014). Antioxidant and anti-inflammatory properties are the two important mechanisms that underlie most of the pharmacological effects of curcumin (Lin, 2007; Marchiani et al., 2014). Moreover, curcumin has been shown to improve systemic markers of oxidative stress, and there is evidence that it can increase serum activities of SOD (Banach et al., 2014; Menon & Sudheer, 2007; Panahi, Sahebkar, Amiri et al., 2012); however, clinical data have not been fully conclusive (DiSilvestro, Joseph, Zhao, & Bomser, 2012; Mohajer et al., 2014). Therefore, the aim of this systematic review and meta-analysis was to assess the impact of curcuminoids supplementation on plasma activities of SOD, catalase, GSH, and lipid peroxides as parameters of oxidative stress.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). PUBMED, Cochrane Library, Scopus, and EMBASE databases were searched using the following search terms in titles and abstracts (also in combination with Medical Subject Headings [MESH] terms): (superoxide dismutase or SOD) and (curcumin or curcuminoids or *Curcuma*). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature search was limited to randomized controlled trials (RCTs) carried out from January 1, 1970 to September 1, 2014. Selected articles were hand searched to identify further relevant studies. Two reviewers (AS and CS) evaluated each article separately. Disagreements were resolved by agreement and discussion with a third party (MB). Uncontrolled studies or those with results that did not consider the main objectives of the meta-analysis were omitted.

2.2. Study selection

2.2.1. Inclusion criteria

Original studies were included if they met the following inclusion criteria: (1) being a randomized clinical controlled trial in either parallel or cross-over design, (2) investigating the impact of purified curcuminoids on plasma/serum activities of SOD, (3) presentation of sufficient information on serum SOD activities at baseline and at the end of study in both curcuminoids and control groups.

2.2.2. Exclusion criteria

The studies were excluded if: (1) they had a non-randomized or uncontrolled design, (2) non-standardized curcuminoids-containing extracts were used, (3) no numerical values were

presented on baseline or follow-up concerning SOD activities, (4) we were unable to obtain adequate details of study methodology or results from the article or the investigators, and, (5) the study was an ongoing trial.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name; (2) year of publication; (3) study location; (4) number of participants in the curcuminoids and control groups; (5) age, gender and body mass index (BMI) of study participants; (6) baseline levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), high-sensitivity C-reactive protein (hs-CRP) and glucose; (7) systolic (SBP) and diastolic blood pressures (DBP); and (8) data regarding baseline and follow-up activities of serum SOD, catalase, GSH, and lipid peroxides.

2.4. Quality assessment

The quality of included studies was assessed using Jadad scale. This scale encompasses randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The overall score of a study according to this scale ranges between 0 and 5, with higher scores indicative of a better quality (Jadad et al., 1996). Studies with Jadad scores of ≤2 and ≥3 were considered as low- and high-quality, respectively (Moher et al., 1999).

2.5. Quantitative data synthesis

Meta-analysis was conducted using Review Manager, version 5.2 (Cochrane Collaboration), and Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) (Borenstein, Hedges, Higgins, & Rothstein, 2005). Serum activities of SOD and catalase were collated in U/mL, and concentrations of GSH and lipid peroxides in μg/mL and nmol/mL, respectively. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = 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. In case of reporting standard error of the mean (SEM), SD was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects. Net changes in measurements (change scores) were calculated for parallel and cross-over trials, 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 compensate for the heterogeneity of studies in terms of curcuminoids formulation used (bioavailability-improved or unformulated), dose of curcuminoids, trial design (parallel or cross-over), duration of curcuminoids supplementation, and demographic characteristics of individual trials (underlying disease, age, gender etc.). In case of double-arm (2 × 2) cross-over trials (Mohajer et al., 2014), each arm was treated as a single study. Effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach (Sahebkar, 2013a, 2013b).

2.6. Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval and Tweedie "trim and fill" and "fail-safe N" methods were used to adjust the analysis for the effects of publication bias (Duval & Tweedie, 2000).

3. Results

3.1. Search results and trial flow

The preliminary screening for probable meaning ruled out articles whose titles and/or abstracts were obviously unimportant. After evaluation, 6 articles met the inclusion criteria and were chosen for the final meta-analysis. Since one of the studies had a 2 × 2 cross-over design, each of the study arms (placebo-curcuminoids or curcuminoids-placebo) was treated as a separate study. Therefore, an overall number of 7 curcuminoids treatment arms were introduced to the meta-analysis. A listing of the study selection procedure is displayed in Fig. 1.

3.2. Characteristics of included studies

In total, 396 participants were randomized, of whom 197 were allocated to curcuminoids supplementation group and 199 to control group in the 6 selected studies (7 treatment arms). The number of participants in these trials ranged from 38 to 100. Included studies were published between 2012 and 2014, and were conducted in the United States and Iran. A range of doses from 80 to 1500 mg/day of curcumin was administered in the included trials. Duration of supplementation curcuminoids ranged between 4 weeks and 8 weeks. Five trials were designed as parallel-group studies as one trial as cross-over study. Demographic and baseline parameters of the included studies are shown in Table 1. Curcuminoids were safe and well-tolerated in all of the RCTs included in this review, with no report of serious adverse events.

3.3. Serum SOD activities

Meta-analysis of data from 6 RCTs showed a significant effect of curcuminoids in increasing serum SOD activities (WMD: 1.15 U/mL, 95%CI: 0.49–1.82, $p = 0.0007$) (Fig. 2). This effect size was robust in sensitivity analysis and omission of each individual study did not have a significant effect (Table 2). In a subgroup analysis, no significant effect was observed in the subset of studies administering curcuminoids for <6 weeks (WMD: 0.75 U/mL, 95% CI: –0.56–2.05, $p = 0.26$), but a significant increase of SOD activities was found in studies with supplementation durations ≥6 weeks (WMD: 1.46 U/mL, 95% CI: 0.60–2.32, $p = 0.0009$) (Fig. 3).

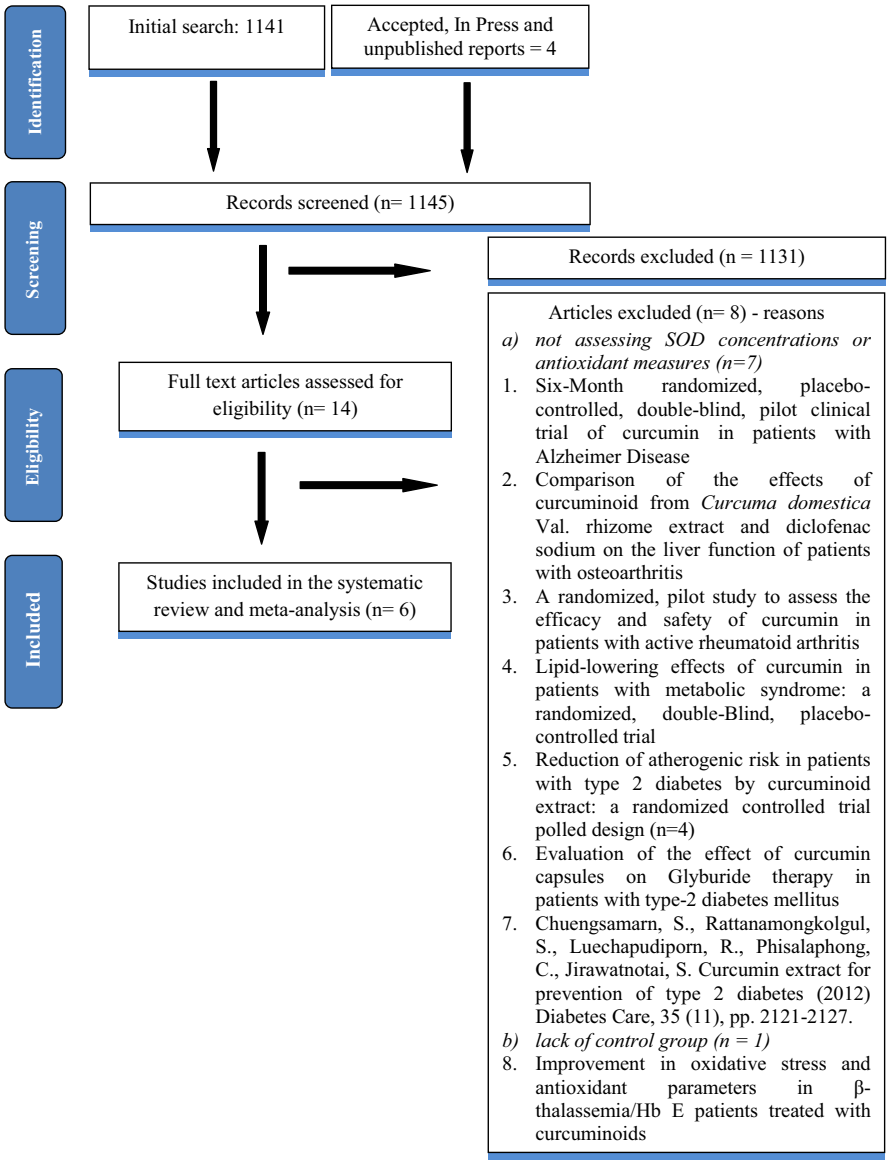

Fig. 1 – Flow chart of the number of studies identified and included into the meta-analysis.

3.4. *Other antioxidant measures*

Changes in serum levels of lipid peroxides, GSH, and activities of catalase were also assessed in relation to curcuminoids supplementation. It was found that curcuminoids significantly reduced serum lipid peroxides (4 RCTs; WMD: –6.35 nmol/mL, 95%CI: –11.06 to –1.64, $p = 0.008$), and increased GSH concentrations (3 RCTs; WMD: 5.39 μg/mL, 95%CI: 1.17–9.60, $p = 0.01$) and catalase activities (3 RCTs; WMD: 51.78 U/mL, 95%CI: 15.71–87.85, $p = 0.005$). Forest plots presenting the impact of curcuminoids on these antioxidant indices are shown in Fig. 4.

3.5. *Publication bias*

Visual inspection of the funnel plot of the study precision (inverse SEM) by effect size (mean difference) suggested a slight asymmetry that was imputed by 1 study using trim-and-fill method. The imputed effect size was 1.09 (95%CI: 0.41–1.77). The "fail safe N" method indicated that 221 theoretically missing studies would be required to make the overall estimated effect size non-significant. Begg's rank correlation (Kendall's Tau with continuity correction = 0.10, Z = 0.30, two-tailed p-value = 0.76) and Egger's linear regression (intercept = 0.68, standard error = 1.65; 95%CI = –3.56–4.92, $t = 0.41$, df = 5.00, two-tailed $p = 0.70$) tests did not show any publication bias. Funnel plot of the impact of curcuminoids on serum SOD activities is illustrated in Fig. 5.

4. Discussion

To the best of our knowledge, the current systematic review and meta-analysis is the first to analyze RCT evidence on the

Table 1 – Demographic characteristics of the included studies.

		DiSilvestro et al. (2012)	Mohajer et al. (2014)	Panahi, Sahebkar, Amiri et al. (2012)	Panahi, Khalili et al. (2014)	Panahi, Beiraghdar et al. (2014)	Panahi, Rahimnia et al. (2014)
Year		2012	2014	2012	2014a	2014b	2014c
Location		USA	Iran	Iran	Iran	Iran	Iran
Jadad score		2	3	3	3	3	3
Design		Randomized double-blind placebo-controlled parallel trial	Randomized double-blind crossover trial	Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial
Duration of trial		4 weeks	4 weeks	8 weeks	8 weeks	4 weeks	6 weeks
Inclusion criteria		Healthy middle aged people (40–60 years old)	Obese subjects	Patients aged 25–65 years presenting solid tumors documented by clinical, paraclinical and histopathological evidence	Patients with metabolic syndrome not receiving lipid-lowering therapy	Subjects suffering from chronic pulmonary complications due to sulfur mustard exposure who were receiving standard respiratory treatments	Patients with degenerative primary knee osteoarthritis with mild-to-moderate severity, bilateral osteoarthritis, and age <80 years
Curcumin form		Optimized curcumin from Curcuma longa root powder	Hard gelatin capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine	Phytosomal form of curcuminoids with soy phosphatidylcholine (lecithin) in a 1:2 weight ratio	Hard gelatin capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine	Hard gelatin capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine	Hard gelatin capsules containing 500 mg C3 Complex (95% curcuminoids) plus 5 mg bioperine
Curcumin intervention		80 mg/day	1000 mg/day	180 mg/day	1000 mg/day	1500 mg/day	1500 mg/day
Participants	Case	19	30	40	50	39	19
	Control	19	30	40	50	39	21
Age (years)	Case	47 ± 5	39 ± 9.0	59.58 ± 14.63	44.80 ± 8.67	50.97 ± 7.27	57.32 ± 8.78
	Control	48 ± 6	39 ± 9.0	58.33 ± 16.10	43.46 ± 9.70	53.97 ± 8.60	57.57 ± 9.05
Male (%)	Case	10.53	10.5*	67.5	54.0	100.0	26.3
	Control	10.53	25.0**	57.5	46.0	100.0	19.0
BMI (kg/m^2)	Case	NS	32.60 ± 3.58	NS	25.46 ± 2.46	28.08 ± 4.82	28.75 ± 3.17
	Control	NS	32.60 ± 3.58	NS	22.80 ± 5.37	25.95 ± 4.03	29.64 ± 4.46
SOD (UI/mL)	Case	48.08 ± 0.77	3.24 ± 1.97[a] 2.81 ± 1.32[b]	0.75 ± 0.33	1.47 ± 0.31	NS	4.03 ± 1.36
	Controls	47.05 ± 0.90	2.5 ± 1.37[c] 3.11 ± 1.46[d]	0.70 ± 0.19	1.70 ± 0.41	NS	4.17 ± 1.39
GSH (µg/mL)	Case	NS	NS	10.69 ± 3.08	NS	11.10 ± 2.76	3.66 ± 0.93
	Control	NS	NS	8.85 ± 1.87	NS	8.85 ± 1.87	3.42 ± 0.99
Serum lipid peroxide (nmole/mL)	Case	NS	NS	19.38 ± 3.08	NS	25.53 ± 3.46	23.04 ± 2.30
	Control	NS	NS	19.56 ± 2.73	NS	24.38 ± 3.18	23.03 ± 2.32
Catalase (UI/mL)	Case	28.97 ± 12.86	NS	14.08 ± 3.13	NS	NS	NS
	Control	27.95 ± 17.31	NS	10.21 ± 1.76	NS	NS	NS

Values are expressed as mean ± SD.
BMI: body mass index; SOD: superoxide dismutase; NA: not applicable, NS: not stated.
* First curcumin-second placebo arm.
** First placebo-second curcumin arm.
[a] Denotes curcuminoids-placebo effect at baseline for period 1.
[b] Denotes curcuminoids-placebo effect at baseline for period 2.
[c] Denotes placebo-curcuminoids effect at baseline for period 1.
[d] Denotes placebo-curcuminoids effect at baseline for period 2.

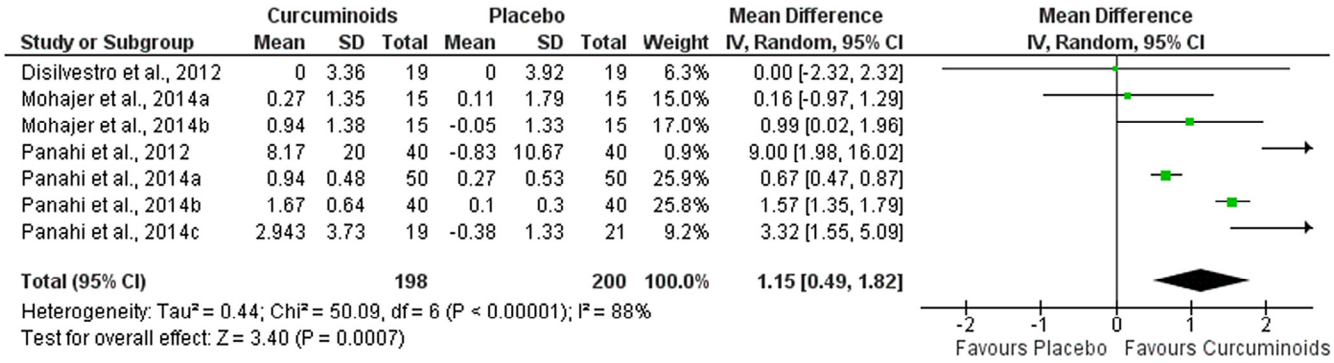

Fig. 2 – Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of curcuminoids on serum activities of superoxide dismutase. Meta-analysis was performed using a random-effect model with inverse variance weighting.

efficacy of supplementation with purified curcuminoids on oxidative stress parameters – plasma activities of SOD and catalase and serum concentrations of GSH and lipid peroxides. The results indicated a significant effect of curcuminoids supplementation on all investigated parameters of oxidative stress.

It has been long confirmed that SOD metalloenzymes, depending on iron, manganese, copper or nickel co-factor used, catalyze the transformation of superoxide anions to hydrogen peroxide and dioxygen and scavenge free oxygen radicals through consecutive reductive and oxidative reactions (Chaudiere & Ferrari-Iliou, 1999). Oral administration of different antioxidants, such as curcuminoids (Shen et al., 2013), anthocyanins (Hashimoto et al., 2010), flavonols and flavan-3-ols (Di Majo et al., 2014) or polyphenols (Michalska et al., 2010; Uto-Kondo et al., 2013), were different strategies for modulating SOD activity or enhancing SOD levels. Curcuminoids are a mixture of curcumin, demethoxycurcumin and bisdemethoxycurcumin obtained from dried rhizomes of the plant *Curcuma longa*, also known as turmeric or curry powder (Zhou, Beevers, & Huang, 2011). In the United States, India, China, Korea, Japan, Iran, Pakistan and South Africa, curcumin is used as a natural dietary supplement for many different diseases (Zhou et al., 2011).

It has been shown that curcumin modulates multiple biochemical pathways and different types of signaling elements, such as adhesion and inflammatory molecules, transcription and growth factors, protein kinases, protein reductases, carrier and drug resistance proteins, receptors, cell-cycle regulatory proteins and many enzymes (Huber et al., 1980; Shehzad, Khan, & Sup Lee, 2012). Curcumin can scavenge different forms of free radicals, such as reactive oxygen and nitrogen species (ROS and RNS, respectively) (Menon & Sudheer, 2007). Another important mechanism for the antioxidant actions of curcuminoids is modulation of the activity of glutathione peroxidase, catalase and SOD, enzymes active in the neutralization of free radicals (Lin, 2007; Marchiani et al., 2014). Furthermore, it has been shown that curcumin inhibits ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthinedehydrogenase/oxidase (Lin, 2007). It has been also shown that curcumin inhibits various molecules involved in inflammation process such as cytosolic phospholipase A2 (Hong et al., 2004), thromboxane (Shah et al., 1999), prostaglandins (Chainani-Wu, 2003), nitric oxide (Johnston & DeMaster, 2003; Moon et al., 2008), elastase, collagenase (Ray, Chattopadhyay, Mitra, Siddiqi, & Chatterjee, 2003), monocyte chemotactic protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1),

Table 2 – Leave-one-out sensitivity analysis of the impact of curcuminoids on serum activities of SOD.

	Quantitative data synthesis						Heterogeneity analysis			
	Curcuminoids group (*n*)	Placebo group (*n*)	Effect size (U/mL)	95% CI	Z-value	*p*-value	Tau²	Q	df (Q)	I²
Overall effect	198	200	1.15	0.49–1.82	3.40	.0007	0.44	50.09	6	88%
Leave-one-out sensitivity analysis										
DiSilvestro et al. (2012)	179	181	1.23	0.54–1.93	3.50	0.0005	0.44	49.26	5	90%
Mohajer et al. (2014)	183	185	1.33	0.61–2.06	3.60	0.0003	0.44	47.56	5	89%
Mohajer et al. (2014)	183	185	1.20	0.44–1.95	3.11	0.002	0.47	50.06	5	90%
Panahi, Sahebkar, Amiri et al. (2012)	158	160	1.08	0.44–1.73	3.29	0.001	0.40	45.19	5	89%
Panahi, Khalili et al. (2014)	148	150	1.35	0.44–2.26	2.91	0.004	0.70	16.85	5	70%
Panahi, Beiraghdar et al. (2014)	158	160	1.06	0.19–1.92	2.39	0.02	0.61	15.44	5	68%
Panahi, Rahimnia et al. (2014)	179	179	0.94	0.27–1.61	2.74	0.006	0.39	43.84	5	89%

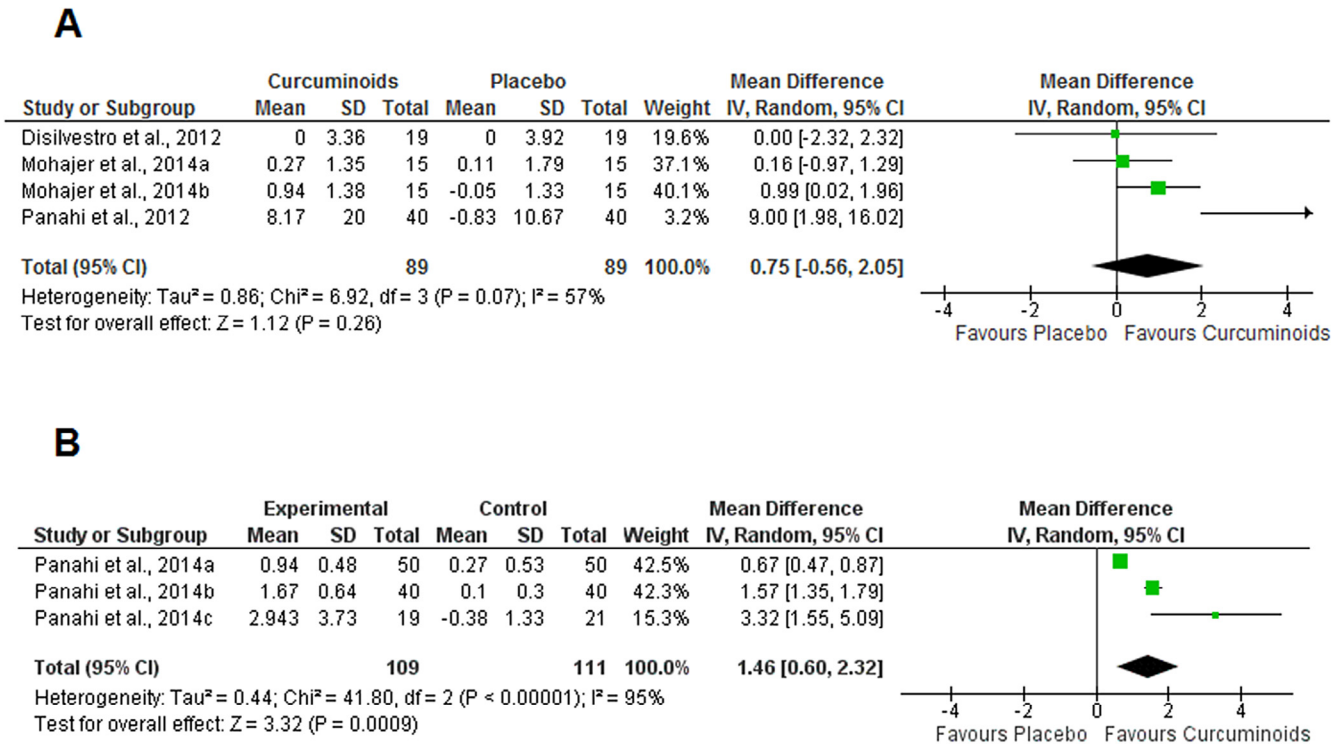

Fig. 3 – Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of curcuminoids on serum activities of SOD in trials with supplementation duration of <6 (A) and ≥6 (B) weeks. Meta-analysis was performed using a random-effect model with inverse variance weighting.

intrahepatic intercellular adhesion molecule-1 (ICAM-1), interferon gamma-induced protein 10 (Kim et al., 2012; Tu, Yao, Xu, & Zhang, 2013), leukotriene B4 (Ammon, Anazodo, Safayhi, Dhawan, & Srimal, 1992), and interleukins – 1, 6, 8 and 12 (Jain, Rains, Croad, Larson, & Jones, 2009; Kang et al., 1999). The antioxidant and free-radical scavenging activities of curcumin are related to the methylene group of the β-diketone (heptadienedione) moiety and to the hydroxyl groups of the compound (Anand et al., 2008).

A major obstacle against the use of curcuminoids in clinical practice is low oral bioavailability, a phenomenon that is due to the hydrophobic nature and rapid metabolism of these phytochemicals (Aggarwal & Sung, 2009). Many approaches have been investigated to increase the bioavailability of curcuminoids, such as obstructing the metabolic pathways by simultaneous administration with other substances, structural manipulation, nanosizing, complexation with phospholipids and encapsulation strategies (Prasad, Gupta, Tyagi, & Aggarwal, 2014). It is interesting to note that all studies that were included in the present analysis took advantage of bioavailability-boosted curcuminoids formulations. Out of the 6 RCTs included, 4 studies co-administered curcuminoids with piperine, which is an alkaloid compound known to improve the pharmacokinetics of various compounds including curcuminoids. Piperine acts by inhibiting hepatic drug metabolizing enzymes, enhancing intestinal perfusion, delaying the gastric emptying time and blocking drug efflux pumps (P-glycoproteins) (Atal, Dubey, & Singh, 1985; Bajad, Bedi, Singla, & Johri, 2001; Han, Chin Tan, & Lim, 2008; Reen et al., 1993). It has been shown that co-administration with piperine enhances the oral bioavailability of curcuminoids by 20 folds (Shoba et al., 1998). One of the included studies used a phytosomal delivery system of curcuminoids that included phosphatidylcholine (Panahi, Beiraghdar et al., 2014). Phosphatidylcholine is another adjuvant that may significantly enhance the intestinal absorption as well as physicochemical stability of curcuminoids to hydrolytic degradation (Cuomo et al., 2011; Marczylo et al., 2007). DiSilvestro et al. used a solid lipid nanoparticle form of curcuminoids with improved solubility, permeability and stability (DiSilvestro et al., 2012). Another possible restriction for therapeutic use of curcumin is the decreased stability in aqueous solution where it goes through fast hydrolysis accompanied by molecular fragmentation at physiological pH (Lin, Pan, & Lin-Shiau, 2000). Taken together, it seems plausible that bioavailability enhancement strategies applied in the included RCTs have an important role in the observed antioxidant effects.

Different synthetic antioxidants such as propyl gallate, tert-butylhydroquinone, butylated hydroxyanisole and butylated hydroxytoluene were created to prevent lipid oxidation as reported by the European Food Safety Authority (EFSA) (Gürtler, 2014). Synthetic antioxidants are popular in fatty packed foods like popcorn, potato chips and snacks, but most of them exert toxic effects or are carcinogenic in high doses (Augustyniak et al., 2010; Wojcik, Burzynska-Pedziwiatr, & Wozniak, 2010). However, curcumin is considered as "*Generally Recognized as Safe*" (GRAS) ingredient by the U.S. Food and Drug Administration, even at high doses between 4000 and 8000 mg/day (Basnet &

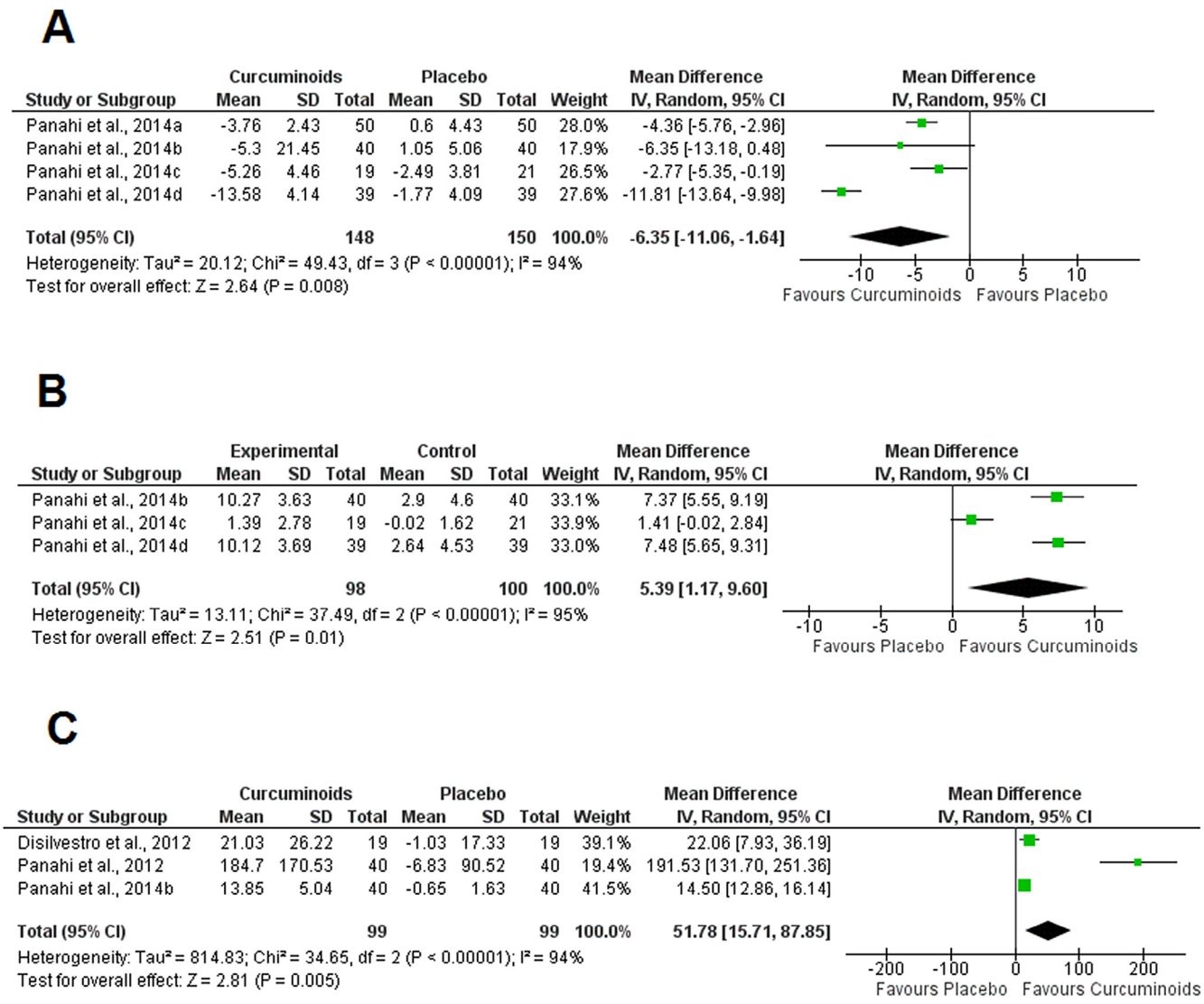

Fig. 4 – Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of curcuminoids on serum concentrations of reduced glutathione (A), lipid peroxides (B), and activities of catalase (C). Meta-analysis was performed using a random-effect model with inverse variance weighting.

Skalko-Basnet, 2011). Despite the fact that curcumin is really active, affordable and well tolerated in all RCTs studied, it is still not authorized as therapy (or even as in any human disease) (Aditya, Shim, Yang, Lee, & Ko, 2014; Amer, Ghattas, Abo-Elmatty, & Abou-El-Ela, 2012; Bartnicki et al., 2013; Gupta, Patchva, Koh, & Aggarwal, 2012; Hamam & Al-Remawi, 2014; Hirofumi, Jinsyo, & Seiichi, 2013).

This meta-analysis has several limitations. Most importantly, the eligible RCTs usually had small populations and short follow-up (up to 8 weeks). The included studies were also heterogeneous with regards to population characteristics, study design, and curcumin dose.

5. Conclusions

In conclusion this systematic review and meta-analysis of RCTs showed a significant effect of curcuminoids in increasing serum SOD activities, catalase activities and GSH concentrations and reduction of serum lipid peroxides. Larger, well-designed studies are needed to validate our findings in strictly selected disorders in order to potentially consider curcumin as an add-on therapy.

Declaration of interest

This meta-analysis was written independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies. No professional writer was involved in the preparation of this meta-analysis.

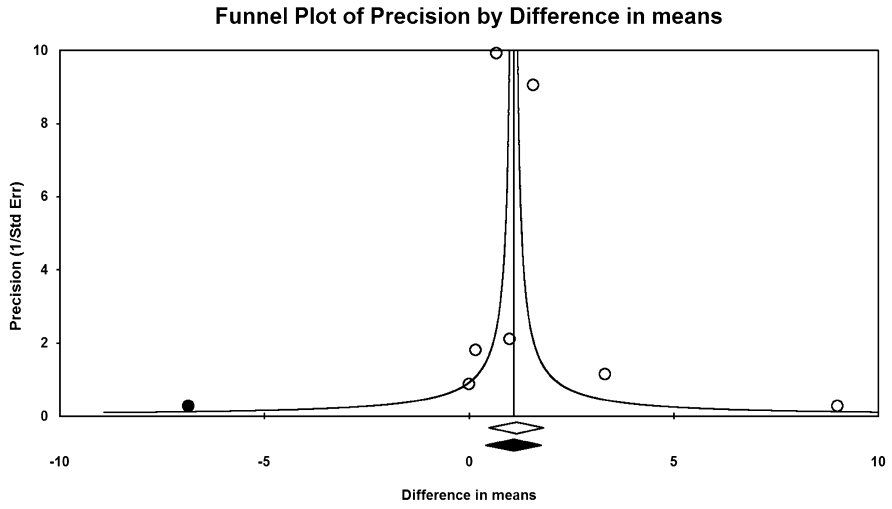

Fig. 5 – Funnel plot detailing publication bias in the studies reporting the impact of curcuminoids on serum activities of superoxide dismutase. Open circles represent observed published studies; closed circles represent imputed unpublished studies.

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