Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The aim of this meta-analysis was to evaluate the efficacy of curcuminoids supplementation on circulating concentrations of IL-6 in randomized controlled trials (RCTs). The search included PubMed-Medline,

Scopus, Web of Science and Google Scholar databases by up to November 01, 2015, to identify RCTs investigating the impact of curcuminoids on circulating IL-6 concentrations. Nine RCTs comprising 10 treatment arms were found to be eligible for the meta-analysis. There was a significant reduction of circulating IL-6 concentrations following curcuminoids supplementation (WMD: −0.60 pg/mL, 95% CI: −1.06, −0.14, p = 0.011). Meta-regression did not suggest any significant association between the circulating IL-6 lowering effects of curcuminoids with either dose or duration of treatment. There was a significant association between the IL-6-lowering activity of curcumin and baseline IL-6 concentration (slope: −0.51; 95% CI: −0.80, −0.23; p = 0.005). This meta-analysis of RCTs suggested a significant effect of curcumin in lowering circulating IL-6 concentrations. This effect appears to be more evident in patients with higher degrees of systemic inflammation

Introduction

Curcuminoids (curcumin, demethoxycurcumin or curcumin I, bisdemethoxycurcumin or curcumin II) are the bioactive dietary polyphenols from turmeric (Curcuma Longa), the most popular spice in Indian cuisine and a major ingredient of curry powders [1]. Several reviews and meta-analyses showed that dietary curcuminoids have various biological activities [2–7], including anti-oxidant [8], anti-inflammatory [3], anti-microbial [9], anti-pruritic [10], hepatoprotective [11], anti-depressant [12], anti-arthritic [13], anti-ischemic [14], lipid-modifying [15,16], metabolic [17], hypouricemic [18], and neuroprotective properties [19]. They also mitigate endothelial dysfunction and improve several clinical and biochemical features of cancer [20–24], giving curcuminoids the potential to be used in clinical practice for a range of human diseases [3,25–27]. Curcuminoids have been tested as a therapeutic option in various diseases such as diabetes, cancer, arthritis, chronic inflammatory and cutaneous diseases, virus infections, Alzheimer's disease and cardiovascular diseases via their multiple pleiotropic effects on genes and cell-signaling pathways [3,5–7]. Most studies on curcuminoids were in-vitro and animal studies; clinical trials have

indicated their safety, tolerability and non-toxicity but small number of patients were enrolled and the real efficacy in humans is at present questionable [3,5,6]. Furthermore, the low availability of these compounds requires the development of formulations with increased solubilization and resistant to inactivation by hydrolysis [5–7]. Cytokines are small molecules with protein or glycoprotein structure (8–80 kDa). They are products of activated immune cells that act as molecular signals between immune competent cells [26]. Among cytokines, interleukin-1 (IL-1), tumor necrosis factor- (TNF-), and interleukin-6 (IL-6) are major inducers of acute phase response [27]. In particular, IL-6 is a multi-functional cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic activities and its potent ability to induce the acute phase response [28]. Interleukin-6 plays a role in the pathogenesis of many human diseases, such as multiple myeloma, rheumatoid arthritis, Castleman's disease, AIDS, mesangial proliferative glomerulonephritis, psoriasis, Kaposi's sarcoma, sepsis, and osteoporosis [28]. Considering its activities, IL-6 appeared to be a viable target for auto-immune disease. Inhibitors of IL-6 were successful in animal models of autoimmune disease paving the way for subsequent studies in humans. Among agents able to inhibit expression and activity of IL-6, curcuminoids proved to have beneficial effects on IL-6 in several in-vitro and animal studies [29–34]. However, clinical studies regarding this effect of curcuminoids in humans have not been fully consistent [29–34]. Hence, the aim of the present meta-analysis was to evaluate the efficacy of curcuminoids supplementation on circulating concentrations ofIL-6 in randomized controlled trials (RCTs) in order to obtain a conclusive result on this potential effect of the compound.

Methods

Search strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and metaanalysis (PRISMA) statement [35]. Medline (http://www.ncbi.nlm. nih.gov/pubmed), SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms

in titles and abstracts (also in combination with MESH terms): (curcumin OR curcuminoid OR curcuminoids OR Curcuma OR Curcuma longa OR turmeric) AND (IL-6 OR interleukin-6 OR "interleukin 6" OR interleukin6 OR IL6 OR "IL 6") AND (random OR randomized OR randomly OR randomization OR "randomized controlled trial" OR "randomized trial" OR "randomized study" OR "random number" OR placebo). The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to studies in English language. The literature was searched from inception to November 01, 2015.

Study selection

Original studies were included if they met the following inclusion criteria: (i) being a controlled trial with either parallel or cross-over design, (ii) investigating the impact of supplementation with curcuminoids or turmeric preparations with known amounts of curcuminoids on circulating IL-6 concentrations, and (iii) presentation of sufficient information on changes in circulating concentrations of IL-6 in the study groups. Exclusion criteria were (i) uncontrolled trials, (ii) inclusion of an active control group in the study design, (iii) observational studies with case-control, cross-sectional or cohort designs, (iv) using non-standardized turmeric extracts with unknown curcuminoids content, (v) trials with treatment durations of < 2 weeks, and (vi) incomplete data on circulating concentrations of IL-6. In case of the latter item, authors of the article(s) were contacted and requested to provide necessary numerical data.

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) study design; 5) number of participants in the curcumin and placebo groups; 5) type and dose of curcumin supplement used; 6) duration of treatment; 7) age, gender and body mass index (BMI) of study participants; 8) inclusion criteria defined in the study; 9) systolic and diastolic blood pressures; and 10) baseline and follow-up IL-6 concentrations.

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [36]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias.

Quantitative data synthesis

Meta-analysis was conducted using Comprehensive MetaAnalysis (CMA) V2 software (Biostat, NJ) [37]. Plasma IL- 6 concentrations were collated in pg/mL. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up—measure at baseline. For crossover trials with a 2 × 2 design, each treatment arm was analysed separately, and net change in each arm was calculated by subtracting the value after control intervention from that reported after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [(SDpre-treatment)2 + (SDpost-treatment)2 − (2R × SDpre-treatment × SDpost-treatment)], assuming a correlation coefficient (R) = 0.5. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects. A random-effects model(using DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design and duration of treatment. Heterogeneity was quantitatively assessed using I 2 index. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. removing one study each time and repeating the analysis [38,39].

Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated WMD and potential confounders including dose and duration of supplementation with curcumin, and baseline IL-6 levels.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, fail-safe N test, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to adjustthe analysis for the effects of publication bias [40].

Results

Flow and characteristics of included studies

Briefly, after multiple databases searching 149 published studies were identified and the abstracts were reviewed. Next, 32 nonoriginal articles were excluded. From the remainder of articles, 85 did not meet the inclusion criteria after assessment of titles and abstracts and were also excluded. Thus, 32 full-text articles were carefully assessed and reviewed for eligibility; of which 23 studies were excluded for not measuring circulating IL-6 concentrations (n = 19), being non-clinical (n = 1), and having a short treatment duration (n = 3). Finally, 9 studies were eligible and included in the systematic review and meta-analysis. The study selection process is shown in Fig. 1. Data were pooled from 9 eligible studies [41–49] comprising 10 treatment arms which included 609 subjects, with 305 in the curcuminoids arm and 304 in the control arm (participants enrolled from the cross-over trial were considered in both arms). Included studies were published between 2008 and 2015. The dose of curcuminoids used changed in the various trials. One study reported effects of curcuminoids 200 mg/day [41], two studies reported effects of curcuminoids 300 mg/day [42,43], three studies of curcuminoids 1 g/day [44–46], two studies of curcuminoids 1.5 g/day [47,48], and one study curcuminoids 6 g/day [49]. The range of intervention periods was from 2 weeks [49] up to 8 months [41]. Study design of almost all included studies was parallel group, except one which was cross-over design [44]. Selected studies enrolled subjects with osteoarthritis [41], knee osteoarthritis

[48], oral lichen planus [49], obesity [44],type 2 diabetes [42,43], metabolic syndrome [46], sulfur mustard intoxication [47], and chronic pruritic skin lesions [45]. Demographic and biochemical characteristics of the evaluated studies are presented in Table 1.

IL-6 assay methods

Different assays methods were used to measure serum IL-6 concentrations. In this regard, most studies [40–42,44–46] determined serum IL-6 levels by enzyme-linked immunoassay. Ganjali et al. [43] analyzed IL-6 concentrations using the Biochip Array Technology on the Randox Evidence Investigator (Randox Laboratories, Belfast, Northern Ireland) by chemiluminescent immunoassay. Only two studies did not provide the method used to determine serum IL-6 levels [47,48].

Risk of bias assessment

According random sequence generation and allocation concealment, six studies were characterized by lack of information (42–46,48) and one study showed high risk of bias (41). Five studies had insufficient information (42,44–46,48) and two exhibited high risk of bias (46,48) with respect to blinding of participants and personnel. In addition, almost all included trials did not provide sufficient information of blinding of outcome assessment (41–46,48,49). However, all included studies showed low risk of bias according to selective reporting and incomplete outcome data. Details of the quality of bias assessment are shown in Table 2.

Effect of curcuminoids on circulating IL-6 concentrations

Overall, the impact of curcuminoids on circulating IL-6 concentrations was reported in 9 RCTs comprising 10 treatment arms. Meta-analysis suggested a significant reduction in plasma IL-6 concentrations following curcuminoids supplementation (WMD: −0.60 pg/mL, 95% CI: −1.06, −0.14, p = 0.011) (Fig. 2). Leave-one out sensitivity analysis showed that this effect size is marginally sensitive to two studies (40,42) (Fig. 2). Subgroup analyses were performed to assess the impact of administered dose and duration of supplementation with curcuminoids, and application of bioavailability-enhanced formulations on the

effect size (Fig. 2). Curcuminoids dose and formulation were not found to significantly affect the IL-6-lowering effect of curcuminoids. However, there was a weaker reduction in circulating IL-6 concentrations in the subset of trials with ≥ 8 weeks of duration (WMD: -0.10 pg/mL, 95% CI: -0.61, 0.41, $p = 0.705$; Figure 3) compared with the subset of studies lasting < 8 weeks (WMD: -1.35 pg/mL, 95% CI: -2.13, -0.58, $p = 0.001$) (Figure 3).

Meta-regression

Random-effects meta-regression was performed to evaluate if changes in circulating IL-6 concentrations are dependent to dose and duration of treatment. Meta-regression analysis did not suggest any significant association between changes in circulating IL-6 levels with either dose (slope: 0.0003; 95% CI: -0.0001, 0.0008; $p = 0.172$) or duration (slope: -0.01; 95% CI: -0.07, 0.05; $p = 0.682$) of treatment (Figure 4).

Publication bias

The funnel plot of standard error versus effect size (mean difference) was slightly asymmetric. "trim and fill" correction suggested one potentially missing study on the left side of funnel plot (Figure 5). Imputation for this potentially missing study yielded an effect size of -0.68 pg/mL (95% CI: -1.13, -0.22). The presence of publication bias was excluded by Egger's linear regression (intercept = -1.14, standard error = 1.57; 95% CI = -4.76, 2.48, $t = 0.73$, df = 8, two-tailed $p = 0.488$) and Begg's rank correlation (Kendall's Tau with continuity correction = 0.04, $z = 0.18$, two-tailed p-value = 0.858) tests. The "fail-safe N" test showed that 109 studies would be needed to bring the WMD down to a non-significant ($p > 0.05$) value.

Discussion

In this meta-analysis, we recorded a significant reduction of circulating IL-6 concentrations following curcuminoids supplementation; this effect does not seem to be dose-dependent, in fact meta-regression did not suggest any significant association between the circulating IL-6-lowering effects of curcuminoids with either dose or duration of treatment. Our results fit with several lines of evidences. At a molecular

and cellular level, curcumin modulates tumor necrosis factor- (TNF-) expression and the cell signaling mediated by TNF- by inhibition of p300/CREB-specific acetyltransferase which leads to repression of acetylation of histone/non histone proteins and hence repression of transcription [50,51]. Curcumin may also be a TNF blocker by binding to TNF directly [52]. Curcumin also inhibits cyclooxygenase-2, signal transducers and activators of transcription (STAT), cyclinD1, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathways [53], as well as IL- 1b and IL-6 expression inhibiting mitogen-activated protein kinase and NF-kB pathways [54]. As regards animal studies, the anti-inflammatory effect of curcumin was first demonstrated in acute and chronic models of inflammation in rats and mice [55], where curcumin suppressed carrageenan-induced edema. Since then, a consistent number of animal models of inflammation have benefited from treatment with curcumin and several mechanisms by which curcumin can exhibit anti-inflammatory activity have been hypothesized [7,52]. In human diseases, extensive clinical trials have addressed the pharmacokinetics, safety and efficacy of curcumin in patients with various inflammatory conditions. An exhaustive list of clinical trials testing the effects of curcumin in various human diseases has been reported by Gupta el al. [56]. Common to most of these studies have been the safety, tolerability and the ability of curcumin to modulate numerous signaling molecules leading to reduced local or even systemic inflammation [7,56]. Interleukin-6, a cytokine featuring redundancy and pleiotropic activity, is one of the most important inflammatory cytokines. Besides its multiple roles in the innate immune system, IL-6 is necessary for the differentiation of T-helper-17 cells [57]; as such, IL-6 is an important factor for the coordination of the innate and acquired immune response [58]. Anomalies in IL-6 production played a pathological role in several autoimmune and chronic inflammatory diseases; for this reason, it has been hypothesized that targeting IL-6 could be an approach to the treatment of these diseases [59]. Furthermore, several anti-IL-6/IL-6 receptor monoclonal antibodies developed for targeted therapy demonstrated promising results in both preclinical studies and clinical trials [60]. In addition, several treatments, including statins, metformin, aspirin, metothrexate, exercise, and others, showed to

reduce systemic inflammation throughout reducing plasma IL-6 levels [61–65]. We reported that curcumin reduced IL-6 by a mean of 0.6 pg/mL; this results might be considered of interest if we look at previous studies in patients with evidence of low-grade systemic inflammation receiving effective consolidated therapies such as statins, metformin and aspirin [61–63]. In these studies, the degree of treatment-mediated IL-6 reduction was comparable to that we observed in the present meta-analysis. Thus, in patients with unstable angina simvastatin reduced plasma IL-6 by 0.4 pg/mL compared to placebo [61]; a 0.35 pg/mL reduction was obtained with metformin in patients with the metabolic syndrome [62]. Finally, in patients with chronic stable angina, aspirin reduced plasma IL-6 by 0.6 pg/mL compared to placebo [63]. As expected, greater plasma IL-6 reductions have been obtained in patients with high-grade systemic inflammation receiving the potent anti-inflammatory methotrexate [64]. In this regard, our meta-regression showed that there was a significant association between the IL-6-lowering activity of curcumin and baseline IL-6 concentration. Therefore, we must consider that the anti-inflammatory effect of curcumin might be more evident in patients with a greater degree of systemic inflammation. Overall, our results of a significant IL-6 reduction by curcumin supplementation support the idea that this nutraceutical may have a role in suppressing pro-inflammatory pathways linked with different diseases. Moreover, clinical trials with curcumin indicate safety, tolerability, and nontoxicity [56]. However, both the clinical efficacy in published trial [56] and the degree of IL-6 lowering in the present meta-analysis is questionable, based, first of all, on the small numbers of patients in each study. Additional limitations of the present meta-analysis need to be considered. Included studies were heterogeneous regarding population characteristics, study design, and duration of supplementation. Nevertheless, the impact of heterogeneity on estimated effect sizes was minimized by choosing a random-effects mode of analysis. Also, only three studies examined the impact of curcumin bioavailability-enhanced formulations on IL-6 [42,43,49]. Active scientific research has been carried out to improve curcumin's pharmacokinetics, systemic bioavailability, biological activity by loading curcumin into nano formulations [56]; now it should

be verified if these novel formulations have stronger IL-6 lowering efficacy. Finally, an overall 0.6 pg/mL reduction of circulating IL- 6 might be considered modest; whether such a reduction might be enough to have a clinical benefit it need to be evaluated in larger clinical trials.

Limitations and strengths

The present meta-analysis has some limitations. Included studies were heterogeneous regarding population characteristics, study design, and duration of supplementation. Nevertheless, the impact of heterogeneity on estimated effect sizes was minimized by choosing a random-effects mode of analysis. In addition, elevated serum IL-6 levels were not among the inclusion criteria of any of the studies considered for this meta-analysis. Finally, most of the included studies had relatively short follow-up durations. Although, no significant association between the IL-6-lowering effect of curcuminoids and treatment duration was observed, the effect of prolonged administration of curcuminoids on circulating IL-6 levels is still not clear. Finally, active scientific research has been carried out to improve curcuminoids' pharmacokinetics, systemic bioavailability, and biological activity by loading curcuminoids into nanoformulations [3]; whether these novel formulations have stronger IL-6 lowering efficacy should be determined. Finally, an overall 0.6 pg/mL reduction of circulating IL-6 might be considered modest; whether such a reduction might translate into a clinical benefit should be evaluated for each possible therapeutic indication in larger clinical trials.

Conclusion

In conclusion, the present meta-analysis of RCTs suggested a significant effect of curcumin in lowering circulating IL-6 concentrations. Despite considerable pharmacologic potential, the clinical efficacy of curcumin is still poorly recognized [3] and this polyphenol has not yet been approved for clinical use in humans. Further studies in larger populations are needed to investigate which patients are best suitable for curcumin supplementation and which formulation should be preferred to increase its anti-inflammatory effects.

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FIGURE LEGENDS

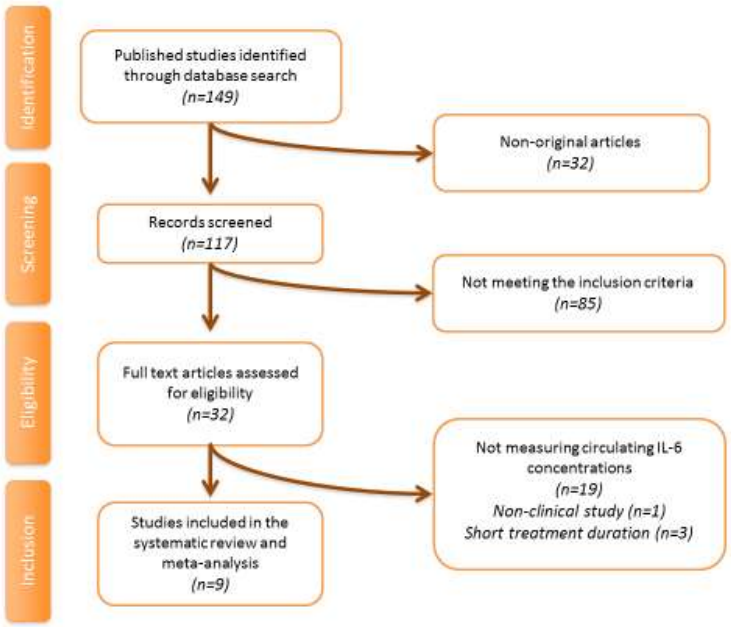
Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of curcuminoids on circulating IL-6 concentrations. Lower plot shows leave-one-out sensitivity analysis.

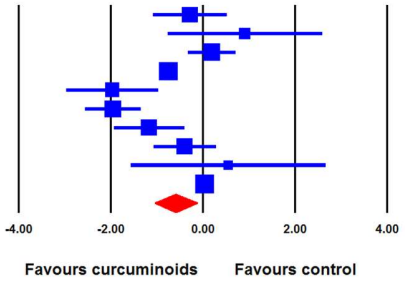
Figure 3. Forest plot displaying subgroup analyses for the impact of treatment dose and duration, and formulation of curcuminoids on the IL-6-lowering activity.

Figure 4. Meta-regression plots of the association between mean changes in circulating IL-6 concentrations with dose and duration of supplementation with curcuminoids. The size of each circle is inversely proportional to the size of the respective study.

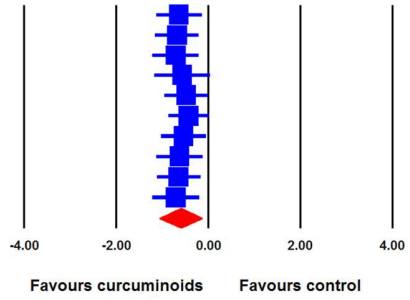
Figure 5. Funnel plot detailing publication bias in the studies reporting the impact of curcuminoids on circulating IL-6 concentrations.



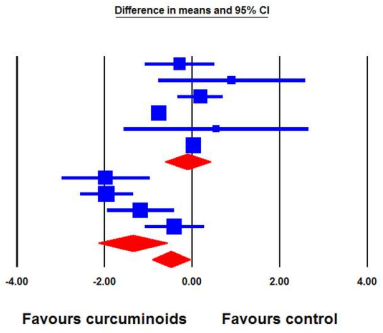
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ganjali et al., 2014a	-0.280	0.406	0.165	-1.075	0.515	-0.690	0.490
Ganjali et al., 2014b	0.910	0.855	0.731	-0.766	2.586	1.064	0.287
Rahimnia et al., 2014	0.190	0.262	0.069	-0.324	0.704	0.724	0.469
Panahi et al., 2014	-0.750	0.084	0.007	-0.914	-0.586	-8.951	0.000
Usharani et al., 2008	-1.970	0.510	0.260	-2.969	-0.971	-3.866	0.000
Panahi et al., 2015	-1.950	0.305	0.093	-2.548	-1.352	-6.389	0.000
Na et al., 2014	-1.170	0.387	0.150	-1.929	-0.411	-3.020	0.003
Belcaro et al., 2010	-0.400	0.343	0.118	-1.073	0.273	-1.165	0.244
Chainani-Wu et al., 2012	0.550	1.076	1.158	-1.559	2.659	0.511	0.609
Panahi et al., 2012	0.035	0.072	0.005	-0.106	0.176	0.488	0.626
	-0.597	0.234	0.055	-1.057	-0.138	-2.549	0.011



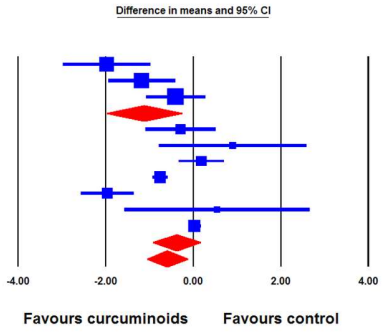
Study name	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ganjali et al., 2014a	-0.632	0.252	0.063	-1.125	-0.139	-2.512	0.012
Ganjali et al., 2014b	-0.675	0.240	0.058	-1.145	-0.205	-2.815	0.005
Rahimnia et al., 2014	-0.705	0.255	0.065	-1.204	-0.205	-2.766	0.006
Panahi et al., 2014	-0.562	0.304	0.093	-1.158	0.035	-1.844	0.065
Usharani et al., 2008	-0.473	0.237	0.056	-0.937	-0.008	-1.993	0.046
Panahi et al., 2015	-0.423	0.223	0.050	-0.861	0.014	-1.895	0.058
Na et al., 2014	-0.532	0.247	0.061	-1.017	-0.047	-2.149	0.032
Belcaro et al., 2010	-0.620	0.254	0.065	-1.119	-0.122	-2.440	0.015
Chainani-Wu et al., 2012	-0.640	0.239	0.057	-1.109	-0.170	-2.672	0.008
Panahi et al., 2012	-0.700	0.255	0.065	-1.200	-0.200	-2.745	0.006
	-0.597	0.234	0.055	-1.057	-0.138	-2.549	0.011



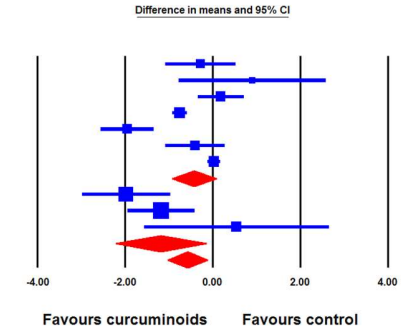
Group by Duration	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
< 8 weeks	Ganjali et al., 2014a	-0.280	0.406	0.165	-1.075	0.515	-0.690	0.490
< 8 weeks	Ganjali et al., 2014b	0.910	0.855	0.731	-0.766	2.586	1.064	0.287
< 8 weeks	Rahimnia et al., 2014	0.190	0.262	0.069	-0.324	0.704	0.724	0.469
< 8 weeks	Panahi et al., 2014	-0.750	0.084	0.007	-0.914	-0.586	-8.951	0.000
< 8 weeks	Chainani-Wu et al., 2012	0.550	1.076	1.158	-1.559	2.659	0.511	0.609
< 8 weeks	Panahi et al., 2012	0.035	0.072	0.005	-0.106	0.176	0.488	0.626
< 8 weeks		-0.099	0.262	0.068	-0.612	0.414	-0.379	0.705
>= 8 weeks	Usharani et al., 2008	-1.970	0.510	0.260	-2.969	-0.971	-3.866	0.000
>= 8 weeks	Panahi et al., 2015	-1.950	0.305	0.093	-2.548	-1.352	-6.389	0.000
>= 8 weeks	Na et al., 2014	-1.170	0.387	0.150	-1.929	-0.411	-3.020	0.003
>= 8 weeks	Belcaro et al., 2010	-0.400	0.343	0.118	-1.073	0.273	-1.165	0.244
>= 8 weeks		-1.352	0.395	0.156	-2.127	-0.576	-3.417	0.001
Overall		-0.481	0.218	0.048	-0.908	-0.053	-2.202	0.028

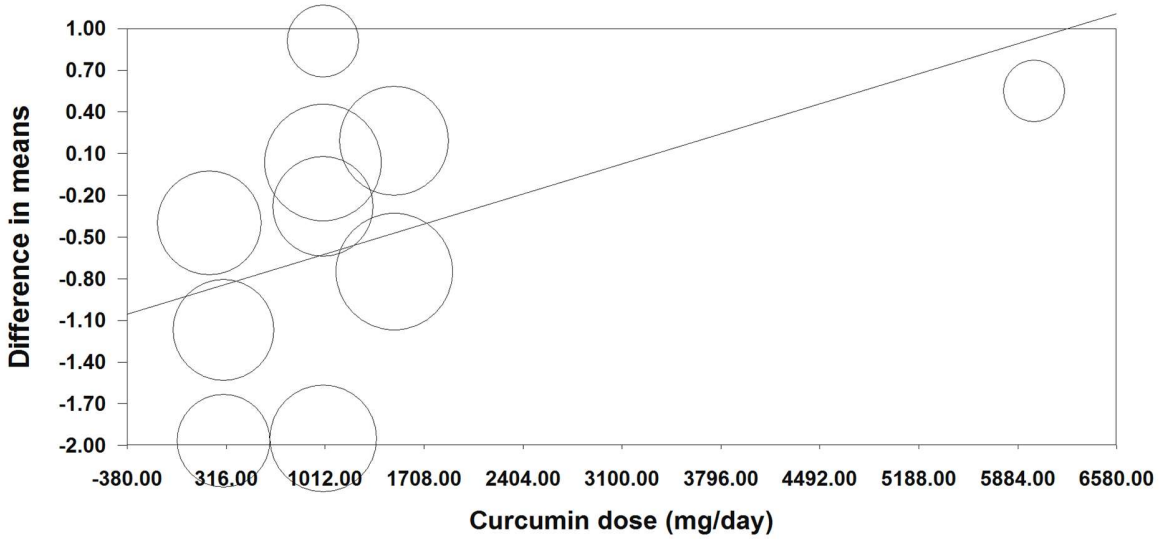


Group by Dose	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
<1000 mg/day	Usharani et al., 2008	-1.970	0.510	0.260	-2.969	-0.971	-3.866	0.000
<1000 mg/day	Na et al., 2014	-1.170	0.387	0.150	-1.929	-0.411	-3.020	0.003
<1000 mg/day	Belcaro et al., 2010	-0.400	0.343	0.118	-1.073	0.273	-1.165	0.244
<1000 mg/day		-1.118	0.437	0.191	-1.974	-0.262	-2.560	0.010
>=1000 mg/day	Ganjali et al., 2014a	-0.280	0.406	0.165	-1.075	0.515	-0.690	0.490
>=1000 mg/day	Ganjali et al., 2014b	0.910	0.855	0.731	-0.766	2.586	1.064	0.287
>=1000 mg/day	Rahimnia et al., 2014	0.190	0.262	0.069	-0.324	0.704	0.724	0.469
>=1000 mg/day	Panahi et al., 2014	-0.750	0.084	0.007	-0.914	-0.586	-8.951	0.000
>=1000 mg/day	Panahi et al., 2015	-1.950	0.305	0.093	-2.548	-1.352	-6.389	0.000
>=1000 mg/day	Chainani-Wu et al., 2012	0.550	1.076	1.158	-1.559	2.659	0.511	0.609
>=1000 mg/day	Panahi et al., 2012	0.035	0.072	0.005	-0.106	0.176	0.488	0.626
>=1000 mg/day		-0.379	0.277	0.077	-0.922	0.164	-1.368	0.171
Overall		-0.591	0.234	0.055	-1.050	-0.132	-2.526	0.012



Group by Formulation	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Formulated	Ganjali et al., 2014a	-0.280	0.406	0.165	-1.075	0.515	-0.690	0.490
Formulated	Ganjali et al., 2014b	0.910	0.855	0.731	-0.766	2.586	1.064	0.287
Formulated	Rahimnia et al., 2014	0.190	0.262	0.069	-0.324	0.704	0.724	0.469
Formulated	Panahi et al., 2014	-0.750	0.084	0.007	-0.914	-0.586	-8.951	0.000
Formulated	Panahi et al., 2015	-1.950	0.305	0.093	-2.548	-1.352	-6.389	0.000
Formulated	Belcaro et al., 2010	-0.400	0.343	0.118	-1.073	0.273	-1.165	0.244
Formulated	Panahi et al., 2012	0.035	0.072	0.005	-0.106	0.176	0.488	0.626
Formulated		-0.426	0.257	0.066	-0.930	0.079	-1.654	0.098
Unformulated	Usharani et al., 2008	-1.970	0.510	0.260	-2.969	-0.971	-3.866	0.000
Unformulated	Na et al., 2014	-1.170	0.387	0.150	-1.929	-0.411	-3.020	0.003
Unformulated	Chainani-Wu et al., 2012	0.550	1.076	1.158	-1.559	2.659	0.511	0.609
Unformulated		-1.184	0.523	0.273	-2.209	-0.159	-2.264	0.024
Overall		-0.574	0.231	0.053	-1.026	-0.121	-2.483	0.013

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0.40
0.10
-0.20
-0.50
-0.80
-1.10
-1.40
-1.70
-2.00
-380.00
316.00
1012.00
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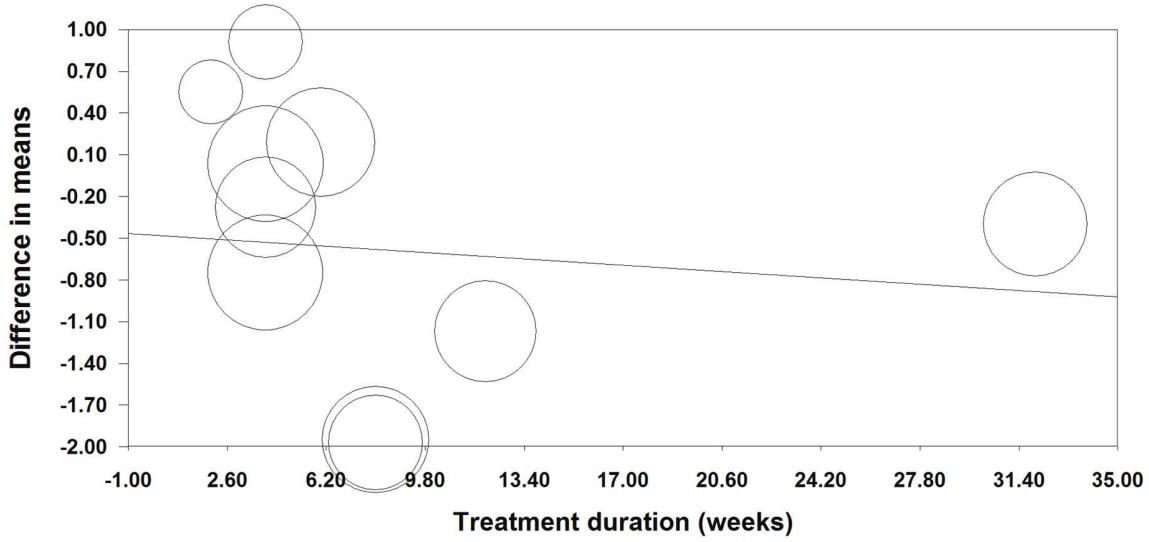
6580.00
Curcumin dose (mg/day)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-1.00
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13.40
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20.60
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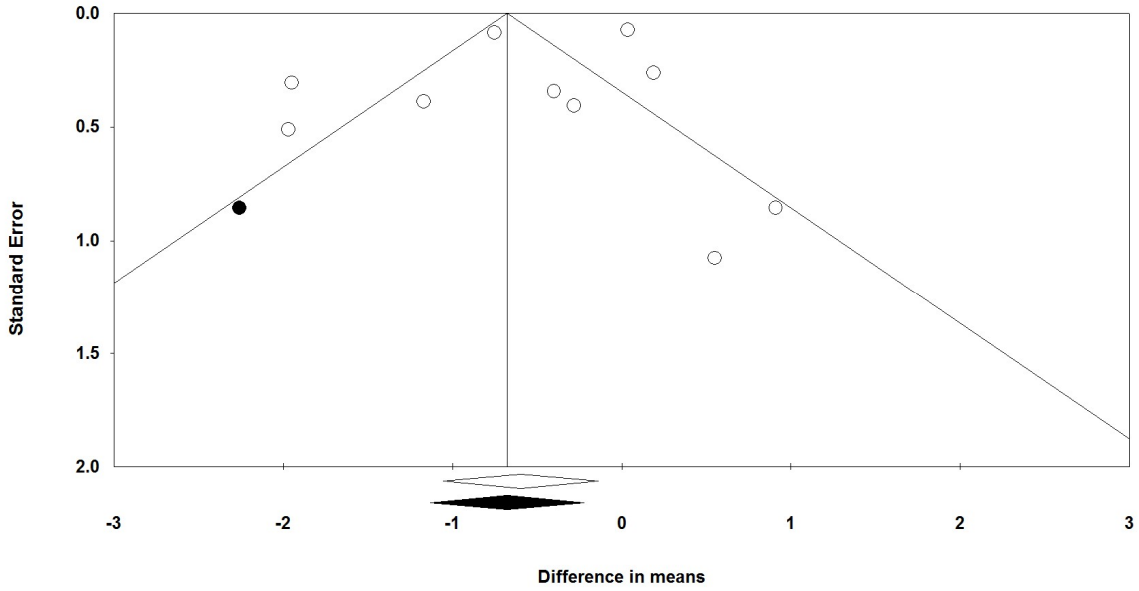
31.40
35.00
Treatment duration (weeks)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-3
-2
-1
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2
3
Difference in means

TABLES

Table 1. Demographic characteristics of the included studies.

Table 2. Risk of bias assessment in the studies considered for meta-analysis.

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI, (kg/m^2)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	C-reactive (mg
Belcaro et al. (2010)	Open-label	Osteoarthritis	8 months								
				50	Curcumin 200 mg/day	43.6±5.5	27 (54.0)	ND	ND	ND	NI
				50	Control	44.2±6	22 (44.0)	ND	ND	ND	NI
Chainani-Wu et al. (2012)	Randomized, double-blind, placebo-controlled	Oral lichen planus	2 weeks								
				10	Curcumin 6 g/day	60.8±8.6	8 (80.0)	ND	ND	ND	2.5 (1.0-
				10	Placebo	56.2±11.7	5 (50.0)	ND	ND	ND	2.0 (1.0-
Ganjali et al. (2014)	Randomized, double-blind, placebo-controlled, cross-over	Obesity	1 month								
				15	Curcumin 1 g/day	ND	ND	ND	ND	ND	NI
				15	Placebo	ND	ND	ND	ND	ND	NI
Na et al. (2014)	Randomized, double-blind, placebo-controlled	Type 2 diabetes	3 months								
				50	Curcumin 300 mg/day	ND	ND	ND	ND	ND	2.71±
				50	Placebo	ND	ND	ND	ND	ND	2.68±
Panahi et al. (2015)	Randomized, double-blind, placebo-controlled	Sulfur mustard intoxication	4 weeks								
				39	Curcumin 1.5 g/day	50.9±7.2	0 (0.0)	28.0±4.8	ND	ND	6.98±
				39	Placebo	53.9±8.6	0 (0.0)	25.9±4.0	ND	ND	8.54±
Rahimnia et al. (2015)	Randomized, double-blind, placebo-controlled	Knee osteoarthritis	6 weeks								
				19	Curcumin 1.5 g/day	57.3±8.7	14 (73.6)	28.7±3.1	ND	ND	5.56±
				21	Placebo	57.5±9.0	17 (80.9)	29.6±4.4	ND	ND	5.00±
Panahi et al. (2012)	Randomized, double-blind, placebo-controlled	Chronic pruritic skin lesions	4 weeks								
				40	Curcumin 1 g/day	47.5±10.7	0 (0.0)	ND	ND	ND	2.58±
				40	Placebo	48.3±8.5	0 (0.0)	ND	ND	ND	2.53±
Sahebkar et al. (2015)	Randomized, double-blind, placebo-controlled	Metabolic syndrome	8 weeks								
				59	Curcumin 1 g/day	44.8±8.6	23 (46.0)	25.4±2.4	135.5±13.1	88.3±7.8	6.52±
				58	Placebo	43.4±9.7	27 (54.0)	22.8±5.3	135.7±14.7	88.7±8.1	7.10±
Usharani et al. (2008)	Randomized, placebo-controlled	Type 2 diabetes	8 weeks								
				23	Curcumin 300 mg/day	55.5±10.7	11 (47.8)	24.6±2.4	130.4±18.5	81.8±10.0	NI
				21	Placebo	49.7±8.1	10 (47.6)	23.9±2.3	126.3±15.4	80.7±7.4	NI

Values are expressed as mean ± SD

*Distribution unspecified

**Median (IQR)

Abbreviations: ND, no data; BMI, body mass index; IQR, interquartile range.

Study	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data
Belcaro et al. (2010)	H	H	L	U	H	U	L
Chainani-Wu et al. (2012)	L	L	L	L	L	U	L
Ganjali et al. (2014)	U	U	L	U	U	U	L
Na et al. (2014)	U	U	L	U	U	U	L
Panahi et al. (2015)	L	L	L	L	L	L	L
Rahimnia et al. (2015)	U	U	L	L	U	U	L
Panahi et al. (2012)	U	U	L	U	U	U	L
Sahebkar et al. (2015)	U	U	L	U	U	U	L
Usharani et al. (2008)	U	U	L	U	H	U	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.