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Effect of Curcumin on IL-6 and IL-8: A Meta-analysis and Systematic Review

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Abstract

Background and objectives: Studies that have investigated the effects of curcumin on the levels of IL-6 and IL-8 are controversial. We performed this meta-analysis to quantitatively evaluate the effects of curcumin on IL-6 and IL-8 regulation.

Methods and study design: The PubMed, Embase, and Cochrane Library (updated to March 2017) databases were searched for related studies. The pooled effects of curcumin treatment on IL-6 and IL-8 were evaluated using a random-effects model. Nine studies comprising a total of 512 subjects were included in the current meta-analysis.

Results: The overall outcome of this meta-analysis suggested that curcumin had no favorable effects on the concentration of IL-6 (-0.80 pg/mL; 95% CI, -1.61 to 0.01 pg/mL; *P*=0.052). Compared with control subjects, subjects treated with curcumin did not show a significant decrease in the concentration of IL-8 (-0.20 pg/mL; 95% CI, -1.02 to 0.62 pg/mL; P=0.639). Subgroup analysis further confirmed that the overall effects of curcumin on the concentrations of IL-6 and IL-8 were not notably affected by the dose or intervention duration of curcumin. Meta-regression analyses did not indicate dose effects of curcumin on IL-6 and IL-8.

Conclusion: This meta-analysis suggested that treatment of curcumin did not significantly reduce the concentrations of IL-6 and IL-8.

Keywords: Curcumin; IL-6; IL-8; Meta-analysis

Introduction

Noncommunicable diseases (NCDs) such as cancers, chronic respiratory diseases and diabetes are significant challenges for global health and have gained considerable attention worldwide [1]. It has been reported that more than 36 million people die from NCDs every year, and this accounts for nearly two-thirds of global deaths [2].

Management of NCDs is a major expenditure of medical resources and is a heavy economic burden to society [3]. In 2012, the World Health Assembly set a health goal of reducing mortality from NCDs by 25% by 2025 [4]. However, the detection, treatment and prevention of NCDs are not fully understood, and the incidence of NCDs is still rising rapidly all over the world.

Inflammation, which is the important and common pathogenic cause for NCDs, is characterized by increasing levels of pro-inflammatory cytokines especially interleukin-6 (IL-6) and interleukin-8 (IL-8) [5]. IL-6 and IL-8 are secreted by a variety of pro-inflammatory cells and are closely involved in acute and chronic inflammation. Furthermore, it had been demonstrated that concentrations of IL-6 and IL-8 are positively correlated with the risk of developing a NCDs [6]. In addition, previous studies have suggested that decreasing the concentrations of pro-inflammatory cytokines could inhibit the deterioration of NCDs and promote the effects of treatment [7,8].

Curcuma longa is a traditional Chinese medicinal herb that has been widely used for a long time as a remedy for the prevention and treatment of chronic diseases [9]. The biological effects of curcuma longa are mainly attributed to the presence of curcumin, which accounts for 77% of the bioactive polyphenolic compound in curcuma longa [10]. Recently, evidence from *in vitro* studies has implied that the beneficial effects of curcumin might result from the down-regulation of IL-6 and IL-8 [11-13]. Meanwhile, a number of results from clinical trials have revealed an interaction between curcumin and pro-inflammatory cytokines [14]. However, the conclusions of these clinical trials have still been controversial as to whether curcumin can reduce the concentrations of IL-6 and IL-8 [15]. Therefore, we performed the current meta-analysis to further explore the changes in IL-6 and IL-8 concentrations during curcumin treatment in order to fully understand the beneficial effects of curcumin.

Methods

Search strategy

We searched the PubMed (updated to March 2017; http://www.ncbi.nlm.nih.gov/pubmed/), Embase (updated to March 2016; http://www.embase.com/) and Cochrane Library (updated to March 2016; http://www.cochrane.org/) databases using the following terms that were searched in the titles and abstracts: (curcuma longa OR turmeric OR curcuma OR curcumin OR curcuminoid OR curcuminoids) AND (IL-6 OR interleukin-6 OR IL-8 OR interleukin-8). References in the reference lists and reviews were hand-searched to further identify articles that examined the effects of curcumin on the concentrations of IL-6 and IL-8.

Study selection

We screened the studies using the following criteria:

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1) the studies were randomized controlled trials in humans with parallel or crossover designs;

2) the subjects were treated with curcumin for >2 weeks;

3) the baseline and endpoint values or the mean differences of IL-6 and IL-8 with SD, SEM or 95% CI were available;

4) the components of the treatment group were described in detail; and 5) the study used a concurrent control group with the only difference between the control and treatment groups being curcumin treatment.

Data extraction and quality assessment

1) When we reviewed the articles that were included in our meta-analysis, the following data were extracted: 1) study characteristics, including the authors, publication year, country, sample size, study design, type of intervention, study duration, and dose;

2) population information, including age and baseline healthy status information; and

3) net changes in the SDs for the concentrations of IL-6 and IL-8. All values were expressed as pg/mL for the concentrations of IL-6 and IL-8.

If the outcomes were reported multiple times at different stages of the trials, only the values that represented the final outcome concentrations at the end of the trials were included in our meta-analysis.

The quality of the included articles was assessed using Cochrane criteria. The assessment items were as follows: adequacy of sequence generation, allocation concealment, blinding, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. A judgment of "yes" indicated a low risk of bias, while a judgment of "no" indicated a high risk of bias, and a judgment of "unclear" indicated an unclear or unknown risk of bias.

Statistical analysis

We conducted our meta-analysis using the STATA program (Version 11; StataCorp, College Station, TX). Intervention effects were defined as the weighted mean difference with the 95% CIs for IL-6 and IL-8. The statistical heterogeneity was estimated using a Cochran's test ($P<0.1$). The I^2 statistic was also calculated, and I^2 >50% indicated a significant heterogeneity among the included studies [16]. If significant heterogeneity was found among trials, we used a random-effects model. Otherwise, we used a fixed-effects model.

We excluded percentage changes in the mean and SD values when we extracted data for our meta-analysis. SD values were calculated from standard errors, 95% CIs, *P* values, or t statistics when they were not directly available. In addition, we assumed a correlation coefficient of 0.5 between the baseline and final values, as suggested by Follmann et al. [17].

Publication bias was assessed using funnel plots and an Egger's test. Subgroup analysis was conducted to exam potential sources of heterogeneity, such as curcumin dose and treatment duration. Additional sensitivity analyses were also performed according to the Handbook for Systematic Review of Interventions of Cochrane software (Version 5.0.2; The Cochrane Collaboration, Oxford, United Kingdom). Furthermore, meta-regression analyses were conducted to investigate the dose-effect relation between curcumin and IL-6 and IL-8.

Results

Results of the literature search

The details of the search strategy process for our meta-analysis are shown in Figure 1. A total of 859 articles were identified in the initial search, and 834 were excluded after careful review of the titles and abstracts. Among the 834 excluded reports, 160 were excluded because they were duplicates and 674 were excluded because they were clearly irrelevant to this meta-analysis. Therefore, 25 articles remained for a more detailed examination. Among these 25 articles, an additional 17 were then excluded for the following reasons: 5 were discarded because they had incomplete data for IL-6 or IL-8, 7 were excluded because they used multiple components, 2 were eliminated because they had repetition of participants, 1 was ruled out because it used an uncontrolled study design, and 1 was excluded because the treatment duration was <1 week. Thus, 9 articles were ultimately selected for inclusion in the meta-analysis, with 8 articles containing findings relevant to IL-6 [18-25] and with 5 articles containing information relevant to IL-8 [20,22,25,26].

Study characteristics

The summary of the studies that were included in our meta-analysis are presented in Table 1. The studies that were included were all randomized controlled trials that were published between 2008 and 2015. The number of subjects included in each study ranged from 20 to 100, and there were 512 subjects in total that were included in the meta-analysis. Of the 9 studies that were included, 8 used a parallel-design while one used a crossover study-design [23]. The average age of the participants varied from 38.3 years old to 59.96 years old (median: 52.47 years). The dose of curcumin ranged from 66.3 mg/day to 6000 mg/day (median: 1000 mg/day). The treatment duration of curcumin varied from 4 weeks to 8 weeks (median: 4 weeks).

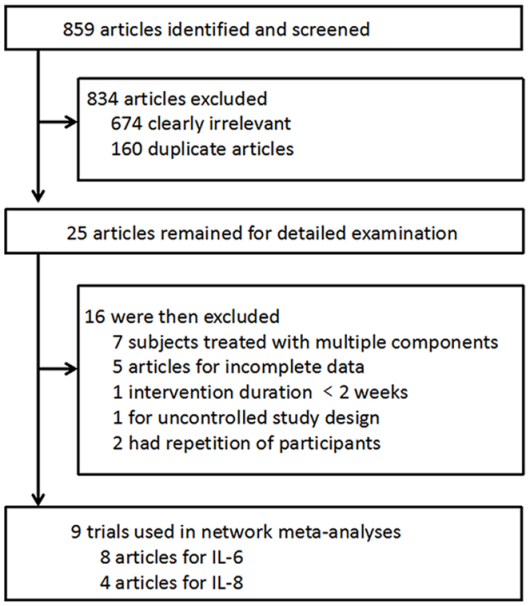

Figure 1: Flow diagram of the study selection procedure showing the number of eligible articles that were included in the meta-analysis.

Author, publication year, country	No. of subjects	Study design	Population Characteristics	Age (years)	BMI(kg/m²)	Treatment group	Control group	Duration
Usharani, 2008. India	44	Parallel	Type 2 diabetes	55.52 ± 10.76 (treatment group) 49.75 ± 8.18 (control group)	24.66 ± 2.42 (treatment group) 23.98 ± 2.35 (control group)	Curcuminoid (600 mg/day)	Placebo	8 weeks
Chainani-Wu, 2011, American	20	Parallel	Oral lichen planus patients	58.50 ± 16.73	NR	Curcuminoid (6000 mg/day)	Placebo	2 weeks
Khajehdehi, 2011. Iran	40	Parallel	Type 2 diabetic nephropathy	52.9 ± 9.2 (treatment group) 52.6 ± 9.7 (control group)	NR	Curcuminoid (66.3 mg/day)	Placebo	8 weeks
Panahi, 2012. Iran	80	Parallel	Chronic cutaneous diseases	47.5 ± 10.7 (treatment group) 48.3 ± 8.5 (control group)	NR	Curcuminoid (1000 mg/day)	Placebo	4 weeks
Panahi, 2014. Iran	80	Parallel	Solid tumors	59.58 ± 14.63 (treatment group) 58.33 ± 16.10 (control group)	NR	Curcuminoid (180 mg/day)	Placebo	8 weeks
Ganjali, 2014. Iran (a)	30	Crossover	Obesity	38.43 ± 10.84	32.60 ± 3.58	Curcuminoid (1000 mg/day)	Placebo	4 weeks
Ganjali, 2014. Iran (b)	30	Crossover	Obesity	38.43 ± 10.84	32.60 ± 3.58	Curcuminoid (1000 mg/day)	Placebo	4 weeks
Rahimnia, 2015. Iran	40	Parallel	Knee osteoarthritis	57.32 ± 8.78 (treatment group) 57.57 ± 9.05 (control group)	28.75 ± 3.17 (treatment group) 29.64 ± 4.46 (control group)	Curcuminoid (1500 mg/day)	Placebo	6 weeks
Panahi, 2015. Iran	78	Parallel	Chronic pulmonary diseases	50.97 ± 7.27 (treatment group) 53.97 ± 8.60 (control group)	28.08 ± 4.82 (treatment group) 25.95 ± 4.03 (control group)	Curcuminoid (1500 mg/day)	Placebo	4 weeks
Panahi, 2016, Iran	100	Parallel	Metabolic syndrome	44.13 ± 8.89	24.13 ± 3.98	Curcuminoid (1000 mg/day)	Placebo	8 weeks

Abbreviations: BMI, body mass index; NR, no report. Values are expressed as the mean ± SD

Table 1: Characteristics of the 9 randomized controlled trials that were included in the meta-analysis.

Data quality

The data quality results are presented in Figures 2 and 3. Information regarding random sequence generation was provided by only two of the studies. Most of the articles (5 of 9) were at a low risk of allocation concealment. Information regarding blinding of outcome assessments was adequately addressed in all the articles and was determined to be low risk in 7 of the studies. 4 articles had a low risk of incomplete outcome data. All included studies had a low risk of blinding, selective reporting and other bias.

Effects of curcumin on the concentrations of IL-6 and IL-8

As is presented in Figure 4, treatment with curcumin did not markedly reduce the concentration of IL-6 (-0.80 pg/mL; 95% CI, -1.61 to 0.01 pg/mL; P=0.052) when compared to the control treatment. In addition, when compared to the control subjects, subjects who were treated with curcumin did not show a significant decrease in the concentration of IL-8, as is shown in Figure 5 (-0.20 pg/mL; 95% CI, -1.02 to 0.62 pg/mL; P=0.639).

Subgroup analysis was performed to further confirm the impact of curcumin dose and treatment duration on the overall effects of curcumin on the concentrations of IL-6 and IL-8. The curcumin doses were divided into high-dose (>1000 mg/day) and low-dose (≤ 1000 mg/day) subgroups. The duration of treatment was classified as either long-term duration (>4 weeks) or short-term duration (≤ 4 weeks). As is shown in Figure 6, subgroup analysis revealed that the concentration of IL-6 was not significantly different between the low-dose subgroup (-0.49 pg/mL; 95% CI, -1.13 to 0.14 pg/mL; P=0.125) and the high-

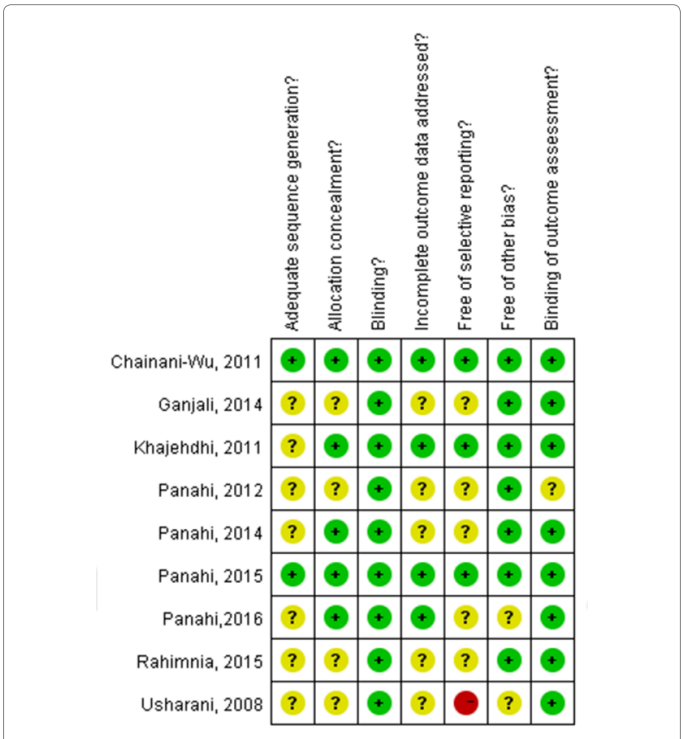

Figure 2: Risk of bias summary graph: judgements of review authors (Low, Unclear and High) for each risk of bias item shown as percentages across all included studies.

dose subgroup (-1.96 pg/mL; 95% CI, -6.28 to 2.35 pg/mL; *P*=0.372). In addition, the concentration of IL-6 was not significantly different between the long duration subgroup (-0.80 pg/mL; 95% CI, -1.68 to 0.09 pg/mL; *P*=0.077) and the short duration subgroup (-0.82 pg/mL; 95% CI, -2.31 to 0.68 pg/mL; *P*=0.286) (Figure 7). Additionally, we failed to find any significant differences in the concentration of IL-8 between the low-dose subgroup (-0.27 pg/mL; 95% CI, -1.31 to 0.77 pg/mL; *P*=0.613) and the high-dose subgroup (0.16 pg/mL; 95% CI, -0.28 to 0.61 pg/mL; *P*=0.477) (Figure 8). Moreover, we did not find any significant differences in IL-8 concentration between the long treatment duration subgroup (0.00 pg/mL; 95% CI, -1.20 to 1.20 pg/mL; *P*=0.999) and the short treatment duration subgroup (-0.29 pg/mL; 95% CI, -1.47 to 0.90 pg/mL; *P*=0.633). (Figure 9) Meta-regression analyses did not indicate dose effects of curcumin on IL-6 and IL-8 (*P*=0.131 for IL-6 and *P* = 0.672 for IL-8). The sensitivity analysis indicated that removing any individual trial did not significantly change the overall effects of curcumin on the concentrations of IL-6 and IL-8.

Publication bias

Funnel plots (Figures 10 and 11) and an Egger's test were conducted to identify any publication bias in the studies included in our meta-analysis. The results indicated that there was no pronounced publication bias in the current meta-analysis (Egger's test: *P*=0.619 for IL-6 and *P*=0.911 for IL-8).

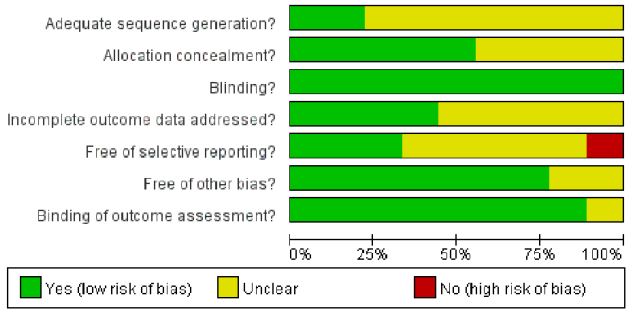

Figure 3: Aggregate of Cochrane risk of bias results.

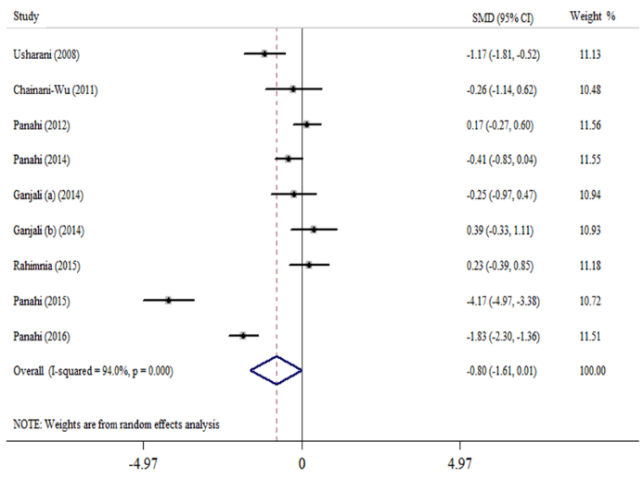

Figure 4: Meta-analysis of the effects of curcumin on the net change of IL-6 (interleukin-6).

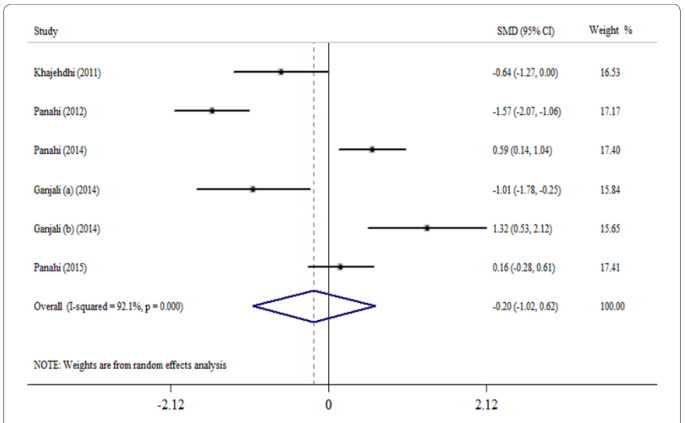

Figure 5: Meta-analysis of the effects of curcumin on the net change of IL-8 (interleukin-8).

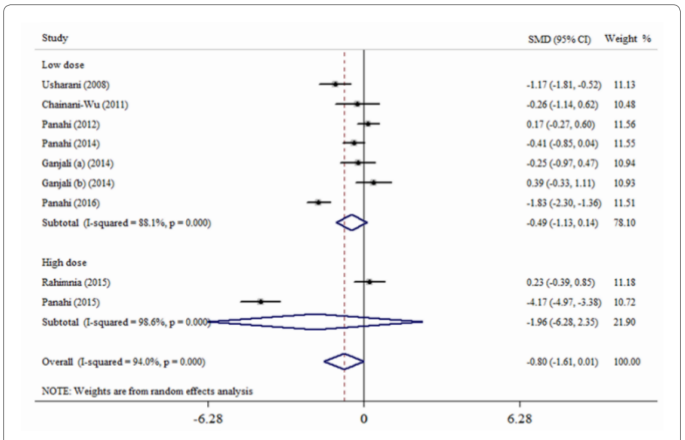

Figure 6: Influence of the dose subgroup on the effects of curcumin treatment on the net change of IL-6 (interleukin-6).

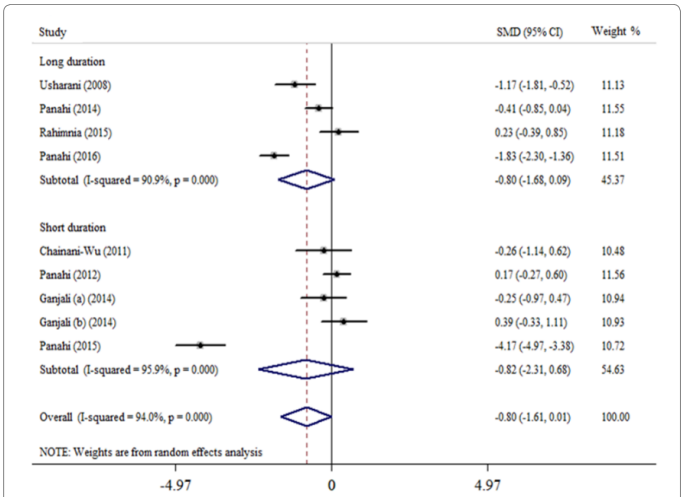

Figure 7: Influence of the treatment duration subgroup on the effects of curcumin on the net change of IL-6 (interleukin-6).

Discussion

Our meta-analysis demonstrated that curcumin had no favorable effects on the concentrations of IL-6 and IL-8. Subgroup analysis found that the overall effects of curcumin on IL-6 and IL-8 were not

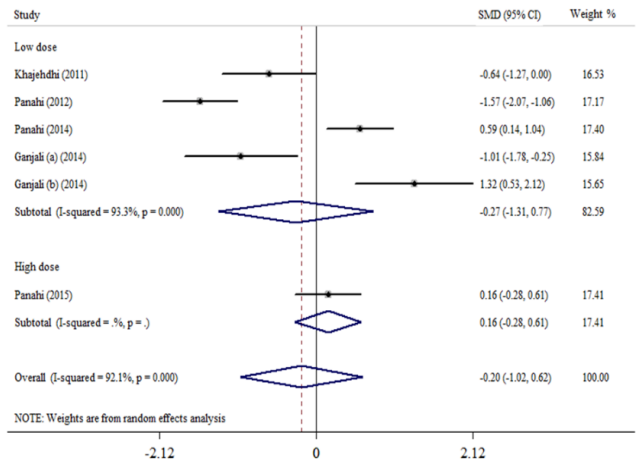

Figure 8: Influence of the dose subgroup on the effects of curcumin treatment on the net change of IL-8 (interleukin-8).

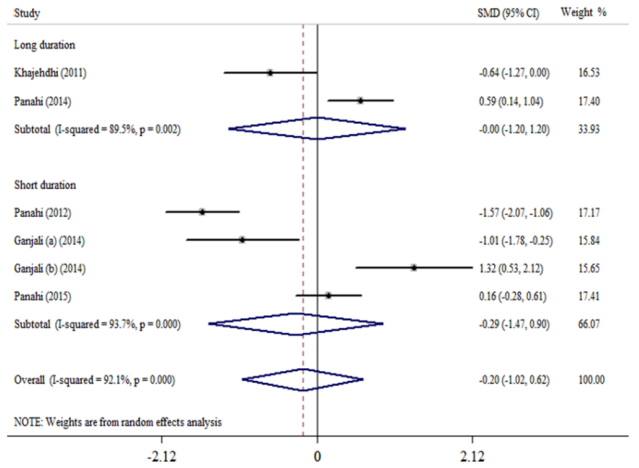

Figure 9: Influence of the treatment duration subgroup on the effects of curcumin on the net change of IL-8 (interleukin-8).

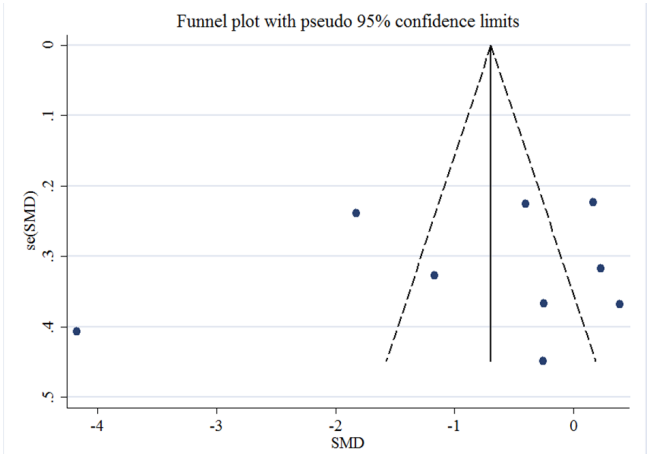

Figure 10: Funnel plot examining the publication bias in the studies that were related to the effects of curcumin on the concentration of IL-6.

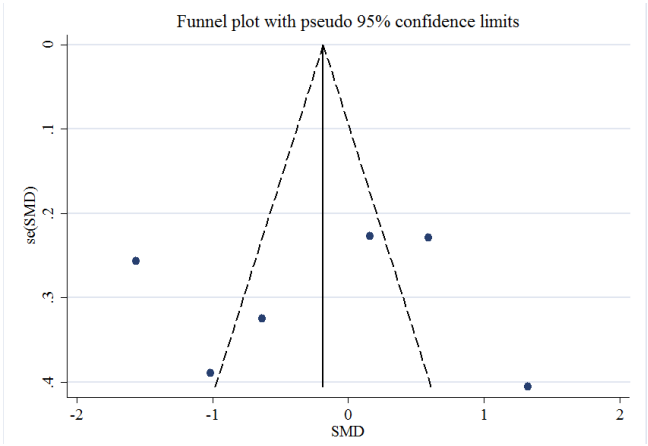

Figure 11: Funnel plot examining the publication bias in the studies that were related to the effects of curcumin on the concentration of IL.

significantly affected by the dose or intervention duration. The result of a sensitivity analysis confirmed that removing any individual trial did not notably change the overall effects of curcumin on the concentrations of IL-6 and IL-8. Our meta-analysis on the effects of curcumin on IL-6 and IL-8 concentrations was limited by the small number of studies that were included.

Curcumin is a type of plant polyphenol that has been suggested to be a highly pleiotropic molecule that interacts with numerous pro-inflammatory cytokines [27-29], particularly with interleukins. The mechanism underlying this interaction appears to primarily involve curcumin's ability to suppress the nuclear factor kappa-B (NF-κB) pathway, which is the master switch in the regulation of the inflammatory response [12,29]. It has been indicated that curcumin's inhibitory effects on NF-κB result from the inhibition of the phosphorylation and degradation of IkBα by IkB kinase (IKK) and the consequent prevention of NF-κB re-localization into the nucleus [30,31]. This effect of curcumin results in the down-regulation of IL-6 and IL-8. Meanwhile, curcumin alleviates IL-6 and IL-8 by increasing the expression of nuclear factor erythroid-2 related factor 2 (Nrf2), which has been negatively correlated with NF-κB and is strongly related to chronic inflammation [32,33]. Moreover, previous evidence has indicated that curcumin can reduce the production of ROS, which plays an important role in the NF-κB pathway and in the occurrence and development of chronic inflammation [34].

Furthermore, a recent meta-analysis of randomized controlled trials investigating the interaction between curcumin and pro-inflammatory cytokines has also provided evidence that treatment with curcumin is able to clearly reduce concentrations of tumor necrosis factor-α (TNF-α) (-4.69 pg/mL; 95% CI, -7.10 to -2.28 pg/mL; $P<0.001$) [35] and C-Reactive Protein (CRP) (-6.44 mg/L; 95% CI, -10.77 to -2.11 mg/L; $P=0.004$) [36]. Similar to TNF-α and CRP, IL-6 and IL-8 are necessary downstream pro-inflammatory cytokines in the NF-κB pathway. In addition, TNF-α is the upstream pro-inflammatory cytokine of IL-6 and interacts with IL-6 and IL-8 directly, and the transcription of CRP in hepatocytes is primarily stimulated by IL-6 [37]. However, in our meta-analysis, we found no significant effects of curcumin on the concentrations of IL-6 and IL-8. Several possibilities could explain our negative findings. The first possibility is that the low bioavailability, rapid metabolism and rapid systemic elimination of curcumin may influence its biological effects in clinical trials [10,13]. A second possibility involves the fact that the inflammation signaling pathways are extremely complex and that there are numerous pro-

inflammatory cytokines downstream of NF-κB, such as L-1β, STAT3 and Wnt/β-catenin [14,38]. The interactions of these cytokines might influence the concentrations of IL-6 and IL-8, which could obscure the treatment effects of curcumin. Third, the participants in the studies that were included in the meta-analysis were patients with obesity, type 2 diabetes, type 2 diabetic nephropathy, solid tumors, knee osteoarthritis, chronic cutaneous diseases and chronic pulmonary diseases. The baseline levels of IL-6 and IL-8 were highly variable in our meta-analysis, which increased the inter-study heterogeneity.

Although the relatively larger number of pooled participants provides stronger statistical power to evaluate the effects of interest, our meta-analysis has several unavoidable limitations. First, the number of studies included in our meta-analysis was limited, and most of them had a small number of participants. Second, the treatment duration of the studies that were included was relatively short (between 4 weeks and 8 weeks). Third, measuring the concentrations of IL-6 and IL-8 was not the primary goal of the included trials, so we cannot rule out the possibility that there were some positive results in other trials that were not reported in these articles. Therefore, more clinical trials are needed that are high quality with larger sample sizes and longer treatment durations and that have a primary goal of measuring IL-6 and IL-8 to accurately assess the changes in IL-6 and IL-8 concentrations following treatment with curcumin.

In conclusion, our meta-analysis revealed that treatment with curcumin did not significantly reduce the concentrations of IL-6 and IL-8, and that subgroup analysis demonstrated that the overall effects of curcumin were not affected by the treatment durations or curcumin doses that were used in the clinical trials. Further high-quality clinical trials are needed in the future to evaluate the effects of curcumin on the concentrations of IL-6 and IL-8.

Acknowledgment

The authors' responsibilities were as follows: S-CH, KL and M-TM: conceived the research idea and drafted the protocol; S-CH, KL, X-HZ and M-TM: selected and screened the trials included in the analysis; S-CH, KL and CK: extracted data, conducted the analysis, and contributed to updating the review. All of the authors contributed to the writing and the revision of the manuscript.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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