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Effect of Curcumin on Circulating Adiponectin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Running title: Curcumin supplementation and adiponectin

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Abstract

Objective: Our objective was to perform a systematic review and meta-analysis on randomized controlled trials (RCTs) assessing the effect of curcumin on serum adiponectin concentration.

Methods: We searched PubMed/Medline, Scopus, ISI Web of Science, Cochrane Library, and Google scholar databases up to April 2019. RCTs conducted among human adults studied the effects of curcumin on serum adiponectin concentrations as an outcome variable was included. The weighted mean differences (WMD) and standard deviations (SD) of change in serum adiponectin levels were calculated. The random effects model was used for deriving a summary of mean estimates with their corresponding SDs.

Results: Out of 313 records, 6 trials that enrolled 652 subjects were included. The pooled results showed that curcumin supplementation significantly increased adiponectin concentrations in comparison with placebo (WMD: 0.82 Hedges' g; 95% confidence interval (CI): 0.33 to 1.30, P<0.001). Greater effects on adiponectin were observed in trials lasting ≤10 weeks (WMD: 1.05 Hedges' g; 95% CI: 0.64 to 1.45, P<0.001).

Conclusion: Curcumin significantly improves adiponectin concentrations. However, due to some limitations in this study, further studies are needed to reach a definitive conclusion about the effect of curcumin on the levels of adiponectin.

Keyword: Curcumin, Adiponectin, Randomized controlled trials, Meta-analysis

Introduction

Metabolic abnormalities and metabolic syndrome are a well-known cause of cardiovascular diseases, whilst insulin resistance is a prominent factor in the aetiology of metabolic syndrome (Qin et al. 2010). Adiponectin is a protein hormone with 244 amino acids that mediates numerous of metabolic processes, including glucose regulation and oxidation of fatty acids (Whitehead et al. 2006), and is an important adipokine produced by adipose tissues and is circulated in high concentrations. Moreover, adiponectin is regarded as a key regulator of insulin sensitivity, ameliorating inflammation of the tissue, recues systemic insulin resistance, and may be used as a predictor of cardiovascular disease (Rodina and Severin 2012). Furthermore, low levels of adiponectin have been found to be correlated with increased risk of diseases, including; diabetes, dyslipidaemia, hypertension and cardiovascular and metabolic syndrome (Rodina and Severin 2012).

Nutraceuticals, or foods with known health-promoting benefits, have been identified as potential interventions for cardiovascular disease, attributable to their lipid-lowering effects (Cicero), amelioration of metabolic syndrome components (Patti), and improvements in vascular function and arterial blood pressure (Patti). Furthermore, attributable to the high costs and side effects associated with traditional pharmacotherapy, attention has been paid to the treatment through herbal medicine (Chuengsamarn, 2012). Curcumin has a pivotal role in reducing complications of diabetes and related metabolic disorders, attributed to antidiabetic, anti-inflammatory, and antioxidant properties and its purported ability to increase circulating adiponectin (Ali Hussain, 2002; Zhang, Fu, Gao, & Liu, 2013). Experimental and clinical studies have reported the effectiveness of curcumin supplementation on hyperlipidaemia and inhibiting atherosclerosis (Calabrese et al., 2008; Zheng et al., 2016). The results of some studies in animal models suggests that curcumin supplementation may decrease total cholesterol, triglycerides, and increase HDL-C (WHO). Curcumin is asserted to regulate the secretion of inflammatory cytokines through proteins and enzymes signalling, resulting in reduced secretion of inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-6), tumour necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) (Babu & Srinivasan, 1997; Jain, Rains, Croad, Larson, & Jones, 2009). In a population of prediabetic participants, curcumin supplementation resulted in enhanced prevention of type II diabetes, improved β-cell function, reduced insulin resistance, and higher levels of circulating adiponectin (Tan, 2004). Moreover, in a study of participants affected by obesity, with type II diabetes, Aggarwal & Harikumar, (2009) reported that curcumin supplementation resulted in

significant a reduction of high sensitivity C-reactive protein (hs-CRP), TNF-α, and IL-6 (Aggarwal & Harikumar, 2009). Further, studies on rodent models suggest that curcumin may conceivably protect against vascular complications of diabetes, and other metabolic disorders, via its effects on Thioredoxin-interacting protein, intercellular adhesion molecule-1, and nitric oxide synthase 2 enzyme expression (Na et al., 2014).

Given the positive role adiponectin has on moderating a number of metabolic processes, the recently reported, positive, biological effects of curcumin supplementation, and the distinct lack of unifying consensus on the topic; our objective was to perform a systematic review and meta-analysis on randomized controlled trials (RCTs) assessing the effect of curcumin on serum adiponectin concentration

Methods

We conducted this meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, which was adhered to during all stages of design, implementation, analysis, and reporting(1).

Data sources and search strategy

We searched multiple electronic databases from the earliest available online indexing year through to April 2019, without language restrictions, including PubMed/Medline, Scopus, ISI Web of Science, Cochrane Library, and Google scholar. The keywords used in our search strategy were ("Curcumin" OR "Curcuma" OR "Curcuminoid" OR "Tumeric" OR "Turmeric") AND ("adipokines" OR "adiponectin" OR "adipocytokines"). Reference lists from all related reviews and original primary studies were also screened to avoid missing any relevant articles.

Study selection

To accelerate the process of screening citations, the search results were imported into a bibliographic database and duplicates were removed automatically (EndNote X6; Thomson Reuters, New York). Subsequently, titles and abstracts screened by two independent authors (A.H and E.Gh) for relevance to the topic. Following this, full-texts of selected articles were retrieved and assessed for eligibility. Studies were included if they were randomized controlled trials of curcumin supplementation that evaluated adiponectin as an outcome. Studies were excluded if participants were children (<18 years) or if they had a concomitant intervention for which effects could not be separated; were of less than 2 weeks' duration; did not report the

baseline and final values of outcome variables (or changes) in both curcumin and control groups; were letters, commentaries, reviews, ecological and animal studies, duplicate publication from the same study, or were published in non-English languages. Unpublished documents and grey literature, such as conference papers, dissertations, and patents were also excluded. Discrepancies were resolved by consensus and discussion with a third, independent, reviewer.

Data extraction

OF the included studies, two authors (A.H and E.Gh) independently extracted the following information into a data spread sheet: first author's last name, publication year, study design, country, participants' gender and mean age of subjects, type of study population, follow-up duration and dose of curcumin supplement. When the values for outcome variable were reported in different time points, data for the end of the trial were extracted. We emailed corresponding authors in cases of any unclear data. Any disagreements between the two reviewers were resolved in consultation with a third investigator (A.A).

Quality assessment

Two authors (A.H and E.Gh) independently evaluated the methodological quality of the included trials using the instrument developed by Jadad et al.(2). Briefly, this scale comprises 3 domains: 1) allocation concealment explanation (maximum of 2 points); 2) double-blinding explanation (maximum of 2 points); and 3) withdrawal explanation and follow-up completeness (maximum of 1 point). In total, a maximum score of 5 points can be achieved and studies with a Jadad score of <3 and ≥ 3 were considered as low and high-quality publications, respectively. Any discrepancies were discussed and resolved by a third investigator (M.P).

Statistical analysis

The difference in the mean values of adiponectin was calculated for all eligible studies and considered as the effect size. The net changes in adiponectin concentrations were estimated as the difference (curcumin minus control) between its changes (end values minus baseline) in the control group and the intervention group. Standard deviation (SD) of the mean difference was calculated using the following formula: SD = square root $[(\text{SD pre-treatment})^2 + (\text{SD post-treatment})^2 - (2 \times R \times \text{SD pretreatment} \times \text{SD post-treatment})]$(3). To ensure the meta-analysis was not sensitive to the selected correlation coefficient (R = 0.5), all analyses were repeated

using correlation coefficients of 0.2 and 0.8. Where a standard error (SE) was only reported, SD was estimated using the following formula: SD = SE × √n (n is the number of subjects in each group). The weighted mean difference (WMD) and its corresponding 95% confidence intervals (CIs), was calculated by conducting random effect model, taking the between study heterogeneity into account. The inconsistency index (I^2) was used to quantify statistical heterogeneity in meta-analyses, and values greater than 50% were considered indicative of high heterogeneity. To find the sources of heterogeneity, subgroup analyses were performed based on the following categories: intervention dosage, duration of follow up, baseline BMI, and mean age of participants. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or group of studies. In addition, plausible publication bias was specified visually by funnel plot and confirmed by the statistical evidence of Egger's test. All statistical analyses were conducted using STATA, version 11.2 (Stata Corp, College Station, TX). P-values less than 0.05 were considered as statistically significant.

Results

Study Selection Process

From 313 potentially relevant citations identified in our structured searches, 229 records were screened (after removing duplicates) and 13 full-text articles were assessed for eligibility. Next, 7 articles were excluded due to the following reasons: studied children (n=1) (4), administered curcumin in combination with other components (n=2) (5, 6), duplicate dataset (n=1) (7), published in non-English language (n=1) (8), and studies that did not provide sufficient data for outcomes (n=2) (9, 10). Finally, 6 trials (11-16) were included in this meta-analysis. The flow chart for selecting studies is presented in Figure 1.

Characteristics of the included studies

Selected studies comprised a total of 652 participants in an intervention (322 participants receiving curcumin treatment) or control groups (330 participants receiving placebo treatment). These articles were published between 2012 and 2019, which among them, three studies were performed in Iran (14-16), two in the Thailand (11, 13), and other study conducted in USA (12). The design of all the nominated trials was parallel. All records examined the effect of curcumin in both genders except for one study (12) that was restricted to men. Participants in these studies were patients with type 2 diabetes (11, 15), pre-diabetic subjects (13), obese men (12), and those with metabolic syndrome (14, 16). The mean age of the participants ranged from 27.1 to 59.37 years old and mean baseline BMI varied from 24.13

to 32.4 kg/m^2. The range of dosage of curcumin supplementation varied from 200 to 1500 mg/day. The duration of intervention was between 6 to 39 weeks in different studies. The general characteristics of the included studies are outlined in Table 1.

According to Jadad scale, all studies had high quality (score ≥ 3). All studies were randomized trials, of them 4 records (11, 14-16) had properly explained the randomization procedure. In addition, all included studies had mentioned blindness whereas only four studies (12, 13, 15, 16) clearly described the blinding procedure. Details concerning a number of participants that dropped out and the reasons for this were reported in all studies. The general characteristics of the included studies are outlined in Table 1.

Effect of curcumin supplementation on circulating adiponectin

The individual trial results and the pooled estimate for the effect of curcumin supplementation on adiponectin are shown in Figure 2. Combining 6 effect sizes from 6 studies based on the random-effects model, we found that curcumin supplementation significantly increased adiponectin (WMD: 0.82 Hedges' g; 95% CI: 0.33 to 1.30, P<0.001) compared to the control group. However, the heterogeneity among the studies was high (I^2=87.2%, P<0.001). To identify the sources of the between-study heterogeneity, subgroup analyses were conducted (Table 2). Mean age of study participants, baseline BMI, and curcumin dosage did not explain this heterogeneity. However, duration of intervention could explain the heterogeneity (I^2=49.5%, P=0.13). In this analysis, we found that the effect of curcumin supplementation on circulating adiponectin was only significant in trials lasting ≤10 weeks (WMD: 1.05 Hedges' g; 95% CI: 0.64 to 1.45, P<0.001). Sensitivity analysis showed that the removal of each trial did not significantly influence the pooled effect of curcumin on adiponectin concentrations. The funnel plot was visually symmetrical (Figure 3) and the result of Egger's test did not show any evidence of publication bias (P=0.91).

Discussion

Curcumin is a bioactive yellow-orange pigment of turmeric and extracted from the rhizomes of Curcuma longa Linn. (Zingiberaceae) (Ravichandran 2013). The therapeutic effects of curcumin and its analogues have been shown efficacious in a number of pathological conditions such as cancer (Mirzaei et al. 2016; Momtazi and Sahebkar 2016), osteoarthritis (Panahi et al. 2014), non-alcoholic fatty liver disease (Rahmani et al. 2016), anxiety and depression (Esmaily et al. 2015), pulmonary diseases (Panahi 2016) and ischemia/reperfusion injury (Sahebkar 2010). Given the purported capability of curcumin to elicit positive, biological

effects, and the known ability of adiponectin to protect against metabolic diseases, our objective was to perform a systematic review and meta-analysis on RCTs assessing the effect of curcumin on serum adiponectin concentration. In accord with this objective, the pooled results showed that curcumin supplementation significantly increased adiponectin concentrations in comparison with placebo; whilst greater effects on adiponectin were observed in trials lasting ≤10 weeks.

Adiponectin is an anti-inflammatory cytokine produced and secreted by adipose tissue. Adiponectin serum level reportedly has an inverse relationship with insulin resistance, dyslipidaemia, cardiovascular disease, and obesity (Tan, 2004; Yang et al., 2002); whilst decreases in adiponectin may resultantly increase the risk of atherosclerotic disease (Rothenbacher, Brenner, Marz, & Koenig, 2005). Adiponectin has a positive effect in reducing the risk of cardiometabolic disease, which is associated with lipid and glucose metabolism, anti-inflammatory, and anti-atherosclerotic properties (Esfahani, Movahedian, Baranchi, & Goodarzi, 2015). The results of some empirical studies have shown that supplementation of curcumin leads to a significant increase in serum adiponectin (Anand et al., 2007; Tan, 2004); whist in patients with metabolic syndrome, Panahi et al showed that supplementing with 1,000 mg of curcumin daily for 8 months increased adiponectin and decreased leptin (Panahi et al., 2016). In another example, consumption of 1,500 mg curcumin daily, for 9-months, in patients affected by pre-diabetes resulted in higher level of adiponectin (Tan, 2004). In the present study, we were able to confirm the veracity of a number of independent studies, highlighting that curcumin supplementation, particularly when consumed for longer than 10 weeks, ay significantly increase adiponectin levels, even when controlling for numerous biological and sociological variables.

Insulin resistance is frequently defined as an impairment of insulin action on glucose, lipid and protein metabolism, and is closely associated with adipose tissue. Excessive visceral and subcutaneous adipose tissue causes adipocyte dysfunction which can result in inflammation through activation of JNK and NFκB. Such inflammation results in impaired adipokine secretion, manifest as decreased adiponectin and increased leptin levels (Castro; Shoelson). Adiponectin and leptin mediate insulin sensitivity through the AMPK (5´AMP-activated protein kinase) pathway. AMPK is considered a ‘master switch’ capable of controlling the energy status in a cell, and its activation resultantly enhances β-oxidation and reduced fatty acid esterification to triglycerides (Vettor). Moreover, several empirical investigations have asserted that leptin-to-adiponectin ratio my conceivably serve as an effective index of insulin resistance and atherogenic risk in both diabetic and non-diabetic

populations (Finucane; Zalatel). Moreover, there are also reports demonstrating the association between leptin-to-adiponectin ratio and low-grade inflammation, carotid *intima media* thickness, arterial stiffness, time of first cardiovascular event and number of metabolic syndrome components (Kappelle). It has been shown that curcumin can influence numerous components of metabolic syndrome, including insulin resistance, low HDL-C, hypertension and obesity. This is due to the reaction of phytochemical materials with various molecular targets, such as transcription factors, receptors, enzymes, growth factors, hormones, cell adhesion molecules, lipoproteins and anti-oxidants, which are involved in the pathophysiology of metabolic syndrome (Panahi et al. 2014; Sahebkar 2014). Qu et al. (2008) reported that culturing curcumin at a concentration of 100 μg/ml increased adiponectin secretion and lessened IL-6 secretion in cultured human adipose tissues (Qu et al. 2008), whilst the effect of curcumin on the expression of adiponectin in rodent models has also been documented. In Bai et al. (2013), 64 mice were trichotomized (control group, a group receiving 50 mg of curcumin and a group receiving 250 mg of curcumin for 11 weeks), and in the group receiving 250 mg of curcumin, a significant increase in adiponectin levels was observed compared to the control group (Bai et al. 2013). In another study in rodent models, Weisberg et al. found that the consumption of 30 % dietary curcumin for 10 weeks increased the adiponectin level (Weisberg et al. 2008).

As reported previously (Panahi; Panahi), and importantly, curcumin supplementation is safe. Moreover, curcumin has been approved by the United States FDA and considered a '*generally recognized as safe'* supplement, whilst its tolerability has been confirmed in several clinical studies. Therefore, owing to its safety and beneficial effects on several features of metabolic syndrome, and results of the present meta-analysis, curcumin may be suggested as a routine supplement for patients with metabolic syndrome, and other metabolic disorders.

Strength and limitations

The primary strength of this study was that this is the first meta-analysis to assess the impact of curcumin supplementation on adiponectin; and given the potential influence on clinical practice, this is a major finding. The evidence base, prior to this meta-analysis, was somewhat equivocal, and required a meta-analytical assessment, which we have provided. We demonstrated that there is sufficient evidence for curcumin supplementation to elicit significant, positive effects on adiponectin levels. A further strength of the current meta-analysis is the accrual of the heterogeneous sample of participants, with a range of demographic status', ethnicities and ages. We were also able to stratify analyses based on both duration of

supplementation and dosage, affording clinicians foresight into expected outcomes based on such information.

Notwithstanding, the current study has some limitations worth considering. The analyses were not restricted to solitarily include patients of one type; although this permitted a larger number of studies and participants to be included for analyses, there may be disease specific modulators to the efficacy of curcumin, which requires further investigation. Some included trials were relatively small in sample size, and it has been asserted by Sterne et al. that it is conceivable for studies with small sample sizes to report bigger effect sizes in intervention arms than studies with larger participant pools (Sterne), nevertheless, this was out of the operational control of the meta-analysis. A further limitation of the present study was the paucity of eligible studies, highlighting the need for a greater number of high-quality RCT's.

Conclusion

In conclusion, this systematic review and meta-analysis of randomized controlled clinical trials suggests that curcumin supplementation moderately increases circulating adiponectin. These findings support potential beneficial effects of curcumin supplementation on pathways related to adipocyte health and adiponectin metabolism.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

None.

Author Contribution

A.H and E.Gh carried out the concept, design, and drafting of this study. A.H AND E.Gh searched databases, screened articles and extracted data. A.H performed the acquisition, analysis, and interpretation of data. C.C critically revised the manuscript. All authors approved the final version of the manuscript. C.C and A.H are the guarantors of this study.

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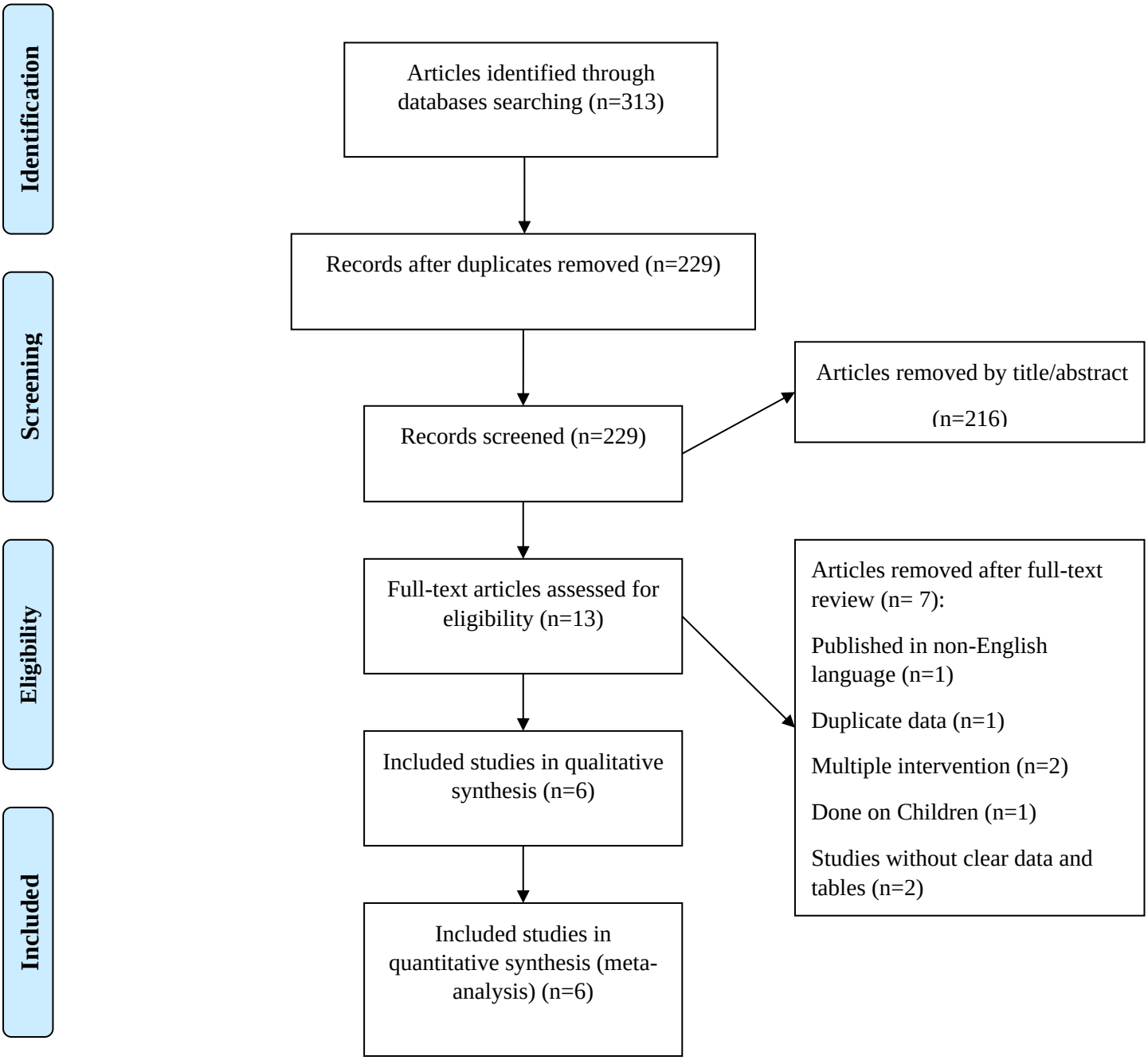
Identification
Screening
Eligibility
Included
Articles identified through databases searching (n=313)
Records after duplicates removed (n=229)
Records screened (n=229)
Articles removed by title/abstract (n=216)
Full-text articles assessed for eligibility (n=13)
Articles removed after full-text review (n= 7):
Published in non-English language (n=1)
Duplicate data (n=1)
Multiple intervention (n=2)
Done on Children (n=1)
Studies without clear data and tables (n=2)
Included studies in qualitative synthesis (n=6)
Included studies in quantitative synthesis (meta-analysis) (n=6)

Figure 1

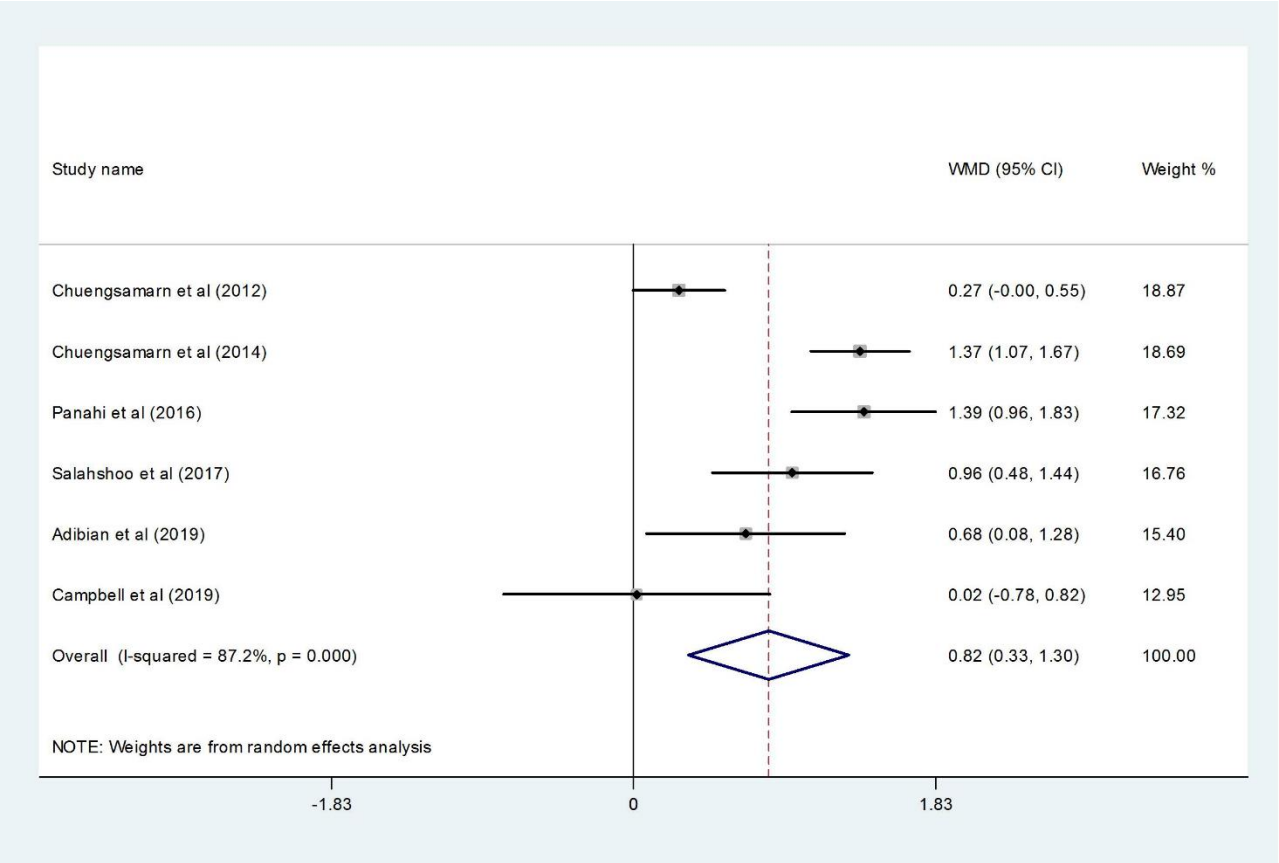
Study name
WMD (95% CI)
Weight %
Chuengsamarn et al (2012)
0.27 (-0.00, 0.55)
18.87
Chuengsamarn et al (2014)
1.37 (1.07, 1.67)
18.69
Panahi et al (2016)
1.39 (0.96, 1.83)
17.32
Salahshoo et al (2017)
0.96 (0.48, 1.44)
16.76
Adibian et al (2019)
0.68 (0.08, 1.28)
15.40
Campbell et al (2019)
0.02 (-0.78, 0.82)
12.95
Overall (I-squared = 87.2%, p = 0.000)
0.82 (0.33, 1.30)
100.00
NOTE: Weights are from random effects analysis
-1.83
0
1.83

Figure 2

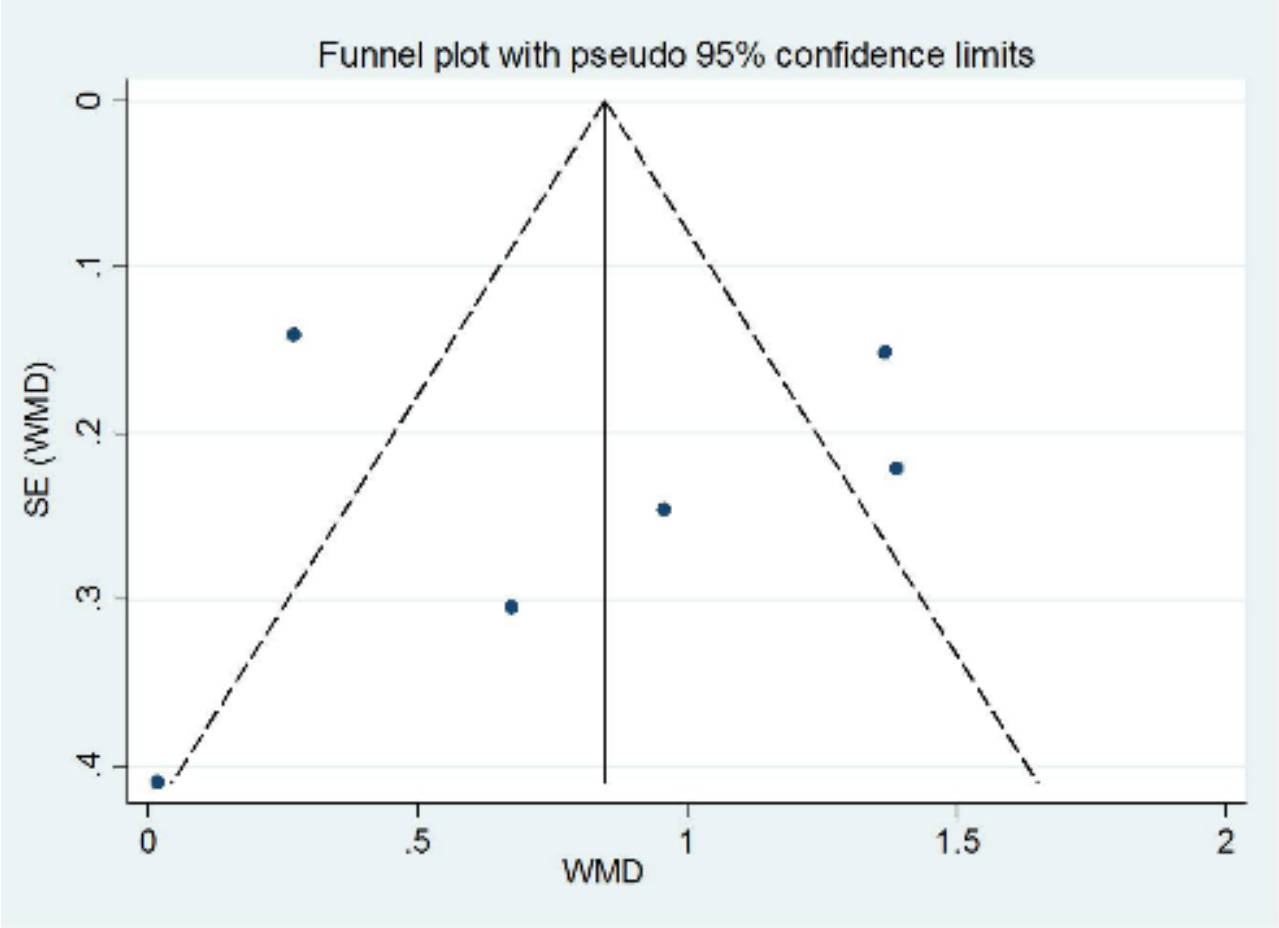
Funnel plot with pseudo 95% confidence limits
SE (WMD)
0
.1
.2
.3
.4
0
.5
1
1.5
2
WMD

Figure 3

Table 1. Characteristics of included trials

First author (publication year)	Country	Sample size	RCT design (Blinding)	Gender	Mean age (years)	Basline BMI (kg/m^2)	Patient Features	Duration (weeks)	Intervention	Comparison	Jadad score
Chuengsamarn et al (2012)	Thailand	201	Parallel (Double)	Both	56.95	26.6	Pre-diabetic	39	1500 mg/d curcuminods	Placebo	4
Chuengsamarn et al (2014)	Thailand	213	Parallel (Double)	Both	59.37	26.96	Type 2 diabetes	26	1500 mg/d curcuminods	Placebo	4
Panahi et al (2016)	Iran	100	Parallel (Double)	Both	44.13	24.13	Metabolic syndrome	8	1000 mg/d curcumin	Placebo	4
Salahshooh et al (2017)	Iran	72	Parallel (Double)	Both	38.2	31.1	Metabolic syndrome	6	1000 mg/d curcumin	Placebo	5
Campbell et al (2019)	USA	22	Parallel (Double)	Men	27.1	32.4	Obese	12	+ fenugreek200 mg/d curcuminoids fiber	Fenugreek fiber	4
Adibian et al (2019)	Iran	44	Parallel (Double)	Both	59.3	28.6	Type 2 diabetes	10	1500 mg/d curcumin	Placebo	5

Abbreviations: RCT, randomized controlled trial

Table 2. Subgroup analysis to assess the effect of curcumin supplementation on adiponectin level.

Sub-grouped by	**No. of trials**	**Effect size[1]**	**95% CI**	**I^2 (%)**	**P for heterogeneity**	**P for between subgroup heterogeneity**
Mean age (year)						**0.14**
<50	3	0.87	0.20, 1.54	77.3	0.01	
≥50	3	0.78	0.00, 1.55	92.9	<0.001	
Mean baseline BMI (kg/m^2)						**0.47**
<30	4	0.93	0.30, 1.56	91.3	<0.001	
≥30	2	0.55	-0.37,1.46	74.1	0.04	
Dose (mg/d)						**0.14**
≤1000	3	0.87	0.20, 1.54	77.3	0.01	
>1000	3	0.78	0.00, 1.55	92.9	<0.001	
Duration (week)						**0.05**
≤10	3	1.05	0.64, 1.45	49.5	0.13	
>10	3	0.59	-0.28, 1.47	93.6	<0.001	

[1]Calculated by Random-effects model
BMI: body mass index