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The effect of curcumin supplementation on circulating adiponectin and leptin concentration in adults: a GRADE-assessed systematic review and meta-analysis of randomised controlled trials

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Abstract

Curcumin is a phytocompound found in the root of turmeric, a common herbal ingredient in many Asian cuisines. The compound contains anti-inflammatory activity, which is mediated through an upregulation of adiponectin and reduction of leptin. Results of randomised controlled trials (RCT) have shown that the effects of curcumin on adipokines are conflicting. Therefore, the current systematic review and meta-analysis of RCT were conducted with the aim of elucidating the role of curcumin supplementation on serum adiponectin and leptin. The search included PubMed, Embase, Cochrane Library, Scopus, Web of Science and Google Scholar from inception to August 2023. For net changes in adipokines, standardised mean differences (SMD) were calculated using random effects models. Thirteen RCT with fourteen treatment arms were eligible for inclusion in this meta-analysis. Curcumin supplementation was effective in increasing serum adiponectin (SMD = 0·86, 95 % CI (0·33, 1·39), $P < 0·001$; $I^2 = 93·1\,\%$, $P < 0·001$) and reducing serum leptin (SMD = −1·42, 95 % CI (−2·29, −0·54), $P < 0·001$; $I^2 = 94·7\,\%$, $P < 0·001$). In conclusion, curcumin supplementation significantly increased circulating adiponectin and decreased leptin levels in adults.

Keywords: **Curcumin: Adipokine: Leptin: Adiponectin: Meta-analysis**

Over the past few decades, research on obesity and metabolic disorders has made significant advances. Adipose tissue is a dynamic endocrine organ that secretes a series of bioactive peptides so-called adipokines, such as adiponectin and leptin which regulate energy balance and create a balance between food intake and energy expenditure as the major contributors to obesity[1]. Adiponectin is the most common circulating hormone secreted by adipocytes. Several metabolic pathways, including the regulation of glucose metabolism, fatty acid oxidation and insulin action, are modulated by adiponectin[1,2]. Previous research has shown that people with CVD, metabolic syndrome (MetS) and type 2 diabetes have reduced adiponectin levels[3]. Decreased incidence of myocardial infarction in men is also associated with high plasma adiponectin levels[4]. Furthermore, adiponectin has been identified as an anti-inflammatory factor as it is negatively associated with the levels of inflammatory cytokines and mediators and free radicals[1,5]. Additionally, it inhibits foam cell growth and the expression of adhesion molecules while increasing nitric oxide production in the endothelium[6,7]. The high molecular weight version of adiponectin, as the most biologically active form of adiponectin, is also recognised as a risk indicator of MetS[8,9]. Leptin acts on the hypothalamus, a region of the brain that controls appetite and energy expenditure. Elevated serum leptin levels signal excessive energy storage to the central nervous system to suppress food intake and increase energy consumption, it also inhibits the secretion of neuropeptide Y and other proteins, which invoke appetite. In addition to its role in regulating appetite and body weight, leptin also plays a role in glucose metabolism. Leptin helps to regulate blood sugar levels by

Abbreviations: MetS, metabolic syndrome; RCT, randomised controlled trials; SMD, standard mean differences.

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promoting glucose uptake into tissues and enhancing insulin sensitivity. Moreover, leptin is related to the so-called 'low-grade inflammatory state' in obese people[10–12].

Curcumin is a principal curcuminoid compound found in turmeric and is a polyphenol that is mainly present in the dried rhizomes of *Curcuma longa L.* The yellowish colour and most of the medicinal properties of turmeric are attributed to this phytochemical and are often used in Asian cuisine[13]. Several studies have shown that curcumin can aid in the treatment of anxiety, arthritis, hyperlipidaemia, inflammatory diseases, oxidative stress, MetS and other illnesses[14–19]. Curcumin has recently been researched as an adjunctive treatment for various illnesses, including telogen effluvium and type 2 diabetes[20]. Curcumin provides antidiabetic benefits by increasing glucose uptake, glycogen synthesis and glycolysis in skeletal muscle, decreasing gluconeogenesis and increasing glycolysis and glycogen synthesis in the liver[21]. Curcumin has also been shown to reduce plasma TAG and cholesterol levels by increasing the activity of lipoprotein lipase and through pathways that alter the expression of genes related to lipid and cholesterol metabolism[22,23].

There is evidence that curcumin may stimulate lipolysis and regulate leptin secretion in rats due to its direct effect on the release of adipokines from adipocytes[24–26]. Moreover, curcumin can inhibit leptin receptor gene expression, as well as interrupts leptin signalling pathways[27–29]. Several meta-analyses have examined the effect of curcumin supplementation on adiponectin and leptin[30–32], although all of these studies were from before 2019. In addition, given the inconsistent findings of curcumin supplementation on adiponectin and leptin[33,34,35] and the lack of a comprehensive meta-analysis, we have further investigated their effects on adipokines in adults. Therefore, the present updated meta-analysis aimed to examine the effects of curcumin supplementation on the of adiponectin and leptin concentrations pooling from the selected randomised controlled trials (RCT) in adults.

Methods

This systematic review meta-analysis was carried out and reported under the Preferred Reporting Items of Systematic Reviews and Meta-Analysis statement guidelines[36]. The protocol of the present study has been approved by the ethics committee of Urmia University of Medical Sciences (identifier: IR.UMSU.REC.1402.213).

Search strategy

Scopus, PubMed, Embase, Cochrane Library, ISI Web of Science databases and Google Scholar were searched for RCT that investigated the effect of curcumin on adipokines (adiponectin and leptin) up to August 2023. We combined MESH and non-MESH terms to discover related studies, using terms such as (curcumin OR curcuminoid OR curcuminoids OR curcuma OR 'curcuma longa' OR tumeric OR turmeric) **AND** (adiponectin OR adipocytokines OR leptin). Two independent reviewers (VM and AHM) screened the articles based on the eligibility criteria. The first step included reviewing the titles and abstracts of the articles. In addition, the full texts of relevant articles were reviewed to determine whether the study was suitable for inclusion in the meta-analysis. All disagreements were resolved by the third author (AHF).

Eligibility criteria

The inclusion criteria were as follows: (1) RCT was used in the research (crossover or parallel design); (2) studies investigating the effects of curcumin on adiponectin and leptin concentrations; (3) studies with adult participants (age 18 years) and (4) studies providing adequate information on the baseline and end-trial plasma adipokines in both intervention and control groups. *In vitro*, *in vivo* and *ex vivo* studies, observational studies, quasi-experimental studies and studies without a control group were excluded from this meta-analysis. The study included only English-language articles.

Data extraction

(1) Name of the first author; (2) year of publication; (3) country where the study was conducted; (4) study design; (5) sample size in each group; (6) intervention assigned to the control group; (7) dose and type of curcumin; (8) intervention duration; (9) mean age, gender and baseline BMI of the participants and (10) the mean and SD of adiponectin and leptin in both intervention and placebo groups at the baseline, at the end of the study, and mean changes were extracted from the selected RCT.

Quality assessment

The risk of bias for each article was assessed using the risk of bias technique developed by the Cochrane collaboration. The tool contains seven items, including: allocation concealment, reporting bias, random sequence generation, attrition bias, performance bias, other sources of bias and detection bias. An 'uncertain risk' value was provided if the data were insufficient to predict the outcome. Each area was assigned a 'high risk' value if the research contained a methodological flaw that could affect the findings. A 'low-risk' grade is assigned if the domain has no defects. A study with all domains of low risk or only one domain of uncertain risk was considered as a high-quality study[37,38]. Two reviewers separately conducted risk of bias assessments.

Statistical analysis

The STATA program (version 16) was used to conduct statistical analysis (Stata Corp.). To assess the effect size for adipokines, SD and mean differences were determined for the intervention and control groups. Furthermore, a random-effects model was used to estimate the standard mean differences (SMD) with 95 % CI[39]. In studies that provided data as interquartile ranges, 95 % CI and SE, they were converted to means + SD. Cochran's Q test was performed to estimate heterogeneity between studies, and I-square (I^2) statistics were employed to evaluate it. I^2 scores above 50·5 % or P values < 0.1 were considered indicative of considerable heterogeneity between studies. We performed a sub-group analysis according to the baseline BMI (<30, ≥30), the study quality (high, low), the intervention duration (≤10, >10 weeks), type of curcumin, sample size (≤50, >50), the health

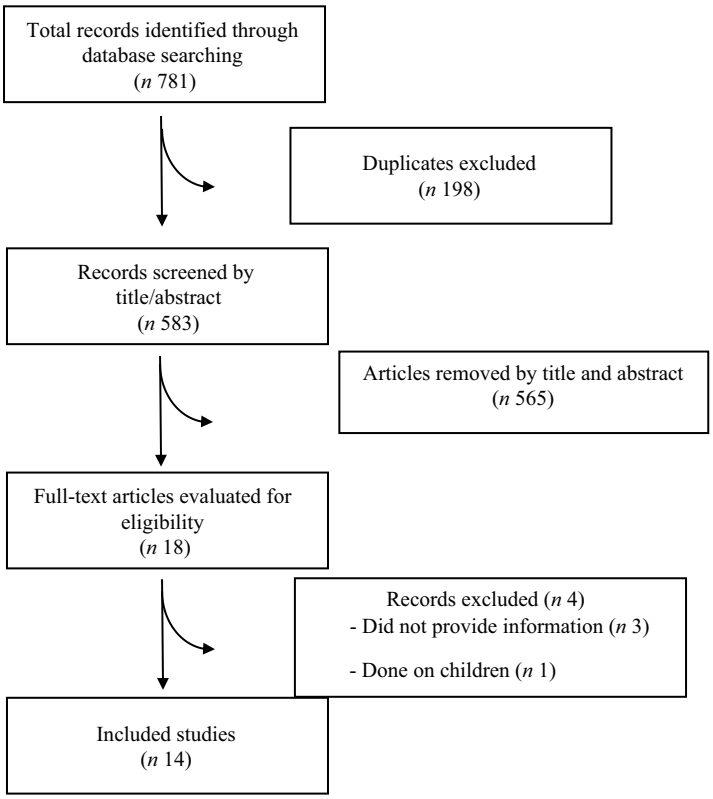

Fig. 1. Flow diagram of study selection.

condition (MetS, type 2 diabetes, non-alcoholic fatty liver disease, obesity and prediabetes) and mean age of participants (≤50, >50 years) to identify potential sources of heterogeneity. Sensitivity analyses were performed using the leave-one-out method to determine the effect of single RCT on the validity of the pooled SMD. Begg's adjusted rank correlation and Egger's regression asymmetry test were applied to examine the results of the small study effect[40,41]. The possible publication bias was assessed by visual inspection of funnel plots. In case of evidence of publication bias, the 'trim and fill' method was performed. *P* values below 0·05 were considered statistically significant in all analyses.

Result

Flow and characteristics of included studies

Following a multi-database search, after screening the titles and abstracts and removing (*n* 565) studies, full-text of eighteen studies were evaluated. Of these, four papers were removed for not assessing plasma adiponectin and leptin levels, and finally, fourteen studies were included in the systematic review and meta-analysis (Fig. 1). Ismail *et al.*'s[42] study was only presented as a systematic review due to the inconsistency of the informations in the tables. Finding showed that 0·5 g/d of curcumin for 4 weeks in obesity adults resulted in a significant reduction in leptin and increased adiponectin. Thus, thirteen RCT comprising fourteeen curcumin treatment arms were included in the final analysis. Included studies were published between 2012[43] and 2022[44]. Studies were conducted in the following countries: Iran[24,33–35,44–47], Thailand[43,48], Japan[49], the USA[50], Egypt[42] and Australia[51]. The range of intervention periods was from 1 week[35] to 9 months[43,48]. The total daily dose of curcumin consumption varied between 50 mg/d[34] and 3000 mg/d[33,46] across the studies. Most of the included RCT conducted in patients with DM[43,45,48,49], Mets[24,44,47], obesity[42,50] and non-alcoholic fatty liver disease[33,34,46]. The characteristics of the selected studies are shown in Table 1.

Risk of bias assessment and quality of evidence

In Table 2, the Cochrane criteria are used to evaluate the risk of bias in the included studies. Of the fourteen RCT included in the present study, nine had high quality[24,33,34,43–46,48,51] and four and one had moderate[35,42,49,50] and low quality[47], respectively. The GRADE quality of adiponectin and leptin evidence has been rated high (Table 3).

Curcumin on adiponectin concentrations

Result from eleven RCT comprising twelve treatment arms[24,34,35,43–50] showed a significant increase of plasma adiponectin concentrations following supplementation with curcumin (SMD = 0·86, 95 % CI (0·33, 1·39), $P < 0·001$) (Fig. 2(a)). The meaningful heterogeneity between trials was decreased by subgrouping based on BMI, health conditions and duration ($I^2 = 93·1$ %, $P < 0·001$). The reducing effect of curcumin on adiponectin levels was higher in MetS patients aged ≤ 50 years (Table 4). Moreover, the overall effects of

Table 1. Study characteristics of included studie

Citation (First author *et al.*)	Year	Location	Health condition	No. of participants in meta-analysis		Age (years)	BMI (kg/m^2)	Dose (mg/d)	Duration (week)
				n_int	n_con				
Chuengsamarn *et al.*[43]	2012	Thailand	Predibetes	119	116	56·9	26·6	1500	38
Chuengsamarn *et al.*[48]	2014	Thailand	T2D	107	106	59·1	27	1500	38
Lopresti *et al.*[51]	2015	Australia	Depression	25	25	48·4	NR	1000	8
Navekar *et al.*[33]	2016	Iran	NAFLD	21	21	42·09	31·81	3000	12
Ismail *et al.*[42]	2016	Egypt	Obesity	15	14	37·5	37·79	500	4
Panahi *et al.*[24]	2016	Iran	MetS	50	50	44·8	25·4	1000	8
Salahshooh *et al.*[47]	2017	Iran	MetS	36	36	37·52	30·67	1000	6
				37	36	40·05	30·66		
Campbell *et al.*[50]	2019	USA	MetS	M: 11	M: 11	27·1	32·4	200	12
Adibian *et al.*[45]	2019	Iran	Obese	21	23	59·3	28·6	1500	10
Mirhafez *et al.*[34]	2019	Iran	T2D	32	29	44·8	30·06	50	8
Funamoto *et al.*[49]	2019	Japan	T2D	15	18	70	25	90	25
Shadnoush *et al.*[35]	2020	Iran	Critically ill patients	31	31	40·77	25·43	500	1
Kalhori *et al.*[46]	2022	Iran	NAFLD	23	23	42	31·8	3000	12
Bateni *et al.*[44]	2022	Iran	MetS	22	21	50	29·9	80	12

NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes.

Table 2. Results of risk of bias assessment for RCT included in the current meta-analysis on the effects of curcumin supplementation on adiponectin and leptin levels

Study	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias	Other sources of bias
Chuengsamarn *et al.*[43]	L	L	L	L	L	L	L
Chuengsamarn *et al.*[48]	L	L	U	L	L	L	L
Lopresti *et al.*[51]	L	L	L	H	L	L	L
Navekar *et al.*[33]	L	L	L	L	L	L	L
Ismail *et al.*[42]	L	U	H	U	L	L	L
Panahi *et al.*[24]	L	L	L	L	U	L	L
Salahshooh *et al.*[47]	U	U	L	U	L	L	U
Campbell *et al.*[50]	L	U	L	L	U	L	L
Adibian *et al.*[45]	L	L	L	L	L	L	L
Mirhafez *et al.*[34]	L	L	L	L	L	L	L
Funamoto *et al.*[49]	L	L	L	L	U	L	U
Shadnoush *et al.*[35]	L	U	L	L	U	L	U
Kalhori *et al.*[46]	L	L	L	L	L	L	U
Bateni *et al.*[44]	L	L	L	L	L	L	L

RCT, randomised controlled trials.
Each study was assessed for risk of bias using the Cochrane risk of bias assessment tool. Domains of assessment were included random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias and other sources of bias. Each domain was scored as 'high risk' if it contained methodological flaws that may have affected the results, 'low risk' if the flaw was deemed inconsequential and 'unclear risk' if information was insufficient to determine. If a study got 'low risk' for all domains, it considered as a high-quality study with totally low risk of bias.

curcumin on adiponectin altered to not significant by excluding the Bateni *et al.*[44] study using one-study removal analysis (SMD = 0·41; 95 % CI (-0·09, 0·90), $P > 0·05$). Egger's and Begg's tests were shown no significant small-study effects ($P = 0·361$ and 0·537, respectively). The trim and fill methods were carried out following the uneven distribution of the funnel plot (SMD = 0·86, 95 % CI (0·33, 1·39), $P < 0·001$) (Fig. 2(b)).

Curcumin on leptin concentrations

Eight RCT[24,33–35,48–51] have investigated the impact of curcumin supplementation on leptin levels. The results showed a significant effect of curcumin supplementation on leptin levels reduction (SMD = −1·42, 95 % CI (−2·29, −0·54); $P < 0·001$) with between-study heterogeneity ($I^2 = 94·7$ %, $P < 0·001$) (Fig. 3). The mean age, sample size, health condition and intervention duration were recognised as sources of heterogeneity. Curcumin supplementation in studies with a sample size of >50 and intervention duration of ≤10 weeks on subjects aged ≤50 years and baseline BMI < 30 led to a higher reduction of leptin levels (Table 4). Sensitivity analysis showed that no single study likely affected the overall effect size. There was no significant publication bias according to the results of Begg's tests ($P = 0·386$).

Discussion

According to our findings, curcumin can be considered as a regulator of metabolic homeostasis from the aspect of balance

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Table 3. GRADE profile of curcumin supplementation for on plasma adipokines

	Summary of findings				Quality of evidence assessment (GRADE)					
Adipokines	No. of patients (trials)		SMD*	95 % CI	Risk of bias†	Inconsistency‡	Indirectness§	Imprecision‖	Publication bias¶	Quality of evidence**
Adiponectin	968	11	0·86	0·33, 1·39	Not serious	Not serious	Not serious	Not serious	Not serious	High
Leptin	627	8	−1·42	−2·29, −0·54	Not serious	Not serious	Not serious	Not serious	Not serious	High

* Presented as standard mean difference (SMD) all outcomes.
† Risk of bias based on the Cochrane risk of bias tool. This tool assesses selection bias, performance bias, detection bias, attrition bias and reporting bias. Five of eight included studies had incomplete outcome data (attrition bias). Half of included studies had performance bias.
‡ Downgraded if there was a substantial unexplained heterogeneity ($I^2 > 50$ %, $P < 0{\cdot}10$) that was unexplained by meta-regression or subgroup analyses.
§ Downgraded if there were factors present relating to the participants, interventions or outcomes that limited the generalisability of the results.
‖ There is evidence of significant effects of flaxseed supplementation on adiponectin and leptin (95 % CI including not zero).
¶ Downgraded if there was an evidence of publication bias using funnel plot that affected overall results detecting by trim and fill analysis.
** Since all included studies were randomised controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria. Quality was graded as high, moderate, low and very low.

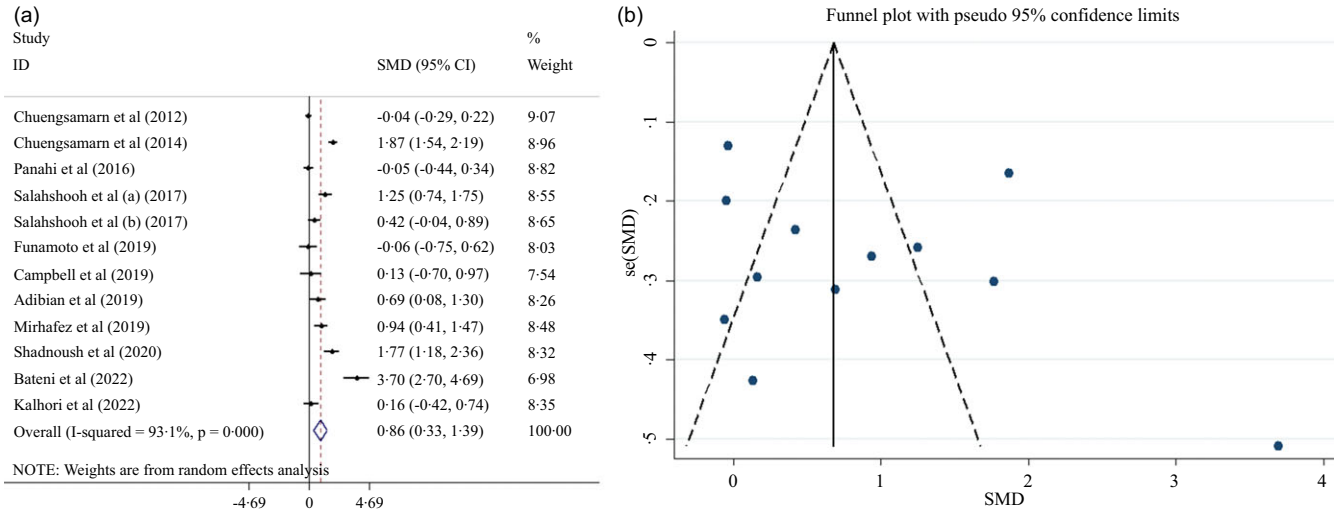

Fig. 2. Forest plot (a) funnel plot with mean difference and 95 % CI and (b) publication bias in the studies, the effects of curcumin supplementation on adiponectin levels.

between different adipokines, which are involved in many metabolic pathways including energy homoeostasis, obesity, inflammation, etc.[52]. Leptin is encoded by the obese (*ob*) gene. Leptin decreases in fasting conditions and increases in conditions of overfeeding to balance energy intake. However, it is known that obese people have hyperleptinaemia and leptin resistance. Also, there is a strong positive relationship between leptin levels and body fat percentage[53]. In addition to leptin resistance, changes in leptin protein function have been identified in obese individuals[54,55]. As a result, combining factors from leptin resistance to changing leptin function is effective in obesity. The decrease found in leptin level following curcumin supplementation can be due to its positive effect on leptin resistance[56]. However, more studies are needed in this regard. Adiponectin has a positive effect on insulin sensitivity, fatty acid oxidation, inflammation and oxidative stress and mitochondrial biogenesis[57]. As a result, a significant increase in adiponectin following curcumin supplementation can have positive effects on body homoeostasis.

There are several meta-analysis studies (three on adiponectin[58–60] and two on leptin[58,61]) that have investigated the effects of curcumin on adipokines. All these meta-analysis studies were from 2019 and earlier. Six additional original studies (five in adiponectin[34,35,44,46,62] and five in leptin[33–35,62,63]) were included in our study to obtain more comprehensive results. Moreover, none of previous meta-analysis studies have performed GRADE assessment to report certainly of evidence. Due to low number of studies, a limited subgroup analysis was performed in previous meta-analysis studies. Our comprehensive subgroup analysis can elucidate different aspects of curcumin effects on adipokines. In both investigated biomarkers, the results of high-quality studies were consistent with the overall results, indicating the validity of the obtained results.

Subgroup analysis revealed that curcumin mainly in the forms with high bioavailability (such as nano-curcumin, phospholipidated curcumin, theracurmin, curcumin+piperine or curcumin+soluble fiber) had increasing and decreasing effects on adiponectin and leptin levels, respectively, especially in patients mean age ≤50 years and BMI < 30 kg/m^2.

More noticeable effects of the highly bioavailable forms of curcumin on adipokines were not a surprising observation. One the biggest problem with curcumin is its poor bioavailability[64]. There are various methods to enhance the bioavailability of curcumin including addition of adjuvant, complexification,

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Table 4. Subgroup analyses for the effects of curcumin supplementation on plasma adipokines

Curcumin on adiponectin levels	No	SMD	95 % CI*	P_{within}†	I^2 (%)‡	$P_{heterogeneity}$§
Overall	12	0·86	0·33, 1·39	<0·001	93·1	<0·001
Age (year)						
≤50	7	1·11	0·39, 1·82	0·003	91·3	<0·001
>50	5	0·53	−0·37, 1·44	0·248	95·5	<0·001
BMI						
<30	7	1·08	0·23, 1·92	<0·001	95·9	<0·001
≥30	5	0·62	0·19, 1·05	<0·001	65·7	0·020
Type of curcumin						
Curcuminoid	3	0·84	−0·50, 2·18	0·218	97·6	<0·001
High bioavailability curcumin	8	0·96	0·30, 1·62	0·004	90·6	<0·001
Turmeric	1	0·16	−0·42, 0·74	0·589	–	–
Health condition						
Mets	4	1·24	0·12, 2·36	0·030	94·5	<0·001
NAFLD	2	0·56	−0·20, 1·32	0·151	73·4	0·053
T2DM	3	0·86	−0·33, 2·06	0·158	93·5	<0·001
Obesity	1	0·13	−0·70, 0·97	0·650	0·0	0·416
Prediabetes	1	−0·04	−0·29, 0·22	0·772	–	–
Critically ill patients	1	1·77	1·18, 2·36	<0·001	–	–
Sample size						
≤50	5	0·88	−0·18, 1·94	0·105	89·8	<0·001
>50	7	0·87	0·20, 1·54	<0·001	94·8	<0·001
Intervention duration (week)						
≤10	6	0·82	0·29, 1·35	0·003	84·9	<0·001
>10	6	0·92	−0·08, 1·92	0·070	96·1	<0·001
Quality study						
Low	5	0·71	0·02, 1·39	0·018	88·1	<0·001
High	7	0·99	0·17, 1·81	0·042	95·2	<0·001
Curcumin on leptin levels						
Overall	8	−1·42	−2·29, −0·54	<0·001	94·7	<0·001
Age (years)						
≤50	6	−2·22	−3·64, −0·81	<0·001	96·1	<0·001
>50	2	−0·72	−0·96, −0·47	<0·001	0·0	0·541
BMI						
<30	3	−7·19	−10·86, −3·51	<0·001	98·3	<0·001
≥30	3	−0·97	−1·55, −0·39	<0·001	54·5	0·111
NR	2	−0·65	−1·90, 0·60	0·308	92·5	<0·001
Type of curcumin						
Curcuminoid	2	−0·39	−1·06, 0·29	0·258	79·8	0·026
High bioavailability curcumin	5	−2·91	−4·67, −1·16	<0·001	96·6	<0·001
Turmeric	1	−1·55	−2·24, −0·86	<0·001	–	–
Health condition						
T2DM	2	−0·72	−0·96, −0·47	<0·001	0·0	0·541
NAFLD	2	−1·07	−1·95, −0·18	0·018	76·2	0·040
Obesity	1	−0·75	−1·62, 0·12	0·904	–	–
MetS	1	−1·27	−1·67, −0·87	<0·001	–	–
Depression	1	0·00	−0·55, 0·56	0·992	–	–
Critically ill patients	1	−35·09	−41·39, −28·79	<0·001	–	–
Sample size						
≤50	4	−0·79	−1·50, −0·08	0·029	75·7	0·006
>50	4	−2·79	−4·43, −1·15	<0·001	97·5	<0·001
Intervention duration (week)						
≤10	4	−3·52	−5·65, −1·39	<0·001	97·6	<0·001
>10	4	−0·92	−1·31, −0·53	<0·001	43·2	0·152
Quality study						
Low	3	−8·45	−12·86, −4·05	<0·001	98·2	<0·001
High	5	−0·72	−1·13, −0·32	<0·001	67·6	<0·001

SMD, standardised mean difference; NR, not reported; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus.
* Obtained from the random-effects model.
† Refers to the mean (95 % CI).
‡ Inconsistency, percentage of variation across studies due to heterogeneity.
§ Obtained from the *Q*-test.

specific formulations and nano-encapsulation[65]. Nanocrystals of curcumin have higher solubility and subsequently bioavailability than curcumin. Colloidal dispersion technology is used to increase bioavailability of curcumin in theracurmin form. Also phospholipid complexes of curcumin and a combination of curcumin with piperine are other ways to improve the bioavailability of curcumin[66]. However, piperine, itself, has various beneficial effects for health including anti-insulin resistance, anti-inflammatory and anti-hepatic steatosis effects[67]. Panahi *et al*. administered 5 mg piperine plus 500

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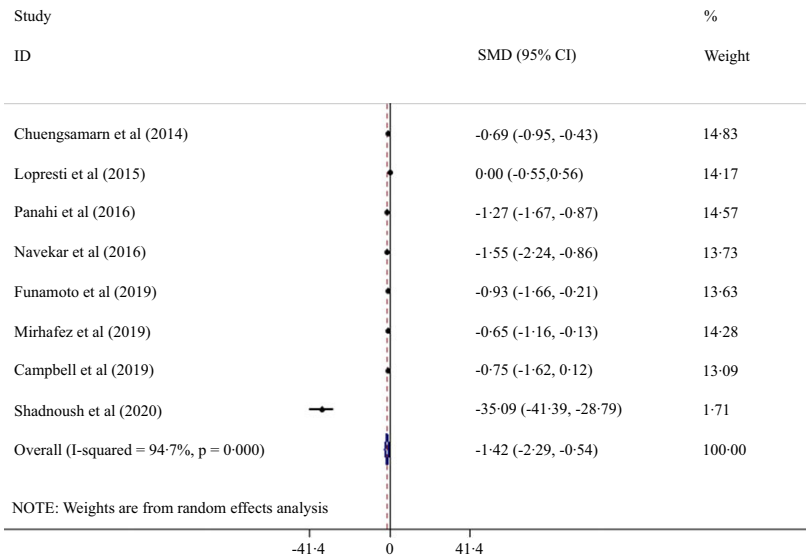

Fig. 3. Forest plot detailing mean difference and 95 % CI of the effects of curcumin supplementation on leptin levels.

mg curcumin twice a day and showed a significant increase in adiponectin and decrease in leptin level[24]. However, there is no clinical trial study investigating the effect of piperine alone on the levels of adipokines. Different mediators are affected by piperine such as NF-κB as a main transcription factor in inflammation and liver X receptor as a transcription factor in lipogenesis. Moreover, piperine inhibited the phosphorylation of insulin receptor substrate-1[67–69]. Therefore, through these pathways, piperine indirectly can regulate metabolism of adipokines.

Seven of seven and five of six studies on patients with a mean age ≤50 years in adiponectin and leptin pooled analyses administered curcumin in the highly bioavailable forms, respectively. Therefore, it cannot be concluded that the effect of curcumin on adipokines was in an age-dependent manner; therefore, all age groups can benefit from curcumin supplementation to decrease leptin and increase adiponectin.

Curcumin had a greater effect on patients with BMI < 30 kg/m^2. It has been found that there is an inverse and direct relationship between BMI and fat mass with adiponectin and leptin levels, respectively[70–72]. As a result, it seems that a higher dose of curcumin and its form with higher bioavailability are needed to affect the level of adipokines significantly in patients with higher BMI compared with normal weight patients.

In terms of study population, subgroup analysis revealed that curcumin supplementation in obese and prediabetes patients led to a non-significant change in adiponectin level. Similar results were observed regarding leptin levels for obese and depressed patients. As with BMI and age, curcuminoid administration with poor bioavailability could explain these inconsistent results compared with other health conditions. Therefore, additional studies on higher bioavailable forms of curcumin are needed to clarify the effect of curcumin on adipokines especially in obese patients. In conclusion, it seems that the prescribed form of curcumin and its dose are the main determinants of the effect of curcumin on adipokines. High doses of curcumin in a highly bioavailable form had a better effect on adipokines level. High doses require toxicological evaluation. However, according to the USA FDA recommendation, curcumin is considered safe supplement (GRAS Notice (GRN) No. 822).

The sample size of included studies is another important factor determining the true effect of curcumin on adipokines. Studies with large sample sizes have more power to show a true effect[73]. However, a very high sample size can also lead to false conclusions[74]. Contradictory results on adiponectin and leptin in different subgroups of intervention duration can be derived by different sample size in both subgroups. In terms of gender, Ostrowska *et al.* reported that serum adiponectin is higher in females[75]. However, as all studies have performed on both genders, subgroup analysis based on gender was not possible. Therefore, additional studies on each gender exclusively are needed.

Different mechanisms have been proposed for the effect of curcumin on adipokines. The anti-inflammatory mechanism of action of curcumin[76] can be one of the possible ways of its effect on the level of adipokines. Studies have shown that inflammation caused by an increase in visceral and subcutaneous fat can lead to suppression of adiponectin production from adipocytes[77]. Inflammatory cytokines such as TNF-α have also stimulatory effects on leptin production[78]. Various studies have pointed out the inhibitory effects of curcumin on NF-κB signalling pathways as the main regulatory switcher of inflammatory pathways in cells[79,80]. Another possible effect of curcumin on adipokines can be related to transcription factors such as peroxisome proliferator-activated receptor-γ (PPARγ)[81], sterol regulatory element-binding transcription factor 1[82], and CCAAT/enhancer-binding protein (C/EBP)[83] which affect the secretion of adipokines[84]. These transcription factors have various functions in the body including regulation of lipid metabolism, insulin sensitivity, inflammation and adipocyte differentiation. Therefore, they can affect the metabolism of adipokines through these actions. Adipokines can also affect the

expression of these transcription factors. However, these effects are contradictory in different studies[85,86]. Moreover, additional studies are needed to discover other molecular targets of curcumin in adipokine-related pathways.

There are some limitations in our study worth noting. First, due to the lack of studies on each gender, subgroup analysis was not performed in this issue. Second, there is a limited number of studies on certain health conditions such as prediabetes, depression and critically ill patients. Further studies on other diseases whose pathogenesis is related to adipokines, such as cardivascular diseases, inflammatory conditions and malignant diseases, are needed to clarify other aspects of curcumin effects on adipokines. Third, only leptin and adiponectin have been investigated in the included studies. Therefore, investigations on the effects of curcumin on other adipokines such as visfatin and resistin seem necessary. Our study also has some worth-noted strengths. First, the present study tried to cover all the limitations of the previous meta-analysis. Second, due to the low risk of bias in the included studies and the appropriate design of the current meta-analysis, quality of our obtained results was high for both leptin and adiponectin. Third, our study was registered in PROSPERO (code: CRD42023393664).

Conclusion

Our results suggest that curcumin supplementation can decrease and increase circulating leptin and adiponectin, respectively. High doses of curcumin (up to 3000 mg/d in tumeric form, 1500 mg/d in curcuminoid form and 1000 mg/d in highly bioavailable form) in a highly bioavailable form including nano-curcumin, phospholipidated curcumin, theracurmin, curcumin+piperine or curcumin+soluble fiber has a better effect on adipokines level. Doses higher than 3000 mg/d need to be evaluated in terms of safety. However, according to the USA FDA recommendation, curcumin is considered safe supplement (GRAS Notice (GRN) No. 822).

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