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Curcumin supplementation contributes to relieving anthropometric and glycemic indices, as an adjunct therapy: A *meta*-research review of *meta*-analyses

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ABSTRACT

Background: Curcumin, a natural polyphenolic compound, can affect anthropometric and glycemic indices; however, the findings of existing *meta*-analyses are controversial.
Study design: The current umbrella *meta*-analysis was performed among present systematic reviews and *meta*-analyses to investigate the effect of curcumin supplementation on anthropometric and glycemic indices.
Methods: A comprehensive systematic search was performed on Embase, PubMed, WOS, Scopus, and Cochrane Library to obtain peer-reviewed papers published before 30/November/2021. meta-analysis was conducted using the random-effects model.
Results: 12 *meta*-analyses were included in the current study. Our results have revealed that the curcumin supplementation can significantly decrease body mass index (BMI) (ES: −0.26; 95 % CI: −0.38, −0.14, $p < 0.001$; $I^2 = 0.0$ %, $P = 0.842$), body weight (BW) (ES: −0.55; 95 % CI: −0.99, −0.12, $p = 0.013$; $I^2 = 81.1$ %, $p < 0.001$), waist circumference (WC) (ES: −0.66; 95 % CI: −1.23, −0.09, $p = 0.023$; $I^2 = 72.4$ %, $p = 0.003$), fasting blood sugar (FBS) (ES: −1.63; 95 % CI: −2.36, −0.89, $p < 0.001$; $I^2 = 88.4$ %, $p < 0.001$), homeostasis model assessment-estimated insulin resistance (HOMA-IR) (ES: −0.38; 95 % CI: −0.48, −0.28, $p < 0.001$;$I^2 = 35.9$ %, $p = 0.142$), hemoglobin A1c (HbA1c) (ES: −0.44; 95 % CI: −0.67, −0.21, $p < 0.001$;$I^2 = 65.0$ %, $p = 0.014$), and insulin (ES: −0.86; 95 % CI: −1.52, −0.21, $p = 0.010$; $I^2 = 92.5$ %, $p < 0.001$).
Conclusion: These findings recommend curcumin supplementation as a favorable intervention to improve anthropometric and glycemic indices.

Abbreviations: **BMI**, Body Mass Index; **BW**, Body Weight; **WC**, Waist Circumference; **FBS**, Fasting Blood Sugar; **HbA1c**, Hemoglobin A1c; **T2DM**, Type 2 Diabetes Mellitus; **GRADE**, Grading of Recommendations, Assessment, Development, and Evaluations; **PCOS**, Polycystic Ovary Syndrome; **FDA**, Food And Drug Administration; **GRAS**, Generally Recognized As Safe; **EFSA**, European Food Safety Authority; **NAFLD**, Nonalcoholic Fatty Liver Disease; **SREBP1**, Sterol Regulatory Element-Binding Protein; **ACAT**, Acyl-CoA, Cholesterol AcylTransferase; **CPT1**, Carnitine PalmitoylTransferase 1; **AMPK**, AMP-activated Protein Kinase; **SIRT1**, Sirtuin 1; **PPAR-γ**, Peroxisome Proliferator-Activated Receptor-Gamma; **CCAAT**, Cytosine-Cytosine-Adenine-Adenosine-Thymidine; **C/EBPα**, Enhancer Binding Proteinα; **GLP-1**, Glucagon-Like Peptide-1; **DPP-4**, DiPeptidyl Peptidase-4; **GLUT**, Glucose Transporter; FNDC5, FibroNectin type 3 Domain-Containing protein 5; **p38MAPK**, p38 Mitogen-Activated Protein Kinase; **ERK**, Extracellular signal-Related Kinase.

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1. Introduction

Obesity has been recognized as a causative factor for insulin resistance and hyperglycemia in type 2 diabetes mellitus (T2DM) (Wellen & Hotamisligil, 2005). Indeed, obesity-mediated T2DM can become a significant healthcare issue by 2030 (Martyn et al., 2008; Wild et al., 2004).

Weight loss and lifestyle modifications are effective strategies for glycemic control; however, diabetes medications must be administered (Chaudhury et al., 2017; Ríos et al., 2015). Numerous pharmacotherapies have been demonstrated to improve glycemic control, but they are also known to cause complications and side effects such as allergic reactions, gastrointestinal problems, acidosis etc. (Ríos et al., 2015; Verma et al., 2018). Hence, nutraceuticals, such as dietary supplements, can be used as adjuncts or alternative treatments for glycemic control (Ríos et al., 2015; Srinivasan, 2005).

Curcumin is a bioactive polyphenol compound from the rhizome of turmeric (Curcuma longa) (Alagawany et al., 2021; Naeini et al., 2022). It has been shown that the significant effects of Curcuma longa are primarily due to curcumin (Pulido-Moran et al., 2016). Natural foods such as curry and mustard sauce contain curcumin, which is also widely used in food processing and cosmetics as a preservative and coloring agent. For the first time in 1949, it was discovered as an antibacterial compound (Simental-Mendía et al., 2019). Asians use it for medical purposes due to its effectiveness and safety (Jalali et al., 2020). Some beneficial effects of curcumin have been revealed, including antidiabetic properties, antioxidant properties, and anti-inflammatory properties (Kalpana & Menon, 2004; Tsuda, 2018). Curcumin can have beneficial roles in some chronic illnesses, e.g., coronary artery disease, atherosclerosis, rheumatoid arthritis, obesity, and T2DM (Aggarwal & Harikumar, 2009; Karimi et al., 2022). The beneficial role of curcumin on glycemic control is due to its inhibitory effect on hepatic gluconeogenesis, glycogenesis, and hyperglycemia-mediated inflammation development (Ghorbani et al., 2014). Besides, it has been reported that curcumin can decrease angiogenesis in adipose tissue (Pivari et al., 2019; Seo et al., 2008), decrease pre-adipocyte differentiation by increasing resting energy expenditure by activating peroxisome proliferator- activated receptor gamma (PPAR-γ((İçer & Tek, 2021; Seo et al., 2008), reduce adipogenic genes expression (Kim et al., 2011; Lee et al., 2009), and inhibit cortisol-mediated central obesity (Hu et al., 2013). The beneficial role of curcumin on glycemic control may be stemmed from its inhibitory effect on the phosphorylation kinase enzyme involved in glycogen storage mobilization (Razavi et al., 2021). It has been demonstrated that curcumin can substantially lower FBS and HbA1c levels (Tabrizi et al., 2018; Wei et al., 2019).

Despite these promising results of curcumin on glycemic control, some studies have indicated that curcumin supplementation can not improve glycemic control (Rahimi et al., 2016; Yang et al., 2014). Although some studies have shown that curcumin can play a pivotal role in the management of obesity or overweight (Akbari et al., 2019; Di Pierro et al., 2015; Rahmani et al., 2016), there are reports indicating that curcumin intake can not affect anthropometric indices such as BMI, BW, and WC (Ghazimoradi et al., 2017; Jafarirad et al., 2019; Jalali et al., 2020; Saadati et al., 2019). Given the inconsistency, the current umbrella *meta*-analysis aimed to investigate the effect of curcumin on glycemic profile and anthropometric parameters.

2. Methods

The current study was performed and reported according to the guiding principle of the preferred reporting items for systematic reviews and *meta*-analysis (PRISMA)(Moher et al., 2015). The protocol of this study has been registered in the international prospective register of systematic reviews (PROSPERO) under number **CRD42022302628**.

2.1. Search strategy

Embase, PubMed, Web of Science, Scopus, and Cochrane Central Library were systematically searched to obtain relevant published before 30th November 2021. The following MeSH and keywords were used:)"curcumin" [Mesh] OR "curcumin"[tiab] OR "curcuminoid"[tiab] OR "turmeric"[tiab]) **AND** ("blood glucose" OR "Glucose" [tiab] OR "Sugar" [tiab] OR "FBS" [tiab] OR "Insulin" [tiab] OR "HOMA-IR" [tiab] OR "insulin resistance" OR "QUICKI" [tiab] OR "insulin sensitivity" [tiab] OR "HbA1c" [tiab] OR "body weight" [tiab] OR "body weight changes" [tiab] OR "body mass index" [tiab] OR "weight loss" [tiab] OR "obesity" [tiab] OR "body weight" [tiab] OR "body mass index" [tiab] OR "BMI" [tiab] OR "waist circumference" [tiab] OR "WC" [tiab]) **AND** ("systematic review" [tiab] OR "*meta*-analysis"). The wild-card term"*" was utilized to increase the sensitivity of our systematic search. Besides, a manual search of the references of eligible studies was done to minimize the risk of missing relevant papers.

2.2. Inclusion and exclusion criteria

Systematic reviews and *meta*-analyses that have provided effect sizes and confidence intervals of curcumin supplementation on anthropometric and glycemic indices have been included in the current umbrella *meta*-analysis. Other studies were excluded from the umbrella *meta*-analysis, including case reports, experimental studies, observational studies, in vitro, ex-vivo, and in vivo investigations have been. Also, the studies that have been published in English languages were included in the current study.

2.3. Study selection

The retrieved records were independently reviewed by two authors in two phases (VM and MK). In the first phase, the titles and abstracts of the papers for the considering to be included in the current study. In the second phase, the full text of the remaining records was reviewed. Any disagreements were resolved via consulting with AHF.

2.4. Data extraction

The following data were extracted from the included papers: the first author's name, sample size, year of publication, curcumin dosage, the duration of the intervention, effect sizes, and the confidence intervals of the effect sizes.

2.5. Quality assessment

We applied the assessment of multiple systematic reviews (AMSTAR) questionnaire to assess the quality of the included studies. The AMSTAR method comprises 11 questions to which reviewers must respond with yes, cannot answer, no, or not applicable. Records with a score of ≥ 8 and 4–7 are considered high and moderate quality, respectively (Shea et al., 2007). Two authors, i.e., VM and MK independently evaluated the methodological quality of the included studies. Any disagreements were resolved via consulting with AHF.

2.6. Data synthesis and statistical analysis

The overall effect size was calculated using the reported effect sizes and confidence intervals. The I^2 statistic and Cochrane's Q test were used to evaluate potential heterogeneity. Significant between-study heterogeneity was defined as an I^2 value > 50 % or $p < 0.1$ for the Q-test. A random-effects model was used if the between-study heterogeneity was significant ($I^2 > 50$ % or $P < 0.1$). Subgroup analyses were done to find possible sources of heterogeneity according to the predefined variables, e.g., curcumin dosage, participants' age, health condition, duration of intervention, and sample size. Sensitivity analysis

was conducted to determine whether the overall effect size was dependent on a specific study. Besides the visual evaluation of the funnel plots, We used Egger's and Begg's tests to investigate potential publication bias (Begg & Mazumdar, 1994; Egger et al., 1997). Trim and fill analysis was used to construct a model without publication bias, displaying a new effect size. STATA version 16.0 was used to conduct all statistical analyses (Stata Corporation, College Station, TX). A $p < 0.05$ was considered significant.

2.7. Certainty of the assessment

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool was used to assess the overall certainty of the evidence in the included *meta*-analyses. The quality of evidence was categorized into four categories based on evaluation criteria, i.e., high, moderate, low, and very low (Guyatt et al., 2008).

3. Results

3.1. Study selection

Following the systematic search on the mentioned databases, 432 records were identified. After removing 97 duplicate papers, the titles and abstracts of the remaining 335 papers were thoroughly reviewed. Afterward, 24 papers were selected for full-text evaluation. Finally, 12 papers met our inclusion criteria and were included in the current study (Akbari et al., 2019; Abdelazeem et al., 2022; Altobelli et al., 2021; Ashtary-Larky et al., 2021; Azhdari, Karandish, & Mansoori, 2019; Chien et al., 2021; Jafarirad et al., 2019; Jalali et al., 2020; Simental-Mendía et al., 2021; Tabrizi et al., 2018; Wei et al., 2019; Zhang et al., 2021). The PRISMA flow chart schematically demonstrates the study selection process (Fig. 1).

3.2. Study characteristics

Participants of these studies had type 2 diabetes mellitus (Altobelli et al., 2021; Zhang et al., 2021), polycystic ovary syndrome (Abdelazeem et al., 2022; Chien et al., 2021; Simental-Mendía et al., 2021), non-alcoholic fatty liver disease (Jafarirad et al., 2019; Jalali et al., 2020; Wei et al., 2019), metabolic syndrome (Akbari et al., 2019; Azhdari et al., 2019; Tabrizi et al., 2018), and cardiovascular disease (Ashtary-Larky et al., 2021). The sample size in the studies ranged between 168 and 2,629. The participants' average age was between 29 and 57.5 years, and the duration of intervention was between 6 and 19 weeks. Administered curcumin dosages were between 0.08 g/day and 1.5 g/day. Table 1 shows the characteristics of the included studies.

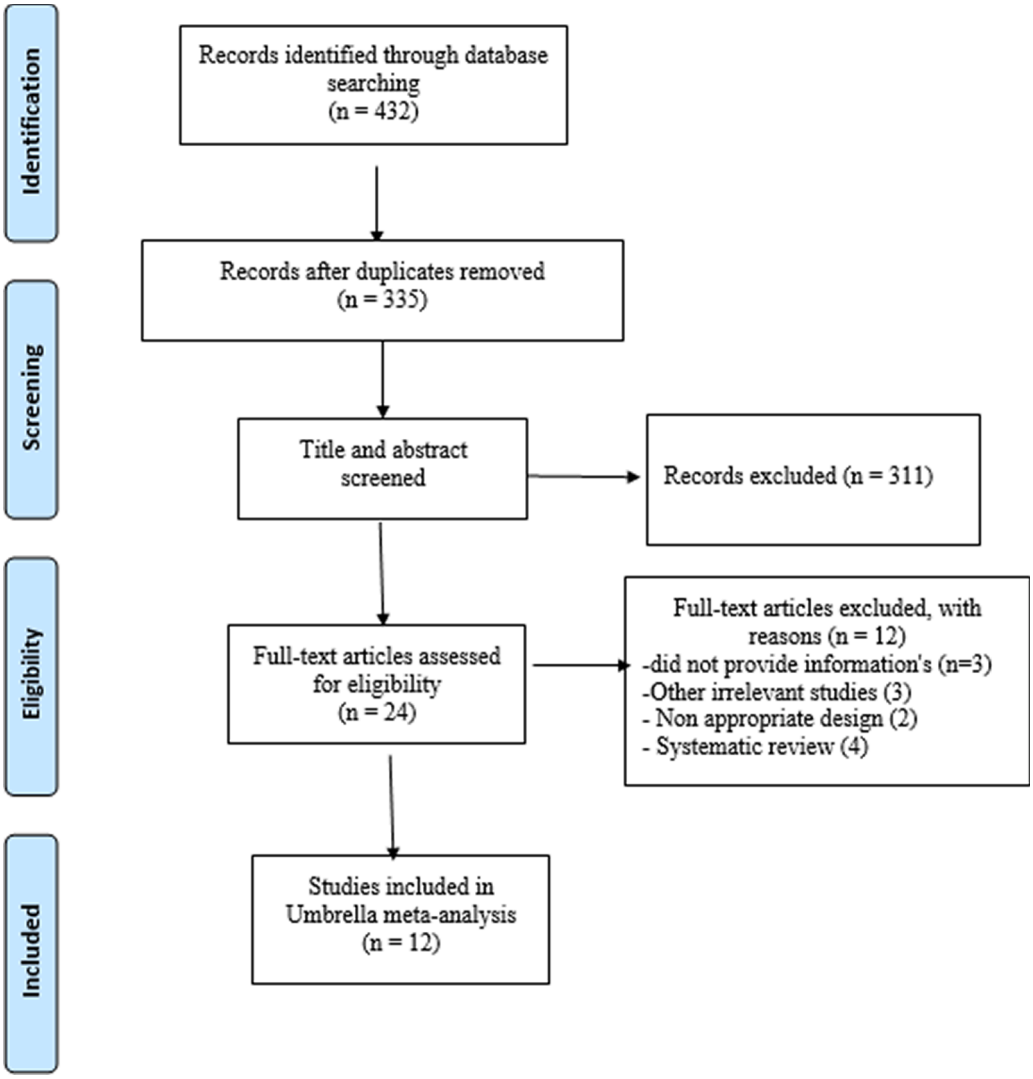

Fig. 1. PRISMA flow diagram of selection studies.

Table 1
Study characteristics of included studies.

Citation (First author et al., year)	No. of Studies in meta-analysis	Country Duration	No. of Participants in Meta-analysis	Mean age	Duration of intervention	Intervention/ daily dose	Quality Assessment Scale and Outcome	Measured outcomes and Results
Abdelazeem et al., 2022	5	USA 10 week	622 with PCOS	29	10 weeks	Curcumin / 0.6–1 g/d	Yes (Cochrane) 3/5 high	BMI → not significant effect Weight → not significant effect WC → not significant effect Insulin → ↓ HOMA-IR → ↓ FBS → ↓
Altobelli et al., 2021	7	Italy NR	954 with T2DM	57.5	Not reported	Curcumin / 0.963–1.2 g/d	No	BMI → not significant effect HOMA-IR → ↓ HbA1C → ↓
Jafarirad et al., 2019	8	Iran 14.5 week	1012 with NAFLD	47.6	10.6–14.6 weeks	Curcumin / 1.1–1.5 g/d	Yes (Cochrane) 7/8 high	BMI → not significant effect Weight → not significant effect WC → not significant effect
Ashtary-larky et al.2021	9	Iran 9.5 week	1114 with CVD	50	9.5 weeks	Curcumin / 0.08–0.8 g/d	Yes (Cochrane) 5/9 high	BMI → not significant effect Weight → not significant effect WC → not significant effect FBS → ↓ HOMA-IR → ↓ Insulin → ↓ HbA1C → not significant effect
Akbari et al.2019	18	Iran 7.8 week	2629 with metabolic syndrome	41.7	7.8–12 weeks	Curcumin / 1.1–1.2 g/d	Yes (Cochrane) 16/18 high	BMI → ↓ Weight → ↓ WC → ↓
Jalali et al., 2020	9	Iran 10.3 week	1921 with NAFLD	33–47	10–11 weeks	Curcumin / 0.16–0.8 g/d	Yes (Jadad) 7/9 high	BMI → not significant effect Weight → not significant effect WC → ↓ FBS → ↓ HOMA-IR → ↓ Insulin → ↓ HbA1C → not significant effect
Wei et al., 2019	4	China 10 week	647 with NAFLD	43.5–46.5	8–10 weeks	Curcumin / 0.75–2 g/d	Yes (Cochrane) 3/4 high	Weight → ↓ FBS → ↓ HOMA-IR → ↓ HbA1C → not significant effect Insulin → not significant effect
Azhdari et al., 2019	7	Iran 6.5 week	244 with metabolic syndrome	43–47	6.5–8.5 weeks	Curcumin / 1.4 g/d	Yes (Cochrane) 6/7 high	WC → not significant effect FBS → not significant effect
Chien et al., 2021	3	Taiwan 10 week	168 with PCOS	30	10 weeks	Curcumin / 1.5 g/d	Yes (Cochrane) 3/3 high	FBS → ↓ HOMA-IR → ↓ Insulin → ↓
Tabrizi et al., 2018	26	Iran 6–13 week	1695 with metabolic syndrome	Not repoered	6–13 weeks	Curcumin / 1–1.1 g/d	Yes (Cochrane) 24/26 high	FBS → ↓ HOMA-IR → ↓ HbA1C → ↓ Insulin → not significant effect
Zhang et al., 2021	12	China 12–14 week	1501 with T2DM	54	12–14 weeks	Curcumin / 0.9–1.1 g/d	Yes (Cochrane) 10/12 high	FBS → not significant effect HOMA-IR → not significant effect

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Table 1 (*continued*)

Citation (First author et al., year)	No. of Studies in meta-analysis	Country Duration	No. of Participants in Meta-analysis	Mean age	Duration of intervention	Intervention/ daily dose	Quality Assessment Scale and Outcome	Measured outcomes and Results
								HbA1C → ↓
Simental-Mendía et al., 2021	5	Iran 6–12 week	296 with PCOS	Not repoered	6–12 weeks	Curcumin/ 0.08–1.5 g/d	Yes (Cochrane) 2/5 high	FBS → ↓ Insulin → ↓ HOMA-IR → ↓

BMI, body mass index; WC, waist circumference; HOMA-IR, homeostatic model assessment for insulin resistance; FBS, fasting blood sugar; PCOS, polycystic ovary syndrome; NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular diseases; T2DM, type 2 diabetes mellitus; NR, not reported.

3.3. Assessing the risk of bias

Suppl. Table 1 shows the results of the AMSTAR questionnaire-based quality assessment of the included studies. Based on the AMSTAR questionnaire, 12 papers were of high quality, and one were of moderate quality.

3.4. The effect of curcumin supplementation on BMI

Curcumin supplementation has significantly decreased body mass index (BMI) (kg/m^2) (ES: −0.26; 95 % CI: −0.38, −0.14, and p < 0.001) (Fig. 2). Besides, the between-study heterogeneity has not been significant (I^2 = 0.0 %, and p = 0.842). The subgroup analysis indicated that the dosage of curcumin supplementation > 1 g/day has a more beneficial effect on decreasing BMI score (Table 2). Based on sensitivity analysis, no significant change has been detected following removing one single study. Based on Begg's test, no significant publication bias has been detected (p = 0.999). Based on GRADE criteria, the related quality of this evidence has been estimated as moderate due to indirectness (**Suppl.** Table 2).

3.5. The effect of curcumin supplementation on BW

Curcumin supplementation has significantly decreased body weight (BW) (kg) (ES: −0.55; 95 % CI: −0.99, −0.12, and p = 0.013) (Fig. 3**A**). However, significant between-study heterogeneity has been detected (I^2 = 81.1 %, and p < 0.001). The dosage of curcumin, duration of intervention, sample size, mean age, and health condition have been identified as sources of the high heterogeneity (Table 2). After excluding the study by Akbari et al. (Akbari et al., 2019), the overall effect of curcumin supplementation on BW has been more remarkable (ES: −0.77; 95 % CI: −1.64, −0.12, and p = 0.013). Begg's test has shown no significant publication bias (p = 0.707). Based on GRADE criteria, the related quality of this evidence has been estimated as moderate due to indirectness (**Suppl.** Table 2).

3.6. The effect of curcumin supplementation on WC

Curcumin supplementation has significantly decreased waist circumference (WC) (cm) (ES: −0.66; 95 % CI: −1.23, −0.09, and p = 0.023) (Fig. 3**B**). Our results have indicated significant between-study heterogeneity (I^2 = 72.4 %, and p = 0.003). The duration of intervention, and age have been identified as sources of high heterogeneity (Table 2). Curcumin supplementation in dosage of ≤ 1 g/day has substantially decreased WC (Table 2). Based on sensitivity analysis, no significant change has been detected following removing one single study. Based on Begg's test, no significant publication bias has been detected (p = 0.707). Based on the GRADE criteria, the overall quality of this evidence has been considered moderate due to a serious indirectness (**Suppl.** Table 2).

3.7. The effect of curcumin supplementation on FBS

Curcumin supplementation has significantly decreased fasting blood sugar (FBS) (mg/dl) (ES: −1.63; 95 % CI: −2.36, −0.89, p < 0.001) (Fig. 4). Our results have shown significant between-study heterogeneity (I^2 = 88.4 %, and p < 0.001). The dosage of curcumin, duration of intervention, sample size, and health condition have been identified as

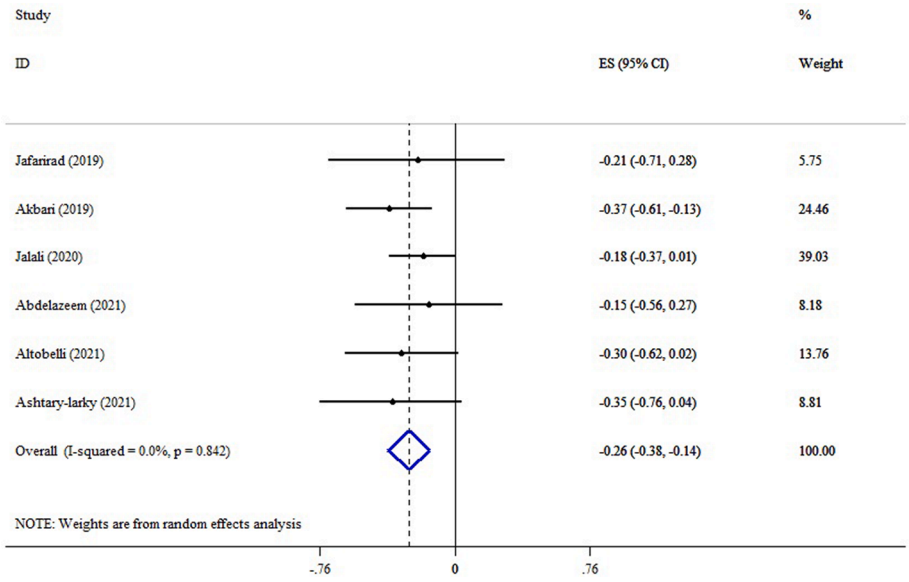

Fig. 2. Forest plot (A) funnel plot with a mean difference and 95% confidence intervals (CIs), the impacts of curcumin supplementation on BMI.

Table 2
Subgroup analysis based on different characteristics.

Variables	No. study	Pooled effect size (95 % CI)	P-value	I^2(%)	P heterogeneity
BMI					
Dosage (g/day)	3	−0.20 (-0.36, −0.04)	0.012	0.0	0.727
≤1 g	3	−0.33 (-0.51, −0.15)	0.000	0.0	0.833
>1 g					
Sample size					
>500	1	−0.37 (-0.61, −0.13)	0.003	-	-
≤500	5	−0.22 (-0.36, −0.08)	0.002	0.0	0.921
Age					
>50	2	−0.32 (-0.57, −0.07)	0.012	0.0	0.848
≤50	4	−0.24 (-0.37, −0.10)	0.001	0.0	0.636
Duration					
> 10 weeks	2	−0.18 (-0.36, −0.01)	0.042	0.0	0.912
≤ 10 weeks	3	−0.32 (-0.51, −0.14)	0.001	0.0	0.660
Not reported	1	−0.30 (-0.62, 0.02)	0.066	-	-
Health condition	2	−0.18 (-0.36, −0.01)	0.042	0.0	0.912
NAFLD	1	−0.30 (-0.62, 0.02)	0.062	-	-
T2DM	1	−0.15 (-0.56, 0.26)	0.479	-	-
PCOS	1	−0.35 (-0.75, 0.05)	0.086	-	-
CVDs	1	−0.37 (-0.61, −0.13)	0.003	-	-
MetS					
Weight					
Dosage (g/day)	3	−1.03 (-2.58, 0.52)	0.192	91.0	0.000
>1 g	3	−0.10 (-0.31, 0.10)	0.325	0.0	0.381
≤1 g					
Sample size					
>500	1	−0.23 (-0.40, −0.07)	0.006	-	-
≤500	5	−0.77 (-1.64, 0.10)	0.084	84.8	0.000
Age					
>50	1	−0.51 (-1.85, 0.83)	0.454	-	-
≤50	5	−0.23 (-0.36, −0.10)	0.000	84.8	0.000
Health condition	3	−0.96 (-2.64, 0.72)	0.066	92.2	0.000
NAFLD	1	−0.50 (-1.17, 0.17)	0.144	-	-
PCOS	1	−0.51 (-1.85, 0.83)	0.454	-	-
CVDs	1	−0.23 (-0.40, −0.07)	0.006	-	-
MetS					
WC					
Dosage (g/day)	3	−0.26 (-0.45, −0.06)	0.010	0.0	0.895
>1 g	3	−1.01 (-1.31, −0.72)	0.000	0.0	0.930
≤1 g					
Sample size					
>500	1	−0.25 (-0.44, −0.05)	0.012	-	-
≤500	5	−0.99 (-1.28, −0.70)	0.000	0.0	0.949
Age					
>50	1	−1.32 (-3.88, 1.24)	0.312	-	-
≤50	5	−0.48 (-0.64, −0.32)	0.001	77.4	0.001
Duration					
>10 weeks	3	−0.63 (-1.33, 0.06)	0.075	88.4	0.000
≤10 weeks	3	−0.78 (-1.99, 0.43)	0.206	0.0	0.744
Health condition	2	−1.00 (-1.30, −0.71)	0.000	0.0	0.933
NAFLD	2	−0.25 (-0.45, −0.06)	0.011	0.0	0.727
MetS	1	−1.32 (-3.88, 1.24)	0.312	-	-
CVDs	1	−1.47 (-4.51, 1.58)	0.344	-	-
PCOS					
FBS					
Dosage (g/day)	6	−1.20 (-1.91, −0.49)	0.001	88.9	0.000
≤1 g	3	−4.00 (-6.78, −1.21)	0.005	33.3	0.223
>1 g					
Sample size					
>500	3	−0.45 (-1.22, 0.33)	0.256	80.3	0.006
≤500	6	−3.13 (-5.24, −1.03)	0.003	91.5	0.000
Age					
>50	2	−8.30 (-25.71, 9.11)	0.350	89.8	0.002
≤50	5	−2.97 (-5.28, −0.65)	0.012	89.6	0.000
Not reported	2	−1.99 (-2.51, −0.99)	0.218	94.5	0.000
Duration					
> 10 weeks	1	−0.28 (-0.62, 0.06)	0.107	-	-
≤ 10 weeks	8	−2.27 (-3.32, −1.22)	0.000	89.8	0.000
Health condition	2	−2.39 (-7.58, 2.81)	0.368	80.1	0.025
NAFLD	3	−3.34 (-4.19, −2.50)	0.000	0.0	0.598
PCOS	1	−0.28 (-0.62, 0.06)	0.174	-	-
T2DM	1	−18.14 (-29.31, −6.97)	0.001	-	-
CVDs	2	−3.56 (-11.74, 4.63)	0.394	71.2	0.063
MetS					
HbA1C					
Sample size					
>500	2	−0.70 (-0.86, −0.54)	0.000	0.0	0.918
≤500	4	−0.29 (-0.45, −0.13)	0.000	0.0	0.420
Age					
>50	2	−0.60(-0.86, −0.33)	0.000	54.8	0.137
≤50	3	−0.22 (-0.45, 0.01)	0.060	0.0	0.427
Not reported	1	−0.35 (-0.63, −0.07)	0.014	-	-
Duration					
> 10 weeks	2	−0.54 (-0.88, −0.20)	0.002	77.6	0.035
≤ 10 weeks	3	−0.22 (-0.45, 0.01)	0.060	0.0	0.427
Not reported	1	−0.42 (-0.75, −0.09)	0.013	-	-
Health condition	2	−0.17 (-0.42, 0.07)	0.158	0.0	0.635
NAFLD	2	−0.60 (-0.86, −0.33)	0.000	54.8	0.137
T2DM	1		0.014	-	-
	1		0.083	-	-

(*continued on next page*)

Table 2 (*continued*)

Variables	No. study	Pooled effect size (95 % CI)	P-value	I^2(%)	P heterogeneity
MetS		−0.35 (-0.63, −0.07)			
CVDs		−0.66 (-1.40, 0.08)			
HOMA-IR					
Dosage (g/day)	5	−0.38 (-0.53,	0.000	45.6	0.118
≤1 g	4	−0.24)	0.000	23.0	0.273
> 1 g		−0.44 (-0.64, −0.24)			
Sample size					
≤500	8	−0.44 (-0.55,	0.000	0.0	0.499
>500	1	−0.33)	0.000	-	-
		−0.28 (-0.33, −0.23)			
Age					
≥50	3	−0.33 (-0.50,	0.000	44.6	0.165
<50	4	−0.16)	0.000	0.0	0.566
Not reported	2	−0.40 (-0.54, −0.26)	0.000	0.0	0.360
		−0.60 (-0.86, −0.33)			
Duration					
> 10	3	−0.49 (-0.75,	0.000	16.6	0.302
weeks	5	−0.24)	0.000	43.9	0.129
≤ 10	1	−0.37 (-0.51,	0.000	-	-
weeks		−0.23)			
Not reported		−0.41 (-0.63, −0.19)			
Health condition	3	−0.46 (-0.71,	0.000	42.4	0.176
PCOS	2	−0.22)	0.201	48.3	0.164
T2DM	2	−0.75 (-1.89,	0.002	0.0	0.590
NAFLD	1	0.40)	0.000	-	-
MetS	1	−0.42 (-0.70,	0.000	-	-
CVDs		−0.15)			
		−0.55 (-0.83, −0.26)			
		−0.28 (-0.33, −0.23)			
Insulin					
Dosage (g/day)	5	−0.94 (-1.66,	0.011	94.3	0.000
≤1 g	2	−0.21)	0.001	0.0	0.625
> 1 g		−1.22 (-1.95, −0.50)			
Sample size					
>500	1	−1.21 (-1.43,	0.000	-	-
≤500	6	−1.00)	0.007	87.4	0.000
		−0.94 (-1.62, −0.26)			
Age					
>50	1	−1.21 (-1.43,	0.000	-	-
≤50	4	−1.00)	0.003	65.9	0.032
Not reported	2	−1.07 (-1.78, −0.37)	0.457	94.9	0.000
		−0.72 (-2.61, 1.17)			
Duration					
> 10	1	−0.49 (-0.81,	0.003	-	-
weeks	6	−0.17)	0.006	92.8	0.000
≤ 10		−1.10 (-1.89,			
weeks		−0.32)			
Health condition	2	−0.51 (-0.83,	0.002	0.0	0.560
NAFLD	3	−0.19)	0.000	0.0	0.671
PCOS	1	−1.62 (-2.13,	0.163	-	-
MetS	1	−1.11)0.21	0.000	-	-
CVDs		(-0.09, 0.50)			
		−1.21 (-1.43, −1.00)			

BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; FBS, fasting blood sugar; PCOS, polycystic ovary syndrome; NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular diseases; T2DM, type 2 diabetes mellitus; NR, not reported.

sources of high heterogeneity following subgroup analysis (Table 2). Subgroup analyses have shown that > 1 g/day of curcumin supplement is associated with a stronger effect on FBS in subjects with PCOS with mean age ≤ 50 years in intervention duration of ≤ 10-week (Table 2). According to sensitivity analysis, no significant change has been detected following removing one single study. Begg's test has indicated no significant publication bias (p = 0.175). According to the GRADE criteria, the overall quality of this evidence was considered moderate due to indirectness (**Suppl.** Table 2).

3.8. The effects of curcumin supplementation on HOMA-IR

Curcumin supplementation has significantly decreased Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (ES: −0.40; 95 % CI: −0.51, −0.29, and p < 0.001) (Fig. 5**A**). Besides, our results have indicated no significant between-study heterogeneity (I^2 = 40.3 %, and p = 0.098). Curcumin supplement > 1 g/day has been more beneficial for subjects with PCOS in intervention duration of > 10-week (Table 2). Based on sensitivity analysis, no significant change has been detected following removing one single study. Begg's test has indicated that there is no significant publication bias (p = 0.251). Based on the GRADE approach, the overall quality of this evidence was moderate due to indirectness (**Suppl.** Table 2).

3.9. The effect of curcumin supplementation on HbA1C

Based on data from 2,240 participants, curcumin supplementation has significantly decreased the hemoglobin A1c (HbA1c) level (ES: −0.44; 95 % CI: −0.67, −0.21, p < 0.001) (Fig. 5**B**). However, our results have detected a significant between-study heterogeneity (I^2 = 65.4 %, and p = 0.014). The mean age, sample size, health condition, and duration had been identified as the source of the high heterogeneity (Table 2). Subgroup analysis has indicated that curcumin supplementation in subjects with T2DM in an intervention duration of > 10 weeks has a more beneficial effect on reducing HbA1C level (Table. 2). According to sensitivity analysis, no significant change has been detected following removing one single study. Begg's test has shown that there is no significant publication bias (p = 0.386). Based on GRADE criteria, the overall quality of this evidence was low due to indirectness and imprecision (**Suppl.** Table 2).

3.10. The effect of curcumin supplementation on fasting insulin

Curcumin supplementation has significantly decreased fasting insulin level (ES: −0.98; 95 % CI: −1.59, −0.37, and p = 0.002) (Fig. 6). Our results have shown a significant between-study heterogeneity (I^2 = 91.7 %, and p < 0.001). Following subgroup analysis, a sample size, age, and health condition have been identified as the sources of the high heterogeneity (Table 2). According to subgroup analysis, curcumin's effect on fasting insulin levels has been more beneficial in subjects with polycystic ovary syndrome (PCOS) with mean age ≤ 50 years in intervention duration of ≤ 10-week (Table 2). Based on sensitivity analysis, no significant change has been detected following removing one single study. Begg's test has demonstrated that there is no significant publication bias (p = 0.999). Based on GRADE criteria, the overall quality of this evidence was low due to indirectness and imprecision (**Suppl.** Table 2).

4. Discussion

Our pooled results have shown that curcumin supplementation can improve anthropometric and glycemic parameters. Results on BMI have been more reliable due to low heterogeneity. Administered dosage, the mean age of participants, health condition, duration of supplementation, and sample size have been the possible sources of high heterogeneity in other studied parameters. Subgroup analysis has revealed that

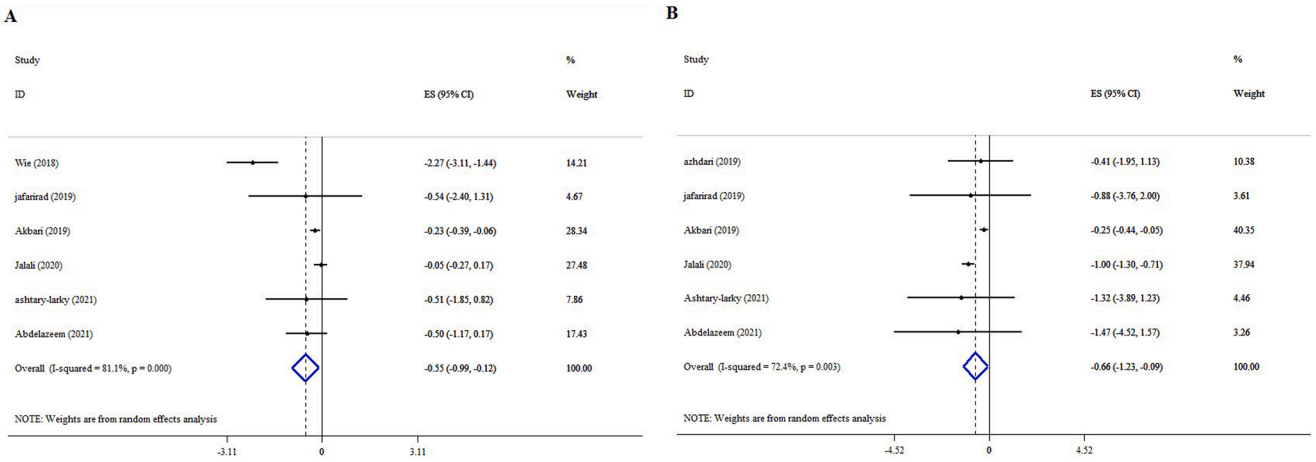

Fig. 3. Forest plot (A) funnel plot with a mean difference and 95% confidence intervals (CIs) (B) funnel plot with a mean difference and 95% confidence intervals (CIs), the impacts of curcumin supplementation on body weight, and WC, respectively.

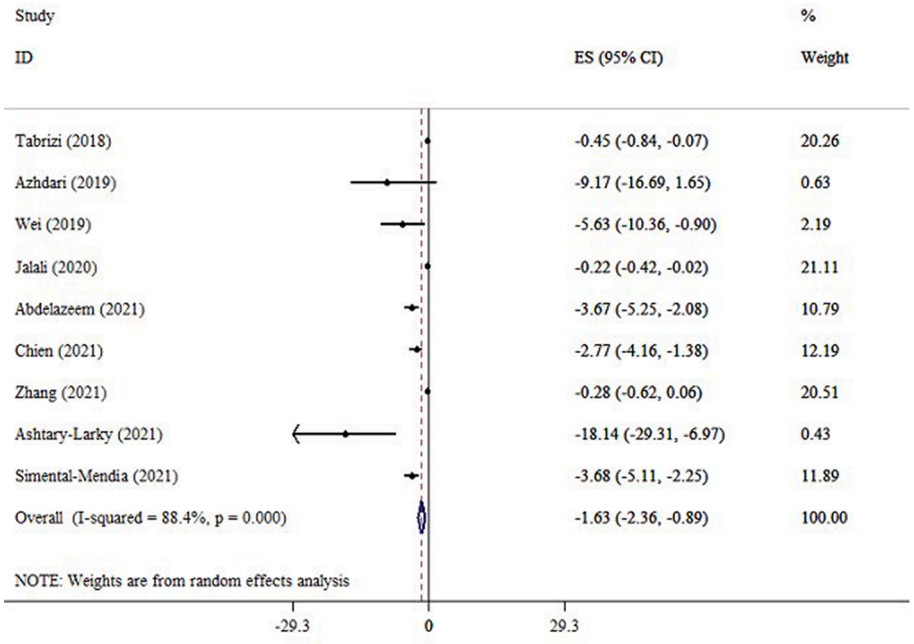

Fig. 4. Forest plot (A) funnel plot with a mean difference and 95% confidence intervals (CIs) (B) publication bias in the studies reporting, the impacts of curcumin supplementation on FBS levels.

curcumin with a dose above 1 g/day has the most beneficial effect on anthropometric and glycemic parameters. This is mostly due to the low bioavailability of curcumin (Kunnumakkara et al., 2017), as a result, high doses are needed for better clinical effects. The US food and drug administration (FDA) has approved curcumin as "generally recognized as safe" (GRAS) (Garg et al., 2019). Lao et al. propsed that the tolerance of curcumin in single oral doses up to 12,000 mg appears to be excellent (Lao et al., 2006). Therefore, the doses in the studies included in the *meta*-analysis are safe. However, based on the European food safety authority (EFSA) recommendation, the administrated dose should not exceed 3 mg/kg/day (Authority, 2014). Some moderate side effects, e.g., nausea, abdominal discomfort, constipation, vertigo, hot flash, hypersensitivity, diuresis, increased duration, and volume of menstrual bleeding, have been reported following the intake of high dose of curcumin (Alsharif & Almuhtadi, 2021).

In terms of the duration of intervention, ≤10-week of curcumin supplementation has the most beneficial effect on anthropometric parameters, insulin, and FBS. However, a longer duration of curcumin supplementation has the same effect on HbA1c and HOMA-IR. It might be due to the fact that insulin sensitivity needs more time to be improved. Besides, HbA1c reflects the glycemic condition over the past three months (Sherwani et al., 2016). Therefore, at least 12-week of curcumin supplementation might be needed to change the HbA1c level. Nevertheless, the beneficial effect of long-term curcumin supplementation on anthropometric measurements has not been the same as its short-term supplementation. Long-term maintenance of weight loss is the primary challenge of obesity management and needs comprehensive improvements in diet and physical activities (Wing & Phelan, 2005).

Subgroup analyses based on health conditions and age have shown that curcumin can be effective in different health conditions and age groups. The most beneficial effect of curcumin on anthropometric measures has been in patients with nonalcoholic fatty liver disease (NAFLD). Besides, the most beneficial of curcumin on FBS, insulin resistance and insulin level has been in patients with PCOS. The most notable improvement in HbA1c level following curcumin supplementation has been in patients with T2DM. Because there is limited number

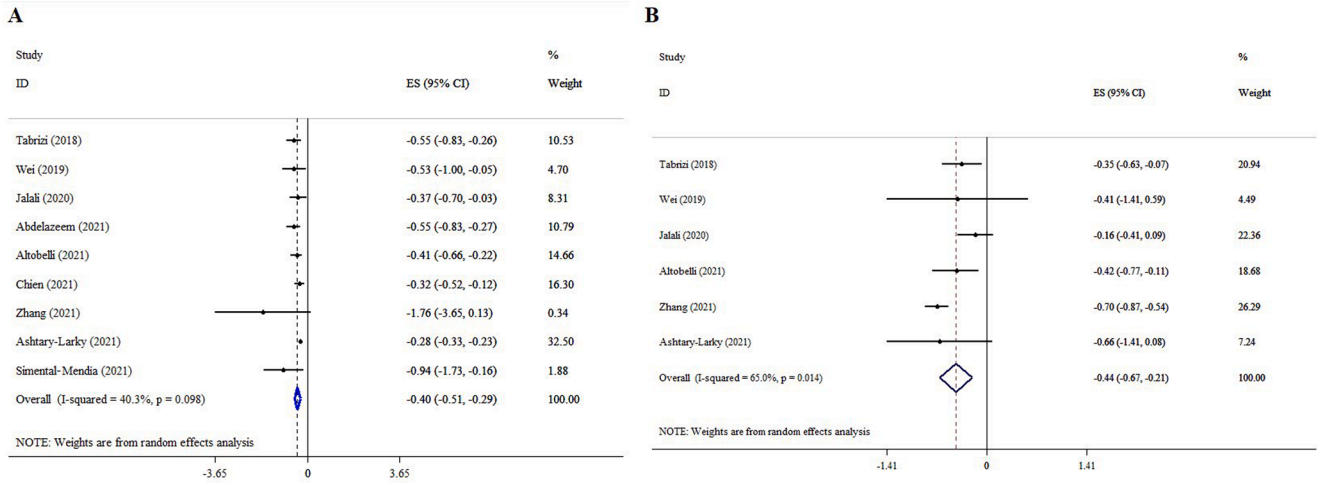

Fig. 5. Forest plot (A) funnel plot with a mean difference and 95% confidence intervals (CIs) (B) funnel plot with a mean difference and 95% confidence intervals (CIs), the impacts of curcumin supplementation on HOMA-IR, and HbA1c, respectively.

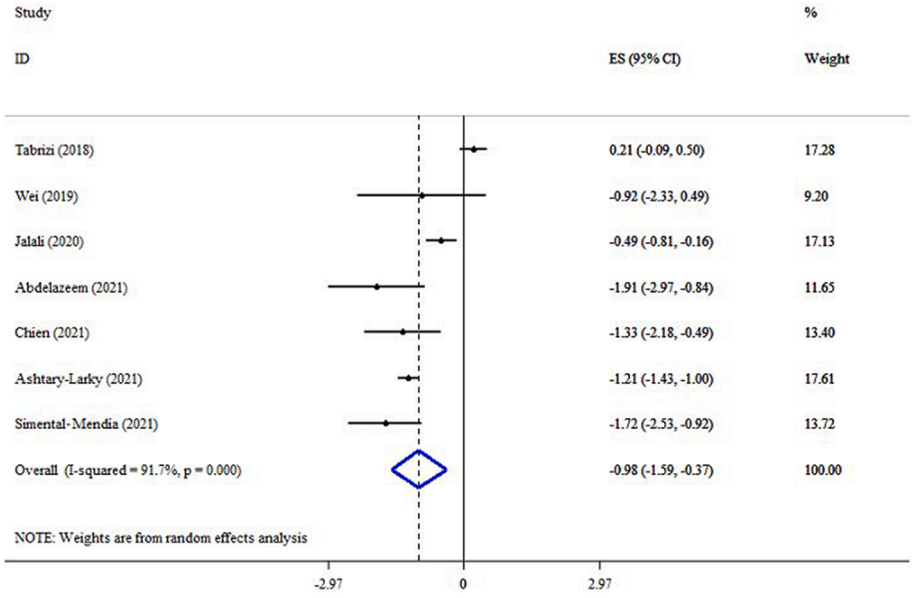

Fig. 6. Forest plot (A) funnel plot with a mean difference and 95% confidence intervals, the impacts of curcumin supplementation on insulin.

of studies on other health conditions, comparison of results between different health conditions cannot be interpreted. In terms of FBS levels, the results on the effectiveness of curcumin supplementation on metabolic syndrome, T2DM, and NAFLD patients were not significant. The studies by Tabrizi et al. (2018), Zhang et al. (2021), and Jalali et al. (Jalali et al., 2020) had the most weight on the final results in metabolic syndrome, T2DM, and NAFLD subgroups, respectively. In all of these studies, low doses of curcumin (≤1 g/day) was investigated. Also, the short duration of curcumin supplementation can be the reason for the insignificant effect of curcumin on HbA1c in NAFLD patients, derived from the studies by Jalali et al. (9-week) (Jalali et al., 2020) and Wei et al. (8-week) (Z. Wei et al., 2019). Concerning the effect of curcumin on HOMA-IR in T2DM patients, the weight of the effect size derived from Altobelli et al.'s study (Altobelli et al., 2021), which investigated the effect of low doses of curcumin (≤1 g/day), have substantially changed the pooled results. Thus, these effect sizes confirm that the effect of curcumin on glycemic indices is dose- and time-dependent.

Our analyses have revealed that the effect of sample size on the final results is not effective enough to change them. Based on the AMSTAR assessment, the quality of included systematic reviews was high. Nevertheless, some included studies consisted of low-quality trials. For instance, included trials in the study by Ashtary et al. (Ashtary-Larky et al., 2021) had high risk of bias. However, the low risk of bias in most of the included studies might not pose questions about the reliability of obtained results in the current umbrella systematic review and *meta*-analysis. Due to the detection of possible sources of heterogeneity, inconsistency is low in our result. Also, effective publication bias is not seen in all studied biomarkers. Notably, because the studied population had different health conditions, our results can have serious indirectness. However, subgroup analyses based on population have minimized the effect of this indirectness. Taken together, the obtained results on the beneficial effect of curcumin supplementation on studied biomarkers are reliable.

Various preclinical studies have investigated the effect of curcumin on anthropometric and glycemic indices at the molecular level. Curcumin can modeluate hepatic lipogenesis through inhibiting the activity of the sterol regulatory element-binding protein (SREBP1) gene as a transcription factor involved in hepatic lipogenesis Moreover, curcumin is involved in regulation of lipid mobilization by increasing the activity of acyl-CoA cholesterol acyltransferase (ACAT) and carnitine

palmitoyltransferase 1 (CPT1) (Pivari et al., 2019). It has been reported that curcumin can suppress angiogenesis in adipose tissue, decrease pre-adipocyte differentiation, and stimulate adipocyte metabolism and apoptosis (Ejaz et al., 2009). Also, curcumin can downregulate the expression of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and cytosine-cytosine-adenine-adenosine-thymidine (CCAAT)/enhancer binding proteinα (C/EBPα) that are the main transcription factors of adipogenesis (Kim et al., 2011; Lee et al., 2009). In contrast, some studies have indicated that curcumin can improve insulin sensitivity via PPAR-γ upregulation (Blanquicett et al., 2010; El-Naggar et al., 2019; Nishiyama et al., 2005; Rinwa et al., 2010). Zou et al. have revealed that dietary curcumin can improve diet-induced adiposity by improving insulin sensitivity and whole body energy metabolism via the fibronectin type 3 domain-containing protein 5 (FNDC5)/p38 mitogen-activated protein kinase (p38MAPK)/extracellular signal-related kinase (ERK) 1/2 pathway (Zou et al., 2021). Curcumin can also suppress 11β-hydroxysteroid dehydrogenase type-1 enzyme, which is involved in cortisol activation and developing central obesity (Hu et al., 2013). The anti-inflammatory properties of curcumin might also explain its beneficial effect on obesity (Varì et al., 2021). The hypoglycemic properties of curcumin can be mediated by its inhibitory effect on phosphorylase kinase, which is involved in glycogenolysis (Razavi et al., 2021). Various in vivo and in vitro studies have highlighted the potent inhibitory effect of curcumin on α-amylase and α-glucosidase (Banuppriya et al., 2018; Butala et al., 2018; Riyaphan et al., 2018). Besides, the stimulatory effect of curcumin on glucagon-like peptide-1 (GLP-1) and its inhibitory effect on dipeptidyl peptidase-4 (DPP-4) may explain its beneficial effect on glycemic control (Cao et al., 2021). Furthermore, it has been reported that curcumin can decrease glucose transporter-1 (GLUT-1) and GLUT-2 activity in adipocytes and hepatic cells, respectively (Mohammadi et al., 2021).

The current GRADE-assessed umbrella systematic review and *meta*-analysis has several strengths. First, we conducted comprehensive subgroup analyses and attempted to find possible sources of heterogeneity and bias. Second, the data quality of the current study was thoroughly evaluated to present reliable results. However, our study also suffers from some limitations. First, due to a limited number of studies that are separately conducted on males and females, subgroup analysis based on sex could not be performed. Second, as studies on health conditions were limited, exact comparison between them and other diseases was not possible. The repetition of some RCTs in different meta-analyses, which can affect the final result. However, further assessments showed that the repeated studies did not have much weight on the final result. Moreover, due to different health statuses in the included studies, indirectness can be possible. Since the type of curcumin (dried drug, oil, and extracts) administered was not reported in most of the included studies, subgroup analysis by type of curcumin was not carried out.

5. Conclusion

Curcumin supplementation can improve anthropometric and glycemic indices in a time- and dose-dependent manner. Administered dose of $>$ 1 g/day of curcumin has the most beneficial effect on anthropometric and glycemic indices. Short duration ($\leq$10-week) of curcumin supplementation has the most decreasing effect on anthropometric parameters, insulin, and FBS. Longer durations of supplementation ($>$10-week) are needed to have the same impact on HOMA-IR and HbA1c. Curcumin can be effective in different health conditions and age groups. With moderate reliability, curcumin supplementation can be administered as the adjuvant therapy in managing hyperglycemia, insulin resistance, and obesity. Quality of evidence on the improving effect of curcumin on HbA1c and insulin level is low.

Ethical statement for solid state ionics

Hereby, I /insert author name/ consciously assure that for the manuscript /insert title/ the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2022.105357.

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