



# Turmeric and curcuminoids ameliorate disorders of glycometabolism among subjects with metabolic diseases: A systematic review and meta-analysis of randomized controlled trials<sup>☆</sup>

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## ABSTRACT

**Background and aims:** Metabolic diseases are globally popular, and a systematic review and meta-analysis of turmeric and curcuminoids on glucose metabolism among people with metabolic diseases was performed.

**Design:** We comprehensively searched Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, the Cochrane Library and two Chinese databases, Wanfang and CNKI for RCTs that focused on the effects of turmeric and curcuminoids on fasting blood glucose (FBG), hemoglobin A1C (HbA1c), fasting serum insulin (FSI) and HOMA-IR among patients with metabolic diseases. The FBG and HbA1c were the main outcomes to be analyzed. With random-effects models, separate meta-analyses were conducted by inverse-variance and reported as WMD with 95% CIs.

**Results:** Evidence from 17 RCTs including 22 trials showed that turmeric and curcuminoids lowered FBG by  $-7.86$  mg/dL (95% CI:  $-12.04$ ,  $-3.67$  mg/dL;  $P = 0.0002$ ), HbA1c by  $-0.38\%$  (95% CI:  $-0.52\%$ ,  $-0.23\%$ ;  $P < 0.00001$ ) and HOMA-IR by  $-1.01$  (95% CI:  $-1.6$ ,  $-0.42$ ;  $P = 0.0008$ ). Moreover, they decreased fasting serum insulin by  $-1.69$  mU/L (95% CI:  $-3.22$ ,  $-0.16$  mU/L;  $P = 0.03$ ) after more than 8 weeks of intervention in a subgroup analysis.

**Conclusions:** Turmeric and curcuminoids decrease FBG, HbA1c and HOMA-IR significantly among subjects with metabolic disease. Additionally, they may have an effect on FSI concentrations if the intervention period is more than 8 weeks. However, attention should be paid to these outcomes due to the significant heterogeneity.

## 1. Introduction

Metabolic diseases include type 2 diabetes mellitus (T2DM) and its complications, pre-diabetes, overweight or obesity, insulin resistance, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases. Overload metabolites, including free fatty acids, glucose, oxidized low-density lipoproteins, cholesterol crystals, and advanced glycation end products, simulate inflammation via different molecular signaling

pathways and induce metabolic disorders [1]. For example, glucose activates Toll Like Receptors to upregulate the MAK and NF- $\kappa$ B signaling pathways, which drive inflammation [2]. In addition, it initiates the NLRP3 inflammasome by activating the transcription factor ChREB and ATP/P2 $\times$ 4 pathway [3]. It is well known that persistent dysglycemia is closely related to the incidence of heart disease, diabetic nephropathy, and retinopathy, which lead to acute myocardial infarction, chronic kidney failure, and blindness. These serious complications

**Abbreviations:** used: C, control group; E, experimental group; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FBG, fasting blood glucose; FSI, fasting serum insulin; HbA1c, hemoglobin A1C; MetS, metabolism syndrome; NAFLD, Non-alcoholic Fatty Liver Disease; RCT, randomized controlled trials; RDC, randomized double-blind crossover; RDP, randomized double-blind parallel; RP, randomized parallel; T2DM, type 2 diabetes mellitus.

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impose a heavy economic burden on families and society. Based on epidemiological research by the International Diabetes Federation, there are more than 536 million adults (aged 20–79 years) with diabetes, which was responsible for 6.7 million deaths in 2021. This number will climb to 643 million and 783 million in 2030 and 2045, respectively. Moreover, 541 million adults have impaired glucose tolerance, which increases the risk of T2DM. The most serious fact is that three in four people with diabetes are in developing countries and states. Nine hundred sixty-six billion dollars have been spent on the treatment of diabetes and its complications [4]. According to recent studies, metabolic disorders, such as overweight, obesity, hyperlipidemia, NAFLD, metabolic syndrome, are connected to dysglycemia. Insulin resistance plays a key role in the development of NAFLD and metabolic syndromes. NAFLD is characterized by excessive fat accumulation in the liver, which induces chronic steatohepatitis, fibrosis, and primary carcinoma. Metabolic syndrome, consisting of obesity, T2DM, and dyslipidemia, is associated with increased inflammatory activity. Ectopic fat accumulation and chronic inflammation, for instance, are risk factors for insulin resistance and diabetes [5–8]. Due to the high incidence and serious complications, it is essential to find a safe, effective, and inexpensive method to ameliorate the disorders of glycometabolism.

Curcuminoids, which are popular spices in India and Southeast Asia, are mainly extracted from turmeric [9]. These are natural polyphenols that consists of curcumin, demethoxycurcumin, and bis-demethoxy curcumin [10]. Over the last few decades, their biological functions have been studied. Some clinical trials reported that curcuminoids played a role in decreasing lipids and uricemia among people with obesity or NAFLD [11,12]. Additionally, research shows that curcuminoids could protect the liver and nervous system [13,14]. Moreover, their anti-inflammatory, anti-ischemic, and anti-arthritis effects have been investigated in animal and human experiments [15–17]. In addition, clinical trials have been performed to explore the hypoglycemic functions of curcuminoids [18,19]. Therefore, using curcuminoids and turmeric may be effective therapies for many diseases such as diabetes, arthritis, hyperuricemia, hyperlipidemia, depression, and metabolic syndrome [20–23]. However, there have been inconsistent results among randomized clinical trials; some have suggested that it lowered hyperglycemia, while others found that it had little effect on glucose metabolism. Although a meta-analysis was conducted to illustrate that curcumin or combined curcuminoids could decrease fasting blood glucose (FBG), hemoglobin A1C (HbA1c), and HOMA-IR levels among patients with dysglycemia, it included a small number of studies (eight studies); thus, the evidence was not strong enough to support any conclusions [24]. Moreover, the high heterogeneity in this meta-analysis further impairs its credibility. Furthermore, it did not study the effects of turmeric and curcuminoids on fasting serum insulin (FSI) concentrations. Finally, the authors did not include trials involving turmeric, in which curcuminoids were the most effective compounds, which may have led to a selection bias. Therefore, we conducted this systematic review and meta-analysis to evaluate the effects of curcuminoids on decreasing hyperglycemia in individuals with metabolic diseases.

## 2. Material and methods

In this article, we followed the methods of Fen Yuan et al., 2019 [25].

### 2.1. Search strategy

We comprehensively searched the Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, Cochrane Library, and two Chinese databases, Wanfang and CNKI, for randomized controlled trials without time or language limitations. The search was performed using the following keywords: 1. curcumin or curcuminoid or curcuminoids or Curcuma or Curcuma longa or turmeric or *C. longa* or *Curcuma domestica*; 2. metabolic syndrome or overweight or obese or obesity or hepatic adipose infiltration or fatty liver or hyperuricemia or

hyperinsulinemia or hyperglycemia or diabetic mellitus or glucose or insulin resistance or glycemic or glycaemic or hypertension or hyperlipidemia or lipid metabolism or dyslipidemia or hypercholesterolemia or hypertriglyceridemia or low-density lipoprotein cholesterol or LDL-c or high-density lipoprotein cholesterol or HDL-c or total cholesterol or TC or triglycerides or TG or adipokine or adiponectin or adiponectins or leptin or leptins; 3. Randomized controlled trial or clinical trial; 4. Humans; 5. Animals; 6. 1 and 2 and 3 and 4; 7. 6 not 5. In addition, we manually searched the references after evaluating similar articles and obtained data from the authors via email. This study was independently performed by Dingkun Wang and Meilin Hu.

### 2.2. Study including standard

After comprehensively reading and discussing, we included studies that met the following criteria: 1) the duration of the intervention was consistently not less than four weeks; 2) turmeric extract or curcuminoids were the only supplements used and were not mixed with other components, and the same mixture was used in the control group; 3) the study participants had metabolic diseases, such as T2DM, pre-diabetes, dyslipidemia, overweight or obesity, metabolism syndrome, or NAFLD; 4) RCTs including parallel and crossover trials were performed among humans rather than animals; 5) all data were accessible, including the baseline and endpoint values or net changes between them with the means, standard deviations (SDs), SEs, number of participants (n), or 95% CIs for the experimental and control groups; 6) all trials reported at least one of following statistics: FBG, HbA1c, fasting serum insulin (FSI), and HOMA-IR; 7) the trials reported comparisons between a treatment group and a control group but not a self-control group; 8) intervention and control groups underwent treatments at the same time; and 9) the participants were adults. The selection of articles was performed by Wenbin Wu and Leyi Ma.

### 2.3. Data collection and quality assessment

Data were extracted from articles included by Jing Gong and checked by Wenya Huang. The contents were as follows: 1) study characteristics including the first author, publication year, study design, oral agent, dosage, period of intervention, and form; 2) participants' information including the continent of residence, average age (mean  $\pm$  SD), baseline FBG (mean  $\pm$  SD), physical condition, and lifestyle; and 3) baseline and endpoint values or net changes in FBG, HbA1c, FSI, and HOMA-IR. Based on the Cochrane Handbook, if a trial included different doses, intervention periods, or oral agents, we divided them into separate trials that were compared with the same control group [26,27]. If a trial contained several treatment groups compared with a control group, we only extracted information regarding the turmeric extract or curcuminoids group and the control group. If a trial was designed with crossover, we only used the first-stage data before the participants were subjected to a washout period [28]. All values were transferred to international standard units. For uncertain data, we obtained the original data by email request and excluded studies for which the authors did not reply.

The quality of the selected studies was assessed using the Cochrane Handbook for Systematic Reviews [26]. The details were related to seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. This assessment was performed by Ke Fang and Lijun Xu.

### 2.4. Data synthesis and statistics

We collected data from the means, SDs, and n in the treatment and control groups. We calculated the means and SDs using a series of conversion formulas if the studies did not provide them directly. For normally distributed data, the formulas were as follows: mean (change) = mean (post-treatment) - mean (baseline); SD (change) = SE  $\times$  square

root of  $n$  or SD (change) = square root ((SD (pre-treatment))<sup>2</sup> + (SD (baseline))<sup>2</sup> - 2 R × SD (pre-treatment) × SD (baseline)), assuming a correlation coefficient (R) = 0.5 [25]. If 95% CIs were available, SDs were calculated using the following transforming formula: SD = square root of  $n \times (\text{upper limit} - \text{lower limit}) / 3.92$  or  $4.128$  when participants were greater than 100 or less than 60 in the intervention and control groups. If the treatment or control groups were divided into different subgroups, we merged the data using the following formulas:  $n$  (merge) =  $n_1 + n_2$ ; mean (merge) =  $(\text{mean}_1 \times n_1 + \text{mean}_2 \times n_2) / (n_1 + n_2)$ ; SD (merge) = square root  $((n_1 - 1) \times (\text{SD}_1)^2 + (n_2 - 1) \times (\text{SD}_2)^2 + ((n_1 \times n_2) / (n_1 + n_2)) \times (\text{mean}_1 - \text{mean}_2)^2)$ . For non-normal distributions, we used the median in place of the mean and obtained SDs by using the following formula: SD = range interquartile / 1.35 if the participants were greater than 100 in each group. If there were fewer than 100 participants, the data were not used to decrease bias [26].

After collecting related data, a meta-analysis was performed using soft RevMan 5. Because of the different doses, intervention periods, and baseline characteristics, the results were expressed as mean differences and 95% CIs with an inverse variance and a random-effects model [27]. Heterogeneity was evaluated using I<sup>2</sup> values and was defined as low, moderate, or high if I<sup>2</sup> values were less than 25%, between 25% and 75%, or more, respectively [29]. Subgroup and meta-regression analyses were conducted to determine the source of heterogeneity if I<sup>2</sup> values were high. Funnel plots and Egger's test were used to examine publication bias using the Stata version 12 software (StataCorp LP). Statistical significance was set at  $p < 0.05$ . This study was performed by Yuan et al.

### 3. Results

#### 3.1. Characteristics of the included studies

In total, 790 articles were identified. After sorting using a file manager, 295 duplicates were excluded. An additional assessment of 495 papers was performed by reading the titles and abstracts, and 393 articles were eliminated for various reasons (reviews or meta-analyses, 75; animal or cell experiments, 204; and no relationship, 114). Finally, 85 studies did not satisfy the selection criteria after comprehensive reading (inclusion of non-metabolic diseases, 35; use of mixed interventions, 34; treatment period less than four weeks, 4; absence of control group, 3; unpublished articles, 2; articles that were neither in English nor in Chinese, 1; conference or supplementary papers, 3; inaccessible paper, 1; child participants, 1; data errors, 1), and 17 studies containing 22 trials were included after overall estimation [10,12,13,17–19,30–40]. A flow diagram and the baseline characteristics of the studies are shown in Fig. 1 and Table 1, respectively. Twenty arms were from Asia, except for two (one from Europe [30] and one from America [31]). Nineteen arms were double-blinded. Apart from one study that was a randomized, double-blinded, crossover trial [31], eighteen of them were randomized controlled, double-blinded, parallel trials. The remaining three trials were non-blinded [10,12,35]. Four articles included six arms in which participants with metabolic syndrome were treated [19,37–39], and two trials recruited participants who were overweight, obese, or hypercholesterolemic [30,31]. Three trials included patients with NAFLD [12,13,40]. In addition, seven studies included eight trials with T2DM patients [10,17,32–36], and one study included three trials with pre-diabetes patients [18]. Additionally, one trial had two intervention groups treated with different oral curcumin agents [39], and three trials had results with different endpoints [17,18,37]. Only one trial found a significant difference in baseline FBG concentrations between the treatment and placebo groups [19]. The intervention periods ranged from 4 weeks to 9 months, and the dose of curcuminoids administered ranged from 46 mg to 1500 mg. All control groups were administered a placebo, except one, in which metformin was consumed by participants in both the intervention and control groups [35]. In addition to the curcuminoids, the administered agents included turmeric, phospholipidated

curcumin, curcuminoid-piperine, and nanocurcumin. Additionally, the oral form in most arms was capsules, except for one in which the participants took tablets [30]. Seventeen studies including 22 trials presented data on FBG concentrations [10,12,13,17–19,30–40]. Eleven articles including 14 arms provided HbA1c data [10,12,13,17–19,32–35,38], and six studies including nine trials reported FSI [12,17,18,32,35,40]. In addition, seven studies including ten trials provided HOMA-IR data [12,17,18,32,34,35,40].

#### 3.2. Quality and publication bias

One study, including three trials, had a high bias regarding incomplete outcome data [18], and two trials allocated concealment with high risk [10,35]. Half of the studies were unclear regarding the process of generating a random sequence [10,12,13,19,30–32,35,36,39]. Moreover, approximately one-third of the studies did not provide a well-described allocation method [12,13,30–32,39,40]. This information is detailed in Table 2. Egger's test showed that publication bias existed in HOMA-IR values ( $P = 0.034$ ), but it did not reveal bias in FBG, HbA1c, or FSI values, with  $P$  values equal to 0.492, 0.334, and 0.803, respectively. Funnel plots of FBG, HbA1c, FSI, and HOMA-IR showed similar trends (funnel figures are shown in Supplemental Figs. 1, 2, 3, and 4, respectively).

#### 3.3. Meta-analysis on fasting blood glucose

Twenty-two trials, including 1137 participants in the intervention group and 1167 in the control group, reported on FBG concentrations [10,12,13,17–19,30–40]. With a random-effects model, it was shown that the use of turmeric and curcuminoids reduced FBG concentrations significantly ( $-7.86$  mg/dL; 95% CI:  $-12.04, -3.67$  mg/dL;  $P = 0.0002$ ). The I<sup>2</sup> value was 90%, and the related  $P$  value was less than 0.00001. The corresponding results are shown in Fig. 2.

#### 3.4. Meta-analysis on HbA1c

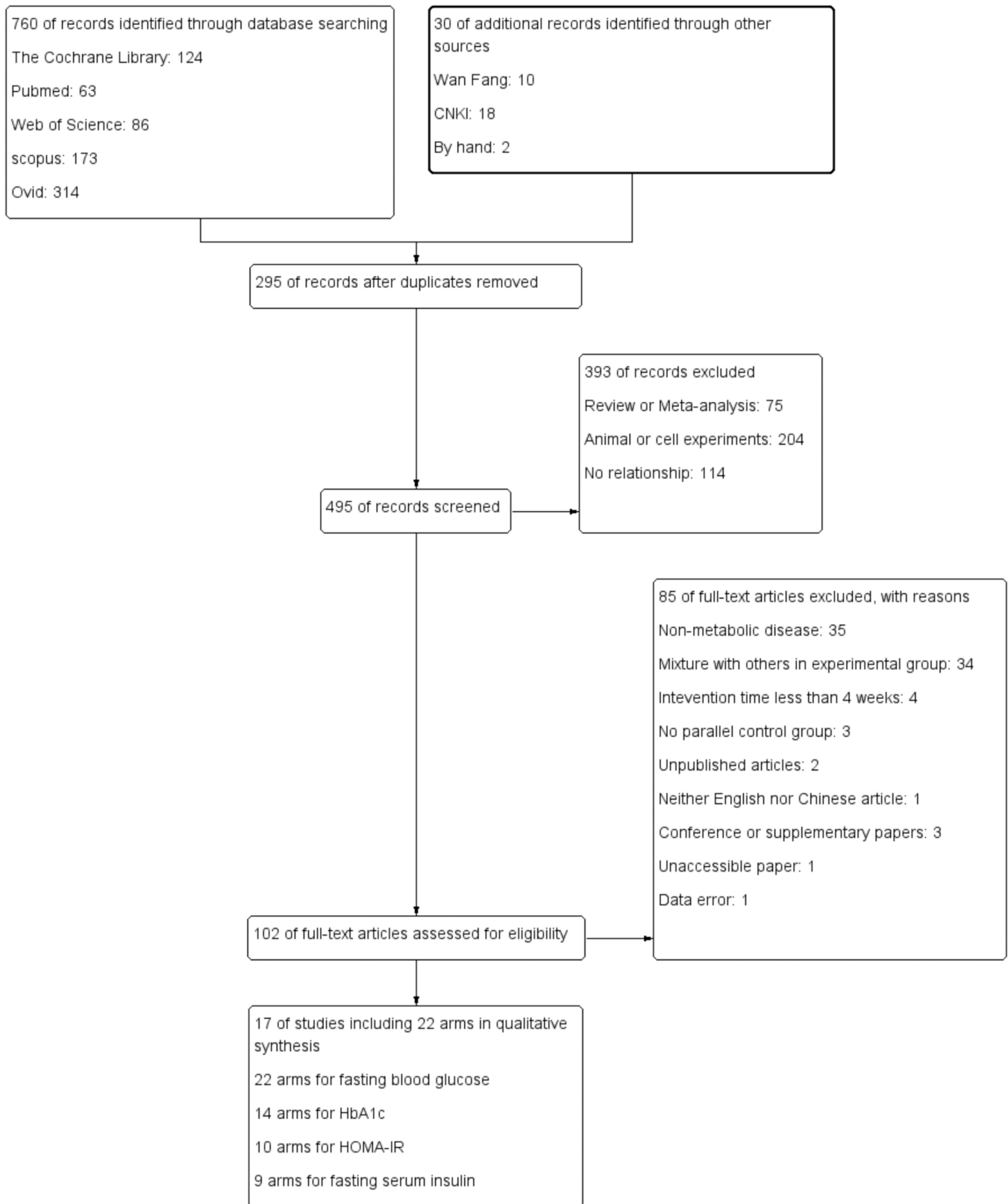
Fourteen trials with 849 participants in the intervention groups and 879 in the control groups reported on HbA1c levels [10,12,13,17–19,32–35,38]. Using a random-effects model, it was shown that the use of turmeric and curcuminoids significantly reduced HbA1c levels significantly ( $-0.38\%$ ; 95% CI:  $-0.52\%, -0.23\%$ ;  $P < 0.00001$ ). The I<sup>2</sup> value was 74%, and the related  $P$  value was significantly less than 0.0001. The corresponding results are shown in Fig. 3.

#### 3.5. Meta-analysis on fasting serum insulin

Six studies, including nine trials with 645 participants in the intervention groups and 675 in the control groups, reported on FSI levels [12,17,18,32,35,40]. With a random-effects model, it was shown that the use of turmeric and curcuminoids slightly reduced FSI concentration ( $-1.21$  mU/L; 95% CI:  $-2.51, 0.08$  mU/L;  $P = 0.07$ ). The I<sup>2</sup> value was 78%, and the related  $P$  value was less than 0.0001. The corresponding results are shown in Fig. 4.

#### 3.6. Meta-analysis on HOMA-IR

Seven studies, including 10 trials with 695 participants in the intervention group and 725 in the control group, reported on HOMA-IR values [12,17,18,32,34,35,40]. Using a random-effects model, it was shown that the use of turmeric and curcuminoids significantly reduced HOMA-IR values ( $-1.01$ ; 95% CI:  $-1.6, -0.42$ ;  $P = 0.0008$ ). The heterogeneity I<sup>2</sup> was 90%, and the related  $P$  value was less than 0.00001. The corresponding results are shown in Fig. 5. These data provide evidence that turmeric and curcuminoids ameliorate insulin resistance.



**Fig. 1.** Database search and studies selections. We searched widely Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, the Cochrane Library and two Chinese databases wanfang and CNKI for RCTs that focused on roles of turmeric and curcuminoids on FBG, hemoglobin A1c(HbA1c), fasting serum insulin and HOMA-IR among patients with metabolic disease. By reading titles, abstracts and thorough studies, we selected 17 studies including 22 arms finally.

**Table 1**  
Characteristics of studies and trials included in this meta-analysis<sup>a</sup>.

First author, year [ref]	Continent	Study design	Physical condition	n (E/C)	Age (y)	Baseline of FBG (mg/dL)	Oral agents	Dose of curcuminoid (mg/d) and form	Period	With original therapy
					mean $\pm$ SD (E/C)	mean $\pm$ SD (E/C)				
Panahi, 2015 [19]	Asia	RDP	MetS	50/50	44.80 $\pm$ 8.67/ 43.46 $\pm$ 9.70	155.46 $\pm$ 40.89/ 136.98 $\pm$ 52.40	Cur-pp	1000; capsule	8 wk	No
Ueng, 2014 [38]	Asia	RDP	MetS	30/29	59.03 $\pm$ 10.10/59.61 $\pm$ 14.09	113.73 $\pm$ 19.28/ 116.10 $\pm$ 24.29	Cmds	1795; capsule	12 wk	Yes
Gilani, 2015a [37]	Asia	RDP	MetS <sup>b</sup>	63/63	42.4 $\pm$ 13.7/ 41.57 $\pm$ 12.8	117 $\pm$ 12.7/ 119.1 $\pm$ 15.3	Turmeric	120; capsule	4 wk	No
Gilani, 2015b [37]	Asia	RDP	MetS <sup>b</sup>	63/63	42.4 $\pm$ 13.7/ 41.57 $\pm$ 12.8	117 $\pm$ 12.7/ 119.1 $\pm$ 15.3	Turmeric	120; capsule	8 wk	No
Salahshooh, 2017a [39]	Asia	RDP	MetS	37/36	40.05 $\pm$ 10.48/38.59 $\pm$ 10.28	103.49 $\pm$ 15.27/ 100.94 $\pm$ 16.74	PHO Cur	200; capsule	6 wk	No
Salahshooh, 2017b [39]	Asia	RDP	MetS	36/36	37.52 $\pm$ 9.47/ 38.59 $\pm$ 10.28	102.00 $\pm$ 14.90/ 100.94 $\pm$ 16.74	UF Cur	1000; capsule	6 wk	No
Shanely, 2012 [31]	America	RDC	OW/OB women	30/31	55.7 $\pm$ 7.67/ 57.7 $\pm$ 8.9	103.68 $\pm$ 20.7/ 100.08 $\pm$ 16.76	Turmeric	112; capsule	4 wk	No
Garg, 2017 [30]	Europour	RDP	Hypercho	18/18	18–70 <sup>c</sup>	95.94 $\pm$ 9.16/ 88.74 $\pm$ 6.87	PHO Cur	200; tablet	4 wk	No
Rahmani, 2016 [13]	Asia	RDP	NAFLD with MetS	37/40	46.37 $\pm$ 11.57/48.95 $\pm$ 9.78	111.65 $\pm$ 34.64/ 116.90 $\pm$ 47.66	Cmds	70; capsule	8 wk	No
Sahebkar, 2016 [12]	Asia	RP	NAFLD	44/43	44.98 $\pm$ 12.59/47.21 $\pm$ 10.29	107.61 $\pm$ 30.26/ 106.61 $\pm$ 25.67	PHO Cur	330; capsule	8 wk	No
Khoshbaten, 2017 [40]	Asia	RDP	NAFLD <sup>d</sup>	21/21	42.09 $\pm$ 7.23/ 40.38 $\pm$ 9.26	92.80 $\pm$ 22.98/ 85.23 $\pm$ 10.06	Turmeric	100; capsule	12 wk	No
Chuengsamarn, 2012a [18]	Asia	RDP	Prediabetic	107/114	56.95 $\pm$ 11.95/57.93 $\pm$ 12.71	103.65 $\pm$ 10.24/ 103.24 $\pm$ 10.46	Cmds	1500; capsule	3 mo	No
Chuengsamarn, 2012b [18]	Asia	RDP	Prediabetic	98/113	56.95 $\pm$ 11.95/57.93 $\pm$ 12.71	103.65 $\pm$ 10.24/ 103.24 $\pm$ 10.46	Cmds	1500; capsule	6 mo	No
Chuengsamarn, 2012c [18]	Asia	RDP	Prediabetic	97/104	56.95 $\pm$ 11.95/57.93 $\pm$ 12.71	103.65 $\pm$ 10.24/ 103.24 $\pm$ 10.46	Cmds	1500; capsule	9 mo	No
Usharani, 2008 [10]	Asia	RP	T2DM	23/21	55.52 $\pm$ 10.76/49.75 $\pm$ 8.18	155.04 $\pm$ 17.94/ 161.19 $\pm$ 19.97	Cmds	600; capsule	8 wk	Yes
Khajehdehi, 2011 [36]	Asia	RDP	T2DM	20/20	52.9 $\pm$ 9.2/ 52.6 $\pm$ 9.7	179.0 $\pm$ 65.5/ 169.54 $\pm$ 76.3	Turmeric	66.3; capsule	2 mo	Yes
Maithili, 2014 [35]	Asia	RP	T2DM <sup>2</sup>	30/30	47 $\pm$ 7.17/ 46.8 $\pm$ 6.1	116 $\pm$ 23/111 $\pm$ 24	Turmeric	46; capsule	4 wk	Yes
Na, 2013 [34]	Asia	RDP	T2DM <sup>3</sup>	50/50	55.42 $\pm$ 6.40/ 54.72 $\pm$ 8.34	154.44 $\pm$ 47.88/ 151 $\pm$ 39.06	Cmds	300; capsule	3 mo	Yes
Kazemi, 2016 [33]	Asia	RDP	T2DM	35/35	56.34 $\pm$ 11.17/60.95 $\pm$ 10.77	135.5 $\pm$ 51.33/ 148.30 $\pm$ 76.41	Nano-Cur	80; capsule	3 mo	Yes
Sahebkar, 2018 [32]	Asia	RDP	T2DM	50/50	43 $\pm$ 8/41 $\pm$ 7	163 $\pm$ 37/174 $\pm$ 33	Cur-pp	500; capsule	3 mo	Yes
Jirawatnotai, 2014a [17]	Asia	RDP	T2DM	107/106	59.16 $\pm$ 11.04/59.98 $\pm$ 10.71	143.83 $\pm$ 36.3/ 139.07 $\pm$ 36.14	Cmds	1500; capsule	3 mo	No
Jirawatnotai, 2014b [17]	Asia	RDP	T2DM	107/106	59.16 $\pm$ 11.04/59.98 $\pm$ 10.71	143.83 $\pm$ 36.3/ 139.07 $\pm$ 36.14	Cmds	1500; capsule	6 mo	No

<sup>a</sup> Ad, adult; Chd, children; C, control group; Cmds, curcuminoids; Cur, curcumin; Cur-pp, curcuminoid-piperine; d, day; E, experimental group; Hypercho, hypercholesterolemia; MetS, metabolism syndrome; n, Number of participants; NAFLD, Non-alcoholic Fatty Liver Disease; PHO, phospholipidated; RDC, randomized double-blind crossover; RDP, randomized double-blind parallel; RP, randomized parallel; T2DM, type 2 diabetes mellitus; Ref, reference; UF, Unformulated; y, year.

<sup>b</sup> Recruiting only males.

<sup>c</sup> The age was presented with overall ranges.

<sup>d</sup> Complying with overweight or obesity.

### 3.7. Subgroup analysis and meta-regressions

We evaluated six subgroups for FBG and HbA1c depending on different physical conditions of participants, doses of curcuminoids, treatment periods, oral agents, baseline FBG concentrations, and treatment with other medications. The results are presented in Table 3. Meta-regressions were performed for FBG and HbA1c values. The intervention

period (regression coefficient:  $-0.7$ ; 95% CI:  $-0.99$ ,  $-0.41$ ;  $P < 0.0001$ ) and dose (regression coefficient:  $-0.009$ ; 95% CI:  $-0.014$ ,  $-0.004$ ;  $P < 0.001$ ) significantly decreased the FBG concentrations.

## 4. Discussion

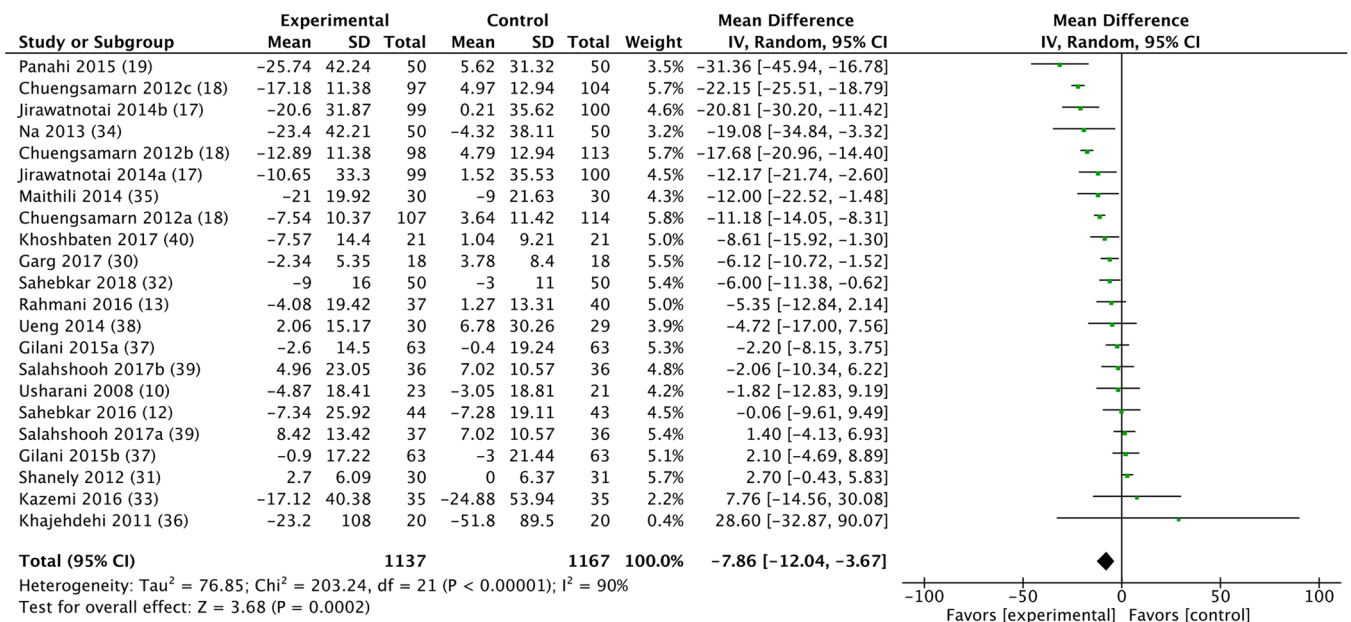
This systematic review and meta-analysis among people with

**Table 2**  
Risk of bias for trials included in the present meta-analysis based on the Cochrane Risk Bias Tool<sup>a</sup>.

First author, year (ref <sup>b</sup> )	Random sequence generation	Allocation concealment	Participant personnel blinding	Outcome assessment blinding	Incomplete outcome data	Selective reporting	other bias
Panahi, 2015 [19]	Unclear	Low	Low	Low	Low	Low	Low
Ueng, 2014 [38]	Low	Low	Low	Low	Low	Low	Low
Gilani, 2015a [37]	Low	Low	Low	Low	Low	Low	Low
Gilani, 2015b [37]	Low	Low	Low	Low	Low	Low	Low
Salahshooh, 2017a [39]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Salahshooh, 2017b [39]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Shanely, 2012 [31]	Unclear	Unclear	Low	Low	Low	Low	Low
Garg, 2017 [30]	Unclear	Unclear	Low	Low	Low	Low	Unclear
Rahmani, 2016 [13]	Unclear	Unclear	Low	Unclear	Low	Low	Low
Sahebkar, 2016 [12]	Unclear	Unclear	Low	Low	Low	Low	Low
Khoshbaten, 2017 [40]	Low	Unclear	Unclear	Low	Low	Low	Low
Chuengsamarn, 2012a [18]	Low	Low	Low	Low	High	Low	Low
Chuengsamarn, 2012b [18]	Low	Low	Low	Low	High	Low	Low
Chuengsamarn, 2012c [18]	Low	Low	Low	Low	High	Low	Low
Usharani, 2008 [10]	Unclear	High	Low	Low	Low	Low	Low
Khajehdehi, 2011 [36]	Unclear	Low	Low	Low	Low	Low	Low
Maithili, 2014 [35]	Unclear	High	Low	Low	Low	Low	Low
Na, 2013 [34]	Low	Low	Low	Low	Low	Low	Low
Kazemi, 2016 [33]	Low	Low	Low	Low	Low	Low	Low
Sahebkar, 2018 [32]	Unclear	Unclear	Low	Low	Low	Low	Low
Jirawatnotai, 2014a [17]	Low	Low	Low	Low	Low	Low	Low
Jirawatnotai, 2014b [17]	Low	Low	Low	Low	Low	Low	Low

<sup>a</sup> The details were related to seven domains which contained random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each category contained low risk, high risk and unclear risk according to the influence of them on the responding studies.

<sup>b</sup> ref, reference number



**Fig. 2.** Forest plot showing the difference in fasting blood glucose changes between experimental and control groups in 22 trials. Under the random-effect model, data are calculated and presented as weighted mean difference and 95% CI with the unit of mg/dL by using generic inverse-variance statistical method. The total means the number of participants in each group. The total means the number of participants in each group. IV, inverse variance.

metabolic diseases revealed that turmeric and curcuminoids decreased FBG, HbA1c, and HOMA-IR levels but had little effect on FSI values. Although the heterogeneities of all the values were high, the stability of these results was validated carefully by removing studies one by one

using RevMan software.

In detail, the level of FBG in the half of the arms with 719 people in the experimental group and 750 in the control group had been decreased by 14.21 mg/dL (95% CI: 18.46, -9.95 mg/dL, P < 0.00001). Although

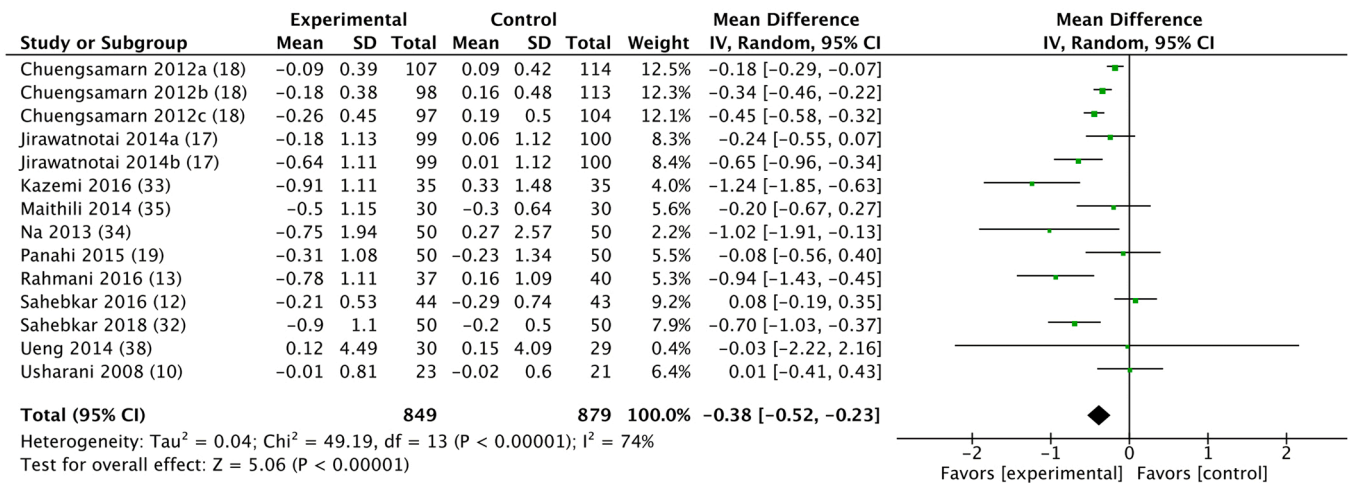


Fig. 3. Forest plot showing the difference in HbA1c changes between experimental and control groups in 14 trials. Under the random-effect model, data are calculated and presented as weighted mean difference and 95% CI by using generic inverse-variance statistical method. The total means the number of participants in each group. IV, inverse variance.

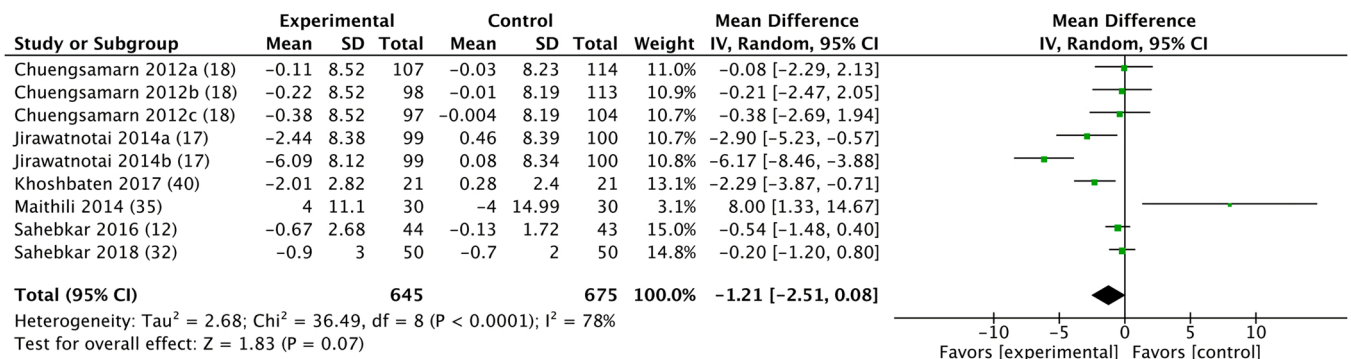


Fig. 4. Forest plot showing the difference in fasting serum insulin changes between experimental and control groups in 9 trials. Under the random-effect model, data are calculated and presented as weighted mean difference and 95% CI with the unit of mU/L by using generic inverse-variance statistical method. The total means the number of participants in each group. IV, inverse variance.

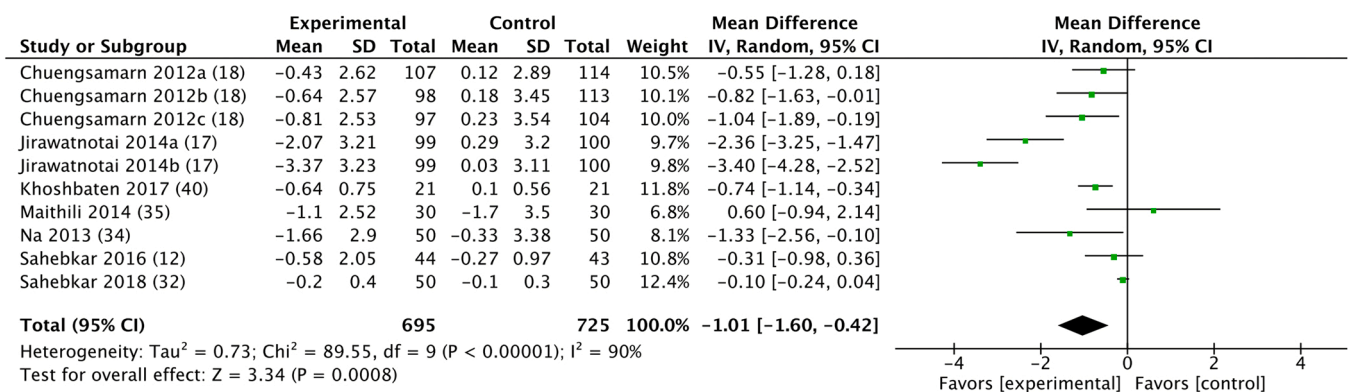


Fig. 5. Forest plot showing the difference in HOMA-IR changes between experimental and control groups in 10 trials. Under the random-effect model, data are calculated and presented as weighted mean difference and 95% CI by using generic inverse-variance statistical method. The total means the number of participants in each group. IV, inverse variance.

high heterogeneity deteriorated the convincing power, a minor change of result had been verified after excluding some trials. However, the remaining arms with 418 people in the experimental group and 417 in the control group showed no effect on FBG without heterogeneity. This result may be due to the low dose of curcumin administered in majority of the trials. Subgroup analysis of FBG in the low-dose group revealed

the results. This could indicate that increasing the daily administered amount is an effective method for improving effectiveness. The use of turmeric and curcuminoids decreased HbA1c levels, which reflects mean blood glucose in three months. However, six trials did not demonstrate any reduction in HbA1c levels, even with a large administration dose. According to a clinical trial, prolonging the administration period

**Table 3**  
Subgroup analysis for FBG, HbA1c<sup>a</sup>.

Subgroup <sup>b</sup>	Trials	n <sup>c</sup> (E/C)	mean difference <sup>d</sup> (mg/dL), 95%CI	Heterogeneity, I <sup>2</sup>	P
1. Total studies (FBG mg/dL)					
Physical condition					
T2DM	11	708/737	-12.88 (-17.49, -8.28)	80%	< 0.00001
non-T2DM	11	429/430	-3.36 (-7.07, 0.34)	71%	0.08
Period of intervention					
> 8 wk	10	676/707	-13.45 (-18.10, -8.80)	81%	< 0.00001
= 8 wk	6	247/246	-5.54 (-12.97, 1.88)	71%	0.14
< 8 wk	6	214/214	-2.11 (-6.13, 1.91)	67%	0.3
Doses of intervention					
High dose	10	689/717	-12.91 (-17.74, -8.08)	85%	< 0.00001
Low dose	12	448/450	-2.84 (-6.28, 0.60)	61%	0.11
Other therapy					
With	7	238/235	-6.47 (-11.25, -1.69)	16%	0.008
Without	15	899/932	-8.46 (-13.49, -3.43)	93%	0.001
Oral agent					
non-traditional agent	8	334/332	-7.82 (-13.75, -1.90)	79%	0.01
traditional agent	16	903/935	-7.82 (-13.75, -1.90)	91%	< 0.00001
Baseline of FBG (Mean mg/dL)					
≥ 126 mg/dL	8	426/426	-11.81 (-19.63, -3.98)	69%	0.003
110 <FBG< 126 mg/dL	5	223/225	-3.35 (-7.54, 0.85)	27%	0.12
≤ 110 mg/dL	9	488/516	-7.35 (-13.85, -0.86)	95%	0.03
2. Total studies (HbA1c %)					
Physical condition					
T2DM	10	688/717	-0.41 (-0.56, -0.26)	73%	< 0.00001
non-T2DM	4	161/162	-0.27 (-0.82, 0.28)	76%	0.33
Period of intervention					
> 8 wk	8	635/666	-0.46 (-0.62, -0.30)	77%	< 0.00001
= 8 wk	5	184/183	-0.20 (-0.60, 0.20)	70%	0.33
< 8 wk	1	30/30	-0.20 (-0.67, 0.27)	Not applicable	0.41
Doses of intervention					
High dose	9	653/681	-0.32 (-0.38, -0.26)	66%	< 0.00001
Low dose	5	196/198	-0.32 (-0.51, -0.12)	84%	0.002
Other therapy					
With	6	218/215	-0.55 (-0.97, -0.13)	68%	0.01
Without	8	631/664	-0.32 (-0.48, -0.17)	77%	< 0.0001
Oral agent					
non-traditional agent	4	179/178	-0.45 (-1.00, 0.09)	87%	0.11
traditional agent	10	670/701	-0.37 (-0.51, -0.23)	66%	< 0.00001
Baseline of FBG (Mean mg/dL)					
≥ 126 mg/dL	7	406/406	-0.50 (-0.80, -0.20)	70%	0.0009
110 <FBG< 126 mg/dL	3	97/99	-0.53 (-1.15, 0.09)	58%	0.1
≤ 110 mg/dL	4	346/374	-0.25 (-0.42, -0.08)	83%	0.004

<sup>a</sup> E/C, experimental/ control group; FBG, fasting blood glucose; FSI, fasting serum insulin; HbA1c.

<sup>b</sup> The subgroup analysis were performed from six fields to discover the source of heterogeneity for FBG and HbA1c.

<sup>c</sup> The number of participants who completed the trials finally in experimental and control groups.

<sup>d</sup> The results were showed in weighted mean difference, 95% CIs and corresponding I<sup>2</sup> value by using generic inverse-variance random-effects models.

improves clinical function [17]. Consequently, a high dose of curcumin should be consumed daily over a half year to lower HbA1c levels significantly. Various animal experiments and clinical trials have demonstrated that curcumin can regulate different signaling pathways to ameliorate insulin resistance, such as activating Nrf2 and heme-oxygenase-1 (HO-1) proteins in the liver, diminishing inflammation and macrophage infiltration to increase insulin sensitivity [41]. This is in accordance with our finding that most of the included studies showed a beneficial effect on HOMA-IR. A series of in vitro studies have shown that curcumin can simulate insulin release by suppressing the JNK pathway [42,43]. Nevertheless, the meta-analysis showed little effect on the FSI. This phenomenon revealed that the curative effect of turmeric and curcuminoids in vitro was not the same as that in vivo, nor was it far from clinical medicine.

Compared with existing reviews and meta-analyses [24], the current meta-analysis is the first to verify the effects of turmeric and curcuminoids on FSI values. Although turmeric and curcuminoids barely decreased the FSI level in totality, a decreased FSI level of 1.69 mU/l (95% CI: -3.22, -0.16 mU/l, P = 0.03) has been proven by prolonging the intervention time to more than eight weeks. However, the stability of this subgroup was poor and could be altered by removing some trials. More studies are needed to improve reliability and provide more

concrete evidence. Conversely, the meta-analysis conducted by Melo showed that the curcumin or combined curcuminoids decreased FBG concentrations by -8.88 mg/dL (95% CI: -5.04, -2.72 mg/dL, P = 0.005) and HbA1c levels by -0.54% (95% CI: -1.09, -0.002%, P = 0.049). However, curcumin or combined curcuminoids did not ameliorate HOMA-IR (1.26; 95% CI: -3.71, -1.19; P = 0.31) in their study, which was inconsistent with our findings which indicated that turmeric and curcuminoids decrease HOMA-IR (1.01; 95% CI: -1.6, -0.42; P = 0.0008). Evidence from our study may be stronger because we included a larger number of trials and applied more rigorous standards as compared with the previous meta-analysis. Moreover, meta-regressions were performed in a previous meta-analysis, and the baseline blood glucose levels and administered agents were found to have a profound influence on FBG concentrations (n = 11; P = 0.01) and HbA1c levels (n = 7; P = 0.04) [24]. Thus, we also initially performed meta-regression regarding oral agents and baseline FBG concentrations to analyze the FBG and HbA1c levels.

Nevertheless, our results showed that neither the administered agents nor the baseline FBG concentrations had significant effects on FBG (n = 22) or HbA1c (n = 14). This controversial result might be due to the different numbers of trials included in our analysis. We evaluated four other factors to detect the source of heterogeneity and found that

only intervention periods and doses had a significant influence on FBG concentrations ( $P < 0.0001$  or  $P < 0.001$ ), indicating that these differences might be the sources of heterogeneity. The corresponding subgroups were further analyzed, and the I<sup>2</sup> values were reduced to 81%, 67%, and 71% in each subgroup at different intervention times. After removing the study conducted by Panahi [19], the I<sup>2</sup> value was 0% in the group of eight weeks. This might have resulted from the highest intervention dosage of curcuminoids being administered in the study in this group. In the group of less than eight weeks, there was a detectable difference and decreased heterogeneity of 67–43% between trials, excluding one small trial [31]. This might be because the trial was conducted with a short intervention time (four weeks) and a low treatment dose (112 mg/day), indicating that both had an obvious effect on FBG concentrations. Additionally, the I<sup>2</sup> value was 85% in the high-dose group and 61% in the low-dose group. The effect of turmeric and curcuminoids on FBG concentrations was significant only in the subgroup of an intervention lasting more than eight weeks or in the subgroup receiving high-dose curcuminoids. Finally, publication bias was discovered in both the previous meta-analyses and our study regarding HOMA-IR values. In the existing meta-analyses, publication bias was eliminated by eliminating one study. After removing the study performed by Sahebkar [32], bias was eliminated ( $P = 0.539$ ) in our study. In addition, two studies that were not published and one that was not written in English or Chinese were excluded, which could be a potential risk for publication bias. We were encouraged that our results indicating the safety and tolerance of both turmeric and curcuminoids were outstanding and that no studies reported serious side effects.

This study has some limitations that should be noted. The most serious limitation of this meta-analysis was the high heterogeneity, which might diminish the reliability of the results [44]. Although we evaluated subgroups of all parameters from the six fields to determine the sources of heterogeneity, this did not work well. The stabilities of nearly half of the subgroups were poor, which may have impaired the credibility of the results. Therefore, high-quality and long-duration randomized controlled trials are necessary. Another shortcoming was that the changes in the means and SDs before and after treatment and between the treatment and control groups were calculated according to a series of formulas in the Cochrane Handbook rather than being directly provided by the authors [26]. These processes might be a potential source of heterogeneity, resulting in the poor accuracy of the results. Moreover, most of the trials were conducted in Asia, which may impair the reliability of the results for people from other continents. However, the present meta-analysis had some advantages. The inclusion criteria were rigorous, and the quality of most of the included studies was high. In addition, funnel plots, meta-regressions, subgroup analyses, and sensitivity analyses were performed to determine and investigate the sources of heterogeneity.

In conclusion, the present meta-analysis suggests that both turmeric and curcuminoids can lower FBG, HbA<sub>1c</sub>, and HOMA-IR levels among patients with metabolic diseases, especially in Asian areas, and their strong effects are more significant when prolonging the intervention time to more than eight weeks and increasing the daily dose to 300 mg. In addition, they may have a positive effect on FSI concentrations, extending the intervention time to more than eight weeks.

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#### CRedit authorship contribution statement

Dingkun Wang and Meilin Hu designed the search strategy and searched the database; Wenbin Wu and Leyi Ma confirmed the inclusion criteria and selected the articles; Jing Gong collected the data; Ke Fang completed the quality assessment that Wenya Huang checked; Fen Yuan finished data synthesis and statistics; Fen Yuan executed writing; Hui Dong and Fuer Lu revised the manuscript carefully. None of the authors has reported any conflicts of interest related to the study.

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#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106121.

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