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EFFECT OF CURCUMIN ON GLYCEMIC CONTROL AND METABOLIC PARAMETERS IN PREDIABETES AND DIABETES

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Abstract: The trend of adding natural medicines for diabetes treatment is uprising. Curcumin, commercially available as mixture of curcuminoids, is one of natural substance which has antidiabetic activities including insulin secretagogue and insulin sensitizer. Possible mechanisms include attenuation of tumor necrosis factor-alpha (TNF-α) and plasma free fatty acid (FFA) as well as activation of peroxisome proliferator-activated receptor gamma (PPAR-γ). This systematic review was aimed to evaluate the effect of curcumin on glycemic control and metabolic parameters in prediabetes and diabetes. Literature review up to November 2017 was undertaken in Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Center for Complementary and Integrative Health (NCCIH), Scopus, ScienceDirect, Web of Science, ProQuest Dissertations and Theses (PQDT), etc. Twelve trials (N=459) met the eligibility criteria and were included. The results indicated that curcuminoids may offer benefits for prediabetes and type 2 diabetes mellitus (T2DM) with tolerable safety profile. Regardless of the varied settings of the included trials, curcuminoids tended to reduce fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) in these populations. Additionally, the improvement was likely observed on lipid profile, such as triglyceride and cholesterol. The available evidence also suggested that giving curcuminoids might be a good strategy to prevent the development of T2DM in prediabetes. Notwithstanding the beneficial effects of curcumin on glycemic control and lipid profile, the recent data may encourage higher quality trials with longer duration to establish the role of curcumin in clinical application, particularly in diabetes management.

Keywords: Curcumin, diabetes, prediabetes, glucose, lipid

บทคัดย่อ **การใช้สารจากธรรมชาติในการรักษาเบาหวานกำลังได้รับความสนใจ เคอร์คิวมิน** (curcumin) **เป็นสารสำคัญของสารสกัดเคอร์คูมินอยด์** (curcuminoids) **พบในผลิตภัณฑ์ขมิ้นชัน ที่สามารถออกฤทธิ์ลดระดับน้ำตาลในเลือด โดยกระตุ้นการหลั่งอินซูลินและเพิ่มความไวต่ออินซูลิน ทั้งนี้กลไก น่าจะเกิดจากผลของการยับยั้งการทำงานของ** tumor necrosis factor-alpha (TNF-α) **และ** plasma free fatty acid (FFA) **รวมถึงกระตุ้นการทำงานของ** peroxisome proliferator-activated receptor gamma (PPAR-γ) **งานวิจัยฉบับนี้มีวัตถุประสงค์เพื่อทบทวนวรรณกรรมอย่างเป็นระบบเกี่ยวกับประสิทธิผลของเคอร์คิวมินในการควบคุมระดับน้ำตาลในเลือดและผลของพารามิเตอร์ทางเมตาบอลิกในผู้ป่วยที่มีภาวะเบาหวานระยะเริ่มต้น** (prediabetes) **และเบาหวาน โดยทำการสืบค้นข้อมูลจากงานวิจัยที่ถูกตีพิมพ์ตั้งแต่อดีตจนถึงเดือนพฤศจิกายน ปี พ.ศ.** 2560 **จากฐานข้อมูลอิเล็กโทรนิกส์ ได้แก่** Pubmed, CENTRAL, CINAHL, NCCIH, Scopus, ScienceDirect, Web of Science **และ** ProQuest Dissertations and Theses (PQDT) **ผลการศึกษา พบงานวิจัยทั้งหมด** 12 **ฉบับที่สอดคล้องกับเกณฑ์คัดเข้า พบว่า เคอร์คูมินอยด์อาจมีประโยชน์ในผู้ป่วยเบาหวานระยะแรกและเบาหวานชนิดที่** 2 **ผู้ป่วยสามารถทนต่อยาได้ดีและมีแนวโน้มที่จะสามารถลดระดับน้ำตาลในเลือดได้ทั้งพลาสมากลูโคสขณะอดอาหาร** (FPG) **และฮีโมโกลบินเอวันซี** (HbA1c) **นอกจากนี้ยังมีผลที่ดีต่อระดับไขมันในเลือด เช่น ไตรกลีเซอร์ไรด์ และคอเลสเตอรอล จากข้อมูลดังกล่าว อาจมีการใช้เคอร์คูมินอยด์ในกลุ่มผู้ป่วยเบาหวานระยะแรก ซึ่งเป็นหนึ่งวิธีที่สามารถช่วยป้องกันการพัฒนาไปสู่โรคเบาหวานชนิดที่** 2 **อย่างไรก็ตาม การศึกษาทางคลินิกในระยะยาวจะเป็นข้อมูลช่วยยืนยันบทบาทของการใช้สารเคอร์คิวมินในทางคลินิกที่ชัดเจน โดยเฉพาะในการรักษาผู้ป่วยเบาหวานต่อไป**

คำสำคัญ: เคอร์คิวมิน, เบาหวาน, ภาวะเบาหวานระยะเริ่มต้น, น้ำตาล, ไขมัน

INTRODUCTION

The incidence of diabetes as chronic disease presented with high level of blood glucose had been rising since almost three decades ago, predominated by type 2 diabetes mellitus (T2DM) (World Health Organization, 2016). T2DM needs effective prevention and management. Prevention is also a good strategy to start in people with prediabetes whose condition is prone to T2DM as their blood glucose levels are between normal and diabetic state (American Diabetes Association, 2017).

Nowadays herbal medicines attract more attention in diabetes treatment. Curcumin, commercially available as mixture of curcuminoids, was mentioned as one of the natural substances which has potential effects in diabetes treatment including insulin secretagogue and insulin sensitizer (Bi *et al.*, 2017; Ghorbani *et al.*, 2014). Based on these mechanisms, curcumin may improve not only glycemic control, but also metabolic parameters such as lipid profile. It is supported by results of clinical trials in people with prediabetes (Chuengsamarn *et al.*, 2012; Rahmani *et al.*, 2016) and diabetes (Chuengsamarn *et al.*, 2012; Chuengsamarn *et al.*, 2014; Jiménez-Osorio *et al.*, 2016; Na *et al.*, 2013; Rahimi *et al.*, 2016; Rahmani *et al.*, 2016). Nevertheless, the available evidence shows inconsistent results. This systematic review was aimed to evaluate the effect of curcumin on glycemic control and metabolic parameters in prediabetes and diabetes.

MATERIALS AND METHODS

This systematic review was conducted without protocol pre-registration to any organization.

Search Strategy and Data Sources

A systematic literature search was performed with inception until November 2017 through MEDLINE (Pubmed), Cochrane Central Register of Controlled Trials (CENTRAL), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), National Center for Complementary and Integrative Health (NCCIH), Scopus, ScienceDirect, Web of Science, ProQuest Dissertations and Theses (PQDT), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), International Standard Randomised Controlled Trial Number (ISRCTN) Registry, BioMed Central, Australian New Zealand Clinical Trial Registry (ANZCTR), Latin American and Caribbean Health Sciences Literature (LILACS), and Google Scholar. The following medical subject heading (MeSH) terms were used; curcumin, curcuma, diabetes mellitus, prediabetic state, hyperglycemia, insulin resistance, hypoglycemic agents, placebos, blood glucose, hemoglobin A glycosylated, triglycerides, cholesterol, LDL, lipoprotein, HDL, and followed by keyword search using "(curcumin extract" OR "curcuminoid" OR "turmeric" OR "curcuma longa" OR "antidiabetics") AND ("prediabetes" OR "impaired glucose tolerance" OR "type 2 diabetes" OR "hyperglycemia" OR "lipid profiles"). Manual search of related citation articles was also carried out.

Study Selection

Eligibility criteria for study selection were (1) randomized controlled trials (RCTs) comparing the effect of curcumin with placebo or any comparator or no treatment in diabetes or prediabetes, (2) curcumin was administered as single extract or curcuminoids mixture or defined composition in turmeric powder or as combined extract with other substance with dominant or equal proportion, (3) reporting glycemic and/ or metabolic parameters such as fasting plasma glucose (FPG) or glycosylated hemoglobin (HbA1c) or lipid profile including triglyceride (TG) or total cholesterol (TC), and (4) published in English. Three reviewers

screened the records independently. One reviewer selected the study by in-depth review. The other two reviewers decided the final eligibility of the selected studies. Conflicts over decision were settled by mutual discussion among reviewers.

Data Extraction and Quality Evaluation

Data extraction was performed by one reviewer and double-checked by the rest two reviewers. Meanwhile, two reviewers assessed the studies' quality. The other reviewer resolved the disagreements between the two reviewers as needed. Studies' quality was assessed by using "Cochrane Risk of Bias Tools" to evaluate seven domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias). The judgment was categorized into 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias (Higgins *et al.*, 2008).

RESULTS AND DISCUSSION

Study selection

We identified a total of 459 records through database searching and other sources including manual search from relevant cited references (Figure 1). We excluded duplication of 84 records. Based on the title and abstract screening, 341 records were excluded, leaving 34 RCTs to be further assessed. There were 22 full texts removed as the following reasons: other condition or diseases (Nakayama *et al.*, 2014; Panahi *et al.*, 2016b; Sengupta *et al.*, 2012; Wickenberg *et al.*, 2010), no baseline values (Neerati *et al.*, 2014), minor proportion of curcumin in combined extracts (Cicero *et al.*, 2017; Grant *et al.*, 2013; Kurian *et al.*, 2014; Mahajan *et al.*, 2015; Mani *et al.*, 1997; Rotman-Pikielny *et al.*, 2014), randomized trial without control group as comparator (Banerji & Banerjee, 2016; Sukandar *et al.*, 2010; Yang *et al.*, 2015), no desired outcomes (Hodai *et al.*, 2016; Lee *et al.*, 2014; Panahi *et al.*, 2016a; Panahi *et al.*, 2017a; Steigerwalt *et al.*, 2012), and were not published in English (Adab *et al.*, 2013; Hodaie *et al.*, 2017; Setiawan *et al.*, 2011). The remaining twelve RCTs met the eligibility criteria and were included in the systematic review.

Study Characteristics and Study Quality

The summary of study characteristics and risk of bias are presented in Table 1 and Table 2, respectively. All studies were from Asian countries, except study by Jiménez-Osorio *et al.* (2016) which was performed in Mexico. Among the twelve studies involved in this systematic review, three studies were conducted in prediabetes with study duration ranging from eight weeks to nine months (Chuengsamarn *et al.*, 2012; Rahmani *et al.*, 2016; Yang *et al.*, 2014). The other nine studies were carried out in diabetic subjects, especially T2DM, within four weeks to six months (Chuengsamarn *et al.*, 2014; Jiménez-Osorio *et al.*, 2016; Khajehdehi *et al.*, 2011; Na *et al.*, 2013; Panahi *et al.*, 2017b; Rahimi *et al.*, 2016; Selvi *et al.*, 2015; Sukandar *et al.*, 2014; Usharani *et al.*, 2008). The preparations used were varied, such as curcuminoids extract (70-1890 mg/day), turmeric powder (confirmed as curcumin 66.3-320 mg/day), or combined with garlic extract (alliin 36-42 mg/day and curcumin 225-255 mg/day).

Outcomes on Glycemic Control and Lipid Profile

The outcomes data on glycemic parameters are presented in Table 3. Assessment on glycemic outcomes in prediabetes revealed that curcumin appeared to decrease FPG by up to

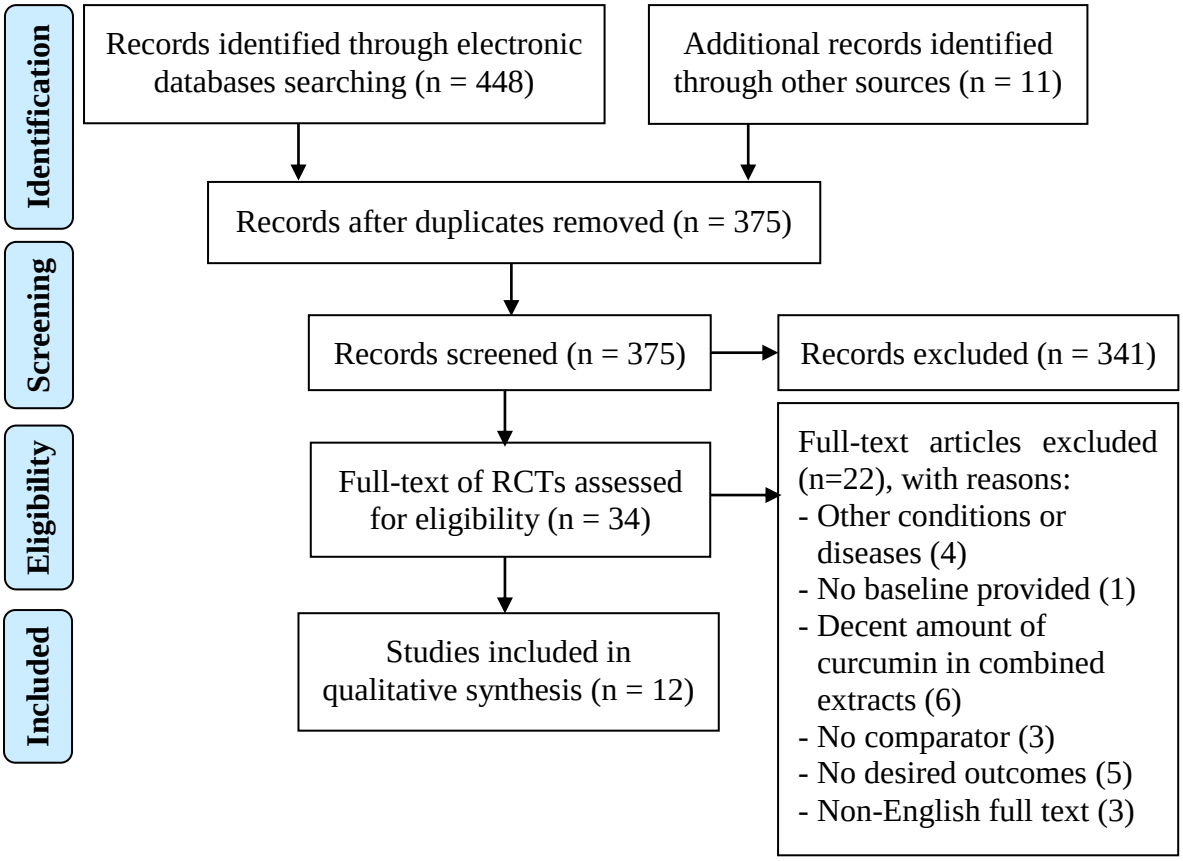

Figure 1. Flow diagram of study selection
RCT: randomized-controlled trial

17 mg/dL compared to placebo which tended to show increase in FPG. Moreover, the trend of effect on HbA1c showed similar direction in all prediabetes studies offering reduction within 0.2-0.8%. Meanwhile, finding in diabetes studies, demonstrated tendency of curcuminoids reducing FPG in all the included studies. Curcumin preparation might reduce FPG in diabetes up to 51 mg/dL compared to control groups. Furthermore, consistent results with similar pattern were found on HbA1c outcomes. The significant reduction from baseline of the intervention group could reach up to 2.3%. In summary, curcuminoids may improve FPG and HbA1c in both prediabetes and type 2 diabetes, regardless the types of preparation used.

Table 4 shows the data on lipid outcomes. Findings in prediabetes revealed that curcuminoids accounted for higher reduction of TG values than placebo which was up to 65 mg/dL. However, TC reduction was less than of TG which was up to only 24 mg/dL. Interestingly in diabetes, the reports showed both increase and decrease in TG. Nevertheless, overall tendency of reduction from baseline might reach 75 mg/dL. The higher decrease was demonstrated by the longer duration of studies. Correspondingly, this trend was also observed in TC. Highest reduction on TC by curcumin was up to 31 mg/dL. These findings indicated favorable effects of curcumin on lipid profile with tendency of obvious reduction in studies with longer duration.

Some studies in prediabetes and diabetes mentioned minor adverse events (AEs) in curcumin groups compared to placebo. For example, gastrointestinal symptoms including constipation, mild diarrhea, stomachae, and nausea (Rahmani *et al*., 2016, Yang *et al*., 2014, Chuengsamarn *et al.*, 2014, Chuengsamarn *et al*., 2012, Usharani *et al*., 2008). Other AEs also existed such as vertigo and itching (Chuengsamarn et al., 2012). However, these AEs were reported as tolerable and not serious.

Table 1. Characteristics of the included studies

Study (Location, Duration)	Inclusion Criteria	Study Arms (n = f + m)
Prediabetes		
Rahmani *et al*. 2016 (Iran, 8 weeks)	MetS, NAFLD (grades 1-3)	Curcumin amorphous dispersion 500 mg/day (curcuminoids 70 mg/day) (n = 19 + 21); Placebo (n = 19 + 21)
Yang *et al*. 2014†† (Taiwan, 12 weeks)	MetS, Asian men or women, taking stable treatment	Curcumin extract (curcuminoids 1890 mg/day) (n = 21 + 12); Placebo (n = 15 + 17)
Chuengsamarn *et al.* 2012† (Thailand, 9 moths)	Naïve prediabetes, age ≥ 35 years	Curcumin capsule (curcuminoids 1.5 g/day) (n = 78 + 42); Placebo (n = 75 + 42)
Diabetes		
Panahi *et al*. 2017b†† (Iran, 12 weeks)	T2DM, age 18-65 years, BMI ≥ 24.0, taking standard care of diabetes	C3 Complex® capsule (curcuminoids 1 g/day) + piperine 10 mg/day (n = 25 + 25); Placebo (n = 24 + 26)
Jiménez-Osorio *et al.* 2016 (Mexico, 8 weeks)	Diabetic/ non-diabetic proteinuric CKD without UTI or HF (class III or IV), age 20-70 years	Diabetic groups: Turmeric capsule (curcumin 320 mg/day) (n = 9 + 19); Placebo (n = 6 + 17)
Rahimi *et al*. 2016†† (Iran, 3 months)	T2DM, taking other necessary medications	Nano-curcumin (nano-micelle) 80 mg/day (n = 18 + 17); Placebo (n = 21 + 14)
Selvi *et al*. 2015*†† (India, 4 weeks)	T2DM, male, age 35-55 years, diabetes duration <2 years, taking metformin	Turmeric powder 2 g/day + metformin 1 g/day (n = 0 + 30); Metformin 1 g/day (n = 0 + 30)
Chuengsamarn *et al*. 2014† (Thailand, 6 months)	Naïve T2DM, age ≥35 years	Curcumin capsule (curcuminoids 1.5 g/day) (n = 57 + 50); Placebo (n = 59 + 47)
Sukandar *et al*. 2014† (Indonesia, 12 weeks)	Naïve T2DM with or without DLP, male or female, age >35 years	Allium curcuma (garlic extract 1.2 g/day + turmericethanolic extract 1.2 g/day or curcumin 225-255 mg/day (n = 17); Glibencamide (n = 12)
Na *et al*. 2013†† (China, 3 months)	Obese or overweight T2DM, age 18-65 years, BMI ≥24.0, on current optimal treatment (OAD or insulin or both + LLD or AHT medication) ≥ 6 months	Curcuminoids capsule 300 mg/day (n = 26 + 24); Placebo (n = 25 + 25)
Khajehdehi *et al*. 2011†† (Iran, 2 months)	Overt type 2 diabetic nephropathy, proteinuria ≥ 500 mg/day, normal kidney function, taking stable ACEI and/ or ARB	Turmeric powder 1.5 g/day (curcumin 66.3 mg/day) (n = 11 + 9); Placebo (n = 7 + 13)
Usharani *et al*. 2008†† (India, 8 weeks)	T2DM, age 21-80 years, stable antidiabetic agents ≥2 months, taking metformin or metformin + sulfonylurea	NCB-02 (C3 curcuminoids preparation) 600 mg/day (n = 11 + 12); Atorvastatin 10 mg/day (n = 11 + 12); Placebo (n = 10 + 11)

*Open-labeled design, †No background therapy, ††Add-on therapy;
DB: double-blinded, OAD: oral antidiabetic drugs, LLD: lipid-lowering drugs, AHT: antihypertensive drugs, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, MetS: metabolic syndrome, NAFLD: non-alcoholic fatty liver disease, T2DM: type 2 diabetes mellitus, CKD: chronic kidney disease, UTI: urinary tract infection, HF: heart failure, DLP: dyslipidemia, BMI: body mass index, n: number of patient, f: female, m: male

Table 2. Risk of bias of the included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Panahi *et al*. 2017b	U	U	L	U	L	L	H
Jiménez-Osorio *et al.* 2016	U	U	L	U	L	L	U
Rahimi *et al*. 2016	L	U	L	U	L	L	L
Rahmani *et al*. 2016	U	L	L	U	L	L	H
Selvi *et al*. 2015	L	H	H	H	L	L	L
Chuengsamarn *et al*. 2014	L	L	L	U	L	L	L
Sukandar *et al*. 2014	U	U	L	U	U	L	H
Yang *et al*. 2014	L	U	L	U	L	L	L
Na *et al*. 2013	L	U	L	L	L	L	L
Chuengsamarn *et al.* 2012	L	L	L	U	L	L	L
Khajehdehi *et al.* 2011	U	L	L	U	L	L	L
Usharani *et al*. 2008	U	U	H	H	L	H	L

H: high risk of bias, L: low risk of bias, U: unclear risk of bias

Table 3. Summary of glycemic outcomes

Study	Arms	FPG (mg/dL)		HbA1c (%)	
		Baseline	Endpoint	Baseline	Endpoint
Prediabetes					
Rahmani et al. 2016	Cur Pcb	111.65 ± 34.64 116.90 ±47.66	107.57 ± 28.34 118.18 ± 47.35**	6.31 ± 1.62* 7.37 ± 1.33	5.53 ± 1.27** 7.53 ± 1.33
Yang *et al.* 2014	Cur Pcb	112.75 ± 18.85 117.53 ± 27.63	114.82 ± 16.15 124.32 ± 11.91	6.32 ± 0.91 6.41 ± 1.03	6.20 ± 0.73 6.56 ± 1.06
Chuengsamarn *et al.* 2012††	Cur Pcb	103.65 ± 0.99 103.24 ± 0.98	86.47 (73-122)* 108.21 (80-138)	5.86 ± 0.04 5.83 ± 0.03	5.60 (4.9-6.8)* 6.02 (5.2-7.5)
Diabetes					
Jiménez-Osorio *et al.* 2016†	Cur Pcb	126.10 ± 9.80 119.70 ± 18.60	120.90 ± 8.80 122.60 ± 11.70	NA	NA
Rahimi *et al.* 2016	Cur Pcb	135.50 ± 51.33 148.30 ± 76.41	120.29 ± 38.01*,** 176.00 ± 61.56	7.59 ± 1.74 7.49 ± 1.75	7.31 ± 1.54*,** 9.00 ± 2.33
Selvi *et al.* 2015	Tur+Met Met	116.00 ± 23.00 111.00 ± 24.00	95.00 ± 11.40** 102.00 ± 18.00**	7.90 ± 1.30 7.80 ± 0.50	7.40 ± 0.90** 7.50 ± 0.70
Chuengsamarn *et al.* 2014†	Cur Pcb	143.83 ± 3.51 138.07 ± 3.51	123.23 ± 2.42 139.28 ± 3.49	7.10 ± 0.12 6.97 ± 0.11	6.46 ± 0.09 6.98 ± 0.11
Sukandar *et al.* 2014†	Al+Cur Gli	192.76 ± 14.59* 250.33 ± 14.55	141.75 ± 9.67** 154.50 ± 24.06**	10.41 ± 0.64 11.86 ± 0.53	8.09 ± 0.37** 7.86 ± 0.45**
Na *et al.* 2013	Cur Pcb	154.44 ± 47.88 151.38 ± 39.06	131.04 ± 31.86* 147.06 ± 37.08	7.77 ± 1.82 7.72 ± 2.12	7.02 ± 2.04* 7.99 ± 2.86
Khajehdehi *et al.* 2011	Tur Pcb	179.00 ± 65.50 169.54 ± 76.30	155.80 ± 90.90 123.60 ± 41.90	NA	NA
Usharani *et al.* 2008	Cur Ato Pcb	155.04 ± 17.94 161.21 ± 19.74 161.19 ± 19.97	150.17 ± 18.84 157.73 ± 16.51 158.14 ± 17.38	8.04 ± 0.85 8.30 ± 0.86 7.82 ± 0.57	8.03 ± 0.76 8.29 ± 0.81 7.80 ± 0.62

*significant difference ($p<0.05$) between groups at corresponding time (baseline or study end)
**significant change ($p<0.05$) from baseline within the same group at study end
All data were presented in mean ± SD otherwise stated as mean and: † ± SEM, †† (minimum-maximum) values
Cur: curcumin, Pcb: placebo, Tur: turmeric group, Met: metformin, Al: alium, Gli: glibenclamide, Ato: atorvastatin, FPG: fasting plasma glucose, HbA1c: glycosylated hemoglobin, NA: not available

Discussion

The results on this systematic review gave the evidence that curcumin may benefit both as single treatment or add-on therapy in prediabetes and T2DM. Curcumin in many forms of preparation tended to improve both glycemic parameters and lipid profile in these popula-

Table 4. Summary of lipid outcomes

Study	Arms	TG (mg/dL)		TC (mg/dL)	
		Baseline	Endpoint	Baseline	Endpoint
Prediabetes					
Rahmani *et al.* 2016	Cur	199.68 ± 91.46*	173.43 ± 95.44	198.59 ± 41.76	174.38 ± 39.56**
	Pcb	160.20 ± 61.94	153.58 ± 50.12	187.78 ± 32.95	196. 82 ± 37.04**
Yang *et al.* 2014	Cur	226.10 ± 64.99	160.79 ± 75.46**	195.10 ± 42.47	175.86 ± 30.63**
	Pcb	159.46 ± 86.28	144.65 ± 56.06	180.07 ± 33.82	167.53 ± 37.6
Diabetes					
Panahi *et al.* 2017b	Cur+Pip	229.78 ± 81.84	205.48 ± 64.52**	217.34 ± 41.60	195.48 ± 33.39**
	Pcb	207.62 ± 54.63	187.06 ± 44.34**	231.04 ± 70.95	213.98 ± 55.12**
Jiménez-Osorio *et al.* 2016†	Cur	155.70 ± 11.00	162.30 ± 13.40	208.50 ± 10.00	218.40 ± 11.50
	Pcb	187.10 ± 22.60	189.00 ± 22.70	231.80 ± 15.90	251.80 ± 22.60
Rahimi *et al.* 2016	Cur	109.00 (94.75)††	131.00 (60.27)†† **	163.40 ± 33.94	158.62 ± 44.06**
	Pcb	142.00 (97.50)	113.00 (58.00)	162.40 ± 38.59	149.00 ± 24.62
Selvi *et al.* 2015	Tur+Met	120.56 ± 37.10	125.70 ± 29.21	184.60 ± 14.60	176.60 ± 14.32
	Met	127.30 ± 33.30	123.40 ± 23.80	181.50 ± 22.30	178.10 ± 24.80
Chuengsamarn *et al.* 2014†	Cur	158.24 ± 9.84	82.98 ± 4.73*	199.43 ± 4.36	168.80 ± 3.89
	Pcb	166.94 ± 9.85	166.87 ± 9.83	195.88 ± 4.29	195.95 ± 4.30
Sukandar *et al.* 2014†	Al+Cur	179.10 ± 21.67	149.75 ± 12.00	240.15 ± 8.01	226.65 ± 7.95*,**
	Pcb	209.56 ± 30.64	186.25 ± 40.11	234.38 ± 6.16	175.63 ± 6.45**
Na *et al.* 2013	Cur	197.51 ± 46.94	157.65 ± 49.60*	236.27 ± 43.70	215.78 ± 41.76
	Pcb	193.97 ± 92.11	186.88 ± 64.43	235.11 ± 47.95	228.15 ± 46.02
Khajehdehi *et al.* 2011	Tur	236.20 ± 146.50	196.70 ± 118.10	214.20 ± 66.50	187.50 ± 59.20
	Pcb	220.40 ± 106.90	190.50 ± 129.90	193.30 ± 45.70	163.70 ± 46.50
Usharani *et al.* 2008	Cur	176.39 ± 27.61	165.26 ± 25.78	195.00 ± 41.16	185.84 ± 34.35
	Ato	182.26 ± 43.85	142.73 ± 17.67**	196.78 ± 35.28	158.69 ± 23.69**
	Pcb	170.14 ± 47.54	168.14 ± 47.10	196.95 ± 35.72	198.76 ± 35.09

*significant difference ($p<0.05$) between groups at corresponding time (baseline or study end)
**significant change ($p<0.05$) from baseline within the same group at study end
All data were presented in mean ± SD otherwise stated as mean and: † ± SEM, †† median interquartile
Cur: curcumin, Pcb: placebo, Pip: piperine, Tur: turmeric group, Met: metformin, Al: alium, Gli: glibenclamide, Ato: atorvastatin, TG: triglyeride, TC: total cholesterol

tions. Basically, curcumin is a polyphenol substance which has pleiotropic activities such as antidiabetes (Prasad *et al.*, 2014). Antidiabetic activities include insulin sensitizer and insulin secretagogue. Possible mechanisms include attenuation of tumor necrosis factor-alpha (TNF-α) and plasma free fatty acid (FFA) as well as activation of peroxisome proliferator-activated receptor gamma (PPAR-γ). The effect on lipid outcomes might be linked with the insulin sensitizing effect of curcumin along with the role of curcumin to normalize human adipose tissue dysfunction (Zhang *et al.*, 2013). All these mechanisms are appropriate for diabetes treatment since insulin resistance and β-cells defect are the hallmark of T2DM (Del Prato *et al.*, 2017). Giving curcumin starting from prediabetic state which is in increased risk of diabetes (American Diabetes Association, 2017) may also become a good strategy to prevent the development of T2DM. Again, the delayed onset on T2DM had been confirmed by Chuengsamarn *et al*. (2012).

To our knowledge, the consensus of generally effective dose to control glycemia and lipids particularly in either prediabetes or diabetes has not been available. However, we may suggest minimum dose of curcumin to be effective in controlling glycemia and lipids is 1.5 g per day as curcumunoids extract in prediabetes. We suggested similar dose for diabetes population, considering the significant magnitude of the outcomes. Should be noted, these doses might be appropriate after comparing with placebo or without giving curcumin to the patients. Additionally, curcumin having tolerable safety profile without serious adverse events had been mentioned by some studies (Chuengsamarn *et al*., 2012, Chuengsamarn *et al*., 2014, Na *et al*., 2013, Rahmani *et al*., 2016, Usharani *et al*., 2008). This matter might become additional advantage given the beneficial effects based on this systematic review.

The overall quality of studies included in this systematic review were of moderate to high. Therefore, this supported the findings in our systematic review to demonstrate the effects of curcumin on glycemic parameters and lipid profile in prediabetes and diabetes. Higher quality and larger trials with much longer duration to establish the role of curcumin in clinical application, particularly in diabetes management, should be encouraged.

CONCLUSION

Curcumin as single supplementation or an add-on treatment, regardless of the types of preparation, possibly improve glycemic control and lipid profile in prediabetes and T2DM with more distinct effects in longer duration of treatment. Nevertheless, higher quality studies are awaited to uphold the role of curcumin in diabetes treatment.

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