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Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis

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Abstract. We conducted a systematic review and meta-analysis to evaluate the effect of Berberine on glucose in patients with type 2 diabetes mellitus and identify potential factors may modifying the hypoglycemic effect. We searched PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database to identify randomized controlled trials that investigated the effect of Berberine. We calculated weighted mean differences (WMD) and 95% confidence interval (CI) for fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated haemoglobin (HbA1c) levels. Twenty-eight studies were identified for analysis, with a total of 2,313 type 2 diabetes mellitus (T2DM) patients. The pool data showed that Berberine treatment was associated with a better reduction on FPG (WMD = –0.54 mmol/L, 95% CI: –0.77 to –0.30), PPG (WMD = –0.94 mmol/L, 95% CI: –1.27 to –0.61), and HbA1c (WMD = –0.54 mmol/L, 95% CI: –0.93 to –0.15) than control groups. Subgroup-analyses indicated that effects of Berberine on blood glucose became unremarkable as the treatment lasted more than 90 days, the daily dosage more than 2 g/d and patients aged more than 60 years. The efficiency of Berberine combined with hypoglycaemics is better than either Berberine or hypoglycaemic alone. The dosage and treatment duration of Berberine and patients' age may modify the effect.

Key words: Berberine, Diabetes, Meta-analysis

DIABETES MELLITUS, a metabolic disorder of the endocrine system, is one of the most common chronic diseases worldwide. There are more than 415 million people with diabetes in the world, and the number will be 642 million by 2040 [1]. Diabetes is an important risk factor for cardiovascular disease and chronic kidney disease [2]. It is responsible for over 5 million deaths [1]. Controlling blood glucose level in people with diabetes will help reduce morbidity and mortality globally [3].

Pharmacological intervention, including oral hypoglycemic agents (OHA) and insulin, is recommended for patients who are unable to reach their glycemic goals by lifestyle modification. Although many new OHAs have been developed, there remain some disadvantages of current treatments. Recently Agarwal *et al.* have reported that the efficacy of anti-diabetic drugs in achieving optimal glycemic control was only 41% among patients [4]. There are a number of potential side effects in currently available anti-diabetic treatments. For example, insulin and insulin secretagogues may increase breast, pancreas, liver and colorectal cancer risk [5], and metformin, the most commonly prescribed OHA, is associated with gastrointestinal discomfort.

Berberine is a traditional Chinese medicine extracted from Chinese rhizomacoptidis, cortex phellodendri, berberis and other plants. It has been used extensively for the treatment of gastrointestinal infections. However, in recent years there has been increased number of studies undertaken in China to examine the treatment effects of Berberine in patients with diabetes, which is probably following the Chinese traditional medicine's "secret prescriptions". Guan *et al.* [6] carried out Berberine *versus* metformin RCT and found Berberine could lower blood glucose, and Zhang *et al.* [7] carried out Berberine *versus* metformin RCT and found Berberine lower blood glucose by increasing insulin receptor expression. But

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some other did not report a significant effect of berberine on glucose, although it reduced blood pressure and cholesterol significantly [8]. A recent systematic literature review [9] showed that berberine with lifestyle intervention was more effective in lowering the level of HbA1c than lifestyle intervention alone or placebo (WMD = –0.71 mmol/L, 95% CI (–0.94, –0.49), $p = 0.001$). Lan *et al.* found that there was substantial heterogeneity in previous studies on the effects of berberine on blood glucose, but it is not clear about what factors caused it. Since Lan *et al.*'s publication, there have been more studies published [10-12]. Numerous studies have shown that Berberine has hypoglycemic effects in the treatment of patients with T2DM, but its efficacy has not been confirmed by large scale and multicenter clinic trials.

We conducted a systematic literature review and a meta-analysis of all randomized controlled trials (RCTs) to assess the hypoglycemic effects of Berberine in patients with T2DM and identify potential factors may modifying the effect.

Materials and Methods

Retrieval strategy and selection criteria

We (Yaping Liang, Xiaojia Xu) searched PubMed, Embase, the Cochrane Library, the China National Knowledge Infrastructure (CNKI), the Wanfang Database, and the Chinese Scientific Journal Database (VIP) for topic-related studies until Decemeber 2017. Ongoing trials reported by ClinicalTrials.gov were also searched. The following search terms were used: ["Berberine" or "Huangliansu" or "Xiaopojian"] and ["type 2 diabetes mellitus (T2DM)" or "non-insulin-dependent diabetes mellitus"]. In addition, the reference lists from articles were manually searched for further studies. Studies were eligible if the following criteria were met: RCTs enrolled patients with T2DM; subjects received Berberine alone or in combination with lifestyle modification or another OHA; the study reported changes of fasting plasma glucose (FPG) or postprandial plasma glucose (PPG) as an outcome indicator. The exclusion criteria were: 1) the results were not presented with exact means and standard deviations of glucose or other information that allowed calculation of means and standard deviations; 2) the study contained subjects with acute or chronic diabetic complications including moderate or severe liver and kidney dysfunction, severe dysfunction of the heart, diabetic ketoacidosis or cardiovascular disease; 3) animal experiments; 4) review or duplicate publications. All articles were independently selected by two reviewers (Mingjuan Yin, Xiaojia Xu) in the sequence of title, abstract, and full text. Any inconsistencies were resolved by discussion until a consensus was achieved.

Data extraction and quality assessment

The following information was extracted from articles: first author, year of publication, study design, sample size, years with T2DM, mean age or age range, intervention measures, dosage, duration and outcomes (FPG and PPG). Extracted data were entered into a standardized Microsoft Excel (Microsoft Corporation, office 2016) file. The quality of the included trials was assessed using the Cochrane risk bias tools (Review Manager 5.3 provided by the Cochrane Collaboration) [13]. Two authors (Yan Zhang, Xiaojia Xu) independently finished extraction and quality assessment after reviewing each article, which was then checked by another author (Yaping Liang). Any disagreements were resolved through discussion and consensus.

Data synthesis and analysis

We examined the efficacy of Berberine or Berberine combined with OHA compared to the control group by weighted mean difference (WMD) with 95% confidence interval (CI).

I^2 statistics and Cochrane's Q test were used to assess the statistical heterogeneity among the included trials. Heterogeneity was assumed to be significant when I^2 statistics >50% or $p < 0.10$ in Cochrane's Q test. A fixed effect model was chosen when no substantial heterogeneity was indicated, otherwise a random effects model was used to incorporate heterogeneity and explain the results cautiously. The overall effect was tested using the Z score.

We investigated clinical heterogeneity by subgroup analyses on the basis of different intervention measures (Berberine with intensive lifestyle intervention *versus* intensive lifestyle intervention or Berberine *versus* placebo, Berberine combined with OHA *versus* the same OHA, Berberine *versus* OHA and Berberine combined with OHA *versus* Berberine), age (<50, 50–60, >60 years), daily dosage (<1.5 g/d, (1.5–2) g/d, >2 g/d) and treatment duration (<90 days, 90 days, >90 days). We did not perform subgroup analysis in other variables because missing values for some studies would have led to their exclusion from statistical analysis.

Additionally, we conducted sensitivity analyses by removing each individual study from the pooled analysis to estimate the influence of each included study. Publication bias was assessed through visual inspection of funnel plot asymmetry. Asymmetry was also tested by Begg rank correlation and Egger regression tests. All reported p values were 2-sided, and $p < 0.05$ was considered significant. All the described statistical analyses were performed using STATA (Stata/SE 12.0).

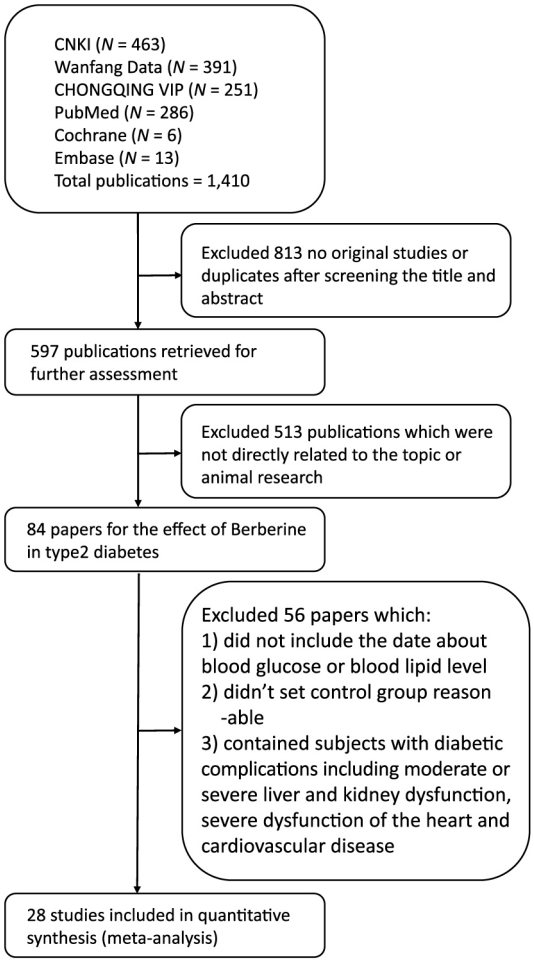

Fig. 1 Flow chart of the strategy used for the selection of studies used in the meta-analysis.

Results

Literature search

The study selection process is shown in Fig. 1. Initial electronic searching retrieved a total of 1,410 citations. Of these, 1,326 were excluded because they were duplicates or irrelevant studies. Of the remaining 84 potentially eligible studies, we included 28 RCTs for our literature review after excluding five which used an unreasonable control group that could induce substantial heterogeneity, nine contained subjects with acute diabetic complications such as moderate or severe liver and kidney dysfunction, and 42 did not report enough data for meta-analysis. The general characteristics of those 28 included studies are presented in Table 1.

Description of included studies

Twenty-eight studies, all conducted in China, with a total of 2,313 T2DM patients were included in this analysis. Five articles [7, 12, 14-16] were published in English and the rest were published in Chinese. Two articles [17, 18] were graduation thesis, and the remaining studies were journal articles. As shown in Table 1, 22 studies adopted a two-armed parallel group design, and other six trials contained three groups, where each group was considered as a separate study in the analysis.

Two trials [14, 15] were designed as double-blind randomized and multicenter trials. Four trials [19-22] did not specify the means of grouping. Most trials diagnosed T2DM according to the 1999 World Health Organization criteria. There were two trials [21, 23] that were conducted before 1999 and diagnosed according to the 1980 World Health Organization criteria.

In these 28 trials, six studies randomized subjects to receive Berberine and lifestyle modification *versus* lifestyle modification alone or with placebo. 13 trials compared a combination of Berberine and one type of OHA with a control of the same OHA, and two trials compared a co-intervention of Berberine and two kinds of OHA with a control of the same OHA. 14 trials compared Berberine and one OHA with Berberine alone. There were four trials that compared a co-intervention of Berberine and OHA with Berberine. Hypoglycemic drugs used as controls included insulin, metformin, glipizide, rosiglitazone, nateglinide, gliclazide, glyburide, glimepiride and acarbose. The outcomes of aspirin group in the study of Xiang *et al.* [24] were not included because aspirin is not directly associated with blood glucose.

The duration of treatment in the diabetes trials ranged from 14 to 730 d. 15 trials lasted for 90 d, one trial lasted for 120 d, and 10 trials lasted for 30–60 d. In addition, the trial reported by Liu 2004 [25] lasted for 14 d and the trial reported by Yin *et al.* [16] lasted for 730 d. Three trials listed the indicators of intervention measures in three stages. For data from the trial reported by Li *et al.* 2007 [26], we chose the index in 60 d, for the trial reported by Ding *et al.* 2013 [22], we selected 90 d and for the trial reported by Guo *et al.* 2006 [27], the index in 30 d was selected.

The dosage of Berberine was generally in the range of 0.3–3.0 g/d. Patients in three trials [11, 12, 28] received Berberine in the range of 0.3–0.6 g/d, and in three trials [19, 23, 29] patients received more than 2.0 g/d. The dose for patients in the trial reported by Gao *et al.* 2002 [30] was 0.04 g/kg/d. For the remaining 21 studies, the daily dosage of Berberine was in the range of 0.9–1.8 g. The total daily Berberine dosage was divided into two or three portions.

Risk of bias

Most of the included trials in this systematic literature review had low to moderate quality, since allocation concealment and blinding was not reported and withdrawal or dropouts were not mentioned. Only two trials were

Table 1 Characteristics of included studies in the meta-analysis

Study	Design	Sample size	Years with T2DM	Mean age	Intervention measures (Test/control group)	dosage (g)	Duraion (days)	Outcomes
Cao 2007 [17]	Randomized	30/30/30	Less than one year	55.3 ± 11.5/53.6 ± 12.9/55.4 ± 10.7	Berberine/ Metformin/ Lifestyle	0.5, TID	90	AB
Gu *et al.* 2010 [14]	Randomized, double-blind, placebo-controlled and multiple-center trial	30/30	Newly diagnosed	51 ± 9/50 ± 10	Berberine/ placebo	0.5, BID	90	AB
Li 2014 [45]	Randomized	60/60	Unknown	45.5 ± 2.5	Berberine/ lifestyle	0.5, TID	90	AB
Ren 2008 [18]	Randomized	31/30	Unknown	47.31 ± 7.51	Berberine/ lifestyle	0.3, TID	90	AB
Xiang *et al.* 2011 [46]	Randomized	20/20/20	Newly diagnosed	35–60	Berberine/ Aspirin/ placebo	0.4, TID	90	AB
Zhang *et al.* 2008 [15]	Randomized, double-blind, placebo-controlled and multiple-center trial	58/52	Newly diagnosed	51 ± 9/51 ± 10	Berberine/ placebo	0.5, BID	90	AB
Li 2008 [47]	Randomized	18/17/17	Unknown	61 ± 12	Berberine, Metformin/ Berberine/ Metformin	0.3, TID	90	AB
Li and Liu 2007 [25]	Randomized	51/51/50	Six months to four years	52 ± 14	Berberine/ Berberine, Glipizide/ Glipizide	0.3, TID	60	AB
Liu 2004 [24]	Randomized	35/33	Unknown	53.2 ± 2.8/55.2 ± 3.6	Berberine, Metformin/ Metformin	0.25–0.5, TID	14	AB
Liu 2013 [20]	Unknown	36/32	Newly diagnosed	47.5 ± 5.5	Berberine, Metformin/ Metformin	0.3, TID	120	AB
Liu and Hu 2008 [48]	Randomized	30/30	More than three months	52.0 ± 9.8/53.1 ± 8.5	Berberine, Metformin/ Metformin	0.3–05, TID	60	AB
Guan *et al.* 2017 [6]	Randomized	53/53	6.3 ± 2.4/6.1 ± 2.4	65.3 ± 3.3/65.7 ± 3.9	Berberine, Metformin/ Metformin	0.2–0.5, TID	30	A
Sheng and Xie 2010 [49]	Randomized	30/30	6 ± 3/5 ± 3	52 ± 9	Berberine, Metformin, Glipizide/ Metformin, Glipizide	0.5, TID	90	A
Yang 2010 [19]	Unknown	24/25	10.3 ± 3.7	54.7 ± 9.4	Berberine, Acarbose/ Acarbose	0.8, TID	90	AB

Table 1 Cont.

Study	Design	Sample size	Years with T2DM	Mean age	Intervention measures (Test/control group)	dosage (g)	Duraion (days)	Outcomes
Ye 2010 [50]	Randomized	40/40	9.6 ± 4.2/10.1 ± 4.5	42.5 ± 8.6/43.5 ± 9.8	Berberine, Metformin, Glimepiride/ Metformin, Glimepiride	0.5, TID	90	AB
Zhang and Yuan 2012 [28]	Randomized	38/38	<5 years 23, 5–10 years 29, >10 years 24	Unknown	Berberine, Metformin/ Metformin	0.5–0.8, TID	90	AB
Zhu *et al.* 2009 [51]	Unknown	55/55/50	5–11 years	42 ± 12	Berberine, Metformin/ Berberine/ Metformin	0.5, TID	90	AB
Zhu *et al.* 2015 [11]	Randomized	59/59	4.5 ± 1.8/4.3 ± 2.0	66.4 ± 7.6/65.6 ± 7.2	Berberine, Glipizide/ Glipizide	0.1, TID	90	AB
Dai *et al.* 2015 [12]	Randomized	39/33	More than two years	53.06 ± 10.36 55.31 ± 11.79	Berberine/ Metformin, Gliclazide	0.1, TID	730	A
Ding *et al.* 2013 [22]	Unknown	32/21	Unknown	49 ± 6/48C9	Berberine/ Insulin	0.6, TID	90	A
Du 2016 [27]	Randomized	37/36	10.9 ± 6.3/11.6 ± 6.9	67.8 ± 4.6/66.5 ± 7.1	Berberine/ Metformin	0.12, TID	28	AB
Gao *et al.* 2002 [29]	Randomized	30/30	Unknown	45 ± 11.8/48 ± 9.7	Berberine/ Xiaoke pill	0.04 g/ (kg·d)	30	A
Guo and Zhao 2006 [26]	Randomized	40/30	Unknown	46.8 ± 5.5/47.2 ± 5.1	Berberine/ Gliclazide	0.4, TID	30	AB
Mai and Li 1997 [21]	Unknown	56/40	Unknown	50	Berberine/ Glyburide	0.5, TID	30	A
Yin *et al.* 2008 [16]	Randomized	15/16	Newly diagnosed	Unknown	Berberine/ Metformin	0.5, TID	35	AB
Yu *et al.* 1996 [23]	Randomized	105/66	1–30 years	Unknown	Berberine/ Gliquidone	0.5–1.0, TID	90	AB
Zhang *et al.* 2010 [7]	Randomized	50/26/21	Unknown	57 ± 8/56 ± 11/49 ± 10	Berberine/ Metformin/ Rosiglitazone	0.5, BID	60	A
Wang 2012 [52]	Randomized	20/20	2–60 years	58	Berberine/ Berberine, Hypoglycemic	0.3, TID	365	A

Note: A: FPG; B: PPG; C: HbA1C.

rated as being at low risk of bias for each aspect assessed. The detailed quality assessments of individual trials are presented in Supplement Fig. 1.

Efficacy of Berberine treatment on FPG

Overall results

A total of 28 clinical studies involving 2,313 participants (1,245 Berberine, 1,068 controls) were included in the analysis to evaluate the effect of Berberine on FPG. As some of them provided their results in multiple subsets, we analyzed their results separately, and thereby had 36 comparisons.

Fig. 2 shows that treatment with Berberine or Berberine combined with OHA was associated with more significant decreases than the control group in FPG (WMD = –0.54 mmol/L, 95% CI (–0.77, –0.30), $p < 0.001$). The sensitivity analysis (Supplement Fig. 2) showed that sequentially excluding each study did not change the

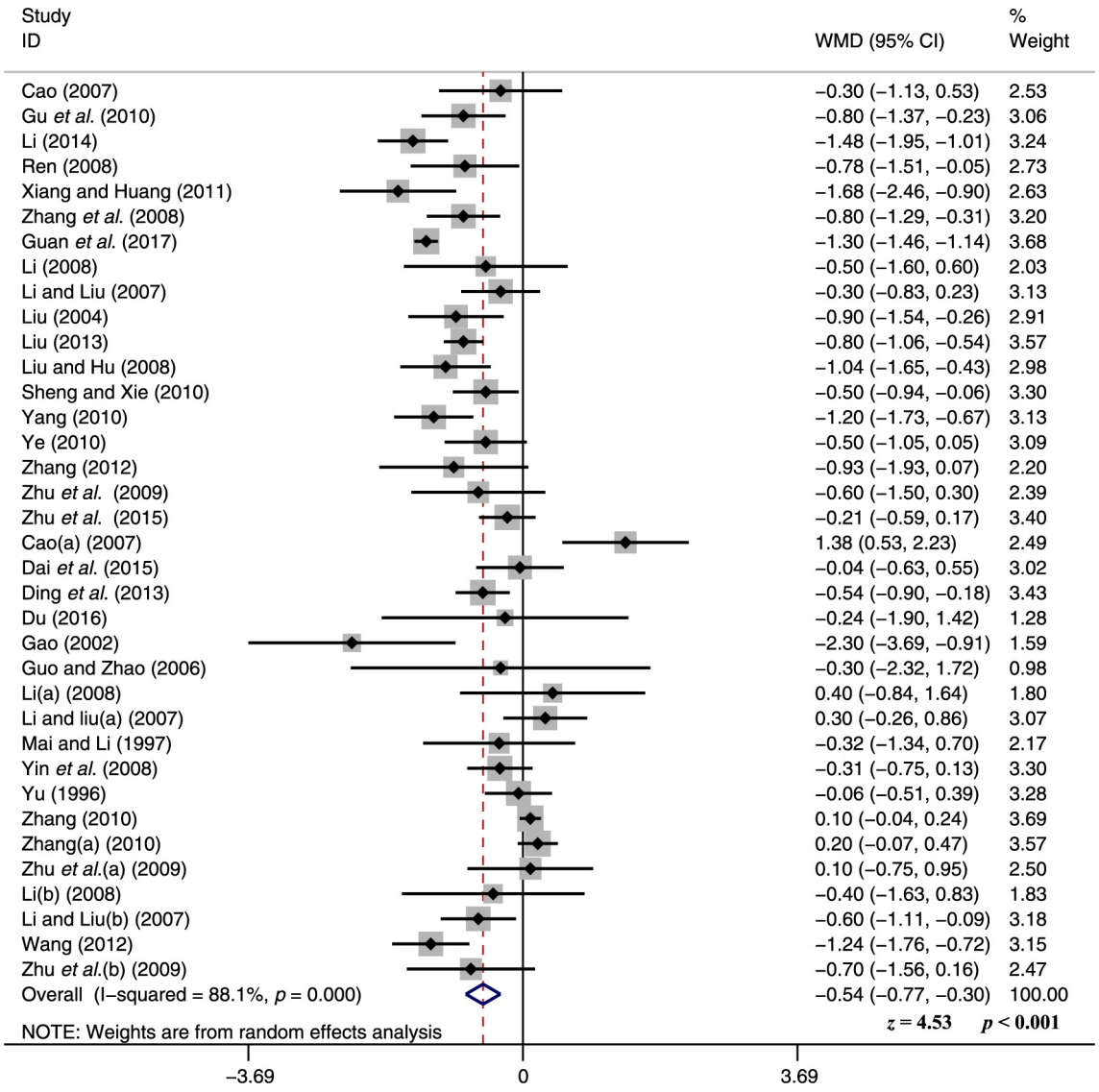

Fig. 2 Forest plots showing weighted mean difference and 95% confidence interval for FPG levels comparing Berberine alone or in combination with OHA to controls in a random effects model.

conclusion. Potential publication bias for change of FPG was not observed in Begg's test ($p = 0.902$) and Egger's test ($p = 0.797$), but in the funnel plots (Supplement Fig. 2).

Subgroup analyses

As there were obvious heterogeneity in the analysis for FPG, we conducted subgroup analysis to minimize the heterogeneity and investigate whether the effects of Berberine treatment on FPG differed according to intervention measures, age, daily dose and duration. Years with T2DM was not explored as a potential modifying factor of effect, because data for this variable were missing for 579/2,313 (25%) patients, and power for subgroup analyses was limited by small sample size in subgroups. The results were presented in Table 2.

Subgroup analysis for intervention measures (Berberine *versus* placebo or lifestyle, Berberine *versus* OHA, Berberine combined with OHA *versus* OHA, Berberine combined with OHA *versus* Berberine) revealed a stronger hypoglycemic effect of Berberine than placebo or lifestyle intervention (WMD = –0.99 mmol/L, 95% CI (–1.37, –0.67), $p < 0.001$). Compared with Berberine or OHA, the combined treatment was associated with more significant decreases in FPG (OHA as control: WMD = –0.75 mmol/L, 95% CI (–1.03, –0.47), $p < 0.001$; Berberine as control: WMD = –0.83 mmol/L, 95% CI (–1.21, –0.46), $p < 0.001$). While, an analysis testing the effects of Berberine *versus* OHA group did not reveal evidence of a statistically significant (WMD = –0.03 mmol/L, 95% CI (–0.27, 0.22), $p = 0.834$). Besides, the effect of Berberine or combined treatment appeared to be similar with control group in participants who aged >60 years old ($p = 0.096$), participants with Berberine daily

Table 2 The results of subgroup analyses

Subgroups	*n*	WMD, mmol/L	95% CI	*p* value	Heterogeneity Between Studies
FPG					
Overall	36	0.54	(–0.77, –0.30)	<0.001	I^2 = 88.1% p < 0.001
Intervention type					
Berberine *vs.* placebo	6	0.99	(–1.37, –0.67)	<0.001	I^2 = 54.7% p = 0.051
Berberine *vs.* OHA	12	0.03	(–0.27, 0.22)	0.834	I^2 = 64.6% p < 0.001
Berberine + OHA *vs.* OHA	14	0.75	(–1.03, –0.47)	<0.001	I^2 = 77.6% p < 0.001
Berberine + OHA *vs.* Berberine	4	0.83	(–1.21, –0.46)	<0.001	I^2 = 19.7% p = 0.291
Daily dosage (g/d)					
<1.5	17	0.38	(–0.76, –0.00)	0.05	I^2 = 71.5% p < 0.001
1.5–2	16	0.7	(–1.53, –0.13)	<0.001	I^2 = 93.2% p < 0.001
>2	3	0.65	(–0.93, –0.36)	0.097	I^2 = 81.5% p = 0.005
Treatment duration (days)					
<90	14	0.51	(–0.95, –0.07)	0.023	I^2 = 93.9% p = 0.552
90	19	0.54	(–0.81, –0.27)	<0.001	I^2 = 71.7% p = 0.234
>90	3	0.72	(–1.27, –0.16)	0.011	I^2 = 78.1% p = 0.373
Age (years)					
<50	7	0.88	(–1.22, –0.54)	0.008	I^2 = 61.7% p = 0.109
50–60	16	0.39	(–0.69, –0.10)	<0.001	I^2 = 84.5% p = 0.269
>60	9	0.45	(–0.98, –0.30)	0.096	I^2 = 82.3% p = 0.433
PPG					
Overall	27	–0.94	(–1.27, –0.61)	<0.001	I^2 = 71.3% p < 0.001
Intervention type					
Berberine *vs.* placebo	6	–1.86	(–2.24, –1.49)	<0.001	I^2 = 0.0% p = 0.591
Berberine *vs.* OHA	8	–0.3	(–1.08, 0.47)	0.441	I^2 = 82.3% p < 0.001
Berberine + OHA *vs.* OHA	10	–0.91	(–1.23, –0.58)	<0.001	I^2 = 30.9% p = 0.162
Berberine + OHA *vs.* Berberine	3	–0.95	(–1.56, –0.34)	0.002	I^2 = 0.0% p = 0.634
Daily dosage (g/d)					
<1.5	12	–0.71	(–1.15, –0.27)	0.001	I^2 = 50.8% p = 0.22
1.5–2	12	–1.34	(–1.71, –0.77)	<0.001	I^2 = 71.5% p < 0.001
>2	3	–0.54	(–1.46, –0.39)	0.255	I^2 = 75.6% p = 0.017
Treatment duration (days)					
<90	9	–0.93	(–1.51, –0.35)	0.002	I^2 = 73.6% p = 0.002
90	17	–0.95	(–1.23, –0.58)	<0.001	I^2 = 73.3% p = 0.572
>90	1	–0.8	(–1.85, –0.25)	0.134	
Age (years)					
<50	5	–1.15	(–1.71, –0.58)	<0.001	I^2 = 47.3% p = 0.180
50–60	10	–1.34	(–1.89, –0.78)	<0.001	I^2 = 73.4% p = 0.571
>60	8	–0.36	(–0.77, –0.05)	0.087	I^2 = 12.5% p = 0.497
HbA1C					
Overall	23	–0.54	(–0.93, –0.15)	0.007	I^2 = 97.7% p < 0.001

Table 2 Cont.

Subgroups	*n*	WMD, mmol/L	95% CI	*p* value	Heterogeneity Between Studies
Intervention type					
Berberine *vs.* placebo	6	–0.67	(–0.90, –0.44)	<0.001	I^2 = 16.0% p = 0.311
Berberine *vs.* OHA	7	–0.16	(–0.46, 0.13)	0.283	I^2 = 84.1% p < 0.001
Berberine + OHA *vs.* OHA	10	–0.67	(–1.29, –0.05)	0.203	I^2 = 97.1% p < 0.001
Daily dosage (g/d)					
<1.5	10	–0.54	(–1.20, 0.11)	0.101	I^2 = 98.9% p < 0.001
1.5–2	11	–0.53	(–0.81, –0.25)	<0.001	I^2 = 66.3% p < 0.001
>2	2	–0.64	(–0.95, –0.34)	<0.001	I^2 = 0.0% p = 0.843
Treatment duration (days)					
<90	6	–0.86	(–1.72, 0.01)	0.048	I^2 = 99.3% p < 0.001
90	15	–0.44	(–0.67, –0.21)	<0.001	I^2 = 60.1% p = 0.001
>90	2	–0.31	(–0.52, –0.11)	0.003	I^2 = 0.0% p = 0.754
Age (years)					
<50	4	–0.39	(–0.56, –0.22)	<0.001	I^2 = 0.0% p = 0.567
50–60	9	–0.45	(–0.71, –0.18)	0.001	I^2 = 84.4% p < 0.001
>60	7	–0.62	(–1.54, 0.31)	0.192	I^2 = 96.4% p < 0.001

dosage <1.5 g (p = 0.05) and >2 g (p = 0.097).

Efficacy of Berberine treatment on PPG

Overall results

20 RCT studies reported the PPG data, involving 1,832 participants (810 Berberine, 1,022 controls). Some of them provided the results in multiple subsets and we analyzed the results separately, thereby resulting in 27 comparisons.

A random model was chosen to pool the effect of Berberine or combined treatment on PPG because of obvious heterogeneity (I^2 = 71.3%, p < 0.001). The results presented in Fig. 3 implied that Berberine or combined therapy resulted in a better reduction of PPG (WMD = –0.94 mmol/L, 95% CI (–1.27, –0.61), p < 0.001) than control groups. Sensitivity analysis (Supplement Fig. 3) revealed that there was no change in the direction of the pooled WMD of PPG when any one study was excluded. The Egger's (p = 0.846) and Begg's test (p = 0.573) for PPG revealed no potential publication bias though the funnel plots for PPG was asymmetric (Supplement Fig. 3).

Subgroup analyses

We preformed subgroup analyses to investigate whether the huge heterogeneity was induced by intervention measures, age, daily dose and duration. Years with T2DM was not explored as a potential modifying factor of effect, because data for this variable were missing for 591/1,832 (32%) patients and power for subgroup analysis was limited by small sample size in subgroups. The results were presented in Table 2.

Subgroup analysis for intervention measures (Berberine *versus* placebo or lifestyle, Berberine *versus* OHA, Berberine combined with OHA *versus* OHA, Berberine combined with OHA *versus* Berberine) revealed a stronger hypoglycemic effect of Berberine than placebo or lifestyle intervention (WMD = –1.86 mmol/L, 95% CI (–2.24, –1.49), p = 0.001). Compared with Berberine or OHA, the combined treatment showed better reduction in PPG (OHA as control: WMD = –0.91 mmol/L, 95% CI (–1.23, –0.58), p < 0.001; Berberine as control: WMD = –0.95 mmol/L, 95% CI (–1.56, –0.34), p < 0.001). While, the difference in the effect of berberine and OHA on PPG was not statistically significant (WMD = –0.30 mmol/L, 95% CI (–1.08, 0.47), p = 0.441). Moreover, the effect of Berberine or combined treatment was not better than control groups in participants aged >60 years old (p = 0.087), participants with Berberine daily dosage >2 g (p = 0.255), the treatment duration more than 90 days (p = 0.134).

Efficacy of Berberine treatment on HbA1C

Overall results

A total of 19 clinical studies reported date on HbA1c involving 1,507 participants (942 Berberine, 865 controls) were included in the analysis. As some of them provided their results in multiple subsets, we analyzed their results separately, and thereby had 23 comparisons.

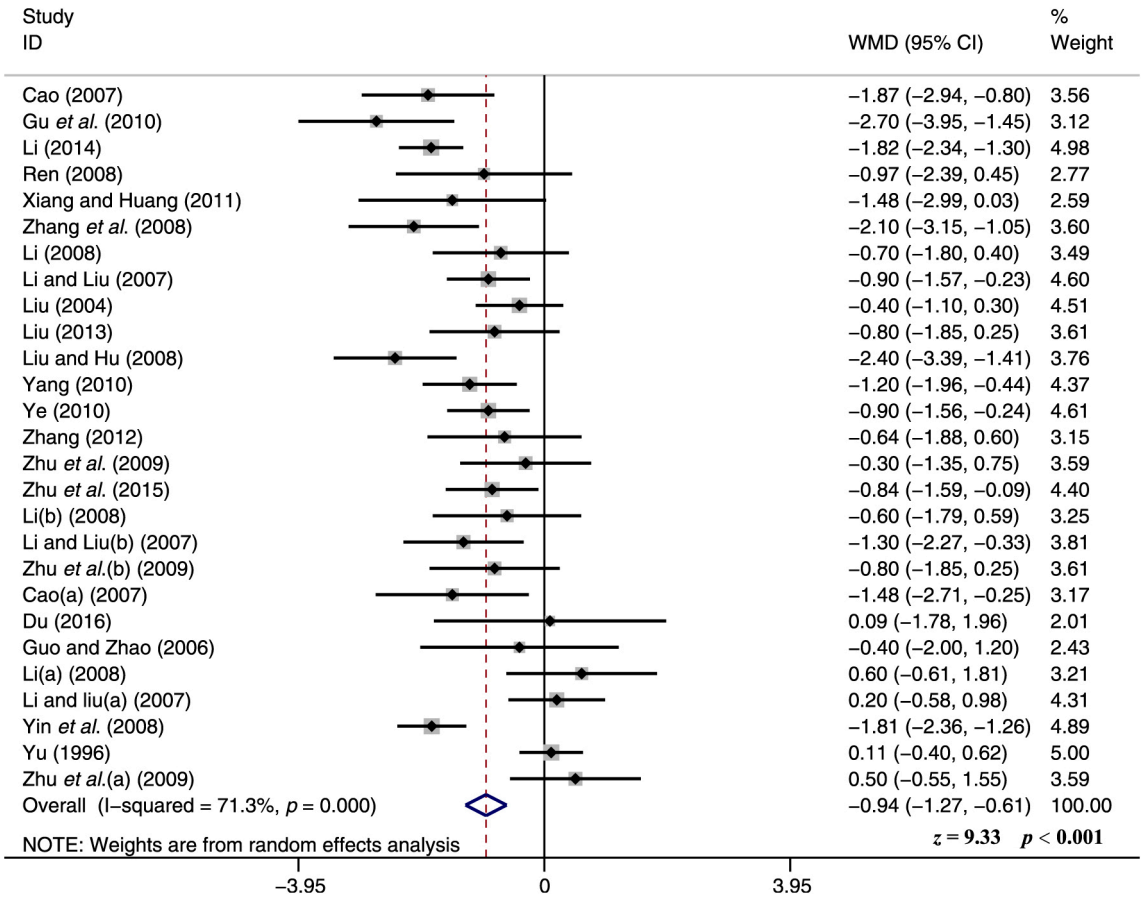

Fig. 3 Forest plots showing weighted mean difference and 95% confidence interval for PPG levels comparing Berberine alone or in combination with OHA to controls in a random effects model.

Fig. 4 shows that treatment with Berberine or Berberine combined with OHA was associated with more significant decreases than the control group in HbA1c (WMD = –0.54 mmol/L, 95% CI (–0.93, –0.15), p = 0.007). The sensitivity analysis (Supplement Fig. 4) showed that sequentially excluding each study did not change the conclusion. Potential publication bias for change of HbA1C was observed in Begg's test (p = 0.045) and Egger's test (p = 0.048) (Supplement Fig. 4).

Subgroup analyses

As there were obvious heterogeneity in the analysis for HbA1C, we conducted subgroup analysis to minimize the heterogeneity and investigate whether the effects of Berberine treatment on HbA1c differed according to intervention measures, age, daily dose and duration. The results were presented in Table 2.

Subgroup analysis for intervention measures (Berberine *versus* placebo or lifestyle, Berberine *versus* OHA, Berberine combined with OHA *versus* OHA) revealed a stronger hypoglycemic effect of Berberine than placebo or lifestyle intervention (WMD = –0.67 mmol/L, 95% CI (–0.908, –0.44), p < 0.001). While, the analyses testing the effects of Berberine or combined treatment *versus* OHA group did not reveal evidence of a statistically significant (Berberine as intervention: WMD = –0.16 mmol/L, 95% CI (–0.46, 0.13), p = 0.283; Combined treatment as intervention: WMD = –0.67 mmol/L, 95% CI (–1.29, –0.05), p = 0.203). Besides, the effect of Berberine or combined treatment appeared to be similar with control group in participants aged >60 years old (p = 0.096), participants with Berberine daily dosage <1.5 g (p = 0.05).

Discussion

This is a meta-analysis of 28 RCTs to evaluate the efficacy of Berberine in the treatment of T2DM patients. The findings of this study suggest that Berberine alone or in combination with OHA significantly improved FPG, PPG and HbA1c in patients with T2DM.

Berberine improved lowering blood glucose (FPG, PPG and HbA1c) when compared with lifestyle modification alone or placebo. Compared to OHA or Berberine alone, combined therapy resulted in a better reduction of FPG and PPG. The significant different effect on HbA1c was not founded between combined and OHA treatment.

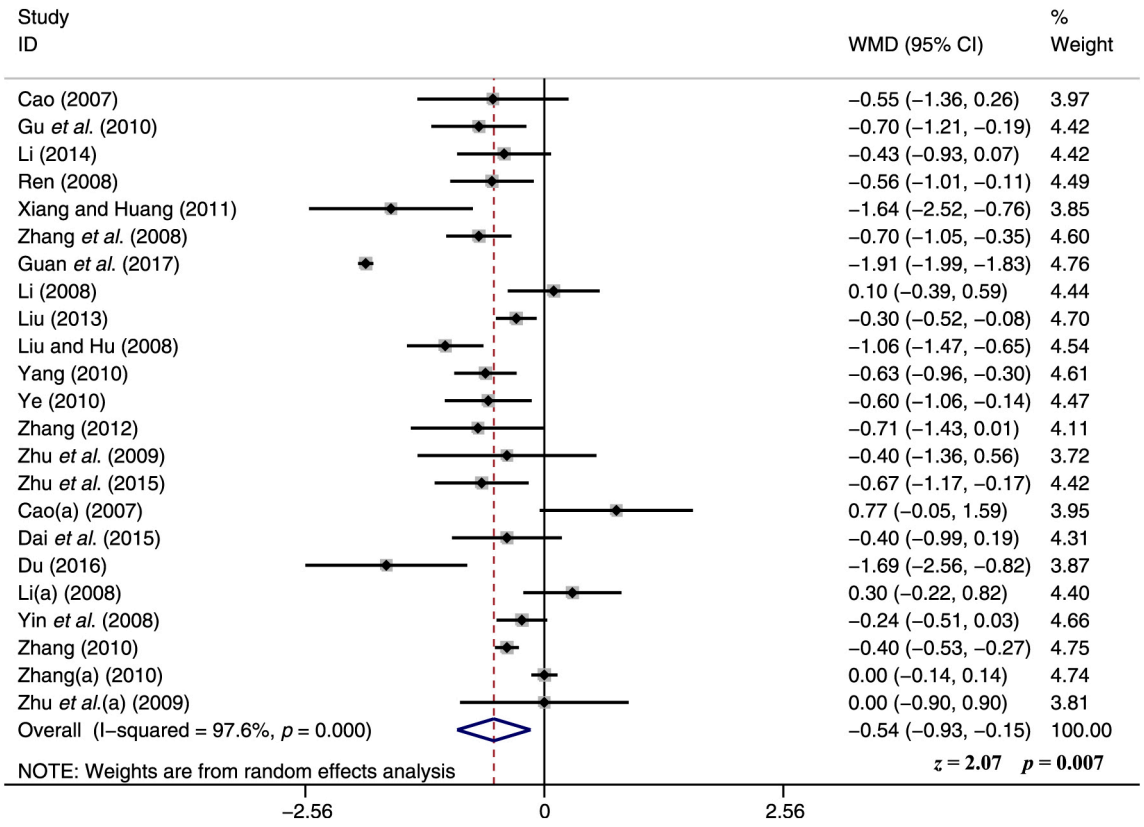

Fig. 4 Forest plots showing weighted mean difference and 95% confidence interval for HbA1c levels comparing Berberine alone or in combination with OHA to controls in a random effects model.

However, in the Berberine *versus* OHA group, there were no significant differences in the effects on FPG, PPG and HbA1c. Two meta-analyses [9, 31] were performed in recent years that attempted to resolve the issue of efficacy and safety of Berberine in T2DM patients. Our results have shown that Berberine or combined treatment appeared to achieve better effects on FPG, PPG and HbA1c levels when patients aged less than 60 years and patients treated with a daily dosage of 1.5–2 g. There was no statistically significant difference in reduction of the level of PPG and HbA1c between two groups when the treatment duration >90 days.

This is the first study which performed subgroup analyses to examine the source of heterogeneity and identify the potential factors which probably affect the effect of Berberine. Compared to previous meta-analysis studies, our analysis added a group (Berberine combined with OHA *versus* Berberine) to compare the effect of combined therapy with Berberine. The Dong *et al.* 2012 [31] study considered 14 trials involving 1,068 patients and set three subgroups. Another systematic literature review added 14 studies, but just four RCT studies focused on T2DM patients and others assessed the effect of Berberine on hyperlipidemia and hypertension patients [9]. For the present study, in an attempt to produce robust results, we defined rigorous inclusion criteria and used a careful search method. Compared to the previous meta-analysis paper [9, 31], we excluded four trials [32-35] because of diabetic complications and moderate or severe liver or kidney dysfunction, and added other 16 trials aimed at evaluating the effect of Berberine in the treatment of T2DM patients. The sample size of each outcome in this meta-analysis is twice as large as previous studies [9, 31]. Exclusion of each single study did not alter the pooled effect of any outcome, which increased robustness to our main findings. Our study therefore provides a more comprehensive picture of the efficacy of Berberine on glucose level in patients with T2DM.

Several factors of the study might have induced heterogeneity. Berberine treatment might have a distinct influence on patients treated with different controls. The treatment duration varied among the eligible studies. Different dosage of Berberine may have inconsistent efficacy. Age is also a vital factor which affects the hypoglycemic effect of Berberine. Accounting for these, we carried out subgroup analyses for FPG and PPG. The results showed that they did not induce significant bias (data shown in Table 2). But the patients with different years suffering from disease might have various responses to the Berberine, and different designation of studies

may have influence on the results. A meta-regression analysis should be done in future to quantify the association of each of above factors with the effect of Berberine on lowering blood glucose in patients with T2DM.

Based on the existing data we have tested our findings for the causal-result relationship between Berberine and lowering glucose according to the following viewpoint:

How consistent are the reported studies?

There is clear consistency among existing RCTs indicating an association between Berberine therapy and blood glucose levels. The glucose-lowering effect of Berberine has also been reported in studies with subjects suffering type 2 diabetes complicated with nonalcoholic-fattyliverdisease (NAFLD) or cerebrovascular disease [17, 35].

Is there experimental evidence?

The anti-diabetic activity of Berberine was first reported in 1988 [36] and its activity has been tested in a number of animal and human studies. Berberine has been found to regulate blood glucose through multiple mechanisms: increasing glucokinase activity [37], increasing insulin secretion and islet regeneration [38], improving insulin resistance [39] and suppressing hepatic gluconeogenesis [40]. There are robust data showing that Berberine exhibits fewer side effects than western medicines in the majority of laboratory and clinical trials. Only a small fraction of patients who were treated with Berberine reported regurgitation, emesis, diarrhea, or constipation [41]. Moreover, Berberine can alleviate a variety of diabetic complications, including diabetic cardiovascular disease, type 2 diabetic nephropathy, and diabetic peripheral neuropathy [42]. The study by Jiang *et al.* 2015 [40] compared the effects of Berberine, metformin and placebo control at the protein level in streptozotocin-induced diabetic rats, and concluded that Berberine inhibited expression of the gluconeogenic proteins phosphor enolpyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase (G-6-Pase) in the liver. Administration of Berberine to KKAy mice reduced FBG levels and Fins by changing the expression of many genes such as adenosine monophosphate-activated protein kinase- (AMPK-) p38, mitogen-activated protein kinase-glucose transporter 4 (MAPK-GLUT4), c-jun N-terminal kinase (JNK) pathway, and peroxisome proliferator-activated receptor α (PPARα) pathway, which was shown in the Zhang *et al.* 2011 study [37]. Moreover, columbamine, a Berberine metabolite, was reported to reduce blood lipid levels by regulating the expression of genes associated with biosynthesis and fatty acid oxidation [43]. Berberine also inhibits cholesterol and TG synthesis in hepatic cells *via* AMPK activation [44]. These findings provide a theoretical basis for our results.

Is the association biologically plausible?

A recent study concluded that metformin, which is a first line oral anti-diabetic agent, alleviates hyperglycemia in T2DM mainly through direct inhibition of hepatic glucose production by AMPK activation [45]. Berberine has also been shown to up regulate protein expression of AMPK. The hypoglycemic effect of Berberine is therefore plausible and unsurprising.

Limitations in this study and recommendations for future research

The limitations of our study are as follows. Firstly, all of the trials were conducted among Chinese T2DM patients. Thus our findings could not be applied to other populations. Secondly, some of the included studies were of poor quality. However, when we included those "good quality" RCT, the findings were not substantially changed. We suggest that further RCTs should focus on double blind and allocation concealment to provide a more convincing conclusion. Thirdly, substantial heterogeneities were present in many subgroups, which may have arisen from the patients' characters, the type and dose of controls, treatment duration, years with T2DM and measurement of outcomes. In addition, differences in the sizes of the experimental and control groups may also create obvious heterogeneities. The results of subgroup analyses should be concluded discreetly because of small sample size in some groups. Fourthly, we could not evaluate the effective rate of Berberine in T2DM patients, since studies calculated the relevant data according to different standards. There is therefore a need for clarification and consistency regarding dosage, timing, and duration in further studies of Berberine treatment in T2DM patients.

In conclusion, the evidence from our systematic literature review and meta-analysis suggests that Berberine (or Berberine combined with OHA) has a significant hypoglycemic effect, which appeared to be similar to the effect of OHA in T2DM patients. When combined with OHA, it achieves a greater reduction of blood glucose than Berberine or OHA. The age of patients, daily dosage of Berberine, and the treatment duration could also affect the efficacy of treatment.

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Disclosure Statement

None of the authors have any potential conflicts of interest associated with this research.

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