

# Efficacy and Safety of Berberine for Prediabetes: A Systematic Evaluation and Meta-Analysis

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## Abstract

**Objective:** To assess the efficacy and safety of berberine in the treatment of prediabetes. **Methods:** We searched the following databases, CNKI, Wan-Fang, VIP, CBM, PubMed, Cochrane Library, Embase, and Medline (OVID) from the databases established to December 2020 in Chinese or English language. Randomized control trials (RCTs) of berberine compared with lifestyle modification, placebo, and/or hypoglycaemics intervention on treating prediabetes were included. Data extraction and paper quality assessment were conducted according to the Cochrane Handbook. RevMan 5.4 was used for the meta-analysis. **Results:** Seven studies involving 859 participants were included in the study and the control groups were all lifestyle modification or metformin treatment. The clinical heterogeneity of the trials was relatively high, and the methodological quality of most trials was generally low. Meta-analysis suggested that berberine could reduce FPG ( $P = 0.001$ ), 2hPG ( $P = 0.001$ ) and HbA1c ( $P = 0.002$ ) levels significantly as compared with lifestyle group. There was no statistical significance between berberine and metformin. No serious adverse effects from berberine were reported. **Conclusions:** Berberine has good efficacy and safety in the treatment of prediabetes. Due to the quality limitations of the included trials, the above conclusions need to be further verified by high-quality, large sample size and multi-center clinical trials.

## Keywords

Berberine, Prediabetes, Efficacy, Safety, Meta-Analysis

## 1. Introduction

Prediabetes refers to the intermediate hyperglycemia state between normal blood

glucose and diabetes [1]. It is also known as impaired glucose regulation (IGR), including impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The epidemiological survey showed that the prevalence of prediabetes was 35.2% [2]. The prevalence among males and females was 37.0% and 33.4% respectively [2]. Prediabetes is considered the most significant risk factor for type 2 diabetes (T2DM). It is estimated that the world's prediabetic population will grow to 470 million by 2030 [3], and about 70% of them will develop diabetes at some point [4]. The damages of hyperglycemia already exist before diabetes. So prediabetes is considered a marker or watershed, which means that the risk of cardiovascular disease, diabetes, microangiopathy, tumor, and dementia will increase in the future [5]. But the blood sugar can be reversed to normal after appropriate treatment. At Present, prediabetic patients mainly depend on lifestyle interventions to prevent or delay diabetes. It is generally considered to be safe and cost-effective. However, only a small number of patients can adhere to their dietary plans and exercise prescriptions and it is reported that about 10% - 20% of prediabetic patients are resistant to the effects of exercise with weight loss [6]. A six-year follow-up study showed that about 50% of the prediabetic patients who had received lifestyle interventions still developed diabetes [7]. Therefore, the guidelines recommend if no satisfactory results are achieved after six months of active interventions, metformin or acarbose should be considered [5]. For young patients having solid financial support and strong health needs, early pharmaceutical interventions are highly recommended [8]. But the high cost and side effects of western medicine limit the clinical application. So it becomes increasingly important to develop cost-effective safe hypoglycemic drugs.

Prediabetes belongs to the “spleen” of traditional Chinese medicine (TCM), which is the philosophy of corrective and preventative action against disease [9] [10]. Berberine (BBR, molecular formula: C<sub>20</sub>H<sub>19</sub>NO<sub>5</sub>, molecular weight: 353.36) is a natural alkaloid extracted from the rhizome of Chinese goldthread (*Coptis chinensis*) and Phellodendron bark (*Cortex phellodendri*) [11] and is well known as the effective drug that can relieve the symptoms of infectious diarrhea. Modern pharmacological studies have confirmed that berberine has significant hypoglycemic and lipid-regulating effects, improving insulin resistance and anti-inflammatory effects [12] [13] [14]. Some clinical trials have also confirmed berberine has the same hypoglycemic effect on prediabetes. But no one has done a systematic evaluation for it. This research used the Cochrane systematic evaluation method and evaluated the efficacy and safety of berberine in treating prediabetes in RCTs. This can provide a critical reference for clinical decision-making.

## 2. Materials and Methods

### 2.1. Search Strategy

We searched the China National Knowledge Infrastructure (CNKI), the Wan-

Fang Database, the Chinese Scientific Journal Database (VIP), the Chinese Bio-Medical Literature Database (CBM), PubMed, Cochrane Library, Embase, and Medline (OVID) from the databases established to December 2020 in any language. Ongoing trials reported by ClinicalTrials.gov were also searched. The following search terms were used: ["Berberine" or "Huangliansu" or "Xiaopojian"] and ["prediabetes" or "pre-diabetes" or "impaired glucose tolerance" or "impaired fasting glucose" or "impaired glucose regulation"]. In addition, the reference lists from articles were manually searched for further studies.

## 2.2. Inclusion Criteria

Studies were included if they fulfilled the following criteria: design of parallel RCT of berberine intervention compared with lifestyle modification, placebo, and/or hypoglycaemics on treating prediabetes, whether allocation concealment and blinding were used or not; Literature is either Chinese or English literature. Some studies contained multiple groups and each comparison group containing berberine was considered as a separate trial in the analysis. Studies were only included if the intervention was given for at least 2 months. Prediabetes was diagnosed by internationally recognized criteria. No sex or age limitation. The diagnosis criteria include WHO 1999 [15], CDS 2013 [16] and ADA 2010 [17].

The primary outcomes consisted of fasting plasma glucose levels (FPG), 2-hour postprandial plasma glucose (2hPG), glycosylated haemoglobin levels A1c (HbA1c) and homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of  $\beta$  cell function (HOMA- $\beta$ ). The secondary outcomes consisted of body mass index (BMI) and adverse effects.

## 2.3. Exclusion Criteria

The exclusion criteria were non-randomized controlled trials and quasi-randomized control trials; abstracts or comments from conference papers; animal studies or comparative studies on different Chinese medicine therapies.

## 2.4. Data Extraction

Literature selecting: read the article title and abstract, eliminated the studies not meeting the inclusion/exclusion criteria. Two reviewers independently assessed trials for inclusion in the review. They extracted data concerning details of the sample size, interventions, duration of treatment, and outcomes by using a standard Microsoft Excel (Microsoft Corporation, office 2016) file. Any disagreements were resolved by consensus, or if required by a third reviewer.

## 2.5. Quality Assessment

The quality of the included trials was assessed using the Cochrane risk bias tools (Review Manager 5.4 provided by the Cochrane Collaboration) [18]. The criteria include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome

data, selective reporting and other bias. We made judgement on each of these criteria relating to the risk of bias: low, high, or unclear (indicating unclear or unknown risk of bias).

## 2.6. Statistical Methods

We used the RevMan 5.4 meta-analysis software to summarize the effects of berberine. Categorical variables used odds ratio (OR) and continuous variables used the mean differences (MD) as analysis statistics. 95% confidence interval (95% CI) was used as the effective size for the combined analysis. The clinical and methodological heterogeneity of the included studies was evaluated with  $X^2$  test and  $I^2$  test. The different berberine interventions and control methods were used for sensitivity subgroup analysis. Reporting bias was explored through funnel plot analysis when the number of included trials exceeded ten. A fixed-effect model was used when the studies in the subgroup were sufficiently similar ( $I^2 < 50\%$ ,  $P > 0.10$ ). Otherwise, a random-effect model was used. When  $P < 0.05$ , it indicated that there was a significant difference between the two groups. Interval estimation and hypothesis test results were shown in the forest plot.

## 3. Results

### 3.1. Literature Search Results

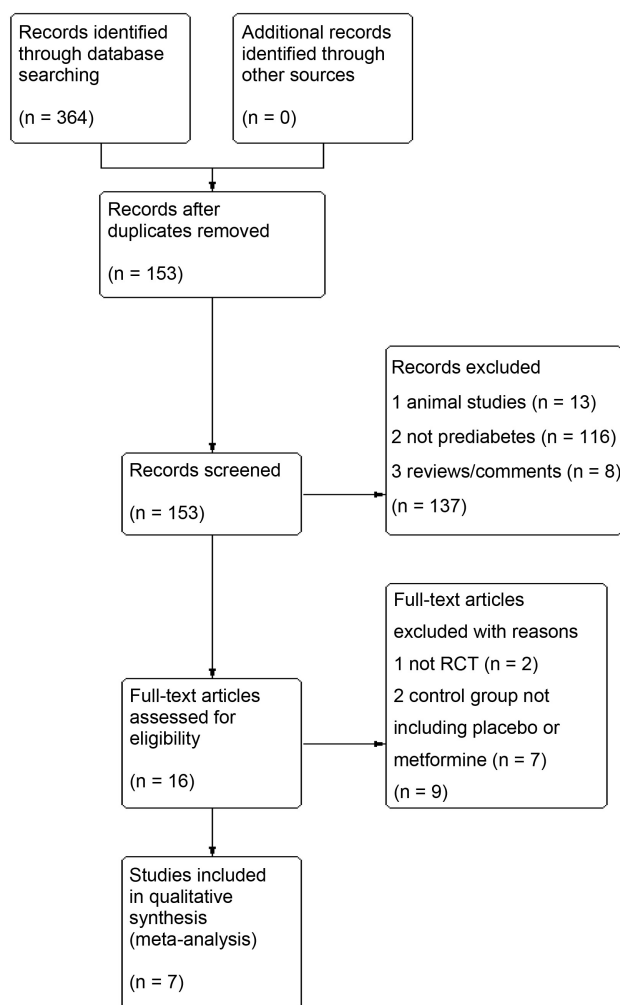
The flowchart of study search results is displayed in **Figure 1**. The primary searches identified a total of 364 references. 153 articles were screened after 211 duplicates of the same articles were removed. According to the inclusion criteria, 146 records were excluded because they were animal studies, not prediabetes, not RCTs, reviews or comments. Finally, seven studies met the eligibility criteria and were included in the systematic review and meta-analysis.

### 3.2. Characteristics of the Included Studies

The seven studies, including six in Chinese and one in English, were published in 2007-2020. All the studies were performed as single center trials and originated from the mainland of China. Six studies [19] [20] [22] [23] [24] [25] adopted two-armed parallel group design. One study [21] adopted three-armed group design, including berberine, lifestyle modification and metformin. One study [23] set a washout period between two treatment periods of berberine vs. lifestyle modification. According to the inclusion criteria, the two studies [21] [23] were analyzed as four trials. A total of 859 prediabetic patients were enrolled. Among them, 431 were in the experimental group and 428 in the control. The baseline consistency of each trial was comparable. See **Table 1**.

### 3.3. Risk of Bias in Included Studies

We used RevMan 5.4 to assess the risk of bias in included seven studies. None of them reported the research plan and sample size estimation method. All the studies mentioned random assignment of participants. But only two studies described



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

**Table 1.** Characteristics of the included trials.

Study	Number of patients (Man/Female)		Intervention		Duration (month)	Outcomes
	Experimental	Control	Experimental	Control		
Ju SB 2007 [19]	46 (28/18)	44 (26/18)	BBR 0.6/d + LM	LM	12	①②③④⑥
Zhang ZJ 2018 [20]	50 (27/23)	50 (32/18)	BBR 0.3 tid + LM	LM	4	①⑥⑦
Chang HY 2020 (1) [21]	80 (45/35)	80 (42/38)	BBR 30 mg tid	LM	6	①②③④⑥⑦
Chang HY 2020 (2) [21]	80 (45/35)	80 (41/39)	BBR 30 mg tid	Met 0.25 tid → 0.5 tid	6	①②③④⑥⑦
Zhang Z 2020 [22]	24 (-/-)	24 (-/-)	BBR 0.2 tid + LM	LM	2	⑥
Wang L 2020 (1) [23]	35 (19/16)	35 (19/16)	BBR 0.3 tid + LM	LM	3	①②③④⑦
Wang L 2020 (2) [23]	34 (19/15)	33 (18/15)	BBR 0.3 tid + LM	LM	3	①②③④⑦
Zhao JQ 2018 [24]	32 (26/6)	32 (24/8)	BBR 0.3 tid + LM	LM	3	①②③⑥
Chen YM 2017 [25]	50 (31/19)	50 (30/20)	BBR 0.5 tid	Met 0.25 tid	6	①②⑥

Note: -, no record; BBR, berberine; LM, lifestyle modification; Met, metformin; ① FPG; ② 2hPG; ③ HbA1c; ④ HOMA-IR; ⑤ HOMA- $\beta$ ; ⑥ BMI; ⑦ adverse effects.

random sequence generation methods, such as random number tables [20] [23]. There was insufficient information to determine whether the randomizations were carried out correctly in the rest of the studies. Only one study described the allocation concealment [22], one study used a single blind [22], and three studies reported the number of withdrawals and drop-outs in each group [19] [22] [23]. None of the studies indicated any other bias. The risk of bias in included studies is shown in **Figure 2**.

### 3.4. Outcome Indicators

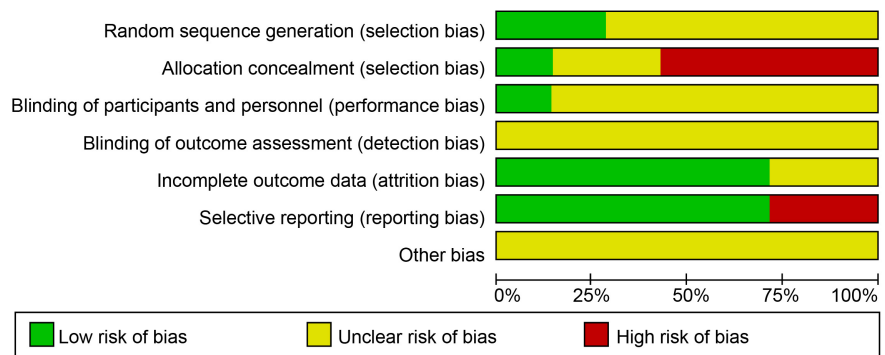
Seven studies (nine trials) were included in the study. The control groups were all lifestyle modification or metformin treatment. Considering that the intervention measures of berberine treatment are different, the influencing factors such as drug dosage and course of treatment can not be combined and analyzed. Therefore, the intervention types of experimental and control groups were analyzed in subgroups, which were divided into berberine vs. lifestyle and berberine vs. metformin. Because some data in Wang L [23] article, our previous research results, were abnormal distribution, the meta analysis was carried out on the basis of the original data.

#### 3.4.1. Efficacy of Berberine Treatment on FPG

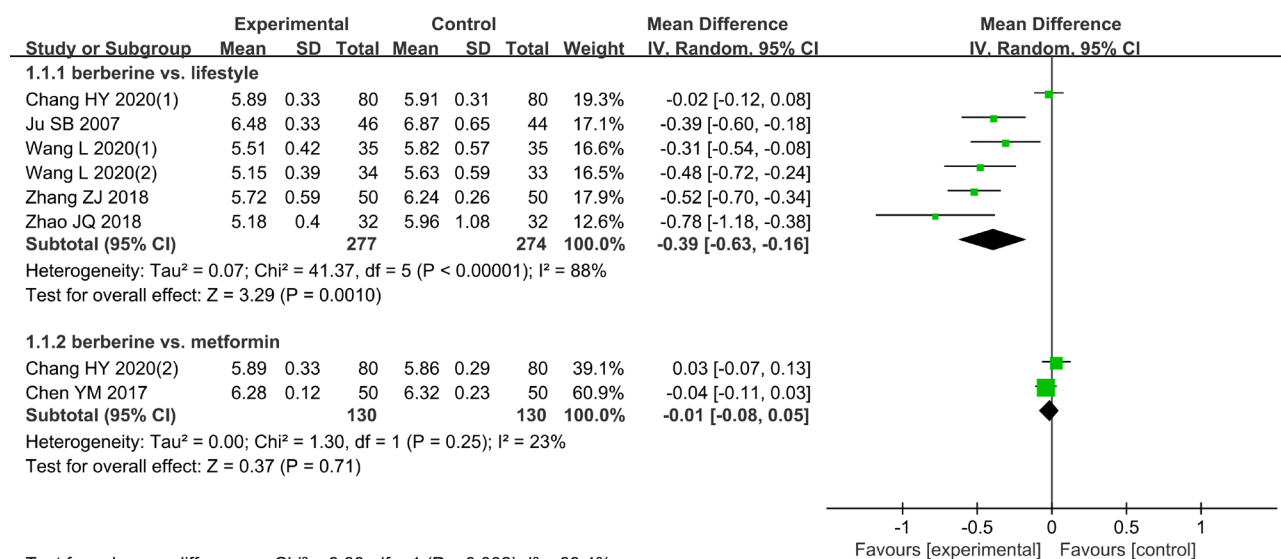
There were six trials that compared the effect of berberine vs. lifestyle on FPG and two trials for berberine vs. metformin. Due to high heterogeneity,  $I^2 > 50\%$ , random-effect (RE) model was used for the analysis. Subgroup analysis showed that berberine significantly reduced FPG level compared with lifestyle group, [MD = -0.39, 95% CI (-0.63, -0.16),  $P = 0.001$ ]. There was no significant difference between berberine and metformin, [MD = -0.01, 95% CI (-0.08, 0.05),  $P = 0.71$ ]. See **Figure 3**.

#### 3.4.2. Efficacy of Berberine Treatment on 2hPG

There were six trials that compared the effect of berberine vs. lifestyle on 2hPG and two trials for berberine vs. metformin. Due to high heterogeneity,  $I^2 > 50\%$ , random-effect (RE) model was used for the analysis. Subgroup analysis showed



**Figure 2.** Risk of bias assessed using RevMan 5.4 according to the guidance in the Cochrane Handbook. Green represents low risk of bias, yellow represents unclear risk of bias, and red represents high risk of bias.



**Figure 3.** Forest plot of outcome measure FPG.

that berberine significantly reduced 2hPG level compared with lifestyle group, [MD = -1.51, 95% CI (-2.43, -0.59),  $P = 0.001$ ]. There was no significant difference between berberine and metformin, [MD = -0.07, 95% CI (-0.29, 0.14),  $P = 0.51$ ]. See **Figure 4**.

### 3.4.3. Efficacy of Berberine Treatment on HbA1c

There were six trials that compared the effect of berberine vs. lifestyle on HbA1c and two trials for berberine vs. metformin. Due to high heterogeneity,  $I^2 > 50\%$ , random-effect (RE) model was used for the analysis. Subgroup analysis showed that berberine significantly reduced HbA1c level compared with lifestyle group, [MD = -0.20, 95% CI (-0.32, -0.08),  $P = 0.002$ ]. There was no significant difference between berberine and metformin, [MD = -0.03, 95% CI (-0.08, 0.02),  $P = 0.22$ ]. See **Figure 5**.

### 3.4.4. Efficacy of Berberine Treatment on HOMA-IR

There were four trials that compared the effect of berberine vs. Lifestyle on HOMA-IR and one trial for berberine vs. metformin. Due to high heterogeneity,  $I^2 > 50\%$ , random-effect (RE) model was used for the analysis. There was no significant difference between berberine and lifestyle or metformin, [MD = -0.13, 95% CI (-0.33, 0.06),  $P = 0.18$ ] and [MD = -0.01, 95% CI (-0.05, 0.03),  $P = 0.64$ ], respectively. See **Figure 6**.

### 3.4.5. Efficacy of Berberine Treatment on HOMA- $\beta$

One trial compared the effect of berberine vs. lifestyle on HOMA- $\beta$ . There was no significant difference between the two groups, [MD = 0.17, 95% CI (-0.03, 0.37),  $P = 0.09$ ]. See **Figure 7**.

### 3.4.6. Efficacy of Berberine Treatment on BMI

There were four trials that compared the effect of berberine vs. lifestyle on BMI

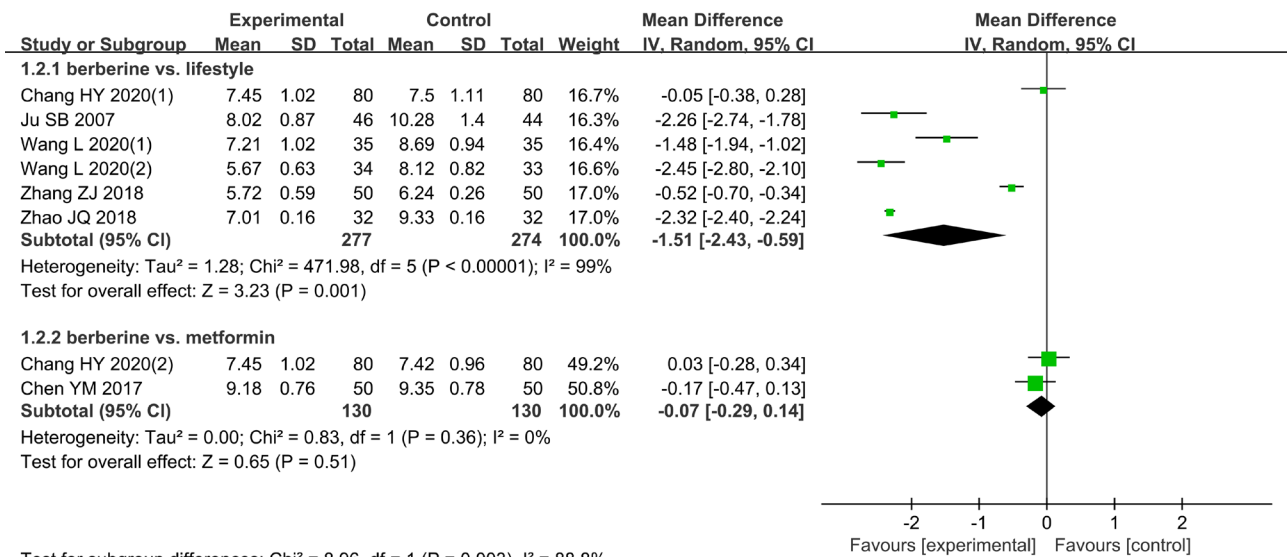


Figure 4. Forest plot of outcome measure 2hPG.

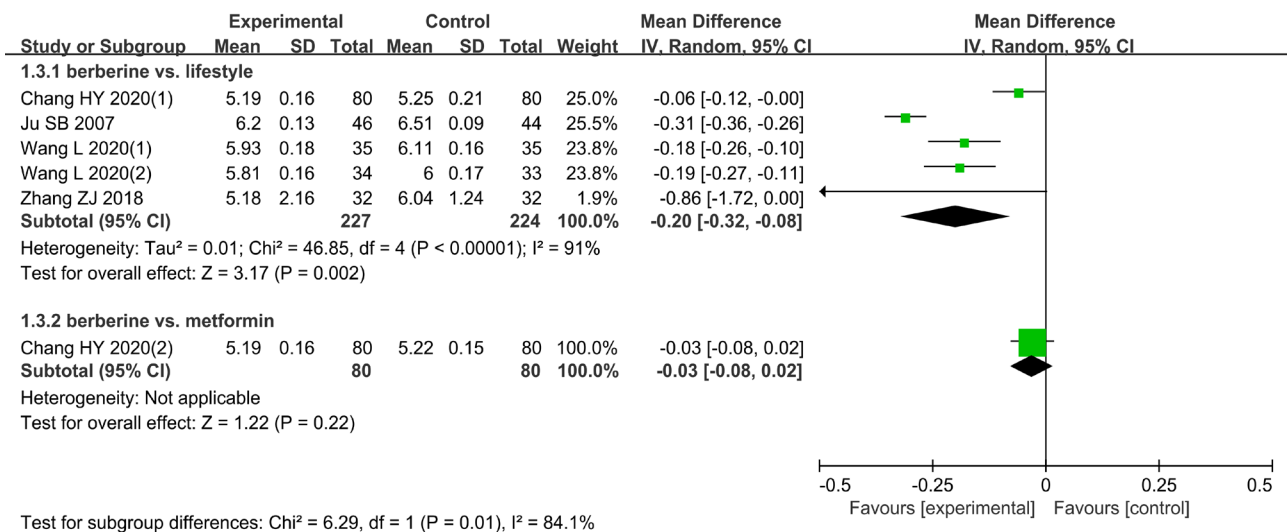


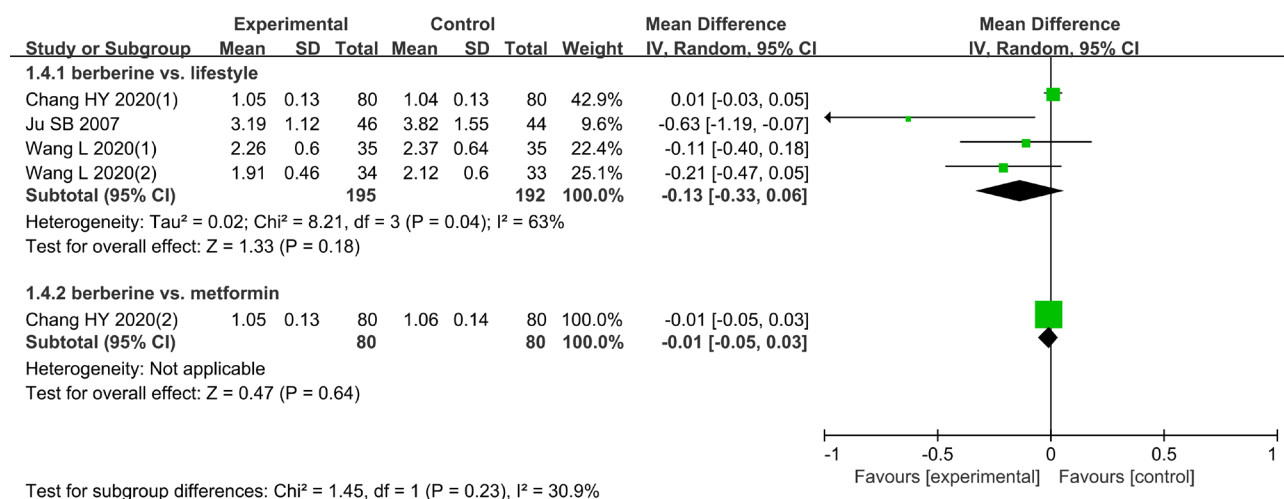
Figure 5. Forest plot of outcome measure HbA1c.

and one trial for berberine vs. metformin. Due to high heterogeneity,  $I^2 > 50\%$ , random-effect (RE) model was used for the analysis. There was no significant difference between berberine and lifestyle or metformin, [MD = -1.14, 95% CI (-2.52, 0.25),  $P = 0.11$ ] and [MD = -0.45, 95% CI (-1.63, 0.73),  $P = 0.45$ ], respectively. See Figure 8.

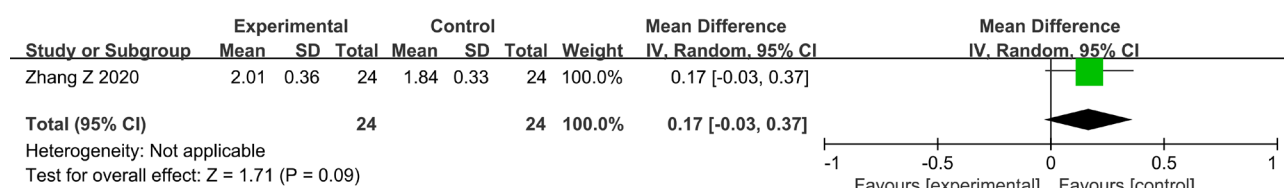
### 3.4.7. Efficacy of Berberine Treatment on Adverse Effects

Five trials reported the number of adverse effects and the other trials only stated slight adverse effects of berberine without clear data. Due to low heterogeneity,  $I^2 < 50\%$ , fixed-effect (FE) model was used for the analysis. Subgroup analysis showed that there was no significant difference between berberine and lifestyle, [MD = 3.75, 95% CI (0.61, 23.2),  $P = 0.15$ ]. Compared with metformin, the

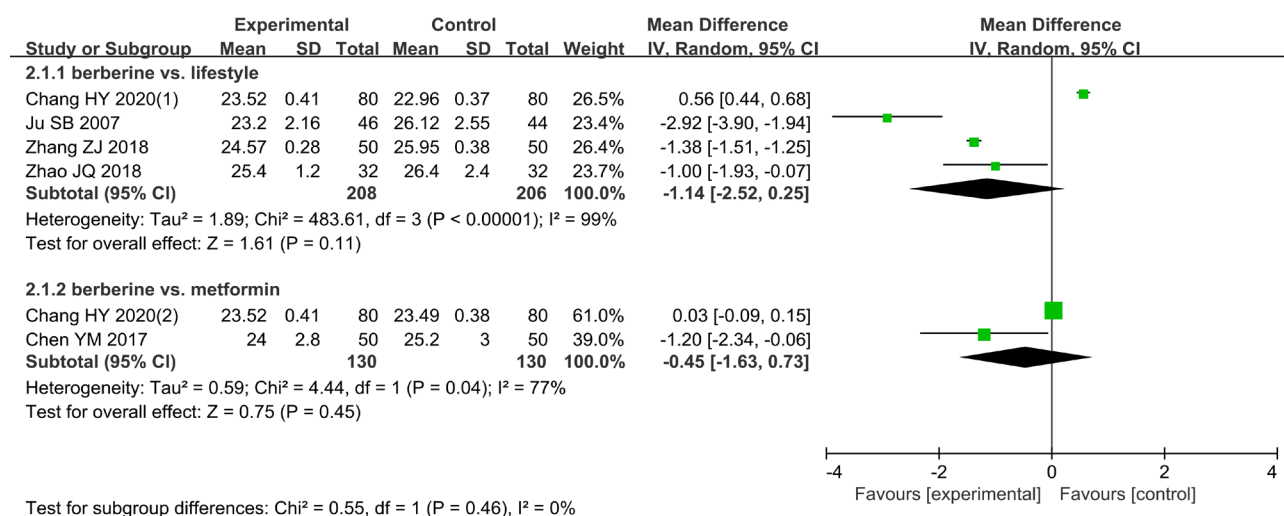




**Figure 6.** Forest plot of outcome measure HOMA-IR.



**Figure 7.** Forest plot of outcome measure HOMA-β.

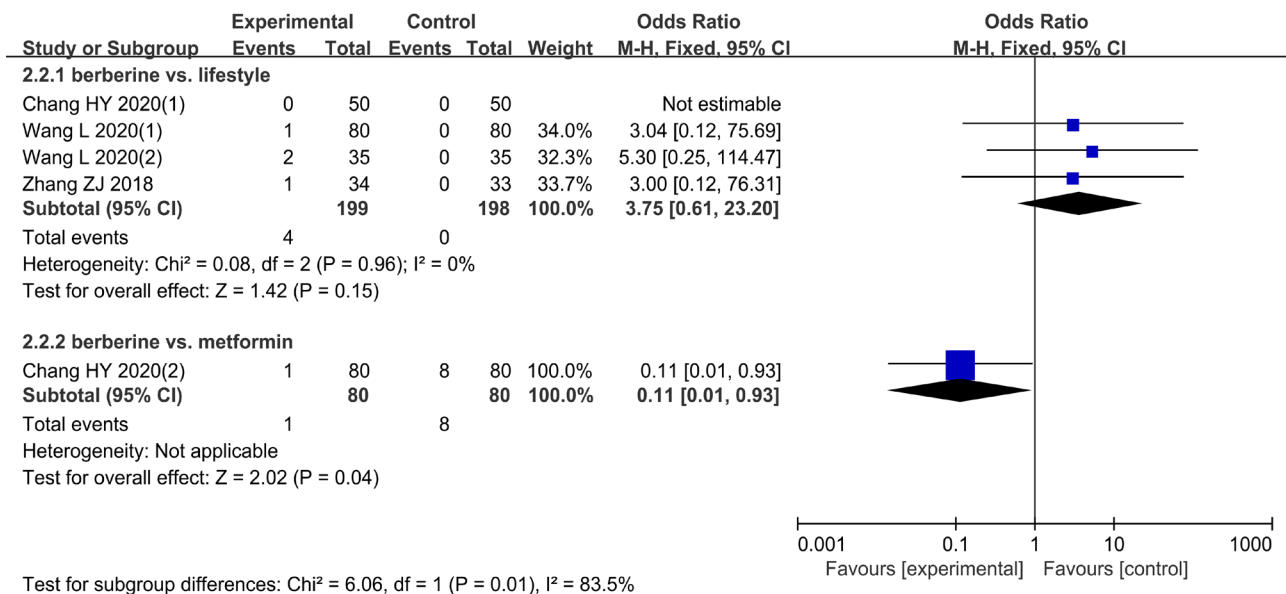


**Figure 8.** Forest plot of outcome measure BMI.

adverse effects rate of berberine was significantly decreased, [MD = 0.11, 95% CI (0.01, 0.93),  $P = 0.04$ ]. All reported events were mild, including constipation, diarrhea, nausea and abdominal distension. No serious adverse effects from berberine were reported. See **Figure 9**.

### 3.5. Sensitivity Analysis

Sensitivity analysis was carried out by eliminating literature one by one. FPG,



**Figure 9.** Forest plot of adverse effects.

HOMA-IR and BMI for the subgroup of berberine vs. Lifestyle, were significantly affected by the article, Chang HY [21]. The results changed from [ $P = 0.001$ ,  $I^2 = 88\%$ , MD =  $-0.39$ , 95% CI ( $-0.63$ ,  $-0.16$ )], [ $P = 0.18$ ,  $I^2 = 63\%$ , MD =  $-0.13$ , 95% CI ( $-0.33$ ,  $0.06$ )] and [ $P = 0.11$ ,  $I^2 = 99\%$ , MD =  $-1.14$ , 95% CI ( $-2.52$ ,  $0.25$ )] to [ $P = 0.00001$ ,  $I^2 = 19\%$ , MD =  $-0.46$ , 95% CI ( $-0.58$ ,  $-0.35$ )], [ $P = 0.04$ ,  $I^2 = 23\%$ , MD =  $-0.23$ , 95% CI ( $-0.44$ ,  $-0.01$ )] and [ $P = 0.0002$ ,  $I^2 = 80\%$ , MD =  $-1.71$ , 95% CI ( $-2.60$ ,  $-0.81$ )], respectively. After excluding the article, berberine could also significantly reduce HOMA-IR and BMI of prediabetes.

### 3.6. Publication Bias Analysis

Owing to the limited number (below ten) of trials included in each analysis, publication bias was not assessed.

## 4. Discussion

### 4.1. Summary and Analysis of Evidence

There have been a lot of clinical studies or reports about berberine in the treatment of T2DM. But it is relatively few studies for prediabetes. At present, no meta-analysis of the efficacy and safety of berberine in prediabetes has been done. In this systematic review, we selected seven clinical studies and the strategy follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A total of 859 participants were involved, of which 431 and 428 were in the experimental and control groups. Our findings upon the seven studies showed that compared with lifestyle group, berberine could lower the level of FPG [MD =  $-0.39$ , 95% CI ( $-0.63$ ,  $-0.16$ ),  $P = 0.001$ ], 2hPG [MD =  $-1.51$ , 95% CI ( $-2.43$ ,  $-0.59$ ),  $P = 0.001$ ] and HbA1c [MD =  $-0.20$ ,

95% CI (-0.32, -0.08),  $P = 0.002$ ]. There was no statistical significance between berberine and metformin. In addition, berberine evaluated in our review generally appeared to be safe. The adverse effects were commonly gastrointestinal discomforts including constipation, diarrhea, nausea and abdominal distension. No serious adverse effects from berberine were reported.

In order to minimize the heterogeneity, we used the subgroup analysis according to different interventions. However, when FPG, 2hPG, HbA1c, HOMA-IR and BMI data were aggregated in the subgroup of berberine vs. lifestyle, the heterogeneity was still high. Then we used the method of eliminating references one by one to carry out the sensitivity analysis. It was found that Chang HY, 2020(1) [21] had the greatest impact on the results. Berberine could also significantly reduce HOMA-IR [ $P = 0.04$ ,  $I^2 = 23\%$ , MD = -0.23, 95% CI (-0.44, -0.01)] and BMI [ $P = 0.0002$ ,  $I^2 = 80\%$ , MD = -1.71, 95% CI (-2.60, -0.81)] after excluding the article. The reason may be that the doses of berberine in this study were significantly lower than those in other studies.

#### 4.2. limitations

This analysis also has several limitations. All the included studies were conducted among Chinese participants in the mainland of China. There was a high risk of selection bias. Although all the studies mentioned random allocation, five studies did not describe the generation of random sequences, and most of the studies did not describe adequate allocation concealment. Only one study described single blindness. Three studies reported withdrawals and drop-outs. So it may lead to selection bias and implementation bias. Potential bias in selection of patients (such as age, gender or blood glucose level at baseline), administration of treatment and assessment of outcomes could lead to overestimation of the therapeutic efficacy of berberine. Moreover, the research approaches of the trials were not described or published in advance. These may lead to follow-up bias and reporting bias. Owing to the limited number (below ten) of trials included in each analysis, publication bias was not assessed. Therefore all of the outcomes should be carefully interpreted based on substantial methodological and clinical diversity.

#### 4.3. Inspiration

This study suggests that the methodological quality of berberine in the treatment of prediabetes is generally low, which may lower the internal authenticity of the results, then affect their external authenticity. High quality RCTs should be carried out, especially scientific and reasonable methodological research design. Attentions should be paid to the design and implementation of clinical studies: 1) Register programmes prior to implementation; 2) Estimate sample size before the study; 3) Report detailedly on random sequence generation, allocation concealment and blinding of participants, researchers and evaluators; 4) Report results and analyze reasons of withdrawals and drop-outs; 5) Large sample sizes

and long-term follow-up are needed to the evaluation of the efficacy and safety of berberine; 6) Report strictly according to CONSORT [26] to improve the levels of evidence and clinical values.

## 5. Conclusion

This study indicates that Berberine has good efficacy and safety in the treatment of prediabetes. Due to the quality limitations of the included trials, the above conclusions need to be further verified by high-quality, large sample size and multi-center RCTs.

## Conflicts of Interest

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

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