Systematic Review and Meta-Analysis

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Efficacy and safety of Shenqi Jiangtang Granules plus oral hypoglycemic agent in patients with type 2 diabetes mellitus

A systematic review and meta-analysis of 15 RCTs

Tianli Li, MM[a,b,c], Hongzheng Li, MM[b,d], Yang Wu, MM[b,c], Qian Wu, MM[d], Guozhen Zhao, MM[a,b], Zhaolun Cai, MM[e], Fenglan Pu, MB[b], Bo Li, MM[a,*]

Abstract

Objective: Shenqi Jiangtang Granules (SQJTG) has been widely used to treat patients with type 2 diabetes mellitus (T2DM). But whether there exists sufficient evidence on the efficacy of SQJTG in the treatment of T2DM is unclear. In order to assess the effects of SQJTG for T2DM, a systematic review and meta-analysis of randomized controlled trials (RCTs) were carried out.

Methods: Eight databases, namely, PubMed, The Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure, Chinese Scientific Journals Full-Text Database, CBM, and Wanfang database were searched up to May 2020. According to the Cochrane standards, the selection of study, the extraction of data, the assessment of study quality, and the analyses of data were carried out strictly. Then a fixed or random effects model was applied to analyze the outcomes.

Results: Fifteen studies (N = 1392) in total conformed the inclusion criteria to this meta-analysis. Two subgroups were identified, based on different dose of SQJTG: oral hypoglycemic agent (OHA) vs OHA plus SQJTG (1 g); OHA vs. OHA plus SQJTG (1.5–3 g). The pooled results showed that, in comparison with OHA, OHA plus SQJTG significantly reduced fasting plasma glucose in both 1 g subgroup and 1.5–3 g subgroup; 2-hour post-meal blood glucose was also greatly reduced in the SQJTG 1 g subgroup and the SQJTG 1.5–3 g subgroup. Compared with OHA, SQJTG 1 g subgroup significantly reduced levels of glycated hemoglobin A1c, as well as the SQJTG 1.5–3 g subgroup. Homeostasis model-insulin resistance index was also reduced in both SQJTG 1 g subgroup and SQJTG 1.5–3 g subgroup; SQJTG group can also significantly reduce the total adverse events especially in reducing the incidence of hypoglycemia.

Conclusions: SQJTG is an effective and safe complementary treatment for T2DM patients. This meta-analysis provides an evidence for the treatment in patients with T2DM. While owing to the high heterogeneity and the trials' small sample size, it's crucial to perform large-scale and strict designed studies.

Abbreviations: 2hPG = 2-hour post-meal blood glucose, ADA = American diabetes association, CHM = Chinese herbal medicine, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin A1c, HOMA-IR = homeostasis model-insulin resistance index, OHA = oral hypoglycemic agent, RCT = randomized controlled trial, SQJTG = Shenqi Jiangtang Granules, T2DM = type 2 diabetes mellitus.

Keywords: Chinese herbal medicine, efficacy, meta-analysis, randomized controlled trials, Shenqi Jiangtang Granules, type 2 diabetes mellitus

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TL and HL contributed equally to this work, and should be regarded as co-first authors.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files.

[a] Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Dongcheng District, [b] Beijing University of Chinese medicine, Chaoyang District, [c] Department of Cardiology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Dongcheng District, [d] Department of Cardiology, Guang'an men hospital, China Academy of Chinese Medical Sciences, Xicheng District, Beijing, [e] Department of Gastroenterology, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, China.

[*] Correspondence: Bo Li, Beijing Hospital of Traditonal Chinese Medicine, Capital Medical University, Beijing, China (e-mail: libo@bjzhongyi.com).

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1. Introduction

Diabetes mellitus (DM) is 1 of the major diseases that endanger human health, and its prevalence is increasing. The latest International Diabetes Federation survey indicated that there were nearly 450 million (aged 18–99) diabetes patients across the world in 2017, and these figures were expected to rise to nearly 700 million by 2045, which used to be far underestimated.[1] In the latest study conducted in 2013, which included 170,287 participants, it was reported that the morbidity of diabetes was 10.9%, with more than 60 percent of those unconscious of their diagnosis.[2] The significant increase in the prevalence of diabetes worldwide is mainly attributed to type 2 diabetes mellitus (T2DM). Persistently high blood sugar levels associated with T2DM can cause systemic vascular damage that affects the heart, eyes, kidneys and nerves, and can lead to complications.[3] It was estimated that about 5 million people between the ages of 20 and 99 died of T2DM in 2017, accounting for approximately 9.9 percent of all causes mortality worldwide.[1] Therefore, good blood glucose control is essential. According to American diabetes association (ADA), For T2DM, metformin should be the preferred drug unless there are contraindications, if the blood glucose control is not good, other OHA can be added.[4] And insulin treatment can be considered when hyperglycemia is severe, especially if catabolic features are present.[4] However, some OHA can cause a few adverse events, including hypoglycemia, Gastrointestinal reactions, dyslipidemia and the gain of weight, et al.[5]

According to Traditional Chinese Medicine, diabetes-related symptoms are named "Xiaoke" disease. In China, "Xiaoke" is widely treated by Chinese herbal medicines (CHMs), and adequate experience has been accumulated.[6,7] Several studies have shown that CHMs have good efficacy in controlling glucose, with fewer adverse events, such as gastrointestinal reactions and hypoglycemic reactions.[8–12] Pharmacological researches have indicated that CHMs can promote glucose uptake and improve insulin sensitivity in 3T3-L1 adipocytes,[13] inhibit β-cell apoptosis and increase β-cell number,[14] and palliate insulin resistance.[15]

Shenqi Jiangtang Granules (SQJTG) is a proprietary Chinese medicine for T2DM approved by China food and drug administration (state medical license number Z10950075), which is composed of 11 herbs such as ginsenosides, schisandrae, astragalus, yam, rehmannia, raspberry, radix ophiopogonis, poria, radix trichosanthis, alisma, wolfberry. SQJTG can treat T2DM with Qi and Yin deficiency symptom like dry throat and thirst, fatigue and no desire to speak, spontaneous perspiration. Some pharmacological studies have indicated that the main components of SQJTG, such as ginsenosides and astragalus, have many effects like gluconeogenesis reduction, improvement of insulin resistance, myocardial protection, lipid regulation, islet cell protection, antioxidation.[16,17]

In recent years, several RCTs have indicated that SQJTG combined with OHA can control blood glucose better with less adverse events than OHA alone.[18–32] In order to objectively evaluate the efficacy and safety of SQJTG in treating T2DM, we performed a systematic review and meta-analysis based on published RCTs.

2. Materials and methods

This work was conducted and reported, based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines.[33] This review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number ID 42020153955). Because we conducted this systematic review and meta-analysis based on published data, it is not necessary for further ethical approval. Furthermore, we analyzed all data anonymously during the whole review process.

2.1. Database and search strategies

Eight databases, namely, PubMed, The Cochrane Library, EMBASE, Web of Science, Chinese National Knowledge Infrastructure, Chinese Scientific Journals Full-Text Database, CBM, and Wanfang database, were searched up to May 20th, 2020. The search was restricted to trials published in Chinese and English. The search strategy was consisted of three facets: the participant (T2DM patients), the intervention (SQJTG) and the type of study design (RCT). The search terms used were (Shenqi Jiangtang Granules OR Shenqi Jiangtang) AND (type 2 diabetes mellitus OR type 2 diabetes OR T2DM) AND (randomized clinical trial OR randomized OR RCT). Citations contained in the retrieved articles were also systematically reviewed to search for additional relevant studies. Two reviewers (Yang Wu and Hongzheng Li) screened Titles and abstracts individually. Any divergence was resolved by Guozhen Zhao.

2.2. Clinical trial selection criteria

Trials were filtrated according to the following inclusion criteria:

(1) The study design was confined to RCTs;
(2) The patients had T2DM diagnosed, conforming with fasting plasma glucose (FPG), 2-hour post-meal blood glucose (2hPG) and glycated hemoglobin A1c (HbA1c) diagnostic criteria, met the criteria of the World Health Organization (1999)[34] or ADA 2010[35] respectively;
(3) The experimental group used SQJTG (Z10950075, China Food and Drug Administration) plus OHA and the control group used OHA. OHA includes biguanides, sulphonylureas, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide receptor agonists.
(4) The outcome should include at least one of the FPG, 2hPG, and HbA1c.

Exclusion criteria were:

(1) duplicates studies;
(2) studies including other treatments, such as acupuncture or other CHMs;
(3) non-RCTs: such as observational study and series case reports;
(4) patients who undergo insulin treatment or take other CHMs;
(5) trials which lack of the detailed description of SQJTG dosage or frequency;
(6) abstracts and reviews without specific data.

2.3. Data extraction

Data were extracted individually by two reviewers (Hongzheng Li and Qian Wu). The extracted data were as followed: basic information (title, authors and publication year); participants and disease (gender, age, disease course and sample size); interventions (dose and frequency of SQJTG, and details of OHA); and outcomes (effective outcomes, adverse events).

2.4. Assessment of risk of bias

The quality of studies was evaluated by applying the Cochrane Risk of Bias (ROB) Tool,[36] which is consisted of seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each item can be judged as low risk, high risk or unclear of bias. And two reviewers (Tianli Li and Hongzheng Li) individually used the ROB tool to evaluate the quality of included RCTs. All divergences in this process were solved by discussion or consultation with Bo Li.

2.5. Types of outcomes

The outcomes we chose were divided into 2 types (main outcomes and secondary outcomes). Main outcomes: We measured the blood glucose using the FPG, 2hPG and HbA1c. According to the World Health Organization 1999 or ADA 2010; Secondary Outcomes: homeostasis model-insulin resistance index (HOMA-IR), adverse events, including hypoglycemia, gastrointestinal reactions, ketoacidosis, rash, emergency complications, incident of emergency department visits and incident of hospitalizations.

2.6. Data statistics and analysis

Data were analyzed by two reviewers (Tianli Li and Hongzheng Li) using Review Manager 5.3 software, which is exploited by the Cochrane Collaboration. The relative risk (RR), mean difference (MD) and 95% confidence interval (95% CI) were calculated. Statistical heterogeneity was assessed by I^2. If the heterogeneity ($P \geq .1$, $I^2 \leq 50\%$) was acceptable, the fixed-effects model was adopted. On the contrary, the random-effects model should be used. A subgroup analysis was conducted on the basis of different doses of SQJTG. Sensitive analysis can be adopted to explore the sources of heterogeneity. When the number of included studies surpasses 10, funnel plots was performed to assess the publication bias.

3. Results

3.1. Description of included trials

We identified 815 records through the original database search. After repeatedly screening, 15 trials[18–32] with 1392 participants were involved in this meta-analysis. The screening process is summarized in a flow diagram (Fig. 1). All studies were conducted in China, and all participants involved were Chinese. All trials lasted from 4 weeks to 6 months were designed as RCT, and compared SQJTG plus OHA with OHA alone. The OHA includes Metformin, Glimepiride, Saxagliptin, Gliquidone, Acarbose, Repaglinide, Sitagliptin, Glipizide, Rosiglitazone and Voglibose. The characteristics of the studies were summarized in detail (Table 1).

3.2. Risk of bias in the included trials

The methodological quality assessed of included studies were low (Fig. 2). 7 of 15 studies[21,22,25,27–30] specified the sequence generation process. No included studies reported allocation concealment. Blinding was all assessed as low risk, as the blinding would not influence the objective outcomes measurement, and all the outcomes we chose are objective. All studies had low attrition bias as all participants were accounted for. For selective reporting bias, due to unavailability of protocols of any included trials, it was assessed as unknown. All included studies claimed baseline comparability, and all these 15 studies reported the inclusion/exclusion criteria. 2 of the included studies[27,32] appeared to have a low risk of for-profit bias as they were sponsored by the government funds, and none were sponsored by the pharmaceutical companies.

3.3. Data analysis

3.3.1. Main outcomes

3.3.1.1. FPG. 14 trials[18–24,25–32] including 1,294 participants reported FPG. As these studies showed significant heterogeneity of results ($I^2 = 67\%$), a statistical analysis of random-effects model was adopted for FPG. Subgroup differences showed no heterogeneity ($p = 0.37$, $I^2 = 0\%$), therefore these RCTs indicated SQJTG combined with OHA was superior to OHA alone (MD, -1.30mmol/L, 95% CI [-1.50 to -1.10], $P = .0002$). For the trials who take SQJTG 1 g per time, three times a day, meta-analysis showed SQJTG combined with OHA was superior to OHA alone (MD, -1.33 mmol/L, 95% CI [-1.63 to -1.04], $P < .00001$). For the trials who take SQJTG 1.5–3 g per time, three times a day, meta-analysis showed SQJTG combined with OHA was also superior to OHA alone (MD, -1.18 mmol/L, 95% CI [-1.36 to -0.99], $P < .00001$). The results showed that T2DM patients who received SQJTG plus OHA were more likely to reduce FPG compared to those who take OHA alone regardless of the SQJTG dosage (Fig. 3).

3.3.1.2. 2hPG. 14 trials[18–31] including 1,352 participants reported 2hPG. As these studies showed no heterogeneity ($I^2 = 36\%$), a statistical analysis of fixed-effects model was adopted. For the trials who take SQJTG 1 g per time, three times a day, meta-analysis showed SQJTG combined with OHA was superior to OHA alone (MD, -1.97 mmol/L, 95% CI [-2.19 to -1.75], $P < 0.00001$). For the trials who take SQJTG 1.5–3 g per time, three times a day, meta-analysis showed SQJTG combined with OHA was also superior to OHA alone (MD, -1.35 mmol/L, 95% CI [-1.71 to -0.99], $P < .00001$). Though subgroup differences showed significant heterogeneity ($P = 0.004$, $I^2 = 88.1\%$), these RCTs indicated SQJTG combined with OHA was superior to OHA alone (MD, -1.81 mmol/L, 95% CI [-1.99 to -1.62], $P < .00001$) (Fig. 4).

3.3.1.3. HbA1c. 13 trials[19–20,22–32] including 1,204 participants reported HbA1c. As these studies showed significant heterogeneity ($P = .002$, $I^2 = 62\%$), a statistical analysis of random-effects model was adopted. For the trials who take SQJTG 1 g per time, three times a day, meta-analysis showed SQJTG combined with OHA was superior to OHA alone (MD, -1.06%, 95% CI [-1.30 to -0.82], $P < .00001$). For the trials who take SQJTG 1.5–3 g per time, three times a day, meta-analysis showed SQJTG combined with OHA was also superior to OHA alone (MD, -0.91%, 95% CI [-1.15 to -0.67], $P < .00001$). Subgroup differences showed no heterogeneity ($P = .38$, $I^2 = 0\%$), therefore, these RCTs indicated SQJTG combined with OHA was superior to OHA alone (MD, -1.00%, 95% CI [-1.17 to -0.83], $P < .00001$) (Fig. 5).

3.3.2. Secondary outcomes

3.3.2.1. HOMA-IR. 5 trials[22,25,26,31,32] including 464 participants reported HOMA-IR. As these studies showed significant

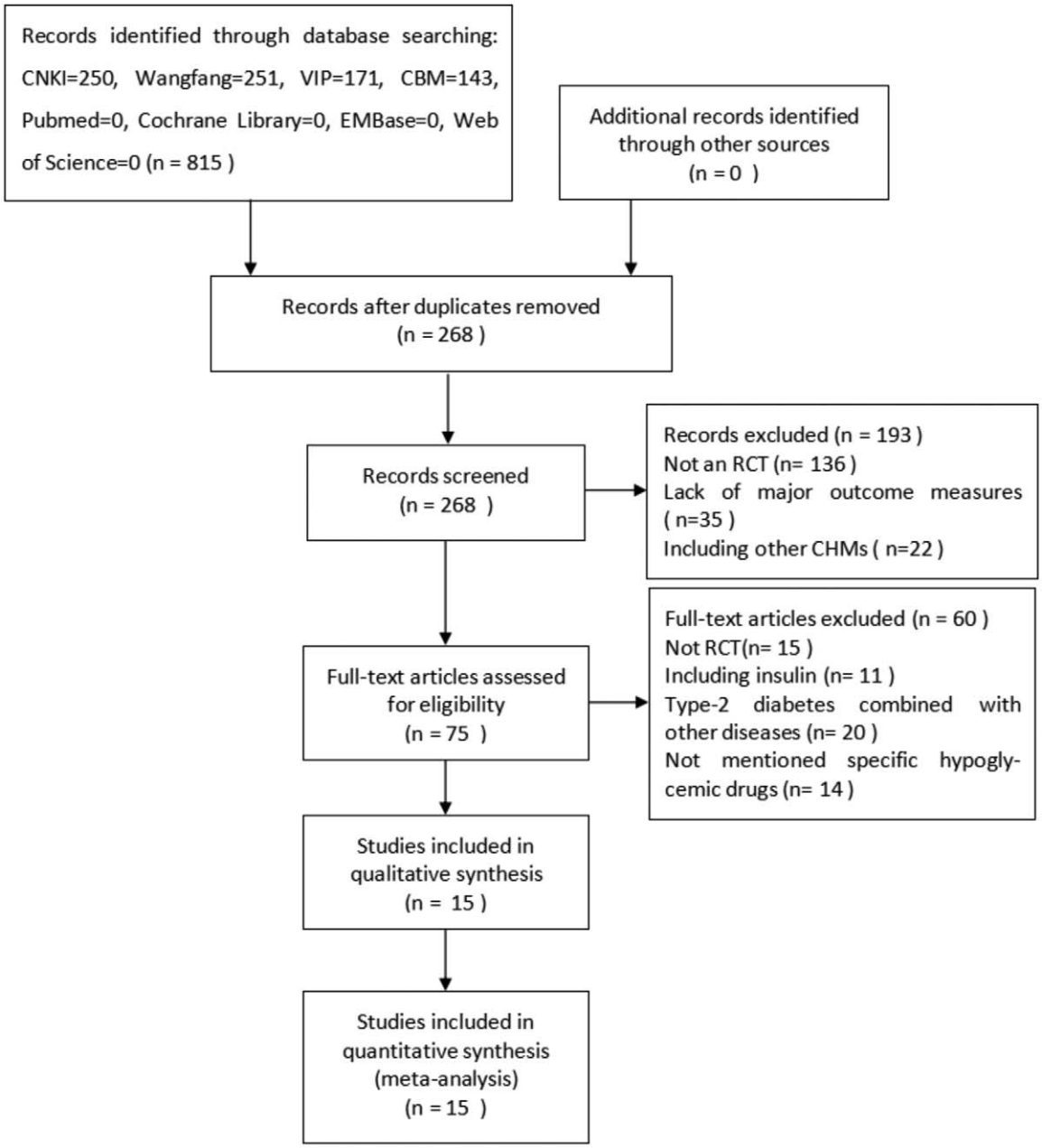

Figure 1. flow diagram of study selection process. *To avoid multiple publications, only the study with the largest sample size was included. If a study was published more than once, only the study with most complete data was included. in case of double counting data from the same trial, any additional publications were excluded.

heterogeneity ($P = .0008$, $I^2 = 79\%$), a statistical analysis of random-effects model was adopted. For the trials who take SQJTG 1g per time, three times a day, meta-analysis showed SQJTG combined with OHA was superior to OHA alone (MD, -0.76, 95% CI [-1.19 to -0.33], $P = .0006$). For the trials who take SQJTG 1.5–3g per time, three times a day, meta-analysis also showed SQJTG combined with OHA was superior to OHA alone (MD, -0.44, 95% CI [-0.66 to -0.22], $P < .0001$) (Fig. 4). Subgroup differences showed no heterogeneity ($P = .20$, $I^2 = 39.4\%$), these RCTs indicated SQJTG combined with OHA was superior to OHA alone (MD, -0.65, 95% CI [-0.91 to -0.39], $P < .00001$) (Fig. 6).

3.3.2.2. Adverse events. Adverse events were reported in 7 trials[19,21,24,25,28–30] including 664 participants (Table 2). The results showed that there were significant differences between the incidence of hypoglycemia (RR, 0.12, 95% CI [0.04, 0.39], $P = .0005$), indicating that SQJTG might have some potential ways to reduce the incidence of hypoglycemia. No statistical significances between two groups in gastrointestinal reactions, including nausea, vomiting, bloating and diarrhea (RR, 1.17, 95% CI [0.40, 3.42], $P = .78$), ketoacidosis (RR, 0.50, 95% CI [0.09, 2.71], $P = .42$), rash (RR, 1.00, 95% CI [0.06, 15.92], $P = 1.00$), emergency complications (RR, 0.60, 95% CI [0.14, 2.49], $P = .48$), incident of emergency-department visits (RR, 0.42, 95%

Table 1

Characteristics and quality of type 2 diabetes patients in included studies.

Study	N (T/C)	Gender (M/F)	Age (years)	Course of disease	Inventions		Outcomes	
					Treatment	Control	Primary	Secondary
Wu JH 2012[18]	68 (34/34)	T:23/11 C:20/14	T:65.5±7.5 C:63.5±6.5	T:13.6±6.8 C:14.3±7.4	SQJTG:2g, tid, 4m + Control	Acarbose: 50 mg, tid, 4mo	①FPG ②2hPG	④HOMA-IR ⑤Adverse Events
Wang ZZ 2013[19]	60 (30/30)	T:16/14 C:15/15	T:59.2±6.5 C:57.1±5.5	T:2.8±2.0 C:3.5±2.5	SQJTG:3g, tid, 8w + Control	Voglibose: 0.2 mg, tid, 8wk	①FPG ②2hPG ③HbA1C	⑤Adverse Events
Zhang L 2019[20]	120 (60/60)	T:31/29 C:33/27	T:57.13±9.86 C:57.46±9.74	T:7.86±2.59 C:7.49±2.38	SQJTG:1g, tid, 12w + Control	Metformin: 0.25g, bid, 12w Glimepiride: 1 mg, qd, 12wk	①FPG ②2hPG ③HbA1C	/
Xia QB 2016[21]	120 (60/60)	T:34/26 C:38/22	T:72.98±5.61C:73.62±6.54	T:3.45±0.37 C:3.26±0.54	SQJTG:1g, tid, 4m + Control	Acarbose: 50 mg, tid, 4mo	①FPG ②2hPG	⑤Adverse Events
Sun Y 201729[22]	96 (48/48)	T:28/20 C:30/18	T:56.27±4.61 C:54.15±4.29	T:4.2±1.3 C:3.9±1.2	SQJTG:1g, tid, 8w + Control	Metformin: 0.25g, tid, 8wk	①FPG ②2hPG ③HbA1C	④HOMA-IR
Chen GY 2011[23]	80 (42/38)	T:22/20 C:20/18	T:51±6 C:49±6	T:11.2±5.8 C:10.9±6.1	SQJTG:1.5g, tid, 8w + Control	Glipizide: 10 mg, tid, 8wk	①FPG ②2hPG ③HbA1C	/
Li GQ 2011[24]	170 (85/85)	T:51/34 C:48/37	T:67.8±8.7 C:65.6±7.7	T:10.4±4.2 C:10.4±3.9	SQJTG:3g, tid, 24w + Control	Gliquidone: 30 mg, tid, 24wk	①FPG ②2hPG ③HbA1C	⑤Adverse Events
Zhang YZ 2019[25]	98 (49/49)	T:29/20 C:31/18	T:59.18±7.66 C:60.27±6.34	T:7.64±1.87 C:7.08±2.41	SQJTG:3g, tid, 12w + Control	SPMHT: 50mg/850 mg, qd, 12wk	②2hPG ③HbA1C	④HOMA-IR ⑤Adverse Events
Sui FL 2019[26]	104 (52/52)	T:22/30 C:21/31	T:54.31±5.11 C:53.25±4.70	T:5.04±1.63 C:4.86±1.33	SQJTG:1g, tid, 3m + Control	Rosiglitazone: 4 mg, qd, 3m Metformin: 0.25g, tid, 3mo	①FPG ②2hPG ③HbA1C	④HOMA-IR
She WJ 2019[27]	74 (37/37)	T:23/14 C:21/16	T:59.24±6.72 C:59.93±5.41	T:9.82±1.75 C:9.91±1.54	SQJTG:1g, tid, 3m + Control	Metformin: 7.5g tid, 3 mo	①FPG ②2hPG ③HbA1C	/
Liu GH 2018[28]	60 (30/30)	T:14/16 C:13/17	T:66.8±10.2 C:67.2±9.4	T:4.3±1.2 C:4.5±1.5	SQJTG:1g, tid, 12w + Control	Metformin: 0.5g, bid, 12wk Gliquidone:30–60 mg,qd, 12wk	①FPG ②2hPG ③HbA1C	⑤Adverse Events
Li W 2015[29]	84 (42/42)	T:27/15 C:26/16	T:63.1±6.6 C:62.8±6.2	T:6.5±2.3 C:6.4±2.1	SQJTG:3g, tid, 4w + Control	Repaglinide: 1 mg, tid, 4wk	①FPG ②2hPG ③HbA1C	⑤Adverse Events
Ren QW 2019[30]	92 (46/46)	T:30/16 C:32/14	T:56.32±3.29 C:57.02±3.58	T:4.69±2.95 C:4.98±3.02	SQJTG:1g, tid, 12w + Control	Saxagliptin: 5 mg, qd, 12 wk	①FPG ②2hPG ③HbA1C	⑤Adverse Events
Wang ZG 2020[31]	126 (64/62)	T:36/28 C:35/27	T:50.53±6.80 C:50.19±6.78	T:5.77±1.29 C:5.82±1.35	SQJTG:1g, tid, 3m + Control	Metformin: 0.25g, bid, 3 mo	①FPG ②2hPG ③HbA1C	④HOMA-IR
Liu HP 2017[32]	40 (20/20)	T:9/11 C:10/10	T:56.55±7.17 C:55.30±7.36	N	SQJTG:3g, tid, 12w + Control	Metformin:0.5g, bid/tid, 12 wk	①FPG ③HbA1C	④HOMA-IR ⑤Adverse Events

HbA1c = glycated hemoglobin A1c, homeostasis model-insulin resistance index SPMHT=Siglitine Phosphate/ Metformin Hydrochloride Tablets, SQJTG=Shenqi Jiangtang Granules.

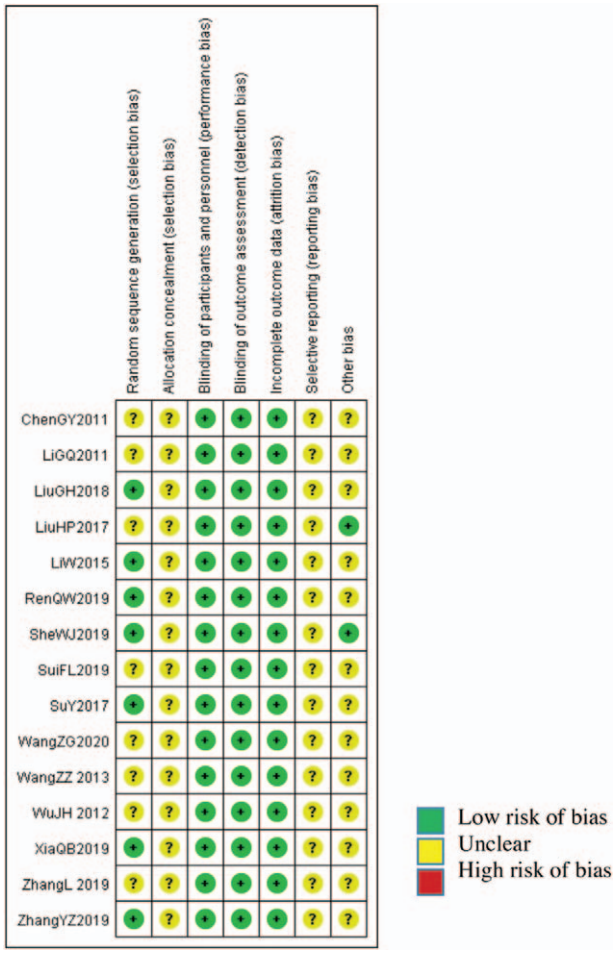

Figure 2. Risk of bias assessment in the included studies based on the Cochrane Handbook. Studies were judged to be high, moderate or low risk of bias according to the assessment of sequence generation of the allocation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.

CI [0.15, 1.17], $P = .10$) or incident of hospitalizations (RR, 0.44, 95% CI [0.14, 1.43], $P = .17$). Moreover, the results suggested that SQJTG can significantly reduce the total adverse events (RR, 0.40, 95% CI [0.26, 0.63], $P < .0001$). It seems to claim SQJTG is safe to be an adjuvant treatment in T2DM.

3.4. Publication bias

A funnel plot was adopted to check the publication bias regarding FPG (Fig. 7), 2hPG (Fig. 8). Through the asymmetry of the graph, we speculated that there might be a potential publication bias.

4. Discussion

4.1. Summary of the evidence and results' explanations

In recent years, the development of hypoglycemic drugs has made a great progress. Oral medications such us metformin, thiazolidinediones (TZD) and sulphonylurea play a vital initial role in T2DM treatment recommended by American Association of Clinical Endocrinology and American College of Endocrinology (AACE/ACE)[37] and Chinese Diabetes Society (CDS).[38] Meanwhile, the exploration of CHMs, artemisinin for example, has already shown that natural herbal medicine can also provide a method for global burden of disease.[39] Similar in the field of treatment for T2DM,[40] SQJTG has been applied for adjuvant treatment of T2DM since being approved by SFDA in China in Feb, 2015. This study aims to reveal the efficacy and safety of SQJTG as a complementary therapy for T2DM. 75 studies claimed RCTs, 15 studies[18–32] with 1392 participants met the selection criteria.

Random blood glucose, fasting blood glucose and Blood glucose at 120 minutes during an oral glucose tolerance test are World Health Organization Diagnostic criteria for dysglycemia. HbA1c, approximates the average blood glucose control over about 3 months, has been regarded as a target for glycemic control with pharmacologic therapy for T2DM.[41] The dominating result showed that SQJTG provided additional benefits for T2DM patient, which demonstrated greater decline in HbA1c, FPF, 2hPG levels compared with control group when applied hypoglycemic drugs as monotherapy. Furthermore, for secondary outcomes, 5 studies[22,25,26,31,32] with 464 participants showed that individuals who used SQJTG plus OHA combination were more effective for ameliorating HOMA-IR.

Adverse events of SQJTG is another concerned outcome. 7 of 15 included trials[19,21,24,25,28–30] reported as it stands. There is no liver or kidney damage observed in all trials. Hypoglycemia, as one of the most common and severe adverse events,[42] can be largely reduced with SQJTG intervention. It turns out that the combination of SQJTG and common OHA can reduce the incidence of adverse events. These results demonstrated that SQJTG is safe and played a synergistic action in the treatment of T2DM.

4.2. Limitations

At least 5 limitations existed in this work. Firstly, the quality of all included studies was low. A random allocation was mentioned in all included studies, whereas, only 7 trials revealed the specific random number table methods. No researches described the detailed methods of allocation concealment, which have led to selection bias and over-estimation of the intervention effects. Secondly, only 15 trials with less than 2000 participants were included in this study. And as for the course of disease, it varied from less than 1 year to more than 13 years, which may probably contribute to high heterogeneity. Moreover, all trials were conducted in China, so subjects outside China might not conform to the findings. Thirdly, obesity is a vital risk factor for T2DM. Weight control has become a momentous factor of all T2DM patients. But in this study, no trial took body mass index (BMI) as an independent factor. Last but certainly not the least, although we conducted a subgroup analysis based on the dosage of SQJTG, the meta-analysis still showed comparatively high heterogeneity for some indicators, such as FPG and HOMA-IR. Through sensitivity analysis of the above results, it was found that the outcomes were stable, and the high heterogeneity might result from the mixture of the large range of Age, course of T2DM, different complications and various medication of control groups.

4.3. Implications for research

Among the eleven herbal compounds of SQJTG, several herbal medicines have already been verified to protect myocardium tissue and improve glucose and lipid metabolism. Ginsenoside

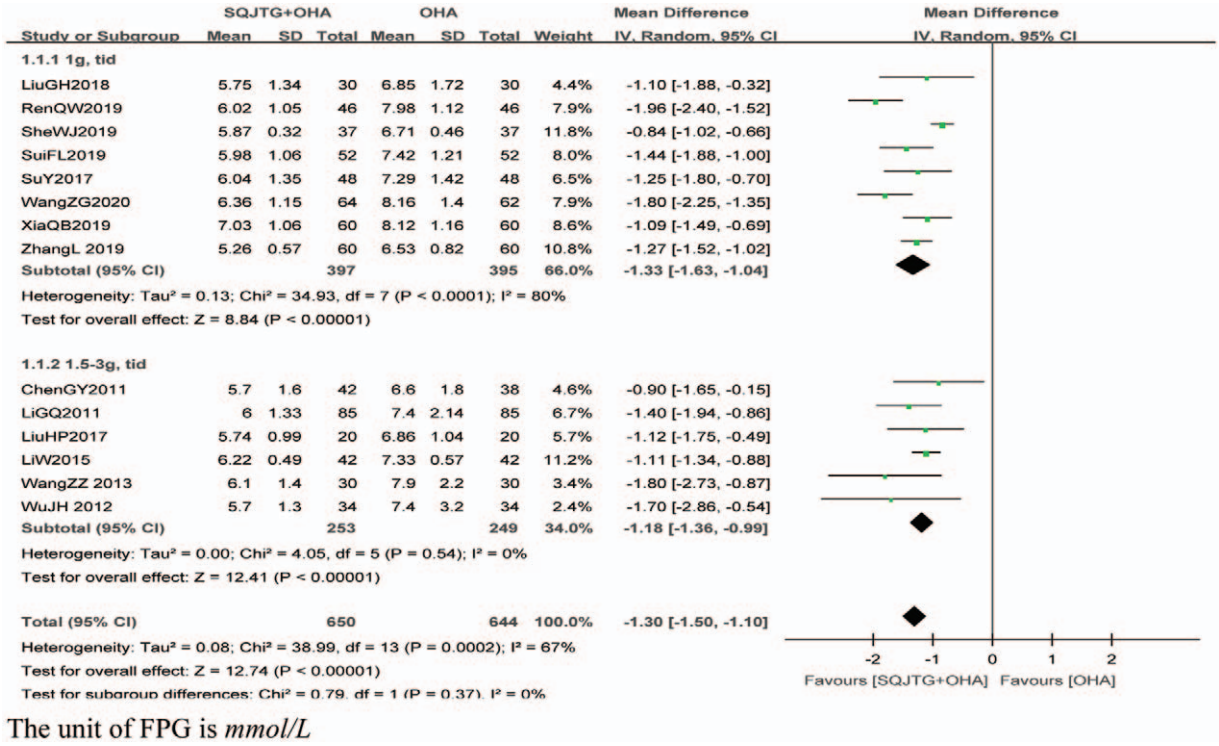

Figure 3. Forest plots of comparison of FPG between two groups. Mean difference of FPG for SQJTG vs OHA was reported in MD and 95% CI. Trials were divided into two subgroups on the basis of different doses of SQJTG: SQJTG (1 g) and SQJTG (1.5–3 g). The unit of FPG is *mmol/L*. 95% CI = 95% credibility interval, FPG = fasting plasma glucose, OHA = oral hypoglycemic agents, SQJTG = Shenqi Jiangtang Granules.

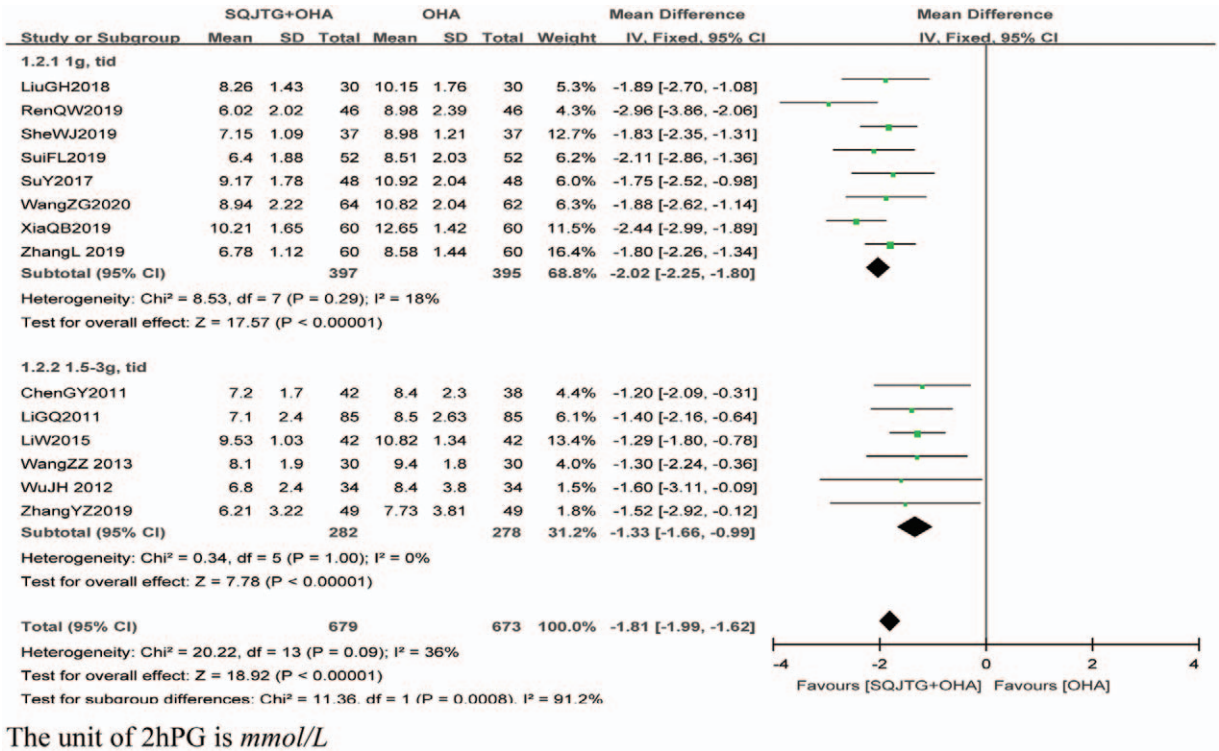

Figure 4. Forest plots of comparison of 2hPG between two groups. Mean difference of 2hPG for SQJTG vs OHA was reported in MD and 95% CI. Trials were divided into two subgroups on the basis of different doses of SQJTG: SQJTG (1 g) and SQJTG (1.5–3 g). The unit of 2hPG is *mmol/L*. 2hPG = 2-hour post-meal blood glucose, 95% CI = 95% credibility interval, OHA = oral hypoglycemic agents, SQJTG = Shenqi Jiangtang Granules.

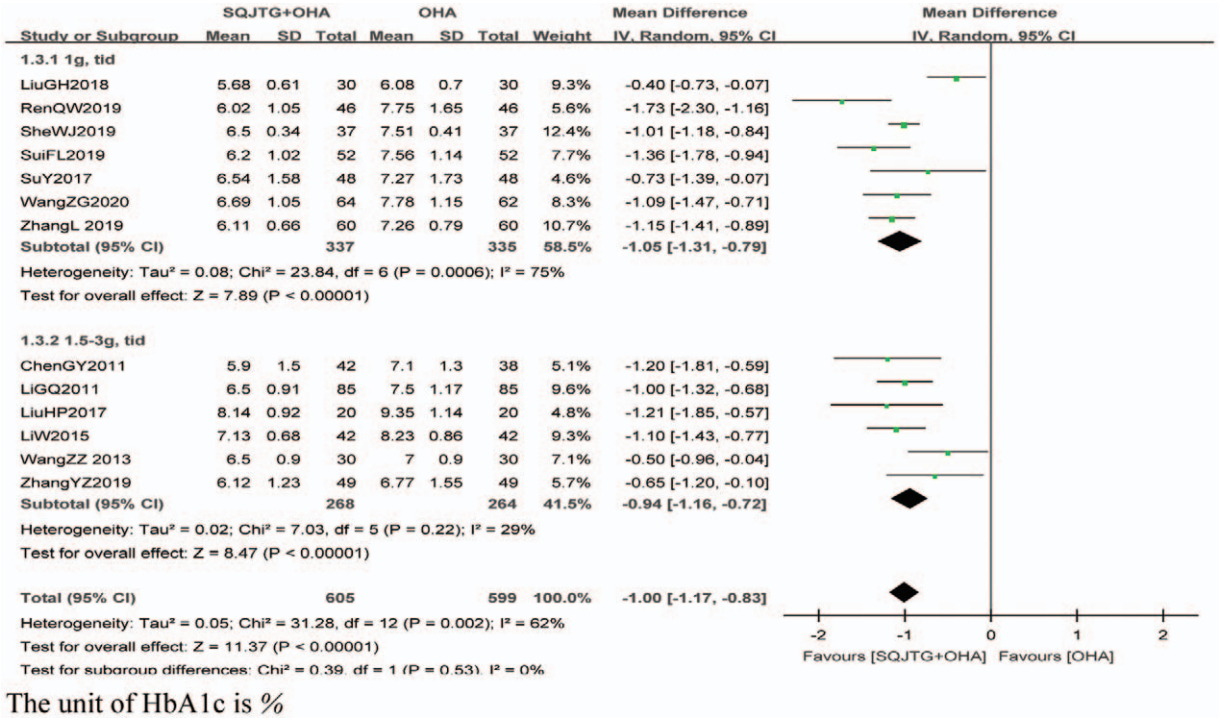

Figure 5. Forest plots of comparison of HbA1c between two groups. Mean difference of HbA1c for SQJTG vs OHA was reported in MD and 95% CI. Trials were divided into two subgroups on the basis of different doses of SQJTG: SQJTG (1 g) and SQJTG (1.5–3 g). The unit of HbA1c is %. 95% CI = 95% credibility interval, HbA1c = glycated hemoglobin A1c, OHA = oral hypoglycemic agents, SQJTG = Shenqi Jiangtang Granules.

Rk3 (G-Rk3), an active ingredient of ginsenosides, may regulate p-ACC, FAS and SREBP-1 to activate the AMPK/Akt signaling pathway to reduce lipid accumulation.[43] Ginsenoside Rb1 may protect against cardiac oxidative stress and inflammation through AMPK/Nrf2/HO-1 signal pathway.[44] And it may synergistically promote fecal β-d-glucosidase activity with Ginseng polysaccharides to display hypoglycemic activity.[45] Astragalus polysaccharides (APS), the main bioactive ingredient extracted from the root of astragalus membranaceus, is widely used in diabetic cardiomyopathy treatment through regulating the expression of ATF6 and PERK related factors of ER stress pathway,[46] activating AMPK pathway to improve insulin sensitivity,[47] and activating SOD2 enzyme to protect cellular mitochondrial ultrastructure, to reduce cell poptosis and inhibit oxidation.[48] Oligosaccharides of Ophiopogonis japonicus shows a speciality on reduce damage on islets,[49] to reduce fasting blood glucose level and improve oral glucose tolerance.[50] It is reported that a kind of polysaccharide extracted purified

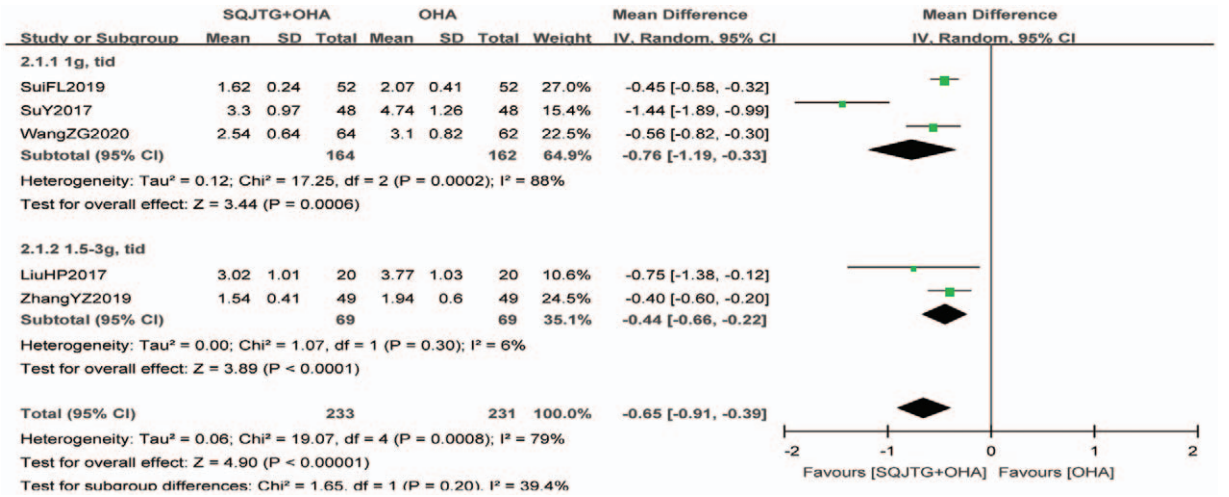

Figure 6. Forest plots of comparison of HOMA-IR between two groups. Mean difference of HOMA-IR for SQJTG vs OHA was reported in MD and 95% CI. Trials were divided into two subgroups on the basis of different doses of SQJTG: SQJTG (1 g) and SQJTG (1.5–3 g). 95% CI = 95% credibility interval, HOMA-IR = Homeostasis model-insulin resistance index, OHA = oral hypoglycemic agents, SQJTG = Shenqi Jiangtang Granules.

Table 2

Comparison of adverse events between two groups.

Types of adverse events	Total events/total number		Risk ratio (95% CI)	*P* value
	Intervention	Control		
hypoglycemia	3/332	25/332	0.12 [0.04, 0.39]	.0005
Gastrointestinal reactions	7/332	6/332	1.17 [0.40, 3.42]	.78
ketoacidosis	2/332	4/332	0.50 [0.09, 2.71]	.42
Rash	1/332	1/332	1.00 [0.06, 15.92]	1.00
Emergency complication	3/332	5/332	0.60 [0.14, 2.49]	.48
Incident of emergency-department visits	5/332	12/332	0.42 [0.15, 1.17]	.10
Incident of hospitalizations	4/332	9/332	0.44 [0.14, 1.43]	.17
In total	25/332	62/332	0.40 [0.26, 0.63]	<.0001

from Schisandra polysaccharide could increase the expression of GLUT-4 to activate AMPK signal pathway in order to improve glucose consumption.[51] There still needs a further multi-factor research to reveal the hazy biological mechanism of SQJTG. Researchers can take the advantages of network pharmacology and systems biology to find the potential interaction of these eleven herbal medicine and assume the possible pathways, then choose several to verify.

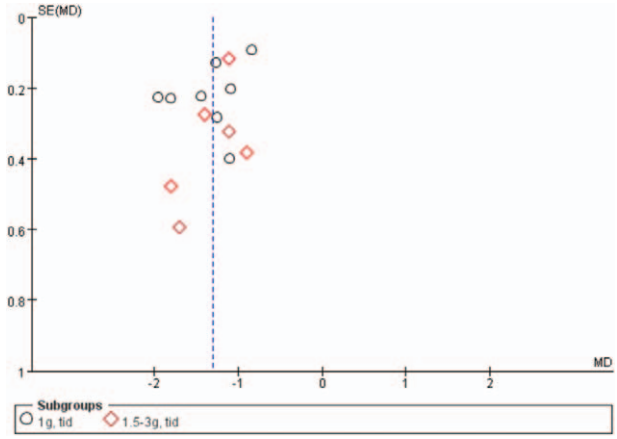

Figure 7. Funnel plot of FPG according to the trials compared with two groups. The funnel plot is a method to assess the potential role of publication bias. If the scatter of points on both sides of the blue line is asymmetric, publication bias is generally considered to exist.

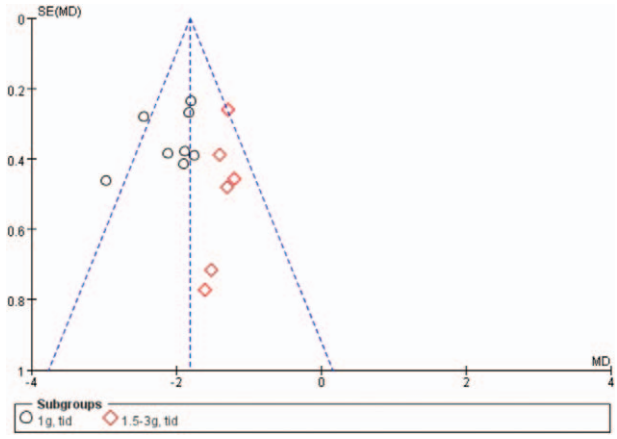

Figure 8. Funnel plot of 2hPG according to the trials compared with two group. The funnel plot is a method to assess the potential role of publication bias. If the scatter of points on both sides of the blue line is asymmetric, publication bias is generally considered to exist.

5. Conclusion

SQJTG intervention tented to be a good complementary drug to have a hypoglycemic effect synergistically, such as HAb1c, FPG and 2hPG, help with HOMA-IR adjusting, reduce adverse events of OHA, especially in reducing the occurrence of hypoglycemia reaction. Clinical trials of sizeable scale samples are still essential for the effectiveness and safety evaluation in the treatment of T2DM. Meantime, mechanism researches should also be conducted to further prove the effectiveness.

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Author contributions

Conceptualization: Tianli Li, Hongzheng Li, Zhaolun Cai.
Critical revisions: Bo Li, Zhaolun Cai.
Data curation: Hongzheng Li.
Formal analysis: Hongzheng Li.
Investigation: Hongzheng Li, Qian Wu.
Literature searches: Hongzheng Li, Yang Wu, Qian Wu.
Methodology: Tianli Li, Hongzheng Li, Yang Wu, Qian Wu, Bo Li.
Project administration: Tianli Li, Bo Li.
Resources: Yang Wu, Fenglan Pu.
Software: Tianli Li, Hongzheng Li, Yang Wu, Fenglan Pu.
Study design: Bo Li, Tianli Li, Hongzheng Li, Guozhen Zhao.
Supervision: Tianli Li, Guozhen Zhao, Zhaolun Cai, Bo Li.
Validation: Zhaolun Cai, Bo Li.
Visualization: Bo Li.
Writing – original draft: Tianli Li, Hongzheng Li, Yang Wu.
Writing – protocol: Tianli Li, Hongzheng Li, Fenglan Pu.
Writing – review & editing: Tianli Li, Hongzheng Li, Zhaolun Cai, Qian Wu.
Writing – search strategy: Hongzheng Li, Yang Wu, Qian Wu.

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