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Efficacy and safety assessment of traditional Chinese medicine for metabolic syndrome

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ABSTRACT

Metabolic syndrome (MetS) is a multifarious metabolic disorder that could severely damage multiple organs. The emergence of MetS has markedly increased medical burden for patients. The treatment of MetS involves multitarget regulation, which is the advantage of traditional Chinese medicine (TCM). Many high-quality studies related to TCM for MetS have been conducted in recent years; however, no overall efficacy analysis has been reported. To evaluate the efficacy and safety of TCM against MetS, we reviewed randomized controlled trials of MetS published in the past decade and then selected and analyzed 16 high-quality articles from over 800 papers. The results showed that TCM might be beneficial in improving body weight as well as in regulating glucose and lipid metabolisms; thus, TCM might be an ideal alternative therapy for MetS management. Treatment safety was also estimated in our analysis. A more elaborately designed and long-term observation of TCM for MetS should be performed in the future.

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of risk factors often diagnosed by the co-occurrence of three out of the four following medical conditions: abdominal obesity, hypertension, hyperglycemia (diabetes mellitus (DM) or impaired glucose regulation) and dyslipidemia (hypertriglyceridemia or low high-density lipoprotein (HDL) cholesterol).[1] The prevalence of MetS in high-income countries is estimated to exceed 25% of the adult population.[2] Moreover, the increased rate of MetS in low-incomed countries is dramatic.[3] MetS is regarded as a risk factor for the development of type 2 diabetes mellitus (T2DM),[4] cardiovascular disease,[5] stroke,[6] polycystic ovary syndrome, non-alcoholic steatohepatitis[7] and cancer,[8] which may all lead to mortality.[9] MetS pandemic may cause heavy social and economic burden. Thus, establishing an effective strategy to prevent MetS is urgent. MetS treatment involves an all-round approach aimed to retard weight gain, improve insulin resistance and dyslipidemia, and control blood glucose and blood pressure.[10–16] Moreover, during treatment, the dosage of each drug must be evaluated because as the disease progresses, conventional agents often gradually lose their efficacy. Novel treatments for MetS, such as sodium glucose transporter-2 inhibitors, seem to be potential candidate drugs, but they need validation.[17]

For the treatment of MetS, traditional Chinese medicine (TCM) has a unique advantage owing to its holism concept and multitarget regulation. Several randomized controlled trials (RCTs)[18–33] have shown the curative effect of TCM on MetS, with some studies focusing on the independent component of MetS. A multicenter, randomized, positive-controlled, R open-label clinical trial proved that the Chinese herb decoction Jiangtangtiaozhi (JTTZ) improves blood glucose and lipid metabolism, as well as reduces body weight.[34] Another study also showed that JTTZ ameliorates T2DM with hyperlipidemia by enriching beneficial bacteria.[35] Furthermore, TCM has been reported to be efficacious and safe for hyperlipidemia-associated diseases, as it mediates lipid metabolism disorders.[36] Regarding obesity, TCM has been reported to be more effective than placebo or lifestyle modification in reducing body weight, showing similar efficacy but fewer side effects compared with antiobesity drugs.[37] Other multicenter RCTs suggested that, compared with conventional pharmaceutical treatment, TCM as an add-on therapy exerts favorable effects on obesity-related hypertension.[38] However, not all of the above-mentioned findings were obtained from a high-quality study with a sufficient number of participants or with subjects precisely diagnosed with MetS. Considering these limitations, we selected high-quality studies (according to the Jadad Scale) published in the past decade to evaluate the efficacy of TCM on MetS through an updated systematic review and meta-analysis.

MATERIALS AND METHODS

Search strategy and data sources

This review was conducted under the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Relevant clinical trials were identified by searching for papers published from January 2009 to December 2019 in the following databases: Web of Science, PubMed, Embase, MEDLINE, Cochrane Library, International Pharmaceutical Abstracts, Global Health, Sinomed, China National Knowledge Internet (CNKI), WanFang and VIP. Search terms included the following: ("metabolic syndrome" or "MetS" or "metabolism syndrome") and ("randomized controlled trial" or "controlled clinical trial" or "random" or "randomly" or "randomized" or "control" or "RCT") and ("TCM" or "traditional Chinese medicine" or "Chinese medicinal herb" or "Chinese herbal medicine" or "decoction" or "formula" or "prescription" or "Chinese patent medicine" or "Chinese patent drug" or "Chinese herbal compound prescription").

Study selection

We included clinical trials that satisfied the following criteria: (1) studies where the participants had a definite diagnosis of MetS and were randomly assigned to receive TCM and Western medicine/placebo; (2) studies with a sample size of ≥60; (3) studies with a treatment duration of ≥12 weeks; (4) studies designed to focus on comparing TCM and Western medicine, or TCM and placebo; (5) studies that included efficacy evaluation on glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG) and 2-hour postprandial blood glucose (2hPG) for blood glucose; body mass index (BMI) and waist circumference (WC) for obesity; total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) cholesterol, and HDL for lipids; as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP) for blood pressure; (6) studies that were designed to be RCTs; and (7) studies where methodological quality was evaluated for each study with the Jadad score from 4 to 7 (the strongest).[39] We excluded clinical studies with the following features: (1) studies that were non-randomized, (2) studies where patients were enrolled with no definite diagnosis, (3) studies that reported only symptomatic changes in patients without laboratory indicators and (4) studies with a Jadad score of <4.

Statistical analysis

Data were analyzed using the RevMan V.5.3 software.[40] Continuous outcomes were pooled for calculation of weighted mean differences accompanied by 95% CIs. Categorical outcomes were pooled for calculation of relative risks (RRs) accompanied by 95% CIs. I^2 statistics were used to measure heterogeneity. A fixed-effect (FE) model was used if I^2 was <50%; otherwise, the random-effect (RE) model was used. Publication bias was explored by means of funnel-plot analysis.

RESULTS

A total of 806 potentially relevant articles were identified during database searching (155 from CNKI, 239 from WanFang, 74 from VIP, 84 from Sinomed, 59 from Web of Science, 50 from PubMed, 50 from MEDLINE, 36 from Cochrane and 59 from Embase). Of these, 372 records were excluded because they were duplicates and 363 were excluded based on the titles and abstracts. A total of 71 articles were extracted from the second-round screening, and, finally, 16 articles remained after the full texts were assessed for eligibility: 14 in Chinese and 2 in English. A flow diagram of the screening is shown in online supplementary figure 1. In total, 1898 patients with MetS from 16 RCTs were included. All characteristics of the included RCTs are displayed in table 1, while the quality assessments and the pharmacological effects of TCM ingredients are summarized in online supplementary tables 1 and 2.

TCM versus placebo

Eleven RCTs that investigated TCM efficacy on MetS were analyzed. Sample sizes ranged from 60 to 169 patients, and the intervention duration was 12 weeks. The methodological quality of the studies was assessed by Jadad scores from 4 to 7. The TCM interventions used for MetS included empirical decoctions and Chinese patent drugs combined with basic treatment, including health education, oral hypoglycemic agents, oral antihypertensive agents, and dyslipidemia drugs.

Results of obesity-related indicators indicated that TCM is more efficacious than placebo in reducing BMI (n=1123, RR −1.01, 95% CI −1.71 to 0.32; figure 1) and that TCM decreases WC (n=851, RR −1.65, 95% CI −2.61 to 0.69; figure 2). Liu and Cui[33] investigated the efficacy of Wenpi Fuzhen decoction in 70 patients with MetS. Patients in the treatment group lost more weight than those in the control group and showed decreases in BMI and WC compared with those in the control group ($p<0.01$ and $p<0.05$). Wang *et al*[25] enrolled 96 patients with MetS with T2DM. All patients were measured for BMI, WC and waist-to-hip ratio (WHtR) to assess obesity; the results showed that these parameters decreased significantly in the treatment group ($p<0.01$) with significant differences compared with the control group ($p<0.05$ and $p<0.01$). The content of each component was also measured; it was shown that patients with central obesity had improved control with Yiqi Huaju formula ($p<0.01$). In a multicenter, randomized, double-blind, parallel-controlled trial, Wang[31] found that the BMI of patients treated with Jiangtang pill significantly declined from 26.68±2.30 to 23.41±2.16 kg/m^2 compared with that of those treated with placebo ($p<0.01$) (table 2).

Regarding blood glucose indicators, the efficacy of TCM in reducing HbA1c is shown in figure 3 (n=820, RR −0.25, 95% CI −0.45 to 0.06). The hypoglycemic effect of TCM on FPG and 2hPG is shown in online supplementary figure 2 (n=1183, RR −0.31, 95% CI −0.40 to 0.22) and in online supplementary figure 3 (n=1062, RR −0.68, 95% CI −0.85 to

Table 1 Summary of the included studies

Study	Subjects (T/C)	Duration	Intervention	TCM outcome				Control	Control outcome			
				BMI/WC	FBG/2hPG/HbA1c	TC/TG/LDL/HDL	SBP/DBP		BMI/WC	FBG/2hPG	TC/TG/LDL/HDL	SBP/DBP
Chen 2011	63/59	12 months	Tianqi Jiangtang capsule+basic treatment	BMI: 26.80±2.61 WC: 94.11±5.99	FBG: 6.12±0.72 2hPG: 8.28±0.27	TC: 5.03±0.93 TG: 1.64±1.10 (39) LDL: 2.92±0.85 HDL:1.46±0.42 (38)	SBP: 127.73±9.19 DBP: 79.52±5.72	Placebo+basic treatment	BMI: 26.50±2.25 WC: 93.68±6.42	FBG: 6.63±0.96 2hPG: 9.18±2.44	TC: 4.93±1.06 TG: 1.69±0.60 LDL: 2.69±0.98 HDL: 1.51±0.63	SBP: 126.17±7.72 DBP: 78.41±6.93
Fan 2012	40/40	12 weeks	Wuling powder+basic treatment	BMI: 23.61±1.37 WC: 83.50±3.80	FBG: 4.85±0.96 2hPG: 10.61±3.54 HbA1c: 6.59±0.94	TC: 3.60±0.67 TG: 1.82±0.72 LDL: 1.73±0.63 HDL: 1.49±0.30	SBP: 128.50±3.72 DBP: 80.67±2.46	Basic treatment	BMI: 24.37±1.32 WC: 86.12±8.24	FBG: 5.08±0.69 2hPG: 11.04±2.34 HbA1c: 6.31±0.70	TC: 3.74±1.20 TG: 1.92±1.06 LDL: 2.18±0.74 HDL: 1.12±0.28	SBP: 138.33±4.64 DBP: 88.80±2.66
Huang 2019	30/31	90 days	Erchen combined with Taohong Siwu decoction+basic treatment	BMI: 27.23±3.13 WC: 92.78±9.04	FBG: 5.43±1.57	TC: 4.18±1.42 TG: 1.26±0.49 LDL: 2.64±0.81 HDL: 1.23±0.29	SBP: 123.61±8.50 DBP: 73.87±7.73	Basic treatment	BMI: 27.08±4.60 WC: 92.72±7.13	FBG: 6.30±1.67	TC: 5.03±0.98 TG: 1.90±1.15 LDL: 2.77±0.78 HDL: 1.13±0.24	SBP: 121.4±10.69 DBP: 74.9±7.49
Lian 2012	83/82	12 weeks	Yi Tang Kang+basic treatment	BMI: 26.60±2.81	FBG: 5.82±0.52 2hPG: 7.33±1.65 HbA1c: 5.83±0.60	TC: 4.92±0.99 TG: 1.68±0.66 LDL: 2.99±0.71 HDL: 1.29±0.31	SBP: 130.55±5.21 DBP: 81.65±3.77	Placebo+basic treatment	BMI: 27.35±2.75	FBG: 5.96±0.68 2hPG: 7.99±1.67 HbA1c: 6.04±0.63	TC: 5.38±1.89 TG: 1.74±0.84 LDL: 3.25±0.74 HDL: 1.34±0.70	SBP: 38.37±8.12 DBP: 86.69±5.20
Liu 2017	35/35	12 weeks	Wenpi Fuzhen decoction+basic treatment	BMI: 26.41±3.25 WC: 89.50±8.22	FBG: 5.72±1.33 2hPG: 7.24±1.87 HbA1c: 5.59±1.23	TC: 4.67±1.12 TG: 2.08±0.81 LDL: 3.32±0.74 HDL: 1.23±0.46	SBP: 133.66±4.97 DBP: 83.01±5.43	Placebo+basic treatment	BMI: 28.78±4.11 WC: 93.99±9.23	FBG:6.36±1.21 2hPG:8.30±2.41 HbA1c:6.13±0.94	TC: 5.22±0.98 TG: 2.50±0.94 LDL: 3.81±0.88 HDL: 1.17±0.32	SBP: 139.84±6.28 DBP: 88.94±6.11
Wang 2012	86/81	12 weeks	Jiangtang pill+basic treatment	BMI: 23.41±2.16	FBG: 5.79±0.66 2hPG: 7.53±1.44 HbA1c: 5.89±0.69	TC: 4.94±0.91 TG: 1.50±0.90 LDL: 3.06±0.67 HDL: 1.23±0.28	SBP: 134.26±8.07 DBP: 84.51±5.04	Placebo+basic treatment	BMI:26.37±2.50	FBG: 5.95±0.60 2hPG: 8.24±1.33 HbA1c: 5.98±0.86	TC: 5.05±0.82 TG: 1.80±1.00 LDL: 3.16±0.62 HDL: 1.27±0.27	SBP: 140.17±9.69 DBP: 88.84±5.57
Wang 2013	60/60	12 weeks	Heye Jiangzhi decoction+basic treatment	BMI: 25.53±1.28 WC: 88.5±3.64	FBG: 6.61±0.95 2hPG: 10.46±3.24	TC: 3.42±1.16 TG: 1.56±0.68 LDL: 1.88±0.72 HDL: 1.70±0.48	SBP: 132.29±9.87 DBP: 82.73±7.72	Basic treatment	BMI: 26.27±2.03 WC: 88.68±7.53	FBG: 6.98±1.37 2hPG: 11.14±2.04	TC: 4.08±0.93 TG: 2.02±1.11 LDL: 1.94±0.57 HDL: 1.56±0.46	SBP: 140.0±14.38 DBP: 86.9±7.56
Wang 2016	48/48	12 weeks	Yiqi Huaju formula+basic treatment	BMI: 25.36±2.32 WC: 88.89±8.83 WHtR: 0.88±0.06	FBG: 6.24±1.31 2hPG: 8.68±2.61 HbA1c: 7.04±1.25	TC: 4.25±0.96 TG: 1.60±0.70 LDL: 2.55±0.70 HDL: 1.16±0.28	SBP: 125.50±5.83 DBP: 78.61±5.40	Placebo+basic treatment	BMI: 27.66±2.21 WC: 97.10±11.00 WHtR: 0.94±0.05	FBG: 7.06±2.08 2hPG: 10.66±3.24 HbA1c: 7.54±1.17	TC: 4.22±0.67 TG: 1.92±0.68 LDL: 2.58±0.52 HDL: 1.10±0.22	SBP: 130.00±9.03 DBP: 81.64±6.22
Yang 2013	40/20	12 weeks	Huayu Fuyuan capsule +basic treatment	WC: 118.40±11.27	FBG: 6.31±0.85	TG: 1.56±0.37 HDL: 1.52±0.38	SBP: 129.60±10.92 DBP: 79.40±7.70	Basic treatment	WC: 117.43±9.42	FBG: 6.70±1.09	TG: 1.81±0.25 HDL: 1.41±0.39	SBP: 131.10±6.24 DBP: 78.70±6.78
Zhang 2014	36/37	12 weeks	Sanhuang Danshen decoction+basic treatment	BMI: 24.96±1.64 WC: 90.17±6.72 WHtR: 0.55±0.04	FBG: 5.56±2.11 2hPG: 7.47±3.20 HbA1c: 6.22±2.10	TC: 4.18±0.80 TG: 1.64±0.45 LDL: 2.66±0.60 HDL: 1.38±0.33		Basic treatment	BMI: 24.85±1.70 WC: 91.84±6.43 WHtR: 0.55±0.04	FBG: 5.81±0.74 2hPG: 7.84±3.33 HbA1c: 7.13±0.90	TC: 4.60±1.10 TG: 2.01±1.51 LDL: 2.75±0.91 HDL: 1.24±0.33	
Zhang 2016	85/84	12 weeks	Yangyin Jiangya capsule+Jiangzhuo Quyu granule+basic treatment	BMI: 23.8±3.1 WC: 88.6±7.2 WHtR: 0.89±0.05	FBG: 5.40±0.55 2hPG: 7.59±0.68 HbA1c: 5.49±0.4	TC: 4.91±0.67 TG: 1.37±0.21 LDL: 2.31±0.57 HDL: 1.45±0.25	SBP: 125.3±5.8 DBP: 78.2±4.8	Basic treatment	BMI: 24.6±2.9 WC: 91.4±7.4 WHtR: 0.93±0.04	FBG: 5.82±0.59 2hPG: 8.17±0.88 HbA1c: 5.85±0.57	TC: 5.06±0.68 TG: 1.58±0.23 LDL: 2.65±0.62 HDL: 1.25±0.28	SBP: 128.8±6.3 DBP: 82.6±5.3
Chen 2014	30/30	12 weeks	Heye Jiangzhi decoction	BMI: 25.03±1.57 WC: 87.87±3.47	FBG: 6.42±0.68 2hPG: 7.50±0.72	TC: 3.71±0.64 TG: 2.13±0.46 LDL: 2.37±0.27 HDL: 1.13±0.10	SBP: 134.63±4.36 DBP: 83.10±4.54	Metformin 0.25g tid, ramipril 5 mg qd, fenofibrate 200 mg qd	BMI: 26.11±1.57 WC: 87.83±3.73	FBG: 6.37±0.58 2hPG: 7.62±0.46	TC: 3.84±0.84 TG: 2.10±0.53 LDL: 2.35±0.24 HDL: 1.05±0.11	SBP: 129.87±3.31 DBP: 79.53±3.89
Ji 2017	33/33	12 weeks	Chaihu Sanren decoction	BMI: 25.77±2.33 WC: 92.47±7.27	FBG: 5.46±0.54	TC: 4.03±0.69 TG: 2.04±0.95 LDL: 2.62±0.81 HDL: 1.12±0.16	SBP: 134.85±9.56 DBP: 80.00±10.00	Pioglitazone hydrochloride tablets 15 mg qd	BMI: 27.85±1.60 WC: 96.85±8.49	FBG: 5.40±1.40	TC: 4.64±1.04 TG: 2.56±1.10 LDL: 3.22±0.75 HDL: 0.98±0.11	SBP: 141.48±9.32 DBP: 85.00±15.00

Continued

Table 1 Continued

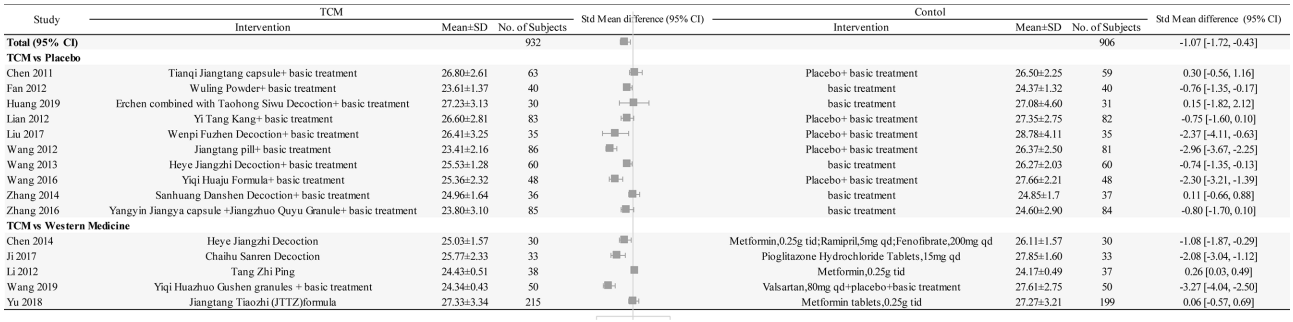
Study	Subjects (T/C)	Duration	Intervention	TCM outcome				Control	Control outcome			
				BMI/WC	FBG/2hPG/HbA1c	TC/TG/LDL/HDL	SBP/DBP		BMI/WC	FBG/2hPG	TC/TG/LDL/HDL	SBP/DBP
Li 2012	38/37	12 weeks	Tang Zhi Ping	BMI: 24.43±0.51 WC: 91.86±6.14	FBG: 5.73±0.39 2hPG: 7.92±0.76 HbA1c: 5.27±0.31	TC: 3.61±1.24 TG: 1.59±0.32 LDL: 2.23±0.72 HDL: 1.06±0.14	SBP: 127.22±8.13 DBP: 80.44±8.58	Metformin 0.25 g tid	BMI: 24.17±0.49 WC: 91.39±5.83	FBG: 5.28±0.27 2hPG: 7.74±0.92 HbA1c: 5.19±0.48	TC: 4.75±1.16 TG: 2.75±0.46 LDL: 3.03±0.33 HD L: 1.05±0.20	SBP: 136.47±8.96 DBP: 79.20±8.83
Wang 2019	50/50	12 weeks	Yiqi Huazhuo Gushen granules+basic treatment	BMI: 24.34±0.43 WHtR: 0.87±0.05	FBG: 6.23±1.31 2hPG: 8.68±2.56 HbA1c: 7.04±1.26	TC: 4.24±0.78 TG: 1.62±0.58 LDL: .54±0.71 HDL: 1.19±0.27	SBP: 125.91±7.12 DBP: 78.47±5.35	Valsartan 80 mg qd+placebo+basic treatment	BMI: 27.61±2.75 WHtR: 0.94±0.048	FBG: 7.06±1.41 2hPG: 10.62±3.24 HbA1c: 7.52±1.36	TC: 4.25±0.68 TG: 1.88±0.44 LDL: 2.55±0.52 HDL: 1.12±0.21	SBP: 130.5 6±7.99 DBP: 79.88±5.43
Yu 2018	215/199	12 weeks	Jiangtang Tiaozhi formula	BMI: 27.33±3.34 WC: 94.73±8.29 HC: 102.02±7.23	FBG: 8.24±2.35 2hPG: 14.52±4.73 HbA1c: 7.51±1.44	TC: 5.06±1.00 TG: 2.79±1.86 LDL: 2.92±0.73		Metformin tablets 0.25 g tid	BMI: 27.27±3.21 WC: 94.98±9.03 HC: 102.67±7.16	FBG: 8.21±2.23 2hPG: 14.83±4.32 HbA1c: 7.57±1.42	TC: 5.21±1.00 TG: 2.82±1.91 LDL: 2.98±0.76	

BMI, body mass index; C, control group; DBP, diastolic blood pressure; FBG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HC, hip circumference; HDL, high-density lipoprotein; 2hPG, 2-hour postprandial blood glucose; LDL, low-density lipoprotein; qd, once per day; SBP, systolic blood pressure; T, treatment group; TC, total cholesterol; TCM, traditional Chinese medicine; TG, triglyceride ; tid, three times per day; WC, waist circumference; WHtR, waist-to-height ratio.

0.50). Analysis of fasting insulin (FINS) revealed that TCM improved islet function (n=343, RR −1.50, 95% CI −2.17 to 0.83; online supplementary figure 4). The efficacy of TCM in improving insulin resistance was observed by homeostasis model assessment of insulin resistance (HOMA-IR) (n=528, RR −0.46, 95% CI −0.68 to 0.25; online supplementary figure 5). In a multicenter RCT,[20] 165 patients with MetS with impaired glucose regulation (IGR) were treated with Yi Tang Kang or placebo. The results showed that Yi Tang Kang effectively lowered FPG and 2hPG (p<0.01), especially 2hPG (p<0.01). Another multicenter, double-blind, placebo-control RCT[32] recruited 112 patients with MetS with impaired glucose tolerance (IGT) who received Tianqi Jiangtang capsule, which was recommended in the China Guideline for Type 2 Diabetes (2017); 55 IGT patients recovered after more than 3 months of treatment. FPG and 2hPG in the treatment group decreased after treatment with Tianqi Jiangtang capsule (p<0.05), and the efficacy of this TCM on 2hPG was more remarkable than that of the control (p<0.05). Wang et al. (2012)[31] also enrolled patients with MetS with IGR who were treated with Jiangtang pill. The data indicated that Jiangtang pill effectively reduced 2hPG, regardless of age difference (p<0.01). Wang et al. (2013)[22] reported that Heye Jiangzhi Decoction decreased FINS (p<0.01) and improved HOMA-IR (p<0.05).

Analysis of blood lipid indicators revealed that TCM reduced cholesterol (n=1073, RR −0.27, 95% CI −0.44 to 0.10; online supplementary figure 6) and diminished TG (n=1133, RR −0.23, 95% CI −0.28 to 0.17; figure 4). Changes in LDL and HDL were also observed, suggesting that TCM decreased LDL (n=1072, RR −0.19, 95% CI −0.27 to 0.11; online supplementary figure 7) and increased HDL (n=1132; RR 0.10; 95% CI 0.02, 0.18; online supplementary figure 8). Wang et al. (2013)[22] showed that Heye Jiangzhi Decoction decreased TC (p<0.01) and increased HDL (p<0.05), with an efficacy rate of 85% in regulating blood lipids. Another survey[23] reported that Erchen combined with Taohong Siwu Decoction showed preponderant efficacy in regulating TC, TG (p<0.01), and LDL (p<0.05), but its effect on HDL was not different than that of placebo (p>0.05). Fan et al (2012)[29] showed that a classical formula of Wuling Powder increased LDL to a greater degree compared with placebo (p<0.01). Zhang et al. (2014)[26] also showed that TCM decoction reduced TG and TC (p<0.05), indicating its potent efficacy in regulating lipid metabolism.

Analysis of blood pressure indicators revealed that TCM decreased SBP (n=1110, RR −4.54, 95% CI −6.90 to 2.19; figure 5) and reduced DBP (n=1110, RR −3.65, 95% CI −5.46 to 1.84; Online supplementary figure 9). Zhang et al. (2016)[30] treated patients with MetS with hypertension with two Chinese patent drugs, namely Yangyin Jiangya capsule and Jiangzhuo Quyu Granule, and their results showed significant decreases in SBP and DBP in the treatment group (p<0.05). Another study[24] investigating the Chinese patent drug Huayu Fuyuan capsule revealed its remarkable effect in regulating SBP (p<0.05).



Study	TCM Intervention	Mean±SD	No. of Subjects	Contol Intervention	Mean±SD	No. of Subjects	Std Mean difference (95% CI)
Total (95% CI)			932			906	-1.07 [-1.72, -0.43]
TCM vs Placebo							
Chen 2011	Tianqi Jiangtang capsule+ basic treatment	26.80±2.61	63	Placebo+ basic treatment	26.50±2.25	59	0.30 [-0.56, 1.16]
Fan 2012	Wuling Powder+ basic treatment	23.61±1.37	40	basic treatment	24.37±1.32	40	-0.76 [-1.35, -0.17]
Huang 2019	Erchen combined with Taohong Siwu Decoction+ basic treatment	27.23±3.13	30	basic treatment	27.08±4.60	31	0.15 [-1.82, 2.12]
Lian 2012	Yi Tang Kang+ basic treatment	26.60±2.81	83	Placebo+ basic treatment	27.35±2.75	82	-0.75 [-1.60, 0.10]
Liu 2017	Wenpi Fuzhen Decoction+ basic treatment	26.41±3.25	35	Placebo+ basic treatment	28.78±4.11	35	-2.37 [-4.11, -0.63]
Wang 2012	Jiangtang pill+ basic treatment	23.41±2.16	86	Placebo+ basic treatment	26.37±2.50	81	-2.96 [-3.67, -2.25]
Wang 2013	Heye Jiangzhi Decoction+ basic treatment	25.53±1.28	60	basic treatment	26.27±2.03	60	-0.74 [-1.35, -0.13]
Wang 2016	Yiqi Huaju Formula+ basic treatment	25.36±2.32	48	Placebo+ basic treatment	27.66±2.21	48	-2.30 [-3.21, -1.39]
Zhang 2014	Sanhuang Danshen Decoction+ basic treatment	24.96±1.64	36	basic treatment	24.85±1.7	37	0.11 [-0.66, 0.88]
Zhang 2016	Yangyin Jiangya capsule +Jiangzhuo Quyu Granule+ basic treatment	23.80±3.10	85	basic treatment	24.60±2.90	84	-0.80 [-1.70, 0.10]
TCM vs Western Medicine							
Chen 2014	Heye Jiangzhi Decoction	25.03±1.57	30	Metformin,0.25g tid;Ramipril,5mg qd;Fenofibrate,200mg qd	26.11±1.57	30	-1.08 [-1.87, -0.29]
Ji 2017	Chaihu Sanren Decoction	25.77±2.33	33	Pioglitazone Hydrochloride Tablets,15mg qd	27.85±1.60	33	-2.08 [-3.04, -1.12]
Li 2012	Tang Zhi Ping	24.43±0.51	38	Metformin,0.25g tid	24.17±0.49	37	0.26 [0.03, 0.49]
Wang 2019	Yiqi Huazhuo Gushen granules + basic treatment	24.34±0.43	50	Valsartan,80mg qd+placebo+basic treatment	27.61±2.75	50	-3.27 [-4.04, -2.50]
Yu 2018	Jiangtang Tiaozhi (JTTZ)formula	27.33±3.34	215	Metformin tablets,0.25g tid	27.27±3.21	199	0.06 [-0.57, 0.69]

Figure 1 Data summary of the high-quality RCTs of TCM interventions for BMI. BMI, body mass index; RCT, randomized controlled trial; TCM, traditional Chinese medicine.

Moreover, Yi Tang Kang[20] led to notable improvement of blood pressure and decreased SBP and DBP (p<0.01).

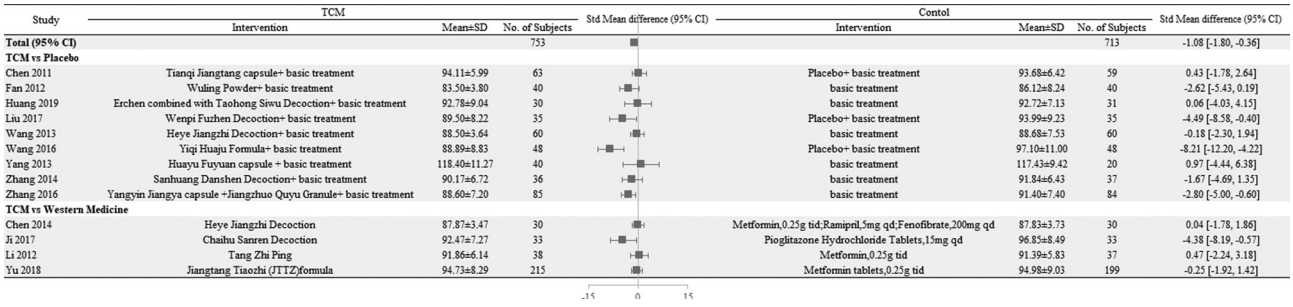
TCM versus Western medicine

Five RCTs comparing the efficacy of TCM with that of Western medicine on MetS were analyzed. The sample sizes ranged from 60 to 414 patients and the treatment duration was 12 weeks. The methodological quality of the studies was assessed by Jadad scores of 4–6. In this comparison, two RCTs[18 27] used Chinese patent drugs as TCM intervention, whereas the others [19,21,28] used empirical decoction. Three RCTs[19 27 28] used single oral hypoglycemic agents as the control group, one[18] used antihypertensive drugs, and one RCT[21] used a combination of oral hypoglycemic agents, oral antihypertensive drugs, and dyslipidemia drugs.

Analysis of obesity-related indicators showed no difference in efficacy between TCM and Western medicine in reducing BMI (n=715, RR −1.19, 95% CI −2.50 to 0.12; figure 1) and no significant difference between their efficacy in reducing WC (n=615, RR −0.36, 95% CI −1.44 to 0.71; figure 2). A total of 70 patients with MetS[21] were assigned to the treatment group (Heye Jiangzhi Decoction) and the control group (Western medicine). After the 12-week treatment, the TCM group showed improvement of BMI compared with that in the metformin-treated group (p<0.05). A multicenter RCT[18] evaluating the effect of Yiqi Huazhuo Gushen granules showed significant (p<0.05) differences in BMI and WHtR between the Yiqi Huazhuo Gushen-treated and valsartan-treated groups. Ji[28] reported that Chaihu Sanren decoction ameliorated central obesity by reducing BMI (p<0.01) and WC (p<0.05), showing higher efficacy than that of pioglitazone hydrochloride tablets.

Analysis of blood glucose indicators revealed no remarkable difference in HbA1c between TCM and Western medicine, as shown in figure 3 (n=589, RR −0.07, 95% CI −0.31 to 0.18). There were no differences in hypoglycemic effect on FPG (n=715, RR −0.01, 95% CI −0.40 to 0.39; Online supplementary figure 2) and 2hPG (n=649, RR −0.10, 95% CI −0.32 to 0.13; online supplementary figure 3) between TCM and Western medicine. Moreover, there were no differences in effect on FINS (n=201, RR −0.03, 95% CI −0.46 to 0.40; Online supplementary figure 4) and HOMA-IR (n=715, RR −0.06, 95% CI −0.33 to 0.20; Online supplementary figure 5) between TCM and Western medicine. A multicenter, randomized, positive-controlled, open-label clinical trial[19] indicated that the Chinese herbal formula JTTZ effectively improved blood glucose metabolism, reducing HbA1c by 0.75±1.32 (95% CI 0.58 to 0.93), FPG by 1.4±2.4 (p<0.001), 2hPG by 2.42±4.53 (p<0.001) and HOMA-IR by 0.19±0.91 (p<0.01). In another study, 80 patients with MetS[27] were randomly assigned to the Tang Zhi Ping group or the metformin group, and the results showed that the Chinese patent drug exerted the same hypoglycemic effect as that of metformin. Furthermore, Ji[28] reported that the Chaihu Sanren decoction had the same hypoglycemic efficacy in improving insulin resistance as that of pioglitazone hydrochloride (p>0.05).

Analysis of blood lipid indicators showed that TCM was more effective than Western medicine in reducing TC (n=715, RR −0.35, 95% CI −0.66 to 0.04; Online



Study	TCM Intervention	Mean±SD	No. of Subjects	Contol Intervention	Mean±SD	No. of Subjects	Std Mean difference (95% CI)
Total (95% CI)			753			713	-1.08 [-1.80, -0.36]
TCM vs Placebo							
Chen 2011	Tianqi Jiangtang capsule+ basic treatment	94.11±5.99	63	Placebo+ basic treatment	93.68±6.42	59	0.43 [-1.78, 2.64]
Fan 2012	Wuling Powder+ basic treatment	83.50±3.80	40	basic treatment	86.12±8.24	40	-2.62 [-5.43, 0.19]
Huang 2019	Erchen combined with Taohong Siwu Decoction+ basic treatment	92.78±9.04	30	basic treatment	92.72±7.13	31	0.06 [-4.03, 4.15]
Liu 2017	Wenpi Fuzhen Decoction+ basic treatment	89.50±8.22	35	Placebo+ basic treatment	93.99±9.23	35	-4.49 [-8.58, -0.40]
Wang 2013	Heye Jiangzhi Decoction+ basic treatment	88.50±3.64	60	basic treatment	88.68±7.53	60	-0.18 [-2.30, 1.94]
Wang 2016	Yiqi Huaju Formula+ basic treatment	88.89±8.83	48	Placebo+ basic treatment	97.10±11.00	48	-8.21 [-12.20, -4.22]
Yang 2013	Huayu Fuyuan capsule + basic treatment	118.40±11.27	40	basic treatment	117.43±9.42	20	0.97 [-4.44, 6.38]
Zhang 2014	Sanhuang Danshen Decoction+ basic treatment	90.17±6.72	36	basic treatment	91.84±6.43	37	-1.67 [-4.69, 1.35]
Zhang 2016	Yangyin Jiangya capsule +Jiangzhuo Quyu Granule+ basic treatment	88.60±7.20	85	basic treatment	91.40±7.40	84	-2.80 [-5.00, -0.60]
TCM vs Western Medicine							
Chen 2014	Heye Jiangzhi Decoction	87.87±3.47	30	Metformin,0.25g tid;Ramipril,5mg qd;Fenofibrate,200mg qd	87.83±3.73	30	0.04 [-1.78, 1.86]
Ji 2017	Chaihu Sanren Decoction	92.47±7.27	33	Pioglitazone Hydrochloride Tablets,15mg qd	96.85±8.49	33	-4.38 [-8.19, -0.57]
Li 2012	Tang Zhi Ping	91.86±6.14	38	Metformin,0.25g tid	91.39±5.83	37	0.47 [-2.24, 3.18]
Yu 2018	Jiangtang Tiaozhi (JTTZ)formula	94.73±8.29	215	Metformin tablets,0.25g tid	94.98±9.03	199	-0.25 [-1.92, 1.42]

Figure 2 Data summary of the high-quality RCTs of TCM interventions for WC. RCT, randomized controlled trial; TCM, traditional Chinese medicine; WC, waist circumference.

Table 2 Representative formula and components and potential mechanisms

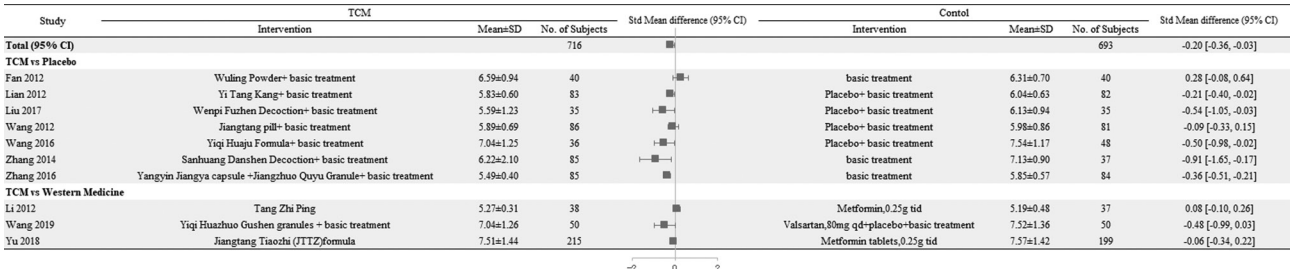
	Formula	Herbs	Main components	Beneficial effects
Chen 2011	Tianqi Jiangtang capsule	*Radix Trichosanthis*, *Radix Astragali seu Hedysari*, *Rhizoma Coptidis*, *Radix Ginseng*, *Herba Dendrobii*, *Fructus Ligustri Lucidi*, *Cortex Lycii*, *Fructus Corni*, *Herba Ecliptae*, *Galla Chinensis*	Berberine, trichosanthin, astragaloside IV, ginseng polysaccharide, ginsenosides, kukoamine A	Antioxidant stress, alleviating insulin resistance; anti-inflammation; reducing fibrosis; increasing insulin sensitivity; reducing fat accumulation in the liver; regulating secretion of insulin and glucagon.
Fan 2012	Wuling powder	*Rhizoma Alismatis*, *Polyporus*, *Poria*, *Rhizoma Atractylodis Macrocephalae*, *Ramulus Cinnamomi*	Alisol A 24-acetate, ergone, grifola polysaccharide, pachyman polysaccharides, polysaccharide of *Atractylodes macrocephala*, atractylenolide I, cinnamaldehyde	Protecting islet, promoting insluin secretion, regulating lipid metabolism, diuresis, decreasing weight, increasing antioxidant activity, inhibiting HMG-CoA reductase, vasodilation
Huang 2019	Erchen combined with Taohong Siwu decoction	*Rhizoma Alismatis*, *Polyporus, Poria, Rhizoma Atractylodis Macrocephalae, Ramulus Cinnamomi*, *Rhizoma Pinelliae Pericarpium Cirri Reticulatae*, *Poria*, *Radix Glycyrrhizae*, *Ginger*, *Fructus Mume*, *Semen Persicae*, *Flos Carthami*, *Radix Angelicae Sinensis*, *Rhizoma Ligustici Chuanxiong*, *Radix Paeoniae Alba*	Alkaloids from *Pinellia ternata*, naringin, tangeretin, pachyman polysaccharides, ursolic acid, citric acid, malic acid, *Angelica sinensis* olysaccharide, ferulic acid, tetramethylpyrazine, total glucosides of paeony	Decreasing PGE-2 and NO, regulating blood lipid metabolism, inhibiting the generation of adipocytes, decreasing weight, enhancing the expression of insulin receptor in liver, antioxidation, antiapoptosis, inhibiting platelet agglutination, antithrombosis, antagonizing ischemic reperfusion injury, vasodilation
Lian 2012	Yi Tang Kang	*Radix Astragali seu Hedysari*, *Poria*, *Rhizoma Alismatis*, *Radix Ginseng Rubra*, *Rhizoma Polygonati*, *Rhizoma Coptidis*, *Radix et Rhizoma Notoginseng*	Astragaloside IV, pachyman polysaccharides, alisol A 24-acetate, arginyl-fructosyl-glucose, arginyl-fructos, *Polygonatum* polysaccharide, berberine, *Panax notoginseng* saponins	Alleviating insulin resistance, promoting insulin release, antioxidation, decreasing weight, improving lipid metabolism, protecting islet, increasing the concentration of cAMP in platelets, blocking calcium influx
Liu 2017	Wenpi Fuzhen decoction	*Radix Codonopsis*, *Poria*, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae*, *Ramulus Cinnamomi*, *Radix Paeoniae Alba, Radix Aucklandiae*, *Radix Aconiti Lateral is Preparata*	*Codonopsis pilosula* polysaccharide, pachyman polysaccharides, polysaccharide of *Atractylodes macrocephala*, atractylenolide I, cinnamaldehyde, total glucosides of paeony, costunolide	Increasing SOD activity, decreasing generation of MDA, regulating blood lipid metabolism, decreasing weight, reducing plasma insulin, inhibiting HMG-CoA reductase, vasodilation, diuresis, decreasing NO and IL-6, inhibiting PTP-1B activity
Wang 2012	Jiangtang pill	*Radix Ginseng Rubra*, *Radix Astragali seu Hedysari*, *Rhizoma Polygonati*, *Poria*, *Rhizoma Coptidis*, *Radix Puerariae*, *Fructus Schisandrae Chinensis*	Arginyl-fructosyl-glucose, arginyl-fructos, astragaloside IV, *Polygonatum* polysaccharide, pachyman polysaccharides, berberine, puerarin, *S. chinensis* lignans	Alleviating insulin resistance, promoting insulin release, antioxidation, decreasing weight, increasing the activity of intracellular LDL receptor, inhibiting β-epinephrine, decreasing NOS
Wang 2013	Heye Jiangzhi decoction	*Folium Nelumbinis*, *Rhizoma Polygonati*, *Radix Polygoni Multiflori*, *Rhizoma Alismatis*, *Pollen Typhae*, *Hirudo*	Nuciferine, *Polygonatum* polysaccharide, stilbene glucoside , alisol a 24-acetate, total flavone in pollen *Typhae*, hirudin	Improving lipidemic disturbance, weight reduction, antioxidative stress, decreasing IGF-1, inhibiting the effect of free fatty acid-induced insulin resistance, antioxidation, anti-inflammatory, immunoregulation, preventing the polymerization of fibrin by thrombin, increasing the CTGFm RNA for anti-fibrosis
Wang 2016	Yiqi Huaju formula	*Radix Astragali seu Hedysari*, *Rhizoma Coptidis*, *Pollen Typhae*, *Herba Artemisiae Scopariae*, *Rhizoma Alismatis*	Astragaloside IV, berberine, total flavone in pollen *Typhae*, coumarins, flavonoids of *Artemisia*, alisol A 24-acetate	Improving insulin resistance, inhibiting the effect of free fatty acid-induced insulin resistance, antioxidation, anti-inflammatory, immunoregulation, vasodilation, reducing visceral fat deposition, promoting the use of glucose in peripheral tissue, promoting insluin secretion, regulating lipid metabolism
Yang 2013	Huayu Fuyuan capsule	*Eupolyphaga seu Steleophaga*, *Hirudo, Radix et Rhizoma Notoginseng*	Total alkaloids from Eupolyphage Sinensis walk, hirudin, *Panax notoginseng* saponins	Regulating blood lipid metabolism, dilating blood vessels, preventing the polymerization of fibrin by thrombin, increasing the CTGFm RNA for antifibrosis, increasing the concentration of cAMP in platelets, blocking calcium influx
Zhang 2014	Sanhuang Danshen decoction	*Radix et Rhizoma Rhei*, *Ramulus Cinnamomi*, *Poria*, *Rhizoma Atractylodis Macrocephalae*, *Rhizoma Alismatis*, *Pericarpium Cirri Reticulatae*, *Radix Salviae Miltiorrhizae*, *Rhizoma Ligustici Chuanxiong*, *Fructus Crataegi*, *Radix Astragali seu Hedysari*, *Radix Rehmanniae Recens*, *Radix Glycyrrhizae*	Emodin, rheidin, cinnamaldehyde, pachyman polysaccharides, polysaccharide of *Atractylodes macrocephala*, atractylenolide I, alisol A 24-acetate, naringin, tangeretin, tanshinone, hawthorn flavonoids, astragaloside IV, catalpol	Regulating blood lipid metabolism, immunoregulation; up-regulating P-glycoprotein; vasodilation, diuresis, inhibiting HMG-CoA reductase, inhibiting PGE-2 release, inhibiting the generation of adipocytes, antiatherosclerosis, promoting GLP-1/GIP secretion

Continued

Table 2 Continued

	Formula	Herbs	Main components	Beneficial effects
Zhang 2016	Yangyin Jiangya capsule+Jiangzhuo Quyu granule	*Carapax et Plastrum Testudinis*, *Radix Paeoniae Alba*, *Radix Ginseng*, *Margarita*, *Haematitum*, *Ramulus Uncariae cum Uncis*, *Spica Prunellae*, *Rhizoma Gastrodiae*, *Calculus Bovis*, *Gypsum Fibrosum*, *Radix et Rhizoma Rhei*, *Flos Sophorae*, *Radix Aucklandiae*, *Fructus Crataegi*, *Semen Raphani*, *Fructus Aurantii Immaturus*, *Cortex Magnoliae Officinalis*, *Pericarpium Cirri Reticulatae*, *Fructus Hordei Germinatus*, *Massa Medicata Fermentata*, *Flos Chrysanthemi*, *Camellia sinensis*	Total glucosides of paeony, ginseng polysaccharide, ginsenosides, rhynchophylline, isorhynchophylline, emodin, rheidin, costunolide, hawthorn flavonoids, naringin, tangeretin, magnolol, honokiol, total flavonoids of *Prunella vulgaris*, gastrodin, taurine	Decreasing NO and IL-6; protecting islet cells, improving myocardial ischemia, vasodilation, blocking calcium influx, regulating blood lipid metabolism, immunoregulation, upregulating P-glycoprotein, inhibiting PTP-1B activity, inhibiting PGE-2 release, inhibiting the generation of adipocytes, promoting the use of glucose by muscle cells, expanding peripheral vessels, promoting the production of NO by endothelial cells
Chen 2014	Heye Jiangzhi decoction	*Folium Nelumbinis*, *Rhizoma Polygonati*, *Radix Polygoni Multiflori*, *Rhizoma Alismatis*, *Pollen Typhae*, *Hirudo*	Nuciferine, *Polygonatum* polysaccharide, stilbene glucoside , alisol A 24-acetate, total flavone in pollen *Typhae*, hirudin	Improving lipidemic disturbance, weight reduction, antioxidative stress, decreasing IGF-1, inhibiting the effect of free fatty acid-induced insulin resistance, antioxidation, anti-inflammatory, immunoregulation, preventing the polymerization of fibrin by thrombin, increasing the CTGFm RNA for antifibrosis
Ji 2017	Chaihu Sanren decoction	*Radix Bupleuri*, *Radix Scutellariae*, *Semen Armeniacae Amarum*, *Semen Coicis*, *Fructus Ammomi Rotundus*, *Cortex Magnoliae Officinalis*, *Rhizoma Pinelliae*, *Talcum*, *Medulla Tetrapanacis*, *Herba Lophatheri*	Saikosaponin, baicalin, amygdalin, coixenolide, *Coix* polysaccharides, magnolol, honokiol, alkaloids from Pinellia Ternata.	Anti-inflammatory, antioxidation; regulating blood lipid metabolism, protecting islet, decreasing TNF-α activity, decreasing PGE-2 and NO
Li 2012	Tang Zhi Ping	*Cortex Mori*, *Rhizoma Alismatis*, *Rhizoma Coptidis*, *Euonymus alatus*, *Radix et Rhizoma Rhei*	Sanggenon, alisol A 24-acetate, berberine, flavonoids of *Euonymus*, emodin, rheidin	Alleviating insulin resistance, decreasing Ang-II, inhibiting myocardial hypertrophy, increasing SOD activity, protecting islet, regulating lipid metabolism, anti-inflammatory, antioxidation, upregulating P-glycoprotein
Wang 2019	Yiqi Huazhuo Gushen granules	*Radix Astragali seu Hedysari*, *Rhizoma Coptidis*, *Pollen Typhae*, *Rhizoma Alismatis*, *Phaseolus radiatus L.*, *Serissa serissoides*, *Radix Aconiti Lateral is Preparata*	Astragaloside IV, berberine, total flavone in pollen *Typhae*, Alisol A 24-acetate	Increasing insulin sensitivity, inhibiting the effect of free fatty acid-induced insulin resistance, antioxidation, anti-inflammatory, immunoregulation, protecting islet, promoting insluin secretion, regulating lipid metabolism
Yu 2018	Jiangtang Tiaozhi formula	*Aloe*, *Rhizoma Coptidis*, *Rhizoma Anemarrhenae*, *Monascus in Oryzae Fructus*, *Momordica charantia L.*, *Radix Salviae Miltiorrhizae*, *Fructus Schisandrae Chinensis*, *Rhizoma Zingiberis*	Barbaloin, arboran A, berberine, *Anemarrhena* Saponin, monacolin K, total saponins from bitter melon, tanshinone, *S. chinensis* lignans	Alleviating insulin resistance, increasing insulin sensitivity, inhibiting glucagon activity, antioxidation, antiplatelet aggregation, inhibiting mTOR and TXNIP activity, inhibiting angiotensin and ACE, inhibiting HMG-CoA reductase, increasing insulin release and islet β cell, antiatherosclerosis, regulating blood lipid metabolism

cAMP, cyclic adenosine monophosphate; CTGF, connective tissue growth factor; GIP, glucose-dependent insulin-stimulating polypeptide; GLP-1, glucagon like peptide-1; HMG-CoA, hydroxymethylglutaryl coenzyme A; IGF-1, insulin-like growth factor-1; IL, interleukin; LDL, low-density lipoprotein; MDA, malondialdehyde; mTOR, mammalian target of rapamycin; NO, nitric oxide; NOS, nitric oxide synthetase; PGE-2, prostaglandin E-2; PTP-1B, proteintyrosinephosphatase1B; SOD, superoxide dismutase; TXNIP, thioredoxin interacting protein.



Study	TCM Intervention	Mean±SD	No. of Subjects	Std Mean difference (95% CI)	Contol Intervention	Mean±SD	No. of Subjects	Std Mean difference (95% CI)
Total (95% CI)			716				693	-0.20 [-0.36, -0.03]
TCM vs Placebo								
Fan 2012	Wuling Powder+ basic treatment	6.59±0.94	40		basic treatment	6.31±0.70	40	0.28 [-0.08, 0.64]
Lian 2012	Yi Tang Kang+ basic treatment	5.83±0.60	83		Placebo+ basic treatment	6.04±0.63	82	-0.21 [-0.40, -0.02]
Liu 2017	Wenpi Fuzhen Decoction+ basic treatment	5.59±1.23	35		Placebo+ basic treatment	6.13±0.94	35	-0.54 [-1.05, -0.03]
Wang 2012	Jiangtang pill+ basic treatment	5.89±0.69	86		Placebo+ basic treatment	5.98±0.86	81	-0.09 [-0.33, 0.15]
Wang 2016	Yiqi Huaju Formula+ basic treatment	7.04±1.25	36		Placebo+ basic treatment	7.54±1.17	48	-0.50 [-0.98, -0.02]
Zhang 2014	Sanhuang Danshen Decoction+ basic treatment	6.22±2.10	85		basic treatment	7.13±0.90	37	-0.91 [-1.65, -0.17]
Zhang 2016	Yangyin Jiangya capsule +Jiangzhuo Quyu Granule+ basic treatment	5.49±0.40	85		basic treatment	5.85±0.57	84	-0.36 [-0.51, -0.21]
TCM vs Western Medicine								
Li 2012	Tang Zhi Ping	5.27±0.31	38		Metformin,0.25g tid	5.19±0.48	37	0.08 [-0.10, 0.26]
Wang 2019	Yiqi Huazhuo Gushen granules + basic treatment	7.04±1.26	50		Valsartan,80mg qd+placebo+basic treatment	7.52±1.36	50	-0.48 [-0.99, 0.03]
Yu 2018	Jiangtang Tiaozhi (JTTZ)formula	7.51±1.44	215		Metformin tablets,0.25g tid	7.57±1.42	199	-0.06 [-0.34, 0.22]

Figure 3 Data summary of the high-quality RCTs of TCM interventions for HbA1c. HbA1c, glycosylated hemoglobin; RCT, randomized controlled trial; TCM, traditional Chinese medicine.

supplementary figure 6). The TG-lowering effect of TCM was not different from that of Western medicine (n=715, RR −0.53, 95% CI −0.64 to 0.42; figure 4). The outcome also showed that TCM was more effective in decreasing LDL (n=715, RR −0.13, 95% CI −0.21 to 0.04; Online supplementary figure 7) and in increasing HDL (n=301, RR 0.08, 95% CI 0.03 to 0.13; Online supplementary figure 8). A study showed that the Heye Jiangzhi decoction[21] regulated lipid metabolism by affecting TC, TG, and LDL, but the effect showed minor difference from that of fenofibrate (p>0.05). In addition, a better response on HDL was reported (p<0.05). Both Yu *et al*[19] and Li *et al*[27] used metformin as treatment for the control group; however, Li *et al* showed higher efficacy in reducing TC, TG and LDL (p<0.05), whereas Yu *et al* reported efficacy similar to that of metformin (p>0.05).

Analysis of blood pressure indicators showed no significant difference between the efficacies of TCM and Western medicine in decreasing SBP (n=301, RR −3.81, 95% CI −10.90 to 3.29; figure 5) and DBP (n=301, RR 0.14, 95% CI −3.21 to 3.50; Online supplementary figure 9). Wang *et al*[18] treated patients with MetS complicated with microalbuminuria (MAU) with Yiqi Huazhuo Gushen granules; the results showed that compared with valsartan, TCM exerted higher efficacy on SBP (p<0.05) but similar efficacy on DBP (p>0.05).

Publication bias

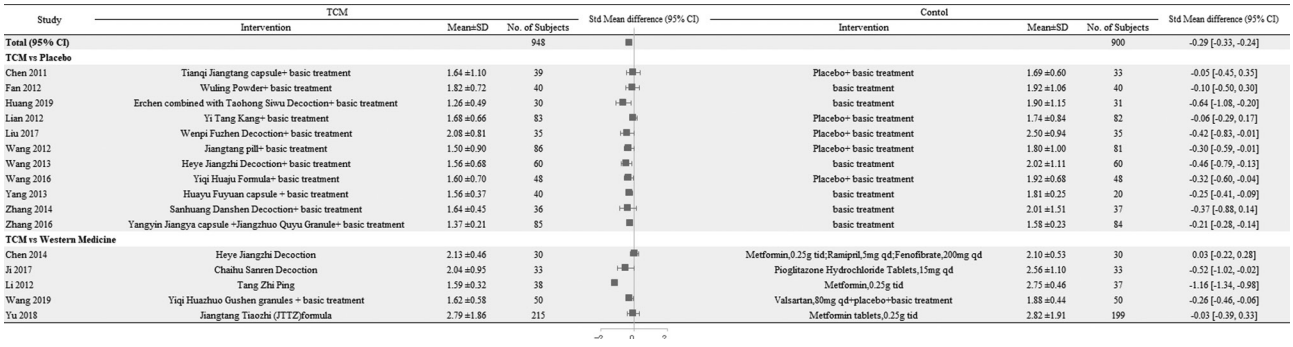
A funnel plot was used to investigate potential publication bias. As shown in online supplementary figures 11–16, the symmetrical dispersion points suggested no publication bias in the comparison of TCM with the control group.

DISCUSSION

The findings described previously showed that TCM exerted efficacy on MetS, according to each studied parameter. Analysis of obesity indicators showed that TCM decreased body weight and WC, with efficacy similar to that of Western medicine. Blood glucose analysis showed that TCM, compared with placebo, exerted a DM-curative effect by lowering HbA1c, FPG, and 2hPG levels, as well as improving islet function and easing insulin resistance. TCM also improved lipid metabolism by reducing TC, TG, and LDL, as well as elevating HDL, with efficacy similar to that of Western medicine. Compared with placebo, TCM also exerted a blood pressure-controlling effect, although this effect was not significantly different from that of Western medicine.

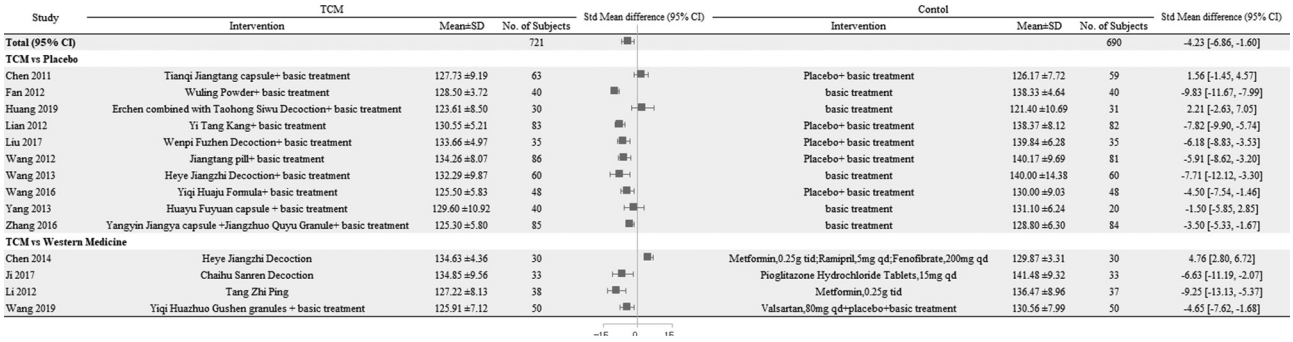
In detail, TCM showed efficacy in decreasing body weight, although its efficacy in decreasing WC or central obesity was not significant. TCM showed significant efficacy in improving glucose metabolism compared with placebo, but this effect was not remarkable compared with that of Western medicine. Moreover, TCM exerted marked efficacy in improving lipid metabolism; it decreases TC, TG, and LDL levels and increases HDL level. However, the efficacy of TCM in controlling blood pressure was not notable. In summary, TCM might be more beneficial for decreasing body weight, as well as regulating lipid and glucose metabolisms for the treatment of MetS.

The first definition of MetS was proposed by the WHO in 1998, in which insulin resistance is regarded as the core factor. The WHO diagnosis criteria of MetS were



Study	TCM Intervention	Mean±SD	No. of Subjects	Std Mean difference (95% CI)	Contol Intervention	Mean±SD	No. of Subjects	Std Mean difference (95% CI)
Total (95% CI)			948				900	-0.29 [-0.33, -0.24]
TCM vs Placebo								
Chen 2011	Tianqi Jiangtang capsule+ basic treatment	1.64 ±1.10	39		Placebo+ basic treatment	1.69 ±0.60	33	-0.05 [-0.45, 0.35]
Fan 2012	Wuling Powder+ basic treatment	1.82 ±0.72	40		basic treatment	1.92 ±1.06	40	-0.10 [-0.50, 0.30]
Huang 2019	Erchen combined with Taohong Siwu Decoction+ basic treatment	1.26 ±0.49	30		basic treatment	1.90 ±1.15	31	-0.64 [-1.08, -0.20]
Lian 2012	Yi Tang Kang+ basic treatment	1.68 ±0.66	83		Placebo+ basic treatment	1.74 ±0.84	82	-0.06 [-0.29, 0.17]
Liu 2017	Wenpi Fuzhen Decoction+ basic treatment	2.08 ±0.81	35		Placebo+ basic treatment	2.50 ±0.94	35	-0.42 [-0.83, -0.01]
Wang 2012	Jiangtang pill+ basic treatment	1.50 ±0.90	86		Placebo+ basic treatment	1.80 ±1.00	81	-0.30 [-0.59, -0.01]
Wang 2013	Heye Jiangzhi Decoction+ basic treatment	1.56 ±0.68	60		basic treatment	2.02 ±1.11	60	-0.46 [-0.79, -0.13]
Wang 2016	Yiqi Huaju Formula+ basic treatment	1.60 ±0.70	48		Placebo+ basic treatment	1.92 ±0.68	48	-0.32 [-0.60, -0.04]
Yang 2013	Huayu Fuyuan capsule + basic treatment	1.56 ±0.37	40		basic treatment	1.81 ±0.25	20	-0.25 [-0.41, -0.09]
Zhang 2014	Sanhuang Danshen Decoction+ basic treatment	1.64 ±0.45	36		basic treatment	2.01 ±1.51	37	-0.37 [-0.88, 0.14]
Zhang 2016	Yangyin Jiangya capsule +Jiangzhuo Quyu Granule+ basic treatment	1.37 ±0.21	85		basic treatment	1.58 ±0.23	84	-0.21 [-0.28, -0.14]
TCM vs Western Medicine								
Chen 2014	Heye Jiangzhi Decoction	2.13 ±0.46	30		Metformin,0.25g tid;Ramipril,5mg qd;Fenofibrate,200mg qd	2.10 ±0.53	30	0.03 [-0.22, 0.28]
Ji 2017	Chaihu Sanren Decoction	2.04 ±0.95	33		Pioglitazone Hydrochloride Tablets,15mg qd	2.56 ±1.10	33	-0.52 [-1.02, -0.02]
Li 2012	Tang Zhi Ping	1.59 ±0.32	38		Metformin,0.25g tid	2.75 ±0.46	37	-1.16 [-1.34, -0.98]
Wang 2019	Yiqi Huazhuo Gushen granules + basic treatment	1.62 ±0.58	50		Valsartan,80mg qd+placebo+basic treatment	1.88 ±0.44	50	-0.26 [-0.46, -0.06]
Yu 2018	Jiangtang Tiaozhi (JTTZ)formula	2.79 ±1.86	215		Metformin tablets,0.25g tid	2.82 ±1.91	199	-0.03 [-0.39, 0.33]

Figure 4 Data summary of the high-quality RCTs of TCM interventions for TG. RCT, randomized controlled trial; TCM, traditional Chinese medicine; TG, triglyceride.



Study	TCM Intervention	TCM Mean±SD	TCM No. of Subjects	Std Mean difference (95% CI)	Contol Intervention	Contol Mean±SD	Contol No. of Subjects	Std Mean difference (95% CI)
Total (95% CI)			721				690	-4.23 [-6.86, -1.60]
TCM vs Placebo								
Chen 2011	Tianqi Jiangtang capsule+ basic treatment	127.73 ±9.19	63		Placebo+ basic treatment	126.17 ±7.72	59	1.56 [-1.45, 4.57]
Fan 2012	Wuling Powder+ basic treatment	128.50 ±3.72	40		basic treatment	138.33 ±4.64	40	-9.83 [-11.67, -7.99]
Huang 2019	Erchen combined with Taohong Siwu Decoction+ basic treatment	123.61 ±8.50	30		basic treatment	121.40 ±10.69	31	2.21 [-2.63, 7.05]
Lian 2012	Yi Tang Kang+ basic treatment	130.55 ±5.21	83		Placebo+ basic treatment	138.37 ±8.12	82	-7.82 [-9.90, -5.74]
Liu 2017	Wenpi Fuzhen Decoction+ basic treatment	133.66 ±4.97	35		Placebo+ basic treatment	139.84 ±6.28	35	-6.18 [-8.83, -3.53]
Wang 2012	Jiangtang pill+ basic treatment	134.26 ±8.07	86		Placebo+ basic treatment	140.17 ±9.69	81	-5.91 [-8.62, -3.20]
Wang 2013	Heye Jiangzhi Decoction+ basic treatment	132.29 ±9.87	60		basic treatment	140.00 ±14.38	60	-7.71 [-12.12, -3.30]
Wang 2016	Yiqi Huaju Formula+ basic treatment	125.50 ±5.83	48		Placebo+ basic treatment	130.00 ±9.03	48	-4.50 [-7.54, -1.46]
Yang 2013	Huayu Fuyuan capsule + basic treatment	129.60 ±10.92	40		basic treatment	131.10 ±6.24	20	-1.50 [-5.85, 2.85]
Zhang 2016	Yangyin Jiangya capsule +Jiangzhuo Quyu Granule+ basic treatment	125.30 ±5.80	85		basic treatment	128.80 ±6.30	84	-3.50 [-5.33, -1.67]
TCM vs Western Medicine								
Chen 2014	Heye Jiangzhi Decoction	134.63 ±4.36	30		Metformin,0.25g tid;Ramipril,5mg qd;Fenofibrate,200mg qd	129.87 ±3.31	30	4.76 [2.80, 6.72]
Ji 2017	Chaihu Sanren Decoction	134.85 ±9.56	33		Pioglitazone Hydrochloride Tablets,15mg qd	141.48 ±9.32	33	-6.63 [-11.19, -2.07]
Li 2012	Tang Zhi Ping	127.22 ±8.13	38		Metformin,0.25g tid	136.47 ±8.96	37	-9.25 [-13.13, -5.37]
Wang 2019	Yiqi Huazhuo Gushen granules + basic treatment	125.91 ±7.12	50		Valsartan,80mg qd+placebo+basic treatment	130.56 ±7.99	50	-4.65 [-7.62, -1.68]

Figure 5 Data summary of the high-quality RCTs of TCM interventions for SBP. RCT, randomized controlled trial; SBP, systolic blood pressure; TCM, traditional Chinese medicine.

formulated on the basis of IGR, DM, or insulin resistance combined with two additional factors, including increased arterial pressure, central obesity, increased plasma TG or decreased HDL, and MAU.[41] In 1999, the European Group for Study of Insulin Resistance thought the definition should include the presence of insulin resistance or fasting hyperinsulinemia, as well as two of the following conditions: hypertension, dyslipidemia, and central obesity.[42] Subsequently, the American National Cholesterol Education Programme Adult Treatment Panel III (ATP III) programme was launched in 2001, establishing criteria that included the presence of three of the following five factors: abdominal obesity, elevated TG, reduced HDL, hypertension, and elevated fasting glucose.[43] Subsequently, the American Association of Clinical Endocrinologists recommended four components of the ATP III standard except WC and emphasized the importance of clinical symptoms.[44] The International Diabetes Federation considered central obesity as the primary risk factor, combined with any two of the following conditions: elevated TG, reduced HDL, elevated blood pressure, elevated FPG, and previous diagnosis of T2DM.[45] Considering the differences between these definitions, the transition from insulin resistance to abdominal obesity might provide insights into the mechanism of MetS.

The Chinese Diabetes Society recommended three or all of the following factors as diagnosis criteria: overweightness or obesity, elevated blood glucose (including FPG or 2hPG), hypertension, and dyslipidemia (including elevated TG, reduced HDL).[41] In 2007, a joint committee of Chinese experts in endocrinology, cardiology, diabetes, and docimasiology released a guideline that proposed the criteria as three or more of the following characteristics: central obesity, elevated TG, reduced HDL, hypertension, elevated blood glucose, and history of diabetes.[46] Though there are differences among these definitions, the definitions are much more suitable for clinical use and for each region.

In our enrolled studies, patients were diagnosed with MetS according to different definitions. Yu *et al*[19] observed the clinical efficacy of TCM on T2DM in terms of obesity and hyperlipidemia, according to the standard of Chinese Diabetes Society.[47] The participants of three trials[20 31 32] were diagnosed with MetS with IGR; in one trial,[30] patients were diagnosed with MetS with hypertension; in another trial, patients were diagnosed with MetS with MAU. Wang *et al*[18] observed the effect of TCM on MetS complicated with MAU. They used a combination of Yiqi Huazhuo Gushen granules and valsartan for 12 weeks and found that the combination showed improved efficacy against MAU ($p<0.05$). Though MAU was not a primary indicator, TCM was shown to decrease urinary microalbumin and delay the progression of MetS. The study also emphasized that attention should be paid to TCM as a secondary and tertiary preventive agent against MetS, as MetS can have various complications.

The RE and FE models were used for sensitivity analysis of the stability of the included studies. As the accurate numbers of each component in every study and the agents used for basic treatment were not provided in detail, we could not measure the effect of these factors on heterogeneity. In addition, different diagnostic criteria and complications might also cause heterogeneity. Moreover, the agents used as control might cause heterogeneity, as Wang *et al*[18] used valsartan; Li *et al*[27] used metformin; and Chen[21] used metformin, ramipril, and fenofibrate. Furthermore, Wang *et al* included patients with MetS with MAU, which might lead to heterogeneity. The patients in some studies[20 21 23 25–28 32] were also selected according to TCM syndrome differentiation and different syndrome patterns. The use of empirical decoction or Chinese patent drugs according to the syndrome differentiation might also cause heterogeneity.

The incidence of adverse events (AEs) was evaluated to assess the safety of TCM. Twelve studies reported AEs and four[18 30–32] did not mention any AE. The incidence of AEs in the TCM and control groups was not significantly different (RR 0.66, 95% CI 0.40 to 1.08; Online supplementary figure 10), suggesting that TCM was generally safe. Details on the AEs are shown in Online supplementary table 2. The main AE observed in treatment group was diarrhea, which might be caused by *Rheum*. Only one patient[26] dropped out of the study owing to diarrhea. Because this symptom did not last long and relative examinations showed kidney or liver injury, TCM as a treatment of MetS was considered safe to a certain degree.

A prominent limitation of the present study was the lack of high-quality RCTs. Though we included studies

with high Jadad scores, there were four RCTs with a Jadad score of 6[18 20 31 33] and only one RCT had a Jadad score of 7.[32] The quality of the included studies would directly and seriously affect the accuracy of a meta-analysis. Besides, the duration of these RCTs was not long enough to provide a strong evidence, and we could not access the long-term efficacy of TCM on MetS-induced complications; future studies should focus on secondary and tertiary preventions. The efficacy of TCM on MetS might be due to weight loss or improvement of insulin sensitivity from the data mentioned previously. However, there is no definite pathological mechanism yet as MetS is the multifactorial disease. We have no idea which factor would accelerate the disease progression faster and the key pathway of treatment. The long-term observation of MetS and each single-factor study might offer references on exploring the mechanism. Regarding the participants, only one RCT[19] included more than 200 patients in each group; thus, the efficacy and the ratio of AEs might be affected by the number of participants. Furthermore, though two RCTs[18 19] were in English, all the participants were Chinese. Thus, the lack of other ethnic groups in the included studies might restrict the scope of their application. Data on cardiovascular events, degree of fatty liver, measurement of MAU, and detailed AEs may provide more persuasive evidence in future meta-analyses.

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