Check for updates

OPEN ACCESS

EDITED BY Shen Xiang-chun, Guizhou Medical University, China

REVIEWED BY Yan Chen, Guizhou Medical University, China Bin Yu, Nanjing University of Chinese Medicine, China

*CORRESPONDENCE Junguo Ren, ⊠ reek2003@163.com

[†]These authors have contributed equally to this work and share first authorship

RECEIVED 06 July 2023 ACCEPTED 18 September 2023 PUBLISHED 28 September 2023

CITATION

Hu L, Qian L, Sun A, Cai G, Gao Y, Yuan Y, Chen X, Jiang Y, Liu J and Ren J (2023), Efficacy of traditional Chinese medicine on diabetic cardiomyopathy in animal models: a systematic review and metaanalysis.

Front. Pharmacol. 14:1253572. doi: 10.3389/fphar.2023.1253572

COPYRIGHT

© 2023 Hu, Qian, Sun, Cai, Gao, Yuan, Chen, Jiang, Liu and Ren. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Efficacy of traditional Chinese medicine on diabetic cardiomyopathy in animal models: a systematic review and meta-analysis

Longxiao Hu^{1,2†}, Longxin Qian^{2†}, Aochuan Sun^{1,2}, Guida Cai³, Yunxiao Gao¹, Yue Yuan¹, Xiaoxiao Chen¹, Yunyao Jiang⁴, Jianxun Liu¹ and Junguo Ren¹*

¹Xiyuan Hospital, Institute of Basic Medical Sciences, China Academy of Chinese Medical Sciences, Beijing, China, ²Beijing University of Chinese Medicine, Beijing, China, ³Institute of Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou, China, ⁴Institute for Chinese Materia Medica, School of Pharmaceutical Sciences, Tsinghua University, Beijing, China

Background: Diabetic cardiomyopathy (DCM) is a severe complication of diabetes that can diminish the quality of life in patients and is a leading cause of death. Research has demonstrated the effectiveness of Traditional Chinese Medicine (TCM) in reducing blood sugar levels and protecting cardiovascular function in both animal models and clinical research studies. Nevertheless, the efficacy of TCM in animal models of DCM has not been analyzed systematically.

Method: We searched the following electronic bibliographic databases: Web of Science, PubMed, Cochrane Library, and CNKI(China National Knowledge Infrastructure). Studies that reported the efficacy of TCM in animals with DCM were included. The literature search was conducted using the terms. The data will be restricted from the year 2013 to 24 April 2023, 24 studies were included in the meta-analysis.

Result: A total of 24 Traditional Chinese Medicine interventions and 2157 animals met the inclusion criteria. The pooled data revealed that TCM interventions resulted in significant improvements in body weight (BW), heart weight (HW) to body weight ratio (HW/BW), triglyceride (TG) and cholesterol (TC) levels, ejection fraction (EF), fractional shortening (FS) and E/A ratio. Subgroup analysis and meta-regression revealed that the type of TCM, duration of intervention, method of modeling, and animal species were potential sources of heterogeneity.

Conclusion: TCM interventions were associated with significant improvements in body weight, heart weight to body weight ratio, triglyceride and cholesterol levels, left ventricular internal dimension in systole, ejection fraction, fractional shortening and E/A ratio. The heterogeneity in the results was found to be potentially due to the type of TCM, duration of intervention, method of modeling, and animal species, as shown in subgroup analysis and meta-regression.

Systematic Review Registration: identifier CRD42023402908

KEYWORDS

diabetic cardiomyopathy, traditional Chinese medicine, animal model, systematic review, meta-analysis

1 Introduction

With the global population aging rapidly and the increasing prevalence of diabetes mellitus, there is a staggering increase in the prevalence of diabetes mellitus-induced cardiomyopathy. This condition is characterized by a higher mortality rate compared to patients without diabetes (Lehrke and Marx, 2017; Nakamura et al., 2022). Cardiovascular diseases are the leading cause of death in this population (Loffroy et al., 2009). Despite significant research advances in diabetes and heart disease, the concept of diabetic cardiomyopathy (DCM) remains controversial and not standardized (Seferovic et al., 2018). Diabetic cardiomyopathy is a cardiac manifestation exclusive to patients with diabetes, which is characterized by left ventricular hypertrophy, diastolic dysfunction, and, in late stages, by significant heart failure and reduced systolic function (Paolillo et al., 2019).

Diabetes mellitus impairs cardiac metabolic flexibility (Jankauskas et al., 2021). Diabetes-related hyperinsulinemia and insulin resistance increase the risk of capillary injuries and can lead to myocardial fibrosis, myocardial hypertrophy, and impaired mitochondrial function. Insulin signaling is reduced in both type 1 diabetes (T1D) and type 2 diabetes (T2D), which is a characteristic feature of these conditions. Additionally, there are changes in other signaling pathways, such as decreased AMPK (AMP-activated protein kinase) signaling and increased PKC (protein kinase C) and MAPK (mitogen-activated protein kinase) signaling. These alterations have detrimental effects on the body's adaptive response (Dillmann, 2019). Furthermore, excessive lipotoxicity from fat deposits or lipid droplets can affect cardiomyocytes, leading to increased oxidative stress and inflammation, ultimately resulting in cardiac fibrosis and hypertrophy (Nakamura et al., 2022). Elevated glucose or fatty acid levels activate NF-KB(Nuclear factor kB) in the myocardium (Lawrence, 2009), which leads to the formation of NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammatory vesicles that release proinflammatory mediators (Shao et al., 2015). High glucose levels also disrupt mitochondrial function, generating ROS(Reactive oxygen species) (He et al., 2021). These ROS cause the aggregation of TXNIP(Thioredoxin-interacting protein) with TRX (Thioredoxin), leading to the activation of the NLRP3 inflammasome. This inflammasome activates caspase-1, which processes pro-inflammatory cytokines IL-1ß and IL-18. ROS further stimulate NF-kB, facilitating the assembly of the NLRP3 inflammasome and cleavage of caspase-1 (Zhou et al., 2011; Couchie et al., 2017). This cascade results in the release of IL-1 β and IL-18, potent inflammatory molecules in diabetes (Figure 1). Activated endothelial cells in diabetes contribute to early myocardial stiffness and diastolic dysfunction (Franssen et al., 2016). In this condition, these cells disrupt the normal functioning of eNOS(endothelial-type nitric oxide synthase), leading to the generation of deleterious substances like superoxide, hydrogen peroxide, and peroxynitrite ions. This process also contributes to a decrease in the levels of NO(nitric oxide), amplifying the detrimental effects on the myocardium (Evan et al., 2019).

To diagnose DCM, clinicians must exclude various contributing factors, including valvular, coronary, hypertensive, or congenital heart disease, along with familial, viral, toxic, or infiltrative cardiomyopathies. Additionally, they must evaluate for glycometabolic disorders before a definitive diagnosis of DCM can be made (Seferović and Paulus, 2015). Non-coding RNAs have emerged as potential diagnostic criteria in the pathogenesis of diabetic cardiomyopathy in recent years (Guo and Nair, 2017).

Currently, there are no specific treatments for DCM, and clinical treatments for diabetes and cardiomyopathy remain separate (Lorenzo-Almorós et al., 2022). However, treatments for diabetes have varying effects on patients with cardiomyopathy. Nakamura et al. (2022) described diabetic treatments including Caloric Restriction, Sulfonylureas, Insulin, Thiazolidinediones, Dipeptidyl Peptidase-4 (DPP4) Inhibitors, and Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor. These treatments can have varying cardiovascular effects. Studies have shown that for diabetics, intensive glycemic control decreases the microvascular complications, while macrovascular complications remain unaffected; it is a complex systemic phenomenon of the disease (Eriksson and Nyström, 2015). SGLT2 can be considered one of the most effective treatments for DCM. However, almost all of these treatments are associated with side effects or limitations, and patients with stable blood glucose levels may still experience adverse effects (Xiao and Luo, 2018). For instance, thiazolidinediones (TZDs) and dipeptidyl peptidase-4 (DPP4) can increase the risk of heart failure (Sc et al., 2015).

The form of DCM leads to overt heart failure with an increased death rate remains to be investigated (Ernande and Derumeaux, 2012). Traditional Chinese medicine (TCM) is widely used to treat disease and preserve health, a series of animal experiments have manifested that TCM can improve glucose metabolism (Wang et al., 2020), reduce the inflammatory response (Meng et al., 2022) and inhibit cardiomyocyte remodeling to relieve symptoms of DCM. However, the efficiency of Traditional Chinese Medicine in animals has not been systematically reviewed, which hinders the treatment of DCM. In order to reveal the effectiveness of TCM in treating diabetic cardiomyopathy using animal studies, here, we performed a systematic review and meta-analysis of these studies, as preclinical evidence.

2 Methods

We performed this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Lorenzo-Almorós et al., 2022). The efficacy outcomes assessed include BW(body weight), HW/BW(heart weight/body weight), BG (blood glucose), TG (triglyceride) levels, serum TC (total cholesterol) levels, LVIDs (left ventricular internal dimension in systole), EF (ejection fraction), FS(fractional shortening), and E/A ratio. Decreased body weight, high heart weight/body weight ratio, high blood glucose, increased triglyceride and serum total cholesterol levels, lower ejection fraction and fractional shortening were considered as indicators of diabetic cardiomyopathy.

2.1 Search strategy

We conducted this report based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. This study was registered with PROSPERO (registration number: CRD42023402908). We searched the following electronic bibliographic databases: Web of Science, PubMed, Cochrane Library, and CNKI(China National Knowledge Infrastructure). Studies that reported the efficacy of TCM in animals with DCM were included. The literature search was conducted using the terms ("Diabetic cardiopathy") OR ("diabetic cardiomyopathy")OR ("Autonomic neuropathy") OR ("microangiopathy") OR ("microvascular disease") AND ("animal" OR" animals" OR "rat" OR" rats" OR" mouse" OR" mice") AND ("Chinese medicine "OR" Chinese herb " OR" herbal " OR " natural drug" OR "Natural Product" OR "traditional Chinese" OR "formula"). The date will be restricted from the year 2013 to 24 April 2023. The English and Chinese languages will be searched only. All searches were performed by two independent researchers (LH and LQ).

2.2 Inclusion and exclusion criteria

The criteria for inclusion in this study consist of animal models with diabetic cardiomyopathy without limitations regarding the construction, design types, randomized controlled trials, sexes and species. All studies that comprise the number of animals used and TCM treatments, including a single Chinese herbal extract (monomer), compounds of several Chinese herbal extracts, and Chinese herbal compounds, were included. Controlled studies with one or more separate control groups and those published in Chinese or English were also included. On the other hand, the exclusion criteria consisted of cell and *in vitro* studies, studies that used other non-TCM treatments, case reports, clinical trials, reviews, and cross-over studies that lacked a separate control group. Furthermore, studies that did not provide data were not included. Two researchers (AS and JR) independently screened the studies, and discrepancies were resolved through discussions.

2.3 Data extraction

Data extraction from the included studies was conducted by two independent researchers (LH and LQ). The following data were extracted from the studies: outcome measures (body weight, HW/ BW, blood glucose, triglyceride, serum total cholesterol, left ventricular end-systolic and end-diastolic diameter, ejection fraction, fractional shortening, and E/A ratio), publication information (author and year), details of treatments administered (dose, route, and duration), and the species of animals used. The study extracted sample size, mean value, and standard deviation (SD)/standard error for the both control and treatment groups for each comparison. In cases where multiple treatment groups shared the same control group, the sample size of the control group was divided by the number of treatment groups for appropriate comparison (Eriksson and Nyström, 2015). If outcomes were measured at more than one time point, we only included data from the last time point (Xiao and Luo, 2018).

2.4 Risk of bias assessment

The included studies were independently assessed for quality by two researchers, and disagreements were resolved through consultation with a third party. The quality of the included studies was evaluated using the SYRCLE (Systematic Review Center for Laboratory Animal Experimentation) Risk of Bias tool. The assessment includes 11 areas that are scored and evaluated separately. These areas are as follows: 1) Random sequence generation; 2) Baseline characteristics; 3) Allocation concealment; 4) Random housing; 5) Blinding; 6) Blinding of participants and personnel; 7) Random outcome assessment; 8) Blinding of outcome assessment; 9) Incomplete outcome data; 10) Selective reporting; 11) Other bias. Any discrepancies that arose during the evaluation were resolved through discussion until a consensus was reached.

2.5 Data analysis

Data were synthesized using either a fixed effects model or a random effects model based on a heterogeneity test. Heterogeneity between studies was explored by Cochran's Q statistic and I²statistic (Diao et al., 2019). All data were analyzed using Review Manager version 5.4 and STATA version 17 packages. Standardized mean differences (SMD) were used as an index of effect for each effect, their point estimates, and 95% confidence intervals. Heterogeneity between included studies was analyzed using the χ^2 test, while the magnitude of heterogeneity was determined quantitatively using I². If heterogeneity between results was not significant ($I^2 \le 50\%$), metaanalysis was performed using a fixed effects model (EF, FS, and E/A). If the heterogeneity between studies was significant ($I^2 > 50\%$), a random effects model was used (body weight, HW/BW, BG, TG, TC, and LVIDs). The study's findings were mainly presented using forest plots, with funnel plots utilized to analyze publication bias. Additionally, sensitivity analyses and Egger's test were carried out (Feidantsis et al., 2018). To further explore the sources of heterogeneity, subgroup analyses should be conducted on the types of Traditional Chinese Medicine (TCM), duration, modeling method, and animal species.

3 Results

3.1 Characteristics of included studies

In this study, a search of 199 publications was conducted, with 168 articles obtained from PubMed, 19 from CNKI, 2 from Web of Science, and 10 from manual search. The duplicates were screened using Endnote 20, resulting in 91 exclusions. Based on the title and abstract assessment, 76 articles were excluded manually, and 8 out of the remaining 32 articles were excluded after reading the full text for



not meeting the inclusion criteria. Eventually, a total of 24 articles were included in this study. Please refer to Figure 2 for the screening process details (Page et al., 2021). Altogether 2157 animals (1088 in the TCM group; 1069 in the control group) were included in this meta-analysis. Ten studies used Sprague Dawley rats, seven studies used Wistar rats, six studies used C57BL/6 J mice, and one study used Kunming mice. Rats weighed between 70–280 g, while C57BL/ 6 J mice and Kunming mice weighed between 23-27.5 and 18–22 g, respectively. The age of the rats was only reported in ten studies and ranged from 6 to 12 weeks. The studies used three different models: High-fat food (HFD) and streptozotocin (STZ) in eleven studies, STZ alone in ten studies, and alloxan in three studies.

Regarding the intervention methods, the researchers identified 24 different types of TCM, including ten compounds and fourteen monomers. The monomers consisted of Berberine (An isoquinoline alkaloid, mainly derived from Rhizoma Coptidis [Ranunculaceae; Coptis chinensis Franch. rhizome]), Curcumin (A yellow curry pigment isolated from Turmeric [Zingiberaceae; Curcuma longa L. root]), Crocin (An extract of Crocus sativus [Iridaceae; Crocus sativus L. flower]), Dioscin (An extract of Dioscoreaceae [Dioscoreaceae; Dioscorea oppositifolia L. rhizome]), Mangiferin (A carboketone glycoside of tetrahydroxypyridone from rhizoma anemarrhenae [Asparagaceae; Anemarrhena asphodeloides Bunge root]), Resveratrol (A non-flavonoid polyphenolic organic compound isolated from the roots of Veratrum grandiflorum [Melanthiaceae; Veratrum grandiflorum root]), Myricetin (A flavonol compound extracted from the bark of Myrica rubra [Myricaceae; Myrica rubra]), Nar (A dihydroflavonoid from pomelo [Rutaceae; Citrus

paradisi Macfadyen L. fruit]), Polydatin (An extract of Plantago Ovata [Plantaginaceae; Plantago ovata Forssk. rhizome]), Rutin (A natural flavonoid glycoside present in Sophora japonica rice [Fabaceae; Styphnolobium japonicum L. buds]), Sal B (the representative component of phenolic acids derived from the Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma]), taxifolin (a flavonoid commonly found in Pseudotsuga taxifolia [Pinaceae; Pseudotsuga menziesii var. menziesii]), triptolide (a most important active ingredient extracted from Tripterygium [Celastraceae, Tripterygium wilfordii Hook.f.]), and Wogonin (an important flavonoid derived from the Scutellaria [Lamiaceae; Scutellaria baicalensis Georgi root]). The intervention durations ranged from 24 to 180 days. Intraperitoneal administration was performed in two of the 24 studies, while gastrointestinal administration was used in the remaining 22 studies. The primary outcome measurements included BW (reported in 11 studies), HW/BW (reported in 7 studies), BG (reported in 15 studies), TG (reported in 7 studies), TC (reported in 10 studies), LVIDs (reported in 6 studies), EF (reported in 8 studies), FS (reported in 8 studies), and E/A (reported in 4 studies). The detailed characteristics of the included studies are shown in Table 1.

3.2 Risk of bias and quality of the included studies

The results of the quality assessment of the 24 included studies are presented in Figure 3. None of the studies reported the random sequence generation, allocation concealment, and blinding of

TABLE 1 Characteristics of included studies.

References	TCM drug	Route	Duration (days)	Species	Weight(g)	Age (weeks)	Model	N (T/C)	Treat	Control	Possible mechanisms	Outcome measures
Chang et al. (2015)	Berberine	i.g	112	Wistar rats	NR	6	HFD + STZ	(8/8)	100 mg/kg/d	Vehicle	The activation of AMPK and AKT was increased, while the activation of GSK3 β was reduced	BG, TG, TC
Guo et al. (2016)	triptolide	i.g	56	SD rats	160–170	6	HFD + STZ	(10/10)	50 μg/kg/d 100 μg/kg/ d 200 μg/kg/d	Vehicle	inhibition of TLR4-induced NF- κ B/IL-1 β immune pathway, suppression of NF- κ B/TNF- α / VCAM-1 mediated inflammatory pathway and downregulation of TGF- β 1/ α -SMA/Vimentin involved cardiac fibrosis	BG, HW/BW, TC
Hou et al. (2016)	Mangiferin	i.g	112	SD rats	220-240	NR	HFD + STZ	(8/8)	20 mg/kg/d	Vehicle	inhibition of ROS overproduction, AGEs/RAGE, and inflammatory activation via deactivating of NF- κB translocation	BG, TG, TC
Li et al. (2020)	Sal B	i.p	112	C57BL/6 J mice	NR	8	STZ	(20/20)	15 mg/kg/d 30 mg/kg/d	Vehicle	promoting the effect of nuclear translocation and DNA methylation of IGFBP3 to raise VEGFA and its receptor VEGFR2	EF, FS, E/A
Shen et al. (2014)	SSYX	i.g	28	Wistar rats	180-220	NR	HFD + STZ	(5/5)	50 mg/kg/d 100 mg/kg/d 200 mg/kg/d	NR	TGF-β1/Smad signaling pathway is involved in diabetic cardiomyopathy and SSYX treatment improves impaired heart function and inhibits fibrosis in diabetes	TC, TG, HW/BW, LVIDs
Shi et al. (2019)	DJC	i.g	56	SD rats	160–200	NR	HFD + STZ	(15/15)	270 mg/kg/d 540 mg/kg/d 1080 mg/kg/d	Water	inhibiting Overexpression of TLR4/MyD88/NF- kB signaling pathway proteins that protects myocardial cells from injury induced by high glucose	BG, TC, HW/BW
Sun et al. (2014)	taxifolin	i.g	28	C57BL/ 6 mice	NR	(6-8)	STZ	(10/10)	25 mg/kg/d 50 mg/kg/ d 100 mg/kg/d	Vehicle	decreasing angiotensin II production, inhibiting NADPH oxidase, and activating JAK2/ STAT3 cascade	BW
Tan et al. (2020b)	polydatin	i.g	56	SD rats	200-220	NR	HFD + STZ	(7/7)	85.71 mg/kg/d	Vehicle	mediating through its inhibition of NADPH oxidase and NF-ĸB activation	E/A, EF, FS
Wang et al. (2021)	FTZ	i.g	30	C57BL/ 6 mice	NR	(8-12)	STZ	(4/4)	3 g (crude drug)/kg/d	Vehicle	1) inhibited the activities of AKT1, ERK, and STAT3	BW, BG, EF, FS, E/A
											(2) decreased the interventricular septal thickness	

(Continued on following page)

TABLE 1 (Continued) Characteristics of included studies.

References	TCM drug	Route	Duration (days)	Species	Weight(g)	Age (weeks)	Model	N (T/C)	Treat	Control	Possible mechanisms	Outcome measures
Wang et al. (2018)	YQHX	i.g	24	SD rats	200–220	NR	HFD + STZ	(6/6)	7.5 mL/kg/d	Vehicle	enhancing the expression of the Bcl-2 protein, inhibiting the expression of Bax and P53, increasing the ratio of Bcl-2 and Bax, and inhibiting the apoptosis of cardiomyocytes	BW, BG, HW/BW
Wei et al. (2019)	Dioscin	i.g	42	SD rats	225-250	8	STZ	(10/10)	100 μg/kg/d 200 μg/kg/d	Saline	modulating the NO-sGC-cGMP- PKG signaling pathway, resulting in improved left ventricle function	BW, HW/BW
Wu et al. (2021)	QLQX	i.g	56	SD rats	NR	NR	STZ	(6/6)	0.5 g/kg/d	Saline	inhibited hyperglycemia-induced cardiomyocyte apoptosis in NRCMs via activating PPARy	LVIDs, E/A
Yao et al. (2021)	ТНЈ	i.g	84	C57BL/ 6 mice	23-25	(8–10)	HFD + STZ	(15/15)	0.125 g/kg/d 0.25 g/kg/ d 0.5 g/kg/d	Vehicle	reducing ROS production and inhibiting NLRP3 activation, thereby blocking the excessive secretion of pro-inflammatory cytokines	BG, TG
Zhang et al. (2018)	Nar	i.g	56	SD rats	230-280	NR	STZ	(8/8)	25 mg/kg/d 50 mg/kg/ d 100 mg/kg/d	Saline	reducing the accumulation of unfolded or misfolded proteins in ER by increasing antioxidant enzyme activity and reducing lipid peroxide production, inhibiting ERS, and reducing the expression of apoptosis-related factors	BW, BG
Zhang et al. (2016)	DOE	i.g	56	Kunming mice	18-22	(8-10)	STZ	(8/8)	75 mg/kg/d 150 mg/kg/d 300 mg/kg/d	Saline	inhibition of oxidative stress, cardiac fibrosis, and downregulation of pro- inflammatory cytokines	BW, HW/BW, BG, TC, TG
Dong et al. (2021)	QGYY	i.g	84	SD rats	180-200	NR	HFD + STZ	(5/5)	5.40 mg/kg/d	Vehicle	improving insulin resistance, inhibiting oxidative stress and inflammatory reaction	BW, BG, TG, TC, LVIDs
Liao et al. (2017)	Myricetin	i.g	180	C57BL/ 6 Mice	23.5-27.5	(8–10)	STZ	(16/12)	200 mg/kg/d	Saline	inhibiting IKB-α/NF-κB/p65 and TGFβ/Smad signaling and enhancing the expression of Nrf2, which accordingly alleviate oxidative stress, inflammation, apoptosis, and fibrosis	BW, BG, LVIDs, EF, FS
Khan et al. (2016)	Wogonin	i.p	112	C57BL/ 6 mice	NR	8	STZ	(16/18)	10 mg/kg/3d	Vehicle	suppressing diabetic-induced cardiomyocyte inflammation and oxidative stress	BG, LVIDs, EF, FS

10.3389/fphar.2023.1253572

(Continued on following page)

References	TCM drug	Route	Duration (days)	Species	Weight(g)	Age (weeks)	Model	N (T/C)	Treat	Control	Possible mechanisms	Outcome measures
Yu et al. (2012)	Curcumin	Orally	112	Wistar rats	70–90	NR	HFD + STZ	(9/9)	100 mg/kg/d 200 mg/kg/d	Vehicle	activating pro-survival signaling pathway Akt/GSK3β in diabetic hearts. Akt promotes cell survival by inhibiting several targets involved in apoptotic signaling cascades	BW, BG, HW/BW, TC, EF, FS
Diao et al. (2019)	resveratrol	i.g	56	SD rats	100-150	NR	HFD + STZ	(10/10)	10 mg/kg/d	Saline	1) inhibit myocardial fibrosis and apoptosis, and contribute to the protection of the cardiac function in DCM rats	EF, FS
											(2) RES promotes mitochondrial biosynthesis and inhibits excessive mitochondrial division	-
Feidantsis et al. (2018)	crocin	Orally	14	Wistar rats	200	NR	STZ	(4/4)	10 mg/kg/d 20 mg/kg/d	Vehicle	1) enhancement of cell protection through upregulation of heat shock response	BW, LVIDs, EF, FS
											2) inhibition of diabetes-induced apoptosis and	_
											3) normalization of cardiac autophagy through activation of AMPK	-
Ganesan et al. (2020)	Rutin	i.g	30	Wistar rats	180-220	NR	alloxan	(6/6)	100 mg/kg/d	Saline	reducing the over-expression of the aquaporin gene preventing the development of metabolic acidosis	TC
Rahimi-Madiseh et al. (2017)	Allium ampeloprasum (AA)	i.g	56	Wistar rats	200-250	NR	alloxan	(12/12)	400 mg/kg/d 800 mg/kg/d	Water	prevent diabetes and associated complications by decreasing the levels of serum lipids, and significantly increasing the activity of antioxidant enzymes, and decreasing serum MDA	BG, TG, TC
Asgary et al. (2014)	cornelian cherry	i.g	28	Wistar rats	190-220	NR	alloxan	(7/7)	2 g/d	NR	Inhibition of a-glucosidase	BG

Sal B, salvianolic acid B; SSYX, shensong yangxin; DJC, danzhi jiangtang; FTZ, fufang zhenzhutiaozhi; YQHX, yiqi huoxue; QLQX, qiliqiangxin; THJ, taohuajing, Nar, naringin; DOE, debdrobium officinale; QGYY, qiguiyaoye; i. g., intragastric injection; i. p., intraperitoneal injection; NR, not reported; HFD, high fat diet; STZ, streptozotocin; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; AKT, protein kinase B; GSK3β, Glycogen synthase kinase 3β; NF-κB, Nuclear factor kappa-B; IL-1β, Interleukin-1β; TNF-α, tumor necrosis factor-a; VCAM-1, vascular cell adhesion molecule-1; TGF-β1, Transforming Growth Factor-β1; a-SMA, α-smooth muscle actin; ROS, reactive oxygen species; AGEs, Advanced Glycation End Products; RAGE, advanced glycosylation end product-specific receptor; IGFBP3, Insulin like growth factor binding protein-3; VEGFA, vascular endothelial growth factor x; VCAM-1, transforming growth factor-β-1; TLR4, Toll-like receptor 4; MyD88, Myeloid differentiation factor 88; NADPH, nicotinamide adenine dinucleotide phosphate; JAK2, Janus kinase 2; ERK, extracellular signal-regulated kinase; STAT3, Signal Transducer and Activator of Transcription 3; Bcl-2, Bcelllymphoma2; Bax, BCL2-Associated X; P53, Cellular tumor antigen p53; NO-sGC-cGMP-PKG, nitric oxide-cyclic guanosine monophosphate)-protein kinase G; NRCMs, neonatal rat cardiomyocyte; PPARγ, peroxisome proliferator-activated receptor y; NLRP3,NOD-like receptor protein 3; HR-a, inhibitor kappa B alpha; Nrf2, nuclear factor erythroid-2-related factor 2; RES, reticuloendothelial system; MDA, malondialdehyde; BW, body weight; BG, blood glucose; TG, triglyceride; TC, total cholesterol; LVIDs, left ventricular end systolic diameter; EF, ejection fraction; FS, fractional shortening.



participants and personnel. However, all the studies reported similar baseline characteristics between the model and control groups. Additionally, all experimental animals were housed in identical conditions, so the placement of animals in all studies can be considered consistent with the principle of randomization. One study had a high risk of bias for incomplete outcome data (attrition bias) due to an unclear number of animals. Eighteen studies reported the random outcome assessment, while 12 studies assessed the blinded methods used for outcome assessment. None of the studies had a selective reporting bias or any other sources of bias. Despite the overall poor quality of these studies, none of them were excluded based on quality or risk of bias assessment.

3.3 Meta-analysis of the efficacy of TCM

3.3.1 Efficacy of TCM on body weight

Eleven studies (341 animals, with 171 in the TCM group and 170 in the control group) assessed body weight and were included in the metaanalysis (Figure 4). The pooled results showed that TCM significantly increased body weight [SMD = 1.69 (1.15,2.22), p < 0.00001; 20 comparisons], despite significant heterogeneity between studies ($\chi^2 =$ 73.10; I² = 74%; df = 19; p < 0.00001). Subgroup analysis indicated a significant correlation (p < 0.001). Among the TCM interventions, Nar, DOE, and crocin had similar efficacy to the control group (p = 0.07, p = 0.05, and p = 0.33, respectively), while the other TCM interventions were associated with significant weight gain (p < 0.05). The forest plot showed that wogonin had a more prominent effect.

3.3.2 Efficacy of TCM on HW/BW

The HW/BW was assessed in 7 studies (303 animals, 155 were in the TCM group and 148 were in the control group), which are included in the meta-analysis (Figure 5). The overall analysis demonstrated a significant reduction in HW/BW with the use of TCM [SMD = -2.23 (-2.74, -1.72), p < 0.00001; 17 comparisons), but with noticeable heterogeneity across trials ($\chi^2 = 42.15$; I² = 62%; df = 16; p = 0.0004). Subgroup analysis displayed a significant correlation (p < 0.01). The efficacy of YQHX was similar to the control group (p = 0.05), while the remaining TCM yielded more obvious results than the control group (p < 0.05).

3.3.3 Efficacy of TCM on blood glucose

A total of 15 studies with 499 animals (253 in the TCM and 246 in the control group) assessed the blood glucose levels, which were incorporated in the meta-analysis (Figure 6). The findings showed that TCM group had significantly lower blood glucose levels compared to the control group [SMD = -2.01 (-2.54, -1.47), p < 0.00001; 27 comparisons) with a high degree of heterogeneity across



studies ($\chi^2 = 133.28$; I² = 80%; df = 26; p < 0.00001). Subgroup analysis indicated a significant correlation between TCM type and effect size (p < 0.00001). Despite DOE, Myricetin, and triptolide having similar efficacy to the control group (p = 0.09, p = 0.10, and p = 0.70, respectively), the remaining TCM had a more pronounced effect on blood glucose reduction than the control group (p < 0.05). The forest map demonstrated mangiferin to be the most effective TCM.

3.3.4 Efficacy of TCM on triglyceride

Eight studies (246 animals; 123 in the TCM group and 123 in the control group) analyzed triglyceride levels, which were included in the meta-analysis (Figure 7). The findings demonstrated that TCM

significantly reduced triglyceride levels [SMD = -1.87 (-2.39, -1.36),p < 0.00001; 16 comparisons) but with noticeable heterogeneity across the studies ($\chi^2 = 36.50$; I² = 59%; df = 15; p = 0.001). Subgroup analysis did not reveal any effect of the TCM type on the results (p = 0.09). While QGYY had similar efficacy to the control group (p = 0.06), the other TCM yielded a more evident reduction in TG than the control group (p < 0.05). The forest map found berberine to have a more marked effect.

3.3.5 Efficacy of TCM on total cholesterol

Ten studies (354 animals; 180 in the TCM group and 174 in the control group) evaluated total cholesterol for inclusion in the meta-

tudy or Subgroup	l Mean	Drug SD	Total	Mean	/lodel SD	Total	S Weight	itd. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl
vifolin(100ma/lua)	25 00	1 94	40	10 77	1 04	10	2 00/	4 90 12 02 6 691	
xitolin(100mg/kg)	20.09	0.09	10	10.77	1.21	10	5.0%	4.60 [2.92, 6.66]	
xitolin(25mg/kg)	19.02	0.90	10	10.77	1.21	10	5.9%	2.04 [1.67, 4.40]	
ubtotal (95% CI)	22.40	1.11	30	10.77	1.21	30	4.5%	2 80 [0 60 5 00]	
eterogeneity: Tau ² =	3.27; Chi ²	= 15.96,	df = 2	(P = 0.0	003); l²	= 87%	14.070	2.00 [0.00, 0.00]	
est for overall effect:	Z = 2.49 (F	9 = 0.01)							
1.2 FTZ	00.40	4.00		00.44	4.04		0.00/	0.00 10.00 4.071	
LZ	26.16	1.29	4	23.14	1.24	4	3.6%	2.08 [0.09, 4.07]	
ubiolal (95% CI)	aliaabla		4			4	3.0%	2.08 [0.09, 4.07]	
eterogeneity: Not ap est for overall effect:	Z = 2.04 (F	P = 0.04)							
1.3 YQHX									
QHX	439.33	25.83	6	329.33	33.12	5	3.3%	3.43 [1.28, 5.58]	
ubtotal (95% CI)			6			5	3.3%	3.43 [1.28, 5.58]	
eterogeneity: Not ap	plicable								
est for overall effect:	Z = 3.13 (F	P = 0.002	2)						
4.4.5									
1.4 Dioscin	247.0	20.4	10	226 4	22.0	10	6 00/	0 76 1 0 16 1 671	<u> </u>
ioscin(100µg/kg)	247.9	30.1	10	226.4	23.9	10	0.0%	0.70 [-0.16, 1.67]	
ubtotal (95% CI)	251.4	24.4	10	226.4	23.9	10	5.9%	0.99 [0.05, 1.93]	•
abtoragonoitur Tou? -	0.00.062	- 0.12	4f - 4 /	B = 0.70). 12 - 00	20	11.0 %	0.07 [0.22, 1.33]	-
sterogeneity: Tau ² =	$7 = 2.60 / \Box$	= 0.12, 0 = 0.000	ur = 1 (a)	r = 0.73); 1~ = 0%	0			
sou or overall ellect:	2 - 2.00 (P	- 0.008)						
1.5 Nar									
ar(100mg/kg)	217.04	15.48	8	193.36	13.94	8	5.4%	1.52 [0.37, 2.67]	
ar(25mg/kg)	194.25	9.08	8	193.36	13.94	8	5.8%	0.07 [-0.91, 1.05]	
ar(50mg/kg)	204.95	12.55	8	193.36	13.94	8	5.7%	0.83 [-0.21, 1.86]	
ubtotal (95% CI)			24			24	16.9%	0.76 [-0.05, 1.57]	
erogeneity: Tau ² =	0.23; Chi ²	= 3.57, c	df = 2 (P = 0.17); ² = 44	%			
est for overall effect:	∠ = 1.84 (F	r = 0.07)	6						
1.6 DOE									
DE(150mg/kg)	27.77	5.79	8	22.64	3.09	8	5.6%	1.05 [-0.02, 2.11]	
DE(300mg/kg)	26.53	3.88	8	22.64	3.09	8	5.6%	1.05 [-0.02, 2.11]	<u> </u>
DE(75mg/kg)	22.72	2.3	8	22.64	3.09	8	5.8%	0.03 [-0.95, 1.01]	
ubtotal (95% CI)	0.00 51/5	0.01	24	D		24	17.0%	0.68 [-0.01, 1.36]	-
sterogeneity: Tau ² = est for overall effect:	U.09; Chi ² Z = 1.94 (F	= 2.61, c P = 0.05)	of = 2 (P = 0.27); I ² = 23	%			
1.7 QGYY	000.0	10.00	-	001	4474	-	4.000	4 00 10 04 0 10	
GTY ubtotal (95% CI)	396.2	18.86	5	361.4	14.74	5	4.3%	1.86 [0.24, 3.48]	
abiotal (35% CI)	nlicable		э			5	4.3%	1.00 [0.24, 3.46]	
eterogeneity: Not ap	7 = 2 24 /F	P = 0 021							
st for overall enect.	2 - 2.24 (P	- 0.02)							
1.8 Myricetin									
yricetin	26.56	2.41	16	21.95	2.34	16	6.1%	1.89 [1.04, 2.74]	
ubtotal (95% CI)			16			16	6.1%	1.89 [1.04, 2.74]	-
eterogeneity: Not ap	plicable								
est for overall effect:	Z = 4.35 (F	o < 0.000	01)						
19 Wogonin									
	29.7	16	16	23.9	12	16	5.2%	4.00 [2.74 5 25]	
odonin	20.1	1.0	16	20.0	1.4	16	5.2%	4.00 [2.74, 5.25]	-
ogonin ibtotal (95% CI)									
btotal (95% CI) terogeneity: Not an	plicable		011						
gonin btotal (95% CI) erogeneity: Not ap t for overall effect:	plicable Z = 6.25 (F	P < 0.000	JUT)						
bgonin Ibtotal (95% CI) Iterogeneity: Not ap st for overall effect:	plicable Z = 6.25 (F	P < 0.000) (10						1
boonin bototal (95% CI) terogeneity: Not ap st for overall effect: .10 Curcumin	plicable Z = 6.25 (P	P < 0.000	,01)	047	40		E 00/		
btotal (95% CI) terogeneity: Not ap st for overall effect: .10 Curcumin rcumin(100 mg/kg)	plicable Z = 6.25 (F 293	25 27	9	247	19	9	5.3%	1.97 [0.80, 3.15]	_ <u></u>
igonin btotal (95% CI) terogeneity: Not ap st for overall effect: .10 Curcumin roumin(100 mg/kg) roumin(200 mg/kg) btotal (95% CI)	plicable Z = 6.25 (F 293 332	25 27	9 9 18	247 247	19 19	9 9 18	5.3% 4.4% 9.8%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08]	
gonin botal (95% CI) erogeneity: Not ap it for overall effect: .10 Curcumin cumin(100 mg/kg) cumin(200 mg/kg) total (95% CI) erogeneity: Tot? =	plicable Z = 6.25 (F 293 332	25 27 = 2 21 - 5	9 9 18	247 247 P = 0.14	19 19): l² = 55	9 9 18	5.3% 4.4% 9.8%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08]	
gonin bototal (95% CI) terogeneity: Not ap st for overall effect: .10 Curcumin ccumin(100 mg/kg) ccumin(200 mg/kg) bototal (95% CI) terogeneity: Tau ² = t for overall effect:	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F	25 27 = 2.21, c P = 0.000	9 9 18 1f = 1 (04)	247 247 P = 0.14	19 19); l² = 55	9 9 18 %	5.3% 4.4% 9.8%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08]	
gonin bottal (95% CI) terogeneity: Not ap it for overall effect: .10 Curcumin cumin(100 mg/kg) cumin(200 mg/kg) stotal (95% CI) erogeneity: Tau ² = it for overall effect:	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F	25 27 = 2.21, c P = 0.000	9 9 18 1f = 1 (04)	247 247 P = 0.14	19 19); I² = 55	9 9 18 %	5.3% 4.4% 9.8%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08]	
ygonin btotal (95% CI) terogeneity: Not ap st for overall effect: .10 Curcumin rcumin(200 mg/kg) btotal (95% CI) terogeneity: Tau ² = st for overall effect: .11 crocin	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F	25 27 = 2.21, c	9 9 18 3f = 1 ()4)	247 247 P = 0.14	19 19); l² = 55	9 9 18 %	5.3% 4.4% 9.8%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08]	
ogonin bibotal (95% CI) aterogeneity: Not ap sts for overall effect: 1.10 Curcumin urcumin(100 mg/kg) urcumin(200 mg/kg) bibotal (95% CI) aterogeneity: Tau ² = sts for overall effect: 1.11 crocin ocin(10mg/kg)	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F 368.5 285 0	25 27 = 2.21, c = 0.000 25.14	9 9 18 3f = 1 (04) 4	247 247 P = 0.14 274.94	19 19); I ² = 55 20.63	9 9 18 %	5.3% 4.4% 9.8%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34]	
ogonin bitotal (95% CI) eterogeneity: Not ap sst for overall effect: 1.10 Curcumin urcumin(100 mg/kg) ubtotal (95% CI) sterogeneity: Tau ² = sst for overall effect: 1.11 crocin bcin(10mg/kg) ubtotal (95% CI)	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F 368.5 285.8	25 27 27 = 2.21, c = 0.000 25.14 77.94	9 9 18 3f = 1 (04) 4 4 8	247 247 P = 0.14 274.94 274.94	19 19); I ² = 55 20.63 20.63	9 9 18 % 4 4 8	5.3% 4.4% 9.8% 2.4% 4.9% 7.3%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34] 0.17 [-1.22, 1.56] 1.62 [-1.65 4.90]	
by the second se	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F 368.5 285.8 4 41: Chi ²	25 27 = 2.21, c = 0.000 25.14 77.94 = 4.47	9 9 18 3f = 1 (04) 4 4 8 1f = 1 (247 247 P = 0.14 274.94 274.94 P = 0.03	19 19); I ² = 55 20.63 20.63): I ² = 75	9 9 18 % 4 4 8	5.3% 4.4% 9.8% 2.4% 4.9% 7.3%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34] 0.17 [-1.22, 1.56] 1.62 [-1.65, 4.90]	
ogonin Jubtotal (95% CI) eterogeneity: Not ap sst for overall effect: 1.10 Curcumin urcumin(200 mg/kg) ubtotal (95% CI) eterogeneity: Tau ² = ust for overall effect: 1.11 crocin ocin(10mg/kg) ocin(20mg/kg) ubtotal (95% CI) eterogeneity: Tau ² = st for overall effect:	plicable Z = 6.25 (F 293 332 0.61; Chi ² + Z = 3.54 (F 368.5 285.8 4.41; Chi ² + Z = 0.97 (F	25 27 = 2.21, c = 0.000 25.14 77.94 = 4.47, c = 0.33)	9 9 18 3f = 1 (04) 4 4 8 8 ff = 1 (247 247 P = 0.14 274.94 274.94 P = 0.03	19 19); I ² = 55 20.63 20.63); I ² = 78	9 9 18 5% 4 4 8 8%	5.3% 4.4% 9.8% 2.4% 4.9% 7.3%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34] 0.17 [-1.22, 1.56] 1.62 [-1.65, 4.90]	
gonin tototal (95% CI) terogeneity: Not ap t for overall effect: .10 Curcumin cumin(100 mg/kg) total (95% CI) erogeneity: Tau ² = it for overall effect: .11 crocin cin(10mg/kg) stotal (95% CI) erogeneity: Tau ² = it for overall effect: .12 crocin cin(20mg/kg) stotal (95% CI) erogeneity: Tau ² = it for overall effect: .1 crocin	plicable Z = 6.25 (F 293 332 0.61; Chi ² + Z = 3.54 (F 368.5 285.8 4.41; Chi ² + Z = 0.97 (F	25 27 = 2.21, c = 0.000 25.14 77.94 = 4.47, c = 0.33)	9 9 18 3f = 1 ()4) 4 4 8 df = 1 (247 247 P = 0.14 274.94 274.94 P = 0.03	19 19); I ² = 55 20.63 20.63); I ² = 78	9 9 18 % 4 4 8 %	5.3% 4.4% 9.8% 2.4% 4.9% 7.3%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34] 0.17 [-1.22, 1.56] 1.62 [-1.65, 4.90]	
ygonin biototal (95% CI) sterogeneity: Not ap st for overall effect: 1.10 Curcumin ircumin(100 mg/kg) biototal (95% CI) terogeneity: Tau ² = st for overall effect: 1.11 crocin scin(20mg/kg) biototal (95% CI) terogeneity: Tau ² = st for overall effect: tal (95% CI)	plicable Z = 6.25 (F 293 332 0.61; Chi ² Z = 3.54 (F 368.5 285.8 4.41; Chi ² Z = 0.97 (F	25 27 = 2.21, c = 0.000 25.14 77.94 = 4.47, c = 0.33)	9 9 18 3f = 1 ()4) 4 4 8 3f = 1 (171	247 247 P = 0.14 274.94 274.94 P = 0.03	19 19); I ² = 55 20.63 20.63); I ² = 78	9 9 18 % 4 4 8 %	5.3% 4.4% 9.8% 2.4% 4.9% 7.3%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34] 0.17 [-1.22, 1.56] 1.62 [-1.65, 4.90]	
ygonin btotal (95% CI) terogeneity: Not ap st for overall effect: .10 Curcumin rcumin(100 mg/kg) total (95% CI) terogeneity: Tau ² = st for overall effect: .11 crocin cin(10mg/kg) btotal (95% CI) terogeneity: Tau ² = st for overall effect: tal (95% CI) terogeneity: Tau ² =	plicable Z = 6.25 (F 293 332 0.61; Chi ² : Z = 3.54 (F 368.5 285.8 4.41; Chi ² : Z = 0.97 (F	25 27 = 2.21, c = 0.000 25.14 77.94 = 4.47, c = 0.33) = 73.10,	9 9 18 df = 1 ()4) 4 4 8 df = 1 (171 df = 1	247 247 P = 0.14 274.94 274.94 P = 0.03	19 19); I ² = 55 20.63 20.63); I ² = 78 00001);	9 9 18 % 4 4 8 % 170 1 ² = 74	5.3% 4.4% 9.8% 2.4% 4.9% 7.3% 100.0%	1.97 [0.80, 3.15] 3.47 [1.89, 5.05] 2.62 [1.17, 4.08] 3.54 [0.74, 6.34] 0.17 [-1.22, 1.56] 1.62 [-1.65, 4.90]	

FIGURE 4

Effects of TCM on body weight(g). Forest plots of the effect size were calculated using SMDs. The horizontal error bars represent the 95% confidence interval of individual studies.

analysis (Figure 8). The combined results demonstrated a significant reduction in total cholesterol levels with TCM usage [SMD = -1.51 (-1.98,-1.04), p < 0.00001; 20 comparisons) but with marked

heterogeneity between studies ($\chi^2 = 64.60$; $I^2 = 71\%$; df = 19; p < 0.00001). Subgroup analysis indicated a significant correlation (p < 0.00001). Whereas QGYY and Rutin showed similar efficacy to

		Drug			Model			Std Maan Difference	Std. Moon Difference
Study or Subgroup	Mean	SD SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.1.1 triptolide									
triptolide(100µg/kg)	3.2	0.08	10	3.5	0.11	10	5.8%	-2.99 [-4.34, -1.63]	
triptolide(200µg/kg)	3.1	0.06	10	3.5	0.11	10	4.6%	-4.32 [-6.06, -2.59] -1.00 [-1.94, -0.05]	
Subtotal (95% CI)	0.1	0.00	30	0.0	0.11	30	17.9%	-2.67 [-4.62, -0.71]	
Heterogeneity: Tau ² = 2 Test for overall effect: Z	.51; Chi² : = 2.67 (P	= 13.25, df = 0.008)	= 2 (P	= 0.001); I² = 85%				
2.1.2 SSYX									
SSYX(100mg/kg)	0.34	0.02	5	0.41	0.03	5	4.3%	-2.48 [-4.35, -0.61]	
SSYX(200mg/kg)	0.32	0.02	5	0.41	0.03	5	3.5%	-3.19 [-5.37, -1.01]	
SSYX(50mg/kg) Subtotal (95% Cl)	0.35	0.02	5 15	0.41	0.03	5 15	4.7% 12.4%	-2.13 [-3.85, -0.40] -2.52 [-3.61, -1.42]	•
Heterogeneity: $Tau^2 = 0$.00; Chi² :	= 0.56, df =	2 (P =	= 0.75); I	² = 0%			[,]	
Test for overall effect: Z	= 4.50 (P	< 0.00001)						
2.1.3 DJC									
DJC(1080mg/kg)	2.65	0.25	15	3.45	0.25	12	6.5%	-3.10 [-4.28, -1.93]	
DJC(270mg/kg)	2.89	0.28	14	3.45	0.25	12	7.3%	-2.03 [-3.01, -1.06]	
Subtotal (95% CI)	2.71	0.22	42	5.45	0.25	36	20.2%	-2.65 [-3.37, -1.93]	◆
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.08; Chi² : = 7.23 (P	= 2.51, df = < 0.00001	: 2 (P :)	= 0.28); I	² = 20%				
2 1 4 YOHX									
YQHX	2.76	0.29	6	3.09	0.05	5	5.7%	-1.38 [-2.77, 0.01]	
Subtotal (95% CI)			6			5	5.7%	-1.38 [-2.77, 0.01]	
Heterogeneity: Not appl Test for overall effect: Z	icable = 1.95 (P	= 0.05)							
2.1.5 Dioscin									
Dioscin(100µg/kg)	3.07	0.21	10	3.27	0.33	10	7.6%	-0.69 [-1.60, 0.22]	
Dioscin(200µg/kg)	3.01	0.25	10	3.27	0.33	10	7.5%	-0.85 [-1.78, 0.07]	•
Heterogeneity: $Tau^2 = 0$.00; Chi ² :	= 0.06, df =	: 1 (P :	= 0.81); I	² = 0%	20	13.176	-0.77 [-1.42, -0.12]	•
l est for overall effect: Z	= 2.33 (P	= 0.02)							
2.1.6 DOE									
DOE(150mg/kg)	0.3377	0.02007	8	0.3929	0.02475	8	5.9%	-2.32 [-3.66, -0.97]	
DOE(300mg/kg) DOE(75mg/kg)	0.3266	0.01523	8	0.3929	0.02475	8	5.1%	-3.05 [-4.61, -1.49] -1 67 [-2 85 -0 48]	
Subtotal (95% CI)	0.0002	0.01001	24	0.0020	0.02110	24	17.5%	-2.22 [-2.99, -1.45]	◆
Heterogeneity: Tau ² = 0	.00; Chi² :	= 1.94, df =	2 (P =	= 0.38); I	² = 0%				
Test for overall effect: Z	= 5.63 (P	< 0.00001)						
2.1.7 Curcumin									
Curcumin(100 mg/kg)	3.52	0.16	9	4.05	0.28	9	6.3%	-2.21 [-3.45, -0.98]	
Curcumin(200 mg/kg)	3.21	0.12	9 18	4.05	0.28	9 18	4.9%	-3.71 [-5.37, -2.06]	
Heterogeneity: $Tau^2 = 0$.57: Chi ² :	= 2.03. df =	: 1 (P :	= 0.15):	² = 51%	10	11.170	-2.00 [-4.01, -1.40]	
Test for overall effect: Z	= 3.85 (P	= 0.0001)	. (.	,,					
Total (95% CI)			155			148	100.0%	-2.23 [-2.74, -1.72]	•
Heterogeneity: Tau ² = 0	.67; Chi² :	= 42.15, df	= 16 (P = 0.00	04); l² = 62	%		_	
Test for overall effect: Z	= 8.58 (P	< 0.00001) df = 6	(P = 0.0	02) 12 - 70	8%			Favours [Model] Favours [Drug]
rescion subdroup differe	ences: Un	i = 20.54.	ui – 0	u= = 0.0	021. 1° = 70	.0 /6			
FIGURE 5	DW//max			fthe off	loot ding	orc = -	المعاملات الما	icing CMDe The heri-	tal arror bars represent the OF% as a fideras
interval of individual st	bw(mg/g	y). ⊦orest p	DIOTS C	n the eff	ect size w	ere ca	iculated u	ising SMUs. The horizon	ital error bars represent the 95% confidence

the control group (p = 0.50, p = 0.17, respectively), the other TCM had a more pronounced effect on reducing TC levels than the control group (p < 0.05). The forest map revealed that DJC was more effective.

3.3.6 Efficacy of TCM on left ventricular internal dimension in systole

Six studies involving 127 animals (63 in the TCM group and 64 in the control group) measured the left ventricular internal dimension in systole (LVIDs) and were included in the

meta-analysis (Figure 9). The pooled results demonstrated that TCM had no significant effect on LVIDs [SMD = -0.54 (-1.42, 0.33), p = 0.22; 9 comparisons] Moreover, there was significant heterogeneity among the studies ($\chi^2 = 37.54$; $I^2 = 79\%$; df = 8; p < 0.00001). Subgroup analysis showed significant correlations (p < 0.00001). Myricetin and wogonin significantly reduced LVIDs compared to controls (p < 0.001). The forest plot indicated that myricetin had the most significant effect on reducing LVIDs.

Study or Subgroup	Mean	Drug SD	Total	Mean	Nodel SD	Total	Weight	Std. Mean Difference IV. Random. 95% Cl	Std. Mean Difference IV. Random. 95% Cl
DJC(1080mg/kg)	13.17	2.45	15	18.65	3.89	12	4.5%	-1.68 [-2.58, -0.78]	-
DJC(270mg/kg)	13.5	2.27	14	18.65	3.89	12	4.5%	-1.60 [-2.50, -0.70]	-
DJC(540mg/kg) Subtotal (95% CI)	13.24	2.96	13 42	18.65	3.89	12 36	4.5%	-1.52 [-2.43, -0.61] -1.60 [-2.12, -1.08]	•
Heterogeneity: Tau ² = 0	.00; Chi ²	= 0.06, d	f = 2 (F	P = 0.97)	; I ² = 0%			,	
Test for overall effect: Z	= 6.01 (F	^o < 0.000	01)						
3.1.2 FTZ	24 54	2	4	20.69	0.40		2.09/	2.01 (2.07	
Subtotal (95% CI)	24.54	Z	4	29.68	2.43	4	3.0%	-2.01 [-3.97, -0.05]	•
Heterogeneity: Not appl	icable								
Test for overall effect: Z	. = 2.01 (F	P = 0.04)							
3.1.3 YQHX									
YQHX Subtotal (95% CI)	27.28	0.77	6	31.07	1.27	5	2.8%	-3.39 [-5.52, -1.26] -3.39 [-5.52, -1.26]	•
Heterogeneity: Not appl	icable								
Test for overall effect: Z	= 3.12 (F	P = 0.002)						
3.1.4 THJ									
THJ(0.125g/kg)	20.14	1.76	7	24.91	2.71	7	3.9%	-1.95 [-3.31, -0.60]	
THJ(0.25g/kg) THJ(0.5a/ka)	18.32	1.15	7	24.91	2.71	7	3.4%	-2.96 [-4.63, -1.30] -2.91 [-4.56, -1.26]	<u> </u>
Subtotal (95% CI)			21			21	10.7%	-2.52 [-3.40, -1.63]	•
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.00; Chi ² = 5.57 (F	= 1.16, d > < 0.000	f = 2 (F 01)	P = 0.56)	; l ² = 0%				
	- 0.07 (1	- 0.000	01)						
3.1.5 Nar	05.40	4.00	0	00.0	1.01	0	0.70/	0.04 (4.00 4.00)	
Nar(25mg/kg)	27.53	1.97	8	28.8	1.01	8	4.3%	-0.77 [-1.79, 0.26]	
Nar(50mg/kg)	26	0.72	8	28.8	1.01	8	3.6%	-3.02 [-4.57, -1.47]	
Subtotal (95% CI) Heterogeneity: Tau ² - 1	41 Chi2	= 8 02 4	24 f = 2 /1	P = 0 02	· 2 = 75%	24	11.6%	-2.11 [-3.67, -0.55]	—
Test for overall effect: Z	= 2.66 (F	P = 0.008	. – 2 (r)	- 0.02)	, 1 - 10%				
3 1 6 DOE	,								
DOE(150ma/ka)	19.2	4.71	8	23.8	2.39	8	4.2%	-1.16 [-2.250.08]	-
DOE(300mg/kg)	19.7	3.4	8	23.8	2.39	8	4.2%	-1.32 [-2.43, -0.21]	-
DOE(75mg/kg) Subtotal (95% Cl)	24	1.98	8 24	23.8	2.39	8 24	4.4%	0.09 [-0.89, 1.07]	•
Heterogeneity: Tau ² = 0	.34; Chi ²	= 4.35, d	f = 2 (F	P = 0.11)	; l² = 54%				
Test for overall effect: Z	= 1.67 (F	P = 0.09)							
3.1.7 Myricetin									
Myricetin	25.3	3.45	16	27.1	2.33	16	4.7%	-0.60 [-1.31, 0.11]	7
Subtotal (95% CI)	icabla		16			16	4.7%	-0.60 [-1.31, 0.11]	•
Test for overall effect: Z	= 1.64 (F	P = 0.10)							
2.4.9 Manania									
Woqonin	13	2.389	16	21.5	3.61	16	4.4%	-2.71 [-3.70, -1.72]	
Subtotal (95% CI)			16			16	4.4%	-2.71 [-3.70, -1.72]	•
Heterogeneity: Not appl Test for overall effect: 7	icable	2 < 0.000	01)						
	- 0.00 (i	- 0.000	01)						
3.1.9 AA	47.040	0 770	40	04.004	4 0000	40	4 40/	4 70 (0.00 0 77)	-
AA(400mg/kg) AA(800ma/ka)	17.312	2.778	12	21.094	1.0983	12	4.4%	-1.73 [-2.69, -0.77] -0.67 [-1.49, 0.16]	
Subtotal (95% CI)			24			24	9.0%	-1.17 [-2.21, -0.13]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 7	.35; Chi ²	= 2.69, d	f = 1 (F	P = 0.10)	; l ² = 63%	•			
resciol overall effect. 2	- 2.21 (1	= 0.03)							
3.1.10 cornelian cherry	y	4 470	-	00 544	7.40	-	0.00/	0.00/5.04 4.001	
cornelian cherry Subtotal (95% CI)	5.262	4.478	7	30.514	7.49	7	3.0%	-3.83 [-5.81, -1.86] -3.83 [-5.81, -1.86]	•
Heterogeneity: Not appl	icable								
Test for overall effect: Z	= 3.80 (F	P = 0.000	1)						
3.1.11 Berberine									
Berberine	7.6	1.25	8	12.6	0.57	8	2.8%	-4.87 [-7.04, -2.69]	—
Heterogeneity: Not appl	icable		8			8	2.8%	-4.87 [-7.04, -2.69]	-
Test for overall effect: Z	= 4.38 (F	o < 0.000	1)						
3.1.12 triptolide									
triptolide(100µa/ka)	27.6	5.7	10	28.2	3	10	4.5%	-0.13 [-1.00, 0.75]	+
triptolide(200µg/kg)	29	3.1	10	28.2	3	10	4.5%	0.25 [-0.63, 1.13]	+
triptolide(50µg/kg)	25.8	6.9	10	28.2	3	10	4.5%	-0.43 [-1.32, 0.46]	-
Heterogeneity: Tau ² = 0	.00; Chi ²	= 1.15, d	f = 2 (F	P = 0.56)	; I² = 0%	50		0.10[-0.01, 0.41]	1
Test for overall effect: Z	= 0.39 (F	P = 0.70)		,					
3.1.13 Mangiferin									
Mangiferin	8.4	0.7	8	19.3	1.2	8	1.2%	-10.49 [-14.79, -6.19]	
Subtotal (95% CI)	licable		8			8	1.2%	-10.49 [-14.79, -6.19]	
Test for overall effect: Z	= 4.78 (F	o < 0.000	01)						
2444.0002	C.								
3.1.14 QGTY QGYY	19.32	1.26	5	28 46	1.41	5	1.5%	-6.17 [-9.86 -2.48]	
Subtotal (95% CI)	.0.02		5	20.40		5	1.5%	-6.17 [-9.86, -2.48]	
Heterogeneity: Not appl	icable	- 0.001	Ň						
est for overall effect: Z	. = 3.28 (F	- = 0.001)						
3.1.15 Curcumin									
Curcumin(100 mg/kg)	13.1	2.2	9	20.6	1.6	9	3.4%	-3.71 [-5.37, -2.06]	
Subtotal (95% CI)	0.7	1.1	18	20.0	1.0	18	5.7%	-5.10 [-8.17, -2.03]	•
Heterogeneity: Tau ² = 3	.66; Chi ²	= 3.81, d	f = 1 (F	P = 0.05)	; l² = 74%	,			
rest for overall effect: Z	. = 3.26 (F	- = 0.001)						
Total (95% CI)			253			246	100.0%	-2.01 [-2.54, -1.47]	• • • • • • • • • • • • • • • • • • •
Heterogeneity: Tau ² = 1	.44; Chi2	= 133.28	, df = 2	26 (P < 0	.00001); I	² = 80 ⁹	%		-10 -5 0 5 10
Test for subaroup different	ences: Ch	ni ² = 94.5	4. df =	14 (P <	0.00001).	² = 85	5.2%		Favours [Model] Favours [Drug]

FIGURE 6

Effects of TCM on blood glucose (mmol/L). Forest plots of the effect size were calculated using SMDs. The horizontal error bars represent the 95% confidence interval of individual studies.

Study or Subgroup	Mean	Drug SD	Total	Mean	Model SD	Total	Weight	Std. Mean Difference IV. Random, 95% Cl	Std. Mean Difference IV. Random, 95% Cl
4.1.1 Berberine							-		
Berberine Subtotal (95% CI)	0.122	0.027	8 8	0.217	0.034	8 8	5.7% 5.7%	-2.93 [-4.45, -1.40] - 2.93 [-4.45, -1.40]	
Heterogeneity: Not app	licable								
Test for overall effect: 2	2 = 3.76	(P = 0.00	02)						
4.1.2 Mangiferin									
Mangiferin	1.4	0.3	8	1.9	0.2	8	6.9%	-1.85 [-3.08, -0.63]	
Heterogeneity: Not ann	licablo		0			0	0.9%	-1.05 [-3.00, -0.03]	
Test for overall effect: 2	Z = 2.96	(P = 0.00	3)						
4.1.3 SSYX									
SSYX(100mg/kg)	1.68	0.0426	5	1.987	0.1273	5	4.0%	-2.92 [-4.98, -0.86]	
SSYX(200mg/kg)	1.835	0.0697	5	1.987	0.1273	5	6.0%	-1.34 [-2.79, 0.11]	
SSYX(50mg/kg)	1.685	0.0538	15	1.987	0.1273	15	4.2%	-2.79 [-4.79, -0.79]	•
Heterogeneity: $Tau^2 = ($	0.06. Chi	2 = 2.13	df = 2	P = 0.3	$(4) \cdot ^2 = 60$	15	14.2 /0	-2.12 [-3.10, -1.00]	
Test for overall effect: 2	z = 3.93	(P < 0.00	01)	(F = 0.5	4), 1 – 0	70			
4.1.4 THJ									
THJ(0.125g/kg)	3.81	0.43	7	4.12	0.52	7	7.6%	-0.61 [-1.69, 0.47]	
THJ(0.25g/kg)	3.15	0.38	7	4.12	0.52	7	6.3%	-1.99 [-3.36, -0.63]	
THJ(0.5g/kg) Subtotal (95% CI)	2.14	0.31	21	4.12	0.52	21	3.8%	-4.33 [-6.49, -2.17]	
Heterogeneity: $Tau^2 = 2$	2 12· Chi	2 = 0.67	df = 21	P = 0.0	08)· I ² = 7	Z1 70%	17.770	-2.11[-3.90, -0.24]	
Test for overall effect: 2	2 = 2.21	(P = 0.03)	() ()	(i = 0.0	00), 1 = 1	070			
4.1.5 DOE									
DOE(150mg/kg)	2.638	0.708	8	4.68	0.716	8	5.9%	-2.71 [-4.17, -1.25]	
DOE(300mg/kg)	2.207	0.529	8	4.68	0.716	8	4.8%	-3.71 [-5.49, -1.94]	
DOE(75mg/kg)	3.094	0.918	8	4.68	0.716	8	6.9%	-1.82 [-3.04, -0.60]	
Heterogeneity: $Tau^2 = ($	30. Chi	2 = 3.06	∠4 df = 2 /	P = 0.2	$2) \cdot ^2 = 3^4$	24 5%	17.770	-2.00 [-3.04, -1.55]	•
Test for overall effect: 2	z = 4.88	(P < 0.00	001)	(r – 0.2	2), 1 – 3.	J 70			
4.1.6 QGYY									
QGYY	1.34	0.42	5	1.98	0.4	5	5.9%	-1.41 [-2.88, 0.06]	
Subtotal (95% CI)			5			5	5.9%	-1.41 [-2.88, 0.06]	
Heterogeneity: Not app Test for overall effect: 2	licable Z = 1.88	(P = 0.06)						
4.1.7 Curcumin									
Curcumin(100 mg/kg)	1.08	0.08	9	1.19	0.14	9	8.0%	-0.92 [-1.90, 0.07]	
Curcumin(200 mg/kg)	0.85	0.11	9	1.19	0.14	9	6.5%	-2.57 [-3.90, -1.25]	
Subtotal (95% CI)			18			18	14.5%	-1.68 [-3.30, -0.07]	
Heterogeneity: Tau ² = ² Test for overall effect: 2	1.01; Chi Z = 2.04	^{i²} = 3.85, (P = 0.04	df = 1 ()	(P = 0.0	5); l² = 74	4%			
4.1.8 AA									
AA(400ma/ka)	4,659	0.6206	12	5,439	0.661	12	8.5%	-1,17 [-2.050.30]	
AA(800mg/kg)	5.097	0.868	12	5.439	0.661	12	8.9%	-0.43 [-1.24, 0.38]	
Subtotal (95% CI)			24			24	17.4%	-0.78 [-1.51, -0.05]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.09; Chi Z = 2.10	^{i²} = 1.50, (P = 0.04	df = 1 ()	(P = 0.2	2); I² = 33	3%			
Total (95% CI)			123			123	100.0%	-1 87 [-2 39 -1 36]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 2 Test for subaroup differ).61; Chi Z = 7.12 ences: (i² = 36.50 (P < 0.00 Chi² = 12.	, df = 1 001) 39. df =	5 (P = (= 7 <i>(</i> P =	0.001); l² 0.09). l²	= 59% = 43.5%	6	-1.01 [2.00, -1.00]	-4 -2 0 2 4 Favours [Model] Favours [Drug]
EICLIPE 7									
Effects of TCM on trig	lyceride	(mmol/l	_). Fore	est plot	s of the e	effect s	ize were	e calculated using SMDs.	The horizontal error bars represent the 95%
connucrice interval Of	manviut	ar stuule							

3.3.7 Efficacy of TCM on ejection fraction

For the ejection fraction, 8 studies (218 animals, 109 were in the TCM group and 109 were in the control group) were included in the meta-analysis (Figure 10). The aggregated results show that TCM significantly increased the ejection fraction [SMD = 2.79 (2.39,3.20), p < 0.00001; 11 comparisons], with moderate heterogeneity between studies (χ^2 = 16.10; I² = 38%; df = 10; p = 0.12). When analyzed with TCM as a subgroup, the difference was not statistically significant (p = 0.05), and all drugs increased the

study or Subgroup	Mean	Drug	Total	Moor	Model	Total	Moinht	N Pandom 05% O	N Rendem 05% C
4 4 0 0 0 0	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
5.1.1 SSYX									
SSYX(100mg/kg)	5.549	0.1984	5	6.094	0.7631	5	4.7%	-0.88 [-2.22, 0.45]	
SSYX(200mg/kg)	5.11	0.3894	5	6.094	0.7631	5	4.3%	-1.47 [-2.96, 0.02]	
SSYX(50mg/kg)	5.915	0.5082	5	6.094	0.7631	5	4.9%	-0.25 [-1.50, 1.00]	
Subtotal (95% CI)			15			15	13.8%	-0.80 [-1.57, -0.02]	\bullet
Heterogeneity: Tau ² = (0.00: Chi ²	= 1.53. d	f = 2(P = 0.46	5): $I^2 = 09$	6			
Test for overall effect: 2	Z = 2.01 (P = 0.04)	- (,,	-			
	(,							
5.1.2 DJC									
$D \left[C \left(1090 m a / k a \right) \right]$	1 64	0.22	15	2 42	0.20	10	E 10/	2 00 [4 26 1 02]	
DJC(1080111g/kg)	1.04	0.22	15	2.43	0.20	12	5.1%	-3.09 [-4.20, -1.92]	
DJC(270mg/kg)	1.96	0.17	14	2.43	0.28	12	5.6%	-2.00 [-2.98, -1.03]	
DJC(540mg/kg)	1.83	0.25	13	2.43	0.28	12	5.5%	-2.19 [-3.22, -1.16]	
Subtotal (95% CI)			42			36	16.2%	-2.36 [-2.98, -1.74]	•
Heterogeneity: Tau ² = 0	0.01; Chi ²	= 2.10, d	f = 2 (P = 0.35	5); l² = 5%	6			
Test for overall effect: 2	Z = 7.47 (P < 0.000	01)						
5.1.3 DOE									
DOE(150ma/ka)	3 167	0.339	8	3 793	0 279	8	4 9%	-1 91 [-3 15 -0 67]	
DOE(300 mg/kg)	2 788	0.48	9	3 703	0.270	8	1.6%	2 42 [3 80 1 04]	
DOE(300mg/kg)	2.700	0.40	0	0.700	0.279	0	4.0 /0	-2.42 [-3.60, -1.04]	
	3.480	0.502	8	3.793	0.279	8	5.5%	-0.71 [-1.74, 0.31]	
Subtotal (95% CI)			24			24	15.0%	-1.60 [-2.63, -0.57]	•
Heterogeneity: Tau ² = 0	0.45; Chi ^a	= 4.40, d	t = 2 ($P = 0.1^{\circ}$	1); $I^2 = 55$	5%			
Test for overall effect: 2	Z = 3.04 (P = 0.002	2)						
5.1.4 QGYY									
QGYY	2.24	0,36	5	2,41	0.35	5	4.8%	-0.43 [-1.70, 0.83]	-+-
Subtotal (95% CI)		0.00	5		0.00	5	4.8%	-0.43 [-1.70, 0.83]	◆
Hotorogonoity: Not ann	licoblo		-			-			
Telefogeneity. Not app									
l est for overall effect: 2	2 = 0.67 (P = 0.50)							
5.1.5 Rutin									
Rutin	6.806	0.196	6	8.583	2.729	6	5.0%	-0.85 [-2.05, 0.36]	
Subtotal (95% CI)			6			6	5.0%	-0.85 [-2.05, 0.36]	\bullet
Heterogeneity: Not app	licable								
Test for overall effect:	7 = 1.38 (P = 0.17							
	_ 1.00 (0.17)							
51644									
A (400mm ///m)	2 000	0 464	10	4 4 2 0	0.007	10	E 20/	2 47 [2 59 4 26]	
AA(400mg/kg)	3.069	0.464	12	4.139	0.367	12	5.3%	-2.47 [-3.58, -1.36]	
AA(800mg/kg)	3.534	0.306	12	4.139	0.367	12	5.7%	-1 73 [-2 69 -0 77]	
Subtotal (95% CI)								-1.75 [-2.05, -0.77]	
			24			24	10.9%	-2.05 [-2.77, -1.32]	◆
Heterogeneity: Tau ² = 0	0.00; Chi ²	= 0.98, d	24 f = 1 (P = 0.32	2); I² = 0%	24	10.9%	-2.05 [-2.77, -1.32]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.00; Chi ² Z = 5.53 (= 0.98, d P < 0.000	24 f = 1(01)	P = 0.32	2); I² = 0%	24 %	10.9%	-2.05 [-2.77, -1.32]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.00; Chi ² Z = 5.53 (= 0.98, d P < 0.000	24 lf = 1 (01)	P = 0.32	2); I² = 0%	24 %	10.9%	-2.05 [-2.77, -1.32]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 2 5.1.7 Berberine	0.00; Chi ^a Z = 5.53 (e = 0.98, d P < 0.000	24 lf = 1 (01)	P = 0.32	2); I² = 0%	24	10.9%	-2.05 [-2.77, -1.32]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine	0.00; Chi ^a Z = 5.53 (1.4	e = 0.98, d P < 0.000 0.23	24 lf = 1 (01) 8	P = 0.32 2.6	2); I² = 0% 0.12	24 % 8	2.2%	-6.18 [-8.84, -3.53]	◆
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI)	0.00; Chi ^a Z = 5.53 (1.4	= 0.98, d P < 0.000 0.23	24 lf = 1 (101) 8 8	P = 0.32 2.6	2); I² = 0% 0.12	24 % 8 8	10.9% 2.2% 2.2%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app	0.00; Chi ^a Z = 5.53 (1.4	e = 0.98, d P < 0.000 0.23	24 lf = 1 (01) 8 8	P = 0.32 2.6	2); I² = 09 0.12	24 % 8 8	10.9% 2.2% 2.2%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall offect	0.00; Chi ² Z = 5.53 (1.4 plicable	= 0.98, d P < 0.000 0.23	24 If = 1 (001) 8 8	P = 0.32 2.6	2); I² = 0% 0.12	24 % 8 8	10.9% 2.2% 2.2%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (= 0.98, d P < 0.000 0.23 P < 0.000	24 lf = 1 (101) 8 8 8	P = 0.32 2.6	2); I ² = 09 0.12	24 % 8 8	10.9% 2.2% 2.2%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5 4 9 krieterit	0.00; Chi ^a Z = 5.53 (1.4 blicable Z = 4.56 (= 0.98, d P < 0.000 0.23 P < 0.000	24 If = 1 (101) 8 8 8	P = 0.32 2.6	2); I ² = 09 0.12	24 % 8 8	10.9% 2.2% 2.2%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide	0.00; Chi ^a Z = 5.53 (1.4 blicable Z = 4.56 (= 0.98, d P < 0.000 0.23 P < 0.000	24 If = 1 (101) 8 8 101)	P = 0.32 2.6	2); I ² = 09 0.12	24 % 8 8	10.9% 2.2% 2.2%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4	= 0.98, d P < 0.000 0.23 P < 0.000 2.2	24 If = 1 (101) 8 8 101) 10	P = 0.32 2.6 6.9	2); I ² = 0% 0.12 0.9	24 % 8 8 8	10.9% 2.2% 2.2% 5.9%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53]	• •
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(200µg/kg)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2	F = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2	24 If = 1 (101) 8 8 8 101) 10 10	P = 0.32 2.6 6.9 6.9	2); I ² = 0% 0.12 0.9 0.9	24 % 8 8 8 10 10	10.9% 2.2% 2.2% 5.9% 5.9%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49]	•
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(50µg/kg)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6	F = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1	24 If = 1 (101) 8 8 8 101) 10 10 10	P = 0.32 2.6 6.9 6.9 6.9 6.9	2); I ² = 0% 0.12 0.9 0.9 0.9 0.9	24 % 8 8 10 10 10	10.9% 2.2% 2.2% 5.9% 5.9% 5.9%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.49]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(200µg/kg) triptolide(50µg/kg) Subtotal (95% CI)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6	F = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1	24 If = 1 (101) 8 8 101) 10 10 10 30	P = 0.32 2.6 6.9 6.9 6.9	2); I ² = 09 0.12 0.9 0.9 0.9	24 % 8 8 10 10 10 30	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ²	F = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 F = 0.12 d	24 If = 1 (101) 8 8 101) 10 10 10 30 If = 2 (P = 0.32 2.6 6.9 6.9 6.9 P = 0.9	2); $ ^2 = 0$? 0.12 0.9 0.9 0.9 1): $ ^2 = 0$?	24 % 8 8 8 10 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(50µg/kg) Subtotal (95% CI) ² = (Test for overall effect =	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (P = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 r = 0.12, d P = 0.27	24 If = 1 (001) 8 8 001) 10 10 10 30 If = 2 (P = 0.32 2.6 6.9 6.9 6.9 P = 0.94	2); I ² = 09 0.12 0.9 0.9 0.9 0.9	24 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (Topug/kg) triptolide(200µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (P = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 T = 0.12, d P = 0.27)	24 If = 1 (001) 8 8 001) 10 10 10 30 If = 2 (P = 0.32 2.6 6.9 6.9 6.9 8.9 P = 0.94	2); ² = 0? 0.12 0.9 0.9 0.9 0.9 1; ² = 0?	24 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.49] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2 5.1.9 Mangiforin	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (P < 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 = 0.12, d P = 0.27)	24 If = 1 (001) 8 8 8 001) 10 10 10 30 If = 2 (P = 0.32 2.6 6.9 6.9 6.9 6.9 P = 0.94	2); ² = 09 0.12 0.9 0.9 0.9 4); ² = 09	24 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 = 0.12, d P = 0.27)	24 ff = 1 (001) 8 8 8 100 100 100 100 300 ff = 2 (P = 0.32 2.6 6.9 6.9 P = 0.94	2); ² = 09 0.12 0.9 0.9 0.9 4); ² = 09	24 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(50µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1	P = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 T = 0.12, d P = 0.27) 0.3	24 if = 1 (001) 8 8 001) 10 10 10 10 30 if = 2 (8 8	P = 0.32 2.6 6.9 6.9 6.9 P = 0.94 4.5	2); l ² = 09 0.12 0.9 0.9 0.9 0.9 4); l ² = 09 0.4	24 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1	= 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.1 = 0.12, d P = 0.27) 0.3	24 If = 1 (001) 8 8 001) 10 10 10 10 10 10 10 10 10 10	P = 0.32 2.6 6.9 6.9 6.9 P = 0.94 4.5	2); l ² = 09 0.12 0.9 0.9 0.9 4); l ² = 09 0.4	24 8 8 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.40] -0.40	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable	P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 F = 0.12, d P = 0.27) 0.3	24 if = 1 (001) 8 8 10 10 10 10 10 30 if = 2 (8 8 8	P = 0.32 2.6 6.9 6.9 P = 0.94 4.5	2); I ² = 09 0.12 0.9 0.9 0.9 0.9 4); I ² = 09 0.4	24 8 8 8 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(50µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (P < 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.1 2.2 2.1 2.2 2.1 P = 0.12, d P = 0.27 0.3 P < 0.000	24 If = 1 (001) 8 8 101) 10 10 10 10 10 10 10 10 10 10	P = 0.32 2.6 6.9 6.9 6.9 6.9 6.9 P = 0.94 4.5	2); ² = 09 0.12 0.9 0.9 0.9 1 ² = 09 0.4	24 % 8 8 8 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (P < 0.98, d $P < 0.000$ 0.23 $P < 0.000$ 2.2 2.2 2.1 $P = 0.12, d$ $P = 0.27)$ 0.3 $P < 0.000$	24 If = 1 (101) 8 8 101) 10 10 10 10 10 10 10 10 10 10	P = 0.32 2.6 6.9 6.9 6.9 P = 0.94 4.5	2); l ² = 09 0.12 0.9 0.9 0.9 4); l ² = 09 0.4	24 % 8 8 8 8 8 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 F = 0.12, d P = 0.27) 0.3 P < 0.000	24 if = 1 (1001) 8 8 1001) 100 100 100 100 300 if = 2 (8 8 8 11)	P = 0.3; 2.6 6.9 6.9 6.9 6.9 8.9 9 8.9 4.5	2); ² = 09 0.12 0.9 0.9 0.9 4); ² = 09 0.4	24 % 8 8 8 8 8 8 8 8 8 8 8	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(200µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mo/kg)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (1.35	P < 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.1 2.2 2.2 2.1 2.2 2.2 2.1 2.2 2.2 2.1 2.2 2.2 2.1 2.2 2.2 2.1 2.2 2.1 0.3 P < 0.0000 0.11	24 If = 1 (1001) 8 8 8 1001) 10 10 10 10 10 10 10 10 10 10	P = 0.32 2.6 6.9 6.9 6.9 6.9 6.9 4.5 4.5	2); ² = 09 0.12 0.9 0.9 0.9 4); ² = 09 0.4	24 % 8 8 8 8 8 10 10 10 10 30 %	10.9% 2.2% 2.2% 5.9% 5.9% 5.9% 17.6% 3.6% 3.6% 3.6%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = 1 Test for overall effect: 2 5.1.9 Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Curcumin(200 mg/kg)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ³ Z = 1.10 (3.1 blicable Z = 4.11 (1.35 1 20	P < 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.2 2.1 P = 0.12, d P = 0.27 0.3 P < 0.000 0.11 0.23	24 if = 1 (101) 8 8 8 101) 10 10 10 10 10 10 10 10 10 10	P = 0.3% 2.6 6.9 6.9 6.9 6.9 6.9 7.49 4.5	2); $ ^2 = 0$? 0.12 0.9 0.9 0.9 1); $ ^2 = 0$? 0.4 0.07 0.27	24 % 8 8 8 8 8 8 8 8 8 8 8 9 9	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6%	-0.28 [-1.77, -1.32] -0.28 [-2.77, -1.32] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.49] -0.40 [-2.53, -1.96] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(200 mg/kg) Curcumin(200 mg/kg)	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (1.35 1.39	P < 0.98, d $P < 0.000$ 0.23 $P < 0.000$ 2.2 2.2 2.1 $F = 0.12, d$ $P = 0.27$ 0.3 $P < 0.000$ 0.11 0.08	24 if = 1 (001) 8 8 8 100 10 10 10 10 10 10 10 10 1	P = 0.3; 2.6 6.9 6.9 6.9 P = 0.9; 4.5 1.49 1.49	2); l ² = 09 0.12 0.9 0.9 0.9 4); l ² = 09 0.4 0.4	24 % 8 8 8 8 8 8 8 8 8 8 8 8 9 9 9	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.4% 5.5%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.36 [-0.00, 0.21]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Curcumin(200 mg/kg) Subtotal (95% CI)	0.00; Chiř Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chiř Z = 1.10 (3.1 blicable Z = 4.11 (1.35 1.39	P < 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.1 2.2 2.1 2.2 2.1 2.2 2.1 2.2 2.1 0.3 P < 0.000 0.11 0.08 0.00	24 if = 1 (10 10 10 10 10 10 10 10 10 10	P = 0.3% 2.6 6.9 6.9 6.9 P = 0.94 4.5 1.49 1.49	2); l ² = 09 0.12 0.9 0.9 0.9 4); l ² = 09 0.4 0.4	24 8 8 8 8 8 10 10 10 30 % 8 8 8 8 8 8 8	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.5% 10.8%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.35 [-2.10, -0.61]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(200µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (5.1.9 Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (1.35 1.39 0.00; Chi ²	P = 0.98, d P < 0.000 0.23 P < 0.000 2.2 2.1 2.2 2.1 2.2 2.1 2.2 2.1 0.3 P = 0.27 0.3 P < 0.000 0.11 0.08 = 0.06, d	24 (f = 1 ((01) 8 8 8 101) 10 10 10 10 10 10 10 10 10 10	P = 0.32 2.6 6.9 6.9 6.9 6.9 6.9 P = 0.94 4.5 1.49 P = 0.87	2); $ ^2 = 0$? 0.12 0.9 0.9 0.9 1); $ ^2 = 0$? 0.4 0.07 0.07 1); $ ^2 = 0$?	24 8 8 8 10 10 10 10 10 30 % 8 8 8 8 8 8 8 8 8 8 8 8 8	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.5% 10.8%	-1.15 [-2.05, -0.17] -2.05 [-2.77, -1.32] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.40 [-1.29, 0.49] -1.45 [-2.51, -0.38] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.35 [-2.10, -0.61]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.10 Curcumin	0.00; Chi ² Z = 5.53 (1.4 0licable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 0licable Z = 4.11 (1.35 1.39 0.00; Chi ² Z = 3.57 (P < 0.98, d $P < 0.000$ 0.23 $P < 0.000$ 2.2 2.2 2.1 $F = 0.12, d$ $P = 0.27$ 0.3 $P < 0.000$ 0.11 0.08 $F = 0.000$ $P = 0.000$	224 (f = 1 ((001) 8 8 8 (001) 10 10 10 10 10 10 10 10 10 10 10 10 10	P = 0.3; 2.6 6.9 6.9 6.9 6.9 P = 0.9; 4.5 1.49 1.49 P = 0.8;	2); $ ^2 = 0$? 0.12 0.9 0.9 1; $ ^2 = 0$? 0.4 0.07 0.07 1); $ ^2 = 0$?	24 % 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.5% 10.8%	-0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.35 [-2.10, -0.61]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Curcumin(200 mg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2	0.00; Chi ² Z = 5.53 (1.4 blicable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 blicable Z = 4.11 (1.35 1.39 0.00; Chi ² Z = 3.57 (P < 0.000 0.23 $P < 0.000$ 2.2 2.2 2.1 $= 0.12, d$ $P = 0.27)$ 0.3 $P < 0.000$ 0.11 0.08 $= 0.06, d$ $P = 0.000$	24 if = 1 (001) 8 8 8 101) 10 10 10 10 10 10 10 10 10 10	P = 0.3; 2.6 6.9 6.9 6.9 4.5 4.5 1.49 1.49 P = 0.8;	2); l ² = 09 0.12 0.9 0.9 0.9 4); l ² = 09 0.4 0.07 0.07 0.07	24 8 8 8 8 8 10 10 10 30 % 8 8 8 8 8 8 8 8 9 9 9 18	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.5% 10.8%	-6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.35 [-2.10, -0.61]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide (100µg/kg) triptolide(200µg/kg) triptolide(200µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.10 Curcumin Curcumin(200 mg/kg) Subtotal (95% CI)	0.00; Chi ² Z = 5.53 (1.4 0licable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 0licable Z = 4.11 (1.35 1.39 0.00; Chi ² Z = 3.57 (P < 0.98, d $P < 0.000$ 0.23 $P < 0.000$ 2.2 2.2 2.1 0.3 $P < 0.000$ 0.11 0.08 $P = 0.000$ $P = 0.000$	24 (if = 1 ((001) 8 8 8 (001) 10 10 10 10 10 30 0 (if = 2 (8 8 8 (1)) 9 9 18 (if = 1 ((4)) 180	P = 0.3% 2.6 6.9 6.9 6.9 6.9 6.9 P = 0.94 4.5 1.49 P = 0.8*	2); $ ^2 = 0$? 0.12 0.9 0.9 0.9 4); $ ^2 = 0$? 0.4 0.07 0.07 1); $ ^2 = 0$?	24 8 8 8 10 10 10 10 10 30 % 8 8 8 8 9 9 9 18 18 174	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.4% 5.5% 10.8%	-1.45 [-2.51, -0.38] -0.28 [-1.17, 0.60] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.35 [-2.10, -0.61]	
Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.7 Berberine Berberine Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.8 triptolide triptolide(100µg/kg) triptolide(50µg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.9 Mangiferin Mangiferin Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 5.1.10 Curcumin Curcumin(100 mg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Test for overall effect: 2 5.1.10 Curcumin Curcumin(200 mg/kg) Subtotal (95% CI) Heterogeneity: Tau ² = (Total (95% CI) Heterogeneity: Tau ² = 0	0.00; Chi ² Z = 5.53 (1.4 0licable Z = 4.56 (6.4 6.2 6.6 0.00; Chi ² Z = 1.10 (3.1 0licable Z = 4.11 (1.35 1.39 0.00; Chi ² Z = 3.57 (0.79; Chi ²	P < 0.98, d $P < 0.000$ 0.23 $P < 0.000$ 2.2 2.2 2.1 $P = 0.27)$ 0.3 $P < 0.000$ 0.11 0.08 $P = 0.000$ $P = 0.000$ $P = 0.000$	24 (if = 1 ((001) 8 8 8 1001) 100 100 100 100 100 100 1	P = 0.3; 2.6 6.9 6.9 6.9 P = 0.9; 4.5 1.49 1.49 P = 0.8; 9 (P < 0	2); l ² = 09 0.12 0.9 0.9 0.9 4); l ² = 09 0.4 0.07 0.07 1); l ² = 09	24 % 8 8 8 8 10 10 10 10 30 % 8 8 8 8 8 9 9 9 18 %	10.9% 2.2% 2.2% 5.9% 5.9% 17.6% 3.6% 3.6% 5.5% 10.8% 100.0%	-0.28 [-1.77, -1.32] -6.18 [-8.84, -3.53] -0.28 [-1.17, 0.60] -0.40 [-1.29, 0.49] -0.18 [-1.06, 0.70] -0.29 [-0.80, 0.22] -3.74 [-5.53, -1.96] -3.74 [-5.53, -1.96] -1.45 [-2.51, -0.38] -1.27 [-2.30, -0.23] -1.35 [-2.10, -0.61] -1.51 [-1.98, -1.04]	

FIGURE 8

Effects of TCM on total cholesterol (mmol/L). Forest plots of the effect size were calculated using SMDs. The horizontal error bars represent the 95% confidence interval of individual studies.

ejection fraction (p < 0.05). The forest plot indicated that wogonin had a more significant effect on increasing ejection fraction than other TCM drugs.

3.3.8 Efficacy of TCM on fractional shortening

The FS was used in 8 studies (218 animals, 109 were in the TCM group and 109 were in the control group), which are

		Drug			Model			Std Moon Difference	Std Mean Difference
Study or Subgroup	Moan	SD	Total	Moan	SD	Total	Weight	IV Pandom 95% Cl	IV Pandom 95% Cl
6 1 1 SSVY	Weatt	50	Total	Wean	50	Total	weight	IV, Random, 5576 CI	
SSVV(100mg/kg)	4.06	0.26	Б	4 02	0 42	5	11 10/	0 07 [1 17 1 21]	
SSTA(10011g/kg)	4.00	0.30	5	4.03	0.43	5	11.170	0.07 [-1.17, 1.31]	
SSYX(200mg/kg)	3.88	0.12	5	4.03	0.43	5	10.2%	-0.43 [-1.69, 0.83]	
SSTA(SUMg/Kg)	4.52	0.10	C 15	4.03	0.43	5 15	10.3%	1.34 [-0.11, 2.79]	
Subtotal (95% Cl)	0.04. 04		7 46 -	2 (D - 0	101.12	- 440/	J2.J /0	0.27 [-0.71, 1.25]	
Test for overall effect:	Z = 0.54	P = 3.3	7, ar = 59)	2 (P = (J. 19); I-	= 41%			
6.1.2 QLQX									
QLQX	2.89	0.23	7	2.89	0.39	8	12.0%	0.00 [-1.01, 1.01]	
Subtotal (95% CI)			7			8	12.0%	0.00 [-1.01, 1.01]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.00	(P = 1.	00)						
6.1.3 QGYY									
QGYY	5.9	0.3	5	6.3	0.3	5	10.4%	-1.20 [-2.62, 0.21]	
Subtotal (95% CI)			5			5	10.4%	-1.20 [-2.62, 0.21]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.67	(P = 0.	09)						
6.1.4 Myricetin									
Myricetin	2.06	0.104	16	2.33	0.081	16	12.0%	-2.82 [-3.84, -1.81]	
Subtotal (95% CI)			16			16	12.0%	-2.82 [-3.84, -1.81]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 5.46	(P < 0.	00001)						
6.1.5 Wogonin									
Wogonin	1.69	0.32	12	2.19	0.17	12	12.1%	-1.88 [-2.87, -0.89]	
Subtotal (95% CI)			12			12	12.1%	-1.88 [-2.87, -0.89]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 3.73	(P = 0.	0002)						
6.1.6 crocin						2	10.00		
crocin(10mg/kg)	3.5	0.3	4	3.5	0.1	4	10.6%	0.00 [-1.39, 1.39]	
crocin(20mg/kg)	3.7	0.5	4	3.5	0.1	4	10.4%	0.48 [-0.94, 1.91]	
Subtotal (95% CI)			8			8	20.9%	0.23 [-0.76, 1.23]	
Heterogeneity: Tau ² =	0.00; Ch	$hi^2 = 0.2$	3, df =	1 (P = 0)	0.63); l²	= 0%			
Test for overall effect:	Z = 0.46	6 (P = 0.	64)						
Total (95% CI)			63			64	100.0%	-0.54 [-1.42, 0.33]	
Heterogeneity: Tau ² =	1.41; Cł	$1i^2 = 37.$	54, df =	= 8 (P <	0.0000	1); l ² = 1	79%		-4 -2 0 2 4
Test for overall effect:	Z = 1.22	(P = 0.)	22)						Favours [Model] Favours [Drug]
Test for subaroup diffe	erences:	Chi ² = 3	31.26. c	lf = 5 (P	? < 0.00	001). I²	= 84.0%		
FIGURE 9									
Effects of TCM on left v	/entricul	ar interi	nal dim	ension	in systo	le (mm)	. Forest p	lots of the effect size we	re calculated using SMDs. The horizontal error
bars represent the 955	% confid	ence in	terval	of indivi	idual st	udies.			

included in the meta-analysis (Supplementary Figure S1). The meta-analysis showed that TCM significantly increased FS compared to control [SMD = 2.72 (2.32, 3.12), p < 0.00001; 11 comparisons), but with substantial heterogeneity among the studies ($\chi^2 = 17.75$; I² = 44%; df = 10; p = 0.06). Subgroup analysis found no significant difference in FS improvement among different TCM drugs (p = 0.06). The forest plot indicated that polydatin had a more significant effect on improving FS compared to other TCM drugs.

3.3.9 Efficacy of TCM on E/A

For the E/A 4 studies (117 animals, 58 were in the TCM group and 59 were in the control group) were included in the meta-analysis (Supplementary Figure S2). The meta-analysis revealed that TCM significantly improved E/A compared to control [SMD = 2.96 (2.41, 3.52; p < 0.00001; 5 comparisons) with moderate heterogeneity between studies ($\chi^2 = 4.88$; I² = 18%; df = 4; p = 0.30). Subgroup analysis found no significant difference in E/A improvement among different TCM drugs (p = 0.20), and each drug significantly improved E/A compared to control (p < 0.05). The effect of QLQX on E/A was not significantly different from the control group (p = 0.07), while the effect of other TCM drugs on E/A was significantly better than control (p < 0.05). The forest plot indicated that polydatin had a more significant effect on improving E/A compared to other TCM drugs.

3.4 Publication bias

The study employed funnel plots (Supplementary Figure S3) and Egger's test (Supplementary Figure S4) to identify potential publication bias. The results show that there was a significant publication bias related to body weight, HW/BW, blood glucose, triglyceride, and total cholesterol (p = 0.003, p < 0.001, p = 0.001, p <

		Drug		I	Model			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
8.1.1 Sal B									
Sal B(15 mg/kg)	75.21	3.31	20	64.05	4.23	20	19.7%	2.88 [1.97, 3.79]	
Sal B(30mg/kg)	77.59	4.21	20	64.05	4.23	20	17.9%	3.14 [2.19, 4.10]	
Subiolai (95% CI)	16 df -	1 (D -	40	12 - 00/		40	37.0%	3.01 [2.35, 3.00]	•
Test for everall effect: 7	. 16, df =	T (P =	0.09);	1~ = 0%					
rest for overall effect. 2	0.95	(F < 0.	00001)						
8.1.2 polydatin									
polydatin	82.59	2.36	7	72.53	3.07	7	4.9%	3.44 [1.61, 5.27]	
Subtotal (95% CI)			7			7	4.9%	3.44 [1.61, 5.27]	
Heterogeneity: Not app	licable								
Test for overall effect: Z	= 3.68	(P = 0.	0002)						
			,						
8.1.3 FTZ									
FTZ	33.62	1.9	4	26.68	3.42	4	3.9%	2.18 [0.14, 4.22]	
Subtotal (95% CI)			4			4	3.9%	2.18 [0.14, 4.22]	
Heterogeneity: Not app	licable								
Test for overall effect: Z	2 = 2.09	(P = 0.	04)						
8.1.4 Myricetin									
Myricetin	76.54	2.39	16	66.72	4.513	16	16.9%	2.65 [1.67, 3.63]	
Subtotal (95% CI)			16			16	16.9%	2.65 [1.67, 3.63]	
Heterogeneity: Not app	licable								
Test for overall effect: Z	= 5.30	(P < 0.	00001)						
8.1.5 Wogonin									
Woqonin	69.5	4.4	12	42.6	5.7	12	5.2%	5.10 [3.33, 6.87]	
Subtotal (95% CI)			12			12	5.2%	5.10 [3.33, 6.87]	
Heterogeneity: Not app	licable								
Test for overall effect: Z	= 5.65	(P < 0.	00001)						
8.1.6 Curcumin									
Curcumin(100 mg/kg)	76.6	2.9	6	68.5	5.2	6	8.0%	1.78 [0.35, 3.20]	
Curcumin(200 mg/kg)	81.8	2.7	6	68.5	5.2	6	4.8%	2.96 [1.13, 4.80]	
Subtotal (95% CI)			12			12	12.8%	2.22 [1.10, 3.35]	
Heterogeneity: Chi ² = 1	.00, df =	1 (P =	: 0.32);	$I^2 = 0\%$					
lest for overall effect: Z	. = 3.87	(P = 0.	0001)						
8 1 7 resveratrol									
resveratrol	68.6	1 82	10	61 2	2 45	10	7 9%	3 28 [1 85 4 72]	
Subtotal (95% CI)	50.0	1.02	10	01.2	2.40	10	7.9%	3.28 [1.85. 4.72]	•
Heterogeneity: Not ann	licable							[, -]	
Test for overall effect: Z	= 4.49	(P < 0.	00001)						
			,						
8.1.8 crocin									
crocin(10mg/kg)	80.42	5.32	4	70.34	1.73	4	3.8%	2.22 [0.16, 4.28]	
crocin(20mg/kg)	73.71	3.89	4	70.34	1.73	4	6.9%	0.97 [-0.57, 2.51]	
Subtotal (95% CI)			8			8	10.7%	1.42 [0.19, 2.65]	
Heterogeneity: Chi ² = 0	.90, df =	1 (P =	0.34);	$I^2 = 0\%$					
Test for overall effect: Z	= 2.25	(P = 0.	02)						
Total (95% CI)			100			100	100 0%	2 79 [2 39 3 20]	◆
Heterogeneity: Chi ² - 1	6 10 df	= 10 /	D = 0.10))· 2 – ⊃	8%	103	100.0 /0		
Test for overall effect: 7	13.10, ul	- 10 (r / (P < /), i`= 3 }	0 /0				-4 -2 0 2 4
Test for subgroup differ	- 13.37 ences: ($hi^2 = 1$	14 05 0	' <i>)</i> {f = 7 / D	= 0.05)	$ ^2 = 5$	0.2%		Favours [Model] Favours [Drug]
	6110 6 3. (, iii -	г т .00. С	<i> /</i> (F	- 0.001	. 1 – 0	0.2 /0		
FIGURE 10									

Effects of TCM on ejection fraction (%). Forest plots of the effect size were calculated using SMDs. The horizontal error bars represent the 95% confidence interval of individual studies.

0.001 and p = 0.006 respectively; Supplementary Figure S3A–E) However, no significant publication bias was found for ejection fraction and fractional shortening (p = 0.910 and p = 0.600, respectively; Supplementary Figure S3F–G). The study did not conduct a publication bias analysis on LVIDs and E/A indicators due to a limited number of included studies.

3.5 Sensitivity analysis

The study conducted sensitivity analyses by individually removing each study to assess its impact on the meta-analysis results. Supplementary Figure S5 shows all effect values falling within the 95% CI of the overall meta-analysis, indicating

TABLE 2 Subgroup analysis of TCM types.

Outcomes	Monomers			Compounds				
	l² (%)	p	SMD [95%CI]	l² (%)	p	SMD [95%CI]		
BW	78	< 0.00001	1.83 [1.15,2.50]	54	0.002	1.29 [0.47,2.11]		
HW/BW	79	< 0.0001	-2.09 [-3.07,-1.12]	0	< 0.00001	-2.37 [-2.80,-1.94]		
BG	89	<0.00001	-2.37 [-3.41,-1.34]	61	< 0.00001	-1.76 [-2.27,-1.24]		
TG	54	< 0.0001	-1.96 [-2.87,-1.04]	62	< 0.00001	-1.86 [-2.50,-1.22]		
ТС	78	0.002	-1.38 [-2.24,-0.51]	54	<0.00001	-1.65 [-2.14,-1.16]		

TABLE 3 Subgroup analysis of duration.

Outcomes	≤56			>56				
	l² (%)	p	SMD [95%CI]	l² (%)	p	SMD [95%CI]		
BW	67	<0.00001	1.33 [0.78,1.89]	61	<0.00001	2.59 [1.70,3.49]		
HW/BW	63	< 0.00001	-2.15 [-2.69,-1.61]	51	0.0001	-2.86 [-4.31,-1.40]		
BG	69	<0.00001	-1.30 [-1.78,-0.82]	85	<0.00001	-3.73 [-5.05,-2.41]		
TG	64	< 0.00001	-1.90 [-2.69,-1.11]	58	< 0.00001	-1.88 [-2.61,-1.16]		
ТС	67	<0.00001	-1.36 [-1.85,-0.87]	81	0.002	-2.26 [-3.69,-0.83]		

comparable effect sizes among studies. The results suggest the statistical validity and reliability of the findings.

3.6 Subgroup analysis

The results show high heterogeneity for BW, HW/BW, BG, TG, and TC. Therefore, subgroup analyses were performed to reveal the sources of heterogeneity, including variations in types of TCM, duration, modeling methods, and animal species.

3.6.1 Effects of TCM types on efficacy

The study conducted subgroup analyses on BW, HW/BW, BG, TG, and TC and categorized TCM into monomers and compounds. Table 2 shows the resulting subgroup analysis. The monomer TCM group showed statistically significant improvements in BW, BG, and TG (p < 0.001), while the compound TCM group showed significant improvements in HW/BW and TC (p < 0.0001). Additionally, subgroup analysis indicated that heterogeneity of BW, HW/BW, BG, and TC was reduced in the compound group, while TG heterogeneity was reduced in the monomer group with statistical significance (p < 0.0001). The findings suggest that heterogeneity among studies might be attributed to differences in TCM types.

3.6.2 Effects of duration on efficacy

The study conducted subgroup analyses for BW, HW/BW, BG, TG, and TC, dividing duration into two subgroups \leq 56 days and >56 days. The subgroup analysis results are provided in Table 3. The TCM intervention duration of \leq 56 days was significantly more effective in improving TG in DCM animals (p < 0.00001), whereas intervention duration >56 days was

significantly better in enhancing BW, HW/BW, BG, and TC (p < 0.01) in DCM animals. However, subgroup analysis results for TC did not show any reduction in heterogeneity. The reduced heterogeneity observed in BW, HW/BW, BG, and TG suggests that duration may be a source of heterogeneity between studies; however, it is not considered a significant contributor to heterogeneity.

3.6.3 Effects of modeling method on efficacy

Subgroup analysis was performed for BW, HW/BW, BG, TG, and TC. We divided the modeling method into three subgroups (STZ, HFD + STZ, and alloxan) for analysis. The results of subgroup analysis are presented in Table 4. Among the subgroups, treatment with a TCM exhibited a statistically significant improvement (p < 0.00001) in BW, HW/BW, and BG of HFD + STZ-induced DCM animals. However, subgroup analysis revealed no significant reduction in heterogeneity in BG and TC of HFD + STZ-induced DCM animals (p < 0.01). On the other hand, BW, HW/BW, and TG presented a reduction in heterogeneity. This reduction may be attributed to the modeling method.

3.6.4 Effects of animal species on efficacy

We performed subgroup analyses for BW, HW/BW, BG, TG, and TC. The animal species are divided into two subgroups (Mice and Rats). Subgroup analysis results are presented in Table 5. The effects of TCM on BW(p < 0.0001), TG (<0.00001), and TC(p < 0.01) were better in DCM mice than in DCM rats. The effects of TCM on HW/BW and BG were better in DCM rats than in DCM mice. Subgroup analysis showed heterogeneity of BW, HW/BW, BG, TG and, TC was reduced. The heterogeneity of BW, HW/BW, BG, TG, and TC may be caused by animal species.

-1.82 [-3.25, -0.40]

-0.78 [-1.51,-0.05]

-1.71 [-2.57,-0.85]

ТG

TC

Outcomes	STZ			HFD + STZ			Alloxan	
	l² (%)	p	SMD [95%CI]	l² (%)	р	SMD [95%CI]	l² (%)	р
BW	75	< 0.00001	1.49 [0.91,2.08]	15	<0.00001	2.51 [1.67,3.35]	-	-
HW/BW	60	0.0002	-1.56 [-2.37,-0.75]	50	<0.00001	-2.52 [-3.08,-1.95]	-	-
BG	73	< 0.0001	-1 48 [-2 20 -0 76]	85	<0.00001	-2.56 [-3.461.67]	78	0.01

48

76

-2.60 [-3.64,-1.55]

-1.60 [-2.63,-0.57]

TABLE 4 Subgroup analysis of the modeling method.

TABLE 5 Subgroup analysis of animal species.

35

55

< 0.00001

0.002

Outcomes	Mice			Rats			
	l² (%)	p	SMD [95%CI]	l ² (%)	p	SMD [95%CI]	
BW	82	<0.0001	1.98 [1.06,2.89]	62	<0.00001	1.41 [0.79,2.04]	
HW/BW	0	< 0.00001	-2.22 [-2.99,-1.45]	67	< 0.00001	-2.23 [-2.83,-1.63]	
BG	72	<0.0001	-1.60 [-2.34,-0.87]	84	<0.00001	-2.30 [-3.03,-1.56]	
TG	68	< 0.00001	-2.34 [-3.38,-1.30]	50	< 0.00001	-1.61 [-2.18,-1.05]	
TC	55	0.002	-1.60 [-2.63,-0.57]	73	<0.00001	-1.50 [-2.04,-0.96]	

< 0.00001

< 0.00001

4 Discussion

4.1 Possible mechanisms of diabetic cardiomyopathy

The pathogenesis of diabetes encompasses various mechanisms that contribute to pancreatic beta-cell dysfunction and insulin resistance, including oxidative stress, endoplasmic reticulum stress, inflammation, autophagy, and DNA methylation (Ganesan et al., 2020). These mechanisms play crucial roles in the development of the disease. When exposed to elevated levels of glucose or fatty acids, the myocardium triggers the activation of NFκB (Rahimi-Madiseh et al., 2017), a protein responsible for regulating immune responses and inflammation. NF-KB promotes the formation of NLRP3 inflammatory vesicles that release proinflammatory mediators (Asgary et al., 2014). Furthermore, heightened glucose levels disrupt mitochondrial function, leading to the generation of ROS (Hu et al., 2022). These ROS cause the aggregation of TXNIP with TRX (Feng et al., 2022), which then bind to NLRP3, initiating the activation of the NLRP3 inflammasome. This inflammasome activates caspase-1, which processes proinflammatory cytokines IL-1β and IL-18. ROS also stimulate NFthereby further facilitating the assembly of the κB, NLRP3 inflammasome and the cleavage of caspase-1 (Egger et al., 1997; Engels et al., 2000). Consequently, this cascade results in the release of IL-1 β and IL-18, potent inflammatory molecules implicated in the pathogenesis of diabetes. In diabetes, activated endothelial cells contribute to the early development of myocardial stiffness and diastolic dysfunction (Petersen and Shulman, 2018). They do so by promoting the uncoupling of endothelial NOS, resulting in the production of superoxide, hydrogen peroxide, and peroxynitrite. Consequently, the levels of NO are reduced (Zhou et al., 2010).

4.2 The efficacy of TCM

-2.56 [-3.46,-1.67]

-1.93 [-2.53,-1.33]

-1.47 [-2.10, -0.84]

33

47

0.04

0.0001

Based on this systematic review and meta-analysis, it is possible to infer that TCM has a significant impact on downregulating BG, TG, and TC in DCM animals, indicating its ability to modulate lipids and blood glucose. Moreover, the TCM treatment was highly effective in reducing myocardial hypertrophy and improving cardiac functions, as evidenced by the significant downregulation of HW/BW and the upregulation of EF, FS, and E/A with statistical significance.

4.3 Subgroup analysis

Table 2 presents the outcome measures, which are divided into two subgroups based on the type of traditional Chinese medicine (TCM): monomer and compound. Based on the results of subgroup analysis, it can be inferred that herbal monomers have a more pronounced impact on BG and TG levels in animals with DCM. Moreover, the treatment of DCM is closely linked to glucolipid metabolism (Montaigne et al., 2021). Thus, these findings imply that individual herbal monomers in TCM may offer greater advantages in enhancing glucose and lipid metaboism compared to TCM compounds.

Table 3 illustrates that even after categorizing the outcome measures into two subgroups based on their duration: ≤56 days and >56 days, a significant level of heterogeneity persisted across most subgroups. This implies that duration has a negligible impact on heterogeneity.

Table 4 showcases the outcome measures, which are categorized into three subgroups based on the animal modeling methods: STZ, HFD + STZ, and alloxan. While there was still some heterogeneity present in all subgroups, reductions were observed. Therefore, we can conclude that the primary source of heterogeneity in the included studies is the modeling approach, which aligns with previous research findings (Chen et al., 2023). The index related to lipid metabolism (TG) displayed significantly better results in the STZ group compared to the HFD + STZ group, potentially due to the impact of the high-fat diet on the measurement outcomes.

Table 5 demonstrates two subgroups, mice and rats, based on animal species. Results suggest that animal species is a contributing factor to heterogeneity, contradicting the outcomes of previous meta-analyses conducted on animal models of diabetes (Chen et al., 2022). Such disparity may stem from the inclusion of different animal strains within the study.

4.4 The possible mechanisms of TCM

4.4.1 Anti-inflammatory action and decrease insulin resistance

The efficacy of wogonin, a herbal medicine traditionally used in mainland China and other Far East regions (Lee et al., 2015), was found to be significant in regulating body weight and EF, as indicated in the forest plot (Figures 4, 10). Wogonin can downregulate ROS-mediated NF- κ B activation (Polier et al., 2011) and reduce hyperglycemia by increasing the transport of phosphorylated Akt and Glut4 to the plasma membrane (PM) in cardiac and skeletal muscle cells. Furthermore, treatment with wogonin resulted in a significant increase in Glut4 expression (Khan and Kamal, 2019). The hypoglycemic efficacy of mangiferin was the most significant among the 24 TCMs included (Figure 5). Previous studies have shown that long-term and short-term mangiferin treatments enhance PDH activity. This is partly due to the reduction of p-PDH levels caused by the downregulation of PDK4 by mangiferin (Apontes et al., 2014).

4.4.2 Antioxidation of TCM

Oxidative stress damage is widely regarded as one of the important pathogenesis of diabetes. Mangiferin, taxifolin, polydatin, Nar, DOE, QGYY, Myricetin and Wogonin they all have significant antioxidant effects in different pathway, One study reported Myricetin attenuated oxidative stress through the acti-vation of the Nrf-2/ARE signal pathway (Liao et al., 2017). taxifolin and polydatin mediate through its inhibition of NADPH oxidase (Sun et al., 2014; Tan et al., 2020a). Nar can reduce the accumulation of unfolded or misfolded proteins in ER by increasing antioxidant enzyme activity and reducing lipid peroxide production, inhibiting ERS and reducing the expression of apoptosis related factors (Zhang et al., 2018). Although the antioxidant mechanism of each medicine is not necessarily the same, there is no doubt that they all have significant antioxidant effects.

4.4.3 Efficacy in cardiac function of TCM

The forest plot analysis demonstrated that polydatin exhibited the exceptional efficacy in cardiac function, specifically in FS and E/A (Supplementary Figure S1, S2). Polydatin, derived from thuja's rhizome and roots (Zhang et al., 2023), is a natural compound with a history of traditional use in treating inflammation, infection, jaundice, skin burns, and hyperlipidemia (Luo et al., 2022). Polydatin stimulates antifibrotic mechanisms and Nrf2-associated signaling pathways, while inhibiting NF-KB improves glycolipid metabolism following its administration (Karami et al., 2022). FTZ can decrease the interventricular septal thickness (Wang et al., 2021). YQHX, QLQX, Myricetin, Curcumin, resveratrol, crocin, can inhibit the apoptosis of cardiomyocytes. Moreover, the TCM treatment was highly effective in reducing myocardial hypertrophy and improving cardiac functions, as evidenced by the significant downregulation of HW/BW and the upregulation of EF, FS, and E/A with statistical significance. Whether the mechanism of TCM to reduce the effects of cell apoptosis and affect more modules.

4.4.4 Other mechanism of TCM

Both hyperglycemia and hyperlipidemia are high-risk factors for diabetic cardiomyopathy. TCM has demonstrated the ability to regulate metabolism, including blood lipid and blood glucose levels. Our included studies have consistently reported the improvement of lipid levels in diabetic animals through TCM intervention, a result also supported by our metaanalysis with p-values less than 0.05 for all differences in Figure 7 and Figure 8. Based on this evidence, we conclude that TCM can effectively improve the disorder of blood lipid metabolism. Furthermore, our findings also indicate that TCM can improve the disorder of blood glucose metabolism, with p-values less than 0.05 for all differences in Figure 6. Moreover, a study (Diao et al., 2019) suggests that resveratrol promotes mitochondrial biosynthesis and inhibits excessive mitochondrial division in DCM, providing additional support for the benefits of TCM in this context.

4.5 Limitation

Most early studies were superficial and primarily concentrated on blood glucose and lipids, with few studies reported on diabetic cardiomyopathy and its mechanisms. The limited literature on diabetic cardiomyopathy could potentially compromise the study's objectivity. Secondly, the quality of the literature acquired for the study was suboptimal, particularly with respect to randomization and blinded implementation. While most studies used the term "randomization," they did not specifically detail the randomization method used. Additionally, none of the studies mentioned the application of blinded methods in the methods section. Thirdly, the high heterogeneity observed in the forest plots is a regular issue in meta-analyses of animal research, partly due to substandard study quality. Additionally, it could stem from various experimental factors, for example, the types of TCM, modeling methods, duration, and animal species.

5 Conclusion

Our study outcomes indicate that Traditional Chinese Medicine significantly improves heart function and controls the levels of blood glucose in animals with DCM, making it a viable treatment option. However, our study had several limitations due to the insufficient number of included studies, poor methodological quality, and a limited number of study animals. We acknowledge that our analysis was based on animal studies, which restricts generalization to humans. Therefore, further high-quality preclinical trials and clinical studies are required to validate our findings before fully applying TCM in the clinical setting.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

LH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing-original draft, Writing-review and editing, Visualization. LQ: Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Writing-original draft, Writing-review and editing. AS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Writing-review and editing. GC: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing-review and editing. YG: Conceptualization, Formal Analysis, Investigation, Project administration, Software, Writing-review and editing. YY: Data curation, Methodology, Project administration, Supervision, Validation, Writing-review and editing. XC: Data curation, Investigation, Project administration, Writing-review and editing. YJ: Supervision, Validation, Visualization, Writing-review and

References

Apontes, P., Liu, Z., Su, K., Benard, O., Youn, D. Y., Li, X., et al. (2014). Mangiferin stimulates carbohydrate oxidation and protects against metabolic disorders induced by high-fat diets. *Diabetes* 63 (11), 3626–3636. doi:10.2337/db14-0006

Asgary, S., Rafieian-Kopaei, M., Shamsi, F., Najafi, S., and Sahebkar, A. (2014). Biochemical and histopathological study of the anti-hyperglycemic and antihyperlipidemic effects of cornelian cherry (Cornus mas L.) in alloxan-induced diabetic rats. *J. Complement. Integr. Med.* 11 (2), 63–69. doi:10.1515/jcim-2013-0022

Chang, W., Zhang, M., Meng, Z., Yu, Y., Yao, F., Hatch, G. M., et al. (2015). Berberine treatment prevents cardiac dysfunction and remodeling through activation of 5'adenosine monophosphate-activated protein kinase in type 2 diabetic rats and in palmitate-induced hypertrophic H9c2 cells. *Eur. J. Pharmacol.* 769, 55–63. doi:10. 1016/j.ejphar.2015.10.043

Chen, R., Ma, K., Li, S., Zhou, X., and Chen, H. (2023). Protective effects and mechanisms of opuntia polysaccharide in animal models of diabetes mellitus: A systematic review and metaanalysis. *J. Ethnopharmacol.* 312, 116490. doi:10.1016/j.jep.2023.116490

Chen, X. M., Yang, W. Q., Wang, X., Chen, C., Qian, Z. M., Wang, S. M., et al. (2022). Effects of natural dihydrochalcones in sweet tea (lithocarpus polystachyus) on diabetes: A systematical review and meta-analysis of animal studies. *Food Funct.* 13 (11), 5899–5913. doi:10.1039/d2fo00245k editing. JL: Methodology, Project administration, Resources, Visualization, Writing-review and editing. RJ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing-original draft, Writing-review and editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the research and evaluation technology system of pharmacology of combination of disease and syndrome (No. CI 2021A04601).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1253572/ full#supplementary-material

Couchie, D., Vaisman, B., Abderrazak, A., Mahmood, D. F. D., Hamza, M. M., Canesi, F., et al. (2017). Human plasma thioredoxin-80 increases with age and in ApoE(-/-) mice induces inflammation, angiogenesis, and atherosclerosis. *Circulation* 136 (5), 464–475. doi:10.1161/circulationaha.117.027612

Diao, J., Wei, J., Yan, R., Fan, G., Lin, L., and Chen, M. (2019). Effects of resveratrol on regulation on UCP2 and cardiac function in diabetic rats. *J. Physiol. Biochem.* 75 (1), 39–51. doi:10.1007/s13105-018-0648-7

Dillmann, W. H. (2019). Diabetic cardiomyopathy. Circ. Res. 124 (8), 1160–1162. doi:10.1161/circresaha.118.314665

Dong, Y., Zhao, Q., Gao, L., and Wang, W. (2021). Molecular mechanism of Astragalus-Angelicae drug pair in the treatment of diabetic cardiomyopathy. *Chin. J. Exp. Formulary* 27 (18), 16–24. doi:10.13422/j.cnki.syfjx.20211118

Egger, M., Smith, G. D., and Phillips, A. N. (1997). Meta-analysis: principles and procedures. *Bmj* 315 (7121), 1533–1537. doi:10.1136/bmj.315.7121.1533

Engels, E. A., Schmid, C. H., Terrin, N., Olkin, I., and Lau, J. (2000). Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat. Med.* 19 (13), 1707–1728. doi:10.1002/1097-0258(20000715)19:13<1707:aid-sim491>3.0.co;2-p

Eriksson, L., and Nyström, T. (2015). Antidiabetic agents and endothelial dysfunction - beyond glucose control. *Basic Clin. Pharmacol. Toxicol.* 117 (1), 15–25. doi:10.1111/ bcpt.12402

Ernande, L., and Derumeaux, G. (2012). Diabetic cardiomyopathy: myth or reality? Arch. Cardiovasc Dis. 105 (4), 218–225. doi:10.1016/j.acvd.2011.11.007

Evangelista, I., Nuti, R., Picchioni, T., Dotta, F., and Palazzuoli, A. (2019). Molecular dysfunction and phenotypic derangement in diabetic cardiomyopathy. *Int. J. Mol. Sci.* 20 (13), 3264. doi:10.3390/ijms20133264

Feidantsis, K., Mellidis, K., Galatou, E., Sinakos, Z., and Lazou, A. (2018). Treatment with crocin improves cardiac dysfunction by normalizing autophagy and inhibiting apoptosis in STZ-induced diabetic cardiomyopathy. *Nutr. Metab. Cardiovasc Dis.* 28 (9), 952–961. doi:10.1016/j.numecd.2018.06.005

Feng, H., Wu, T., Zhou, Q., Li, H., Liu, T., Ma, X., et al. (2022). Protective effect and possible mechanisms of artemisinin and its derivatives for diabetic nephropathy: A systematic review and meta-analysis in animal models. *Oxid. Med. Cell Longev.* 2022, 5401760. doi:10.1155/2022/5401760

Franssen, C., Chen, S., Unger, A., Korkmaz, H. I., De Keulenaer, G. W., Tschöpe, C., et al. (2016). Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. *JACC Heart Fail* 4 (4), 312–324. doi:10.1016/j. jchf.2015.10.007

Ganesan, D., Albert, A., Paul, E., Ananthapadmanabhan, K., Andiappan, R., and Sadasivam, S. G. (2020). Rutin ameliorates metabolic acidosis and fibrosis in alloxan induced diabetic nephropathy and cardiomyopathy in experimental rats. *Mol. Cell Biochem.* 471 (1-2), 41–50. doi:10.1007/s11010-020-03758-y

Guo, R., and Nair, S. (2017). Role of microRNA in diabetic cardiomyopathy: from mechanism to intervention. *Biochim. Biophys. Acta Mol. Basis Dis.* 1863 (8), 2070–2077. doi:10.1016/j.bbadis.2017.03.013

Guo, X., Xue, M., Li, C. J., Yang, W., Wang, S. S., Ma, Z. J., et al. (2016). Protective effects of triptolide on TLR4 mediated autoimmune and inflammatory response induced myocardial fibrosis in diabetic cardiomyopathy. *J. Ethnopharmacol.* 193, 333–344. doi:10.1016/j.jep.2016.08.029

He, F., Huang, Y., Song, Z., Zhou, H. J., Zhang, H., Perry, R. J., et al. (2021). Mitophagy-mediated adipose inflammation contributes to type 2 diabetes with hepatic insulin resistance. *J. Exp. Med.* 218 (3), e20201416. doi:10.1084/jem.20201416

Hou, J., Zheng, D., Fung, G., Deng, H., Chen, L., Liang, J., et al. (2016). Mangiferin suppressed advanced glycation end products (AGEs) through NF-κB deactivation and displayed anti-inflammatory effects in streptozotocin and high fat diet-diabetic cardiomyopathy rats. *Can. J. Physiol. Pharmacol.* 94 (3), 332–340. doi:10.1139/cjpp-2015-0073

Hu, T., Yue, J., Tang, Q., Cheng, K. W., Chen, F., Peng, M., et al. (2022). The effect of quercetin on diabetic nephropathy (DN): A systematic review and meta-analysis of animal studies. *Food Funct.* 13 (9), 4789–4803. doi:10.1039/d1fo03958j

Jankauskas, S. S., Kansakar, U., Varzideh, F., Wilson, S., Mone, P., Lombardi, A., et al. (2021). Heart failure in diabetes. *Metabolism* 125, 154910. doi:10.1016/j.metabol.2021. 154910

Karami, A., Fakhri, S., Kooshki, L., and Khan, H. (2022). Polydatin: pharmacological mechanisms, therapeutic targets, biological activities, and health benefits. *Molecules* 27 (19), 6474. doi:10.3390/molecules27196474

Khan, S., and Kamal, M. A. (2019). Wogonin alleviates hyperglycemia through increased glucose entry into cells via AKT/GLUT4 pathway. *Curr. Pharm. Des.* 25 (23), 2602–2606. doi:10.2174/1381612825666190722115410

Khan, S., Zhang, D., Zhang, Y., Li, M., and Wang, C. (2016). Wogonin attenuates diabetic cardiomyopathy through its anti-inflammatory and anti-oxidative properties. *Mol. Cell Endocrinol.* 428, 101–108. doi:10.1016/j.mce.2016.03.025

Lawrence, T. (2009). The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb. Perspect. Biol. 1 (6), a001651. doi:10.1101/cshperspect.a001651

Lee, W., Ku, S. K., and Bae, J. S. (2015). Anti-inflammatory effects of baicalin, baicalein, and wogonin *in vitro* and *in vivo*. *Inflammation* 38 (1), 110–125. doi:10.1007/s10753-014-0013-0

Lehrke, M., and Marx, N. (2017). Diabetes mellitus and heart failure. *Am. J. Med.* 130 (6), S40–s50. doi:10.1016/j.amjmed.2017.04.010

Li, C. L., Liu, B., Wang, Z. Y., Xie, F., Qiao, W., Cheng, J., et al. (2020). Salvianolic acid B improves myocardial function in diabetic cardiomyopathy by suppressing IGFBP3. J. Mol. Cell Cardiol. 139, 98–112. doi:10.1016/j.yjmcc.2020.01.009

Liao, H. H., Zhu, J. X., Feng, H., Ni, J., Zhang, N., Chen, S., et al. (2017). Myricetin possesses potential protective effects on diabetic cardiomyopathy through inhibiting ikba/nfkb and enhancing Nrf2/HO-1. Oxid. Med. Cell Longev. 2017, 8370593. doi:10. 1155/2017/8370593

Loffroy, R., Bernard, S., Sérusclat, A., Boussel, L., Bonnefoy, E., D'Athis, P., et al. (2009). Noninvasive assessment of the prevalence and characteristics of coronary atherosclerotic plaques by multidetector computed tomography in asymptomatic type 2 diabetic patients at high risk of significant coronary artery disease: A preliminary study. *Arch. Cardiovasc Dis.* 102 (8-9), 607–615. doi:10.1016/j.acvd.2009.04.007

Lorenzo-Almorós, A., Cepeda-Rodrigo, J. M., and Lorenzo, Ó. (2022). Diabetic cardiomyopathy. *Rev. Clin. Esp. Barc.* 222 (2), 100–111. doi:10.1016/j.rceng.2019.10.012

Luo, J., Chen, S., Wang, L., Zhao, X., and Piao, C. (2022). Pharmacological effects of polydatin in the treatment of metabolic diseases: A review. *Phytomedicine* 102, 154161. doi:10.1016/j.phymed.2022.154161

Meng, T., Li, X., Li, C., Liu, J., Chang, H., Jiang, N., et al. (2022). Natural products of traditional Chinese medicine treat atherosclerosis by regulating inflammatory and oxidative stress pathways. *Front. Pharmacol.* 13, 997598. doi:10.3389/fphar.2022.997598

Montaigne, D., Butruille, L., and Staels, B. (2021). PPAR control of metabolism and cardiovascular functions. *Nat. Rev. Cardiol.* 18 (12), 809–823. doi:10.1038/s41569-021-00569-6

Nakamura, K., Miyoshi, T., Yoshida, M., Akagi, S., Saito, Y., Ejiri, K., et al. (2022). Pathophysiology and treatment of diabetic cardiomyopathy and heart failure in patients with diabetes mellitus. *Int. J. Mol. Sci.* 23 (7), 3587. doi:10.3390/ijms23073587

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj* 372, n71. doi:10.1136/bmj.n71

Paolillo, S., Marsico, F., Prastaro, M., Renga, F., Esposito, L., De Martino, F., et al. (2019). Diabetic cardiomyopathy: definition, diagnosis, and therapeutic implications. *Heart Fail Clin.* 15 (3), 341–347. doi:10.1016/j.hfc.2019.02.003

Petersen, M. C., and Shulman, G. I. (2018). Mechanisms of insulin action and insulin resistance. *Physiol. Rev.* 98 (4), 2133–2223. doi:10.1152/physrev.00063.2017

Polier, G., Ding, J., Konkimalla, B. V., Eick, D., Ribeiro, N., Köhler, R., et al. (2011). Wogonin and related natural flavones are inhibitors of CDK9 that induce apoptosis in cancer cells by transcriptional suppression of Mcl-1. *Cell Death Dis*. 2 (7), e182. doi:10. 1038/cddis.2011.66

Rahimi-Madiseh, M., Heidarian, E., Kheiri, S., and Rafieian-Kopaei, M. (2017). Effect of hydroalcoholic Allium ampeloprasum extract on oxidative stress, diabetes mellitus and dyslipidemia in alloxan-induced diabetic rats. *Biomed. Pharmacother.* 86, 363–367. doi:10.1016/j.biopha.2016.12.028

Scirica, B. M., Braunwald, E., Raz, I., Cavender, M. A., Morrow, D. A., Jarolim, P., et al. (2015). Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 132 (15), e198. doi:10.1161/cir. 00000000000330

Seferović, P. M., and Paulus, W. J. (2015). Clinical diabetic cardiomyopathy: A two-faced disease with restrictive and dilated phenotypes. *Eur. Heart J.* 36 (27), 1718–1727. doi:10.1093/eurheartj/ehv134

Seferovic, P. M., Petrie, M. C., Filippatos, G. S., Anker, S. D., Rosano, G., Bauersachs, J., et al. (2018). Type 2 diabetes mellitus and heart failure: A position statement from the heart failure association of the European society of cardiology. *Eur. J. Heart Fail* 20 (5), 853–872. doi:10.1002/ejhf.1170

Shao, B. Z., Xu, Z. Q., Han, B. Z., Su, D. F., and Liu, C. (2015). NLRP3 inflammasome and its inhibitors: A review. *Front. Pharmacol.* 6, 262. doi:10.3389/fphar.2015.00262

Shen, N., Li, X., Zhou, T., Bilal, M. U., Du, N., Hu, Y., et al. (2014). Shensong Yangxin Capsule prevents diabetic myocardial fibrosis by inhibiting TGF- β 1/Smad signaling. J. Ethnopharmacol. 157, 161–170. doi:10.1016/j.jep.2014.09.035

Shi, H., Wang, L., Fang, Z. H., Ni, Y. Q., Shen, A. L., Liu, P. P., et al. (2019). Experimental study on effect and mechanism of Danzhi Jiangtang Capsules on diabetic myocardial injury. *Zhongguo Zhong Yao Za Zhi* 44 (23), 5159–5165. doi:10.19540/j. cnki.cjcmm.20191015.401

Sun, X., Chen, R. C., Yang, Z. H., Sun, G. B., Wang, M., Ma, X. J., et al. (2014). Taxifolin prevents diabetic cardiomyopathy *in vivo* and *in vitro* by inhibition of oxidative stress and cell apoptosis. *Food Chem. Toxicol.* 63, 221–232. doi:10.1016/j. fct.2013.11.013

Tan, Y., Zhang, Z., Zheng, C., Wintergerst, K. A., Keller, B. B., and Cai, L. (2020b). Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. *Nat. Rev. Cardiol.* 17 (9), 585–607. doi:10.1038/s41569-020-0339-2

Tan, Y. Y., Chen, L. X., Fang, L., and Zhang, Q. (2020a). Cardioprotective effects of polydatin against myocardial injury in diabetic rats via inhibition of NADPH oxidase and NF-κB activities. *BMC Complement. Med. Ther.* 20 (1), 378. doi:10.1186/s12906-020-03177-y

Wang, J., Ma, Q., Li, Y., Li, P., Wang, M., Wang, T., et al. (2020). Research progress on Traditional Chinese Medicine syndromes of diabetes mellitus. *Biomed. Pharmacother.* 121, 109565. doi:10.1016/j.biopha.2019.109565

Wang, L, Wu, H, Deng, Y., Zhang, S., Wei, Q., Yang, Q., et al. (2021). FTZ ameliorates diabetic cardiomyopathy by inhibiting inflammation and cardiac fibrosis in the streptozotocin-induced model. *Evid. Based Complement. Altern. Med.* 2021, 5582567. doi:10.1155/2021/5582567

Wang, X., Huang, J., Wang, S., and Ni, Q. (2018). The Chinese herb yi-qi-huo-xue protects cardiomyocyte function in diabetic cardiomyopathy. *Evid. Based Complement. Altern. Med.* 2018, 7316840. doi:10.1155/2018/7316840

Wei, Q., Zhu, T., Xiao, X., Sun, L., Zhang, Z., and Huang, T. (2019). Dioscin attenuates myocardial damages in diabetic rats maybe by regulating NO-sGC-cGMP-PKG pathway. *Ann. Clin. Lab. Sci.* 49 (1), 97–104.

Wu, X., Zhang, T., Lyu, P., Chen, M., Ni, G., Cheng, H., et al. (2021). Traditional Chinese medication qiliqiangxin attenuates diabetic cardiomyopathy via activating PPARγ. *Front. Cardiovasc Med.* 8, 698056. doi:10.3389/fcvm.2021.698056 Xiao, E., and Luo, L. (2018). Alternative therapies for diabetes: A comparison of western and traditional Chinese medicine (TCM) approaches. *Curr. Diabetes Rev.* 14 (6), 487–496. doi:10.2174/1573399813666170519103230

Yao, R., Cao, Y., Wang, C., Xu, L., Zhang, X., Deng, Y., et al. (2021). Taohuajing reduces oxidative stress and inflammation in diabetic cardiomyopathy through the sirtuin 1/nucleotide-binding oligomerization domain-like receptor protein 3 pathway. *BMC Complement. Med. Ther.* 21 (1), 78. doi:10.1186/s12906-021-03218-0

Yu, W., Wu, J., Cai, F., Xiang, J., Zha, W., Fan, D., et al. (2012). Curcumin alleviates diabetic cardiomyopathy in experimental diabetic rats. *PLoS One* 7 (12), e52013. doi:10. 1371/journal.pone.0052013

Zhang, Y. F., Meng, N. N., Li, H. Z., Wen, Y. J., Liu, J. T., Zhang, C. L., et al. (2018). Effect of naringin on oxidative stress and endoplasmic reticulum stress in diabetic cardiomyopathy. *Zhongguo Zhong Yao Za Zhi* 43 (3), 596–602. doi:10.19540/j.cnki.cjcmm.2018.0013

Zhang, Z., Sun, Z., Jia, R., Jiang, D., Xu, Z., Zhang, Y., et al. (2023). Protective effects of polydatin against bone and joint disorders: the *in vitro* and *in vivo* evidence so far. *Nutr. Res. Rev.*, 1–12. doi:10.1017/s0954422423000082

Zhang, Z., Zhang, D., Dou, M., Li, Z., Zhang, J., and Zhao, X. (2016). Dendrobium officinale Kimura et Migo attenuates diabetic cardiomyopathy through inhibiting oxidative stress, inflammation and fibrosis in streptozotocin-induced mice. *Biomed. Pharmacother.* 84, 1350–1358. doi:10.1016/j.biopha.2016.10.074

Zhou, R., Tardivel, A., Thorens, B., Choi, I., and Tschopp, J. (2010). Thioredoxininteracting protein links oxidative stress to inflammasome activation. *Nat. Immunol.* 11 (2), 136–140. doi:10.1038/ni.1831

Zhou, R., Yazdi, A. S., Menu, P., and Tschopp, J. (2011). A role for mitochondria in NLRP3 inflammasome activation. *Nature* 469 (7329), 221–225. doi:10.1038/ nature09663