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Research article

Pharmacological mechanisms of Taohe Chengqi decoction in diabetic cardiovascular complications: A systematic review, network pharmacology and molecular docking

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ABSTRACT

Background: Diabetic cardiovascular complications are the leading cause of diabetes-related deaths. These complications place an enormous and growing burden on global health systems and economies. The objective of this study was to conduct a systematic review on the therapeutic mechanisms of Taohe Chengqi Decoction (THCQD) in the treatment of diabetic cardiovascular complications. To predict the potential mechanisms of action of THCQD on diabetic cardiovascular complications using network pharmacology, and to validate these predictions through molecular docking analysis.

Methods: To collect relevant animal experiments, we searched a total of 6 databases. Eligibility for the study was determined based on inclusion and exclusion criteria. Data extraction was then performed on the literature. Methodological quality of animal studies was assessed using SYRCLE criteria. Based on network pharmacology, intersecting genes for THCQD and diabetic cardiovascular complications were obtained using Venny, PPI analysis and topology analysis of intersecting genes were performed; GO and KEGG were used for enrichment analysis and prediction of new targets of action. Molecular docking techniques were employed to model the interactions between drug components and target genes, thereby validating the results of network pharmacology predictions.

Results: A total of 16 studies were finally identified that fit the direction of this review. Included 6 studies of the myocardium, 1 study of the aortic arch, 5 studies of the femoral artery, 4 studies of the thoracic aorta. THCQD exhibited anti-inflammatory, anti-fibrotic and anti-atherosclerotic effects on cardiovascular complications in diabetic rats. Network pharmacology results showed that C0363 (Resveratrol), C0041 (Emodin), and C1114 (Baicalein) were the key components in the treatment of diabetic cardiovascular complications by THCQD. PPI results showed that INS, AKT1, TNF, ALB, IL6, IL1B as the genes that interact with the top 6. KEGG enrichment analysis identified the AGE-RAGE signaling pathway in diabetic complications as the most prominent pathway enriched by THCQD for diabetic cardiovascular complications genes. The results of molecular docking showed that the key active components demonstrated favorable interactions with their corresponding target genes.

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Conclusion: In conclusion, the results of both basic and web-based pharmacological studies support the beneficial effects of the natural herbal formulation THCQD on diabetic cardiovascular complications. This decoction has anti-inflammatory and antifibrotic properties and is effective in ameliorating diabetic cardiovascular disease. The network pharmacology results further support these ideas and identify the AGE-RAGE signaling pathway in diabetic complications as possibly the most relevant pathway for THCQD in the treatment of diabetic cardiovascular complications. The extent of the therapeutic potential of all-natural herbal components in the treatment of diabetic cardiovascular disease merits further investigation.

Abbreviations

DM	Diabetes mellitus
DCM	diabetic cardiomyopathy
HYP	hydroxyproline
GLUT4	glucose transporter protein-4
GSH-Px	glutathione peroxidase
MDA	malondialdehyde
TGF-β1	transforming growth factor β1
CTGF	connective tissues growth factor
TGF-β:	Transforming Growth Factor β
IGF-1	Insulin-Like Growth Factor-1
TLR-2	Toll Like Receptors-2
TLR-4	Toll Like Receptors-4
VCAM-1	Vascular Cell Adhesion Molecule-1
MCP-1	Monocyte Chemoattractant Protein-1
AGEs	Advanced Glycosylation End products
RAGEs	Receptor of Advanced Glycation End products
eNOS	endothelial Nitric Oxide Synthase
GSH-Px	glutathione peroxidase
VSMC	vascular smooth muscle cells
NO	Nitric Oxide

Trial registration

The study has been registered at PROSPERO (CRD42023392260).

1. Introduction

Diabetes mellitus (DM) is a very common and increasingly significant chronic disease. In recent years, the prevalence of DM has been increasing worldwide, and the number of people with DM is expected to reach 700 million worldwide by 2045 [1,2]. The high prevalence of DM, the deaths caused by DM, and the health expenditures associated with the complications of diabetes continue to rise globally, placing a serious burden on society, finances, and health systems [3–5]. Cardiovascular complications of diabetes, including coronary heart disease and peripheral vascular disease, as well as microvascular complications, are major contributors to the burden associated with DM [6,7]. Approximately 70–75 % of patients with diagnosed coronary artery disease have DM or abnormalities in blood glucose [8]. Diabetic cardiovascular complications already account for more than half of DM mortality [9]. Diabetic cardiovascular complications have become a very heavy and unavoidable problem.

Taohe Chengqi Decoction (THCQD) is a well-known herbal formula that first recorded in the *Treatise on Miscellaneous Diseases of Typhoid Fever* (circa 200 AD). THCQD is composed of Peach Seed, Rhubarb, Cassia twig, Licorice Root, and Mirabilite. Studies have found that the combination of herbs in THCQD can improve glucose metabolism and lower high blood sugar levels in diabetic patients [10–13]. Research confirms that THCQD improves vascular endothelial function in diabetic patients [14], and alleviation of oxidative damage in kidney and heart tissues of diabetic rats by scavenging oxygen free radicals and anti-lipid peroxidation effects [15]. In recent years, a very large number of scholars have confirmed the protective effect of THCQD on diabetic cardiovascular complications, and much scientific evidence has been found regarding its mechanisms. To our knowledge, the protective mechanism of THCQD for diabetic cardiovascular disease has not been systematically summarized.

In this review, we provide a systematic review of the mechanism of action of THCQD for the treatment of diabetic cardiovascular complications, a broad overview of existing studies, and a summary of the combined use of herbal therapies. In addition, we

comprehensively analyzed the chemical constituents in THCQD and used the network pharmacology approach to predict its potential mechanisms for the treatment of diabetic cardiovascular complications. Molecular docking was utilized to confirm the interactions between key components and their corresponding target genes.

2. Materials and methods

This systematic review was based on the latest PRISMA guidelines. The study has been registered at PROSPERO (CRD42023392260).

2.1. Literature search

A total of 6 databases were searched to collect relevant animal experiments, including 2 English databases (PubMed and EMBASE) and 4 Chinese databases (CNKI, WanFang, VIP, SinoMed). Searches were conducted until December 31, 2022, and updated prior to submission of the paper. The related terms were as follows: ("taohechengqi"[Title/Abstract]) AND ("diabetes mellitus"[MeSH Terms] OR "diabetes complications"[MeSH Terms] OR "diabet*"[Title/Abstract] OR "IDDM"[Title/Abstract] OR "NIDDM"[Title/Abstract] OR "MODY"[Title/Abstract] OR "T1DM"[Title/Abstract] OR "T2DM"[Title/Abstract] OR "T1D"[Title/Abstract] OR "T2D"[Title/Abstract]) AND ("Animal Experimentation" OR "rat*"). The literature collection was conducted by a researcher (ZHANG) for all published studies up to the cut-off date. The complete search strategy is presented in Appendix 1.

2.2. Study selection

2.2.1. Inclusion criteria

Animals: 1. STZ induced diabetes model; 2. Cardiovascular-related content in the study results. Interventions: Herbs for THCQD, Chinese herbal soup. Comparators: 1. STZ induced diabetes model; 2. The rearing conditions and living environment were the same as those of the experimental group. 3. Did not receive any therapeutic measures.

2.2.2. Exclusion criteria

Model: 1. No accurate description of the model; 2. Human studies; 3. In vitro studies. Interventions: 1. No accurate description of the composition of THCQD used; 2. Finished drugs whose existence of interest relationship cannot be confirmed; 3. Failure to follow animal ethics. Comparators: 1. Control group was given the treatment before the end of the experiment. 2. Control group lived in a different environment than the experimental group and may have experienced treatment that would appear to be harmful. 3. Non-STZ-induced diabetes model.

2.2.3. Data extraction

Two investigators (CAO and ZHANG) independently read and assessed the literature. In case of any disagreements, the literature was reassessed by a third researcher (YANG) to decide whether to be included in the analysis. Data were extracted from all included studies, which included: 1.The method for inducing the diabetes model; 2. The rat species used; 3. The intervention mode; 4. The method of administration; 5. The composition of the THCQD formulation; 6. Description of the results and the mechanism of action involved in the study. For studies without data descriptions, we contacted the corresponding author via their email address to obtain the data. To ensure the completeness and accuracy of the data, one researcher (ZHANG) extracted the data, and another researcher (CAO) double-checked the data.

2.3. Quality assessment

Two reviewers evaluated the methodological quality of the animal studies using SYRCLE [16] criteria, which assessed the following ten items: 1. adequate sequence generation; 2. baseline characteristics; 3. allocation concealment; 4. randomized housing; 5. blinding (performance bias); 6. randomized outcome assessment; 7. blinding (detection bias); 8. incomplete outcome data; 9. selective outcome reporting; 10. other sources of bias. The results of the bias assessment will be presented using graphs and charts, indicating the level of risk of bias (high, low, or unclear) for each of the ten items in each trial.

2.4. Data analysis

The included studies were categorized based on the site of the study, and a count was made of the medications used in conjunction with THCQD. The results were only categorized and described, without providing quantitative statistics.

2.5. Gene targets of THCQD and diabetic cardiovascular complications

The HIT database [17] were utilized to screen the active ingredients present in THCQD. The target genes obtained from the HIT database were combined, and then the target genes of THCQD were obtained after removing the duplicate entries.

To obtain the target genes for Diabetic cardiovascular complications, the term "Diabetic cardiovascular complications" was entered into the GeneCards database (https://www.genecards.org/). Select target genes with relevance score greater than 10.0.

2.6. Intersecting genes and "drug-target-intersecting genes-disease" network construction

Use bioinformatics (https://www.bioinformatics.com.cn/) to make a jvenn diagram to get the drug gene-disease gene intersection. The "drug-target-intersecting genes-disease" network constructionwas built by Cytoscape 3.9.1 software. Sorting the compounds by their degree values to identify key components.

2.7. PPI network construction and topology analysis

The PPI network was constructed using the STRING database [18] and analyzed using Cytoscape 3.9.1 software. The intersection genes were imported into the STRING database, and the species type was set to "Homo sapiens", hide disconnected nodes in the network, and export the PPI network images and TSV files. The obtained TSV files were imported into Cytoscape 3.9.1 software to construct the network. The genes were sorted according to the degree value, and the core targets were screened according to the degree value.

2.8. GO functional enrichment and KEGG pathway enrichment analysis

Enrichment analysis was conducted utilizing the DAVID database [19] to identify enriched biological processes (BP), molecular functions (MF), cellular components (CC), and KEGG pathways of the intersecting genes. The results of the top 20 were presented visually by bioinformatics.

2.9. Molecular docking

Molecular docking of key compounds to their corresponding targets was conducted to validate the results of network pharmacology. The PDB database (https://www1.rcsb.org/) and Uniprot database [20] were used to find and download the molecular structure files and 3D structure models of the target proteins. The molecular structures of target compounds were downloaded from PubChem, and PyMOL 2.3.0 was utilized for operations including the removal of water molecules and proto-ligands from the downloaded target proteins. Ligand molecules were optimized to their minimal energy conformations using Chem3D Ultra 11.0 for molecular mechanics. Pre-processed target proteins were hydrogenated using AutoDock Tools 26, followed by hydrogenation and torsional bond assignment of the optimally conformed ligands from molecular mechanics. The target protein and ligand molecules were subjected to molecular simulation of docking using AutoDock Vina software (https://vina.scripps.edu/). The docking algorithm was Lamarckian Genetic Algorithm, the docking mode was semi-flexible docking, the exhaustiveness was set to 8, and the maximal number of conformations in the output was set to 9, to obtain the docking binding free energy as well as docking Result file. The free binding energy is less than −5 kcal/mol, the binding is excellent, and less than −7 kcal/mol, the binding is strong. PyMOL2.3.0 software was used to visualize the docking results of this group.

3. Results

3.1. Included studies

A total of 179 records were retrieved from the selected database. After removing duplicates, 83 records remained. The titles and abstracts of the articles were read carefully, and 48 records were excluded based on the inclusion and exclusion criteria approach. The full text of the remaining 35 records was read, and 19 records were excluded. 16 studies were finally identified that fit the direction of this review. **As shown in Flow Chart.**

Table 1
Summary table of literature.

Study	Diabetic model	Intervention	Composition	Results
LI Saimei [21]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group 4 Water extracted alcoholic sedimentation group 5 n-Butanol group 6 Ethyl acetate group 7 Diamicron group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae	Improvement of the ultrastructure of myogenic fibers and mitochondria in cardiac myocytes of diabetic rats
LI Saimei [22]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group 4 Water extracted alcoholic sedimentation group 5 n-Butanol group 6 Ethyl acetate group 7 Diamicron group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae	Taohe Chengqi decoction decreases myocardial HYP content and reduces myocardial type III collagen mRNA expression
LI Saimei [23]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group 4 Water extracted alcoholic sedimentation group 5 n-Butanol group 6 Ethyl acetate group 7 Diamicron group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae	Damectin and n-butanol groups improve the structure of elastic membrane in the aortic arch of diabetic rats and improve the morphology of mid-membrane smooth muscle cells and mitochondria
CHU Quan-gen [24]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group 4 Water extracted alcoholic sedimentation group 5 n-Butanol group 6 Ethyl acetate group 7 Diamicron group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae	Taohe Chengqi decoction stabilizes myocardial GluT4 mRNA expression in the heart
CHU Quan-gen [25]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group 4 Water extracted alcoholic sedimentation group 5 n-Butanol group 6 Ethyl acetate group 7 Diamicron group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae	Taohe Chengqi decoction increases Na + -K + -ATPase and Ca2+-ATPase activities in diabetic rat cardiac myocytes
WANG Jun [26]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction high dose group 4 Taohe Chengqi decoction medium dose group 5 Taohe Chengqi decoction low dose group 6 Metformin group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae	Taohe Chengqi decoction reduces the expression of TGF-β1 and CTGF in the femoral artery of diabetic rats
DING Zhi-ming [27]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group 4 Metformin hydrochloride group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis	Taohe Chengqi decoction reduces the expression of collagen I and III in femoral arteries.

(*continued on next page*)

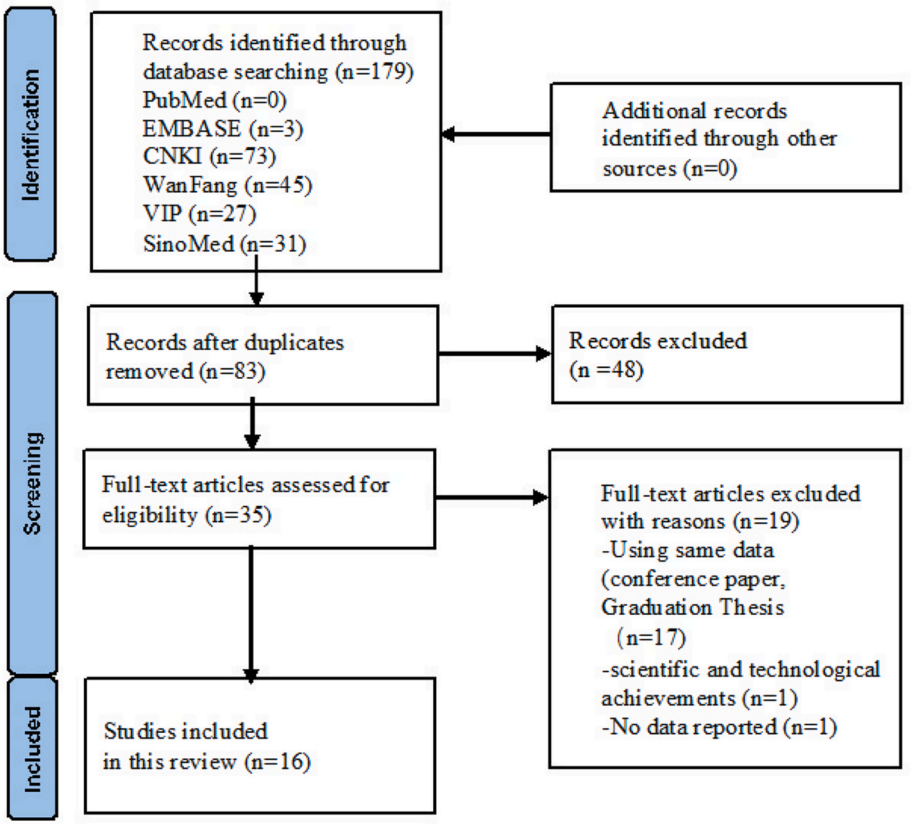
Table 1 (*continued*)

Study	Diabetic model	Intervention	Composition	Results
			Rehmannia glutinosa Radix scrophulariae	
LI Jing [28]	STZ induced diabetes	1 Normal group 2 Diabetes group 3 Taohe Chengqi decoction group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae Salviae Miltiorrhizae	Taohe Chengqi decoction enhances GSH-Px activity in heart tissue and reduces MDA content antioxidant effect
DENG Xiao-feng [29]	STZ induced diabetes	1 Normal group 2 Model group 3 Taohe Chengqi decoction Group A 4 Peach Nucleus Cheng Qi Tang Group B 5 Taohe Chengqi decoction Group C 6 Metformin group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa Radix scrophulariae Salviae Miltiorrhizae cooked Rhubarb Asarum	Decreased VCAM-1, MCP-1, NF-κB in thoracic aorta; decreased NF-κ B mRNA, MCP-1 mRNA, VCAM-1 mRNA expression in thoracic aorta
XU Yang [30]	High fat and high sugar diet induced diabetes model	1 Normal group 2 Model group 3 Taohe Chengqi decoction high dose group 4 Tao Nucleus Cheng Qi Tang medium dose group 5 Tao Nucleus Cheng Qi Tang low dose group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite	Taohe Chengqi decoction intervention reduces TGF-β expression in diabetic rats TGF-β expression and IGF-1 expression in the femoral artery of rats
XU Yang [31]	High fat and high sugar diet induced diabetes model	1 Normal group 2 Model group 3 Taohe Chengqi decoction high dose group 4 Tao Nucleus Cheng Qi Tang medium dose group 5 Tao Nucleus Cheng Qi Tang low dose group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite	Taohe Chengqi decoction intervention reduces TLR-2 and TLR-4 expression in the lower limb femoral artery vasculature of diabetic rats TLR-4 expression
XU Shuai [32]	STZ induced diabetes	1 Normal group 2 Model group 3 Taohe Chengqi decoction Group A 4 Taohe Chengqi decoction Group B 5 Taohe Chengqi decoction Group C 6 Aminoguanidine hydrochloride group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Rehmannia glutinosa Radix Ophiopogonis Radix scrophulariae cooked Rhubarb Asarum	Taohe Chengqi decoction reduces the production of AGEs and the expression of receptor RAGE mRNA in the thoracic aorta.
XU Yang [33]	STZ induced diabetes	1 Normal group 2 Model group 3 Taohe Chengqi decoction Group A 4 Taohe Chengqi decoction Group B	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite	Taohe Chengqi decoction decreases the expression of TLR-2 and TLR-4, decreases the content of TGF-β and increases the content of IGF-1 in the femoral artery of diabetic rats
GU Yu-mei [34]	STZ induced diabetes	1 Normal group 2 Model group 3 Taohe Chengqi decoction Group I 4 Taohe Chengqi decoction Group II 5 Metformin group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Radix Ophiopogonis Rehmannia glutinosa	Taohe Chengqi decoction reduces PI3K(P85) mRNA and Akt mRNA expression in the thoracic aorta of diabetic rats and inhibits the development of atherosclerosis in the thoracic aorta

(*continued on next page*)

Table 1 (*continued*)

Study	Diabetic model	Intervention	Composition	Results
			Radix scrophulariae Salviae Miltiorrhizae Asarum	
XU Shuai [35]	STZ induced diabetes	1 Model group 2 Taohe Chengqi decoction Group A 3 Taohe Chengqi decoction Group B 4 Taohe Chengqi decoction Group C 5 Metformin group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Rehmannia glutinosa Radix Ophiopogonis Radix scrophulariae cooked Rhubarb Asarum	Taohe Chengqi decoction enhances eNOS mRNA expression in the thoracic aorta of diabetic rats
ZHANG Ya-nan [36]	STZ induced diabetes	1 Normal group 2 Model group 3 Taohe Chengqi decoction low dose group 4 Taohe Chengqi decoction high dose group 5 Metformin Hydrochloride Group	Peach Seed Rhubarb Cassia twig Licorice Root Mirabilite Astragalus membranaceus Rehmannia glutinosa Radix Ophiopogonis Salviae Miltiorrhizae	Taohe Chengqi decoction reduces NLRP3, ASC, Caspase-1 and p–NF–κB p65 protein expression in myocardial tissue of diabetic rats



3.2. Characteristics of the study

In this review, a total of 16 studies were included [21–36]. Included 6 studies of the myocardium [21,22,24,25,28,36], 1 study of

the aortic arch [23], 5 studies of the femoral artery [26,27,30,31,33], 4 studies of the thoracic aorta [29,32,34,35]. The period of inclusion in the study was from 2005 to 2022. The results are shown in Table 1.

3.3. Cardiovascular protection mechanism of THCQD in diabetic rats

3.3.1. Effects of THCQD on the myocardium in diabetic rats

6 studies [21,22,24,25,28,36] reported significant effects of THCQD on myocardium in diabetic rats. Compared with the model group, the use of THCQD improved the ultrastructure of cardiomyocytes [21]. Reduced myocardial hydroxyproline (HYP) content and decreased myocardial type III collagen mRNA expression [22]. And stabilized myocardial glucose transporter protein-4 (GLUT4) mRNA expression [24]. Increased Na^{+}-K^{+}-ATPase and Ca^{2+}-ATPase activities in cardiomyocytes [25]. Enhanced myocardial glutathione peroxidase (GSH-Px) activity and reduced malondialdehyde (MDA) content [28]. Decreased NLRP3, ASC, Caspase-1, and p–NF–κB p65 protein expression in myocardium [36]. These findings suggest that THCQD has a protective effect on the myocardium of diabetic rats, potentially improving cardiac function and reducing the negative effects of diabetes on heart tissue.

3.3.2. Effect of THCQD on the aortic arch in diabetic rats

One study [23] reported a significant effect of THCQD on the aortic arch in diabetic rats. Compared with the model group, THCQD improved the internal elastic membrane structure within the aortic arch and improved the morphology of mid-membrane smooth muscle cells and mitochondria in diabetic rats [23]. These improvements suggest that THCQD may have a beneficial impact on the vascular health of diabetic rats, particularly in the aortic arch region.

3.3.3. Effects of THCQD on the femoral artery in diabetic rats

Five studies [26,27,30,31,33] reported significant effects of THCQD on the femoral arteries in diabetic rats. Compared with the model group, THCQD decreased the expression of collagen I and III in the femoral arteries [27]. Decreased the expression of transforming growth factor β1 (TGF-β1) and connective tissues growth factor (CTGF) [26]. Decreased the expression of Transforming Growth Factor β (TGF-β) and increased the expression of Insulin-Like Growth Factor-1 (IGF-1) in femoral arteries [30]. Decreased the expression of Toll Like Receptors-2 (TLR-2), Toll Like Receptors-4 (TLR-4) expression in femoral arteries [31]. Decreased femoral artery TLR-2 and TLR-4 expression, reduced TGF-β content and elevated IGF-1 content in femoral arteries [33]. These findings suggest that THCQD may have therapeutic potential in improving vascular health by modulating key growth factors and immune response markers in the femoral arteries of diabetic rats.

3.3.4. Effects of THCQD on the thoracic aorta in diabetic rats

Four studies [29,32,34,35] reported significant effects of THCQD on the thoracic aorta in diabetic rats. Compared with the model group, THCQD decreased the expression of Vascular Cell Adhesion Molecule-1 (VCAM-1), Monocyte Chemoattractant Protein-1 (MCP-1) and NF-κB protein in the thoracic aorta; decreased the expression of NF-κB mRNA, MCP-1 mRNA, and VCAM-1 mRNA expression [29]. Decreased the expression of PI3K (P85) mRNA and Akt mRNA [34]. Reduced Advanced Glycosylation End products (AGEs) and decreased expression of Receptor of Advanced Glycation End products (RAGEs) mRNA [32]. And increased expression of endothelial Nitric Oxide Synthase (eNOS) mRNA in the thoracic aorta [35]. Overall, these studies suggest that THCQD may exert beneficial effects on the thoracic aorta of diabetic rats by reducing inflammation, modulating key signaling pathways, and improving vascular function.

Table 2
Risk of bias for included studies.

Study	a	b	c	d	e	f	g	h	i	j
LI Saimei [21]	Y	U	U	U	U	U	U	N	N	N
LI Saimei [22]	Y	U	U	U	U	U	U	N	N	N
LI Saimei [23]	Y	U	U	U	U	U	U	N	N	N
CHU Quan-gen [24]	Y	U	U	U	U	U	U	N	N	N
CHU Quan-gen [25]	Y	U	U	U	U	U	U	N	N	N
WANG Jun [26]	Y	U	U	U	U	U	U	N	N	N
DING Zhi-ming [27]	Y	U	U	U	U	U	U	N	N	N
LI Jing [28]	U	U	U	U	U	U	U	N	N	N
DENG Xiao-feng [29]	Y	Y	U	U	U	U	U	N	N	N
XU Yang [30]	U	Y	U	U	U	U	U	N	N	N
XU Yang [31]	U	Y	U	U	U	U	U	N	N	N
XU Shuai [32]	Y	Y	U	U	U	U	U	N	N	N
XU Yang [33]	U	Y	U	U	U	U	U	N	N	N
GU Yu-mei [34]	U	Y	U	U	U	U	U	N	N	N
XU Shuai [35]	U	U	U	U	U	U	U	U	U	U
ZHANG Ya-nan [36]	U	Y	U	U	U	U	U	N	N	N

a: Sequence generation; b: Baseline characteristics; c: Allocation concealment; d: Random housing; e: Blinding (performance bias); f: Random outcome assessment; g: Blinding (detection bias); h: Incomplete outcome data; i: Selective outcome reporting; j: Other sources of bias; Y: yes; N: no; U: unclear.

Table 3
THCQD chemical composition.

Id	Pref Name	CAS	Pubchem ID	Smiles
C1125	Baicalin	CAS:21967-41-9	CID:64982	OC(=O)[C@H]1O[C@@H](Oc2cc3oc(cc(=O)c3c(c2O)O)c2ccccc2)[C@@H]([C@H]([C@@H]1O)O)O
C0485	Wogonin	CAS:632-85-9	CID:5281703	COC1=C(C=C(C2=C1OC(=CC2=O)C3=CC=CC=C3)O)O
C1221	Catechol	CAS:120-80-9	CID:289	C1=CC=C(C(=C1)O)O
C1114	Baicalein	CAS:491-67-8	CID:5281605	C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O
C1178	Beta-Sitosterol		CID:222284	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
C1237	Chrysin	CAS:480-40-0	CID:5281607	C1=CC=C(C=C1)C2=CC(=O)C3=C(C=C(C=C3O2)O)O
C0267	Oroxylin A	CAS:480-11-5	CID:5320315	COC1=C(C2=C(C=C1O)OC(=CC2=O)C3=CC=CC=C3)O
C0263	Oleic Acid	CAS:112-80-1	CID:445639	CCCCCCCCC=CCCCCCCCC(=O)O
C0189	Linoleic Acid	CAS:60-33-3	CID:5280450	CCCCC/C=C\C/C=C\CCCCCCCC(=O)O
C0843	Abscisic Acid	CAS:21293-29-8	CID:5375199	OC(=O)/C=C(\C=C\C1(O)C(=CC(=O)CC1(C)C)C)/C
C0447	Thymol	CAS:89-83-8	CID:6989	CC1=CC(=C(C=C1)C(C)C)O
C1162	Benzaldehyde		CID:240	O=Cc1ccccc1
C0259	Octanol	CAS:111-87-5	CID:957	CCCCCCCCO
C1218	Carvacrol	CAS:499-75-2	CID:10364	CC(c1ccc(c(c1)O)C)C
C0064	Eugenol	CAS:97-53-0	CID:3314	COC1=C(C=CC(=C1)CC=C)O
C0839	(2E,4E)-Deca-2,4-Dienal	CAS:25152-84-5	CID:5283349	CCCCCC=CC=CC=O
C0808	5,7-Dihydroxy-2-(4-Hydroxyphenyl)-2,3-Dihydrochromen-4-One		CID:932	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
C0041	Emodin	CAS:518-82-1	CID:3220	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)O
C0397	Serotonin	CAS:50-67-9	CID:5202	NCCc1c[nH]c2c1cc(O)cc2
C0377	Rutin	CAS:153-18-4	CID:5280805	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O)O
C0881	Aloe-Emodin		CID:10207	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)CO
C0306	Physcion	CAS:521-61-9	CID:10639	COc1cc(O)c2c(c1)C(=O)c1c(C2=O)c(O)cc(c1)C
C1240	Chrysophanol	CAS:481-74-3	CID:10208	Cc1cc(O)c2c(c1)C(=O)c1c(C2=O)c(O)ccc1
C0369	Rhein	CAS:478-43-3	CID:10168	C1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)C(=O)O
C0090	Gallic Acid	CAS:149-91-7	CID:370	C1=C(C=C(C(=C1O)O)O)C(=O)O
C0045	Epicatechin Gallate	CAS:1257-08-5	CID:107905	Oc1cc(O)c2c(c1)O[C@@H]([C@@H](C2)OC(=O)c1cc(O)c(c(c1)O)O)c1ccc(c(c1)O)O
C1220	Catechin		CID:1203	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
C0356	Quinalizarin	CAS:81-61-8	CID:5004	Oc1c(O)ccc2c1C(=O)c1c(C2=O)c(O)ccc1O
C0339	Purpurin	CAS:81-54-9	CID:6683	Oc1c(O)cc(c2c1C(=O)c1ccccc1C2=O)O
C0912	Anthraquinone	CAS:84-65-1	CID:6780	O=C1c2ccccc2C(=O)c2c1cccc2
C0119	Hesperidin	CAS:520-26-3	CID:10621	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC(=C(C=C5)OC)O)O)O)O)O)O)O)O)O
C0110	Glycyrrhizin	CAS:103000-77-7	CID:14982	CC1(C2CCC3(C(C2(CCC1OC4C(C(C(C(O4)C(=O)O)O)O)OC5C(C(C(C(O5)C(=O)O)O)O)O)O)C)C(=O)C=C6C3(CCC7(C6CC(CC7)(C)C(=O)O)C)C)C)C
C1125	Baicalin	CAS:21967-41-9	CID:64982	OC(=O)[C@H]1O[C@@H](Oc2cc3oc(cc(=O)c3c(c2O)O)c2ccccc2)[C@@H]([C@H]([C@@H]1O)O)O
C0114	(−)-Epicatechin		CID:72276	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
C0203	Magnolol	CAS:528-43-8	CID:72300	C=CCc1ccc(c(c1)c1cc(CC=C)ccc1O)O
C0126	Honokiol	CAS:35354-74-6	CID:72303	C=CCC1=CC(=C(C=C1)O)C2=CC(=C(C=C2)O)CC=C
C0243	Naringin	CAS:10236-47-2	CID:442428	CC1C(C(C(C(O1)OC2C(C(C(OC2OC3=CC(=C4C(=O)CC(OC4=C3)C5=CC=C(C=C5)O)O)CO)O)O)O)O)O)O
C1243	Cinnamic Acid	CAS:621-82-9	CID:444539	C1=CC=C(C=C1)C=CC(=O)O
C0363	Resveratrol	CAS:501-36-0	CID:445154	C1=CC(=CC=C1C=CC2=CC(=CC(=C2)O)O)O
C0073	Ferulic Acid	CAS:1135-24-6	CID:445858	COc1cc(/C=C/C(=O)O)ccc1O
C0308	Piceatannol	CAS:10083-24-6	CID:667639	Oc1cc(/C=C/c2ccc(c(c2)O)O)cc(c1)O
C1203	Caffeic Acid	CAS:331-39-5	CID:689043	C1=CC(=C(C=C1C=CC(=O)O)O)O
C1114	Baicalein	CAS:491-67-8	CID:5281605	C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O
C0364	Resveratrol 4′-Methyl Ether	CAS:33626-08-3	CID:6255462	COc1ccc(cc1)/C=C/c1cc(O)cc(c1)O
C0618	Sennoside A	CAS:81-27-6	CID:73111	OC[C@H]1O[C@@H](Oc2cccc3c2C(=O)c2c([C@@H]3[C@H]3c4cc(cc(c4C(=O)c4c3cccc4O[C@@H]3O[C@H](CO)[C@H]([C@@H]([C@H]3O)O)O)O)O)C(=O)[O-])cc(cc2O)C(=O)[O-])[C@@H]([C@H]([C@@H]1O)O)O
C0714	Rhaponticin	CAS:155-58-8	CID:637213	OC[C@H]1O[C@@H](Oc2cc(/C=C/c3ccc(c(c3)O)OC)cc(c2)O)[C@@H]([C@H]([C@@H]1O)O)O
C0775	Rhapontigenin	CAS:500-65-2	CID:5320954	COC1=C(C=C(C=C1)C=CC2=CC(=CC(=C2)O)O)O
C1241	Cianidanol		CID:9064	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
C0045	Epicatechin Gallate	CAS:1257-08-5	CID:107905	Oc1cc(O)c2c(c1)O[C@@H]([C@@H](C2)OC(=O)c1cc(O)c(c(c1)O)O)c1ccc(c(c1)O)O

(*continued on next page*)

Table 3 (*continued*)

Id	Pref Name	CAS	Pubchem ID	Smiles
C0188	Linalool	CAS:78-70-6	CID:6549	CC(=CCCC(C)(C=C)O)C
C1243	Cinnamic Acid	CAS:621-82-9	CID:444539	C1=CC=C(C=C1)C=CC(=O)O
C1242	Cinnamaldehyde	CAS:104-55-2	CID:637511	C1=CC=C(C=C1)C=CC=O
C1259	Coumarin	CAS:91-64-5	CID:323	C1=CC=C2C(=C1)C=CC(=O)O2
C0419	Styrene	CAS:100-42-5	CID:7501	C=CC1=CC=CC=C1
C0333	Protocatechuic Acid	CAS:99-50-3	CID:72	C1=CC(=C(C=C1C(=O)O)O)O
C0532	Procyanidin B2	CAS:29106-49-8	CID:122738	C1C(C(OC2=C1C(=CC(=C2C3C(C(OC4=CC(=CC(=C34)O)O)C5=CC(=C(C=C5)O)O)O)O)O)C6=CC(=C(C=C6)O)O)O
C0193	Liquiritin	CAS:551-15-5	CID:503737	C1C(OC2=C(C1=O)C=CC(=C2)O)C3=CC=C(C=C3)OC4C(C(C(C(O4)CO)O)O)O)O
C0041	Emodin	CAS:518-82-1	CID:3220	CC1=CC2=C(C(=C1)O)C(=O)C3=C(C2=O)C=C(C=C3O)O
C0152	Isoliquiritigenin	CAS:961-29-5	CID:638278	C1=CC(=CC=C1C=CC(=O)C2=C(C=C(C=C2)O)O)O
C0156	Isoquercetin	CAS:482-35-9	CID:5280804	OC[C@H]1O[C@@H](Oc2c(oc3c(c2 = O)c(O)cc(*c*3)O)c2ccc(c(*c*2)O)O)[C@@H]([C@H]([C@@H]1O)O)O
C1208	Calycosin	CAS:20575-57-9	CID:5280448	COc1ccc(cc1O)c1coc2c(c1 = O)ccc(*c*2)O
C0333	Protocatechuic Acid	CAS:99-50-3	CID:72	C1=CC(=C(C=C1C(=O)O)O)O
C0914	Apigenin	CAS:520-36-5	CID:5280443	C1=CC(=CC=C1C2 = CC(=O)C3=C(C=C(C=C3O2)O)O)O
C0044	Enoxolone	CAS:471-53-4	CID:10114	O=C1C=C2[C@@H]3C[C@](C)(CC[C@]3(C)CC[C@]2([C@]2([C@H]1[C@@]1(C)CC[C@@H](C([C@@H]1CC2)(C)C)O)C)C(=O)O
C0124	Hispidulin	CAS:1447-88-7	CID:5281628	COc1c(O)cc2c(c1O)c(=O)cc(o2)c1ccc(*cc*1)O
C0109	Glycyrol	CAS:23013-84-5	CID:5320083	COc1c(CC=C(C)C)c(O)cc2c1c1oc3c(c1c(=O)o2)ccc(*c*3)O
C1278	Daidzein	CAS:486-66-8	CID:5281708	C1=CC(=CC=C1C2 = COC3=C(C2=O)C=CC(=C3)O)O
C0164	Kaempferol	CAS:520-18-3	CID:5280863	C1=CC(=CC=C1C2 = C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
C0083	Formononetin	CAS:485-72-3	CID:5280378	COC1=CC=C(C=C1)C2=COC3=C(C2=O)C=CC(=C3)O
C0074	Fisetin	CAS:528-48-3	CID:5281614	C1=CC(=C(C=C1C2 = C(C(=O)C3=C(O2)C=C(C=C3)O)O)O)O
C0291	Paraben		CID:3702506	Oc1ccc(*cc*1)C(=O)O
C0108	Glycybenzofuran	CAS:1253641-15-4	CID:46934435	COc1c(CC=C(C)C)c(O)cc(c1c1oc2c(c1C)ccc(*c*2)O)O
C0838	8-Prenylnaringenin	CAS:53846-50-7	CID:480764	CC(=CCc1c(O)cc(c2c1O[C@@H](CC2=O)c1ccc(*cc*1)O)O)C
C0090	Gallic Acid	CAS:149-91-7	CID:370	C1=C(C=C(C(=C1O)O)O)C(=O)O
C0312	Pinocembrin	CAS:480-39-7	CID:68071	Oc1cc2O[C@@H](CC(=O)c2c(*c*1)O)c1ccccc1
C0114	(−)-Epicatechin		CID:72276	C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O
C0105	Glabridin		CID:124052	Oc1ccc(c(*c*1)O)[C@@H]1COc2c(C1)ccc1c2C=CC(O1)(C)C
C1239	Chrysoeriol	CAS:491-71-4	CID:5280666	COc1cc(ccc1O)c1cc(=O)c2c(o1)cc(cc2O)O
C0110	Glycyrrhizin	CAS:103000-77-7	CID:14982	CC1(C2CCC3(C(C2(CCC1OC4C(C(C(C(O4)C(=O)O)O)O)O)OC5C(C(C(C(O5)C(=O)O)O)O)O)C)C(=O)C=C6C3(CCC7(C6CC(CC7)(C)C(=O)O)C)C)C)C
C0242	Naringenin	CAS:480-41-1	CID:439246	Oc1ccc(cc1)[C@@H]1CC(=O)c2c(O1)cc(cc2O)O
C0089	Galangin	CAS:548-83-4	CID:5281616	C1=CC=C(C=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
C0935	Astragalin	CAS:480-10-4	CID:5282102	OC[C@H]1O[C@@H](Oc2c(oc3c(c2 = O)c(O)cc(*c*3)O)c2ccc(*cc*2)O)[C@@H]([C@H]([C@@H]1O)O)O
C0045	Epicatechin Gallate	CAS:1257-08-5	CID:107905	Oc1cc(O)c2c(*c*1)O[C@@H]([C@@H](C2)OC(=O)c1cc(O)c(c(*c*1)O)O)c1ccc(c(*c*1)O)O
C1243	Cinnamic Acid	CAS:621-82-9	CID:444539	C1=CC=C(C=C1)C=CC(=O)O
C1259	Coumarin	CAS:91-64-5	CID:323	C1=CC=C2C(=C1)C=CC(=O)O2
C0013	Dibenzoylmethane	CAS:120-46-7	CID:8433	O=C(*c*1*ccccc*1)CC(=O)c1ccccc1
C1178	Beta-Sitosterol		CID:222284	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
C0905	Anethole	CAS:104-46-1	CID:637563	CC=CC1=CC=C(C=C1)OC
C0377	Rutin	CAS:153-18-4	CID:5280805	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O
C0101	Genistein	CAS:446-72-0	CID:5280961	C1=CC(=CC=C1C2 = COC3=CC(=CC(=C3C2=O)O)O)O
C0053	Esculetin	CAS:305-01-1	CID:5281416	C1=CC(=O)OC2=CC(=C(C=C21)O)O
C0836	8-Prenylapigenin	CAS:72357-31-4	CID:10246505	CC(=CCc1c(O)cc(c2c1oc(cc2 = O)c1ccc(*cc*1)O)O)C
C0602	2,3,9,10-Tetramethoxy-6,8,13,13A-Tetrahydro-5H-Isoquinolino[2,1-B] Isoquinoline	CAS:2934-97-6	CID:5417	COc1cc2CCN3C(c2cc1OC)Cc1c(C3)c(OC)c(*cc*1)OC
C0493	Licochalcone D	CAS:144506-15-0	CID:10473311	COc1c(/C=C/C(=O)c2ccc(c(*c*2)CC=C(C)C)O)ccc(c1O)O
C0808	5,7-Dihydroxy-2-(4-Hydroxyphenyl)-2,3-Dihydrochromen-4-One		CID:932	C1C(OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O
C0185	Licoagrochacone A		CID:5318998	CC(C)(C=C)C1=C(C=C(C(=C1)C=CC(=O)C2=CC=C(C=C2)O)OC)O
C0262	Oleanolic_Acid		CID:10494	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)O)C)C2C1)C)C(=O)O)C
C0462	Tromethamine	CAS:77-86-1	CID:6503	OCC(CO)(CO)N

3.4. Herbs used in combination with THCQD

THCQD has been used in combination with other herbs when used to in the treatment of diabetic cardiovascular disease. 3 studies [30,31,33] used only the fixed herbal formula of THCQD. 13 studies [21–29,32,34–36] used other herbs in combination with THCQD. 12 studies [21–29,32,34,35] used Astragalus membranaceus, Radix Ophiopogonis, Rehmannia glutinosa and Radix scrophulariae in combination with THCQD; 4 studies [28,29,34,36] added Salviae Miltiorrhizae; 4 studies [29,32,34,35] added Asarum; and three studies [29,32,35] added cooked Rhubarb.

3.5. Quality assessment

Of the included literature, 9 studies (56 %) mentioned the method of random assignment. 7 studies (44 %) reported baseline characteristics of the animals. All studies had no studied that mentioned allocation concealment, randomized housing, blinding (performance bias), randomized outcome assessment, and blinding (detection bias). All but one study was unclear, others had complete outcome data results and no other sources of bias. The results are presented in Table 2.

3.6. Gene targets of THCQD and diabetic cardiovascular complications

Peach kernel, Rhubarb, Cassia twig, Licorice Root and Mirabilite were imported into the HIT database. And 17 compounds and 227 genes were obtained from the Peach Seed, 31 compounds and 414 genes from the Rhubarb, 8 compounds and 54 genes from the Cassia twig, 41 compounds and 380 genes from the Licorice Root, and 1 compound and 5 genes from the Mirabilite. The chemical composition is shown in Table 3, the network of component targets is shown in Appendix 2.

The term “Diabetic cardiovascular complications” was entered into the GeneCards database, select the relevance score greater than 10.0. A total of 1831 target genes were obtained. The results are shown in Appendix 3.

3.7. Intersecting genes and “drug-target-intersecting genes-disease” network construction

275 intersecting genes were obtained using Venny 2.1. The mappings were analyzed using the network analysis plugin and the compounds with the top degree values were C0363 (Resveratrol), C0041 (Emodin), C1114 (Baicalein), ranked according to their degree values. The gene intersection were shown in Fig. 1, and the “drug-target-intersecting genes-disease” network was shown in

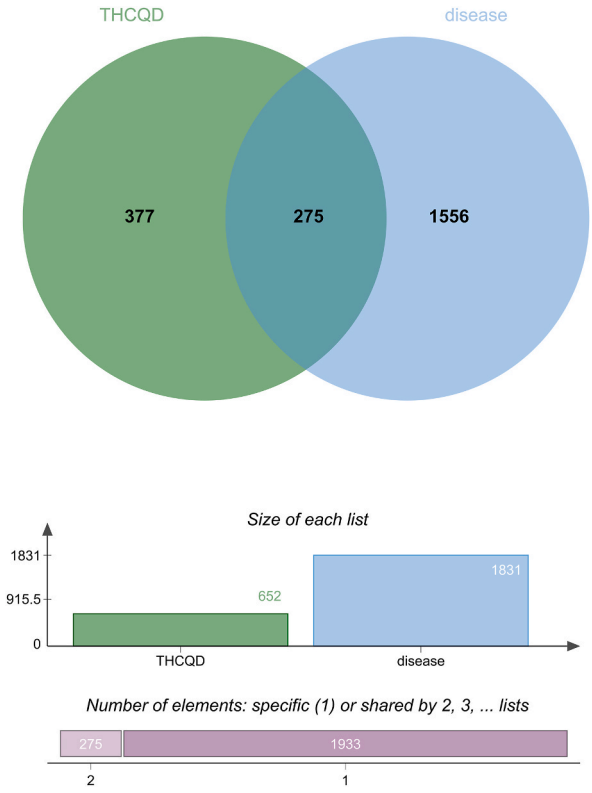


Fig. 1. THCQD-disease gene intersection.

Appendix 4.

3.8. PPI network construction and topology analysis

The PPI network display was obtained using STRING database, 275 genes were imported, hide disconnected nodes in the network, 269 nodes and 9312 edges were obtained. Export the PPI network data and import the data into Cytoscape 3.9.1 software for analysis. The genes were ranked according to the degree value, and the top degree values were INS, AKT1, TNF, ALB, IL6, IL1B, etc. The PPI results were shown in Appendix 5, the topology analysis results were shown in Fig. 2, and the topology analysis information were shown in Table 4.

3.9. GO functional enrichment and KEGG pathway enrichment analysis

A total of 1196 BPs, 101 CCs and 210 MFs were obtained from GO functional enrichment. The results of enrichment analysis were sorted according to *P*-value, The top 3 BPs focused on positive regulation of gene expression, response to hypoxia, positive regulation of transcription from RNA polymerase II promoter. The top 3 CCs focused on extracellular space, extracellular region, cell surface. The top 3 MFs focused on enzyme binding, identical protein binding, cytokine activity. A total of 192 KEGG pathways were obtained, and sorted according to the *P*-value, KEGG pathways were mainly concentrated in AGE-RAGE signaling pathway in diabetic complications, Pathways in cancer, Lipid and atherosclerosis, Fluid shear stress and atherosclerosis, etc. The top 10 bars of BP, CC, MF and the top 20 bars of KEGG were made as bubble plots, see Figs. 3 and 4; examples of pathways with minimal *P*-value in KEGG see Fig. 5.

3.10. Molecular docking

Molecular simulations of the docking process between key components and target genes were performed using AutoDock Vina v.1.2.0 software. This analysis aimed to obtain the binding free energies and the corresponding docking result files. The binding energy data are presented in Table 5. It is important to note that the smaller the binding energy observed in molecular docking, the stronger the binding affinity between the compound and the target protein. The molecular docking results for the three compounds with the six core protein receptors indicated that Resveratrol was able to form strong interactions with all six core protein receptors. Detailed results of the molecular docking are provided in Figs. 6 and 7.

4. Discussion

Taohe Chengqi Decoction is a very commonly used herbal combination for the treatment of diabetes mellitus, and THCQD is also frequently used for the treatment of diabetic cardiovascular complications. This review summarizes the mechanism of THCQD in treating diabetic cardiovascular complications. Although the number of studies is limited, most of the findings suggest that THCQD does have a beneficial effect on diabetic cardiovascular complications (Fig. 8).

4.1. THCQD improves myocardial function in diabetic rats

A study by Li [22] found that in diabetic rat model, myocardial fibrosis occurred with increased HYP content and increased expression of type I and III collagen in the myocardium, and that THCQD could counteract fibrosis by reducing myocardial HYP content and decreasing myocardial type III collagen mRNA expression. And Li [21] observed by electron microscopy that THCQD could improve the ultrastructure of myogenic fibers and mitochondria in diabetic rat cardiac myocytes. Heart Injuries in DCM is

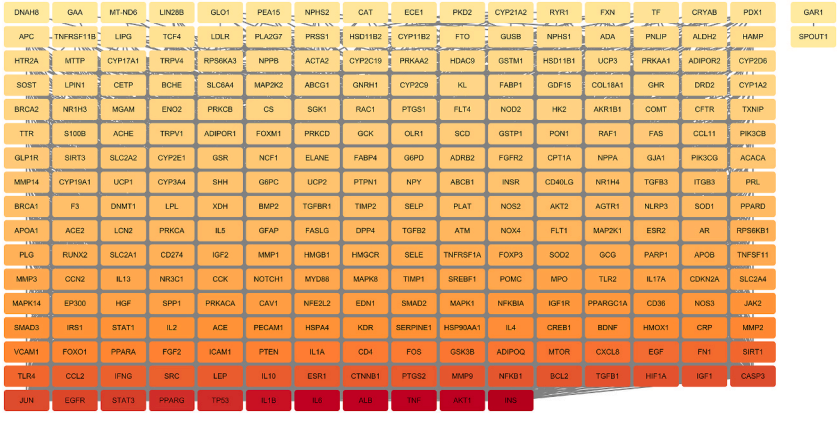


Fig. 2. Topology analysis.
The genes in the figure are sorted by degree, the genes marked in red, the redder the color the larger the degree.

Table 4
Topology analysis information.

Name	Stress	Degree	TopologicalCoefficient
INS	49006	221	0.295989
AKT1	41802	210	0.306749
TNF	40022	209	0.309836
ALB	42916	208	0.306517
IL6	38444	208	0.310566
IL1B	29264	192	0.325971
TP53	28822	181	0.329435
PPARG	27470	179	0.329756
STAT3	20972	170	0.346548
EGFR	21884	165	0.337564
JUN	17580	161	0.358608
CASP3	17880	160	0.355428
HIF1A	16086	156	0.361998
TGFB1	16402	156	0.360188
IGF1	16386	156	0.356072
BCL2	16292	154	0.360853
NFKB1	15054	153	0.368167
MMP9	15408	153	0.363621
PTGS2	16178	151	0.363089
ESR1	16846	150	0.357082
CTNNB1	17688	150	0.352352
IL10	14088	149	0.366772
LEP	17906	148	0.347231
SRC	13432	147	0.365588
CCL2	14084	145	0.368234
IFNG	12540	145	0.3708
TLR4	12200	141	0.375432
SIRT1	13706	140	0.358512
FN1	12166	139	0.376308
EGF	10858	138	0.373946
CXCL8	9436	133	0.384598
MTOR	10988	131	0.375682
ADIPOQ	12322	130	0.352337
GSK3B	10978	129	0.371186
CD4	10158	127	0.386879
FOS	10042	127	0.383641
IL1A	7848	124	0.394887
PTEN	8614	122	0.385772
ICAM1	6932	122	0.398855
FGF2	6840	121	0.393678
PPARA	10646	119	0.360713
VCAM1	6330	118	0.396936
FOXO1	13896	118	0.370835
MMP2	7066	117	0.406798
CRP	8440	116	0.367326
HMOX1	9102	114	0.408127
IL4	5032	113	0.415085
BDNF	8264	113	0.39065
CREB1	10860	113	0.395146
KDR	6348	111	0.394049
HSP90AA1	8416	111	0.374693
SERPINE1	5644	111	0.40254
PECAM1	5298	110	0.407063
HSPA4	9734	110	0.387775
ACE	18020	109	0.369604
IL2	5366	108	0.408635
STAT1	4720	108	0.414006
IRS1	7706	107	0.365088
SMAD3	5180	107	0.41683
JAK2	5116	107	0.41068
NOS3	13142	105	0.39632
CD36	6562	104	0.381252
PPARGC1A	14988	103	0.355865
IGF1R	5046	102	0.393055
NFKBIA	3952	102	0.42127
MAPK1	8278	100	0.391635
SMAD2	3988	100	0.421565
EDN1	8316	100	0.404885

(*continued on next page*)

Table 4 (*continued*)

Name	Stress	Degree	TopologicalCoefficient
CAV1	8730	97	0.406311
NFE2L2	4376	97	0.410458
PRKACA	15114	96	0.376703
SPP1	3656	94	0.41784
MAPK14	4302	93	0.410557
EP300	4996	93	0.389313
HGF	3270	93	0.418188
SLC2A4	8478	90	0.369686
MPO	3990	90	0.39106
IL17A	2318	90	0.438507
TLR2	2708	90	0.431595
CDKN2A	3312	90	0.423248
SREBF1	7234	89	0.356912
TIMP1	3100	89	0.430078
POMC	14284	89	0.363182
NOTCH1	3228	88	0.428059
MYD88	2566	88	0.431252
MAPK8	2838	88	0.43737
CCK	3130	87	0.436077
NR3C1	6332	86	0.40397
CCN2	2932	86	0.428302
IL13	2080	86	0.434543
MMP3	2224	85	0.442353
TNFSF11	2522	84	0.438606
APOB	6138	83	0.339732
PARP1	2726	81	0.422502
GCG	3814	81	0.390152
SOD2	18696	80	0.378267
SELE	2362	79	0.42691
TNFRSF1A	2170	79	0.433225
FOXP3	1804	79	0.447632
HMGCR	5628	77	0.350747
MMP1	1832	77	0.443698
HMGB1	1986	77	0.44928
CD274	1548	76	0.447112
IGF2	4016	76	0.412162
SLC2A1	5408	75	0.422545
PLG	2566	75	0.430579
RPS6KB1	2094	75	0.446439
RUNX2	2468	75	0.438
AR	2230	73	0.426376
ESR2	2812	72	0.431881
FLT1	1498	72	0.458012
MAP2K1	1356	72	0.461165
NOX4	2156	71	0.43512
ATM	2010	70	0.434647
TGFB2	1542	69	0.445892
DPP4	2344	68	0.411485
FASLG	1054	68	0.470362
PRKCA	1908	66	0.432549
IL5	1310	66	0.434363
GFAP	1876	66	0.440143
LCN2	1798	65	0.432729
APOA1	5480	64	0.349691
PPARD	3970	64	0.430284
ACE2	2252	64	0.436897
SOD1	21996	64	0.399639
AGTR1	3842	62	0.414578
NLRP3	1164	62	0.453226
PLAT	3532	61	0.458763
TIMP2	792	61	0.474198
SELP	958	61	0.42981
TGFBR1	1278	61	0.456336
AKT2	1452	61	0.421286
NOS2	5984	61	0.444867
BMP2	1174	60	0.459073
XDH	3754	59	0.402942
LPL	2718	58	0.340419
F3	1478	58	0.42923

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Table 4 (*continued*)

Name	Stress	Degree	TopologicalCoefficient
DNMT1	900	58	0.466446
BRCA1	1286	57	0.428715
NR1H4	2068	57	0.375452
TGFB3	774	57	0.463816
PRL	2062	57	0.418162
ITGB3	1906	57	0.391926
CD40LG	530	56	0.468524
INSR	1556	55	0.386014
ABCB1	1998	54	0.406553
NPY	2192	54	0.363232
UCP2	1486	54	0.376799
PTPN1	1070	54	0.457842
SHH	592	52	0.477626
CYP3A4	6400	52	0.322372
G6PC	1662	52	0.338842
UCP1	1308	51	0.3724
CYP19A1	7142	51	0.400646
MMP14	400	50	0.470388
ACACA	1602	49	0.308905
NPPA	3950	49	0.405593
GJA1	2426	49	0.458284
PIK3CG	818	49	0.45776
CPT1A	1116	48	0.350032
ADRB2	3274	48	0.415802
FGFR2	902	48	0.388505
FABP4	966	47	0.401298
G6PD	6652	47	0.314295
NCF1	940	47	0.441226
ELANE	532	47	0.446306
GSR	8432	47	0.397485
CYP2E1	2890	46	0.389381
SLC2A2	1368	46	0.357662
SIRT3	3544	46	0.439346
GLP1R	930	44	0.410906
RAF1	584	44	0.433498
FAS	2258	44	0.4915
PIK3CB	700	44	0.412789
CCL11	292	44	0.465819
PON1	1842	43	0.342511
GSTP1	2880	43	0.351056
SCD	680	43	0.369479
OLR1	522	42	0.434016
GCK	816	40	0.346469
PRKCD	546	40	0.436454
FOXM1	898	40	0.420866
ADIPOR1	626	38	0.437874
TRPV1	1252	38	0.456745
ACHE	896	37	0.425061
S100B	448	37	0.474785
TTR	912	36	0.382752
TXNIP	526	36	0.468764
CFTR	1754	35	0.383673
COMT	1744	34	0.259076
AKR1B1	4368	34	0.363269
HK2	5742	33	0.394057
NOD2	112	33	0.484972
RAC1	414	33	0.442496
PTGS1	3238	33	0.453838
SGK1	660	33	0.429156
FLT4	212	33	0.493608
CS	2446	32	0.302083
MGAM	5396	32	0.365709
ENO2	686	32	0.418132
PRKCB	438	32	0.42981
NR1H3	262	31	0.412725
CYP1A2	1346	30	0.301667
DRD2	1830	30	0.340304
GHR	244	30	0.456955
GDF15	180	30	0.498958

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Table 4 (*continued*)

Name	Stress	Degree	TopologicalCoefficient
COL18A1	88	30	0.479416
BRCA2	296	30	0.427404
FABP1	382	29	0.330629
KL	310	29	0.473599
CYP2C9	908	28	0.286951
ABCG1	288	28	0.391446
GNRH1	1582	28	0.396154
MAP2K2	150	28	0.472647
SLC6A4	1400	27	0.327713
CETP	628	26	0.346003
LPIN1	360	26	0.374886
BCHE	536	26	0.40638
SOST	306	26	0.521484
CYP2D6	1170	25	0.214661
UCP3	198	25	0.366275
PRKAA1	242	25	0.381176
ADIPOR2	184	25	0.465238
GSTM1	1076	24	0.295704
HSD11B1	2016	24	0.3167
HDAC9	110	24	0.460676
PRKAA2	216	23	0.38359
CYP2C19	656	22	0.228381
NPPB	122	22	0.447117
ACTA2	124	22	0.448789
TRPV4	422	22	0.368806
RPS6KA3	788	22	0.479899
MTTP	58	21	0.329109
CYP17A1	1488	21	0.287032
ALDH2	952	20	0.19532
HTR2A	316	20	0.289394
HAMP	844	20	0.5368
ADA	94	19	0.486475
PNLIP	170	19	0.377873
NPHS1	218	18	0.461505
GUSB	126	18	0.516276
FTO	84	15	0.452058
HSD11B2	836	14	0.286876
CYP11B2	560	14	0.25
LDLR	184	14	0.300912
PRSS1	106	14	0.374052
PLA2G7	148	14	0.452478
TCF4	120	13	0.551489
LIPG	96	12	0.286568
TNFRSF11B	44	12	0.424309
APC	30	11	0.619939
CRYAB	22	10	0.508642
TF	286	10	0.319828
PDX1	8	10	0.430126
FXN	44	9	0.373016
RYR1	80	8	0.317551
ECE1	20	7	0.438837
PKD2	188	7	0.354978
CAT	60	7	0.33887
CYP21A2	8	7	0.3053
NPHS2	0	6	0.526812
GLO1	14	6	0.383202
PEA15	20	6	0.410185
LIN28B	2	5	0.660944
MT-ND6	8	3	0.516779
GAA	0	2	0.601852
DNAH8	0	1	0
GAR1	0	1	0
SPOUT1	0	1	0

associated with myocardial fibrosis, which is characterized by ventricular remodeling and interstitial fibrosis, ultimately leading to heart failure [37]. High blood glucose levels can alter cardiac metabolism and function, leading to cardiac stiffness, as well as systolic and relaxation dysfunction [38]. Moreover, persistent hyperglycemia increases the inflammatory response, which exacerbates myocardial fibrosis [39]. Cardiac fibrosis impairs the contractile function of the heart and leads to impaired ventricular relaxation, which eventually leads to ventricular hypertrophy, reduced cardiac output, and heart failure [40]. In healthy cardiac tissue, the

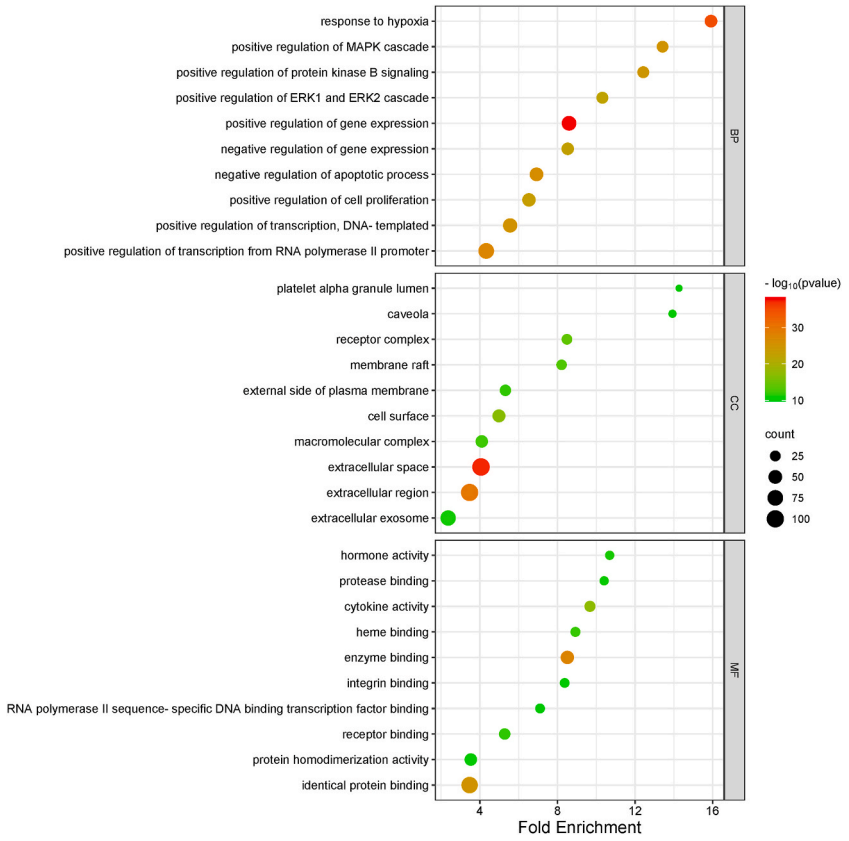

Fig. 3. Top 10 GO functionality enrichment.
BP: biological process, CC: cellular composition, MF: molecular function. The colors range from red to green, with redder colors representing smaller P-value. Bubble size represents the number of basic enrichment, the larger the bubble the more gene enrichment.

extracellular matrix plays a key role in maintaining the structural integrity of the heart, and HYP, a collagen-synthesizing extracellular matrix, is increased in the cardiac tissue of type 2 diabetic rats [41]. Cardiac tissue is mainly composed of collagen I (85 %) and collagen III (11 %) [42], and myocardial fibrosis alters the normal myocardial structure, with increased expression of collagen types I and III leading to cardiac remodeling and consequent myocardial dysfunction [43–45].

The THCQD could stabilize myocardial GLUT4 mRNA expression [24], thereby increasing myocardial glucose utilization and improving myocardial energy balance. Data show that diabetic patients are more prone to myocardial ischemia reperfusion injury (MIRI) [46,47], and MIRI-triggered arrhythmias may lead to myocardial infarction [48]. That is important in patients with diabetic myocardial ischemia. GLUT4 is a glucose transporter responsible for the uptake of glucose into the myocardium. In the case of diabetes, the level of GLUT4 is affected, thus promoting an increase in blood glucose [49] and a decrease in the ability of the myocardium to utilize glucose, which affects myocardial energy balance and consequently abnormal cardiac function. That THCQD could improve myocardial function by increasing cardiomyocyte Na^{+}-K^{+}-ATPase and Ca^{2+}-ATPase activities. Abnormal regulation of Ca^{2+} is one of the important reasons for the development of DCM. Increased intracellular Ca^{2+} concentration is the main stimulus for smooth muscle contraction [50]. Abnormal Ca^{2+} is the main cause of decreased contractility and slow diastole in DCM myocardium, triggering arrhythmias and cellular changes [51]. Increased intracellular Ca^{2+} with decreased K^{+} can decrease membrane potential and enhance vasoconstrictor response [52].

THCQD could reduce the expression of NLRP3, ASC, and Caspase-1 in myocardial tissue, delay the progression of DCM, reduce p–NF–κB p65 protein expression, and inhibit the activation of NLRP3 inflammatory vesicles [36]. Oxidative stress injury is considered to be one of the major causes of the development of cardiovascular complications in diabetic patients [53]. The development of DCM consists of a hidden subclinical period characterized by damage and abnormalities at the cellular and molecular levels, as well as initial diastolic dysfunction followed by the development of systolic dysfunction, ultimately leading to heart failure [54,55]. GSH-Px is an important peroxidolytic enzyme that protects the structure and function of cell membranes from peroxide disruption and damage, both of which play a crucial role in the balance of oxidation and antioxidation in vivo [56]. MDA content is an important indicator of the body's antioxidant capacity [57]. Increase the activity of GSH-Px and reduce the content of MDA [28], by inhibiting oxidative stress, thus protecting myocardial tissue. Chronic inflammation caused by hyperglycemia is the main feature of DM [58]. Immunoregulation and inflammatory responses play a crucial role in the initiation and development of DCM [59,60]. NLRP3 inflammatory vesicles are multiprotein complexes that coordinate the innate immune response, while activation of unregulated NLRP3 inflammatory vesicles in

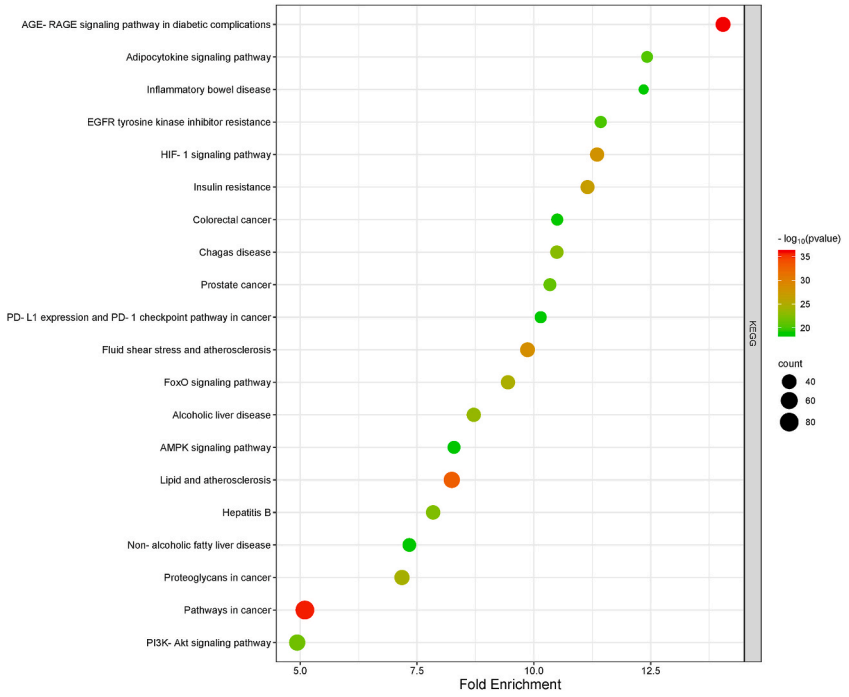

Fig. 4. Top 20 KEGG pathway enrichment analysis.
The colors range from red to green, with redder colors representing smaller *P*-value. Bubble size represents the number of basic enrichment, the larger the bubble the more genes are enriched.

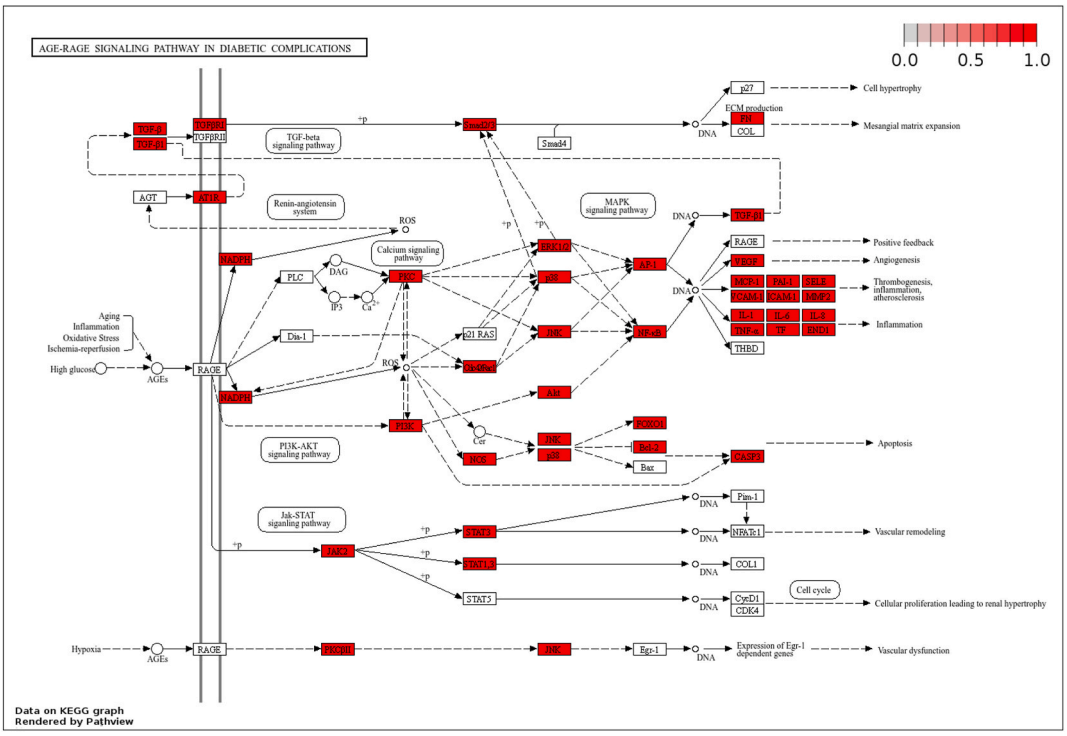

Fig. 5. Examples of pathways with minimal *P*-value in KEGG.
The red markers in the figure show the position of the target gene in the pathway. May 14, 2024.

Table 5
Combining energy data.

Ligand	Protein	Energy (kcal/mol)
Resveratrol	INS	−6.2
	AKT1	−5.6
	TNF	−8.4
	ALB	−9.2
	IL6	−5.9
	IL1B	−6.7
Emodin	INS	
	AKT1	−6.7
	TNF	−9.3
	ALB	
	IL6	
	IL1B	−7.4
Baicalein	INS	
	AKT1	−6.1
	TNF	−9.3
	ALB	
	IL6	−6.3
	IL1B	

pathological responses can lead to unexpected immune and inflammatory pathological conditions [61]. NLRP3 inflammatory vesicles are composed of NLRP3, ASC, and Caspase-1 [62], and the inflammatory factors released upon activation can lead to an inflammatory response in the heart, resulting in myocardial pathological changes such as cardiac hypertrophy and myocardial fibrosis [63,64]. p–NF–κB p65 activates NLRP3 and contributes to the regulation of inflammatory cytokines [65,66]. By inhibiting the NF-κB pathway, oxidative stress and apoptosis can be suppressed [67]. This leads to anti-fibrotic and oxidative stress inhibiting effects.

4.2. Protective effect of THCQD on the aortic arch in diabetic rats

Li [23] observed by electron microscopy that THCQD improved the elastic membrane structure within the aortic arch and reduced mitochondrial swelling within the mesangial smooth muscle cells in diabetic rats. Previous studies show changes in aortic structure in diabetic rat models [68,69], with increased permeability of damaged aortic endothelial cells, damaged mitochondrial membranes within mid-membrane smooth muscle cell membranes, and swollen mitochondria.

4.3. Anti-fibrosis and anti-atherosclerosis of THCQD in diabetic rat femoral artery

THCQD can decrease the expression of collagen I and III in femoral arteries [27]. Vascular fibrosis requires the accumulation of collagen, fibronectin and other extracellular matrix components in the vessel wall [70]. THCQD can decrease TGF-β1 and CTGF expression in the femoral artery of diabetic rats [26]. Overexpression of TGF-β is associated with the pathogenesis of diabetic microvascular and macrovascular complications [71], and TGF-β promotes extracellular matrix deposition leading to vascular fibrosis [72]. CTGF is a secreted protein that plays a major role in angiogenesis and fibrosis [73,74]. The expression of this protein is efficiently induced by TGF-β [75]. CTGF is thought to be both closely associated with vascular fibrosis [76] and to act as a downstream effector of TGF-β, mediating at least part of its pro-fibrotic activity [77,78]. Increased expression of TGF-β1 and CTGF is thought to be related to the mechanisms of fibrosis [79]. These may be the mechanisms through which THCQD exerts its protective effects against diabetic vascular fibrosis.

THCQD can decrease the content and expression of TGF-β and increase the expression of IGF-1 in the femoral arteries of diabetic rats [30,33]. IGF-1 can promote angiogenesis and neovascularization [80,81], and IGF-1 can stimulate smooth muscle proliferation in early atherosclerosis [82] and has a protective effect against atherosclerosis [83]. Toll-like receptors may play an important role in the process of arterial fibrosis [84,85] and atherosclerosis [86,87]. TLR-2 and TLR-4 are central to the progression of atherosclerosis [88,89]. TLR-2 and TLR-4-mediated inflammation are involved in the formation of atherosclerotic calcification [90–92] and contribute to the development of atherosclerosis [93–95]. Just THCQD can decrease TLR-2 and TLR-4 expression in the femoral artery vasculature. These evidences above suggest that THCQD has a protective effect on femoral artery fibrosis and atherosclerosis.

4.4. Anti-inflammatory and vasoprotective effects of THCQD in thoracic aorta of diabetic rat

One of the key factors of vasculopathy and inflammatory response includes VCAM-1 and MCP-1 [96–98]. NF-κB activation triggers reactive oxygen species accumulation and inflammation [99]. Inflammatory factors such as MCP-1 and VCAM-1 are involved in the pathophysiological process of DCM [100,101]. THCQD could reduce the expression of VCAM-1, MCP-1, and NF-κB proteins in the thoracic aorta of diabetic rats, and reduce the expression of NF-κB mRNA, MCP-1 mRNA, and VCAM-1 mRNA in the thoracic aorta [29], thereby reducing inflammation.

THCQD can reduce the production of AGEs and decrease the expression of RAGE mRNA in the thoracic aorta of diabetic rats [32]. THCQD may exhibit a protective effect on the thoracic aorta by reducing the expression of RAGE and AGEs. Specific receptor binding of

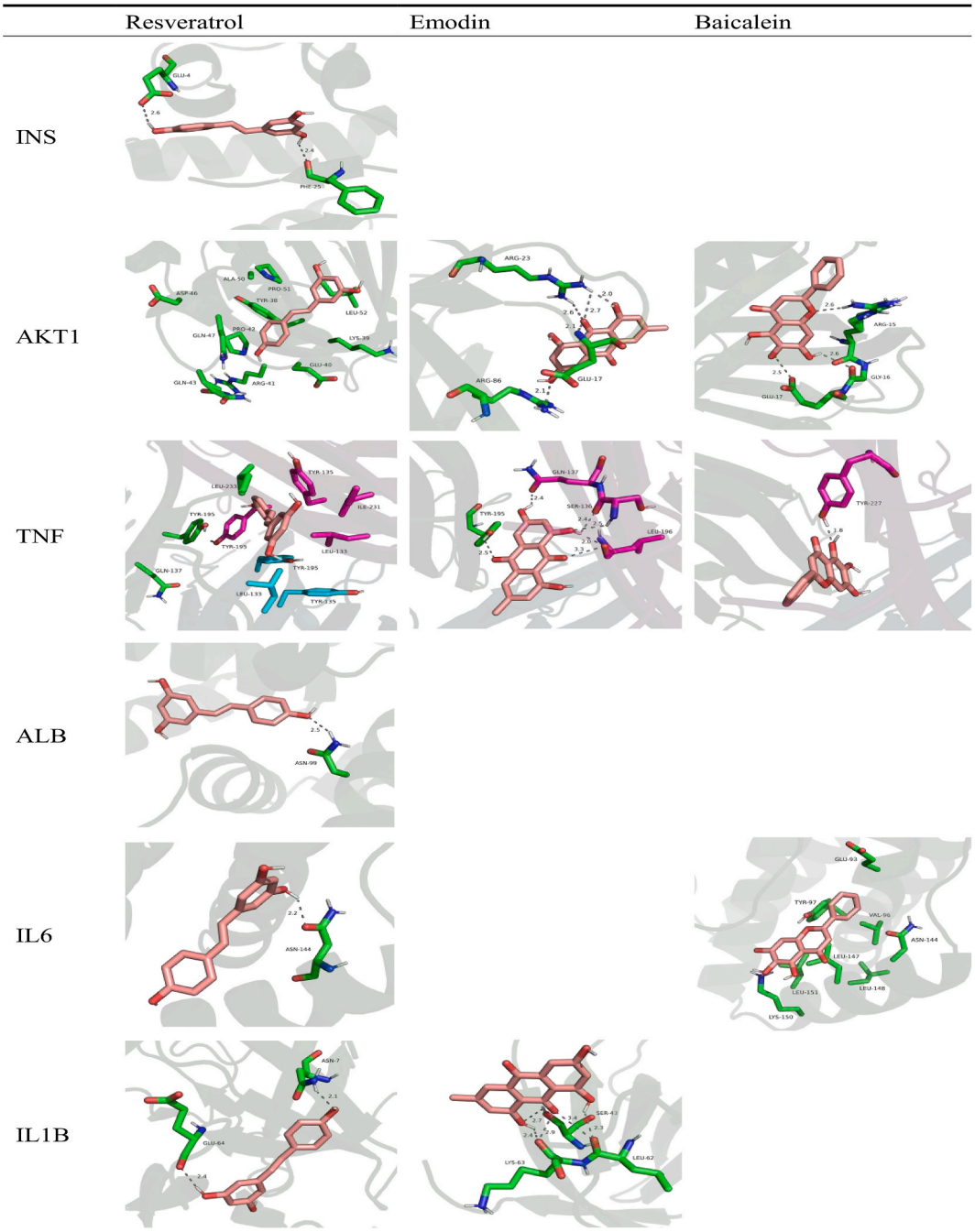

Fig. 6. Molecular docking results of key components with target genes.

RAGE and AGEs is important in the function of atherosclerotic vascular smooth muscle cells (VSMC) [102]. AGEs and oxidative stress are considered to be key factors in the development of cardiovascular disease and diabetic complications [103,104]. Accelerated formation of AGEs is associated with the pathogenesis of diabetic macrovascular complications [71]. Also AGEs are thought to play a role in the development and progression of atherosclerosis [105]. RAGE is produced through non-enzymatic glycosylation reactions and is thought to be a major causative factor in triggering diabetic vascular complications [106].

THCQD can decrease the expression of PI3K (P85) mRNA and Akt mRNA in the thoracic aorta of diabetic rats [34]. Vascular endothelial cells have the function of regulating vascular tone, and vascular endothelial cell dysfunction is an important pathological feature of several cardiovascular diseases, which is mainly characterized by a decrease in endothelium-dependent vasodilatory function with varying degrees of inflammatory response and elevated levels of oxidative stress [107,108]. Nitric Oxide (NO) mediated

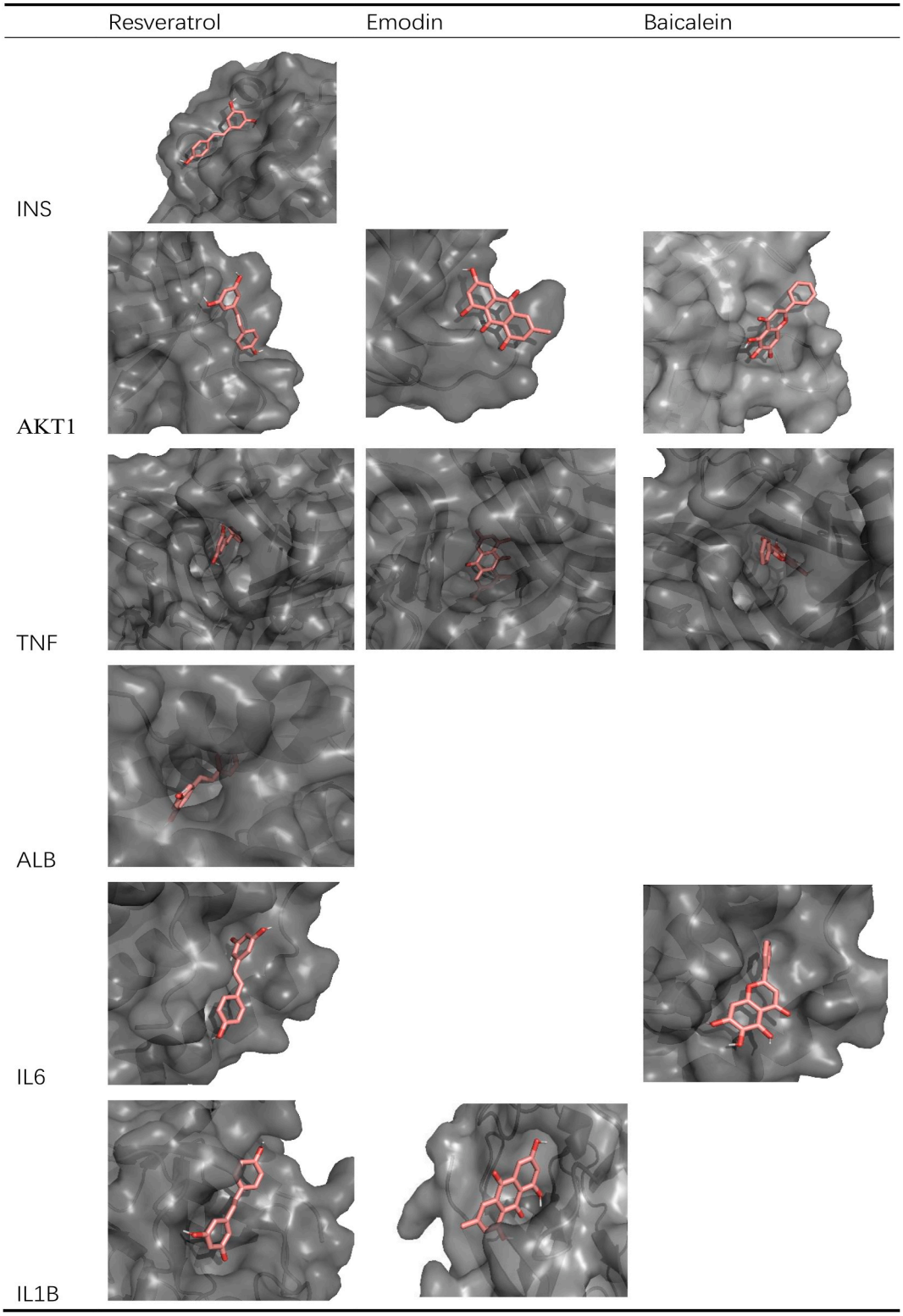

Fig. 7. Receptor-ligand binding region.

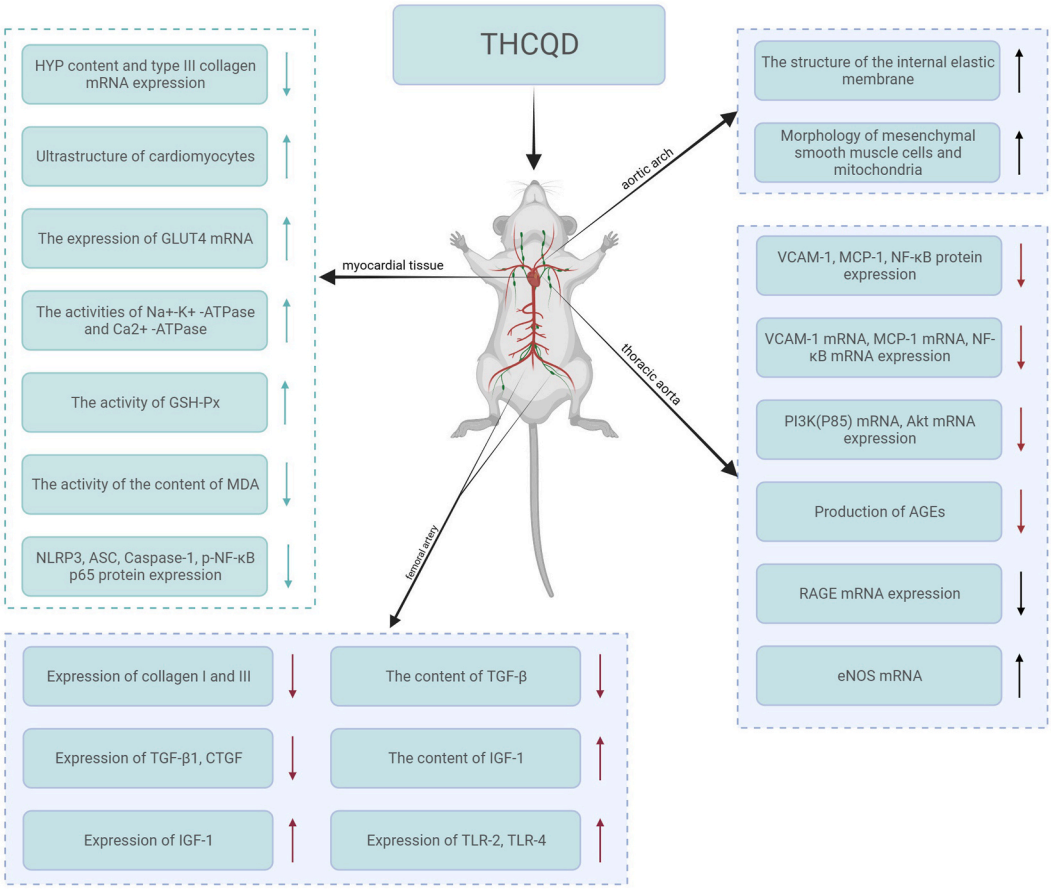

Fig. 8. Mechanism of THCQD for diabetic cardiovascular complications.

by vascular eNOS production has strong anti-inflammatory effects [109]. THCQD can increase the expression of eNOS mRNA in the thoracic aorta [35]. eNOS-mediated anti-inflammatory effects are closely related to the PI3K-Akt signaling pathway [110]. PI3K-Akt is an important intracellular signaling pathway that mediates endothelial cell proliferation, migration, and survival and plays an important role in angiogenesis [111,112]. The Akt cascade response initiated by tyrosine kinases, immune cell receptors, cytokine receptors, G protein-coupled receptors, and PI3K-stimulated PIP3 generation activation may further influence the immune inflammatory response [113,114]. Research shows that, inhibition of PI3K and Akt expression attenuates injury-induced vascular VSMC proliferation, thereby affecting the further development of atherosclerosis [115]. There are may be the mechanism by which THCQD can improve diabetic atherosclerosis.

4.5. Herbs used in combination with THCQD

THCQD contains Peach Seed as a drug, and some studies have confirmed that Peach Seed can improve the level of macrovascular fibrosis in diabetes [116,117]. Moreover, the combination of herbs containing Peach Seed can treat cardiovascular diseases and improve atherosclerosis [118,119]. THCQD was used in combination with other herbs when used to improve diabetic cardiovascular disease. Of all the studies included in this review, 3 studies [30,31,33] used only fixed combinations of THCQD. 13 studies [21–29,32,34–36] used THCQD in combination with other herbs. 12 studies [21–29,32,34,35] added Astragalus membranaceus, Radix Ophiopogonis, Rehmannia glutinosa and Radix scrophulariae to THCQD. The Radix Ophiopogonis, Rehmannia glutinosa and Radix scrophulariae form a traditional Chinese herbal formula called “Zengye Decoction”. Zengye Decoction is from “Identification of Warm Disease” (written in 1798) and has been used to treat diabetes since the Qing Dynasty, and research [120,121] has shown that Zengye Decoction exerts significant hypoglycemic effects in type 2 diabetes by improving insulin resistance. 4 studies [29,32,34,35] added Salviae Miltiorrhizae. The Salviae Miltiorrhizae is effective in the treatment of diabetic complications and anti-fibrosis [122–124]. In addition, Salviae Miltiorrhizae is also very effective in improving MIRI [125,126]. Four studies [29,32,34,35] added Asarum. Asarum has anti-inflammatory and cardiovascular protective effects [127,128]. And three studies [29,32,35] added cooked Rhubarb. Cooked Rhubarb is the result of the concoction of Rhubarb and the concoction of cooked Rhubarb can reduce the diarrhea effect of Rhubarb.

4.6. Network pharmacology and molecular docking

In this study, we used network pharmacology to further predict the targets of action of THCQD for the treatment of diabetic cardiovascular complications. The results of "drug-target-intersecting genes-disease" showed that Resveratrol, Emodin, and Baicalein were the most critical compounds for THCQD in the treatment of diabetic cardiovascular complications. Resveratrol is a natural product with anti-oxidative stress, anti-inflammatory, and pancreatic β-cell protection properties, and may ameliorate diabetic cardiovascular complications through multiple signaling pathways [129]. Emodin is the main constituent of rhubarb, which is widely used in the treatment of cardiovascular diseases and has very excellent antifibrotic properties [130,131]. Baicalein is a flavonoid that has been shown to improve insulin resistance, combat oxidative stress and protect cardiomyocytes. These three compounds show great potential in the treatment of diabetic cardiovascular complications.

The results of PPI protein interactions and topology analysis, we screened the top 6 target genes INS, AKT1, TNF, ALB, IL6, IL1B by degree value. INS is the only human insulin-encoding gene that regulates insulin synthesis and secretion. Insulin resistance not only leads to hyperglycemia, but also to atherosclerosis, hypertension, and endothelial dysfunction, all of which are risk factors for cardiovascular complications [132]. AKT1 is a molecule that plays a key role in cell signaling and is involved in the regulation of a variety of processes including cell growth, survival, metabolism and differentiation. The effects of AKT1 on diabetes and cardiovascular complications are bidirectional. Activation of AKT1 benefits vascular repair and regeneration, improves mitochondrial function, and reduces oxidative stress, but excessive activation leads to diminished cellular response to insulin and promotes the development of atherosclerosis. The ALB gene is the genetic code for human albumin. The assessment and management of albumin levels are crucial for the effective management of cardiovascular risk in patients with diabetes [133]. TNF, IL6 and IL1B play key roles in the development of cardiovascular complications in diabetes, and their role in the AGE-RAGE signaling pathway in diabetic complications is critical for the course of diabetic complications.

Among the KEGG results, the most relevant to the target was AGE-RAGE signaling pathway in diabetic complications. The AGE-RAGE signaling pathway in diabetic complications, Fluid shear stress and atherosclerosis, Lipid and atherosclerosis are the important pathways in the prevention and treatment of cardiovascular complications in diabetes. This corroborates the results of our systematic review. The AGE-RAGE pathway can elicit a variety of intracellular signals. With the binding of O_2 to NADPH oxidase to generate ROS leading to the activation of MAPKs (p38, ERK, JNK), PI3K-AKT and JAK-SATAT, which leads to the activation of transcription factors (NF-κB, ERK1) and further promotes the expression of various pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and genes related to atherosclerosis (VCAM-1, tissue factor, VEGF, and RAGE) [134,135]. As suggested by the results in the systematic review, THCQD can positively affect both the activation, transduction (NF-κB) and product components (VCAM-1, VEGF, RAGE) in this pathway.

This study utilized molecular docking to analyze the relationship between key components and target genes. Combined with free energy data, it was found that there is a significant binding affinity between the key components and target genes. Specifically, the binding free energy data in Table 5 shows that Resveratrol can form strong interactions with all six core protein receptors. This may be the key component of THCQD in treating diabetic cardiovascular complications. Furthermore, the detailed docking images displayed in Figs. 6 and 7 provide intuitive evidence for understanding the molecular mechanism of action between the key components and target genes. In particular, the docking results clearly demonstrate the hydrogen bonds and hydrophobic interactions between the components and receptors, which are crucial for their pharmacological effects. With these findings, we have gained a deeper understanding of the role of THCQD in the treatment of diabetic cardiovascular complications.

5. Conclusion

In summary, Taohe Chengqi Decoction (THCQD) has shown promising therapeutic effects in the treatment of diabetic cardiovascular complications. The review indicates that THCQD improves myocardial function, reduces fibrosis, and exhibits anti-inflammatory and anti-atherosclerotic properties. Network pharmacology and molecular docking studies have identified key compounds like Resveratrol, Emodin, and Baicalein that target critical pathways in diabetic complications. Future research should focus on elucidating the long-term clinical outcomes of THCQD treatment and optimizing its formulation for maximal efficacy and safety.

6. Limitations and prospects

While providing valuable insights, this review has some limitations. First, a limited number of studies were included, which may limit the generalizability of the conclusions we draw. Second, some of the studies had quality issues in reporting baseline characteristics, description of randomization methods, and other key study designs. In addition, although network pharmacology is based on network analysis in systems biology, the results derived from it still need to be validated by animal experiments to ensure its scientific validity and reliability. In spite of these limitations, THCQD, an all-natural herbal formula, shows promising potential in the treatment of diabetic cardiovascular disease. With ongoing research in this field, discoveries about the underlying mechanisms of its positive effects on cardiovascular health are anticipated. By identifying such mechanisms, THCQD's therapeutic effects can be better understood, paving the way for improved treatment strategies for diabetic cardiovascular disease, benefiting many patients worldwide.

Statement

The exact experimental data were not available in the original literature retrieved (results were given in figures), and therefore the

data could not be obtained for Meta-analysis. Therefore, sections 12, 13a, 13b, 13e, 13f, and 20d of the PRISMA 2020 checklist were not reported in this article.

Ethics approval and consent to participate

Not Applicable.

Consent for publication

All the authors agreed to the manuscript's publication.

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Availability of data and material

The dataset used in this study is available upon reasonable request from the corresponding author.

CRediT authorship contribution statement

ZHANG Chun-peng: Writing – review & editing, Writing – original draft, Software, Data curation. **CAO Tian:** Writing – review & editing, Writing – original draft, Data curation. **YANG Xue:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ZHANG Chun-peng and CAO Tian contributed equally to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33308.

References

[1] P. Saeedi, I. Petersohn, P. Salpea, et al., Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition, Diabetes Res. Clin. Pract. 157 (2019) 107843, https://doi.org/10.1016/j.diabres.2019.107843.

[2] D.R. Whiting, L. Guariguata, C. Weil, J. Shaw, IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030, Diabetes Res. Clin. Pract. 94 (3) (2011) 311–321, https://doi.org/10.1016/j.diabres.2011.10.029.

[3] K. Ogurtsova, J.D. da Rocha Fernandes, Y. Huang, et al., IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040, Diabetes Res. Clin. Pract. 128 (2017) 40–50, https://doi.org/10.1016/j.diabres.2017.03.024.

[4] G.L. Plosker, D.P. Figgitt, Repaglinide : a pharmacoeconomic review of its use in type 2 diabetes mellitus, Pharmacoeconomics 22 (6) (2004) 389–411, https://doi.org/10.2165/00019053-200422060-00005.

[5] N.H. Cho, J.E. Shaw, S. Karuranga, et al., IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045, Diabetes Res. Clin. Pract. 138 (2018) 271–281, https://doi.org/10.1016/j.diabres.2018.02.023.

[6] C. Abi Khalil, R. Roussel, K. Mohammedi, N. Danchin, M. Marre, Cause-specific mortality in diabetes: recent changes in trend mortality, Eur J Prev Cardiol 19 (3) (2012) 374–381, https://doi.org/10.1177/1741826711409324.

[7] J.L. Harding, M.E. Pavkov, D.J. Magliano, J.E. Shaw, E.W. Gregg, Global trends in diabetes complications: a review of current evidence, Diabetologia 62 (1) (2019) 3–16, https://doi.org/10.1007/s00125-018-4711-2.

[8] E. Standl, K. Khunti, T.B. Hansen, O. Schnell, The global epidemics of diabetes in the 21st century: current situation and perspectives, Eur J Prev Cardiol 26 (2_suppl) (2019) 7–14, https://doi.org/10.1177/2047487319881021.

[9] W. Mao, Y. Fan, X. Wang, et al., Phloretin ameliorates diabetes-induced endothelial injury through AMPK-dependent anti-EndMT pathway, Pharmacol. Res. 179 (2022) 106205, https://doi.org/10.1016/j.phrs.2022.106205.

[10] Z. Zhen, The effect of modified Taohe Chengqi decoction on diabetes and the blood glucose level, Clinical Journal of Chinese Medicine 9 (27) (2017) 48–50, https://doi.org/10.3969/j.issn.1674-7860.2017.27.021.

[11] J. Kang, S. Ma, The effect of modified Taohe Chengqi Decoction in treating Type 2 diabetes mellitus, Inner Mongolia Journal of TCM 35 (17) (2016) 7, https://doi.org/10.3969/j.issn.1006-0979.2016.17.007.

[12] J. Meng, X. Zheng, F. Zhang, et al., Effect of flavored Taohe Chengqi Decoction on insulin resistance of obese diabetic patients, J Integr Tradit Chin West Med. 31 (15) (2022) 2126–2129.

[13] W. Mao-qing, W. Yu-hua, Y. Yu, Comprehensive analysis of the effect of adding Taohe Chengqi Decoction in treating patients with diabetes mellitus (type 2) and the effect on patients' blood glucose levels, Chan Pharma 31 (7) (2019) 83–84, https://doi.org/10.3969/j.issn.1006-3765.2019.07.033.

[14] W. Qi, J. Lei, Therapeutic efficacy and effect on vascular endothelial function and serum inflammatory factor in the treatment of type 2 diabetes mellitus with blood stasis and vein syndrome by adding flavored peach kernel and Cheng Qi Tang, Western Chin Med 35 (7) (2022) 6–10, https://doi.org/10.12174/j.issn.2096-9600.2022.07.02.

[15] L. Jing, G. Chao, H. Lian-lian, L. De-yi, C. Hui-liang, Antioxidant protection of liver, kidney and heart tissues in STZ diabetic rats by adding Taohe Chengqi Decoction, Anhui Agri Sci 41 (30) (2013) 12052–12054+12058, https://doi.org/10.13989/j.cnki.0517-6611.2013.30.094.

[16] C.R. Hooijmans, M.M. Rovers, R.B. de Vries, M. Leenaars, M. Ritskes-Hoitinga, M.W. Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med. Res. Methodol. 14 (2014) 43, https://doi.org/10.1186/1471-2288-14-43.

[17] D. Yan, G. Zheng, C. Wang, et al., Hit 2.0: an enhanced platform for herbal ingredients' targets, Nucleic Acids Res. 50 (D1) (2022) D1238–d1243, 10.1093/nar/gkab1011.

[18] D. Szklarczyk, A.L. Gable, D. Lyon, et al., STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, Nucleic Acids Res. 47 (D1) (2019) D607–d613, https://doi.org/10.1093/nar/gky1131.

[19] B.T. Sherman, M. Hao, J. Qiu, et al., DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update), Nucleic Acids Res. 50 (W1) (2022) W216–w221, https://doi.org/10.1093/nar/gkac194.

[20] U. Consortium, UniProt: the Universal protein Knowledgebase in 2023, Nucleic Acids Res. 51 (D1) (2023) D523–d531, https://doi.org/10.1093/nar/gkac1052.

[21] L. Sai-mei, W. Ling-ni, C. Quan-gen, et al., Effects of adding peach kernel Chengqi Tang and its different extracts on the ultrastructure of cardiac myocytes in diabetic rats, J Beijing Univ Tradit Chin Med (3) (2005) 48–51, https://doi.org/10.3321/j.issn:1006-2157.2005.03.015.

[22] L. Sai-mei, C. Quan-gen, M. Wei, et al., Effects of adding Taohe Chengqi decoction and different extracts on myocardial fibrosis in diabetic rats, J Nangjing Univ Tradit Chin Med (4) (2005) 236–239, https://doi.org/10.3969/j.issn.1000-5005.2005.04.012.

[23] L. Sai-mei, C. Quan-gen, M. Wei, L. Jia-jie, G. You-heng, W. Zhi-gao, Effects of adding peach kernel Cheng Qi Tang and its extract on ultrastructure of aortic arch in diabetic rats, J Guangzhou Univ Tradit Chin Med (2) (2005) 134–137, https://doi.org/10.3969/j.issn.1007-3213.2005.02.014.

[24] C. Quan-gen, L. Sai-mei, M. Wei, X. Qiu-ying, J. Hong-lan, G. You-heng, Effects of adding Taohe Chengqi decoction and its different extracts on GluT4 mRNA expression in cardiac myocytes of diabetic rats, Chinese Journal of Basic Chinese Medicine (12) (2006) 912–914, https://doi.org/10.3969/j.issn.1006-3250.2006.12.014.

[25] C. Quan-gen, L. Sai-mei, M. Wei, X. Qiu-ying, J. Hong-lan, G. You-heng, Effect of adding Taohe Chengqi decoction and its different extracts on calcium transport in diabetic rats' cardiomyocytes, J Chin Trad Med Infor (6) (2006) 43–45, https://doi.org/10.3969/j.issn.1005-5304.2006.06.021.

[26] W. Jun, X. Yang, Y. Xiang-ke, Z. Xue-yong, D. Zhi-ming, Expression of TGF-β1 and CTGF in experimental diabetic rats with macroangiopathy and the intervention effect of Chinese medicine, J Tianjin Chin Med 29 (3) (2012) 266–269, doi: CNKI:SUN:TJZY.0.2012-03-026.

[27] D. Zhi-ming, W. Hai-kuo, W. Jun, Expression of collagen proteinI and III in angiopathy of rats with diabetes and intervention with Chinese medicine, J Tianjin Chin Med 29 (6) (2012) 573–575.

[28] L. Jing, G. Chao, H. Lian-lian, L. De-yi, C. Hui-liang, Antioxidant protection of liver, kidney and heart tissues in STZ diabetic rats by adding peach kernel Cheng Qi Tang, Journal of Anhui Agri 41 (30) (2013) 12052–12054+12058, https://doi.org/10.13989/j.cnki.0517-6611.2013.30.094.

[29] D. Xiao-feng, Experimental Study on the Prevention of Diabetic Macroangiopathy Based on NF-Kb Pathway with the Addition of Peach Kernel Cheng Qi Tang and its Reformulation, Guangzhou University of Chinese Medicine, 2016 [Docter].

[30] X. Yang, W. Jun, Influence of Taohe Chengqi decoction on expressions of TGF - β and IGF - 1 in lower Limb femoral vessels of diabetes rats, J Liaoning TCM 43 (2) (2016) 418–420+448, https://doi.org/10.13192/j.issn.1000-1719.2016.02.075.

[31] X. Yang, W. Jun, W. Hai-kuo, Study on the effect of Peach Kernel Cheng Qi Tang on Toll-like receptor pathway in diabetic rats with macrovascular fibropathy, J Tianjin Chin Med 33 (5) (2016) 299–302, https://doi.org/10.11656/j.issn.1672-1519.2016.05.11.

[32] X. Suai, *Experimental study on the Prevention and Treatment of T2DM Macroangiopathy in Rats Based on AGEs-RAGE with Spiked Peach Kernel Cheng Qi Tang* [Docter], Guangzhou University of Chinese Medicine, 2017.

[33] X. Yang, W. Jun, Effect of peach kernel Cheng Qi Tang on the expression of Toll-like receptors in rat diabetic macrovasculature, J Chin Integr Chin and West Med Surg 23 (1) (2017) 60–64, https://doi.org/10.3969/j.issn.1007-6948.2017.01.017.

[34] G. Yu-mei, Z. Zhang-zhi, X. Shuai, D. Xiao-feng, Effects of adding Taohe Chengqi decoction on blood glucose, lipids and macrovascular lesions in diabetic rats, New Chinese Medicines and Clinical Pharmacology 28 (5) (2017) 583–587, https://doi.org/10.19378/j.issn.1003-9783.2017.05.006.

[35] X. Shuai, L. Wei-chi, L. Hua-jun, Z. Zhang-zhi, F. Qiu-yuan, L. Bao-ling, The effects of different formulae of Peach Kernel Cheng Qi Tang on atherosclerosis in type 2 diabetic rats. Paper Presented at: National TCM Diabetes Conference of the Diabetes Branch of the Chinese Academy of Traditional Chinese Medicine (19th), 2018.

[36] Z. Ya-nan, D. Ying-jun, X. Hua-zhou, L. Zi-liang, S. Qiu-jun, The effect of adding peach kernel Cheng Qi Tang on NLRP3 inflammatory vesicles in rats with diabetic cardiomyopathy, J Chin Exper Form 28 (16) (2022) 59–65, https://doi.org/10.13422/j.cnki.syfjx.20220780.

[37] M. Liu, T. Peng, L. Hu, et al., N-glycosylation-mediated CD147 accumulation induces cardiac fibrosis in the diabetic heart through ALK5 activation, Int. J. Biol. Sci. 19 (1) (2023) 137–155, https://doi.org/10.7150/ijbs.77469.

[38] M.S. El Hayek, L. Ernande, J.P. Benitah, A.M. Gomez, L. Pereira, The role of hyperglycaemia in the development of diabetic cardiomyopathy, Arch Cardiovasc Dis 114 (11) (2021) 748–760, https://doi.org/10.1016/j.acvd.2021.08.004.

[39] J. Liu, J. Lu, L. Zhang, et al., The combination of exercise and metformin inhibits TGF-β1/Smad pathway to attenuate myocardial fibrosis in db/db mice by reducing NF-κB-mediated inflammatory response, Biomed. Pharmacother. 157 (2023) 114080, https://doi.org/10.1016/j.biopha.2022.114080.

[40] A.O. Mocumbi, J.R. Stothard, P. Correia-de-Sá, M. Yacoub, Endomyocardial fibrosis: an update after 70 Years, Curr. Cardiol. Rep. 21 (11) (2019) 148, https://doi.org/10.1007/s11886-019-1244-3.

[41] R.A. Elrashidy, S.E. Ibrahim, Cinacalcet as a surrogate therapy for diabetic cardiomyopathy in rats through AMPK-mediated promotion of mitochondrial and autophagic function, Toxicol. Appl. Pharmacol. 421 (2021) 115533, https://doi.org/10.1016/j.taap.2021.115533.

[42] K. Maruyama, K. Imanaka-Yoshida, The pathogenesis of cardiac fibrosis: a review of recent progress, Int. J. Mol. Sci. 23 (5) (2022), https://doi.org/10.3390/ijms23052617.

[43] B. Li, Z. Zheng, Y. Wei, et al., Therapeutic effects of neuregulin-1 in diabetic cardiomyopathy rats, Cardiovasc. Diabetol. 10 (2011) 69, https://doi.org/10.1186/1475-2840-10-69.

[44] C.J. Li, L. Lv, H. Li, D.M. Yu, Cardiac fibrosis and dysfunction in experimental diabetic cardiomyopathy are ameliorated by alpha-lipoic acid, Cardiovasc. Diabetol. 11 (2012) 73, https://doi.org/10.1186/1475-2840-11-73.

[45] T. Peng, M. Liu, L. Hu, et al., LncRNA Airn alleviates diabetic cardiac fibrosis by inhibiting activation of cardiac fibroblasts via a m6A-IMP2-p53 axis, Biol. Direct 17 (1) (2022) 32, https://doi.org/10.1186/s13062-022-00346-6.

[46] T. Miki, T. Itoh, D. Sunaga, T. Miura, Effects of diabetes on myocardial infarct size and cardioprotection by preconditioning and postconditioning, Cardiovasc. Diabetol. 11 (2012) 67, https://doi.org/10.1186/1475-2840-11-67.

[47] L.C. Godoy, M.E. Farkouh, Surgical vs percutaneous coronary revascularization in patients with diabetes following an acute coronary syndrome, J. Diabetes 11 (7) (2019) 610–612, https://doi.org/10.1111/1753-0407.12917.

[48] M. Majidi, A.S. Kosinski, S.M. Al-Khatib, et al., Implications of ventricular arrhythmia "bursts" with normal epicardial flow, myocardial blush, and ST-segment recovery in anterior ST-elevation myocardial infarction reperfusion: a biosignature of direct myocellular injury "downstream of downstream", Eur Heart J Acute Cardiovasc Care 4 (1) (2015) 51–59, https://doi.org/10.1177/2048872614532414.

[49] A. Jafri, S. Sharma, N. Khurana, M. M, U. Singh, K. Luthra, Herbal anti-hyperglycemic compound increases expression of glucose transporter molecules in diabetic rats, J. Diabetes Metabol. 10 (2019), https://doi.org/10.35248/2155-6156.19.10.824.

[50] Y.M. Searls, R. Loganathan, I.V. Smirnova, L. Stehno-Bittel, Intracellular Ca2+ regulating proteins in vascular smooth muscle cells are altered with type 1 diabetes due to the direct effects of hyperglycemia, Cardiovasc. Diabetol. 9 (2010) 8, https://doi.org/10.1186/1475-2840-9-8.

[51] T. Smani, I. Gallardo-Castillo, J. Ávila-Médina, M.F. Jimenez-Navarro, A. Ordoñez, A. Hmadcha, Impact of diabetes on cardiac and vascular disease: role of calcium signaling, Curr. Med. Chem. 26 (22) (2019) 4166–4177, https://doi.org/10.2174/0929867326666170523140925.

[52] Y. Sun, C. Wang, N. Zhang, F. Liu, Melatonin ameliorates hypertension in hypertensive pregnant mice and suppresses the hypertension-induced decrease in Ca (2+)-activated K(+) channels in uterine arteries, Hypertens. Res. 44 (9) (2021) 1079–1086, https://doi.org/10.1038/s41440-021-00675-5.

[53] H. Wan, S. Zhao, Q. Zeng, et al., CircRNAs in diabetic cardiomyopathy, Clin. Chim. Acta 517 (2021), https://doi.org/10.1016/j.cca.2021.03.001.

[54] V. Chavali, S.C. Tyagi, P.K. Mishra, Predictors and prevention of diabetic cardiomyopathy, Diabetes Metab Syndr Obes 6 (2013) 151–160, https://doi.org/10.2147/dmso.S30968.

[55] I. Falcão-Pires, A.F. Leite-Moreira, Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment, Heart Fail. Rev. 17 (3) (2012) 325–344, https://doi.org/10.1007/s10741-011-9257-z.

[56] R. Margis, C. Dunand, F.K. Teixeira, M. Margis-Pinheiro, Glutathione peroxidase family - an evolutionary overview, FEBS J. 275 (15) (2008) 3959–3970, https://doi.org/10.1111/j.1742-4658.2008.06542.x.

[57] C. Mas-Bargues, C. Escrivá, M. Dromant, C. Borrás, J. Viña, Lipid peroxidation as measured by chromatographic determination of malondialdehyde. Human plasma reference values in health and disease, Arch. Biochem. Biophys. 709 (2021) 108941, https://doi.org/10.1016/j.abb.2021.108941.

[58] A.R. Saltiel, J.M. Olefsky, Inflammatory mechanisms linking obesity and metabolic disease, J. Clin. Invest. 127 (1) (2017) 1–4, https://doi.org/10.1172/jci92035.

[59] O. Lorenzo, B. Picatoste, S. Ares-Carrasco, E. Ramírez, J. Egido, J. Tuñón, Potential role of nuclear factor κB in diabetic cardiomyopathy, Mediat. Inflamm. 2011 (2011) 652097, https://doi.org/10.1155/2011/652097.

[60] E. Teixeira-Lemos, S. Nunes, F. Teixeira, F. Reis, Regular physical exercise training assists in preventing type 2 diabetes development: focus on its antioxidant and anti-inflammatory properties, Cardiovasc. Diabetol. 10 (2011) 12, https://doi.org/10.1186/1475-2840-10-12.

[61] E.I. Elliott, F.S. Sutterwala, Initiation and perpetuation of NLRP3 inflammasome activation and assembly, Immunol. Rev. 265 (1) (2015) 35–52, https://doi.org/10.1111/imr.12286.

[62] T. Strowig, J. Henao-Mejia, E. Elinav, R. Flavell, Inflammasomes in health and disease, Nature 481 (7381) (2012) 278–286, https://doi.org/10.1038/nature10759.

[63] Y. Zheng, L. Xu, N. Dong, F. Li, NLRP3 inflammasome: the rising star in cardiovascular diseases, Front Cardiovasc Med 9 (2022) 927061, https://doi.org/10.3389/fcvm.2022.927061.

[64] K. Nakahira, J.A. Haspel, V.A. Rathinam, et al., Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome, Nat. Immunol. 12 (3) (2011) 222–230, https://doi.org/10.1038/ni.1980.

[65] Z. Zhong, A. Umemura, E. Sanchez-Lopez, et al., NF-κB restricts inflammasome activation via elimination of damaged mitochondria, Cell 164 (5) (2016) 896–910, https://doi.org/10.1016/j.cell.2015.12.057.

[66] I.S. Afonina, Z. Zhong, M. Karin, R. Beyaert, Limiting inflammation-the negative regulation of NF-κB and the NLRP3 inflammasome, Nat. Immunol. 18 (8) (2017) 861–869, https://doi.org/10.1038/ni.3772.

[67] J. Zhai, Z. Li, H. Zhang, et al., Berberine protects against diabetic retinopathy by inhibiting cell apoptosis via deactivation of the NF-κB signaling pathway, Mol. Med. Rep. 22 (5) (2020) 4227–4235, https://doi.org/10.3892/mmr.2020.11505.

[68] L. Tao, L. Zong-han, Early ultrastructural changes in the aorta of experimental type II diabetic rats and the factors affecting them, J Chin Atherosclerosis (Z1) (1994) 92–96.

[69] Z. Min, Z. Hui-ju, W. Xiao-ying, L. Shi-kun, Z. Dong-mei, Ultrastructural and functional changes in the aorta of diabetic rats and the effect of cloxacin on them, J Chin Diabetes (2) (2001) 28–31, https://doi.org/10.3321/j.issn:1006-6187.2001.02.007.

[70] B. Toffoli, R.J. Pickering, D. Tsorotes, et al., Osteoprotegerin promotes vascular fibrosis via a TGF-β1 autocrine loop, Atherosclerosis 218 (1) (2011) 61–68, https://doi.org/10.1016/j.atherosclerosis.2011.05.019.

[71] J.R. Rumble, M.E. Cooper, T. Soulis, et al., Vascular hypertrophy in experimental diabetes. Role of advanced glycation end products, J. Clin. Invest. 99 (5) (1997) 1016–1027, https://doi.org/10.1172/jci119229.

[72] S. Wei, L. Li-bing, L. Jiang-yang, Role of TGF-β, MMPs and TIMPs in persistent atrial fibrillution associated with rheumatic mitral stenosis, Med J Vhia PLA 39 (8) (2014) 614–617, doi: CNKI:SUN:JFJY.0.2014-08-004.

[73] X. Shi-Wen, A. Leask, D. Abraham, Regulation and function of connective tissue growth factor/CCN2 in tissue repair, scarring and fibrosis, Cytokine Growth Factor Rev. 19 (2) (2008) 133–144, https://doi.org/10.1016/j.cytogfr.2008.01.002.

[74] E.E. Moussad, D.R. Brigstock, Connective tissue growth factor: what's in a name? Mol. Genet. Metabol. 71 (1–2) (2000) 276–292, https://doi.org/10.1006/mgme.2000.3059.

[75] A. Leask, D.J. Abraham, The role of connective tissue growth factor, a multifunctional matricellular protein, in fibroblast biology, Biochem. Cell. Biol. 81 (6) (2003) 355–363, https://doi.org/10.1139/o03-069.

[76] J.M. Hughes, E.J. Kuiper, I. Klaassen, et al., Advanced glycation end products cause increased CCN family and extracellular matrix gene expression in the diabetic rodent retina, Diabetologia 50 (5) (2007) 1089–1098, https://doi.org/10.1007/s00125-007-0621-4.

[77] I.E. Blom, R. Goldschmeding, A. Leask, Gene regulation of connective tissue growth factor: new targets for antifibrotic therapy? Matrix Biol. 21 (6) (2002) 473–482, https://doi.org/10.1016/s0945-053x(02)00055-0.

[78] R.A. Kanaan, M. Aldwaik, O.A. Al-Hanbali, The role of connective tissue growth factor in skeletal growth and development, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 12 (12) (2006) 277–281.

[79] J. Gu, X. Liu, Q.X. Wang, et al., Angiotensin II increases CTGF expression via MAPKs/TGF-β1/TRAF6 pathway in atrial fibroblasts, Exp. Cell Res. 318 (16) (2012) 2105–2115, https://doi.org/10.1016/j.yexcr.2012.06.015.

[80] Y.L. Cho, S.M. Hur, J.Y. Kim, et al., Specific activation of insulin-like growth factor-1 receptor by ginsenoside Rg5 promotes angiogenesis and vasorelaxation, J. Biol. Chem. 290 (1) (2015) 467–477, https://doi.org/10.1074/jbc.M114.603142.

[81] S.M. Jacobo, A. Kazlauskas, Insulin-like growth factor 1 (IGF-1) stabilizes nascent blood vessels, J. Biol. Chem. 290 (10) (2015) 6349–6360, https://doi.org/10.1074/jbc.M114.634154.

[82] A. Sirbu, H. Nicolae, S. Martin, et al., IGF-1 and insulin resistance are major determinants of common carotid artery thickness in morbidly obese young patients, Angiology 67 (3) (2016) 259–265, https://doi.org/10.1177/0003319715586499.

[83] Y. Higashi, S. Gautam, P. Delafontaine, S. Sukhanov, IGF-1 and cardiovascular disease, Growth Hormone IGF Res. 45 (2019) 6–16, https://doi.org/10.1016/j.ghir.2019.01.002.

[84] S. Dunzendorfer, H.K. Lee, P.S. Tobias, Flow-dependent regulation of endothelial Toll-like receptor 2 expression through inhibition of SP1 activity, Circ. Res. 95 (7) (2004) 684–691, https://doi.org/10.1161/01.Res.0000143900.19798.47.

[85] C. Monaco, S.M. Gregan, T.J. Navin, B.M. Foxwell, A.H. Davies, M. Feldmann, Toll-like receptor-2 mediates inflammation and matrix degradation in human atherosclerosis, Circulation 120 (24) (2009) 2462–2469, https://doi.org/10.1161/circulationaha.109.851881.

[86] A.N. Seneviratne, C. Monaco, Role of inflammatory cells and toll-like receptors in atherosclerosis, Curr. Vasc. Pharmacol. 13 (2) (2015) 146–160, https://doi.org/10.2174/1570161113116660160.

[87] J. Lin, V. Kakkar, X. Lu, Essential roles of toll-like receptors in atherosclerosis, Curr. Med. Chem. 23 (5) (2016) 431–454, https://doi.org/10.2174/0929867323666151207111408.

[88] A. Kapelouzou, S. Giaglis, M. Peroulis, et al., Overexpression of toll-like receptors 2, 3, 4, and 8 is correlated to the vascular atherosclerotic process in the hyperlipidemic rabbit model: the effect of statin treatment, J. Vasc. Res. 54 (3) (2017) 156–169, https://doi.org/10.1159/000457797.

[89] L. Chávez-Sánchez, M.G. Garza-Reyes, J.E. Espinosa-Luna, K. Chávez-Rueda, M.V. Legorreta-Haquet, F. Blanco-Favela, The role of TLR2, TLR4 and CD36 in macrophage activation and foam cell formation in response to oxLDL in humans, Hum. Immunol. 75 (4) (2014) 322–329, https://doi.org/10.1016/j.humimm.2014.01.012.

[90] G.L. Lee, C.C. Yeh, J.Y. Wu, et al., TLR2 promotes vascular smooth muscle cell chondrogenic differentiation and consequent calcification via the concerted actions of osteoprotegerin suppression and IL-6-mediated RANKL induction, Arterioscler. Thromb. Vasc. Biol. 39 (3) (2019) 432–445, https://doi.org/10.1161/atvbaha.118.311874.

[91] G.L. Lee, Y.W. Chang, J.Y. Wu, et al., TLR 2 induces vascular smooth muscle cell migration through cAMP response element-binding protein-mediated interleukin-6 production, Arterioscler. Thromb. Vasc. Biol. 32 (11) (2012) 2751–2760, https://doi.org/10.1161/atvbaha.112.300302.

[92] G.L. Lee, T.L. Liao, J.Y. Wu, K.K. Wu, C.C. Kuo, Restoration of 5-methoxytryptophan protects against atherosclerotic chondrogenesis and calcification in ApoE (-/-) mice fed high fat diet, J. Biomed. Sci. 28 (1) (2021) 74, https://doi.org/10.1186/s12929-021-00771-1.

[93] W. Li, A.E. Sama, H. Wang, Role of HMGB1 in cardiovascular diseases, Curr. Opin. Pharmacol. 6 (2) (2006) 130–135, https://doi.org/10.1016/j.coph.2005.10.010.

[94] P. Doddapattar, C. Gandhi, P. Prakash, et al., Fibronectin splicing variants containing extra domain A promote atherosclerosis in mice through toll-like receptor 4, Arterioscler. Thromb. Vasc. Biol. 35 (11) (2015) 2391–2400, https://doi.org/10.1161/atvbaha.115.306474.

[95] A.H. Schoneveld, I. Hoefer, J.P. Sluijter, J.D. Laman, D.P. de Kleijn, G. Pasterkamp, Atherosclerotic lesion development and Toll like receptor 2 and 4 responsiveness, Atherosclerosis 197 (1) (2008) 95–104, https://doi.org/10.1016/j.atherosclerosis.2007.08.004.

[96] D.H. Kong, Y.K. Kim, M.R. Kim, J.H. Jang, S. Lee, Emerging roles of vascular cell adhesion molecule-1 (VCAM-1) in immunological disorders and cancer, Int. J. Mol. Sci. 19 (4) (2018), https://doi.org/10.3390/ijms19041057.

[97] S.L. Deshmane, S. Kremlev, S. Amini, B.E. Sawaya, Monocyte chemoattractant protein-1 (MCP-1): an overview, J. Interferon Cytokine Res. 29 (6) (2009) 313–326, https://doi.org/10.1089/jir.2008.0027.

[98] V. Pulito-Cueto, S. Remuzgo-Martínez, F. Genre, et al., Elevated VCAM-1, MCP-1 and ADMA serum levels related to pulmonary fibrosis of interstitial lung disease associated with rheumatoid arthritis, Front. Mol. Biosci. 9 (2022) 1056121, https://doi.org/10.3389/fmolb.2022.1056121.

[99] P.H. Hung, Y.C. Hsu, T.H. Chen, C.L. Lin, Recent advances in diabetic kidney diseases: from kidney injury to kidney fibrosis, Int. J. Mol. Sci. 22 (21) (2021), https://doi.org/10.3390/ijms222111857.

[100] X. Guo, M. Xue, C.J. Li, et al., Protective effects of triptolide on TLR4 mediated autoimmune and inflammatory response induced myocardial fibrosis in diabetic cardiomyopathy, J. Ethnopharmacol. 193 (2016) 333–344, https://doi.org/10.1016/j.jep.2016.08.029.

[101] D. Wang, P. Luo, Y. Wang, et al., Glucagon-like peptide-1 protects against cardiac microvascular injury in diabetes via a cAMP/PKA/Rho-dependent mechanism, Diabetes 62 (5) (2013) 1697–1708, https://doi.org/10.2337/db12-1025.

[102] L. Mao, R. Yin, L. Yang, D. Zhao, Role of advanced glycation end products on vascular smooth muscle cells under diabetic atherosclerosis, Front. Endocrinol. 13 (2022) 983723, https://doi.org/10.3389/fendo.2022.983723.

[103] Z. Amri, I.B. Amor, A. Zarrouk, et al., Anti-glycation, antiplatelet and antioxidant effects of different pomegranate parts, BMC Complement Med Ther 22 (1) (2022) 339, https://doi.org/10.1186/s12906-022-03824-6.

[104] V. Srikanth, Z. Arvanitakis, Type 2 Diabetes and Dementia, 2018.

[105] S. Singh, B.V. Siva, V. Ravichandiran, Advanced Glycation End Products: key player of the pathogenesis of atherosclerosis, Glycoconj. J. 39 (4) (2022) 547–563, https://doi.org/10.1007/s10719-022-10063-x.

[106] T. Azegami, T. Nakayama, K. Hayashi, et al., Vaccination against receptor for advanced glycation end products attenuates the progression of diabetic kidney disease, Diabetes 70 (9) (2021) 2147–2158, https://doi.org/10.2337/db20-1257.

[107] D.T.N. Huynh, K.S. Heo, Therapeutic targets for endothelial dysfunction in vascular diseases, Arch Pharm. Res. (Seoul) 42 (10) (2019) 848–861, https://doi.org/10.1007/s12272-019-01180-7.

[108] A. Daiber, S. Steven, A. Weber, et al., Targeting vascular (endothelial) dysfunction, Br. J. Pharmacol. 174 (12) (2017) 1591–1619, https://doi.org/10.1111/bph.13517.

[109] U. Förstermann, W.C. Sessa, Nitric oxide synthases: regulation and function, Eur. Heart J. 33 (7) (2012) 829–837, https://doi.org/10.1093/eurheartj/ehr304, 837a-837d.

[110] A. Daiber, N. Xia, S. Steven, et al., New therapeutic implications of endothelial nitric oxide Synthase (eNOS) function/dysfunction in cardiovascular disease, Int. J. Mol. Sci. 20 (1) (2019), https://doi.org/10.3390/ijms20010187.

[111] J. Karar, A. Maity, PI3K/AKT/mTOR pathway in angiogenesis, Front. Mol. Neurosci. 4 (2011), https://doi.org/10.3389/fnmol.2011.00051.

[112] P. Abeyrathna, Y. Su, The critical role of Akt in cardiovascular function, Vasc. Pharmacol. 74 (2015) 38–48, https://doi.org/10.1016/j.vph.2015.05.008.

[113] M. Kashiwada, P. Lu, P.B. Rothman, PIP3 pathway in regulatory T cells and autoimmunity, Immunol. Res. 39 (1–3) (2007) 194–224, https://doi.org/10.1007/s12026-007-0075-2.

[114] P.T. Hawkins, L.R. Stephens, PI3K signalling in inflammation, Biochim. Biophys. Acta 1851 (6) (2015) 882–897, https://doi.org/10.1016/j.bbalip.2014.12.006.

[115] C. Liu, T. Su, F. Li, et al., PI3K/Akt signaling transduction pathway is involved in rat vascular smooth muscle cell proliferation induced by apelin-13, Acta Biochim. Biophys. Sin. 42 (6) (2010) 396–402, https://doi.org/10.1093/abbs/gmq035.

[116] Z. Yu, L. Guo-tao, L. Zeng-zhen, X. Yang, W. Jun, Effects of peach kernel on TRIB3 gene and Toll like receptor signaling pathway in rats with diabetic macrovascular fibrosis, J Chin TCM and Pharmacy. 34 (12) (2019) 5670–5674, doi: CNKI:SUN:BXYY.0.2019-12-039.

[117] X. Yang, W. Jun, The effect of tao-He-Cheng-Qi decoction on vascular expression of toll-like receptor 2, toll-like receptor 4, transforming growth fator-beta and insulin-like growth fator-1 in rats with diabetes, J Chin Surgery of Integr Trad and West Med 23 (1) (2017) 60–64, https://doi.org/10.3969/j.issn.1007-6948.2017.01.017.

[118] Y. Wang, Q. Jia, Y. Zhang, J. Wei, P. Liu, Taoren honghua drug attenuates atherosclerosis and plays an anti-inflammatory role in ApoE knock-out mice and RAW264.7 cells, Front. Pharmacol. 11 (2020) 1070, https://doi.org/10.3389/fphar.2020.01070.

[119] Y. Cao, Y. Liu, T. Zhang, W. Lei, B. Zhang, Comparative analysis on single- and multiherb strategies in coronary artery atherosclerosis therapy, Cardiol. Res. Pract. 2021 (2021) 6621925, https://doi.org/10.1155/2021/6621925.

[120] M. Wang, S.Q. Chang, Y.S. Tian, G.Q. Zhang, J. Qi, Zengye decoction ameliorates insulin resistance by promoting glucose uptake, Rejuvenation Res. 23 (5) (2020) 367–376, https://doi.org/10.1089/rej.2019.2228.

[121] Z. Liu, W. Kuang, X. Xu, et al., Putative identification of components in Zengye Decoction and their effects on glucose consumption and lipogenesis in insulin-induced insulin-resistant HepG2 cells, J. Chromatogr., B: Anal. Technol. Biomed. Life Sci. 1073 (2018) 145–153, https://doi.org/10.1016/j.jchromb.2017.12.019.

[122] C. Junren, X. Xiaofang, Z. Huiqiong, et al., Pharmacological activities and mechanisms of hirudin and its derivatives - a review, Front. Pharmacol. 12 (2021) 660757, https://doi.org/10.3389/fphar.2021.660757.

[123] L. Ke, C. Zhong, Z. Chen, et al., Tanshinone I: pharmacological activities, molecular mechanisms against diseases and future perspectives, Phytomedicine 110 (2022) 154632, https://doi.org/10.1016/j.phymed.2022.154632.

[124] H. Zhong, D.Y. Li, S.Y. Wang, et al., Tanshinone IIa attenuates vascular calcification through inhibition of NF-κB and β-catenin signaling pathways, Sheng Li Xue Bao 74 (6) (2022) 949–958, https://doi.org/10.13294/j.aps.2022.0086.

[125] Y. Yang, M. Shao, J. Yao, et al., Neocryptotanshinone protects against myocardial ischemia-reperfusion injury by promoting autolysosome degradation of protein aggregates via the ERK1/2-Nrf2-LAMP2 pathway, Phytomedicine 110 (2022) 154625, https://doi.org/10.1016/j.phymed.2022.154625.

[126] D. Gong, T. Yuan, R. Wang, et al., Network pharmacology approach and experimental verification of Dan-Shen Decoction in the treatment of ischemic heart disease, Pharm. Biol. 61 (1) (2023) 69–79, https://doi.org/10.1080/13880209.2022.2152059.

[127] H. Liu, C. Wang, The genus Asarum: a review on phytochemistry, ethnopharmacology, toxicology and pharmacokinetics, J. Ethnopharmacol. 282 (2022) 114642, https://doi.org/10.1016/j.jep.2021.114642.

[128] H. Liu, S. Li, X. Huan, et al., The antinociceptive and anti-inflammatory potential and pharmacokinetic study of significant alkamides ingredients from Asarum Linn, J. Ethnopharmacol. 297 (2022) 115569, https://doi.org/10.1016/j.jep.2022.115569.
[129] M. Su, W. Zhao, S. Xu, J. Weng, Resveratrol in treating diabetes and its cardiovascular complications: a review of its mechanisms of action, Antioxidants 11 (6) (2022) 1085, https://doi.org/10.3390/antiox11061085.
[130] X. Dong, J. Fu, X. Yin, et al., Emodin: a review of its pharmacology, toxicity and pharmacokinetics, Phytother Res. 30 (8) (2016) 1207–1218, https://doi.org/10.1002/ptr.5631.
[131] Jia X. HaoShang, H. Liu, X. Zhang, Y. Shao, A comprehensive review of emodin in fibrosis treatment, Fitoterapia 165 (2023) 105358, https://doi.org/10.1016/j.fitote.2022.105358.
[132] S. Zhang, L. Gao, S. Li, et al., Association of non-insulin-based insulin resistance indices with disease severity and adverse outcome in idiopathic pulmonary arterial hypertension: a multi-center cohort study, Cardiovasc. Diabetol. 23 (1) (2024) 154, https://doi.org/10.1186/s12933-024-02236-9.
[133] N.A. ElSayed, G. Aleppo, V.R. Aroda, et al., 10. Cardiovascular disease and risk management: standards of care in diabetes-2023, Diabetes Care 46 (Suppl 1) (2023) S158–s190, https://doi.org/10.2337/dc23-S010.
[134] N.A. Calcutt, M.E. Cooper, T.S. Kern, A.M. Schmidt, Therapies for hyperglycaemia-induced diabetic complications: from animal models to clinical trials, Nat. Rev. Drug Discov. 8 (5) (2009) 417–429, https://doi.org/10.1038/nrd2476.
[135] J.S. Huang, J.Y. Guh, H.C. Chen, W.C. Hung, Y.H. Lai, L.Y. Chuang, Role of receptor for advanced glycation end-product (RAGE) and the JAK/STAT-signaling pathway in AGE-induced collagen production in NRK-49F cells, J. Cell. Biochem. 81 (1) (2001) 102–113, https://doi.org/10.1002/1097-4644(20010401)81:1<102::aid-jcb1027>3.0.co;2-y.