The Mechanism of Action of Qihuang Jiangtang Capsule in the Treatment of Type 2 Diabetes Based on Network Pharmacology and Molecular Docking Technology

Mengmeng Ji1 Yanan Yu2 Jiarui Wu3 Jun Liu2 Yanhua Jiang2 Zhiwei Jing2

1 School of Life Sciences, Ningxia University, Ningxia Yinchuan China
2 Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China
3 School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing, China

Abstract

Objective

Our objective was to investigate the potential mechanism of action of Qihuang Jiangtang capsule (QHJTC) in the treatment of type 2 diabetes mellitus (T2DM) through network pharmacology and molecular docking.

Methods

The active components of materia medica in the formula of QHJTC were searched on the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform and Encyclopedia of Traditional Chinese Medicine. The targets related to the active components were obtained via PubChem database. The targets related to T2DM were retrieved through the GeneCards database. The targets corresponding to the active components and diabetes mellitus were uploaded to the Venn diagrams website to get the Venn diagram, and the intersecting targets were the potential targets of QHJTC in treating T2DM. The active components and potential targets were imported into Cytoscape 3.7.2 software to construct the active component–potential target network, and the key compounds and targets were screened by the Network Analyzer module in the Tools module. The potential targets were imported into the STRING database to obtain the interaction relationships, so as to analyze and construct the protein–protein interaction (PPI) network by Cytoscape 3.7.2 software. The intersecting targets were introduced into Metascape for gene ontology (GO) functional enrichment analysis and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analysis. The top 20 signaling pathways obtained by the KEGG pathway enrichment analysis and the related targets and the corresponding targets were analyzed by using Cytoscape 3.7.2 software to construct the “active component–important target-key pathway network ” for the intervention of T2DM with QHJTC. The molecular docking of active components and core targets was performed with AutoDock software.

Results

A total of 237 active components and 281 related targets were obtained from QHJTC, as well as 1 362 T2DM targets and 155 potential targets of QHJTC in treating...
Introduction

According to the World Health Organization, diabetes is a chronic metabolic disease characterized by elevated blood sugar levels which can cause serious damage to the heart, blood vessels, eyes, kidneys, and nerves over time. At present, the most common type of diabetes mellitus is type 2 diabetes mellitus (T2DM), which occurs when the body develops resistance to insulin or produces insufficient insulin. In the past 30 years, the prevalence of T2DM has increased significantly,¹ and China has become the country with a large number of diabetes patients.²,³ At present, the world has reached a goal to inhibit the growth in the number of people with diabetes and obesity by 2025. As the only patented traditional Chinese medicine approved by the China Food and Drug Administration (CFDA) of the People’s Republic of China in 2017, Yidaokang Qihuang Jiangtang capsule (QHJTC) can treat diabetes and its complications from the root and has a broad market prospect. Pharmacological and clinical studies have confirmed that QHJTC can repair damaged islet tissue, increase insulin release, and reduce blood glucose.⁴ In this study, network pharmacology and molecular docking were used to investigate the potential mechanism of QHJTC in the treatment of T2DM, so as to provide a theoretical basis for further study of the active components of QHJTC.

Materials and Methods

Screening of Main Active Components and Related Targets of Qihuang Jiangtang Capsule

By searching the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://old.tcmsp-e.com/tcmsp.php)⁵ and the Encyclopedia of Traditional Chinese Medicine (ETCM, http://www.tcmip.cn/ETCM/index.php/Home/Index/index.html),⁶ the chemical composition of Xiyangshen (Panacis Quinquefolii Radix), Zhimu (Anemarrhenae Rhizoma), Shigao (Gypsum Fibrosorum), Kuguacong (dried bitter gourd), Canjian (silkworm cocoon), Huangqi (Astragali Radix), Shanyao (Dioscoreae Rhizoma), Dihuang (Rehmanniae Radix), Xuan Shen (Scrophulariae Radix), Bei Shashen (Glehniae Radix), Maidong (Ophiopogonis Radix), Yuzhu (Polygonati Odorati Rhizoma), Huangjing (Polygonati Rhizoma), Tianhuafen (Trichosanthis Radix), Ji’nejin (Galli Gigerii Endothelium Corneum), Huangqizi (Lycii Fructus), Gouqizi (Lycii Fructus), Nyu Zhenzi (Ligustri Lucidi Fructus), and Yinyanghuo (Epimedii Folium) was collected, through literature search.⁷,⁸ The bioactive components of QHJTC with oral bioavailability ≥30% and herb likeness ≥0.18 were screened.⁹ The related targets of the active components were obtained using PubChem database (https://pubchem.ncbi.nlm.nih.gov).

Type 2 Diabetes Mellitus-Related Targets and Potential Targets of Qihuang Jiangtang Capsule in the Treatment of Type 2 Diabetes Mellitus

The GeneCards database (https://www.genecards.org/) was searched with “type 2 diabetes mellitus” as a keyword to obtain T2DM-related targets. The targets corresponding to the active components of QHJTC and the T2DM targets were imported into the Venn diagrams website (http://bioinformatics.psb.ugent.be/) to draw the Venn diagram. The intersecting targets should be the potential target of QHJTC in the treatment of T2DM.

Construction of Active Component-Potential Target Network Diagram

The active components and potential targets of QHJTC were introduced into Cytoscape 3.7.2 software to construct the active components–potential targets network. The key components and key targets were screened out by topology analysis via the Network Analyzer module in the Tools module.

Construction of Protein–Protein Interaction Network

The potential targets were imported into STRING database, “multiple proteins” was selected, the species was limited to “homo sapiens”, and the interaction relationship was obtained. The interaction relationship was imported into Cytoscape 3.7.2 software to analyze and construct protein–protein interaction (PPI) network.

Enrichment Analysis

The gene ontology (GO) functional enrichment analysis and Kyoto encyclopedia of gene and genome (KEGG) pathway enrichment analysis of potential targets were carried out through Metascape (https://metascape.org/).

Conclusion

QHJTC can treat T2DM through multi-components, multi-targets, and multi-paths.
Construction of Active Components—Important Target-Key Pathway Network
The top 20 signal pathways obtained by KEGG pathway enrichment analysis and the corresponding active components of targets and related targets were imported into Cytoscape 3.7.2 software to construct the “active components—important targets-key pathways” network of QHJT in treating T2DM.

Molecular Docking
The structure of the key components was downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) and saved in SDF format. The SDF format file was transformed into .mol2 format file by Chem 3D software and imported into Autodock Tools 1.5.6 for hydrogenation, charging, and other processing. The protein conformations of important targets were screened from RCSB PDB database (https://www.rcsb.org/). There were three screening conditions: the biological source of protein structure was human; the protein structure was obtained by X-crystal diffraction; and the crystal resolution of protein was 3Å. The screened proteins were treated by removing water and small molecules, and hydrogenation, charging, and combining nonpolar hydrogen were carried out in Autodock Tools 1.5.6 software. Molecular docking was carried out with Autodock Vina 1.5.6. The receptor ligand was sorted and screened according to the binding energy.

Results
Screening of Active Components and Related Targets of Qihuang Jiangtang Capsule
Through TCMSP, ETCM, and literature searching and screening, 237 active components of QHJT were obtained, including 11 from Xiyangshen (Panacis Quinquelifolii Radix), 15 from Zhimu (Anemarrhenae Rhizoma), 3 from Canjian (silkworm cocoon), 20 from Huangqi (Astragali Radix), 20 from Shanzhuyu (Corni Fructus), 16 from Shanyao (Dioscoreae Rhizoma), 2 from Dihuang (Rehmanniae Radix), 2 from Tianhufan (Trichosanthis Radix), 16 from Maidong (Ophiopogonis Radix), 9 from Xuanshen (Scrophulariae Radix), 8 from Bei Shashen (Glehniae Radix), 8 from Yuzhu (Polygonati Odorati Rhizoma), 12 from Huangqin (Polygonati Rhizoma), 14 from Huanglian (Coptidis Rhizoma), 45 from Gouqizi (Lycii Fructus), 13 from Nyu Zhenzi (Ligustri Lucidi Fructus), and 496 from Yinyanghuo (Epimedi Foliuim). After removing the repeated targets, there were a total of 281 targets (Table 1).

Type 2 Diabetes Mellitus Targets and Potential Targets of Qihuang Jiangtang Capsule in the Treatment of Type 2 Diabetes Mellitus
A total of 1,362 T2DM-related targets were found through GeneCards database. The targets corresponding to the active components of QHJT and the T2DM targets were imported into the Venn diagrams platform to get the Venn diagram. There were 155 intersecting targets, which were the potential targets of QHJT in treating T2DM (Fig. 1).

Active Components—Potential Targets Network
The active components and potential targets of QHJT were introduced into Cytoscape 3.7.2 software to construct the active components—potential targets network. The network had 316 nodes (150 active components nodes and 166 target nodes) and 1,995 lines, and each line represented the interaction between the active compound and the target. The topology analysis of the network was carried out through the “Network Analyze” function of Cytoscape 3.7.2 software, and it was found that there were 32 key active components with topological degree >10, including quercetin, kaempferol, β-sitosterol, luteolin, stigmasterol, anhydroicaritin, diosgenin, isorhamnetin, formononetin, baicalin, etc. There were 49 key targets with topological degree >10, including prostaglandin-endoperoxide synthase 2 (PTGS2), PTGS1, protein kinase CAMP-activated catalytic subunit α (PRKACA), adrenoceptor β2 (ADRB2), SCN5A, serine protease 1 (PRSS1), ADRB1, peroxisome proliferator-activated receptor γ, tumor necrosis factor (TNF), intercellular adhesion molecule 1, vascular endothelial growth factor A (VEGFA), tumor protein p53 (TP53) (Fig. 2).

Protein–Protein Interaction Network
The interaction relationship was obtained by importing the 155 potential targets into STRING database, and the PPI network was analyzed and constructed by Cytoscape 3.7.2 software. The network consisted of 155 nodes and 3,266 lines. The node represented the target protein, and the line represented the interaction between proteins. The degree value represented the number of lines connected to one node, and the more the lines, the greater the correlation. It can be used to evaluate the importance of each node in the network. The larger the node is and the darker the color is, the more important the node is. The average degree value of nodes in the network was 42.14, of which 63 nodes were
| Materia medica | Mol ID | Active components | OB /% | DL | Targets (n) |
|---------------|-------|-------------------|-------|----|-------------|
| Huangqi (Astragali Radix) | MOL000239 | jaranol | 50.83 | 0.29 | 12 |
| | MOL000354 | isorhamnetin | 49.60 | 0.31 | 35 |
| | MOL000371 | 3,9-di-O-methylhissolin | 53.74 | 0.48 | 22 |
| | MOL000378 | 7-O-methylisoumorculatol | 74.69 | 0.30 | 44 |
| | MOL000380 | (6αR,11αR)-9,10-dimethoxy-6α,11α-dihydro-6H-benzofuran-3,2-c)chromen-3-ol | 64.26 | 0.42 | 21 |
| | MOL000392 | formononetin | 69.67 | 0.21 | 38 |
| Shanyao (Dioscoreae Rhizoma) | MOL001559 | piperlonguminine | 30.71 | 0.18 | 11 |
| | MOL000322 | kadsurenone | 54.72 | 0.38 | 26 |
| | MOL005430 | hancinone C | 59.05 | 0.39 | 21 |
| | MOL000546 | diosgenin | 80.88 | 0.81 | 16 |
| | MOL005465 | AIDS180907 | 45.33 | 0.77 | 12 |
| Xiyangshen (Panacis Quinquefolii Radix) | MOL000358 | beta-sitosterol | 36.91 | 0.75 | 37 |
| | MOL005344 | ginsenoside rh2 | 36.32 | 0.56 | 12 |
| | MOL006980 | papaverine | 64.04 | 0.38 | 20 |
| Shudihuang (Rehmanniae Radix Praeparata) | MOL000449 | stigmasterol | 36.91 | 0.75 | 21 |
| Maidong (Ophiopogonis Radix) | MOL000296 | hederagenin | 36.91 | 0.75 | 21 |
| Huangjing (Polygonati Rhizoma) | MOL001792 | DFV | 32.76 | 0.18 | 12 |
| | MOL002714 | baicalein | 33.52 | 0.21 | 36 |
| | MOL002959 | 3'-methoxydaidzein | 48.57 | 0.24 | 18 |
| | MOL004941 | (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one | 71.12 | 0.18 | 14 |
| Zhimu (Anemarrhenae Rhizoma) | MOL000422 | kaempferol | 41.88 | 0.24 | 61 |
| | MOL004497 | hippeastrine | 51.65 | 0.62 | 11 |
| Xuanshen (Scrophulariae Radix) | MOL002222 | sugiol | 36.11 | 0.28 | 17 |
| Huanglian (Coptidis Rhizoma) | MOL001454 | berberine | 36.86 | 0.78 | 16 |
| | MOL002894 | berbberrubine | 35.74 | 0.73 | 12 |
| | MOL002897 | epiberberine | 43.09 | 0.78 | 11 |
| | MOL002903 | (R)-canadine | 55.37 | 0.77 | 30 |
| | MOL002904 | berlambine | 36.68 | 0.82 | 19 |
| | MOL000785 | palmatine | 64.6 | 0.65 | 18 |
| Bei Shashen (Glehniae Radix) | MOL001956 | cnidilin | 32.69 | 0.28 | 12 |
| | MOL000098 | quercetin | 46.43 | 0.28 | 150 |
| Gouqizi (Lycii Fructus) | MOL005406 | atropine | 45.97 | 0.19 | 25 |
| | MOL008400 | glycitein | 50.48 | 0.24 | 22 |
| | MOL009650 | Atropine | 42.16 | 0.19 | 27 |
| Shanzhuyu (Corni Fructus) | MOL008457 | tetrahydroalstonine | 32.42 | 0.81 | 27 |
| Nyu Zhenzi (Ligustri Lucidi Fructus) | MOL004576 | taxifolin | 57.84 | 0.27 | 11 |
| | MOL005147 | lucidumoside D_qt | 54.41 | 0.47 | 17 |
| | MOL000006 | luteolin | 36.16 | 0.25 | 57 |
| Yinyanghuo (Epimedii Folium) | MOL003044 | chryseriol | 35.85 | 0.27 | 17 |
| | MOL003542 | 8-isopentenyl-kaempferol | 38.04 | 0.39 | 28 |
| | MOL004373 | anhydroicaritin | 45.41 | 0.44 | 36 |
| | MOL004380 | Chomoerythrin, 1,6-didehydro-3,15,16-trimethoxy, (3,beta)- | 39.14 | 0.49 | 38 |
| | MOL004391 | 8-(3-methylbut-2-ethyl)-2-phenyl-chromone | 48.54 | 0.25 | 30 |

Abbreviations: DL, drug likeness; OB, oral bioavailability; DFV, the synonyms are Liquiritigenin or (2S)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one.
greater than the average value, including AKT serine/threonine kinase 1 (AKT1), interleukin-6 (IL-6), VEGFA, TNF, TP53, caspase 3 (CASP3), mitogen-activated protein kinase 1 (MAPK1), PTGS2, matrix metalloproteinase-9, MAPK8, etc.

**Enrichment Analysis**

The 155 intersecting targets were imported into Metascape database for GO functional enrichment analysis and KEGG pathway enrichment analysis. A total of 471 items were obtained by GO analysis, including 248 involved in biological processes (BP), mainly related to response to inorganic substances, trauma, lipopolysaccharide, organic circulation complex cell response, apoptosis pathway, extracellular stimulation response, oxygen level response, positive regulation of cell migration, active oxygen metabolism process, steroid hormone response, regulation of cell stress response, and negative regulation of cell proliferation; 125 involved in molecular functions (MF), including protein domain specific binding, protein kinase binding, DNA-transcription factor binding, oxidoreductase activity, serine hydrolase activity, kinase activity, growth factor binding, adrenergic receptor activity, antioxidant activity, and TNF receptor superfamily binding; 98 involved in cell components, mainly related to membrane raft, cystic cavity, extracellular matrix, receptor complex, perinuclear region, cell membrane, dendrites, adhesion plaque, and so on. There were 299 signal pathways obtained by KEGG pathway enrichment analysis, mainly related to cancer pathway, advanced glycosylation end products (AGEs)-receptor of AGEs (RAGE) signal transduction pathway, IL-17 signal pathway, p53 signal pathway, insulin resistance and nuclear factor-kappa B (NF-κB) signal pathway, VEGF signal pathway, thyroid hormone signal pathway, estrogen signal pathway, sphingolipid signal pathway, and so on. Bar and bubble charts of the top 20 items were drawn (►Figs. 4 and 5).

**Active Component–Important Target–Critical Pathway Network and Its Analysis**

The top 20 signal pathways obtained by KEGG analysis and related targets as well as the corresponding active components of related targets were introduced into Cytoscape 3.7.2 software to construct the active component–important target–critical pathway network of QHJTC in treating T2DM and were screened under the condition of degree value ≥7 (median). The network had 322 nodes, including 115 active component nodes, 170 target nodes, and 20 pathway nodes after deleting the free targets, and had 1,699 lines with an average value of 10.55. There were 29 active components with a degree value greater than the average value, including quercetin, luteolin, kaempferol, β-sitosterol, isorhamnetin, formononetin, 7-methyl ribonuclein, baicalin, anhydroicaritin, 8-isoprene-flavonoids, stigmasterol, tetrahydroalstonine, diosgenin, daidzein, stamens isoalloones, and so on. There were 46 targets with a degree value greater than the average value, including PTGS2, PTGS1, PRKACA, NOS2,
PRSS1, ADRB2, AR, SCN5A, ESR1, NR3C2, GSK3B, CASP9, and so on. There were 18 signal pathways with the degree value greater than the average value, which were proteoglycan in cancer, cancer pathway, IL-17 signal pathway, sphingolipid signal pathway, VEGF signal pathway, AGE-RAGE signal transduction pathway in diabetic complications, platinum resistance, estrogen signal pathway, malaria, measles, p53 signal pathway, thyroid hormone signal pathway, gap junction, insulin resistance, serotonin-containing synapses, transcriptional disorders in cancer, longevity regulation pathway, and NF-κB signal pathway (►Fig. 6).

Molecular Docking
Quercetin, kaempferol, β-sitosterol, luteolin, and baicalein were docked with AKT1, BAX, BCL2, CASP3, PTGS2, CCND1, IL6, and MTOR. The docking binding energy of them was less than 0 kcal·mol⁻¹, indicating that the key components in QHJTC can spontaneously bind to the core targets. The docking results were visualized by Pymol software (►Table 2, ►Fig. 7).

Discussion
T2DM belongs to the category of “dispersion-thirst” in TCM and is the syndrome of root vacuity and tip repletion due to the lack of congenital constitution, emotional imbalance, improper diet, and so on. The pathogenesis of dispersion thirst has been understood in traditional Chinese medicine, which holds that yin deficiency and dryness heat are its basic pathogenesis. The more deficient yin is, the more exuberant dryness heat is, and the more exuberant dryness heat is, the more deficient yin is, so the two are cause and effect to each other throughout the whole process of the disease. Clearing heat and moistening dryness, nourishing yin and engendering liquid are the treatment method of the disease. Case Records as a Guide to Clinical Practice (Lin Zheng Zhi Nan Yi An) points out that dispersion thirsts was just due to yin depletion and yang hyperactivity as well as deficiency of fluid with exuberant heat. QHJTC is derived from four classic formulas of TCM, that is, Renshen Baihu decoction from Treatise on Cold Damage (Shang Han Lun), Xiaoke Formula from Danxi’s Experiential Therapy (Dan Xi Xin Fa), Shashen Maidong decoction from Systematic Differentiation of Warm Diseases (Wen Bing Tiao Bian), and Liuwei Dihuang Pill from Essentials from the Golden Cabinet (Jin Gui Yao Lue). QHJTC consists of 20 kinds Chinese materia medica, with Canjian (silkworm cocoon), Huangqi (Astragali Radix), Shanyao (Dioscoreae Rhizoma) and Xiyangshen (Panacis Quinquefolii Radix) as the principal herbs, Shudihuang (Rehmanniae Radix Praeparata), Maidong (Ophiopogonis Radix), Zhimu (Anemarrhenae Rhizoma), Huanglian (Coptidis Rhizoma), Shigao (Gypsum Fibrosum), Huangjing (Polygonati Rhizoma), Xuanshen (Scrophulariae Radix), Bei Shashen (Glehniae Radix), Tianhuafen (Trichosanthis Radix), Yuzhu (Polygonati Odorati Rhizoma) as minister herbs, Gouqizi (Lycii Fructus), Kuguagan (dried bitter gourd) and Shanzhuyu (Corni Fructus) as assistant herbs, with Ji’neijin (Galli Gigerii Endothelium Corneum), Nyu Zhenzi (Ligustri Lucidi Fructus) and Yinyanghuo (Epimedii Folium) as the guide herbs, all of which can have the effects of boosting qi and nourishing yin, engendering body liquid, and clearing heat for qi and yin vacuity resulting in heat syndrome, such as fatigue, thirst with liking for drinking water, large appetite with rapid hungering, and copious urine. Modern clinical studies have
Fig. 4 GO enrichment analysis.
shown that Renshen Baihu decoction can reduce blood sugar, blood lipids, and promote the improvement of quality of life.\textsuperscript{13} Xiaoke formula can continuously inhibit the activity of adenosine 5'-monophosphate (AMP)-activated protein kinase by Sirtuin 1 (SIRT1) to decrease the activity of oxidase and oxidative stress, and then reduce blood glucose and promote microcirculation.\textsuperscript{14} Yu Nyu decoction combined with Shashen Maidong decoction has a definite effect on diabetic patients of fire excess from yin deficiency, which can reduce the levels of serum Vaspin and Omentin-1 and improve blood glucose metabolism.\textsuperscript{15} Liuwei Dihuang Pill is a classic prescription for nourishing yin and tonifying the kidney. It plays a role in the prevention and treatment of diabetes, such as antioxidant injury, reducing blood glucose, improving insulin resistance, and alleviating diabetic complications and has a significant protective effect on the vascular system of diabetes patients. Its mechanism may be related to increasing the level of serum adiponectin or upregulating the expression of adiponectin receptors (AdipoR1 and AdipoR2).\textsuperscript{16}

In this study, a total of 237 active components and 281 related targets were obtained from QHJTC. Through GeneCards database, 1,362 T2DM targets were found, including 24 from Gouqizi (Lycii Fructus), 18 from Yinyanghuo (Epimedii Folium), 14 from Huangqi (Astragali Radix), 12 from Shanzhuyu (Corni Fructus), 11 from Zhimu (Anemarrhenae Rhizoma), 11 from Huanglian (Coptidis Rhizoma), 10 from Shanyao (Dioscoreae Rhizoma), 9 from Nyu Zhenzi (Ligustri Lucidi Fructus), 8 from Bei Shashen (Glehniae Radix), 8 from Huangjing (Polygonati Rhizoma), 6 from Xiyangshen (Panacis Quinquefolii Radix), 6 from Yuzhu (Polygonati Odorati Rhizoma), 5 from Xuanshen (Scrophulariae Radix), 4 from Maidong (Ophiopogonis Radix), 2 from Shudihuang (Rehmanniae Radix Praeparata), 1 from Canjian (silkworm cocoon), and 1 from Tianhuafen (Trichosanthis Radix). The active component–potential target network had 298 nodes and 1,995 lines. It was found that there were various interactions among herbs in QHJTC and the same compound can act on different targets, different compounds on the same target to form a complex network, which fully reflected the multicomponent and multitarget therapeutic mechanism of QHJTC as a compound preparation of traditional Chinese medicine. The topological analysis of the active component–potential target network showed that there were 32 active components with a degree value greater than 10, including 7 from Yinyanghuo (Epimedii Folium), 5 from Zhimu (Anemarrhenae Rhizoma), 6 from Huangqi (Astragali Radix), 4 from Huanglian (Coptidis Rhizoma), 2 from Huangjing (Polygonati Rhizoma), 2 from Gouqizi (Lycii Fructus), 2 from Shanyao (Dioscoreae Rhizoma), 1 from
Xuanshen (Scrophulariae Radix), 1 from Shanzhuyu (Corni Fructus), 1 from Nyu Zhenzi (Ligustri Lucidi Fructus), 1 from Maidong (Ophiopogonis Radix). Quercetin belonging to the active component of Yinyanghuo (Epimedii Folium) had the greatest degree value, so it is speculated that the key herb of QHJTC in treating T2DM may be Yinyanghuo (Epimedii Folium). The related chemical constituents of Shigao (gypsum fibrosum), Kuguagan (dried bitter gourd) and Ji-neijin (Galli Gigerii Endothelium Corneum) were not found in TCMSP and ETCM database, and the related chemical components were not found in the literature, but in the clinical application of QHJTC, Shigao (Gypsum Fibrosum) as minister herbs, Kuguagan (dried bitter gourd) as assistant herb, and Ji-neijin (galli Gigerii Endothelium Corneum) as guide herb were essential herbs to assist Canjian (silkworm cocoon), Huangqi (Astragal Radix), Shanyao (Dioscoreae Rhizoma), and Xiyangshen (Panacis Quinquefolii Radix) to replenish qi and nourish yin. Network topology analysis showed that PTGS2, PTGS1, PRKACA, ADRB2, SCN5A, PRSS1, and so on were the core targets. PTGS2, also known as cyclooxygenase 2, plays a major role in the occurrence and development of T2DM. PTGS2 produces prostaglandins, which negatively regulate glucose-stimulated insulin secretion and act as mediators of inflammatory response. Genetic correlation studies have shown that ADRRs gene variation is associated with T2DM. Quercetin, kaempferol, β-sitosterol, luteolin, phytosterol, anhydroicaritin, diosgenin, isorhamnetin, for-mononetin, and baicalein are the main active components. Quercetin is a kind of flavonol compound, which is widely distributed in the plant world. It has a variety of biological activities and extensive pharmacological effects, such as antioxidant, anti-inflammation, antivirus, antitumor, hypoglycemic, lipid-lowering, immune regulation, and so on, which is of very important clinical significance in the treatment of bacterial infection, viral infection, tumor, diabetes, hyperlipidemia, and immune system diseases.

### Table 2 Molecular docking results

| Compounds   | Target protein | Binding free energy/kcal·mol⁻¹ |
|-------------|----------------|-------------------------------|
| quercetin   | AKT1           | -6.7                          |
| quercetin   | BAX            | -6.8                          |
| quercetin   | BCL2           | -7.1                          |
| quercetin   | CASP3          | -7.8                          |
| quercetin   | PTGS2          | -9.1                          |
| quercetin   | CCND1          | -7.9                          |
| quercetin   | IL6            | -7.2                          |
| kaempferol  | AKT1           | -6.6                          |
| kaempferol  | BAX            | -6.9                          |
| kaempferol  | BCL2           | -6.9                          |
| kaempferol  | CASP3          | -7.9                          |
| kaempferol  | PTGS2          | -8.9                          |
| β-sitosterol| BAX            | -7.6                          |
| β-sitosterol| BCL2           | -7.1                          |
| β-sitosterol| CASP3          | -6.4                          |
| β-sitosterol| PTGS2          | -9.5                          |
| luteolin    | AKT1           | -6.8                          |
| luteolin    | CASP3          | -8.1                          |
| luteolin    | PTGS2          | -9.4                          |
| luteolin    | CCND1          | -7.7                          |
| luteolin    | IL6            | -7.2                          |
| diosgenin   | AKT1           | -7.7                          |
| diosgenin   | MTOR           | -10.5                         |
| baicalein   | AKT1           | -7.2                          |
| baicalein   | BAX            | -7.0                          |
| baicalein   | BCL2           | -7.7                          |
| baicalein   | CASP3          | -7.9                          |
Pharmacological studies have shown that quercetin can activate fibroblast growth factor 21 (FGF21) / MAPK signal pathway to effectively reduce peripheral insulin resistance and blood glucose in T2DM rats.\(^{20}\) Based on network pharmacology and molecular docking technology, it is shown that quercetin may act on NOS3, CYP1B1, NOS2, and other core targets to regulate toll-like receptor signal pathway, MAPK signal pathway, insulin signal pathway, and so on.\(^{21}\) A total of 471 items were obtained by GO functional enrichment analysis of 155 intersecting targets. The BP are mainly involved in the responses to inorganic substances, trauma, lipopolysaccharide, cellular responses to nitrogen compounds, apoptosis pathway, active oxygen metabolism, and so on. MF are mainly about protein domain-specific binding, protein kinase binding, DNA-transcription factor binding, cytokine receptor binding, oxidoreductase activity, serine hydrolase activity, nuclear receptor activity, protease binding, phosphatase binding, and so on. Cell components are mainly membrane raft, capsule cavity, extracellular matrix, endoplasmic reticulum cavity, protein kinase complex, cell membrane, dendrite, adhesion spot, lipid vacuole, organelle membrane cavity and so on. A total of 299 signal pathways were obtained by KEGG pathway enrichment analysis, mainly related to cancer pathway, AGE-RAGE signal transduction pathway in diabetic complications, IL-17 signal pathway, p53 signal pathway, insulin resistance, and so on. The pathogenesis of T2DM is related to insulin resistance (IR) and β-cell dysfunction. IR refers to the decrease of the biological effect of insulin, which leads to the decrease of glucose uptake and metabolism, including the decrease of insulin sensitivity and responsiveness. It is the initial factor of T2DM, which runs through the whole disease course, and its mechanism is complex. Traditional Chinese medicine can act on multiple targets related to the pathogenesis of IR, so as to slow down and prevent IR.\(^{22}\) QHJTC can effectively reduce the levels of blood glucose and blood lipids in patients with mild T2DM by reducing IR and improving islet function.\(^{23}\) It can also improve hemorheological indexes and has a significant effect on the prevention and treatment of diabetic complications.\(^{24}\) Diabetic model rats were used to explore the hypoglycemic effect of QHJTC and its effect on islet function and pancreatic tissue changes. The results showed that QHJTC could significantly reduce blood glucose in alloxan-induced hyperglycemic rats, significantly reduced the glucose tolerance curve of diabetic

**Fig. 7** Molecular docking results.

BCL2 with Baicalin (Affinity = -7.7 kcal\(\cdot\)mol\(^{-1}\))

BAX with beta-Sitosterol (Affinity = -7.6 kcal\(\cdot\)mol\(^{-1}\))

PTGS2 with beta-Sitosterol (Affinity = -9.5 kcal\(\cdot\)mol\(^{-1}\))

AKT1 with Diosgenin (Affinity = -7.7 kcal\(\cdot\)mol\(^{-1}\))

MTOR with Diosgenin (Affinity = -10.5 kcal\(\cdot\)mol\(^{-1}\))

CASP3 with Luteolin (Affinity = -8.1 kcal\(\cdot\)mol\(^{-1}\))

IL6 with Luteolin (Affinity = -7.2 kcal\(\cdot\)mol\(^{-1}\))

CCND1 with Quercetin (Affinity = -7.9 kcal\(\cdot\)mol\(^{-1}\))

- Chinese Medicine and Natural Products  Vol. 2  No. 3/2022  © 2022. The Author(s).
rats, and significantly improve the results of glucose tolerance in diabetic rats. It could also promote insulin secretion in rats with high glucose, improve the islet function of diabetic rats, and repair pancreatic tissue damage caused by alloxan.\textsuperscript{25} AGE-RAGE signal pathway is an important link in the occurrence and development of diabetic nephropathy.\textsuperscript{26} Traditional Chinese medicine has the advantages of overall regulation, multi-channel and multitarget in the treatment of diabetic nephropathy, which can improve the progression of diabetic nephropathy by blocking AGES-RAGE signal pathway, but the mechanism and target are not clear. Quercetin, kaempferol, \( \beta \) -sitosterol, luteolin, and baicalein docked with AKT1, BAX, BCL2, CASP3, PTGS2, CCND1, IL6, and MTOR all have docking binding energies \(<0\) kcal-mol\(^{-1}\), indicating that the key components of QHJTC could spontaneously bind to the core target.

**Conclusion**

QHJTC can treat T2DM through multicomponents, multi-targets, and multipathways, which provides references and a theoretical basis for further revealing the pharmacological mechanism of QHJTC.

**CRediT Authorship Contribution Statement**

**Ji Mengmeng**: Analyzing the data and wrote the draft manuscript. **Yanan Yu, Jiariu Wu, Jun Liu, Yanhua Jiang**: Providing technical support, revised the manuscript. **Zhiwei Jing**: Designing the study, directed and financially supported the study and revising the manuscript.

**Funding**

This work was supported by the National Natural Science Foundation of China (82074584) and the National Key Innovative Talents Training Project Of Traditional Chinese Medicine (2019-128).

**Conflict of Interest**

The authors declare no conflict of interest.

**References**

1. Wang X, Strizich G, Hu Y, Wang T, Kaplan RC, Qi Q. Genetic markers of type 2 diabetes: progress in genome-wide association studies and clinical application for risk prediction. J Diabetes 2016;8(01):24–35
2. Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). Chin J Diabetes Mellitus 2021;13(04):315–409
3. Hu C, Jia W. Diabetes in China: epidemiology and genetic risk factors and their clinical utility in personalized medication. Diabetes 2018;67(01):3–11
4. Qiao GQ. Chinese medicine medicine powder for treating diabetes: CN101406627A[P]. 2009–04–15.
5. Ru J, Li P, Wang J, et al. TCMS: a database of systems pharmacology for drug discovery from herbal medicines. J Cheminform 2014;6:13
6. Xu HY, Zhang YQ, Liu ZM, et al. ETCM: an encyclopaedia of traditional Chinese medicine. Nucleic Acids Res 2019;47(D1):D976–D982
7. Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China: 2005 ed. Peking: Chemical Industry Press Co., Ltd.; 2005:63
8. Li XZ, Wang XX. Determination of trace element content in gypsum of different origins. Zhong Yao Cai 1990;13(04):35–36
9. Na Z, Ji-Jun S, Jian-Wu HE, et al. Discovery and study on potential effect of herbal pair of Uncariae Ramulus cum Uncis–Eucommiae Cortex on pregnancy hypertension based on network pharmacology and molecular docking. Zhongguo Zhongyao Zazhi 2020;45(22):5393–5402
10. Huang GW, Chen FC, Liu Y, et al. Predictive analysis of active compounds in Qinsu Capsule for prevention of COVID-19 based on network pharmacology and molecular docking. Shanghai J Tradit Chin Med 2020;54(10):1–11
11. Fan XT, Wu C, Li J, et al. Research on the potential mechanism of Shiyi Qingwen Pill against COVID-19 based on network pharmacology and molecular docking. Lishizhen Med Mater Med Res 2021;32(01):206–210
12. Chen YL, Sun ZL. Discussion on the identification and prevention and control strategies of the related ethnic specific risk factors in diabetic lifestyle. Chin J Diabetes Mellitus 2018;10(05):310–313
13. Meng QJ. The effect of Renshen Baihu decoction in the treatment of type 2 diabetes mellitus and its mechanism. J Med Theory Pract 2018;31(10):1455–1456
14. Chen WY, Yao ZY, Hu H. Clinical study on modified Xiaoke prescription for atherosclerotic disease of the lower extremities induced by type 2 diabetes with excessive heat impairing body fluid syndrome. J New Chin Med 2019;51(09):122–124
15. Wu XM, Lin WY, Zhang YX, et al. Curative effect of Yu'nv dection combined with Shashen Maidong Decoction on Yin-deficiency and fire-hyperactivity type diabetes mellitus and its influence on serum vaspin and omentin-1. J Sichuan Tradit Chin Med 2021;39(02):113–116
16. Zhang L, Fang ZH. Research progress of Liuwei Dihuang pills in treating diabetes mellitus. Clin J Tradit Chin Med 2018;30(12):2328–2331
17. Konheim YL, Wolford JK. Association of a promoter variant in the inducible cyclooxygenase-2 gene (PTGS2) with type 2 diabetes mellitus in Pima Indians. Hum Genet 2003;113(05):377–381
18. Pinelli M, Giacchetti M, Acquaviva F, et al. Beta2-adrenergic receptor and UCP3 variants modulate the relationship between age and type 2 diabetes mellitus. BMC Med Genet 2006;7:85
19. Liu SW, Liu JY. Advances in the pharmacological effects of quercetin. Chin J Lung Dis Electron Ed 2020;13(03):418–421
20. Ge L, Cai YJ, Wang ZD. Effect of quercetin on insulin resistance and FGFR1/MAPK signaling pathway in type 2 diabetic rats. China Pharm 2019;22(03):418–421
21. Ren L, Wang KJ, Zong Y. Mechanism of quercetin in treatment of type 2 diabetes mellitus based on network pharmacology and molecular docking method. Herb Eval Res 2020;43(10):1964–1970
22. Sun FH, Wang QH, Qiu ZL, et al. Research progress of mechanisms of traditional Chinese medicine in treatment of insulin resistance of type 2 diabetes mellitus. Med Recapitul 2018;24(20):4068–4072, 4077
23. Testa JL, Su RR, Liu HL, et al. Clinical effect analysis of QHJTC on primary type 2 diabetes mellitus and its effect on islet function. Zhonghua Zhongyi Yaoxuan 2021;39(06):236–239
24. Tang SM, Yang ZM, Chen WQ, et al. Astrogalus polysaccharide improves type 2 diabetes mellitus in rats by protecting islet \( \beta \) cells. Acad J Second Mil Med Univ 2017;38(01):2406–2409
25. Chen YY, Cui WW, Liu HL, et al. Effect of Qihuang Jiangtang Capsule on blood glucose regulation and pancreatic tissue in diabetes model rats. Chin J Tradit Chin Med 2021 Accessed September 06, 2022, at: https://kns.cnki.net/kcms/detail/21.1546.R.20211203.2033.042.html
26. Yang CM, Yang ZX, Ma XL. The mechanism of AGES-RAGE signaling pathway in diabetic nephropathy and the progress of Chinese medicine treatment. Acta Chin Med 2019;34(09):1864–1868