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Based on Network Pharmacology and Molecular Docking, Explore the Molecular Mechanism of Modified Xiao-xian-xiong Decoction in the Treatment of T2DM

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Abstract: Objective: Based on network pharmacology and molecular docking, explore the mechanism of Modified Xiao-Xian-Xiong Decoction (MXD) formula in treating type 2 diabetes (T2DM). Methods: Using the traditional Chinese medicine system pharmacology technology platform (TCMSP) to select the main active ingredients of rhubarb, coptis, pinellia and trichosanthis and its corresponding action targets; the relevant target genes in the Gene Cards database for T2DM, Mapping the drug active component targets to the T2DM targets; use R language to draw the Wayne diagram of small breast soup with flavor applied on T2DM; Cystoscope 3.8.2 Visual mapping software can be used to construct a network model of "drug active ingredient-target"; meanwhile, intersection target protein interaction network (PPI) using STRING database, the key proteins were selected; again, the gene ontology GO enrichment analysis and the Kyoto Encyclopedia of Genes and Genome (KEGG) pathway enrichment analysis were performed in the R language. Finally, molecular docking was performed to further verify the efficient binding of the selected compounds to the core target. Results: 54 active components of the flavor formula acting on T2DM were selected after selection; GO analysis shows that the biological function of Xiaoxianxiong Decoction in treating T2DM potential genes mainly involves transcriptional regulation, oxidative stress, protein binding and inflammatory reaction; the enrichment of KEGG pathway shows that the pathways affected by Xiaoxianxiong Decoction Jiawei Recipe in treating T2DM mainly include tumor necrosis factor (TNF) signal pathway, phosphatidylinositol oxygen 3 kinase/protein kinase B (PI3K/Akt) signal pathway, calcium ion signal pathway and nuclear transcription factor-κB(NF-κB) Signal path, etc. Molecular docking results showed that the core compounds such as quercetin, rheate, berberine, and baicalein had a strong affinity with the T2DM core genes. Conclusion: The mechanism of Xiaoxianxiong Decoction in treating T2DM may be to inhibit the secretion of inflammatory factors, participate in anti-inflammatory reaction, reduce oxidative stress, and activate PI3K /Akt /NF-κB and other signal pathways to participate in anti-inflammatory and antioxidant reactions, improve insulin resistance, and increase insulin sensitivity and reduce blood glucose.

1. Introduction

As a common endocrine system disease, diabetes not only has a high incidence but also more complications. According to the latest data from the International Diabetes Alliance, more than 460 million diabetics occurred worldwide in 2019 and are expected to exceed 700 million in 2045, T2DM is the main disease [1,2]. The etiology and pathogenesis of T2DM are not clear at present, but the pathophysiology has been well studied [3,4]. It is mainly characterized by the decline of insulin's ability to regulate glucose metabolism (insulin resistance) and the relative reduction of insulin secretion caused by the functional defects of the β cells in the pancreatic islet. Thus, the pathogenesis basis of T2DM is thought to be associated with insulin resistance [5-8].

The original recipe of Xiao-Xian-Xiong Decoction is composed of melon wilt, coptis and pinellia, which has the effect of clearing heat and resolving phlegm and dispersing wide chest knot [9]. It is mainly used for under heart fullness and discomfort caused by phlegm heat interaction or chest nodules. The results of recent years show that Xiao-Xian-Xiong Decoction can significantly improve the clinical symptoms of diabetic patients, reduce their blood glucose, and the insulin sensitivity of patients improves [10,11]. In addition, it also shows that it has the effects of treating digestive system diseases, cardiovascular diseases, anti-tumor and calming nerves [12]. Academician Tong Xiaolin put forward the clinical strategy of state-target syndrome differentiation, which made Xiao-Xian-Xiong Decoction widely used in the treatment of diabetes and its complications [13]. This study used network pharmacology and molecular docking to explore the protective effect and potential mechanism of T2DM rats, aiming to provide some experimental basis for the clinical application of diabetes prevention.

2. Materials and Methods

2.1. TCMSP Screening for Drug-active Ingredients

TCMSP (http://tcmspw.com/tcmsp. The php) is the most commonly used Chinese herbal medicine system pharmacology platform, contains most of the Chinese herbal medicine information and can be used for data analysis, first we use TCMSP platform to obtain Modified Xiao-Xian-Xiong Decoction (Rhubarb, Coptis, Pinellia and Trichosanthes), according to the oral bioavailability (OB 30%) and drug (DL 0.18) filter and screen out active compounds that meet the requirements.

2.2. Target Prediction of Type 2 Diabetes

In the Gene Cards database (http://www.genecards.org/) take diabetes as the relevant target, set the action target of Modified Xiao-Xian-Xiong Decoction obtained from tcmsp database as "drug", and the diabetes target gene obtained from gene cards database as "disease". Map the two, use R language to get the drug target network, and draw the Wayne diagram of drug targets. The intersection in the figure is the possible intersection target of the active ingredients in Xiaoxianxiong Tang Jiawei recipe for treating T2DM.

2.3. Construction and Analysis of the Chemical Composition-action Target Network of TCM

By using the target normalization database UniProt (https://www.uniprot). The name (target name) of the obtained drug component target and the disease target is uploaded respectively, and the protein species is set to Homo sapiens (Human) to obtain the standard gene name of its target. Cytoscape3.8.2, as a visual mapping software, can intuitively analyze the mechanism of action of

drug therapy for diseases. The node represents the medicinal chemical components and potential action targets of TCM, and the edge shows the connection between TCM components and its action targets, building a compound component-target network.

2.4. Construction of PPI Network and Core Target Screening

The string database can be used to analyze the interaction between proteins, import the predicted target of Modified Xiao-Xian-Xiong Decoction for the treatment of diabetes into the string database, and limit the research species to homon sapiens, the low interaction score is set to the highest confidence ("highest confidence <0.900>"). Discrete targets are hidden, and other parameters remain default settings. The PPI network of Xiaoxianxiong Decoction on T2DM is obtained. Finally, the R script is used to count and sort the protein interaction links obtained in STRING database, and output the target gene with the largest number of connections, that is, the core target.

2.5. GO Functional Analysis and KEGG Pathway Enrichment Analysis

The drug-disease intersection gene was corrected to the official name (official gene symbol) using R language, and then "DOSE" and "Bioconductor" in R language were used for data processing. Finally, the data processing results were drawn as GO functional analysis and bubble chart of KEGG pathway enrichment analysis in R language, with a set threshold of $P<0.05$.

2.6. Molecular Docking

Molecular docking was performed to further validate the efficient binding of the selected compounds to the core target. Structure of the small-molecule compounds was obtained from the TCMSP acquisition mol2 format. The crystal structures of the candidate target were obtained from the PDB database (https://www.rcsb.org/). The receptor structure was modified by AutodockTools 1.5.6 21 (dehydrofed) and exported to pdbqt format. After defining the grid at the active site of the acceptor protein, the docking program was performed by AutoDock-Vina 1.1.2, and the output score was shown as kcal/mol. PyMOL 2.3.0 and BIOVIA Discovery Studio 2016 were applied to the result processing and visualization.

3. Results

3.1. Efficacy Components Selected by TCMSP and Their Corresponding Targets

There were four traditional Chinese medicines in Rhubarb, Coptis, Pinellia and Trichosanthes. These four medicinal compounds were obtained in TCMSP, OB 30% and DL 0.18 were set, and 54 effective compounds corresponding to 110 targets were selected.(in table 1)

Table 1: Active ingredients selected by TCMSP

	Mol ID	Molecule Name	OB (%)	DL
Coptis	MOL001454	berberine	36.86	0.78
	MOL013352	Obacunone	43.29	0.77
	MOL002894	berberrubine	35.74	0.73
	MOL002897	epiberberine	43.09	0.78
	MOL002903	(R)-Canadine	55.37	0.77
	MOL002904	Berlambine	36.68	0.82
	MOL002907	Corchoroside A_qt	104.95	0.78
	MOL000622	Magnograndiolide	63.71	0.19
	MOL000762	Palmidin A	35.36	0.65

	MOL000785	palmatine	64.6	0.65
	MOL000098	quercetin	46.43	0.28
	MOL001458	coptisine	30.67	0.86
	MOL002668	Worenine	45.83	0.87
	MOL008647	Moupinamide	86.71	0.26
	MOL001755	24-Ethylcholest-4-en-3-one	36.08	0.76
Pinellia	MOL002670	Cavidine	35.64	0.81
	MOL002714	baicalein	33.52	0.21
	MOL002776	Baicalin	40.12	0.75
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000449	Stigmasterol	43.83	0.76
	MOL005030	gondoic acid	30.7	0.2
	MOL000519	coniferin	31.11	0.32
	MOL006936	10,13-eicosadienoic	39.99	0.2
	MOL006937	12,13-epoxy-9-hydroxynonadeca-7,10-dienoic acid	42.15	0.24
	MOL006957	(3S,6S)-3-(benzyl)-6-(4-hydroxybenzyl)piperazine-2,5-quinone	46.89	0.27
	MOL003578	Cycloartenol	38.69	0.78
	MOL006967	beta-D-Ribofuranoside, xanthine-9	44.72	0.21
	MOL001494	Mandenol	42	0.19
Trichosanthes	MOL002881	Diosmetin	31.14	0.27
	MOL004355	Spinasterol	42.98	0.76
	MOL005530	Hydroxygenkwanin	36.47	0.27
	MOL006756	Schottenol	37.42	0.75
	MOL007165	10α-cucurbita-5,24-diene-3β-ol	44.02	0.74
	MOL007171	5-dehydrokarounidiol	30.23	0.77
	MOL007172	7-oxo-dihydrokaro-unidiol	36.85	0.75
	MOL007175	karounidiol 3-o-benzoate	43.99	0.5
	MOL007179	Linolenic acid ethyl ester	46.1	0.2
	MOL007180	vitamin-e	32.29	0.7
	MOL002235	EUPATIN	50.8	0.41
Rheum	MOL002251	Mutatochrome	48.64	0.61
	MOL002259	Physciondiglucoside	41.65	0.63
	MOL002260	Procyanidin B-5,3'-O-gallate	31.99	0.32
	MOL002268	rhein	47.07	0.28
	MOL002276	Sennoside E_qt	50.69	0.61
	MOL002280	Torachrysone-8-O-beta-D-(6'-oxayl)-glucoside	43.02	0.74
	MOL002281	Toralactone	46.46	0.24
	MOL002288	Emodin-1-O-beta-D-glucopyranoside	44.81	0.8
	MOL002293	Sennoside D_qt	61.06	0.61
	MOL002297	Daucosterol_qt	35.89	0.7
	MOL002303	palmidin A	32.45	0.65
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000471	aloe-emodin	83.38	0.24
	MOL000554	gallic acid-3-O-(6'-O-galloyl)-glucoside	30.25	0.67
	MOL000096	(-)-catechin	49.68	0.24

3.2. The Intersection Target of MXD and T2DM

The T2DM-related target genes were first retrieved from the Gene Cards database. Disease-drug Wayne plots were drawn using the R language. Figure 1 below: there are 179 intersection targets between MXD and T2DM.

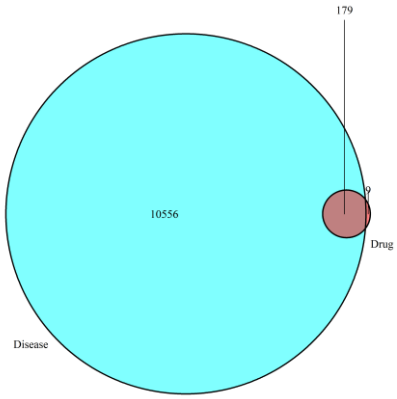


Figure 1: Disease drug Wayne diagram

3.3. Network Construction and Analysis Results

The Uniport database yielded 74 total of human target genes, and constructed the active components and acting targets into a network map by Cytoscape 3.8.2, as shown in Figure 2, contains 128 nodes (54 active components and 74 related targets) and 662 lines, with the left quadrangle representing the active component, the right quadrangle representing the relevant target, and the line representing the relationship between the active component and the relevant target. It is reported that the degree and the betweenness of the intermediate value are positively related to the importance of the active ingredient, that is, the larger the value, the more important the corresponding node is in this network diagram. The results showed that quercetin, stigmasterol, berberine, berberine β glutosterol and other compounds play a pivotal role in the network diagram with sarcomavirus 17 oncogene, protein kinase AKT1, mitogen activated protein kinase and other target proteins, which may be the key active components and target proteins.

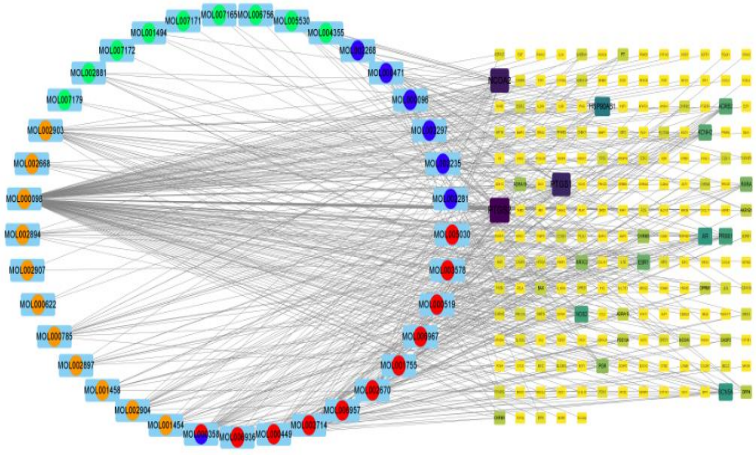
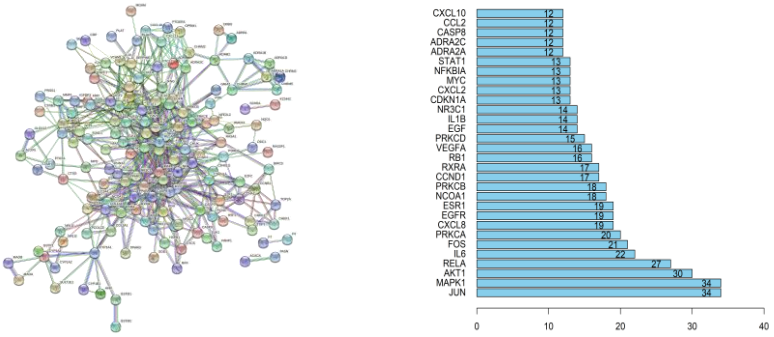


Figure 2: Active ingredient target network diagram

3.4. Construction of Target Protein Interaction Network and Key Target Screening Results

To further investigate the mechanism of action of T2DM, the 179 mapped intersection targets were subjected to PPI network analysis through the STRING database, as shown in Figure 3. There are 121 targets in the network that can have protein interactions. The top 30 targets are selected to draw the core target bar map and draw the core target network map by script.



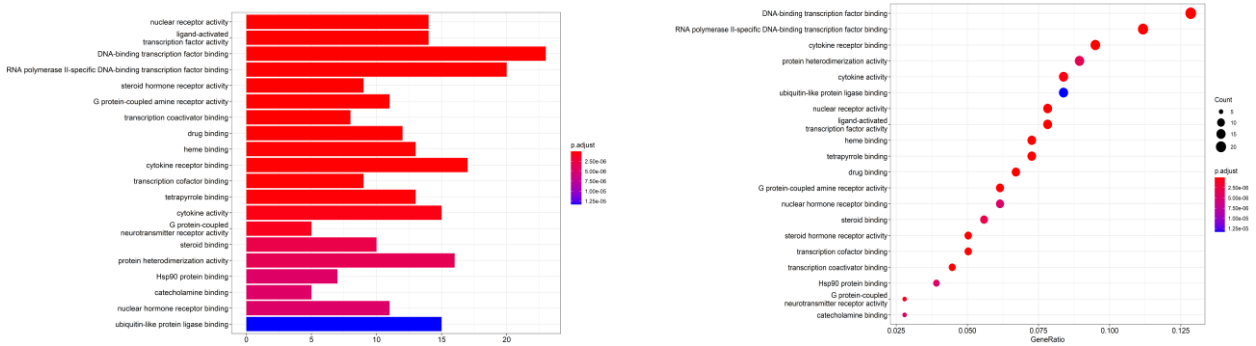
1) 2)

Note: Figure 1) is the PPI network diagram; Figure 2) is the target point bar chart

Figure 3: Target protein network diagram of MXD for T2DM

3.5. Results of the GO Functional Analysis

The 179 intersection genes of MXD-T2DM affect 185 biological processes (P<0.01, FDR<0.01), and selected the top 20 functional information with P value, see Figure 4. It shows that the active components of MXD are mainly enriched in response to drugs, positive transcriptional regulation of RNA polymerase II promoter, coping with LPS, positive regulation of DNA template transcription, aging, response to hypoxia, positive regulation of vasoconstriction, response to toxic substances, positive regulation of angiogenesis, response to ethanol and inflammatory response.



1) 2)

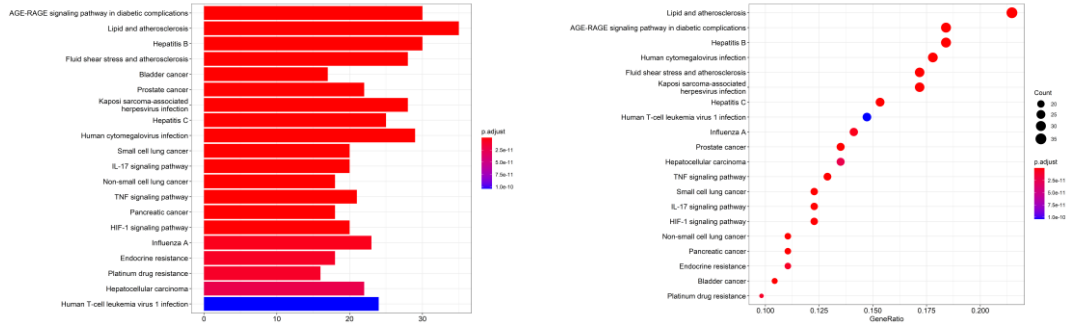
Note: Figure 1) is bar chart; Figure 2) is bubble chart

Figure 4: GO enrichment analysis for bar plots and bubble plots

3.6. KEGG Thoroughfare

Results of KEGG enrichment pathway analysis The KEGG pathway enrichment analysis found that, The 179 intersection target genes were significantly enriched on the 30 pathways (P<0.05), as shown in Figure 5, Six of the most meaningful pathways include the tumor necrosis factor (TNF) signaling pathway, The Toll-like receptor-like signaling pathway, Phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) signaling pathway, Cooline kinase receptor 2 (ErbB) signaling

pathway, Calcium ion signaling pathway and the nuclear transcription factor-κB (NF-κB) signaling pathway, it suggested that the MXD treated T2DM by acting multiple pathway.



1) 2)

Note: Figure 1) is bar chart; Figure 2) is bubble chart

Figure 5: KEGG path analysis histogram and Bubble Diagram

3.7. Molecular Docking

In this study, based on the energy matching between the top 3 core targets with large Degree values in the PPI network and the three active components, the optimal configuration was selected based on the docking score, as shown in Table 2. The binding energy below-7kcal/mol indicates that the docking results are stable, indicating that most of the ligands can bind well to the receptor. Binding energy below-7kcal/mol indicates stable docking results. According to the docking scoring and the results shown in Figure 6-9, an AKT1-baicalein interaction exists to form a binding pocket.residues GLN: 414 and SERA: 259 form hydrogen bonds to facilitate structure stabilization, while forming Pi-Pi Stacked and Pi-Pi T-shaped bonds with TYRA: 263 and TYRA: 417, while others can also form van der Waals forces; IL1 β and rhein interact to form a binding pocket. The residues GLUA: 64, L L 1 B: 64, LYSA: 65, LEUA: 62, TYRA: 68 and SERA: 5 form hydrogen bonds to stabilize the structure, the Pi-Alkyl bond with PROA: 91, G L U A: 64 and the Pi-Sigma bond, van der Waals force; ESR1-bertin. The residues ARGB: 503 of berberine and ESR1 form a hydrogen bond, To contribute to the structural stability, Also forming a Pi-Sigma bond with ALAB: 493, LEUB: 495, and GLNB: 441, Others can also form a van der Waals force; The presence of PPARA-quercetin interactions, Residues ARGA of quercetin and PPARA: 434, ARGA: 388, TYRA: 311, ARGC: 388, GLYC: 390, and LEUC: 391 form hydrogen bonds, To contribute to the structural stability, The Pi-Pi T-shaped and Pi-Alkyl bonds are also formed together with TYRA: 311 and VALC: 394.

Table 2: The Autodock Vina scoring results

		affinity(kcal/mol)
baicalein	AKT1 (7NH5)	-7.8
rhein	IL-1β	-7.3
berberine	ESR1 (1ERR)	-7.7
quercetin	PPARA(1KKQ)	-7.9

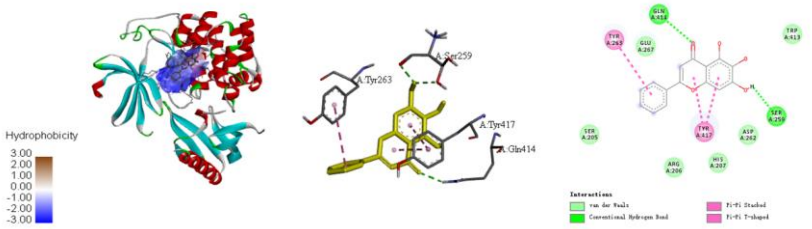


Figure 6: AKT1-baicalein

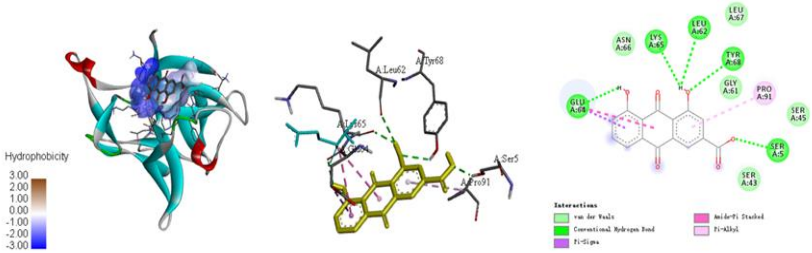


Figure 7: I L-1β and lubriate

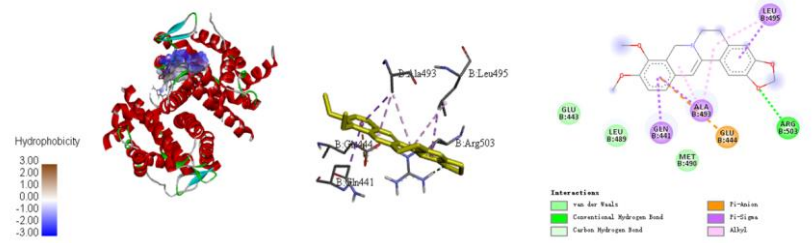


Figure 8: ESR1-Aberberine

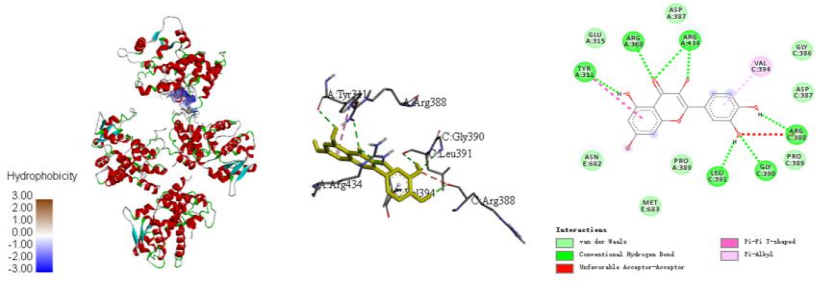


Figure 9: PPARA-quercetin

4. Discussion

Network pharmacology is a kind of scientific research method of biological system information, it can collect multiple pharmacology information, through system biology means, analyze the specific biomolecular network, and mining drugs, genes, drugs, proteins, diseases, etc, to discover the molecular mechanism of drug action, explore and mining new targets and new role [14,15]. In this study, network pharmacology and molecular docking techniques were used to study the action mechanism of "multi-cause, multi-effect and multi-target" treatment in T2DM, in order to provide new research ideas for T2DM treatment. Xiao-Xian-Xiong Decoction from the “Shang Han Lun”, which trichosanthis “heart moisten lung, phlegm heat”, can clear heat moisten dryness, and liver

slow urgent [16,17]; coptis "bitter cold heat besides ruffian", in addition to relieving heat and swelling, it also has the effect of protecting liver and promoting gallbladder [18,19]; pinellia "xin dry phlegm knot", in addition to heat phlegm, it can also reduce the liver of the gas machine, modern medical research found that it has to improve the liver internal amino transaminase activity [20-22]. On this basis, increase the Rheum "clear heat and diarrhea, cool blood and detoxification", thus strengthening the Xiao-Xian-Xiong Decoction clearing heat and cleansing phlegm. Rheum has the function of protecting the liver, which can not only promote the regeneration of liver cells, but also promote the discharge of toxins in the body. In clinical practice, it is blindly recognized as a traditional Chinese medicine with a good effect of liver protection and liver protection [23-25].

This study under the blessing of network pharmacology technology, combined multiple pharmacology platform and gene database, screening out the key active ingredients, build the drug-disease network and target GO analysis and KEGG analysis, through molecular docking technology of related molecular docking and core target, systematically explore the mechanism of the treatment of T2DM. In this study, 54 active components in MXD were collected, and the key compounds for T2DM included baicalein, baicalin, quercetin, β -sitosterol, bilirubin, berberine, berine, etc. In the GO analysis of T2DM, 185 biological processes were obtained, among which the response to LPS, oxidative stress response, and regulation of apoptotic signaling pathways were all associated with T2DM. KEGG pathway enrichment analysis showed that T2DM treatment mainly involves tumor necrosis factor (TNF) signaling, Toll-like receptor signaling, phosphatidylinositol 3 kinase/ protein kinase B (PI3K/Akt) signaling, cooline kinase receptor 2 (ErbB) signaling, calcium ion signaling and nuclear transcription factor-κB (NF-κB) signaling. The PPI network was constructed based on the STRING database, 30 core targets were selected, and the analysis found that AKT1, IL-1β, IL-6, JUN, MAPK1, ESR1, and PPARA are the key core targets of the network, and may play a key role in the treatment of T2DM. The combined molecular docking results showed that the four compounds bind quite well to AKT1, IL-1β, ESR1, and PPARA among, Quercetin docking with PPARA, The stronger the interaction is, The compound conformation is also becoming more stable, Moreover, AKT1-baicalein, IL-1β, rheic acid and ESR1-berberine scores were very stable, studies have shown, Baicalein, by downregulating the gene expression of Caspase-1, ASC, IL-1β and IL-6 genes, Upregulation of the HO-1 protein expression, Inhibition of the activation of the NLRP3 inflammasome exerts an anti-inflammatory effect [26,27]; Quercetin upregulates the cellular activity and insulin secretion of INS-1, Also has the effect of improving diabetes mellitus [28,29]; The rhein intervention treatment could significantly ameliorate the damage of the diabetic kidney tissue in db/db mice, Inhibition of the wnt/β-catenin pathway protein expression in a high-glucose environment, It may be one of the action mechanisms of rhein acid against diabetes [30-32]; Alberberine may, by increasing GPR43 and TGR5 activity, Upregulation of GCG and PC1/3 mRNA expression, Promoting GLP-1, as well as insulin secretion, Lower your blood sugar. It can be known that the treatment of diabetes is combined by multiple components and multiple ways.

5. Conclusions

In conclusion, the key components screened through network pharmacology have relatively stable combination with AKT1, MAPK1, IL-1β and IL-6. Through the method of network pharmacology combined with molecular docking, and the comprehensive discussion and analysis of each network and database, the molecular mechanism of MXD in treating T2DM through multi-component, multi target and multi way was fully discussed, the method is relatively complete, and the screening results are mostly supported by relevant literature. Later, cell or animal experiments should be conducted on the prediction results to provide new ideas and references for

relevant basic and clinical research.

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References

[1] Lin Zhiqin, Shi Laner, Zheng Meisi, Zhu Zhangzhi. Network pharmacological mechanism of the treatment of type 2 diabetes. Journal of Guangzhou University of Traditional Chinese Medicine, 2021, 38 (04): 791-796.
[2] Gong Chengjun, Ma Xiaoyan. Exploring the mechanism of renal depression in treating diabetic nephropathy based on network pharmacology. World Traditional Chinese medicine: 1-7 [2021-03-17]. http://kns.cnki.net/kcms/detail/11.5529.R.20210305.1708.072.html.
[3] LanXiaoBu, Zhou Gang, Sun Yuhong. Progress in the pathogenesis of diabetes complications and its drug therapy. Journal of Clinical Rational Drug Use, 2021, 14 (05): 178-181.
[4] Li Xiuyun, Zhang Xinyou, Wu Diyao, Pan Shumao, Ding Liang, Liu Mengling. Literature analysis of TCM compound network pharmacology studies. China Pharmacy, 2021, 32 (02): 182-189.
[5] Pan Li, Liu Weizhong. Understanding and treatment progress of type 2 diabetes mellitus and its complications in Traditional Chinese and Western medicine. Clinical Journal of Traditional Chinese Medicine, 2021, 33 (01): 162-166.
[6] Yang Qian, Yang Lixia, Qiu Lianli, Zhang Dinghua, Shi Xiaowei. Progress in TCM treatment of prediabetes. Clinical Research of TCM, 2021, 13 (01): 137-141.
[7] Yang Haoyu, Yang Yingying, Zhang Pei. Analysis of the inheritance mode of "square test-target set by drugs". Journal of Traditional Chinese Medicine, 2021, 36 (01): 103-105.
[8] Mutarpu, Du Yingjie. Progress in traditional Chinese and Western medicine research of obese type 2 diabetes mellitus. Xinjiang Traditional Chinese Medicine, 2020, 38 (06): 73-76.
[9] Wu Xuemin, Wang Han, Luo Jinli, Park Chunli. The use of state target syndrome differentiation in phlegm dampness and heat obesity-cassia seed, car front son, la seed, radish seed, Wei son. Liaoning Traditional Chinese Medicine Journal, 2020, 47 (12): 4-6.
[10] Lei Lei, Lin Zhili, Wang Linlin, Zhao De, Wang You, Li Fangting. Kinetic mechanism of pancreatic islet inflammation during the pathogenesis of type 2 diabetes mellitus. Scientific Bulletin, 2020, 65 (35): 4139-4148.
[11] Ding Qi again, Zheng Yujiao, Gou Xiaowen, Zhao Linhua. Tong Xiaolin's innovation of two diagnosis and treatment modes on Typhoid and Miscellaneous Diseases. Journal of Traditional Chinese Medicine, 2020, 35 (09): 1838-1842.
[12] Li Jia, Song Dynasty, Wu Xinping, Hao Xuliang. On typhoid fever "Summary" and application of prescriptions. Chinese Journal of Basic Medicine of Traditional Chinese Medicine, 2020, 26 (08): 1052-1053+1109.
[13] Shi Laner, Nie Zhongchao, Zhang Wenjing, Zheng Meisi, Liu Chuang, Zhu Zhangzhi. Pharmacological mechanism of type 2 diabetes based on network pharmacology. Chinese Journal of Experimental Prescription Medicine, 2020, 26 (04): 198-206.
[14] Shi Laner, Nie Zhongchao, Zhang Wenjing, Zheng Meisi, Lin Zhiqin, Zhu Zhangzhi. Exploring the mechanism of action of type 2 diabetes based on network pharmacology. Chinese Journal of Experimental Prescription Medicine, 2019, 25 (18): 160-166.
[15] Zhang Limin, Zou Lianxia, Wu Zuqiang, Zhang Xueying, Tan Yi, Feng Deyong. Effect of small chest soup on insulin resistance index and β cell function in patients with prediabetes. Journal of Chengdu University of Traditional Chinese Medicine, 2018, 41 (04): 52-55.
[16] Ye Minghua. Clinical analysis of 60 patients with pre-diabetic sputum heat mutual junction syndrome. Chinese and foreign medical treatment, 2018, 37 (19): 156-159+162.
[17] Gu Yuerong. Progress in clinical application and experimental research of breast decoction. Continuing Medical Education, 2018, 32 (06): 148-150.
[18] Wang Wenyi, Wang Xiaofei. Research progress in TCM treatment of diabetic nephropathy. Everyone Health, 2018 (12): 98.
[19] Jiang Xia. TCM treatment of chronic complications of diabetes mellitus. China Pharmaceutical economics, 2014, 9 (02): 75-76.
[20] Wu Qingting, Ma Xingyu, Xie Xuejiao. Recent situation of clinical application research of Xiao-Xian-Xiong Decoction. Hunan Journal of Traditional Chinese Medicine, 2020, 36 (06): 169-171.
[21] Xu Shisheng, Guo Kangxiao, Zang Jinglei, Zhou Yu. Design, synthesis, and lipid-lowering activity analysis of

tetrahydroberberine compounds. Chemical Design Communications, 2020, 46 (11): 134-135.
[22] Fang Xingyue, Liu Qibing, Yang Xiao, Yi Guohui, Fan Haofei, Huang Jing. Study on improving vascular endothelial cell damage by tetrahydroberberine. Journal of Hainan Medical College, 2020, 26 (15): 1146-1151+1158.
[23] Ji Yubin, Liu Xin, Yu Lei, Dou Limin, Zhang Xiaopo. Progress in the pharmacological effects of Tetrahydroberberine. Chinese herbal medicine, 2017, 48 (24): 5270-5275.
[24] Li Wenwen, Zhong Dapeng, Zhang Wei, Ren Li, Cheng Ying. Protective effects and mechanism of quercetin on islet β cell injury in diabetic rats. Journal of Guangxi Medical University, 2021, 38 (02): 298-303.
[25] Yang Jiayi, Peng Linlin, Ning Jianping. Effect of rhein on ILK/Snail signaling in the mesenchymal transdifferentiation of renal tubular epithelial cells in rats with diabetic nephropathy. Chinese Journal of Physicians, 2020, 22 (06): 875-880,885+875-880, 885.
[26] Qingyu Guo. Macroin improves exercise endurance in obese mice by upregulating the AMPK-Sirt1 signaling pathway. Nanjing University, 2020.
[27] Xia Jingsheng, Wang Qian, Zou Geely, Cai Yu, Li Ying. Molecular mechanism by which berberine promotes glucagon-like peptide secretion in type 2 diabetic rats. Medical Guide, 2021, 40 (04): 442-449.
[28] Yao Qiong, Ye Taisheng, Zhang Yingwen, Wang Xiuping, Peng Yanfang, Ke Haoliang. Based on the functional mechanism of network pharmacology and Akt1/mTOR autophagy pathway of Astragalus galk. World Science and Technology-Modernization of Traditional Chinese Medicine, 2021, 23 (08): 2699-2710.
[29] Rong Xiaozhe, Lin Shuai Jun, Wang Rui. Based on the exploration of PI3K/AKT signaling pathway, the intervention effect of total flavonoids on glycolipid metabolism and oxidative stress damage in type 2 diabetic rats was investigated. The World Journal of Integrated Traditional Chinese and Western Medicine, 2020, 15(11): 2041-2048.DOI:10.13935/j.cnki.sjzx.201116.
[30] Zhang Limin, Feng Deyong, Zou Lianxia, Wu Zuqiang, Zhang Xueying, Tan Yi. Effects of small breast soup on phlegm dampness and heat constitution of prediabetes. Journal of Hunan University of Traditional Chinese Medicine, 2018, 38 (04): 467-469.
[31] Li Bin, Fan Yuan, Li Xin. Progress in TCM Treatment of Insulin Resistance in Type 2 DM based on PI3K/Akt signaling pathway. Chinese patent medicine, 2017, 39 (01): 151-154.
[32] Wang Ze. Based on the regulation of SIRT1 / NF- κ B signaling by miR-34a, the mechanism of Qingfang to improve hepatic insulin resistance in type 2 diabetes. China Academy of Traditional Chinese Medical Sciences, 2020.