

Evaluation of Synergistic Effect of Predicted Network Pharmacology of Berberine in Type 2 Mellitus Diabetes Treatment

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Abstract

Objectives: Based on the compounds-target-disease network theory, network pharmacology are new approaches for systematic studying the diseases, revealing the mystery of active compounds synergistic effect and investigating the mechanism of Traditional Chinese Medicines (TCM). The potential pharmacodynamic material basis and network regulation mechanism of berberine in diabetes and related chronic diseases are studied.

Methods: The corresponding ID number of berberine was checked in the PubChem database. The putative targets of diabetes and related chronic diseases were found through the IPA commercial database combined with OMIM database. Finally, it established a berberine-target genes-diseases network by Cytoscape. Graph-based techniques are examined by the network diffusion methods to predict berberine-target genes-diseases network and influence the transmission in networks.

Results: The corresponding gene of berberine were found in the IPA database, and the effective targets for diabetes and related chronic diseases were obtained by combining OMIM. It is confirmed that berberine worked on 45 putative targets, such as APOA1, VEGFA, PPARG, PRKCB, TNF etc. These drug-target networks involve about 20 diseases such as diabetes, high blood pressure, coronary heart disease, cardiac arrhythmia, depression, neuro division, and so on. On the basis of above similarities and interaction data for gene and targets; a new gene or target get its interaction profile respectively; a new gene is one that has unknown targets and in the similar manner a new target is the one which has no known interactions with any genes and proposed efficient way to understand berberine pathways mechanisms.

Conclusion: The common putative targets of diabetes and related chronic diseases are identified from the molecular

level, established the berberine-drug target prediction-disease pharmacology network. This method may offer an efficient way to understand the berberine, multi-targets and multiple pathways mechanisms of berberine for treatment of diabetes and related chronic diseases.

Keywords: Berberine; Network pharmacology; Diabetes; Chronic diseases

Introduction

Berberine is the main active ingredient of *Coptidis*. It can be extracted from traditional Chinese medicines such as *Coptis*, *Phellodendron* and *Berberis sargentiana*. It is an alkaloid and is often used as an anti-infective and anti-inflammatory drug for bacterial gastroenteritis. It is also used for gastrointestinal tract such as dysentery and other digestive diseases. Recent studies have shown that berberine also plays an important role in the treatment of medical diseases, oncological diseases, and antidiabetics and antihyperlipidemic [1-4]. The therapeutic effect of berberine is mainly manifested in its pharmacological effects such as blood sugar lowering, blood lipids, anti-inflammatory and anti-oxidation, and it has well relief and protection for diabetes complications such as diabetes and diabetic nephropathy, diabetic cardiovascular disease and diabetic peripheral neuropathy. Based on the therapeutic effect of berberine, this study mainly analyzes the numerous network-coordinated therapeutic effects of berberine, focusing on the network mechanism of berberine in the treatment of diabetes and other chronic diseases.

Diabetes is a group of metabolic diseases characterized by hyperglycemia and characterized by disorders of glucose metabolism. It is caused by defects in insulin secretion and its biological effects. Hyperglycemia can cause lesions in various tissues of the body, especially chronic damage and dysfunction of the eyes, kidneys, heart, and nerves. In recent years, the

incidence of diabetes has continued to rise worldwide, and the World Health Organization (WHO) international diabetes federation survey shows that there are nearly 4 billion people with diabetes worldwide [5,6]. Diabetes has become the third non-infectious chronic disease that threatens human health after cardiovascular disease and cancer on a global scale, and the number of diabetic patients in China is increasing [7].

Diabetes belongs to the category of Chinese medicine, and it has a long history of using traditional Chinese medicine to treat diabetes. Many studies have also shown that Chinese medicine also plays an important role in the treatment of diabetes. The study of berberine (also known as berberine) in traditional Chinese medicine for the treatment of diabetes has received increasing attention [8]. It has also been found that berberine can reduce the levels of fasting blood glucose, postprandial blood glucose, glycosylated hemoglobin and triglycerides in patients with type 2 diabetes, and its hypoglycemic and lipid-lowering effects may be multi-target. At present, there are more studies on berberine molecular, but the mechanism of action is not very clear. In this paper, the network pharmacology method was used to establish the berberine-multi-gene-multi-disease network model by means of the Ingenuity Pathway Analysis (IPA) commercial database and the Online Mendelian Inheritance in Man (OMIM) open-source database to elucidate the mechanism of action of the main components of berberine. It lays a further molecular theoretical foundation for the treatment of diabetes and other chronic diseases by berberine, multi-target, and multi-path.

Materials and Methods

Determination of berberine and diabetes related genes

This study strives to accurately determine the mechanism of action of berberine molecules in the treatment of diabetes and

other chronic diseases at the genetic level. Therefore, this study first determined the corresponding relationship between berberine molecule and the corresponding genes of diabetes and other chronic diseases. The specific implementation process is as follows: The CID number of berberine molecule is imported into the Ingenuity Pathway Analysis (IPA) commercial database, and the search range is determined at the time of inquiry. The selected species, the direct or indirect interactions were determined, and the target gene information corresponding to the introduced berberine molecule was finally retrieved. Table 1 shows the genes corresponding to berberine inquired by the Ingenuity Pathway Analysis (IPA) commercial database. Then look for all other genetic information for diabetes and other chronic diseases in the human Mendelian genetic database, the Online Mendelian Inheritance in Man (OMIM) open-source database. Finally, the genes searched by the two databases are matched by the gene ID, and the genetic information of the two databases is extracted by the common gene ID number to extract the common gene obtained from the two databases, so that the chemical component-gene-correspondence of disease can be obtained. Related studies indicate that there are 15 susceptibility genes for type 2 diabetes in Chinese population: *ADIPOQ*, *CDH13*, *CDNK2B*, *GLIS3*, *GRB14*, *HHEX*, *HNF1A*, *IRS1*, *KCNQ1*, *PAX4*, *PEPD*, *PPARG*, *RASGRP1*, *SLC30A8*, *TCF7L2*. The query found that three genes in Table 1 are type 2 diabetes susceptibility genes in the Chinese population, namely *ADIPOQ*, *PPARG* and *IRS1*.

Table 1: Related genes of berberine.

Berberine	<i>ADIPOQ</i>	<i>SCARB1</i>	<i>NOS2</i>	<i>IL10</i>	<i>ERBB2</i>	<i>CDK2</i>
Berberine	<i>APOA1</i>	<i>STAT1</i>	<i>PCSK9</i>	<i>IL6</i>	<i>FOXO1</i>	<i>CDK4</i>
Berberine	<i>APOB</i>	<i>STAT3</i>	<i>PON1</i>	<i>INSR</i>	<i>GCG</i>	<i>CYP1A2</i>
Berberine	<i>AR</i>	<i>TGFB1</i>	<i>PPARA</i>	<i>IRS1</i>	<i>GRK2</i>	<i>CYP2E1</i>
Berberine	<i>BIRC5</i>	<i>TH</i>	<i>PPARG</i>	<i>LDLR</i>	<i>HIF1A</i>	<i>CYP3A5</i>
Berberine	<i>CASP1</i>	<i>TNF</i>	<i>PRKAA1</i>	<i>MAPT</i>	<i>HMGB1</i>	<i>CYP4A11</i>
Berberine	<i>CASP3</i>	<i>TP53</i>	<i>PRKCZ</i>	<i>MMP2</i>	<i>HMGCR</i>	<i>ENDOG</i>
Berberine	<i>CCL2</i>	<i>VEGFA</i>	<i>PTGER2</i>	<i>MMP9</i>	<i>HRAS</i>	

Construct berberine-gene-disease correlation

In this paper, the network model of berberine-multi-gene-multiple diseases was established by the professional network analysis software which named Cytoscape. The network model includes three network nodes which are the active components

of berberine, related target genes and diabetes and other chronic diseases. The connection between nodes and nodes indicates that there is interaction between the two nodes, so the three kinds of nodes have a total of five correspondences, namely berberine active ingredient-target gene-diseases, target

gene-berberine active ingredient-target genes, diseases-target genes-diseases, diseases-target genes-berberine active ingredients, target genes-diseases-targets gene. The network model of berberine-multi-gene-multiple diseases was established through the above five corresponding interactions, and then the mechanism of action of berberine and corresponding diseases could have analyzed.

Network diffusion models: Graph-based techniques are examined by the network diffusion methods to predict berberine-target genes-diseases network and influence the transmission in networks. To train a network can well classify, we require a list of previously known berberine-target genes-diseases network. In other way we want to predict the new network interaction which is not based on existing training data. The data which represents the gene and the target involved in network is also needed for this purpose. Neighborhood methods perform predictions on the basis of functions that are relatively simple. More accurately, on the basis of previous similarities and interaction data for gene and targets, a new gene or target can get its interaction profile respectively, a new gene is one that has unknown targets and in the similar manner a new target is the one which has no known interactions with any genes.

Result

Analysis of berberine related gene

The genes corresponding to berberine found in the Ingenuity Pathway Analysis (IPA) commercial database are shown in Table 1. We can see that the number of target genes corresponding to berberine is 45, that is, berberine can regulate the expression of 45 genes such as *APOA1*, *VEGFA*, *PPARG*, *PRKCZ*, *TNF*, and so on. Berberine have different prevention and treatment effects on the diseases involved in these genes. There are three diabetes susceptibility genes are susceptibility genes associated with type 2 diabetes in the Chinese population, which are the *ADIPOQ* gene, the *PPARG* gene, and the *IRS1* gene, respectively.

In addition to the direct relationship between the *ADIPOQ* gene and type 2 diabetes in the Chinese population, the protein encoded by this gene is also closely related to the formation of fatty liver. The *PPARG* gene is a peroxisome proliferator-activated receptor gamma-encoding gene, which belongs to the nuclear receptor peroxisome proliferator-activated receptor subfamily. It can bind to the retinoid receptor to form a heterodimer, and the binding of DAN regulates the transcription of a variety of genes. *PPARG* is mainly responsible for the catabolism of lipids, and is also associated with a variety of

diseases, including obesity, diabetes, arteriosclerosis and cancer. *PPARG* is expressed in different degrees in tissues such as fat, liver, skeletal muscle, kidney, and pancreas. It is activated by binding to ligands, and activates or inhibits genes by interacting with *PPAR* Response Elements (PPREs) in the promoter of the target gene. The transcription of thus participate in a variety of physiological and pathological processes in the body, including adipocyte differentiation, inflammatory response, apoptosis, obesity, atherosclerosis and cancer. *PPARG* can be activated by fatty acids and plays an important role in insulin sensitivity and fat production. An increase in *PPARG* activity increases the absorption of fatty acids and the accumulation of fat, which in turn produces obesity. *IRS1* is the major substrate for insulin receptor kinase. *IRS1* contains multiple sites of tyrosine phosphorylation that phosphorylate to bind to proteins containing the SH domain, thereby mediating insulin-induced metabolism and growth-promoting signals. *IRS1* mediates insulin signaling on the one hand, but *IRS1* overexpression or some serine phosphorylation also leads to insulin resistance.

Statistical analysis of diabetes related gene

The genes associated with diabetes and other chronic diseases were searched by the Online Mendelian Inheritance in Man (OMIM) open source database. The genes found are shown in Table 2. It can be seen that the number of genes associated with different diseases is also different, wherein the number of genes associated with hypertension is 23, the number of genes associated with diabetes is 13, and the number of genes associated with depression is 6, the number of genes associated with arrhythmia is 7 and so on. The chronic diseases mentioned in this study mainly include chronic diseases such as hypertension, depression, coronary heart disease, and arrhythmia. Among the genetic information in Table 1, three genes (*ADIPOQ* gene, *PPARG* gene and *IRS1* gene) are directly related to type 2 diabetes in the Chinese population. Table 2 shows that the number of genes associated with diabetes is 13. The data in Table 2 is directly from the disease, directly query the genetic information related to it, here contains the genetic information directly related and indirectly related. At the same time, because there are multiple genes may be related to a variety of diseases, such as *PPARG* gene in addition to lipid catabolism, but also related to a variety of diseases, including obesity, diabetes, adipocyte differentiation, inflammation, apoptosis, arteriosclerosis and cancer.

Table 2: Diabetes and other chronic diseases correspond to other genes.

Disease	Number of gene	Disease	Number of gene	Disease	Number of gene
Anxiety	1	Depression	4	Tension	1
Blues	1	Depressive	1	The neuroses syndrome	2
Care	3	Diabetes	13	Heart failure	7

Chest distress	2	Dyspnea	2	High blood pressure	15
Concern	3	Eacute myocardial infarction	11	Insomnia	1
Hypertension	8	Fear	1	Neuro division	6
Depressed	1	Palpitation	1		

Berberine-multi-gene-multiple disease network analysis

In order to study the regulation of berberine on diabetes and other chronic diseases, berberine was subjected to component-multi-gene-multiple disease analysis. There are many gene targets that can be regulated by berberine from IPA database. We integrate with the genes corresponding to the diseases queried by OMIM, and finally use Cytoscape software to map out the main component of berberine-multi-gene-multi-disease network. The model is shown in Figure 1. In the figure, the innermost layer is represented by a light blue diamond-shaped node, which is a berberine molecule; the purple rectangular node represents the target gene information that can be regulated by berberine; and the green elliptical node represents other disease information corresponding to the target gene. The components, genes, and diseases are not layered in the figure, and are intended to show other diseases of gene regulation clearly. It can be clearly seen from the figure that berberine mainly regulates the expression of 45 genes such as *APOA1*, *VEGFA*, *PPARG*, *PRKCZ*, *TNF*, etc., which associated with and diabetes and other chronic diseases. The main diseases are diabetes, hypertension, coronary heart disease, disorders, depression, schizophrenia, etc. Among them, the *APOA1* gene encodes serum apolipoprotein A1, which is a protective factor for atherosclerosis. Its content and contrast value are important for the prevention and judgment of atherosclerosis and cardiovascular disease. The full name of *VEGFA* is vascular endothelial growth factor A, which is widely distributed in many tissues of the human body, such as gland, liver, lung, kidney, heart machine, etc., which plays a key role in tumor angiogenesis and invades tumors. *PPARG* gene is involved in a variety of diseases. *PPARG* gene is responsible for lipid catabolism, and chronic diseases related to obesity, diabetes, adipocyte differentiation, inflammatory response, apoptosis, arteriosclerosis and cancer.

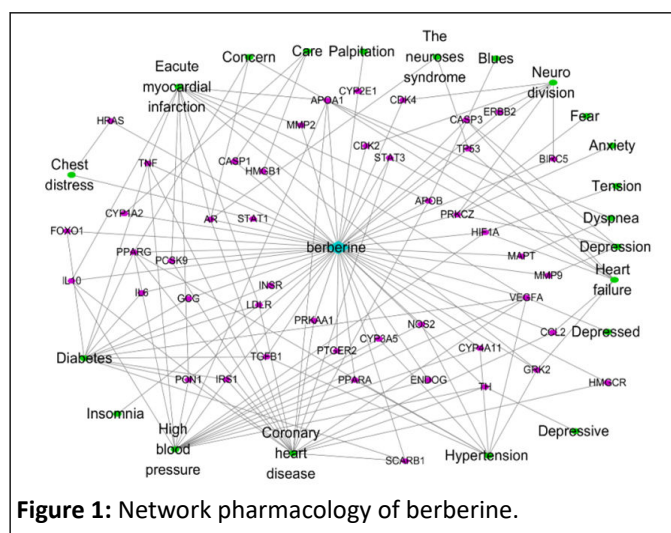


Figure 1: Network pharmacology of berberine.

Molecular docking

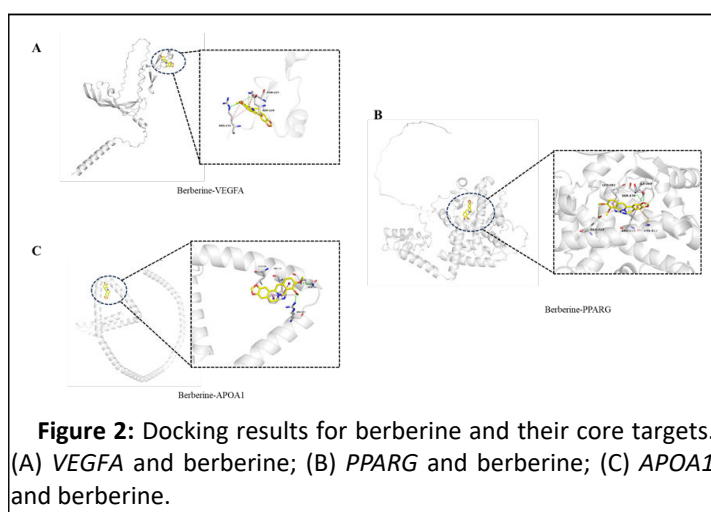
Due to the complex diversity of its constituents, traditional Chinese medicines often have a complicated mechanism of action in treating diseases. According to the theory of receptors, the chemical composition of traditional Chinese medicine is still the material basis of biological activity, and its role is to interact with other active functional receptors. Therefore, computer and other professional software can be used to simulate the direct interaction between components and target molecules. This has become a common research method in the field of drug research, and is gradually being applied to the research of traditional Chinese medicine [9-16].

Therefore, the berberine can regulate more genes and some of them for partial molecular docking verification. Here the berberine molecule and serum apolipoprotein A1, vascular endothelial growth factor A protein, peroxidation which encoding by *APOA1*, *VEGFA*, *PPARG* genes performed molecular docking on the interaction between the receptor and the protein target. In this paper, the Autodock Vina program is used for semi-flexible molecular docking calculations, that is, only the conformation of the berberine molecule is changed during the docking process, and the structure of the receptor protein remains unchanged. The position of the lattice box of the receptor binding site in the docking process is set in the position reported in the literature, and finally the optimal binding conformation is found based on the semi-empirical free energy function. Through molecular docking, it was found that the berberine molecule has a strong interaction with the above three target proteins, docking scores are shown in Table 3, docking results for berberine and their core targets shown in

Figure 2. Therefore, we combined the Ingenuity Pathway Analysis (IPA) database and the Online Mendelian Inheritance in Man (OMIM) database to provide a network model for the regulation of diabetes and other chronic diseases by berberine,

Table 3: Molecular docking scores (kcal/mol).

Ligands	Receptors		
	APOA1	VEGFA	PPARG
Berberine	-7.2	-6.6	-9.4



KEGG enrichment analysis

The above molecular docking technique verified the interaction between the berberine molecule and the target protein molecules encoded by the three genes *APOA1*, *VEGFA* and *PPARG*, and proved that there is a strong interaction between

which has certain guiding significance for subsequent scientific research.

between them. For the network mechanism of berberine, we performed KEGG pathway enrichment analysis on all target genes corresponding to berberine. The pathway enrichment map is shown in Table 4. The pathway enrichment map shows the pathways involved in the 45 genes of the berberine component corresponding to the target. In each pathway, the target gene realizes its regulatory function through its upstream and downstream genes, thus completing its intricate pathway to disease treatment. In this study, an *APOA1* gene closely related to adipokines and diabetes was selected, and its KEGG pathway related to diabetes was analyzed, as shown in Figures 3-5. For each pathway, it contains extremely complicated upstream and downstream regulation relationships. Therefore, we only give the enrichment analysis of the KEGG pathway. The corresponding regulation process of each pathway will be given one by one in future research. At the same time, this study gave the distribution of the biological pathways of type 2 diabetes susceptibility genes in Chinese population corresponding to berberine, as shown in Table 5.

Table 4: KEGG pathway enrichment table of berberine corresponding to target.

Category	Term	Genes	Benjamini
KEGG_PATHWAY	Pathways in cancer	<i>PTGER2, IL6, MMP9, ERBB2, PPARG, TP53, FOXO1, BIRC5, STAT1, CDK4, MMP2, TGFB1, STAT3, CDK2, CASP3, HIF1A, VEGFA, N</i>	4.30E-11
KEGG_PATHWAY	Hepatitis B	<i>CASP3, IL6, TNF, MMP9, TP53, BIRC5, CDK4, STAT1, TGFB1, CDK2, STAT3</i>	4.40E-07
KEGG_PATHWAY	Insulin resistance	<i>PPARA, PRKCZ, IL6, TNF, FOXO1, PRKAA1, INSR, IRS1, STAT3</i>	6.60E-06
KEGG_PATHWAY	Non-alcoholic fatty liver disease	<i>PPARA, CASP3, IL6, TNF, PRKAA1, CYP2E1, ADIPOQ, INSR, IRS1, TGFB1</i>	5.5E-06
KEGG_PATHWAY	FoxO signaling pathway	<i>IL6, FOXO1, PRKAA1, INSR, IRS1, TGFB1, CDK2, IL10, STAT3</i>	1.50E-05

KEGG PATHWAY	Proteoglycans in cancer	<i>CASP3, HIF1A, TNF, MMP9, ERBB2, VEGFA, TP53, MMP2, TGFB1, STAT3</i>	1.70E-05
KEGG_PATHWAY	Pancreatic cancer	<i>ERBB2, VEGFA, TP53, CDK4, STAT1, TGFB1, STAT3</i>	2.20E-05
KEGG_PATHWAY	Toxoplasmosis	<i>CASP3, TNF, LDLR, NOS2, STAT1, TGFB1, IL10, STAT3</i>	2.60E-05
KEGG_PATHWAY	Bladder cancer	<i>MMP9, ERBB2, VEGFA, TP53, CDK4, MMP2</i>	2.90E-05
KEGG_PATHWAY	HIF-1 signaling pathway	<i>IL6, HIF1A, ERBB2, VEGFA, NOS2, INSR, STAT3</i>	2.00E-04
KEGG_PATHWAY	Inflammatory Bowel Disease (IBD)	<i>IL6, TNF, STAT1, TGFB1, IL10, STAT3</i>	2.60E-04
KEGG_PATHWAY	AMPK signaling pathway	<i>HMGCR, PPARG, FOXO1, PRKAA1, ADIPOQ, INSR, IRSI</i>	4.80E-04
KEGG_PATHWAY	Adipocytokine signaling pathway	<i>PPARA, TNF, PRKAA1, ADIPOQ, IRSI, STAT3</i>	4.60E-04
KEGG_PATHWAY	Pertussis	<i>CASP3, IL6, TNF, NOS2, CASP1, IL10</i>	4.90E-04
KEGG_PATHWAY	Hepatitis C	<i>PPARA, TNF, LDLR, TP53, SCARB1, STAT1, STAT3</i>	6.20E-04
KEGG_PATHWAY	Type II diabetes mellitus	<i>PRKCZ, TNF, ADIPOQ, INSR, IRSI</i>	1.30E-03
KEGG_PATHWAY	Malaria	<i>IL6, CCL2, TNF, TGFB1, IL10</i>	1.60E-03
KEGG_PATHWAY	Amoebiasis	<i>CASP3, IL6, TNF, NOS2, TGFB1, IL10</i>	2.10E-03
KEGG_PATHWAY	Chagas disease (American trypanosomiasis)	<i>IL6, CCL2, TNF, NOS2, TGFB1, IL10</i>	2.20E-03
KEGG_PATHWAY	Tuberculosis	<i>CASP3, IL6, TNF, NOS2, STAT1, TGFB1, IL10</i>	2.60E-03
KEGG_PATHWAY	Leishmaniasis	<i>TNF, NOS2, STAT1, TGFB1, IL10</i>	2.50E-03
KEGG_PATHWAY	Herpes simplex infection	<i>CASP3, IL6, CCL2, TNF, TP53, STAT1, CDK2</i>	3.00E-03
KEGG_PATHWAY	Measles	<i>IL6, TP53, CDK4, STAT1, CDK2, STAT3</i>	4.5E-03
KEGG_PATHWAY	African trypanosomiasis	<i>IL6, APOA1, TNF, IL10</i>	5.20E-03
KEGG_PATHWAY	Prostate cancer	<i>AR, ERBB2, TP53, FOXO1, CDK2</i>	7.00E-03
KEGG_PATHWAY	Rheumatoid arthritis	<i>IL6, CCL2, TNF, VEGFA, TGFB1</i>	7.00E-03

KEGG PATHWAY	MicroRNAs in cancer	<i>CASP3, MMP9, ERBB2, VEGFA, TP53, IRS1, STAT3</i>	8.00E-03
KEGG_PATHWAY	PI3K-Akt signaling pathway	<i>IL6, VEGFA, TP53, PRKAA1, CDK4, INSR, IRS1, CDK2</i>	9.5E-03
KEGG_PATHWAY	NOD-like receptor signaling pathway	<i>IL6, CCL2, TNF, CASP1</i>	1.20E-02
KEGG_PATHWAY	TNF signaling pathway	<i>CASP3, IL6, CCL2, TNF, MMP9</i>	1.40E-02
KEGG_PATHWAY	Amyotrophic Lateral Sclerosis (ALS)	<i>CASP3, TNF, TP53, CASP1</i>	1.60E-02
KEGG_PATHWAY	Legionellosis	<i>CASP3, IL6, TNF, CASP1</i>	2.20E-02
KEGG_PATHWAY	Insulin signaling pathway	<i>PRKCZ, FOXO1, PRKAA1, INSR, IRS1</i>	2.50E-02
KEGG_PATHWAY	PPAR signaling pathway	<i>PPARA, APOA1, PPARG, ADIPOQ</i>	2.50E-02
KEGG PATHWAY	Colorectal cancer	<i>CASP3, TP53, BIRC5, TGFB1</i>	2.60E+00
KEGG_PATHWAY	Apoptosis	<i>CASP3, TNF, ENDOG, TP53</i>	2.60E-02
KEGG_PATHWAY	p53 signaling pathway	<i>CASP3, TP53, CDK4, CDK2</i>	2.90E-02
KEGG_PATHWAY	Hypertrophic Cardiomyopathy (HCM)	<i>IL6, TNF, PRKAA1, TGFB1</i>	3.50E-02
KEGG PATHWAY	Transcriptional misregulation in cancer	<i>IL6, MMP9, PPARG, TP53, FOXO1</i>	3.60E-02
KEGG_PATHWAY	Small cell lung cancer	<i>TP53, NOS2, CDK4, CDK2</i>	4.10E-02
KEGG_PATHWAY	Influenza A	<i>IL6, CCL2, TNF, STAT1, CASP1</i>	4.70E-02

Table 5: Distribution of susceptibility gene biological pathways in type 2 diabetes in Chinese population.

Gene	Pathway
<i>ADIPOQ</i>	Non-Alcoholic Fatty Liver Disease (NAFLD); AMPK signaling pathway; PPAR signaling pathway; Type II diabetes mellitus
<i>PPARG</i>	Pathways in cancer; AMPK signaling pathway; PPAR signaling pathway; Transcriptional misregulation in cancer
<i>IRS1</i>	Insulin resistance; Non-Alcoholic Fatty Liver Disease (NAFLD); FoxO signaling pathway; MicroRNAs in cancer; PI3K-Akt signaling pathway; Insulin signaling pathway

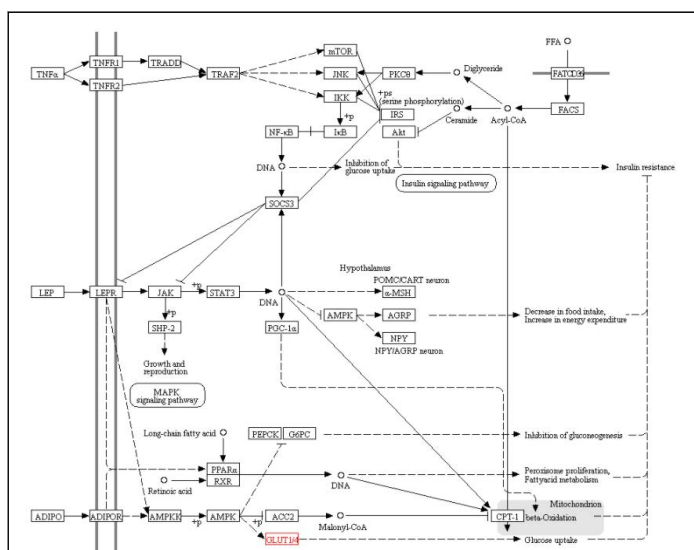


Figure 3: Adipocyte signal pathway map involved in *ADIPOQ*.

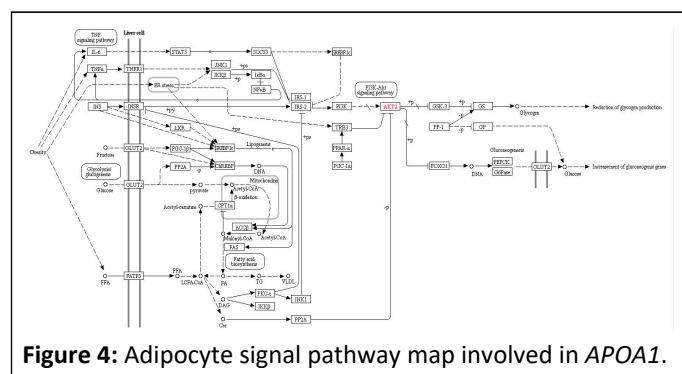


Figure 4: Adipocyte signal pathway map involved in *APOA1*.

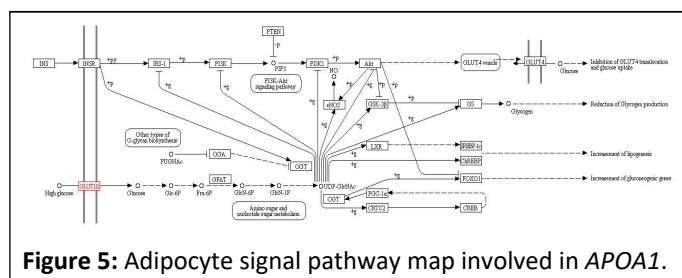


Figure 5: Adipocyte signal pathway map involved in *APOA1*.

Network visualization

Network visualization as an experimental study aid, may be used to demonstrate the berberine-target genes-diseases bipartite network. Examining the network visually may provide some evidences or understandings which may be difficult to reach otherwise. For example, by examining closely the visualized network carefully for hints, it is possible to tell why certain interactions have low prediction score. The user may use the edge width or coloring edges with a color scale to specify how high or low the prediction scores may be. This particular example is demonstrated in Figure 6.

Network diffusion model

The methods which involves investigation of graph-based techniques to predict new interactions falls in the network diffusion category. It is named as such because it is predominant in this category. Network-Based Inference (NBI) applies network

diffusion on the berberine-target genes-diseases bipartite network corresponding to the interaction matrix Y to perform predictions. The working of network diffusion is according to: $\hat{Y} = WY$.

Where $W \in \mathbb{R}^{n \times n}$ is the weight matrix defined as:

$$w_{ij} = \frac{1}{\Gamma(i,j)} \sum_{l=1}^m \frac{Y_{il}Y_{jl}}{\kappa(t_l)}$$

Where Γ is the diffusion rule, and $k(x)$ denotes the degree of node x in the berberine-target genes-diseases bipartite network. While in NBI case, the Γ rule is given by $\Gamma = k(d_j)$.

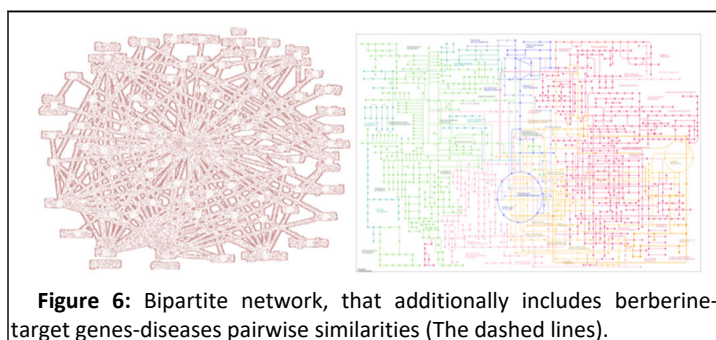


Figure 6: Bipartite network, that additionally includes berberine-target genes-diseases pairwise similarities (The dashed lines).

Discussion

In this paper, the network pharmacology research method was used to analyze the network model of berberine regulating diabetes and other chronic diseases, and the molecular docking method was used to verify the mechanism. It was found that berberine can regulate the expression *APOA1*, *VEGFA*, *PPARG*, *PRKCB*, *TNF*, etc. which involves diabetes, hypertension, coronary heart disease, arrhythmia, depression, schizophrenia and other diseases.

Conclusion

In summary, this paper uses the computational method to study the network model of berberine-multi-gene-multiple diseases, avoiding the barriers that are difficult to obtain in the chemical composition of traditional Chinese medicine, and provides calculation hypothesis and experimental direction for further research. This method reduce the amount of experimental work, which in turn reduces the cost of new drug development and research in the future. Therefore, the use of network to study the role of TCM in treating diseases and preventing disease has given new scientific connotations to traditional Chinese medicine. At the same time, this result has a good reference for the study of complex diseases based on metabolic pathways.

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Competing and Conflicting Interests

The authors declare no competing financial interest.

References

1. Song J (2008) New progress in clinical application and research of Xiaochai. *Mod Med Health* 24:1652-1655

2. Li H, Chai X, Li X F (2008) Clinical use and adverse reactions of berberine. *Armed Police Med* 19:661-662
3. Pang B, Zhao LH, Zhou Q, Zhao TY, Wang H, et al. (2015) Application of berberine on treating type 2 diabetes mellitus. *Int J Endocrinol* 2015:905749
4. Liu C, Wang Z, Song Y, Wu D, Zheng X, et al. (2015) Effects of berberine on amelioration of hyperglycemia and oxidative stress in high glucose and high fat diet-induced diabetic hamsters *in vivo*. *Biomed Res Int* 2015:313808
5. Tai N, Wong FS, Wen L (2015) The role of gut microbiota in the development of type 1, type 2 diabetes mellitus and obesity. *Rev Endocr Metab Disord* 16:55-65
6. El-Kaissi S, Sherbeeni S (2011) Pharmacological management of type 2 diabetes mellitus: An update. *Curr Diabetes Rev* 7:392-405
7. Fan LY, Du JL (2012) Diabetes hazards and prevention. *Pract J Intern Med* 26:56-59
8. Yin J, Xing H, Ye J (2008) Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism* 57:712-717
9. Hood L, Heath JR, Phelps ME, Lin B (2004) Systems biology and new technologies enable predictive and preventative medicine. *Science* 306(5696):640-643
10. di Ventura B, Lemerle C, Michalodimitrakis K, Serrano L (2006) From *in vivo* to *in silico* biology and back. *Nature* 443(7111):527-533
11. Ekins S (2004) Predicting undesirable drug interactions with promiscuous proteins *in silico*. *Drug Discov Today* 9:276-285
12. Wu DH, Xu XJ (2009) Computer simulation of the mechanism of qi and blood circulation of traditional Chinese medicine. *J Phys Chem* 25:446-450
13. Huang Q, Qiao X, Xu X (2007) Potential synergism and inhibitors to multiple target enzymes of Xuefu Zhuyu Decoction in cardiac disease therapeutics: A computational approach. *Bioorg Med Chem Lett* 17:1779-1783
14. Qin H, Xuebing Q, Xiaojie X (2007) Chemical analysis of effective components of Chinese herbs. *Comput Appl Chem* 24:41-44
15. Xu X (2006) New concepts and approaches for drug discovery based on traditional Chinese medicine. *Drug Discov Today Technol* 3:247-253
16. Xu X (1999) Study on computer simulation for Chinese traditional compound medicine. *Prog Chem* 11:202-204