# **Research** Article

# Network Pharmacology Analysis of Traditional Chinese Medicine Formula *Xiao Ke Yin Shui* Treating Type 2 Diabetes Mellitus

# Jiewen Zhou, Qiuyan Wang, Zhinan Xiang, Qilin Tong, Jun Pan, Luosheng Wan D, and Jiachun Chen

Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Huazhong University of Science and Technology, Hangkong Road 13#, Wuhan 430030, China

Correspondence should be addressed to Luosheng Wan; wanluosheng@hust.edu.cn and Jiachun Chen; homespringchen@mail.hust.edu.cn

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*Xiao Ke Yin Shui* (XKYS) formula is a traditional Chinese medicine formula treating type 2 diabetes mellitus (T2DM). XKYS formula consists of four herbs, i.e., Coptidis rhizoma, Liriopes radix, bitter melon, and Cassiae semen. Herein, the chemical profiles of four herb extracts were investigated, and further analysis of the underlying mechanism of XKYS formula treating T2DM was performed using network pharmacology. The main components were selected for our network-based research. Targets of XKYS formula were mainly collected from two databases, SwissTargetPrediction and Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), and the text-mining method was also implemented. T2DM relating genes and therapeutic targets were collected from five databases. Subsequently, STRING and Cytoscape were employed for the analysis of protein-protein interaction (PPI) networks. Functional annotation and pathway analysis were conducted to investigate the functions and relating pathways of target genes. The content of 12 compounds in the herb extracts was determined. With the analysis of PPI networks, a total of 76 genes were found to be important nodes and could be defined as the main target genes regulated by XKYS formula in the treatment of T2DM and its complications. Components in XKYS formula mainly regulate proteins including protein kinase B (Akt), phosphatidylinositol 3-kinase (PI3K), insulin receptor substrate (IRS), and tumor necrosis factor (TNF). XKYS formula exerts therapeutic effects in a synergetic manner and exhibits antidiabetic effect mainly via reducing insulin resistance. These findings could be guidelines in the further investigation of this formula.

# 1. Introduction

Diabetes mellitus (DM) is now recognized as a complex metabolic disorder, and type 2 diabetes mellitus (T2DM) is the most common type of diabetes [1]. Nowadays, different kinds of therapies are applied in the treatment of diabetes, including insulin and other oral medications. Such therapies may be promising in glycemic control but could also cause side-effects like hypoglycemia or gastrointestinal dysfunction [2]. Thus, more and more people have turned their attention to herbal medicine or diet-based therapies, seeking for safer and more cost-effective complementary medicine for T2DM [3–6].

Traditional Chinese medicine (TCM) is a rich resource, possessing data that can still be hints for the development of new drugs. The focus of the current study, *Xiao Ke Yin Shui* (XKYS) formula, is recorded in *Bencaogangmu* (compendium of Materia Medica). XKYS formula contains four herbs, namely, Coptidis rhizoma (dried rhizomes of *Coptis chinensis* Franch.), Liriopes radix (the dried tuberous roots of *Liriope spicata* (Thunb.) Lour. var. *prolifera* Y. T. Ma), bitter melon (the immature fresh fruits of *Momordica charantia* L.), and Cassiae semen (the dried seeds of *Cassia obtusifolia* L.). All these herbs are widely used in clinical practice treating diabetes [7]. Several ingredients in these four herbs are generally accepted as the main bioactive components in the treatment of T2DM and its complications, i.e., alkaloids in Coptidis rhizoma, polysaccharides in Liriopes radix, triterpenoids and polysaccharides in bitter melon, and anthraquinone and naphthopyrone in Cassiae semen [8–11]. Thereby, herb extracts were prepared aiming to yield bioactive fractions containing ingredients mentioned above. The mixture of these herb extracts may be a satisfying alternative for the treatment of T2DM.

In XKYS formula, a single component may be responsible for the therapeutic effect through different pathways, and some components may act on the same targets as well. For example, isoquinoline alkaloids from Coptidis rhizoma like berberine are generally recognized as activators of adenosine 5'-monophosphate- (AMP-) activated protein kinase (AMPK) but could also exert therapeutic effects on T2DM through inhibition of protein tyrosine phosphatase 1B (PTP1B) and peroxisome proliferator-activated receptor gamma (PPARy) [12-14]. Polysaccharides of Liriopes radix and extracts of Cassiae semen could ameliorate glycemic control through activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway [15, 16]. Triterpenoids in bitter melon are proved to be AMPK activators while polysaccharides are inhibitors of PPARy [17, 18]. These findings, however, could not fully explain the synergetic effects of XKYS formula in the treatment of T2DM and its complications.

Nowadays, researchers have been aware that the "one key, one lock" mode is insufficient to decipher the drug actions, especially in those complex diseases. Network pharmacology, however, analyzing drugs and drug targets in a systemic manner may provide us with novel insights into drug actions [19]. The key ideas of network pharmacology share much with the basic disciplines of TCM, making it a useful tool in the research of TCM [20]. In addition, rapid development of biomedical big data, like TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform), has facilitated such research [21]. Thus, a network-based pharmacological analysis could provide us with a comprehensive understanding towards the significance of each component, target, and pathway.

In brief, this study provided chemical profiles for the extracts of four herbs. And, network pharmacology analysis was applied to understand the underlying mechanisms of XKYS formula in the treatment of T2DM and its complications.

#### 2. Materials and Methods

2.1. Materials and Reagent. Coptidis rhizoma, Liriopes radix, fresh bitter melon, and Cassiae semen were authenticated by Professor Jiachun Chen (School of Pharmacy, Huazhong University of Science and Technology, or HUST). Voucher specimens of these herbs were deposited in Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, HUST.

The four herb extracts were total alkaloids of Coptidis rhizoma (TACR), Liriopes radix polysaccharides (LRP), bitter melon extract (BME), and Cassiae semen extract (CSE), respectively. Detailed preparation methods for the extracts were reported in Supplementary Materials (Part 1).

Acetonitrile ( $CH_3CN$ ) was purchased from Sigma Aldrich (USA). Water was deionized water. Hydrochloric acid, methanol, phosphate buffer, anthrone, sulfuric acid, fructose, glucose, and formic acid (HCOOH) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China).

HPLC analysis of TACR, BME, and CSE was performed on the Agilent 1260 system with Agilent TC-C18 (250 mm × 4.6 mm, 5  $\mu$ m) columns. HPLC analysis of LRP was performed on the Hitachi L-2130 system with an Agilent TC-C18 (250 mm × 4.6 mm, 5  $\mu$ m) column. Content of total carbohydrate was determined on an ultraviolet-visible spectrophotometer, UV-1750 (Shimazu, Japan).

Epiberberine, coptisine, palmatine, berberine, and aurantio-obtusin were purchased from National Institute for Food and Drug Control. Cassiaside, rubrofusarin-6-O- $\beta$ -D-gentiobioside, glucoaurantio-obtusin, and cassiaside C were purchased from Chengdu MUST Bio-technology Co. Ltd. (Sichuan, China). Momordicoside L,  $7\beta$ ,25-dihydrocucurbita-5,23(*E*)-dien-19-al-3-O- $\beta$ -D-allopyranoside, and momordicoside F<sub>2</sub> were self-prepared (Supplementary Materials, Part 2, Figures S1 and S2). The purity of each standard was >98%.

2.2. Analysis of Four Herb Extracts. The analysis of TACR was conducted using the reported method [22].

The total carbohydrate content of LRP was examined using anthrone-sulfuric acid method according to the previous report [23].

Monosaccharide composition analysis of LRP was performed using the HPLC method after derivation with 1-pheny-3-methyl-5-pyrazolone (PMP), and the detailed method was reported in Supplementary Materials (Part 3) [24]. The mobile phase was 20:80 (v:v) CH<sub>3</sub>CN-H<sub>3</sub>PO<sub>4</sub> buffer (pH 7.0). The flow rate was 1.0 ml/min. The injection volume was 20  $\mu$ l. Column temperature was held constant at 25°C. The UV detection wavelength was 250 nm.

The total carbohydrate content of BME was examined using anthrone-sulfuric acid method according to the previous report [23].

HPLC analysis of BME was conducted with the mobile phase consisting of CH<sub>3</sub>CN (A) and water (B). The elution program was 0 min 20%A, 10 min 30%A, 30 min 50%A, and 50 min 70%A. The flow rate was 1.0 ml/min. Column temperature was held constant at 25°C. The detector was evaporative light scattering detector (ELSD), with the evaporator temperature at 60°C and nebulizer temperature at 40°C. The flow rate of nitrogen was 1.6 l/min. The standard (10, 20  $\mu$ l) and sample (20  $\mu$ l) dissolved in 70% methanol were subjected to HPLC analysis.

HPLC analysis of CSE was carried out according to the previous report [25].

2.3. Construction of Protein-Protein Interaction (PPI) Networks of XKYS Formula Treating T2DM and Its Complications. To identify the corresponding targets of the main components of XKYS formula, several approaches combined with chemometric method, information integration, and data-mining were implemented. These components, except polysaccharides, were submitted to TCMSP and SwissTargetPrediction server to find component-target interaction information. TCMSP mainly predicts drug-target interactions with random forest (RF) and support vector machine (SVM) method, while SwissTargetPrediction is a 2D/3D similarity measurement of small molecules [26, 27]. All components, as well as the aglycon of the glycosides, were also submitted to PubMed, SciFinder, and Google Scholar for the text-mining of component-target information. And all targets were submitted to the UniProt database (http://www.uniprot.org) for validation of their gene names. Hereby, a target gene list of XKYS was obtained through *in silico* investigation.

Another gene list relating to T2DM was established after screening of five databases, including DrugBank database (http://www.drugbank.ca/), Online Mendelian Inheritance in Man (OMIM, http://www.omim.org/), Kyoto Encyclopedia of Genes and Genomes (KEGG, https://www.kegg.jp), Therapeutic Target Database (TTD, https://db.idrblab.org/ ttd/), and Text-mined Hypertension, Obesity, and Diabetes Candidate Genes database (T-HOD, http://bws.iis.sinica.edu. tw/THOD/). And all genes and targets were submitted to the UniProt database for validation of their gene names.

Two gene lists were submitted to STRING. The STRING server generated a "Combined Score" ranged from 0 to 1 for each interaction. The higher the score is, the greater the confidence of the interaction. In STRING, an interaction >0.4 means "medium confidence" and >0.7 means "high confidence" [28].

The obtained PPI networks were intersected using Cytoscape 3.2.1, and interactions with score >0.7 were collected, generating a new PPI network, i.e., the PPI network of XKYS formula treating T2DM and its complications.

2.4. Gene Ontology (GO) Functional Annotation and KEGG Pathway Analysis. To elucidate the function of the targets and their role in signaling transduction, the Database for Annotation, Visualization and Integrated Discovery (DA-VID) was used to analyze the GO function and KEGG pathway of the main target genes of XKYS formula in the treatment of T2DM and its complications. The biological process, cellular component, molecular function, and the pathway involved were also described.

2.5. Component-Target-Pathway Network Construction. The network model of component-target-pathway was established using Cytoscape 3.2.1. In this network, nodes represent components (C), targets (T), or pathways (P), and edges represent the interaction of C-T or T-P. Based on the results of KEGG enrichment analysis and C-T database, the C-T-P interactions were shown to provide an overview on the mechanisms of XKYS formula in the treatment of T2DM and its complications.

## 3. Results

3.1. Determination of Main Component Contents of Four Herb Extracts. Four isoquinoline alkaloids, three cucurbitane-

type triterpenoids, two anthraquinones, and three naphthopyrones were determined using HPLC. Results of the HPLC analysis are shown in Table 1 and Figure 1, and the structures were also reported (Table 2). The total content of carbohydrate in LRP was determined to be 96.5% while BME 10.8%. The composition of LRP was also determined as fructose: glucose, 20.7:1.

3.2. Screening of Main Components from Four Herb Extracts and Construction of PPI Networks. The screening of 19 components (Table 2) in XKYS had led to the acquisition of 216 targets, while 602 genes relating to the pathophysiology of T2DM were also collected (Supplementary Materials, Tables S1 and S2). All the gene names in two lists were uploaded to STRING, respectively. The XKYS PPI network consists of 216 proteins and 2070 interactions, whereas T2DM, 602 proteins and 11595 interactions (Figures 2(a) and 2(b)). Each interaction has a Combined Score >0.4. By intersecting these two networks, all interactions with high confidence (>0.7) were picked, generating a new PPI network.

The new network consists of 76 genes, representing the main target genes regulated by XKYS formula in the treatment of T2DM. In addition, among these genes, some genes like AKT1, mitogen-activated protein kinase 1 (MAPK1), tumor necrosis factor (TNF) were also found to be important genes involved in the progression of diabetic complications [29–31]. Thus, these genes could also be regarded as the main target genes regulated by XKYS formula in the treatment of T2DM and its complications (Figure 2(c), Table 3).

The new PPI network contains 76 nodes and 333 edges (Figure 2(c)). In this network, nodes represent targets, while edges, the interactions of proteins. And degree, a topological parameter describing the importance of a node, stands for the number of edges connecting to the node. The higher the degree, the more important the target in the network is.

As can be seen in Figure 2(c), important targets were painted red and located centrally in the network. AKT1, PI3KCG, MAPK1, LEP, IRS1, and PPARG were the top six genes regarding their degree.

3.3. GO Functional Annotation and KEGG Pathway Analysis. GO functional annotation was performed on 76 target genes, and the top 20 GO terms (P < 0.01) were selected based on  $-\log P$  values (Figure 3). GO enrichment analysis indicated that these 76 target genes are responsible for glucose homeostasis, platelet activation, regulation of insulin secretion, cellar response to hypoxia, and cellular response to insulin stimulus (Figure 3(a)). These biological processes are related to molecular functions including, steroid hormone receptor activity, protein kinase activity, protein serine/threonine (Ser/Thr) kinase activity, enzyme binding, and drug binding (Figure 3(b)). And, these processes occur mainly in caveola, cytosol, plasma membrane, nucleoplasm, and receptor complex (Figure 3(c)).

KEGG pathway analysis was conducted for further exploration of these targets as shown in Figure 3(d). These

Extracts	Constituents	Content (mg/g)
TACR	Epiberberine	55.0
	Coptisine	135.1
	Palmatine	99.7
	Berberine	354.7
BME	Momordicoside L	1.9
	7β,25-Dihydrocucurbita-5,23( <i>E</i> )-dien-19-al3-O-	1.0
	$\beta$ -D-allopyranoside	1:0
	Momordicoside F <sub>2</sub>	1.9
CSE	Cassiaside	40.0
	Rubrofusarin 6-O- $\beta$ -D-gentiobioside	32.0
	Glucoaurantio-obtusin	46.1
	Cassiaside C	27.4
	Aurantio-obtusin	22.2

TABLE 1: Content of components in herb extracts determined using HPLC.





FIGURE 1: HPLC spectra of four herb extracts. (a) TACR: M1, epiberberine; M2, coptisine; M3, palmatine; M4, berberine. (b) Monosaccharide composition of LRP. Fructose : glucose = 20.7 : 1. (c) BME: M7, momordicoside L; M8,  $7\beta$ , 25-dihydrocucurbita-5, 23(E)-dien-19al-3-O- $\beta$ -D-allopyranoside; M10, momordicoside F<sub>2</sub>. (d) CSE: M12, cassiaside; M14, rubrofusarin-6-O- $\beta$ -D-gentiobioside, M16, glucoaurantio-obtusin; M17, aurantio-obtusin; M18, cassiaside C.

targets were highly enriched in insulin resistance (IR), insulin pathway, adipocytokine pathway, AMPK pathway, T2DM, forkhead box protein O (FoxO) pathway, nonalcoholic fatty liver disease (NAFLD), mammalian target of rapamycin (mTOR) pathway, hypoxia-inducible factor 1 (HIF-1) pathway, glucagon pathway, and so on. These pathways are highly relevant to the development of T2DM and its complications, and XKYS formula may exert therapeutic effects through pathways mentioned above.

3.4. Composition-Target-Pathway Network Construction. A total of 76 genes were defined as the main target genes regulated by XKYS formula in the treatment of T2DM and its complications. These genes were kept, and other entries were omitted in the database of C-T. The combination of C-T and T-P databases had led to a C-T-P network (Figure 4), providing us with an overview on the therapeutic effects of XKYS formula. In addition, the degree of each node is presented in Supplementary Materials Table S3.

The inner cycle represents the main components of XKYS formula. Nodes painted in red were key components interacting with a larger number of targets. Among all of these 19 components, alkaloids from Coptidis rhizoma were regarded as the key components in the treatment of T2DM and its complications.

The middle cycle represents the main target genes regulated by XKYS formula. When painted in red, the corresponding targets are regulated by more components and participate in more pathways. It could be observed that

No.	Name	CAS No.	Molecular formula	Structure	Herb
M1	Epiberberine	6873-09-2	C <sub>20</sub> H <sub>18</sub> NO <sub>4</sub>	OCH <sub>3</sub> OCH <sub>3</sub> OCH <sub>3</sub> OCH <sub>3</sub>	Coptidis rhizoma
M2	Coptisine	3486-66-6	C <sub>19</sub> H <sub>14</sub> NO <sub>4</sub>		Coptidis rhizoma
M3	Palmatine	3486-67-7	C <sub>21</sub> H <sub>22</sub> NO <sub>4</sub>	H <sub>3</sub> CO CH <sub>3</sub> H <sub>3</sub> CO CH <sub>3</sub>	Coptidis rhizoma
M4	Berberine	2086-83-1	C <sub>20</sub> H <sub>18</sub> NO <sub>4</sub>	H <sub>3</sub> CO OCH <sub>3</sub>	Coptidis rhizoma
M5 M6	Liriopes radix polysaccharides Bitter melon polysaccharides	N/A N/A	N/A N/A	N/A N/A	Liriopes radix Bitter melon
M7	Momordicoside L	81348-83- 6	C <sub>36</sub> H <sub>58</sub> O <sub>9</sub>	онс но онс о-β-Glc	Bitter melon
M8	7 $\beta$ ,25-Dihydrocucurbita-5,23( <i>E</i> )-dien-19-al- 3-O- $\beta$ -D-allopyranoside	912329- 04-5	C <sub>36</sub> H <sub>58</sub> O <sub>9</sub>	онс онс он	Bitter melon

TABLE 2: Structures of components in four herb extracts.

TABLE 2: Continued.

No.	Name	CAS No.	Molecular formula	Structure	Herb
М9	3,7,25-Trihydroxycucurbita-5,23-dien-19-al	85372-65- 2	$C_{30}H_{48}O_4$	ОНС ОНС ОН	Bitter melon
M10	Momordicoside F <sub>2</sub>	81348-82- 5	C <sub>36</sub> H <sub>58</sub> O <sub>8</sub>	АШ-В-О	Bitter melon
M11	5 $\beta$ ,19-Epoxycucurbita-6,23-diene-3 $\beta$ ,25-diol	81910-41- 0	$C_{30}H_{48}O_3$	но	Bitter melon
M12	Cassiaside	13709-03- 0	$C_{20}H_{20}O_{10}$	O OH O-β-Glc	Cassiae semen
M13	Norrubrofusarin	3566-98-1	$C_{14}H_{10}O_5$	О ОН ОН	Cassiae semen
M14	Rubrofusarin 6-O- $\beta$ -D-gentiobioside	24577-90- 0	C <sub>27</sub> H <sub>32</sub> O <sub>15</sub>	O OH O-β-GIc-β-GIc O OCH <sub>3</sub>	Cassiae semen
M15	Rubrofusarin	3567-00-8	C <sub>15</sub> H <sub>12</sub> O <sub>5</sub>	O OH OH O OH OH OCH <sub>3</sub>	Cassiae semen

8

TABLE 2: Continued.



N/A = not applicable.

PI3KR1, PI3KCG, AKT, and TNF are key genes regulated by XKYS formula. This result agreed with that obtained from PPI analysis.

The outer cycle represents the top 20 pathways enriched. Pathways containing the most target genes were in red. IR, AMPK pathway, insulin pathway, and pathway in cancer are the key pathways. This result was familiar to that obtained from KEGG pathway analysis.

# 4. Discussion

TCM formulae are usually hard to decipher due to its mode of action, namely, "network target, multicomponents" [20]. T2DM is also a complex metabolic disorder with changes in various pathways. XKYS formula and T2DM can be considered as two networks and explained with the help of network pharmacology.

According to C-T-P network, alkaloids from Coptidis rhizoma are the main components in XKYS formula that exert antidiabetic effects. Results also indicated that around 64% of the content in TACR could be determined using the HPLC method. Among these isoquinoline alkaloids determined, berberine accounted for  $\sim$ 35% of the fraction and was also

proved to be a key node in the C-T-P network. Berberine has a wide range of biological activities, among which anti-hyperglycemic and anti-hyperlipidemia are two major benefits in the treatment of T2DM [8]. Berberine could activate AMPK via inhibition of mitochondrion respiratory complex I instead of the regulation of calcium/calmodulin-dependent protein kinase kinase beta (CaMKK $\beta$ ), leading to the reduction of IR and amelioration of lipid metabolism [13, 32]. Momordicoside L and its analogue were detected in BME and interesting enough, and the agylcon of Momordicoside L could activate AMPK through CaMKK $\beta$ , which was distinct from the mechanism of berberine [17]. This could be a good evidence of synergetic effect presented by this formula.

LRP are highly enriched according to its total content of carbohydrate. Our previous studies had found that LRP could upregulate the insulin signaling pathway and exert therapeutic effects in diabetic rodents through activation of PI3K/Akt signaling pathway [15, 23]. Aurantio-obtusin, along with its glycosides, accounted for ~6.8% of CSE and was shown to be an important component in the C-T-P network. Previous reports had indicated that aurantioobtusin may offer therapeutic effects in hypertension through the PI3K/Akt-eNOS (endothelial nitric oxide



FIGURE 2: Protein-protein interaction networks. The mapping of PPI network was generated by the STRING server. (a) PPI network of genes regulated by XKYS formula (217 nodes, 2070 edges). (b) PPI network of genes relating to the pathophysiology of T2DM (602 nodes, 11595 edges). (c) 76 main target genes regulated by XKYS formula in the treatment of T2DM and its complications. This network contains 76 nodes and 333 edges. As shown in the color bar, nodes in red could be considered as important and nodes in green are less important in this network. The degree value of each node in Figure 2(c) is presented in Table 3.

synthase) pathway, implying a possible mechanism in the treatment of diabetic complications of XKYS formula [33].

As can be seen in the C-T-P network, AKT1, PI3KCG, PI3KR1, and TNF were key genes regulated by XKYS formula in the treatment of T2DM and its complications. Proteins expressed by genes AKT1, PI3KCG, and PI3KR1 were all important members in the signaling transduction of PI3K/Akt. This signaling pathway is of great significance in the progression of T2DM due to its role in glucose metabolism [34]. The PI3K/Akt signaling pathway is also responsible for the regulation of the signaling pathway like MAPK, FoxO, and nuclear factor kappa B (NF- $\kappa$ B). These pathways play important roles in the regulation of protein synthesis, cell survival, differentiation, proliferation, and apoptosis and are highly related to the proliferation and regeneration of islet  $\beta$ -cells [29].

TABLE 3: Main targets regulated by XKYS formula in the treatment of T2DM and its complications.

AKC         Data Sector         Data Sector         PIC 20         PIC 20         PIC 20           Phosphatighinostiol 4.5-biophosphate 3-kmase         PIC 3CG         P48736         24           Phosphatighinostiol 4.5-biophosphate 3-kmase         PIC 3CG         P48736         24           Leptin         IEP         P1159         22           Leptin         IEP         P1159         22           Perosione proliferator activated receptor gamma         PPARG         P72331         21           Tumor necrosis factor         TNF         P01375         20           Glucagon         GCC         P01275         17           Prostaglandin G/H synthase, catohtelia         NOS3         P29744         16           Phosphatighinositol 3-kinase regulatory suburit         PIC 32         BCL2         P10415         15           Eatrogen receptor         ISSR         P06213         15         15           Insulin receptor         ISSR         P06213         15           Intriculuin-4         PARA         Q07669         13           Intriculuin-4         Parabaging factor activated receptor gamma         PPARA         Q07669         13           Intriculuin-4         Pareceptor         ISSR         P06213<	Protein name	Gene name	Unipro ID	PPI network degree
Phospharial-files and solutions of the second secon	RAC-alpha serine/threonine-protein kinase	AKT1	P31749	27
Calight: submit gamma isoformPIRSC GPA73624LeptinIERP3558622LeptinIEPP413922Mingen-activated protein kinas 1MAPK1P2348222Peroxione proliferitor activated receptor gammaPPARGP733121Tumor necrosis factorTNFP0137520GlucagonGCGP0127517Porotighendin GH1 synthas 2PTGS2P2353417Nitric-oxide synthase, endothelialNOS3P2947416Posphaltdylinouido 3-kinase regulatory submitPKRRP2798616Appotosi regulator Bcl 2BCL2P1041515Bindin receptorISSRP0021315Mingen-activated protein kinase 14MAPK14Q1653915Mingen-activated protein kinase 14MAPK14Q0786913Peroxione proliferator activated receptor alphaPPARGCIAQ91BK213Peroxione proliferator activated receptor gammaPPARGCIAQ91BK213Peroxione proliferator activated receptor gammaPARGCIAQ91BK213Candit denokine 2CCL2P150010Protein kinase C dela typePKCDQ90585510Natrix metalloproteinase-9MIP9P1478010Protein kinase C dela typePRCCIP17529Leptin receptor.ARP17939Protein kinase C dela typePKCAP17529Protein kinase C dela typePRCAP17938 <td>Phosphatidylinositol 4,5-bisphosphate 3-kinase</td> <td></td> <td>T 517 15</td> <td>27</td>	Phosphatidylinositol 4,5-bisphosphate 3-kinase		T 517 15	27
Insulin receptor substrate i IEF INTERNATION INTERNATIONI INTERNATION INTERNAT	catalytic subunit gamma isoform	PIK3CG	P48736	24
LepinLEPP4115922Mitogen-activated protein kinse 1MAPK1P2848222Perotsione profiferator activated receptor gammaPPARGP3723121GlucagonGCGP0117517Prostaglandin G/H synthase.P76S2P333417Nitri-coide synthase, endotheliaNOS3P2947416Proshglutifity for galaxie regulatory subunitP1K3R1P2796616aphaApptois regulator Bc1-2BCL2P1041515Extreger receptorESR1P0337215Insulin receptorINSRP0611315Mitogen-activated protein kinase 14MAPK14Q1639913Provisione profiferator-activated receptor alphaPPARGQ97UBK213Peroxisome profiferator-activated receptor alphaPPARAQ0786913Peroxisome profiferator-activated receptor gammaPPARGCIAQ97UBK213Peroxisome profiferator-activated receptor gammaPPARGCIAQ97UBK213Peroxisome profiferator-activated receptor gammaPPARGCIAQ97UBK213Peroxisome profiferator-activated receptor gammaPPARGCIAQ97UBK213Peroxisome profiferator-activated receptor alphaPPARAQ0786913Heme oxygenase 1SUR11Q96011115Soluce carrier faith 22CCL2P135001010Protein kinase 2CCL2P135001010Protein kinase 2MIPPP1477801010 <t< td=""><td>Insulin receptor substrate 1</td><td>IRS1</td><td>P35568</td><td>22</td></t<>	Insulin receptor substrate 1	IRS1	P35568	22
Mitogen-activated protein kinase 1MAPK1P2848222Proxisone profilerator activated receptor gammaPPARGP9733121Tumor necrosis factorGCGP0137520GlucagonGCGP0137520Prostaglandin G/H synthase 2PTGS2P333417Nitric-oxide synthase, endothelialNOS3P2847416Phosphatidylinositol 3-kinase regulatory subunitPIK3R1P2798616JaphaDRSRP0621315Insulin receptorESR1P0337215Insulin receptorISR1P033915Insulin receptorIL84MAPK14Q01633915Interlexin, 4MAPK3P2236115Provisome profiferator-activated receptor alphaPPARGAQ90786913Provisome profiferator-activated receptor agamaPPARGAQ90786913Portosiome profiferator-activated receptor gammaPPARGAQ90786914Solute carrier family 2, facilitator diguose transporterSLC2A4P1467211C C motif chemokine 2CCL2P135001010ProtornobinF2P007341010NAD -dependent protein deactylase sirtuin-1SIRT1Q96E8610NAD -dependent protein in	Leptin	LEP	P41159	22
Perokisone proliferator activated receptor gamma PPARG P37231 21 Timor necrosis factor TNF P01375 20 Glucagon CCG P01275 17 Prostaglandin G/H synthase 2 P7SS2 P3S34 17 Nitri-oxide synthase, endothelial NOS3 P2474 16 Phosphatidylinoutiol 3-kinase regulatory submit PIK3R1 P27986 16 Japha Apoptosis regulator R4-2 BCL2 P10415 15 Extrogen receptor FSR1 P03372 15 Insuln receptor INSR P06213 15 Mitogen-activated protein kinase 14 MAPK14 Q16539 15 Mitogen-activated protein kinase 3 MAPK3 P27361 15 Interlexikn-4 P2786 92361 11 Soluc carrier family 2, facilitate glucose transporter SLC2A4 P14672 11 C-C motif chemokine 2 CCL2 P15500 10 Protornobin P2 P0875 9 P104700 10 Protein kinase C della type P187CD 096655 10 ND d-gendenic protein acetylase situin-1 SIREF1 P36956 10 Androgen receptor AR LEPR P4857 9 I -Piosphatidylinostol 4.5 bisphosphate PLCG1 P19174 9 Protein kinase C della type P187CD 94555 9 I -Piosphatidylinostol 4.5 bisphosphate PLCG1 P19174 9 Protein kinase C dalla type P1771 9 P1791 P18831 9 Actry-CoA carboxylase ILEPR P4857 9 I -Piosphatidylinostol 4.5 bisphosphate C PLCG1 P19174 9 Protein kinase C dalla type P1771 9 P1791 P18931 9 Acty-CoA carboxylase ILEPR P4877 9 I -Piosphatidylinostol 4.5 bisphosphate C PLCG1 P19174 9 Protein kinase C dalla type P1878 9 P17051 P171 9 P18051 9 P17051 9 P1705	Mitogen-activated protein kinase 1	MAPK1	P28482	22
Tamor necrosis factorTNFP0137520GlocagonGCGP0127517Prostaglandin G/H synthase 2PTGS2P333417Nitric-oxide synthase, endothelialNOS3P2947416Phosphatidylinositol 3-kinase regulatory subunitPK3R1P2798616alphaPK3R1P037215Istrogen receptorESR1P037215Insulin receptorESR1P037215Indigen activated protein kinase 3MAPK14Q1653915Mitogen activated protein kinase 4MAPK14Q0151913Proxisome proliferator-activated receptor aphaPPARGCLAQ90786913Proxisome proliferator-activated receptor gammaPPARGCLAQ90786913Portoxione roliferator-activated glacose transporterSLC2A4P1467211Solute carrier family 2, facilitated glacose transporterSLC2A4P1467211Solute carrier family 2, facilitated glacose transporterSLC2A4P1467210ProthornobinF2P007341010ProthornobinF2P007341010NaD dependent protein deacetylase sirtuin-1SIRTIQ96E8610NAD dependent protein deacetylase sirtuin-1SIRTIQ96E8610NAD dependent protein deacetylase sirtuin-1SIRTIQ96E8610NAD dependent protein deacetylase sirtuin-1SIRTIQ96E8610NAD dependent protein face tylase sirtuin-1SIRTIQ96E8610 <tr< td=""><td>Peroxisome proliferator activated receptor gamma</td><td>PPARG</td><td>P37231</td><td>21</td></tr<>	Peroxisome proliferator activated receptor gamma	PPARG	P37231	21
GlucagonGCGP0127517Prostaglandin G/H synthase 2PTGS2P3354417Nitri-oxide synthase, endothelialNOS3P2947416alphaProsphatidylnostiol 3-kinase regulatory subunitPTGS2P1041515alphaBCL2P104151515Estrogen receptorFSR1P0337215Insulin receptorINSRP0621315Mitogen-activated protein kinase 14MAPK14Q1653915Interleukin -4P27861314Peroxisome profilerator-activated receptor alphaPPARAQ0786913Peroxisome profilerator-activated receptor gammaPPARAQ9UBK213Concurritor 1-alphaPAAGC1AQ9UBK211Heme oxygenase 1HMOX1P0960111Solut carrier family 2, facilitate glucose transporterSLC2A4P1467211member 4CCCCL2P1300010Proteinkinase C delia typePRKCDQ0565510ND-dependem protein dacetylase sirtuin-1SIRT1Q96F8610Sterol regulatory element-binding protein 1SREFF1P3695610Adrogen receptorARLEPRP483579Ploophadietstrase gamma-1PICCGP19749Potein kinase C alpha typePRKCAP17529Potein kinase C alpha typePRKCAP17529Potein kinase C alpha typePRKCAP17529Protein kinase C alpha typePRKCA	Tumor necrosis factor	TNF	P01375	20
Prostaglandin G/H synthase 2 PTGS2 P3354 17 Mitric-oxide synthase, endothelial NOS3 P3474 16 Phosphatidylinositol 3. kinase regulatory subunit p1K3R1 P27986 16 Apoptosis regulator Bcl-2 BCL2 P10415 15 Estrogen receptor FSR1 P03372 15 Insulin receptor Kinase 14 MAPK14 Q16539 15 Mitogen-activated protein kinase 14 MAPK14 Q16539 15 Interleukin-4 IL4 P05112 14 Peroxisome profilerator-activated receptor alpha PPARA Q07869 13 Peroxisome profilerator-activated receptor agama PPARGC1A Q9UBK2 13 Herne oxygenase 1 HMOX1 P09601 11 Solute carrier family 2, facilitated glucose transporter MMOX1 P09601 10 Protonionin P12 P00734 100 Matrix metaloproteinase -9 MMP9 P14780 10 Protonionin P12 P00734 10 Matrix metaloproteinase -9 MMP9 P14780 10 Protonionin P12 P00734 10 Matrix metaloproteinase -9 MMP9 P14780 10 Protonionin P12 P00734 10 Matrix metaloproteinase -9 MMP9 P14780 10 Protonionin P2 P00734 10 Matrix metaloproteinase -9 MMP9 P14780 10 Protonic kinase C delta type PRKCD Q05635 10 ND-dopendeminositi 4,5-bisphosphate P1CG 1 P1974 9 Protonic kinase C delta type PRKCA P17252 9 Protonic kinase C delta type PRKCB P0577 9 Leptin receptor LEP-R LEPR P1873 9 Patotic kinase C heat type PRKCB P0577 9 Leptin receptor LEP-R P1874 9 Protonic kinase C heat type PRKCB P0577 9 Leptin receptor ALPARA RXRA P19733 9 Acetyl-CA C ACI3083 8 Tumo necrosis factor ligand superfamily member 6 FASLG P18973 9 Protoin kinase C heat type PRKCA P1755 6 Glucokinase C heat type PRKCA P1755 6 Glucokinase catalytic subunit PRKAA1 Q11311 7 Glucose-6-phosphatase catalytic subunit PRKAA2 P54466 6 Glucokinase C eption	Glucagon	GCG	P01275	17
Nitric oxide synthase, endothelialNOS3P2947416alphaPIK3RIP2798616alphaBCL2P1641515Estrogen receptorESR1P0337215Insulin receptorINSRP0621315Mitogen-activated protein kinase 14MAPK14Q1653915Mitogen-activated protein kinase 3MAPK3P2736115Interleukin 4IL4P0511214Peroxisome proliferator-activated receptor gammaPPARAQ0786913Peroxisome proliferator-activated glucose transporterSLC2A4P1467211Memo sygenase 1EZP007341010ProthrambinF2P007341010Prothinkanes C delta typePRKCDQ0565510NDA-dependent protein 1SREBF1P3695610Androgen receptorARP102759Protein kinase C alpha typePRKCAP17329Protein kinase C alpha typePRKCAP17339<	Prostaglandin G/H synthase 2	PTGS2	P35354	17
Phosphatdylinostiol 3-kinase regulatory subunit phosphatdylinostiol 4-kinase regulatory subunit Apoptosis regulator Bel-2 Brogen receptor Estragen receptor Insulin receptor Insulin receptor NNR P06213 Insulin receptor NNR P06213 Interleukin-4 Protein kinase 14 MAPK14 Q16539 Interleukin-4 Protein kinase 3 MAPK3 PPARG Q07869 Interleukin-4 Peroxisome proliferator-activated receptor alpha PPARG AQ07869 POBME Peroxisome proliferator-activated receptor alpha PPARG AQ07869 POBME Peroxisome proliferator-activated receptor gamma PPARGC1A POBME Peroxisome proliferator-activated receptor gamma PPARGC1A POBME Peroxisome proliferator-activated receptor gamma PPARGC1A POBME POBME POBME POBME PARGC1A POBME POBME POBME POBME PARGC1A POBME POBME POBME PARGC1A POBME POBME POBME PARGC1A POBME POBME POBME PARGC1A POBME POBME POBME PARGC1A POBME POBME PARGC1A POBME POBME PARGC1A POBME POBME PARGC1A POBME POBME PARGC1A POBME PARGC1A POBME POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A POBME PARGC1A PISOPA PARGC1A PISOPA PARGC1A PISOPA PARGC1A PISOPA PARGC1A PISOPA PARGC2 PISOPA PARGC3 PISOPA PISOPA PARGC3 PISOPA PISOPA PISOPA PARGC3 PISOPA	Nitric-oxide synthase, endothelial	NOS3	P29474	16
appa approximate and the second secon	Phosphatidylinositol 3-kinase regulatory subunit	PIK3R1	P27986	16
Appinos regulator here2 be12 profiles and here2 be12 profiles and here2 between the set of the set	Apontosis regulator Rel 2	PCI 2	D10415	15
Lategen receptor ten insuin receptor in Kins (C)	Estrogen recentor	DCL2 ESD 1	P10415 D03372	15
Intam ICCP 00 Transfer 1 (2015) 12 (2015) 13 (2015) 15 (2015) 14 (2015) 15 (	Insulin receptor	INSP	P06213	15
Integrinativated protein kinase 3 MAPK3 P27361 15 Interleakin-4 IL4 P05112 14 Peroxisome proliferator-activated receptor gamma PARGC1A Q9UBK2 13 Peroxisome proliferator-activated receptor gamma PARGC1A Q9UBK2 13 Peroxisome proliferator-activated receptor gamma PARGC1A Q9UBK2 13 Heme oxygenase 1 HMOX1 P09601 11 C-C motif chemokine 2 CCL2 P13500 10 C-C motif chemokine 2 CCL2 P13500 10 Prothrombin P2 P00734 10 Matrix metalloproteinase-9 MMP9 P14780 10 Prothrombin P2 P00734 10 Matrix metalloproteinase-9 MMP9 P14780 10 Protein kinase C delta type PRKCD Q05655 10 NAD-dependent protein deacetylase sirtuin-1 SIRT1 Q96EB6 10 Sterol regulatory element-binding protein 1 SREFIP P36956 10 Androgen receptor LEP R LEPR P48357 9 1-Phosphatikylinositol 4.5-bisphosphate PLCGI P1974 9 Protein kinase C alpha type PRKCA P17252 9 Protein kinase C alpha type PRKCA P1733 8 Tumor necrosis factor ligand superfamily member 6 FASIG P48033 8 Tumor necrosis factor ligand superfamily member 6 FASIG P48023 8 Tumor necrosis factor ligand superfamily member 6 FASIG P48023 8 Tumor necrosis factor ligand superfamily member 6 FASIG P48023 8 Tumor necrosis factor ligand superfamily member 6 FASIG P48023 8 Tumor necrosis factor kapa-8 kinase subunit IKBKB 014920 7 Nitric coide synthase, inducible NOS2 P35228 7 5-Hydroxytryptamine receptor 2C (by homology) HTR2C P28335 6 5-Hydroxytryptamine receptor 2A (by homology) HTR2A P28233 5 5-Hydroxytryptamine receptor 2A (by homology) HTR2A P28233 5 5-Hydroxytryp	Mitogen activated protein kinase 14	MADK1/	016539	15
Interieukin-4Interieukin-4Interieukin-4Peroxisome proliferator-activated receptor gamma Peroxisome proliferator-activated receptor Protin kinase C dela type PerkCD PerkCD PerkCD Possione protein deacetylase sirtuin-1 StRIT Protein kinase C dela type PerkCD PerkCD PerkCD Possione protein deacetylase sirtuin-1 StRIT PerkED PerkECA Possione protein deacetylase sirtuin-1 Protein kinase C alpha type PerkCA PerkCA Protein kinase C alpha type PerkCA PerkCA Protein kinase C alpha type PerkCA PerkCA Protein kinase C alpha type PerkCA PerkCA Pervetin phosphatase nonreceptor type PerkCA Pervetin kinase-3 beta Cachocylase 1 Pervetin kinase-3 beta Pervetin kinase c alpha type- PerkCA PerkCA Pervetin phosphatase nonreceptor type 1 PerkVI PerkVI Pervetin kinase-3 beta PerkCB PerkCB Portein kinase-3 beta PerkCB Portein kinase-3 beta PerkCA PerkCB Portein kinase-3 beta PerkCA PerkCB Portein kinase-3 beta PerkCA PerkCA PerkCA PerkCB PerkCA PerkCB PerkCA PerkC	Mitogen-activated protein kinase 3	MAPK3	P27361	15
Provisione proliferator-activated receptor alpha PPARA Q07869 13 Peroxisome proliferator-activated receptor gamma PPARGCIA Q9UBK2 13 Peroxisome proliferator-activated receptor gamma PPARGCIA Q9UBK2 13 Heme oxygenase 1 HMOX1 P0600 11 Solute carrier family 2, facilitated glucose transporter KIX P14672 11 C.C. motif chemokine 2 CCL2 P13500 10 Prothrombin E2 P00734 10 Matrix metalloproteinase-9 MMP9 P14780 10 Prothrombin P2 PRKCD Q05655 10 NAD-dependent protein deacetylase sirtuin-1 SIRTI Q96EB6 10 Sterol regulatory element-binding protein 1 SREEFI P36956 10 Androgen receptor LEP-R LEPR P48357 9 1-Phosphatidyfinositol 4,5-bisphosphate PICCG1 P19174 9 Protein kinase C alpha type PRKCA P17252 9 Protein kinase C alpha type PRKCA P17252 9 Protein kinase C bata type PRKCA P17252 9 Protein kinase C alpha type PRKCA P17252 9 Protein kinase C alpha type PRKCA P17252 9 Protein kinase C alpha type PRKCA Q13085 8 Turmor nerrosis factor ligand superfamily member 6 FASLG P48033 8 Furnor nerrosis factor ligand superfamily member 6 FASLG P48033 8 Furnor nerrosis factor ligand superfamily member 6 FASLG P48033 8 Glucogen synthase kinase-3 beta G5K3B P49841 7 Inhibitor of nuclear factor kapa-8 kinase subunit KEKE 014920 7 Nitric oxide synthase, inducible NOS2 P35228 7 S'-AMP-activated protein kinase catalytic subunit PKKAA1 Q13131 7 Glucose-6 phosphatase Glucose-6 phosphatase catalytic subunit PRKAA2 P54646 6 Glucose-6 phosphatase G6FC P35575 6 S'-MProstrix kinase catalytic subunit PRKAA2 P54646 6 Glucose-6 phosphatase G5K3B P49841 7 Inhibitor of nuclear factor kapa-8 kinase subunit HTR2C P28335 6 S'-AMP-activated protein kinase catalytic subunit PRKAA2 P54646 6 Glucose-6 phosphatase G6FC P35575 5 S-Glucokinase G7 GCK P35575 5 S-Hydroxytryptamine receptor 2A (by homology) HTR2A P28233 5 S-Hydroxytryptamine recepto	Interleukin-4	II 4	P05112	13
Peroxisone proliferator-activated receptor gamma PPARGCIA Q9UBK2 13 Peroxisone proliferator-activated receptor gamma PPARGCIA Q9UBK2 13 Heme oxygenase 1 Solute carrier family 2, facilitated glucose transporter SLC2A4 P14672 11 Solute carrier family 2, facilitated glucose transporter SLC2A4 P14672 11 C-C motif chemokine 2 CCL2 P13500 10 Prothrombin E2 P00734 10 Matrix metalloproteinase-9 MMP9 P14780 10 Protein kinase C delta type PRKCD Q05655 10 ND-dependent protein deacetylase sirtuin-1 SIRT1 Q96EB6 10 Sterol regulatory element-binding protein 1 SREBF1 P36956 10 Androgen receptor AR P10275 9 Leptin receptor, LEP-R LEPR P48357 9 1-Phosphatidylinositol 4,5-bisphosphate PLCGI P19174 9 Protein kinase C abla type PRKCB P05771 9 Protein kinase C beta type PRKCB Q02156 8 Tumor necrosis factor ligand superfamily member 6 PASLG P48023 8 Tumor necrosis factor ligand superfamily member 6 PASLG P48023 8 Tumor necrosis factor ligand superfamily member 6 PASLG P48023 8 Tumor necrosis factor ligand superfamily member 6 PASLG P48023 8 Tumor necrosis factor kappa-B kinase subunit IKBKB 014920 7 S'-AMP-activated protein kinase catalytic subunit PKKAA1 Q13131 7 eta Mite oxide synthase, inducible NOS2 P35228 7 S'-AMP-activated protein kinase catalytic subunit PKKAA1 P189793 5 S-Hydroxytryptamine receptor 2C (by homology) HTR2A P28375 5 S-Hydroxytryptamine receptor 2C (by homology) HTR2A P28323 5 S-Hydroxytryptamine receptor 2A (by homology) HTR2A P3855 5 S-Hydroxytryptamine receptor 2A (by homology	Perovisome proliferator-activated receptor alpha	PPARA	007869	13
Coactivator 1-alphaPPARCCIAQ9UBR213Heme oxygenase 1HMOX1P0960111Heme oxygenase 1HMOX1P0960111Coccentric chemokine 2CCL2P1350010ProthombinF2P0073410ProthombinF2P0073410Prothin Kinase C delta typePRKCDQ0565510NAD-dependent protein deacetylase sirtuin-1SIRT1Q96EB610Sterol regulatory element-binding protein 1SREBF1P3695610Adrogen receptorARP1077591Leptin receptor, LEP-RLEPRP4355799Leptin receptor, LEP-RLEPRP4355799Protein kinase C alpha typePRKCAP1725299Protein kinase C alpha typePRKCAP1725299Protein kinase C beta typePRKCAP1725299Protein kinase C alpha typePRKCAP1725299Protein kinase C alpha typePRKCAP1725299Tumor necrosis factor ligand superfamily member 6FASLGP4802388Protein kinase C beta typePRKCBQ0215688Glycogen synthase kinase: albeitIKBKBQ1492077Nitric oxide synthase kinase: albeitIKBKBQ149207Nitric oxide synthase kinase: albeit subunitPRKAA1Q131317Glycogen synthase kinase: albeit subunitPRKAA1Q13131 <t< td=""><td>Peroxisome proliferator-activated receptor apria</td><td>1171101</td><td>20/009</td><td>15</td></t<>	Peroxisome proliferator-activated receptor apria	1171101	20/009	15
Heme expenses 1HMOX1P0960111Solute carrier family 2, facilitated glucose transporter member 4SLC2A4P1467211Solute carrier family 2, facilitated glucose transporter member 4SLC2A4P1467211C-C motif chemokine 2CC1.2P1350010ProthrombinF2P0073410Matrix metalloproteinase-9MMP9P1478010NAD-dependent protein deacetylase sirtuin-1SIRT1Q96EB610Sterol regulatory element-binding protein 1SREBF1P3695610Androgen receptorARP102759Leptin receptor, LEP-RLEPRP483579L-Phosphatdiylinositol 4,5-bisphosphateP102759Protein kinase C alpha typePRKCAP12529Protein kinase C beta typePRKCBP057719Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Acteryl-CoA carboxylase 1ACACAAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Tortein kinase C epsilon typeQRKCEQ021568Glucose-6-phosphataseGGPCP3557565'-AMP-activated protein kinase catalytic subunitRKKA1Q131317Glucose-6-phosphataseGGPCP3557555-Hydroxytryptamine receptor 2C (by homology)HTR2AP2823355-Hydroxytryptamine receptor 2C (by homology)HTR2AP2823355-Hydroxytryptamine receptor 2	coactivator 1-alpha	PPARGC1A	Q9UBK2	13
Solute carrier family 2, facilitated glucose transporter member 4SLC2A4P1467211C-C motif chemokine 2CCL2P1350010ProthenkinseF2P0073410Matrix metalloproteinase-9MMP9P1478010NAD-dependent protein deacetylase sirtuin-1SIRTIQ96EB610Sterol regulatory element-binding protein 1SREBF1P3695610Adrogen receptorARP102759Leptin receptor, LEP-RLEPRP4835791-Phosphatidylinositol 4.5-bisphosphatePLCGIP191749phosphodiesterase gamma-1PRKCAP172529Protein kinase C dalpa typePRKCAP172529Protein kinase C beta typePRKCBP057719Protein kinase C beta typePRKCBP197339Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor figand superfamily member 6FASLGP480238Protein kinase C esplon typePRKCEQ011568Glycogen synthase, inducibleNOS2P3522875'-MP-activated protein kinase catalytic subunit alpha-1PRKAA1Q131317Glucoace-6-phosphataseG6PCP3557565'-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-MP-activated protein kinase catalytic subunit alpha-2PKAA2P546466GlucokinaseGCKP355755GlucokinaseGCKP355755 <td>Heme oxygenase 1</td> <td>HMOX1</td> <td>P09601</td> <td>11</td>	Heme oxygenase 1	HMOX1	P09601	11
member 4SUC2A4P1872P1872C-C motif chemokine 2CCL2P1350010C-C motif chemokine 2CCL2P1350010Matrix metalloproteinase-9MMP9P1478010MAtrix metalloproteinase-9PRKCDQ0565510NAD-dependent protein deacetylase sirtuin-1SIRTIQ96EB610Sterol regulatory element-binding protein 1SREBF1P3695610Androgen receptorLP-RLEPRP483579Leptin receptor, LEP-RLEPRP483579L-Phosphatidylinositol 4.5-bisphosphateP10CG1P191749Protein kinase C alpha typePRKCAP172529Protein kinase C beta typePRKCBP057719Protein kinase C beta typePRKCBP057719Protein kinase C beta typePRKCBQ013058Tumor necrosis factor ligand superfamily member 6FASLGP480238Tortein kinase C epsilon typePRKKEEQ021558Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kapa-B kinase subunitIKBKBO149207Nitric oxide synthase, inducibleNOS2P352287S'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317GlucokinaseGCKP355756S'-Hydroxytryptamine receptor 2C (by homology)HTR2AP282335S'-MAP-activated protein kinase catalytic subunitPRKAA2P546466<	Solute carrier family 2, facilitated glucose transporter	SI COA A	D14672	11
C-C motif chemokine 2 CCL2 P13500 10 Prothrombin F2 P00734 10 Matrix metalloproteinase-9 MMP9 P14780 10 Protein kinase C delta type PRKCD Q05655 10 NAD-dependent protein deacetylase sirtuin-1 SIRT1 Q96EB6 10 Sterol regulatory element-binding protein 1 SREBF1 P36956 10 Androgen receptor AR P10275 9 Leptin receptor, LEP-R LEPR P48357 9 Leptin receptor, LEP-R LEPR P48357 9 Protein kinase C alpha type PKCCB P05771 9 Protein kinase C beta type PKKCA P1752 9 Tryosine-protein phosphatase nonreceptor type 1 PTPN1 P18031 9 Protein kinase C alpha type PKKCB P05771 9 Tyrosine-protein phosphatase nonreceptor type 1 PTPN1 P18031 9 Retinoic acid receptor RXR-alpha RXRA P19793 9 Acetyl-CoA carboxylase 1 ACACA Q13085 8 Tumor necrosis factor ligand superfamily member 6 FASLG P48023 8 Protein kinase C epsilon type PKKCE Q02156 8 Glycogen synthase kinase-3 beta GSK3B P48941 7 Inhibitor of nuclear factor kappa-8 kinase subunit KBKB 014920 7 S'-AMP-activated protein kinase catalytic subunit PKAA11 Q13131 7 Glucose-6-phosphatase (Ley homology) HTR2C P35575 6 S'-AMP-activated protein kinase catalytic subunit PRKAA2 P34646 6 Mittochondrial brown fat uncoupling protein 1 UCP1 P25874 6 Beta-2 drenergic receptor 2.0 (by homology) HTR2C P35575 5 S-Hydroxytryptamine receptor 2.0 (by homology) HTR2A P28223 5 S-Hydroxytryptamine receptor 2.0 (by homology) HTR2A P35578 5 HTR2B P41995 5 S-Hydroxytryptamine receptor 2.0 (by homology) HTR2A P38557 5 S-Hydroxytryptamine receptor 2.0 (by homology) HTR2A P38558 5 S-Hydroxytr	member 4	SLC2A4	P14072	11
ProthrombinF2P0073410Matrix metalloproteinase-9MMP9P1478010Protein kinase C delta typePRKCDQ0565510NAD-dependent protein deacetylase sirtuin-1SIRT1Q96EB610Sterol regulatory element-binding protein 1SIREBF1P3695610Androgen receptorARP102759Leptin receptor, LEP-RLEPRP483579-Phosphatidylinositol 4,5-bisphosphatePLCG1P191749phosphodiesterase gamma-1PLCG1P191739Protein kinase C alpha typePRKCAP172529Protein kinase C abta typePRKCBP057719Trosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glucose-6-phosphataseG6PCP352287S'-AMP-activated protein kinase catalytic subunitT11glucose-6-phosphataseG6PCP355756S'-Hydroxytryptamine receptor 2C (by homology)HTR2CP28336S'-MAP-activated protein kinase catalytic subunitT11glucosi-6-phosphataseGCKP3557555S-Hydroxytryptamine receptor 2A (by homology)HTR2AP36466 <t< td=""><td>C-C motif chemokine 2</td><td>CCL2</td><td>P13500</td><td>10</td></t<>	C-C motif chemokine 2	CCL2	P13500	10
Matrix metalloproteinase-9MMP9P1478010Protein kinase C delta typePKKCDQ0565510NAD-dependent protein deacetylase sirtuin-1SIRT1Q96EB610Sterol regulatory element-binding protein 1SREBF1P3695610Androgen receptorARP102759Leptin receptor, LEP-RLEPRP4835791-Phosphatidylinositol 4,5-bisphosphatePLCG1P191749phosphodiesterase gamma-1PKCAP175229Protein kinase C alpha typePKKCBP057719Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBQ149207Vitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317Glucose-6-phosphataseG6PCP3557565'-Mydroxytryptamine receptor 2A (by homology)HTR2AP2823355-Hydroxytryptamine receptor 2A (by homology)HTR2AP2823355-Hydroxytryptamine receptor 2A (by homology)HTR2AP3555855-Hydroxytryptamine receptor 2A (by homology)HTR2AP355585 <t< td=""><td>Prothrombin</td><td>F2</td><td>P00734</td><td>10</td></t<>	Prothrombin	F2	P00734	10
Protein kinase C delta type PRKCD Q05655 10 NAD-dependent protein deacetylase sirtuin-1 SIRTI Q96EB6 10 Sterol regulatory element-binding protein 1 SIRTI Q96EB6 10 Androgen receptor AR P10275 9 Leptin receptor, LEP-R LEPR P48357 9 1-Phosphatidylinositol 4,5-bisphosphate PLCG1 P19174 9 Protein kinase C alpha type PKCA P17252 9 Protein kinase C beta type PRKCB P05771 9 Tyrosine-protein phosphatase nonreceptor type 1 P17N1 P18031 9 Retinoic acid receptor XRR-alpha RXRA P19793 9 Acetyl-CoA carboxylase 1 ACACA Q13085 8 Tumor necrosis factor ligand superfamily member 6 FASLG P48023 8 Glycogen synthase kinase-3 beta GSK3B P49841 7 Inhibitor of nuclear factor kappa-B kinase subunit KBKB 014920 7 Nitric oxide synthase, inducible NOS2 P35228 7 5'-AMP-activated protein kinase catalytic subunit PRKAA1 Q13131 7 Glucose-6-phosphatase (G6PC P35575 6 5'-AMP-activated protein kinase catalytic subunit PRKAA1 Q13131 7 Glucose-6-phosphatase (G6PC P35575 6 5'-AMP-activated protein kinase catalytic subunit PRKAA1 Q13131 7 Glucose-6-phosphatase GG6PC P35575 6 5'-AMP-activated protein kinase catalytic subunit PRKAA2 P5464 6 Mitochondrial brown fat uncoupling protein 1 UCP1 P25874 6 Beta-2 adrenergic receptor 2A (by homology) HTR2A P28233 5 5'-AMP-activated protein kinase catalytic subunit PKAA2 P54646 5 Glycoximase GCK P35575 5 Glucokinase GCK P35575 5 Glucokinase GCK P35575 5 Flydroxytryptamine receptor 2A (by homology) HTR2A P28223 5 5-Hydroxytryptamine receptor 2A (by homology) HTR2A P28223 5 5-Hydroxytryptamine receptor 2A (by homology) HTR2A P28223 5 5-Hydroxytryptamine receptor 2A (by homology) HTR2A P35558 5 Flydroxytryptamine receptor 2	Matrix metalloproteinase-9	MMP9	P14780	10
NAD-dependent protein deacetylase sirtuin-1SIRTIQ96EB610Androgen receptorARP102759Leptin receptor, LEP-RLEPRP4835791-Phosphatidylinositol 45-bisphosphateP10759phosphodiesterase gamma-1PICGIP191749Protein kinase C balpa typePRKCAP172529Protein kinase C bat typePRKCAP172529Protein kinase C bat typePRKCAP170539Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207betaNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317alpha-1UCP1P258746Glucose-6-phosphataseGCKP355575Glucok-fordiral brown fat uncoupling protein 1UCP1P258746GlucokinaseGCKP3555755S-Hydroxytryptamine receptor 2A (by homology)HTR2AP282235S-Hydroxytryptamine receptor 2A (by homology)HTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolicPCK1P355585Protoxio	Protein kinase C delta type	PRKCD	Q05655	10
Sterol regulatory element-binding protein 1SREBF1P3695610Androgen receptorARP102759Leptin receptor, LEP-RLEPRP4835791-Phosphatidylinositol 4.5-bisphosphatePLCG1P191749phosphodiesterase gamma-1PLCG1P191749Protein kinase C alpha typePRKCAP172529Protein kinase C beta typePRKCBP057719Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207betaNOS2P35228755'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317Glucose-6-phosphataseG6PCP3557565'-Mydraxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunitPKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2GCKP35557555-Hydraxytryptamine receptor 2A (by homology)HTR2AP282355-Hydraxytryptamine receptor 2B<	NAD-dependent protein deacetylase sirtuin-1	SIRT1	Q96EB6	10
Androgen receptorARP102759Leptin receptor, LEP-RLEPRP4835791-Phosphatidylinositol 4,5-bisphosphatePLCG1P191749phosphodiesterase gamma-1PRKCAP172529Protein kinase C alpha typePRKCBP057719Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKB0149207Nitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317Glucose-6-phosphataseG6PCP3557565-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunitPKKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRA2P481255S-Hydroxytryptamine receptor 2A (by homology)HTR2AP28235S-Hydroxytryptamine receptor 2A (by homology)HTR2AP35585Forphosphoenolpyruvate carboxykinase, cytosolicPCKIP355585 <td>Sterol regulatory element-binding protein 1</td> <td>SREBF1</td> <td>P36956</td> <td>10</td>	Sterol regulatory element-binding protein 1	SREBF1	P36956	10
Leptin receptor, LEP-RLEPRP4835791-Phosphotidylinositol 4,5-bisphosphatePLCG1P191749phosphodiesterase gamma-1PLCG1P191749Protein kinase C alpha typePRKCAP172529Protein kinase C beta typePRKCBP057719Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207Nitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317Glucose-6-phosphataseG6PCP3557565'-MP-activated protein kinase catalytic subunitPRKAA2P546466alpha-1UCP1P2587466Mitochondrial brown fat uncoupling protein 1UCP1P2587555-Hydroxytryptamine receptor 2A (by homology)HTR2AP2823355-Hydroxytryptamine receptor 2A (by homology)HTR2BP4159559Phosphoenolpyruvate carboxykinase, cytosolicPCK1P3555859Presting PARDQ0318159Adenos	Androgen receptor	AR	P10275	9
1-Phosphatidylinostiol 4,5-bisphosphatePLCG1P191749phosphodicisterase gamma-1PRKCAP172529Protein kinase C alpha typePRKCBP057719Tyrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Glycogen synthase kinase C apsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207Stritic oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317alpha-1Glucose-6-phosphataseG6PCP3557565'-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunitPRKAA2P546466alpha-2GlucokinaseGCKP355575GlucokinaseGCKP355575S-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolicPCK1P355585CfTP)P2657ADORA1P305424Alpha-2A adrenergic receptor A1ADORA1P305424 </td <td>Leptin receptor, LEP-R</td> <td>LEPR</td> <td>P48357</td> <td>9</td>	Leptin receptor, LEP-R	LEPR	P48357	9
Protein kinase C alpha type PRKCA P17252 9 Protein kinase C beta type PRKCB P05771 9 Tyrosine-protein phosphatase nonreceptor type 1 PTPN1 P18031 9 Retinoic acid receptor RRR-alpha RXRA P19793 9 Acetyl-CoA carboxylase 1 ACACA Q13085 8 Tumor necrosis factor ligand superfamily member 6 FASLG P48023 8 Protein kinase C epsilon type PRKCE Q02156 8 Glycogen synthase kinase-3 beta GSK3B P49841 7 Inhibitor of nuclear factor kappa-B kinase subunit IKBKB 014920 7 Nitric oxide synthase, inducible NOS2 P35228 7 5'-AMP-activated protein kinase catalytic subunit PRKAA1 Q13131 7 Glucose-6-phosphatase G6PC P35575 6 5'-AMP-activated protein kinase catalytic subunit PRKAA2 P54646 6 S'-AMP-activated protein kinase catalytic subunit PRKAA2 P54646 6 Mitochondrial brown fat uncoupling protein 1 UCP1 P25874 6 Beta-2 adrenergic receptor 2A (by homology) HTR2A P28223 5 5-Hydroxytryptamine receptor 2A (by homology) HTR2B P41595 5 F-Hydroxytryptamine receptor 2B HTR2B P41595 5 F-Hydroxytryptamine receptor 4DRA2A P08913 4 Alpha-2A adrenergic receptor 4DRA2B P18089 4	1-Phosphatidylinositol 4,5-bisphosphate	PLCG1	P19174	9
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FixedFixedFixedFixedFixedTryrosine-protein phosphatase nonreceptor type 1PTPN1P180319Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207Vitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317alpha-1GGPCP3557565'-AMP-activated protein kinase catalytic subunitPRKAA2P5464665'-AMP-activated protein kinase catalytic subunitPRKAA2P546466alpha-2GGPCP3557555Hydroxytryptamine receptor 2C (by homology)HTR2CP2833555-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolicPCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894<	Protein kinase C alpha type	PRICA	P17232 D05771	9
Tristine-protection type 1FTFNFT80-19Retinoic acid receptor RXR-alphaRXRAP197939Acetyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207betaNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317alpha-1GfCCP3557565'-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunitPRKAA2P546466alpha-2GCKP3557555GlucokinaseGCKP35557555'-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355'-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolicPCK1P355585(GTP)P25874ADORA1P305424Adrenergic receptor A1ADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2BP180894	Turosina protain phosphatasa nonrecentor tura 1	P KKCD DTDN1	P03771 D18031	9
Initial active for receptor appliesInitialInitialInitialInitialAcctyl-CoA carboxylase 1ACACAQ130858Tumor necrosis factor ligand superfamily member 6FASLGP480238Protein kinase C epsilon typePRKCEQ021568Glycogen synthase kinase-3 betaGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKB0149207betaNOS2P352287S'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317alpha-1Glucose-6-phosphataseG6PCP3557565'-AMP-activated protein kinase catalytic subunitPRKAA2P546466alpha-2GCKP3555755Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolicPCK1P355585(GTP)PCK1P3555855Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	Retinoic acid receptor RXR-alpha	RXRA	P19793	9
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Initial inclusion lactor lactor is a primiter of the initial of t	Tumor necrosis factor ligand superfamily member 6	FASIG	P48023	8
Arton MinorReferenceGSK3BP498417Inhibitor of nuclear factor kappa-B kinase subunitIKBKBO149207Nitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunitPRKAA1Q131317alpha-1GGKCP3557565'-AMP-activated protein kinase catalytic subunitPRKAA2P2833565'-AMP-activated protein kinase catalytic subunitPRKAA2P546466alpha-2CP1P2587466GGKCP3557556GGKP3557555Glucose-ceptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunitPRKAA2P546466alpha-2GGKP35575556GGKP35575556GGKP35575557GGKP35575557GGKP35575557GGKP35575559SGGKP3557555-Hydroxytryptamine receptor 2A (by homology)HTR2BP4159559Phosphoenolpyruvate carboxykinase, cytosolicPCK1P3555859Phosphoenolpyruvate carboxykinase, cytosolicPCK1P3555859Peroxisome proliferator-activated receptor deltaPARDQ031815Adenosine receptor A1ADORA1P305424<	Protein kinase C ensilon type	PRKCE	O02156	8
OrderOrderOrderOrderInhibitor of nuclear factor kappa-B kinase subunit betaIKBKBO149207Nitric oxide synthase, inducibleNOS2P352287S'-AMP-activated protein kinase catalytic subunit alpha-1PRKAA1Q131317Glucose-6-phosphataseG6PCP3557565'-AMP-activated protein kinase catalytic subunit alpha-1PRKAA2P2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPDARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	Glycogen synthase kinase-3 beta	GSK3B	P49841	7
betaIKBKBOl 49207Nitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunit alpha-1PRKAA1Q131317Glucose-6-phosphataseG6PCP3557565'-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	Inhibitor of nuclear factor kappa-B kinase subunit			_
Nitric oxide synthase, inducibleNOS2P3522875'-AMP-activated protein kinase catalytic subunit alpha-1PRKAA1Q131317Glucose-6-phosphataseG6PCP3557565'-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Witochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	beta	IKBKB	O14920	7
5'-AMP-activated protein kinase catalytic subunit alpha-1PRKAA1Q131317Glucose-6-phosphataseG6PCP3557565-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	Nitric oxide synthase, inducible	NOS2	P35228	7
alpha-1CHARMANCHARMANCHARMANGlucose-6-phosphataseG6PCP3557565-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	5'-AMP-activated protein kinase catalytic subunit	PRKAA1	013131	7
Glucose-6-phosphataseG6PCP3557565-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	alpha-1	I KKAAI	Q15151	7
5-Hydroxytryptamine receptor 2C (by homology)HTR2CP2833565'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	Glucose-6-phosphatase	G6PC	P35575	6
5'-AMP-activated protein kinase catalytic subunit alpha-2PRKAA2P546466Mitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2B adrenergic receptorADRA2BP180894	5-Hydroxytryptamine receptor 2C (by homology)	HTR2C	P28335	6
alpha-2InternalPotenceMitochondrial brown fat uncoupling protein 1UCP1P258746Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolicPCK1P355585(GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptorADRA2BP180894	5'-AMP-activated protein kinase catalytic subunit	PRKAA2	P54646	6
Mitochondrial brown fat uncoupling protein 1UCP1P258/46Beta-2 adrenergic receptorADRB2P075505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptorADRA2BP180894	alpha-2		Descrit	,
Beta-2 adrenergic receptorADRB2P0/5505GlucokinaseGCKP3555755-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894	Mitochondrial brown fat uncoupling protein 1	UCP1	P25874	6
GlucokinaseGCKP3555/55-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894	Beta-2 adrenergic receptor	ADRB2	P0/550	5
5-Hydroxytryptamine receptor 2A (by homology)HTR2AP2822355-Hydroxytryptamine receptor 2BHTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894		GCK	P3555/	5
S-Frydroxytryptamine receptor 2BFTR2BP415955Phosphoenolpyruvate carboxykinase, cytosolic (GTP)PCK1P355585Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894	5-Hydroxytryptamine receptor 2A (by nomology)	HIK2A UTD2D	P28223	5
Prosphoenopyruvate carboxykinase, cytosonePCK1P355585(GTP)Peroxisome proliferator-activated receptor deltaPPARDQ031815Adenosine receptor A1ADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894	Desphaenolpuruwata carboxylringga gytagolia	ПТК2В	P41595	5
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Adenosine receptor AlADORA1P305424Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894	Peroxisome proliferator-activated receptor delta	PPARD	003181	5
Alpha-2A adrenergic receptor (by homology)ADRA2AP089134Alpha-2B adrenergic receptorADRA2BP180894	Adenosine receptor A1	ADORA1	P30542	4
Alpha-2B adrenergic receptorADRA2BP180894	Alpha-2A adrenergic receptor (by homology)	ADRA2A	P08913	4
	Alpha-2B adrenergic receptor	ADRA2B	P18089	4

TABLE 3: Continued.

Protein name	Gene name	Unipro ID	PPI network degree
Alpha-2C adrenergic receptor	ADRA2C	P18825	4
D(2) dopamine receptor (by homology)	DRD2	P14416	4
Hepatocyte nuclear factor 1-alpha	HNF1A	P20823	4
Mitogen-activated protein kinase 10	MAPK10	P53779	4
Glucocorticoid receptor	NR3C1	P04150	4
Acyl-CoA desaturase	SCD	O00767	4
Solute carrier family 2, facilitated glucose transporter member 1	SLC2A1	P11166	4
Mitochondrial uncoupling protein 2	UCP2	P55851	4
Carnitine O-palmitoyltransferase 1, liver isoform	CPT1A	P50416	3
D(1A) dopamine receptor	DRD1	P21728	3
3-Hydroxy-3-methylglutaryl-coenzyme A reductase	HMGCR	P04035	3
Prostacyclin receptor	PTGIR	P43119	3
Superoxide dismutase (Cu-Zn)	SOD1	P00441	3
Aldose reductase	AKR1B1	P15121	2
Cyclin-dependent-like kinase 5	CDK5	Q00535	2
Aromatase	CYP19A1	P11511	2
Corticosteroid 11-beta-dehydrogenase isozyme 1	HSD11B1	P28845	2
Transcription factor AP-2-alpha	TFAP2A	P05549	2
Vitamin D3 receptor	VDR	P11473	2
Angiotensin-converting enzyme	ACE	P12821	1
Dipeptidyl peptidase 4	DPP4	P27487	1
Prostaglandin G/H synthase 1	PTGS1	P23219	1





FIGURE 3: GO functional annotation and KEGG analysis of 76 target genes. Biological process (a), molecular function (b), cellar components (c), and KEGG pathways (d) were sorted according to  $-\log P$  values (P < 0.01). P value was calculated using a modified Fisher exact test, which ranges from 0 to 1. P value = 0 represents perfect enrichment. For each diagram, the x-axis presents GO or KEGG terms, whereas the y-axis is the  $-\log P$  value of each term.

Tumor necrosis factor (TNF) is a cytokine that could be secreted by macrophages and adipose cells. It can induce IR by downregulation of the activity of PI3K/Akt signaling pathway. It has also been reported that MAPK and NF- $\kappa$ B signaling pathways are stimulated by TNF and further regulates inflammatory response, oxidative stress, and apoptosis [31].

As shown in KEGG pathway analysis, 23 out of 76 targets were found to participate in IR, ranking no. 1 according to its –log *P* value. Other pathways on the KEGG list were adipocytokine pathway, AMPK pathway, insulin pathway, T2DM, FoxO pathway, NAFLD, etc. And, this finding was further approved by the C-T-P network. All of these signaling pathways are all highly related to IR. Thus, we could make a preliminary inference from this result that the most important mechanism of XKYS formula in the treatment of T2DM may be reducing IR.

IR is a condition in which the target organs are insensitive to insulin. Long-term of unhealthy diet and lacking exercises could cause overweight or even obesity. Overweight or obese patients are in metabolic disorder states with excessive fat accumulation [35]. Some experts had put forward a hypothesis that obesity is a chronic condition of inflammation [36]. Adipocytokines like TNF and interleukin-6 (IL-6) could inhibit the binding of insulin receptor (InsR) and insulin receptor subunit (IRS). IRS would be degraded under such conditions. In addition, inflammation response and oxidative stress interact as both cause and effect, causing the damage of islet  $\beta$ -cells and diabetic microangiopathy and then leading to the onset of T2DM and its complications [37]. Moreover, the activity of AMPK in skeletal muscles and liver reduces in IR conditions, causing decreased oxidation of free fatty acids and a lower intake of glucose, which in turn deteriorating glycemic control [38]. The FoxO pathway is one of those key factors in the transition from IR to the damage of islet  $\beta$ -cells. The dysfunction of  $\beta$ -cells is caused by various factors, including oxidative stress and inflammatory response. The FoxO pathway is highly related to the risk factors mentioned above [39].

In addition, the pathway in cancer was also an important pathway enriched in the C-T-P network (Figure 4). For one thing, diabetes is a risk factor for carcinogenesis due to hyperinsulinemia, hyperglycemia, and fat-induced chronic inflammation [40]. For another, components in XKYS formula like isoquinoline alkaloids and cucurbitane-type triterpenoids were reported to possess antitumor activities through pathways participating in the pathophysiology of



FIGURE 4: Component-target-pathway network of XKYS formula in the treatment of T2DM and its complications. Nodes in red are considered as important, and the green nodes are considered as less important. The degree of each node was presented in Supplementary Materials Table S3.

both diabetes and cancer [41, 42]. Thus, such correlation was also presented in C-T-P network.

It should also be noted that the PI3K/Akt signaling pathway is also regarded as a key regulator in the development of diabetic complications [29]. And, among those pathways enriched, the hypoxia-inducible factor 1 (HIF-1) pathway and vascular endothelial growth factor (VEGF) pathway are considered to be important factors involved in the development of diabetic complications [43, 44].

The network-based pharmacological analysis has shown that XKYS formula could regulate the glucose and lipid metabolism and alleviate IR mainly through insulin, AMPK, adipocytokine, and FoxO pathway. And, this formula could also be used in the treatment of diabetic complications due to its effect on PI3K/Akt, HIF-1, and VEGF pathways.

This study provided an overview on the antidiabetic effects of XKYS formula in a holistic manner. However, in vivo and in vitro experiments are required to offer more information about the mechanisms of XKYS formula.

# 5. Conclusion

Components in XKYS formula mainly regulate proteins including Akt, PI3K, IRS, and TNF. XKYS formula exerts

therapeutic effects in a synergetic manner and exhibits antidiabetic effect mainly via reducing IR. These findings could be guidelines in the further investigation of this formula.

#### Abbreviations

AKI:	Protein kinase B
AMPK:	Adenosine 5'-monophosphate (AMP)
	activated protein kinase
BME:	Bitter melon extract
CaMKKβ:	Calcium/calmodulin-dependent protein
	kinase kinase beta
CSE:	Cassiae Semen extract
DM:	Diabetes mellitus
FoxO:	Forkhead box protein O
GO:	Gene ontology
HIF-1:	Hypoxia-inducible factor 1
InsR:	Insulin receptor
IR:	Insulin resistance
IRS:	Insulin receptor subunit
KEGG:	Kyoto encyclopedia of genes and genomes
LRP:	Liriopes radix polysaccharides
mTOR:	Mammalian target of rapamycin

NAFLD:	Nonalcoholic fatty liver disease
NF- $\kappa$ B:	Nuclear factor kappa B
PI3K:	Phosphatidylinositol 3-kinase
PPARy:	Peroxisome proliferator-activated receptor
	gamma
PPI:	Protein-protein interaction
T2DM:	Type 2 diabetes mellitus
TACR:	Total alkaloids of Coptidis rhizoma
TCM:	Traditional Chinese medicine
TCMSP:	Traditional Chinese medicine systems
	pharmacology database and analysis platform
TNF:	Tumor necrosis factor
VEGF:	Vascular endothelial growth factor
XKYS	Xiao Ke Yin Shui formula.
formula:	

# **Data Availability**

The data used to support the findings of this study are included within the article and the Supplementary Materials.

# **Conflicts of Interest**

The authors declare that there are no existing conflicts of interest.

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#### **Supplementary Materials**

Figure S1: structures of M7, M8, and M10. Figure S2: HPLC spectra of M7 (A), M8 (B), and M10 (C) and bitter melon extract (D). Table S1: *in silico* screening results of XKYS. Table S2: the gene list collected from online resources relating to T2DM. Table S3: information of each node in the component-target-pathway network. (*Supplementary Materials*)

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