Study on the Mechanism of Liuwei Dihuang Pill s Formula in Treating Parkinson's Disease Based on Network Pharmacology

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Research

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Abstract

Background: Parkinson's Disease (PD) is a common neurodegenerative disease in middle-aged and elderly people. Liuwei Dihuang Pill (LWDH Pills) has good effect on Parkinson's disease but the mechanism of action is not clear. Network pharmacology is the result of integrating the basic theories and research methods of medicine, biology, computer science, bioinformatics and other disciplines, which can systematically and comprehensively reflect the mechanism of drug intervention in disease network.

Methods: Obtained the main components and targets of herbs in LWDH Pills through Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database, and screen the active components of traditional Chinese medicine according to ADME; The PD-related targets were obtained from Gencards, OMIM, TTD, DRUGBANK databases. Used Jvenn to take the intersection of targets of LWDH Pills and PD-related targets, use the String platform to analyze protein interactions, construct a PPI network and explore potential protein functional modules in the network. The Metascape platform was used to performe KEGG pathway and GO Function enrichment analysis. Finally, the Cytoscape software was used to construct the drug-components-target network.

Results: After screening and de-weighting, 210 effective active ingredients of LWDH Pills, 204 drug targets, 4333 diabetic nephropathy disease targets, and 162 drug-disease targets were obtained by the intersection of Jvenn. GO and KEGG enrichment analysis showed that these targets are involved in neuron death, G protein-coupled amine receptor activity, reactive oxygen species metabolic process, membrane raft, MAPK signaling pathway, cellular senescence and other biological processes. Drug-components-target shows that the hub components of Liuwei Dihuang Pills were quercetin, Stigmasterol, kaempferol, and beta-sitosterol

Conclusion: LWDH Pill has the characteristics of multi-component, multi-target and multi-pathway for the treatment of PD. The hub components may be quercetin, Stigmasterol, kaempferol, and beta-sitosterol, and may be through pairing hub targets such as AKT1, VEGFA, IL6, etc. to regulate Neuron death, G protein-coupled amine receptor activity, reactive oxygen species metabolic process, membrane raft, MAPK signaling pathway, cellular senescence to play a role in the treatment of PD

Introduction

Parkinson's disease (PD) is a common neurological disorder in the middle and old age, characterized by progressive degeneration of dopaminergic neurons in the substantia nigra and pathological changes in the formation of lewy bodies, biochemical changes in the decrease of dopamine (DA) transmitters in the striatum region, imbalance of dopamine and acetylcholine transmitters in the striatum region, motor symptoms such as tremor, myotonia, motor retardation, postural balance disorder and sleep disorders, olfactory disorders, autonomic nervous dysfunction, cognitive and mental disorders [1]. Epidemiological research shows that the prevalence of PD over 60 years old in Europe and the United States reaches 1%, and over 4% are over 80 years old. The prevalence rate of people over 65 years old in China is 1.7%, which is similar to European and American countries [2-3]. Drug therapy is the first choice for the treatment of PD. Levodopa is the standard treatment and the most effective symptomatic drug in the treatment of PD [4]. However, levodopa cannot completely cure Parkinson's disease, the long-term efficacy of the drug gradually worsens and brings a series of side effects [5].

Traditional Chinese medicine (TCM) has more than 2,000 years of experience in treating Parkinson's disease. TCM believes that kidney yin deficiency is the key to the onset of Parkinson's disease. Liuwei Dihuang Pills (LWDH Pills) is a classic kidney-tonifying prescription created by Qian Yi, a famous doctor in the Northern Song Dynasty. Liuwei Dihuang Pills contains six herbal medicine: Rehmanniae Radix Praeparata (Shudihuang, SDH), Rhizoma Dioscoreae (Shanyao,

SY), Cornus Officinalis Sieb (Shanzhuyu, SZY), Poria Cocos, (Fuling, FL), Cortex Moutan (Mudanpi, MDP), Alisma Orientale (Zexie, ZX). Clinical practice has proved that Liuwei Dihuang Pills was effective in treating PD, it can improve autonomic symptoms in patients with PD[6-7]. However, the six traditional Chinese medicines in Liuwei Dihuang Pills have complex chemical components, and their targets and mechanisms for the treatment of PD are not clear.

Network pharmacology (NP) was first proposed by British scholar Andrew L. Hopkins in 2007. NP is based on the rapid development of systems biology and multi-directional pharmacology. The new idea of drug design, which can expand the available drugs. Target space is one of the new strategies for new drug discovery [8]. It is based on the "disease-gene-target-drug" interaction network foundation, through the analysis of genes, proteins, diseases, drugs and other information in existing databases, combined with existing literature data, the use of professional network to build analysis software and structural biology Methods such as science and computational chemistry systematically and comprehensively reveal the intervention and influence of drugs on the disease network, thereby revealing the secret of the synergistic effect of drugs on the human body [9]. The holistic and systematic characteristics of its research strategy have the same goal as the theory of traditional Chinese medicine in diagnosing and treating diseases from a holistic perspective. It is very suitable for studying the relationship between various drug components and disease targets in traditional Chinese medicine. Thus, NP is widely used in the research of Chinese medicine. LI [10]used HERB BIOMAP data collection, target map clustering, network target analysis and other methods to determine the anti-diabetic activity of the traditional Chinese medicine Gegen Qinlian Decoction. 4-Hydroxymethylphenytoin increased insulin secretion in RIN-5F cells and improved 3T3-L1 fat cells. Insulin resistance lays the foundation for the treatment of diabetes in the future. Zhang [11] through molecular docking and network analysis, clarified the main active compounds, targets of action and various pharmacological mechanisms of Reduning injection in the treatment of upper respiratory tract infections, including inhibiting virus replication and directly acting on the key to regulating the life cycle of respiratory viruses Protein, indirectly regulates the host immune system, etc. ZENG Q et al. [12] conducted network pharmacological analysis on Chaihu Shugan Powder and screened out 152 active ingredients, predicting that sapogenin F, sapogenin G, sapogenin C, leucoflorin, hesperidin, and hesperidin have good Through the enrichment analysis of GO and KEGG, it was found that it reduces Abeta-induced neuronal cell death and PC12 cell apoptosis through the PI3K-AKT signaling pathway, suggesting that it may have a therapeutic effect on Alzheimer's disease.

Materials And Methods

Collection of Compounds and Target Prediction of LWDH Pills

Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmspw.com/tcmsp.php) is an open source database that specializes in analyzing traditional Chinese herbal medicines, which integrates pharmacodynamics, pharmacokinetics, target prediction, and genomics[13]. We obtained compounds of each herbals in LWDH Pills from TCMSP platform with the search terms "Shudihuang", "Shanyao", "Shanzhuyu", "Fuling", "Mudanpi", "Zexie". Before targets prediction, used absorption, distribution, metabolism, and excretion (ADME) to select biologically active compounds that contribute to its therapeutic effect, while those with poor pharmacological properties and poor drug capabilities are removed[14]. We chose oral bioavailability (OB) ≥30%, and drug-likeness (DL) ≥0.18 as the ADME parameters. The target of LWDH Pill was also obtained through the TCMSP platform, The selected active compounds were collected in respective target databases to relate to their target.

Predicting target of PD

We obtained the PD-related target from four databases: (1) Durg Bank (https://go.drugbank.com/. Version 5.1.8)[15], which is a comprehensive, free-to-access, online database containing information on drugs and drug targets. As both a bioinformatics and a cheminformatics resource. (2) Therapeutic Target Database (TTD, http://db.idrblab.net/ttd/,

Updated June 1st , 2020)[16], it is a database to provide information about the known and expected therapeutic protein and nucleic acid targets,the targeted disease, pathway information and the corresponding drugs directed at each of these targets. (3) Gene Cards (https://www.genecards.org/, Version 5.0)[17], which is an online database that provides detailed information about all genes that have been annotated and predictable by humans, and automatically integrates gene-centric data from about 100 data sources. Including genome, transcriptome, proteome, genetics, clinical and functional information. (4) Online Mendelian Inheritance in Man (OMIM, https://omim.org/. Updated January 19, 2021)[18], it isis a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 15,000 genes. We used "Parkinson's disease" as a keyword to screen disease targets in each database, and summarize the obtained targets and remove duplicate values. Finally, use the Uniprot database to standardize the obtained targets.

Protein-Protein Interaction Network Construction and Module Screening

In order to clarify the interaction between the related targets of Liuwei Dihuang Pills and the PD-related targets, Jvenn (http://jvenn.toulouse.inra.fr/app/index.html) was used to take the intersection of them and draw the Venn diagram to obtain drug-disease, which were the targets of Liuwei Dihuang Pill in the treatment of Parkinson's disease. STRING (https://string-db.org/, Version 11.0) is a database of known and predicted protein-protein interactions[19]. The interactions include direct (physical) and indirect (functional) associations; they stem from computational prediction, from knowledge transfer between organisms, and from interactions aggregated from other (primary) databases. We submitted the target in the intersection to the STRING to identify protein-protein interaction information, and use Cytoscape (Version 3.8.0) to visualize the network, which is an open source software platform for visualizing molecular interaction networks and biological pathways and integrating these networks with annotations, gene expression profiles and other state data[20]. Moreover, in order to more accurately analyze the action mechanism of LWDH Pills in treating dyslipidemia, it is necessary to further identify its important modules. The important modules and targets were screened from the PPI network with degree cutoff=2, max. Depth=100, k-core=2, and node score cutoff = 0.2 by using the Molecular Complex Detection (MCODE) plug-in Cytoscape. P- value ≤ 0.05 was considered as a significant difference..

KEGG Pathway and GO Function Enrichment Analysis

We applied Gene Ontology (GO) enrichment and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis to systematically analysed the biological functions of drug-disease targets[21-22]. Metascape (https://metascape.org/)[44] can perform enrichment analysis on targets. which integrates multiple authoritative functional databases such as GO, KEGG, Uniprot, etc., and supports annotation, enrichment analysis. We submitted these targets to the Metascape to perform GO and KEGG Pathway enrichment analysis. P-value ≤ 0.01 was considered as a significant difference.

Construction and Analysis of drug-component-target Network

Input the relationship between the active components of LWDH Pills and drug-disease targets into Cytoscape software to construct a drug-component-target network. Use the network analyzer analysis tool of Cytoscape software to analyze the network characteristic parameters, including Degree, Betweenness Centrality (BC) and ClosenessCentrality (CC), to screen the hub components and targets of LWDH Pill and the relationship between them.

Results

Collection of Compounds and Target Prediction of LWDH Pills

A total of 475 compounds of six herbs in LWDH Pills were obtained from TCMSP database. After the two key ADME parameters of OB≥30% and DL≥0.18 are screened and duplicate values are removed, we got 210 active compounds, Including 19 compounds of FL, 32 compounds of MDP, 43 compounds of SY, 132 compounds of SZY, 2 compounds of SDH, 7 compounds of ZX (figure 1). Finally, we obtained 204 targets of LWDH Pills through compiling the corresponding targets of active compounds of six herbs using TCMSP database.

Predicting target of PD

We searched the four databases of Genecards, OMIM, TTD, and DrugBank respectively, and the numbers of PD-related targets were 3827, 526, 89, and 202 respectively. Summarize the obtained targets and remove duplicate values, and finally got 4333 PD-related targets.

Protein-Protein Interaction Network Construction and Module Screening

We submitted targets of LWDH Pills and PD-related targets to Jvenn to draw a Venn diagram (figure 2), and we obtained 162 drug-disease targets. Based on the analysis results of these drug-disease targets from STRING online database, we used Cytoscape software to constructed a PPI network with 160 nodes and 2800 edges (figure 3). We use the network analyzer analysis tool of Cytoscape software to analyze the network, and adjust the size of each target in the PPI network according to the degree value. The color of edges is based on the combined score between the targets, the larger the combined score, the darker the color. After obtaining the PPI network, we use the MCODE plug-in CytoScape software to analyze the interaction relationship through the molecular complex detection algorithm, and obtain the module (figure 3). According to P value, the biological processes with the 3 best scores in the Module are retained respectively to describe their functions (table 1).

Table 1 LWDH Pills-PD targets PPI network function description

Module	Function description	Log10 (P)
Module1	G protein-coupled amine receptor activity	-20.7
Module2	MAPK signaling pathway	-13.88
Module3	apoptotic signaling pathway	-10.02

KEGG Pathway and GO Function Enrichment Analysis

We use Metascape database to perform enrichment analysis on the above drug-disease-related targets, including GO biological process (BP), GO cellular component (CC), GO molecular function (MF) and KEGG pathways. Then, we saved the top 20 results of each item, and made bubble charts for further analysis (figure 4). It can be seen that these targets enrich on many biological processes, and the LWDH Pills preparation can regulate various biological processes in the body to achieve the purpose of treating PD. Among them, the most closely related biological processes include neuron death, G protein-coupled amine receptor activity, reactive oxygen species metabolic process, membrane raft, MAPK signaling pathway, cellular senescence.

Construction and Analysis of Drug-Component-Target Network

According to the screened drug-disease targets and their pairing relationship with active ingredients, 23 active components of 210 active ingredients can be targeted to PD-related targets (table 2). Input the relationship between these active components and drug-disease target into Cytoscape software, we got drug-component-target network with 186 nodes and 379 edges (figure 5). We use the network analyzer analysis tool of Cytoscape software to analyze the

network characteristic parameters to get Betweenness Centrality (BC), ClosenessCentrality(CC), Degree of each component. We predicted that quercetin (BC = 0.70528, CC = 0.61056, Degree= 117) is the main component of Liuwei Dihuang Pills in the treatment of Parkinson's disease, followed by Stigmasterol (BC = 0.08635, CC = 0.38144, Degree= 68), kaempferol (BC = 0.13884, CC = 0.41761, Degree= 45), and beta-sitosterol (BC = 0.10312, CC = 0.39278, Degree= 31).

Table 2 Characteristic parameters of network nodes for the main active ingredients of LWDH Pills

Mol ID	molecule name	Attribution Herbs	Betweenness Centrality	ClosenessCentrality	Degree
MOL000098	quercetin	MDP	0.70528	0.61056	117
MOL000449	Stigmasterol	SY,SZY,SDH	0.08635	0.38144	68
MOL000422	kaempferol	MDP	0.13884	0.41761	45
MOL000358	beta-sitosterol	SZY	0.10312	0.39278	31
MOL000296	hederagenin	FL	0.03611	0.36926	16
MOL000322	Kadsurenone	SY	0.04245	0.36926	16
MOL000546	diosgenin	SY	0.05697	0.36634	14
MOL005430	hancinone C	SY	0.03033	0.36489	13
MOL001559	piperlonguminine	SY	0.01517	0.35783	8
MOL005465	AIDS180907	SY	0.02240	0.35645	7
MOL005440	Isofucosterol	SY	0.02585	0.35509	6
MOL005530	Hydroxygenkwanin	SZY	0.00230	0.35509	6
MOL000492	(+)-catechin	MDP	0.00614	0.35373	5
MOL001736	(-)-taxifolin	SY	0.00070	0.35238	4
MOL002879	Diop	SZY	0.00091	0.35238	4
MOL007374	5-[[5-(4-methoxyphenyl)-2-furyl]methylene]barbituric acid	MDP	0.01481	0.35238	4
MOL001494	Mandenol	SZY	0.00027	0.35104	3
MOL000273	(2R)-2-[(3S,5R,10S,13R,14R,16R,17R)-3,16-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl]-6-methylhept-5-enoic acid	FL	0.00273	0.34972	2
MOL001495	Ethyl linolenate	SZY	0.00013	0.34972	2
MOL002464	1-Monolinolein	ZX	0.00013	0.34972	2
MOL003137	Leucanthoside	SZY	0.01081	0.34972	2
MOL005481	2,6,10,14,18-pentamethylicosa-2,6,10,14,18-pentaene	SZY	0.00004	0.34972	2
MOL005503	Cornudentanone	SZY	0.00004	0.34972	2

Discussion

PD is a common neurodegenerative disease in middle-aged and elderly people. Because of its high prevalence, high disability rate, and chronic disease course, it has gradually become an important science and social issue in the field of population and health. DA receptor dysregulation is the pathophysiological basis of PD.However, there are still many confusions in its pathogenesis. It is currently believed that factors such as mitochondrial dysfunction caused by

oxidative stress, abnormal protein folding caused by endoplasmic reticulum stress, neuroinflammation, microbiota-gut-brain axis and related gene changes are closely related to the occurrence and development of PD[23].

In this study, we collected the targets of LWDH Pills and the targets of PD from multiple databases, combined them to obtain 162 targets of Liuwei Dihuang Pills for the treatment of PD, then we constructed PPI network and screening module. By observing the network, we can know that the important genes are AKT1, VEGFA, IL6. Basic research shows that AKT1 regulates pathological angiogenesis, vascular maturation and permeability in vivo[24]. VEGFA is a highly specific vascular endothelial cell growth-promoting factor, which can promote the increase of vascular permeability, the degeneration of extracellular matrix, the migration, proliferation and angiogenesis of vascular endothelial cells[25]. IL6 is a pleiotropic cytokine with a wide range of functions. IL-6 can regulate the growth and differentiation of a variety of cells, has the function of regulating immune response, acute phase response and hematopoietic function, and plays an important role in the body's anti-infection immune response[26]. Furthermore, we screened the module in the PPI and described its function. The module is a potential subject of the PPI network. The density of subnet connections is high, and there are few connections in the area. Therefore, the module is considered to be a collection of biological significance. This collection has two meanings. One is a protein complex (protein complex).), that is, multiple proteins work together to form a complex and then play a biological role; one is a functional module, such as proteins located in the same pathway, which interact more closely [27]. The results showed that the function of modules is related to G protein-coupled amine receptor activity, MAPK signaling pathway, and apoptosis signaling pathway. Previous studies have shown that DA receptors belong to the family of G protein-coupled receptors (GPCRs), DA receptors are regulated by G protein coupled receptor kinases (GRKs) and arrestins. Research on specific gene knockout mice suggests that GPCRs may be selectively phosphorylated by certain subtypes of GRKs and also selectively bind to certain arrestins subtypes[28-29]. In the striatum, the D1 receptor mostly binds to arrestin3, while the D2 receptor mostly binds to arrestin2[30-31]. Neuroinflammation is one of the important causes of DA neuron degeneration. Basic research showed that p38 mitogen-activated protein kinase (p38MAPK) signaling pathways are also involved in the immune inflammatory response of PD. And the apoptosis signaling pathway is one of the pathogenesis of PD that scholars currently consider.

Subsequently, we performed KEGG pathway and GO function enrichment analysis on these targets. According to q-value, the more important ones are neuron death, G protein-coupled amine receptor activity, reactive oxygen species metabolic process, membrane raft, MAPK signaling pathway, cellular senescence. Some of them are the same as the biological function of modules. Furthermore, neuron death is the pathological basis of PD. The reactive oxygen species metabolic process and membrane raft may be related to mitochondrial dysfunction and thus participate in the occurrence and development of PD. Astrocytes are the bridge connecting neurons and blood vessels, and are involved in activities such as underdevelopment, neurotransmitter transmission, brain metabolism, and blood flow regulation[32-33]. The maintenance of the mitochondrial respiratory chain function of astrocytes is very important for the energy balance of the brain and the production of antioxidants that protect neurons. HOEKSTRA et al. [34] found that the expression of DRP1 in astrocytes in the brain of PD patients was reduced; knocking out DRP1 in astrocytes cultured in vitro significantly affected mitochondrial morphology and spatial positioning in astrocytes. It may interfere with the uptake of Ca2+-coupled glutamate to produce hepatotoxicity and affect the survival of PD neurons. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can be used in U373 MG human star glue Accumulate in the mitochondria of tumor cells, inhibit the synthesis of mitochondrial respiratory chain complex I, causing severe symptoms of PD[35].

Finally, we constructed and analyzed the drug-component-target network to predict the hub component of LWDH Pills in the treatment of Parkinson's disease and their mechanisms. According to the degree, BC, and CC of the drug-component-target network, we predict that quercetin, Stigmasterol, kaempferol, and beta-sitosterol are the hub components of LWDH Pills. Quercetin has an antioxidant effect and can prevent cell damage induced by oxidative stress. Quercetin can effectively inhibit the transcription activity of cyclooxygenase 2 promoter, which can catalyze the production of

arachidonic acid into prostaglandins (PGs) and other inflammatory substances, stimulate cell proliferation. Quercetin has a certain anti-inflammatory activity, and its anti-inflammatory effect is related to its strong oxidative effect [36]. Through metabolism in the body, the metabolites produced by quercetin have important anti-inflammatory effects[37]. Stigmasterol has anti-inflammatory and antioxidant effects, Panda et al.[38] found that stigmasterol can reduce blood glucose concentration by reducing the release of thyroxine and increasing the concentration of insulin in the blood. At the same time, by reducing liver lipid peroxidation, increase the activity of catalase (CAT), Superoxide dismutase (SOD), glutathione (GSH) to exert its antioxidant activity. Pandith et al. [39] found that stigmasterol has anti-inflammatory effects, which can significantly reduce the inflammatory factor cycloxygenase-2 (COX-2) and inducible nitric oxide synthesis stimulated by lipopolysaccharide (LPS). Enzyme (iNOS) mRNA expression, while exerting its anti-inflammatory effect by reducing the release of PGE2 and NO. Basic research shows that computers have anti-oxidant, anti-tumor, anti-infection and other biological activities. Moreover, Wu Can[40] showed through animal experiments that campers will have a certain effect on the structure of mitochondria, and at the same time it will also have an inhibitory effect on the mitochondrial respiratory chain. Beta-sitosterol has anti-inflammatory, anti-oxidant and promotes the proliferation and differentiation of embryonic neural stem cells. Yin et al. [41] reacted Beta-sitosterol with organic acids to generate the derivative Beta-sitosterol-2-naphthoyl ester, and found that it can inhibit the expression of TLR4 and NF-κB to cause SOD in mice with acute liver injury, GSH level increases, MDA content decreases, and at the same time enhances the expression of NRF-2 and HO-1 to inhibit oxidative stress. Liao et al. [42] beta-sitosterol can inhibit the production of CAS1 and the activation of the MAPK signaling pathway by inhibiting the activation of the inflammasome NLRP3 in epidermal cells and macrophages, leading to TNF-α, IL-1beta, and MAPK signaling pathways in cells. The production of IL-6 and IL-8 is significantly reduced, thus playing an anti-inflammatory effect. Furthermore, beta-sitosterol in the diet can smoothly pass through the blood-brain barrier and be deposited on the brain cell membrane. Mahmoudi et al. [43] found that after treating embryonic neural stem cells with beta-sitosterol-containing Alyssum hologram, the expression of NOTCH1, HES-1, KI-67, and NICD proteins were significantly up-regulated, which promoted the proliferation and differentiation of embryonic neural stem cells.

Conclusion

In summary, based on network pharmacology technology and methods, this study explained the effective active ingredients of LWDH Pills and their related targets and pathways for the treatment of PD, and explained its multi-component, multi-target, and multi-component treatment for PD. The hub components may be quercetin, Stigmasterol, kaempferol, and beta-sitosterol, and may be through pairing core targets such as AKT1, VEGFA, IL6, etc. to regulate Neuron death, G protein-coupled amine receptor activity, reactive oxygen species metabolic process, membrane raft, MAPK signaling pathway, cellular senescence to play a role in the treatment of PD. That provides a reference for in-depth exploration of the pharmacological effects of LWDH Pills. Because some bioinformatics data inventory is limited, it cannot contain all the active ingredients and targets in LWDH Pills, so this article still has certain limitations. The next step is to use clinical or animal experiments for deeper exploration.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets obtained from TCMSP, Durg Bank, Gene Cards, TTD, OMIM.

Competing interests

The authors declare that there is no potential conflicts of interest.

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Authors' contributions

All authors contributed to study conception and design, Lin Dongtao is responsible for data collection. Analysis of data and visualization of results were conducted by writing Dongtao Lin and Yudan Zeng. The manuscript Was written by Dongtao Lin. Deyu Tang, Yongming Cai were responsible for revising the manuscript. All authors read and approved the final manuscript.

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Figures

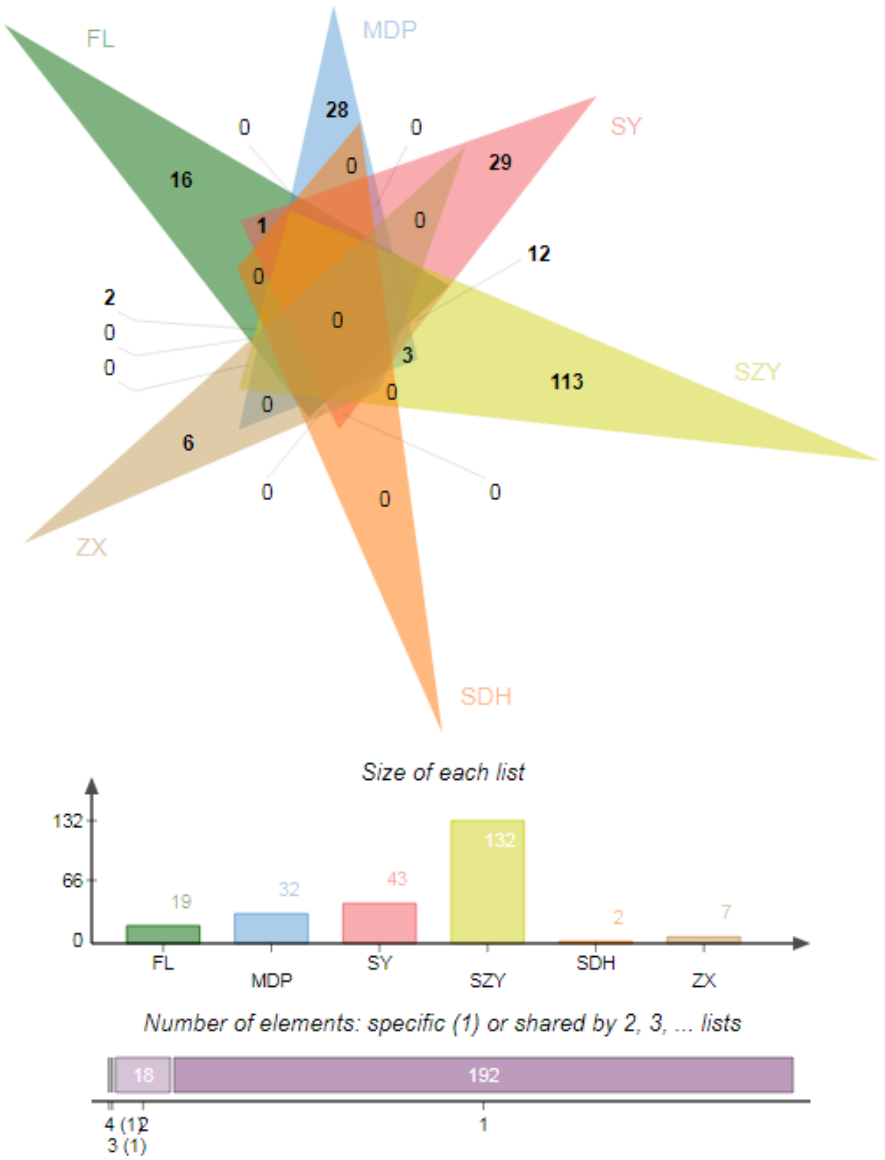

Figure 1

active compounds of six herbs in LWDH Pill

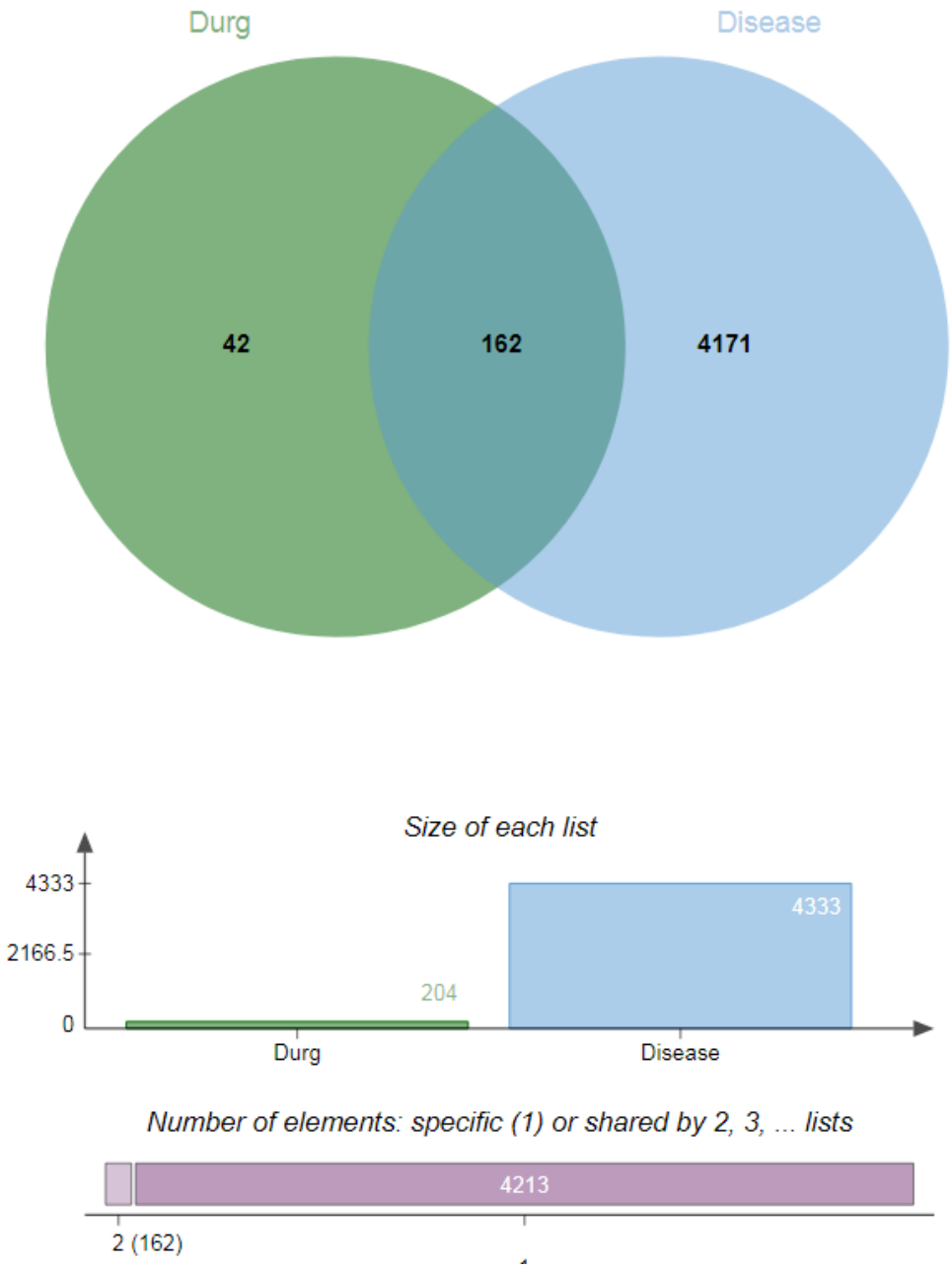

Figure 2

Venn diagram of PD-related targets and targets of LWDH Pills

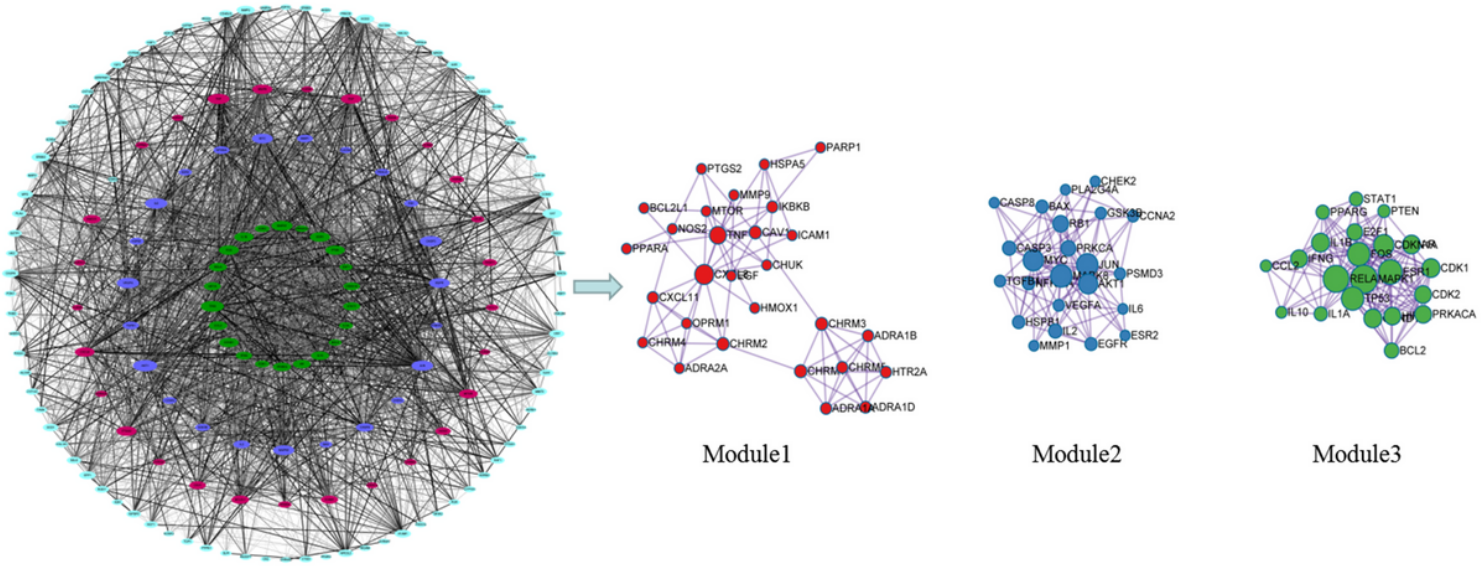

Figure 3

LWDH Pills-PD target PPI network and module. The nodes represents the target, the edges represents the matching short relation, and the size of nodes represents the degree, color of edges represents combined score.

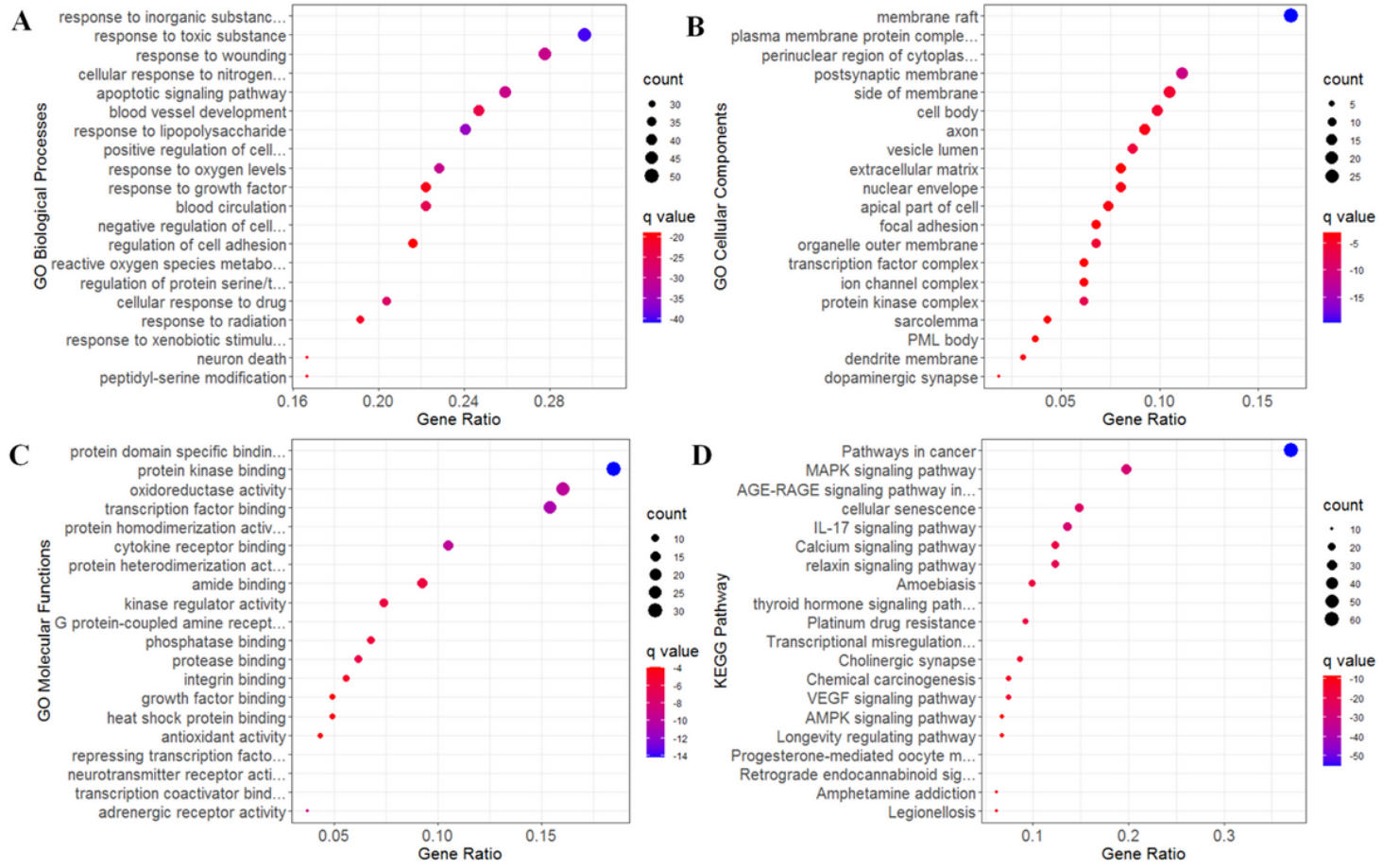

Figure 4

Results of enrichment analysis

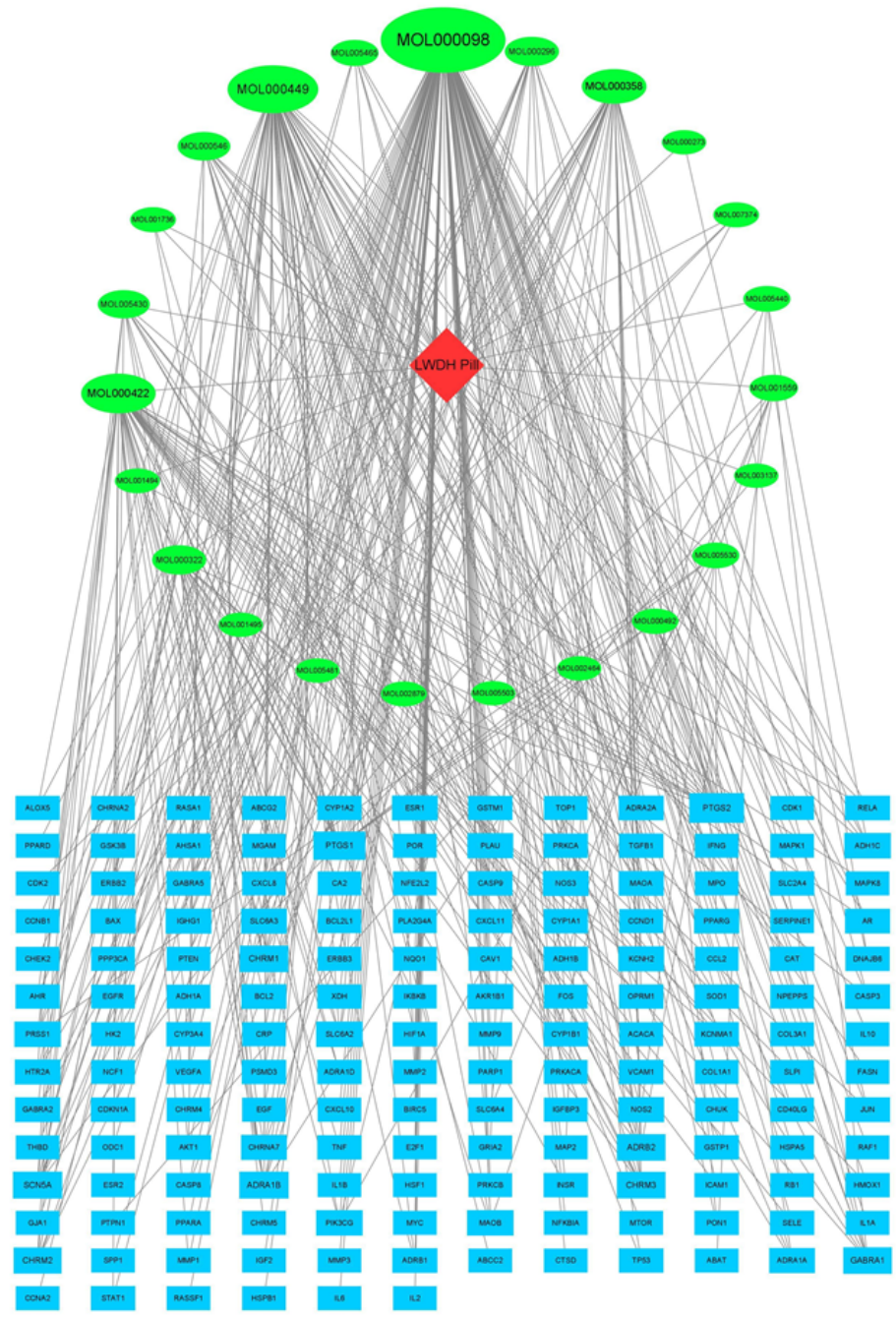

Figure 5

Drug-Components-Targest Network. The circular nodes represent the components, the rectangular nodesthe represent the drug-disease targets, the diamond node represents LWDH Pills, The edges represents the matching short relation, and the size of nodes represents the degree.