Progress in the Application of Network Pharmacology in Mongolian Medicine Research

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Abstract This paper summarizes the status quo of Mongolian medicine research, the basic research ideas and contents of network pharmacology, the latest development of network pharmacology technology in the field of Mongolian medicine research, the application progress, future development direction and existing problems in the research of Mongolian medicine, so as to provide new ideas and new methods for the scientific research of traditional medicine.

Key words Mongolian medicine, Network pharmacology, Research, Application, Progress

1 Introduction

In the early 13th century, the tribes of Mongolia were combined to form a new Mongolian nationality under the leadership of Genghis Khan, and changed the original tribal name to the ethnic name^[1]. By learning and drawing lessons from traditional medical theories and experiences, the Mongolian people have gradually formed a set of complete, reasonable and scientific medication methods and drug resources, constituting a unique Mongolian iatrology and pharmacology, popularly known as Mongolian medicine^[2]. Mongolian medicine is not only an important part of ethnic medicine, but also the most precious traditional medicine of the Mongolian people. Many researchers have made great efforts to the modernization, industrialization and standardization of Mongolian medicine^[3]. So far, the research and development of Mongolian medicine has made a qualitative leap in the improvement of preparations, pharmacological mechanisms, quality standards and new drug research and development^[4]. In the pharmacological research of Mongolian medicine, more achievements have been made by interpreting traditional effects with modern pharmacology, and new breakthroughs have also been made in the basis of pharmacodynamics and mechanism of action^[5]. Mongolian medicine has made improvements on traditional dosage forms with green and natural as a unique feature [6]. At present, the industrial production technology of tablet, powder, paste, granule, decoction, pill, oral liquid and other preparations is relatively mature^[7]. In addition, new dosage forms such as soft capsules and dropping pills have been developed, some of which have been applied in clinic. With the vigorous development of pharmaceutical industry, the research on the modernization of ethnic medicine has also made great progress. The medicinal property theory of Mongolian

to explain the function, application and property law of medicine^[8]. Unfortunately, there is a lack of attention to the theory of Mongolian medicine properties in the study of the chemical composition and pharmacological mechanism of Mongolian medicine, and there are few written records of Mongolian medicine effects. The experience of Mongolian medication in the past dynasties was mostly handed down by oral instruction^[9], while the basic ingredients of Mongolian medicine were unclear, and the safety and effectiveness of Mongolian medicine was questioned. The descriptions of medicinal properties were different in various books or even not recorded^[10], and traditional literatures had not been comprehensively collated and analyzed. The pharmacology, toxicology and compatibility laws had not been thoroughly explained, resulting in slow development of new drugs[11]. The research on efficacy and medicinal properties is basically limited to China, which restricts the development and research of Mongolian medicine and the inheritance and development of Mongolian medicine theories. Network pharmacology is a multidisciplinary approach that combines the knowledge of systems biology, bioinformatics, network technology and other disciplines^[12]. Based on systems biology theory, a complex network relationship model is established by network analysis and other technologies to clarify the connection between drugs and targets and their role in treating specific diseases, providing an innovative method for predicting the multicomponent, multi-target and mechanism of action of drugs [13]. Through systematic and comprehensive research, the influence of active ingredients of drugs on disease targets and the molecular correlation between drugs and diseases are explored, so as to further understand the mechanism of action of drugs and provide a guidance for the development of new drugs and clinical diagnosis and treatment [14-15]. It has also been widely used in the study of pharmacodynamic mechanism of compound drugs^[16-17]. This paper briefly introduces the status quo of Mongolian medicine research, the basic research ideas and contents of network pharmacology, the application status, future development direction and existing problems of network pharmacology in the research field of

medicine is the core of Mongolian medicine and a unique concept

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Mongolian medicine, in order to provide some references for the scientific research of traditional medicine.

2 Introduction to network pharmacology

In 2007, Andrew L. Hopkins at the University of Dundee in the United Kingdom first proposed a novel approach for drug research, network pharmacology. This technology can be used to study the network of biological systems by selecting specific signal nodes to design drug molecules with multiple targets [18]. It is a virtual computing method based on high-throughput omics to retrieve network databases and conduct data analysis, and systematically studies the construction of biological information networks and network topology analysis, which is in line with the "holistic view" of traditional medicine^[19]. Network pharmacology extrapolates the degree of association between targets and networks to determine the impact of drugs on diseases and the possibility of intervention^[20]. The research of network pharmacology reflects systematicness and globality, which is in line with the overall concept of "correspondence between man and universe" and "people-oriented" emphasized in Chinese and Mongolian medicine, as well as the concept of disease prevention and treatment in Mongolian medicine, and provides new strategies and methods for the modernization research of Mongolian medicine^[21].

3 Research ideas of network pharmacology

The disciplines including pharmacology, bioinformatics, computer technology science and network biology form the basis of network pharmacology, whose research ideas are usually integrating data \rightarrow establishing network prediction models \rightarrow analyzing pharmacological mechanisms \rightarrow analyzing diseases^[22].

- 3.1 Integration and collection of chemical components In network pharmacology, there are three methods of chemical composition aggregation that are most commonly used today. (i) Online database retrieval. All the chemical components of the study object are collected, but the record range of a database is limited. (ii) Literature retrieval. It can refer to and make use of the research information on chemical components of relevant medicinal materials in the literature. Although literature collection and sorting leads to a heavy workload, it can make up for the shortcomings of database retrieval. (iii) Experimental testing. Components in drugs or blood can be analyzed by fingerprint and high-resolution mass spectrometry [23].
- **3.1.1** Component analysis by database. Online databases for pharmacodynamic material basis such as Swiss Target Prediction, TCMID, PubChem and TCMSP platforms are all databases for information on common pharmacological chemical components, and can collect all the chemical components contained in the database, but due to the limitation of the content included in the database, the research basis of chemical component is weak^[24]. Fu Xuyang et al. [25] screened out 90 action targets of Mongolian medicine Zhonglun-5 in the treatment of rheumatoid arthritis via TCMSP and TCMID databases, and found that Akt1, MAPK9, STAT1,

MAPK8, Bcl-2, MAPK14 and STAT3 were the key targets of Zhonglun-5 for the treatment of rheumatoid arthritis. Meantime, its mechanism of action was discussed combined with the literatures, and it was predicted that the drug played an anti-inflammatory role by inhibiting the inflammatory response. Zhang Ying et al. [26] screened out 117 intersection targets of the active ingredients, targets and disease targets from the four components of Mongolian medicine Caoguo Siwei Decoction powder using TCMSP, GeneCards, DisGeNET and OMIM databases, obtained the potential targets of Mongolian medicine Caoguo Siwei Decoction powder in the treatment of migraine, and further constructed the network chart and PPI. Core targets such as VEGFA, PTGS2 and AKT1 were screened by network topology analysis, and AKT and FoxO signaling pathways were analyzed. Li Jing et al. [27] obtained 86 component targets from Oxytropis myriophylla via TCMID. The enrichment analysis of O. myriophylla in the treatment of acute bronchitis and asthma showed that the targets were closely related to biological processes, cellular hypoxia response and inflammatory response. Moreover, there was strong binding activity between the target tumor necrosis factor-α and the target of O. myriophylla.

3.1.2 Establishing component analysis database. The component analysis method can be established to utilize the information of chemical components of relevant medicinal materials in the literature. In spite of relatively heavy workload, it can make up for the deficiency of database retrieval. The method of establishing chemical component bank is not universal and is not applicable to processed or complex processed drugs, because processing will lead to changes in the content and structure of compounds. The original plant is very different from the chemical substance base, so the established chemical component database is not the real material base, but the material base that actually gets into the patient's body and works^[28]. Tian Xianting et al. ^[29] confirmed that there were 29 kinds of chemical components of Erwei Duzhong decoction migrating to blood by HPLC-Q-Exactive MS/MS assay. He Xiaolei et al. [30] predicted the target of each component of Erwei Duzhong decoction through Swiss Target Prediction platform, and screened 25 active components in total, including 278 targets for drugs and diseases, and the core targets included albumin, tumor necrosis factor-α, AKT1, EGFR, SRC, etc. The molecular docking of the core target and core components indicated that Erwei Duzhong decoction interacted with ALB, TNF-α, AKT1 and other targets through vulgarin, 7-hydroxycoumarin and ferulic acid, and regulated PI3K/Akt, EGFR and other signaling pathways to treat postmenopausal osteoporosis. Huang Yujia et al. [31] found some unpredicted active substances in Anshen Buxin Liuwei pills through TCMSP database and combined with literature reports, and identified 59 core targets and 99 signaling pathways. Molecular docking results showed that 10 active ingredients, such as betulinic acid and stigmasterol, had good binding ability with AKT1, APP, ALB, MAPK3, VEGFA and MAPK1. The in vitro test showed that the activity of BV2 cells increased significantly after administration compared to the model group. Anshen Buxin Liuwei pills can regulate the mRNA expression of each core target, and may exert the antidepressant effect mainly through the signaling pathway such as hydroxytryptamine synapses and related core targets. Sun Guoyuan *et al.* [9] collected the chemical components of Flos Gentianae Dahuricae based on the literature [32], and screened out 23 active components using SwissTarget Prediction database and predicted 27 action targets. The results showed that Flos Gentianae Dahuricae mainly involved in key proteins such as PTGS2, and exerted anti-inflammatory effects through oxidative stress response and regulation of TNF- α signaling pathway.

3.1.3 Experimental detection. Mongolian medicine components that enter the blood and migrate in the body can be detected by experimental methods. According to the physiological process of the human body, the special material base combination of Mongolian medicine is determined, which will have a certain impact on the absorption of drugs in the blood. Although experimental measurements can not fully describe all the chemical components, the information obtained by this method is more realistic and easier to relate to the components in the blood which are widely regarded as the material basis for drug efficacy. Obviously, an experimental method is not comprehensive enough to analyze chemical components, and other means are needed, such as literature search, to discover new ingredients in real time and include them in the component analysis, truly reflecting the "component library" of the intrinsic characteristics of medicinal materials. Predicting by network pharmacology, Xu Xiujuan et al. [33] proved the analgesic effect of Mongolian medicine Binglang Shisanwei pills through cell test; it acted on thermal targets such as TRPA1 and TRPV1 to balance the interaction between receptors and ligands in nerve tissue, and regulated the tryptophan channel and the response of GMP-PKG to inflammatory mediators. Zhang Dongxu et al. [34] predicted the therapeutic effect of Nuangong Qiwei pills on dysmenorrhea through network pharmacology, and its mechanism of action involved 68 potential targets, in which IL-6, PTGS2, TNF, TP53 and other protein interaction networks were the core targets. The results of animal test showed that the low, medium and high dose groups of Nuangong Qiwei pills showed a significant reduction in the number of twisting reactions in rats. Compared with the positive group, the high-dose group significantly reduced the expression of peroxidase synthetase 2 related protein COX-2 and the level of PGF2α in uterine tissue, and regulated the tension of uterine smooth muscles by down-regulating the PTGS2 target, thus effectively relieving dysmenorrhea symptoms. Zhang Chunyan et al. [8] predicted 62 targets of Mongolian medicine Qiwei Qinggan powder with anti-liver fibrosis effect by using network pharmacology, 10 of which were core targets. In GO enrichment analysis, three aspects were involved: cell components, molecular functions and biological processes. KEGG enrichment results showed that PPAR, Rap1, AMPK and MAPK were related to the occurrence and development of liver fibrosis. The active ingredients Quercetin, Luteolin and Kaempferol were verified to be closely related to Akt1, PIK3R1 and MAPK1 paths through molecular docking. In animal test, observation by Masson staining demonstrated that the administration group significantly reduced the proliferation of fiber tissue, and effectively reduced the infiltration degree of inflammatory cells, thereby improving the fibrosis of liver tissue. Qiwei Qinggan powder down-regulated the expression of α -SMA, Collagen1, PI3K and Akt. In the cell culture test, the serum containing Qiwei Qinggan powder could increase the apoptosis rate of HSC-T6 cells.

3.2 Construction of Mongolian medicine-component-disease-target network model Network pharmacology is a multidisciplinary interdisciplinary science developed on the basis of pharmacology, computational science and systems bioinformatics to study the complex relationships among diseases, targets, components and drugs. The influence of cells and organs on body functions can be understood at the molecular level, and drug targets can be identified efficiently and quickly, so as to design safe and effective multi-target drugs^[35]. It can broaden the vision of drug research and greatly promote the modernization research of traditional drugs^[36]. Wang Kai et al. [37] screened out 104 disease and drug intersection targets of Zadi-5 through network pharmacology database, and constructed a "medicine-chemical componenttarget-disease" network by combining 67 active ingredients and 104 potential targets of Zadi-5. The network diagram had 178 nodes and 1 275 edges (Fig. 1). There were 10 key targets in multiple signaling pathways.

Zhang Yanan et al. [12] predicted the sites of action of Cynomorium songaricum ethyl acetate extract on disease targets and drug targets through network pharmacology, and obtained 2 common targets and 3 related pathways. A "composition-target-disease" interactive network was constructed to display the complex nootropic network of C. songaricum ethyl acetate extract (Fig. 2). Huang Xianju et al. [38] screened the active ingredients of Zhachong Shisanwei pills and the related targets of anti-rheumatic inflammation from network pharmacological database. Using Cytoscape 3.2.1 software, the relationship network of composition, target and disease of Zhachong Shisanwei pills was constructed (Fig. 3).

3.3 Construction and analysis of PPI network The protein-protein interaction (PPI) network is implemented through the construction of STRING (https://www.string-db.org/) database^[39]. Biological networks collaborated with network pharmacological analysis can predict possible adverse reactions of drugs and predict possible new targets for drugs. The establishment of PPI network can deeply explore the molecular mechanism of diseases and dig out the genes that cause diseases^[40]. Pengsigerexi et al. [41] imported 297 intersection targets of Mongolian medicine Sanwei Alatanqiqige powder for the treatment of functional dyspepsia into the STRING database, plotted the PPI network diagram using PPI network analysis and Cytoscape software (Fig. 4), and predicted the mechanism of action by network pharmacology and molecular docking. Chen Ying et al. [42] screened 34 active com-

ponents and 110 targets of Sulongga-4 granules, 74 of which were potential targets. A PPI network was constructed using network pharmacological data platform (Fig. 5). Through the analysis of biological processes, 87 items were obtained, while 117 pathways were aguired through KEGG path analysis. Ge Shasha et al. [43] screened out 16 compounds with high activity in Mongolia medicine Siwei Shiliu powder through TCMSP database and chemical professional database, predicted and analyzed 35 targets related to the regulation of hyperlipidemia, and analyzed 12 clustering results with String, with the highest being 3.06, including four items of lipid metabolism, steroid metabolism, cholesterol metabolism and sterol metabolism, and 31 enrichment pathways associated with KEGG (Fig. 6). The results demonstrated that Mongolian medicine Siwei Shiliu powder played a role in the treatment of hyperlipidemia by interfering in fatty acid metabolism, hormone regulation and immune stability.

3.4 GO and KEGG enrichment analysis of key targets and KEGG enrichment analysis of key targets is widely applied in network pharmacology studies to identify genes or proteins that are significantly enriched in signaling pathways most likely to be regulated by drugs. Common open source integration tools are used to facilitate GO annotation and KEGG path enrichment analysis [44]. Meantime, GraphPad Prism 8.0 can be used to draw bar charts and path charts, and clusterprofiler is employed to obtain the latest version of KEGG database annotations for enrichment analysis in real time, in order to obtain more accurate and effective enrichment annotation results^[45]. Chen Siyuan et al. [46] screened out 22 active ingredients and 36 core targets of Mongolian medicine Shudage-4 in the treatment of gastritis through network pharmacology combined with molecular docking technology, conducted GO functional enrichment analysis via DAVID database, and listed the top 10 functional information paths of -lgP ranking in the analysis results. By querying the KEGG database, a total of 61 paths were retrieved, and the first 15 pathways with the lowest P value were selected. The results showed that the active component targets of Shudage-4 were distributed in different pathways to achieve coordination. He Xiaolei et al. [30] obtained 25 active ingredients and 278 targets of drugs and diseases in Erwei Duzhong decoction by searching literature, and the core targets were ALB, TNF-α, AKT1, EGFR, SRC, etc. KEGG pathway enrichment and GO function enrichment analysis of Erwei Duzhong decoction interfering with postmenopausal osteoporosis genes were performed by Metascape, and bubble charts and bar charts were plotted using the online mapping tool "Weishengxin". Among the 179 pathways obtained, the first 20 pathways, such as cancer pathway, PI3K/Akt signaling pathway and steroid hormone biosynthesis, were the most significant. Shan Chengbin et al. [47] used network pharmacology to analyze biomolecular networks when studying the role of Gurigumu-7 in the treatment of liver diseases. Potential targets were screened out by R software and performed GO enrichment, and a total of 125 items were obtained. After screening with $P \leq 0.05$, 144 signal pathways of great significance were obtained.

4 Application of network pharmacology in Mongolian medicine research

4.1 Predicting potential targets Bai Yinglu *et al.* [48] screened 60 active ingredients, involving 311 target genes, through network pharmacology combined with molecular docking technology when discussing the potential molecular mechanism of Mongolian medicine Bawei Sanxiang powder in treating chronic heart failure. The active ingredients screened were conducted molecular docking with proteins via Autodock _ vina software. Molecular docking data showed that there was a significant binding effect between target active components and receptor proteins. Tunuomula et al. [49] found 22 potential chemical components in Mongolian medicine Tegexidegegi (Tangniaole) powder by referring to literature and combining with network pharmacology, predicted drug targets and disease targets, and obtained 472 potential targets through crosscomparison, 21 of which were identified as core targets. KEGG pathway enrichment analysis and molecular docking with Autodock software showed that AKT1, MAPK1 and MAPK3 had good binding ability with their corresponding active components. Hao Xiaogiong et al. [50] screened 58 active ingredients of Mongolian medicine Garidi-13 through TCMSP database and obtained 114 potential targets for the treatment of stroke. Network pharmacological analysis suggested that Garidi-13 played a protective role in 27 pathways, including interleukin-17 signaling pathway and nuclear factor KB signaling pathway, and identified key potential targets: NOS3, ACE, IL6, TNF, SERPINE1, VEGFA, IL1β, MMP9, CXCL8, TP53 and MAPK1, etc.

Clarifying effective substances Chemical separation of drugs is followed by activity screening or efficacy evaluation, and biological behaviors of different targets, cells and organs are studied at the gene and molecular level to reveal the intervention mechanism of drug molecules on them, so as to clarify the efficacy of different compounds in drugs and the mechanism of action in the treatment of diseases^[51]. A network can be built through network pharmacology to predict the efficacy of a drug or the relationship between an efficacy and its chemical component. Hou Jian et al. [52] searched through TCMSP database and screened out the active ingredients in Mongolian medicine Sanzi decoction and their related targets. With the help of network topology analysis, the important target genes of Sanzi decoction in the treatment of rheumatoid arthritis were revealed, including IL-6, TNF, AKT1, VEGFA, IL-1\(\beta\), etc. In addition, quercetin, kaempferol, ellagic acid and β -sitosterol were also identified as important active components. A total of 2 281 results were obtained in GO enrichment analysis, including 2 107 results in biological processes, 44 results in cell components, and 130 results in molecular functions. These results were mainly related to the physiological processes such as response to lipopolysaccharides, response to bacterial-derived molecule and reactive oxygen metabolism. KEGG pathway enrichment analysis showed that there were 160 signaling pathways,

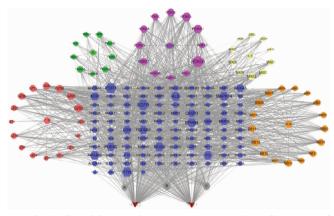


Fig. 1 "Medicine-chemical component-target-disease" network of Zadi-5

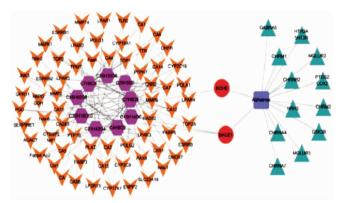


Fig. 2 "Composition-target-disease" interactive network of *Cynomorium songaricum* ethyl acetate extract

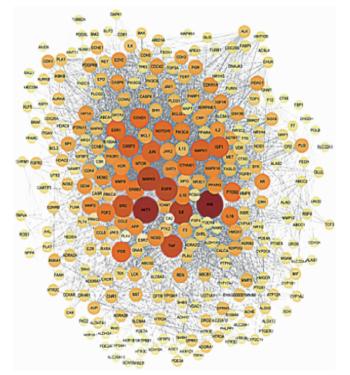


Fig. 3 Network diagram of "component-target-disease" of Zhachong Shisanwei pills

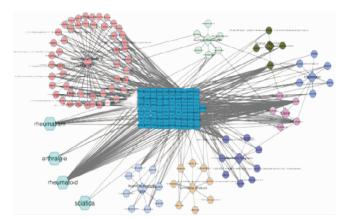


Fig. 4 PPI network diagram

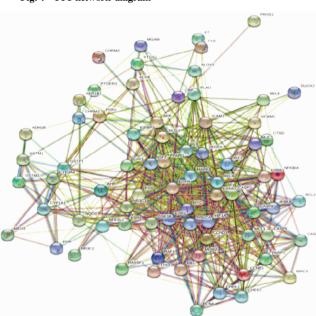


Fig. 5 PPI network of Sulongga-4 granules in the treatment of diarrhea

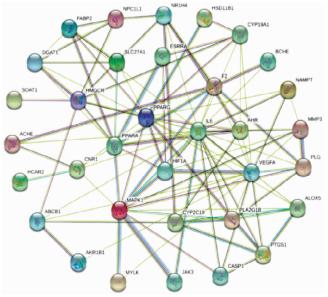


Fig. 6 Target interaction network

including AGE-RAGE, NF-KB and interleukin-17 signaling pathways. Wu Qinghua et al. [53] screened 177 chemical components from Mongolian medicine Cymbaria using network pharmacological database, and confirmed the structure of 90 chemical components, among which 34 chemical components had significant effects on 61 biological processes such as regulating protein kinase activity, while Akt1 and TNF-α were the key targets in these biological processes. It was predicted by molecular docking technology that these components had high binding activity to the key target Akt1. After validation of cell models in vitro, catalpol showed a hypoglycemic effect, and increased the levels of p-Akt (Ser473) / Akt, PPARα and PPARδ while reducing the expression level of FABP4 protein, thereby regulating glycolipid metabolism and improving hepatic insulin resistance. Tan Zhenzhen et al. [54] searched the chemical components and target sites of Mongolian medicine Eligen-7 through network pharmacological database, and built a network diagram of components and targets. The PPI core network was constructed by searching the targets related to liver fibrosis. GO functional enrichment analysis showed that 110 GO items were selected when P < 0.05. Thirty pathways were screened out by KEGG enrichment analysis, and the P values of these pathways were also less than 0.05.

4.3 Clarifying the mechanism of drug action In biological networks, disease mechanisms are associated with drug properties. Although the concepts in network pharmacology and traditional medicine are expressed differently, they both reflect the concept of biological balance, and their understanding of the molecular mechanism of diseases is closely related to the regulatory mechanism of biological network [55]. In the field of pharmaceutical research, network pharmacology has become a common research method to predict the active components and mechanism of action of drugs^[56]. Yu Kai et al. ^[57] determined the active components of Mongolian medicine Erdun-Uzil by studying relevant literatures, and screened out the bioactive components and corresponding targets. The targets of active components were mapped and intersected with the targets associated with epilepsy to construct the PPI network. On this basis, 47 core targets were selected and a network diagram of "component-key target-pathway" was constructed. MMP9, EGFR and MAOA showed high binding ability when docking with 3-methylcyclopentadecanone and luteolin. The results indicated that Erdun-Uzil treated epilepsy by inhibiting the mRNA expression of epidermal growth factor to increase the expression of epilepsy apoptosis factor, promoting the expression of inhibitory neurotransmitters in the brain, and preventing the synchronous discharge of neurons in the brain through various ways. Wan Quan et al. [58] obtained 20 active ingredients and 175 action targets of Mongolian medicine Sanwei Tanxiang decoction through network pharmacology. Key active components such as quercetin showed high binding activity with key targets such as MAPK3. DAVID enrichment analysis covered the correlation of B-cell receptor, AGE-RAGE and Toll-like receptor signaling pathways. Sanwei Tanxiang decoction acted on different targets in a variety of ways and treated ischemic heart disease through multiple signaling pathways. Zhu Xiaoling et al. [59] searched Mongolian medicine to treat sticky blight and traditional Chinese medicine to treat blight through literature review and TCMSP database. The targets of the selected chemical components were retrieved, and the disease targets that played a role in the novel coronavirus infection in different infection stages were screened. A network including components and targets as well as PPI network was established to further study the mechanism of action of active components in the treatment of novel coronavirus infection through GO enrichment analysis and KEGG pathway analysis. The results of network pharmacology combined molecular docking showed that tetrahydroberberine and semilicoisoflavone had good binding ability with ACE2, and effectively inhibited the transmission of novel coronavirus by acting on multiple targets and pathways.

5 Conclusions

As the most important part of traditional medicine, Mongolian medicine plays an irreplaceable role in medical treatment, hygiene and health care. Because of its low toxicity, high efficiency and relative economy, Mongolian medicine has become the key medicine to safeguard the life safety of the people of this nation and this region. The research of network pharmacology mainly depends on the existing database, and the accuracy and reliability of prediction are directly affected by the accuracy and reliability of the databases. At present, there are few databases covering the chemical components of Mongolian medicine, and the information of compounds contained in some databases is not accurate enough, while the data quality needs to be further screened. Even if the original plant of medicinal materials is the same, the metabolites in the plant body will also be very different in case of different harvesting years and seasons. Moreover, the results obtained under different experimental targets are not the same, which will also lead to the instability of the accuracy of the data, thus directly affecting the results of network pharmacological analysis. The study of Mongolian medicine network pharmacology should be based on traditional pharmaceutical knowledge or drug sources, and various factors should be fully analyzed to minimize the influence on the analysis results. In addition, due to the lack of chemical, biological and pharmacological data of Mongolian medicine and the weak basic research on ethnic medicine in the early stage, it has not been extensively and deeply studied, and the research on network pharmacology of Mongolian medicine also started late. Therefore, there are few research results of Mongolian medicine network pharmacology based on public database model, especially there are certain challenges in the subsequent test. In recent years, with the continuous progress of science and technology, network pharmacology has made great breakthroughs in genome, proteomics and other fields related to diseases and drugs. With the continuous improvement in computer technology, software and database, the development prospect of network pharmacology will be promising in the future.

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