MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
KYIV NATIONAL UNIVERSITY OF TECHNOLOGIES AND DESIGN
Faculty of Chemical and Biopharmaceutical Technologies
Department of Biotechnology, Leather and Fur

QUALIFICATION THESIS

on the topic **The effect of Ginkgo biloba on uric acid metabolism genes**
First (Bachelor's) level of higher education
Specialty 162 "Biotechnology and Bioengineering"
Educational and professional program "Biotechnology"

Completed: student of group BEBT-21
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APPROVE
Head of Biotechnology, Leather and Fur Department, Professor,
Dr. Sc., Prof.
_____Olena MOKROUSOVA
«___»_____2025

ASSIGNMENTS
FOR THE QUALIFICATION THESIS
Ma Xianghong

1. Thesis topic **The effect of Ginkgo biloba on uric acid metabolism genes**

Scientific supervisor Dr. Sc., Prof. Tetiana Shcherbatiuk

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2. Initial data for work: assignments for qualification thesis, scientific literature on the topic of qualification thesis, materials of Pre-graduation practice

3. Content of the thesis (list of questions to be developed): literature review; object, purpose, and methods of the study; experimental part; conclusions

4. Date of issuance of the assignments 05.03.2025

WORK CALENDAR

№	The name of the stages of the qualification thesis	Terms of performance of stage	Note on performance
1	Introduction	until 11 April 2025	
2	Chapter 1. Literature review	until 20 April 2025	
3	Chapter 2. Object, purpose, and methods of the study	until 30 April 2025	
4	Chapter 3. Experimental part	until 11 May 2025	
5	Conclusions	until 15 May 2025	
6	Draw up a bachelor's thesis (final version)	until 25 May 2025	
7	Submission of qualification work to the supervisor for feedback	until 27 May 2025	
8	Submission of bachelor's thesis to the department for review (14 days before the defense)	28 May 2025	
9	Checking the bachelor's thesis for signs of plagiarism (10 days before the defense)	01 June 2025	Similarity coefficient ____% Citation rate ____%
10	Submission of bachelor's thesis for approval by the head of the department (from 7 days before the defense)	04 June 2025	

I am familiar with the task:

Student _____ Ma Xianghong

Scientific supervisor _____ Tetiana SHCHERBATIUK

Abstract

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Objective: To explore the mechanism of *Ginkgo biloba* in the treatment of hyperuricemia based on network pharmacology, and to verify the experimental results by molecular docking technique. How: The common target genes of *ginkgo biloba* active components and hyperuricemia were found using TCMSP, Uniprot and Weishengxin-based databases, and the PPI network diagram of key targets was drawn. GO and KEGG enrichment was carried out using David database, and molecular docking was carried out through Discovery Studio software. Predict the binding degree of major compounds to key targets. Result: Through screening, 21 kinds of *ginkgo biloba* active ingredients were obtained, with 290 potential targets and 1391 hyperuricemia disease targets. Through comparison, 91 same targets were found between hyperuricemia and *ginkgo biloba*, and several key targets TP53, TNF, IL6, PPARG, IL1B and CASP3 were screened for molecular docking. The docking results showed that TP53, TNF, PPARG and CASP3 had good binding activity with isorhamnetin, beta-sitosterol, formononetin and (-)-epigallocatechin-3-gallate. It is predicted that the key targets of *ginkgo biloba* in the treatment of hyperuricemia may be TP53, TNF, PPARG and CASP3. The results of KEGG pathway enrichment analysis showed that *ginkgo biloba* may treat hyperuricemia through several signaling pathways, including TNF signaling pathway, cancer signaling pathway, and AGE-RAGE signaling pathway in diabetic complications. Conclusion: Multiple active components in *ginkgo biloba* fruit have a network mechanism of synergistic action on hyperuricemia through multi-component, multi-target and multi-pathway, which may be through action on core target genes such as TP53, TNF, PPARG and CASP3. And then regulate cancer

signaling pathway, TNF signaling pathway, P53 signaling pathway and other pathways to play a therapeutic role in hyperuricemia.

Key words: Ginkgo biloba, Hyperuricemia, Network pharmacology, Molecular docking, Action mechanism

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INTRODUCTION

Uric acid is actually the final product of purine metabolism in the body. Uric acid is metabolized in the liver. The glycoside metabolism generates 5-phosphoribose, which is converted into phosphoribose pyrophosphate by PRPP synthase, and then into inosine monophosphate **Ошибка! Источник ссылки не найден.**. The intermediate products are adenosine monophosphate esters and guanine monophosphate esters, purine nucleotides used for DNA and RNA synthesis, and inosine, the latter of which is converted into hypoxanthine by purine nucleoside phosphorylase. Xanthine oxidase is an enzyme inhibited by allopurinol, which can convert hypoxanthine to xanthine and then xanthine to uric acid [1]. The uric acid produced and excreted in the human body every day are in a balanced state. If too much high-purine and high-nutrition food is consumed, the excess uric acid cannot be excreted through the kidneys and will be carried into the blood and deposited in other tissues and organs. If this continues for a long time, it will "harm" multiple organs in the body. Gout, diabetes, stroke, coronary heart disease, uric acid nephrolithiasis and renal function impairment are all related to hyperuricemia [3]. Hyperuricemia is a common metabolic disease, and its incidence rate has been on the rise worldwide in recent years. Hyperuricemia is caused by the disorder of purine substance metabolism in the human body, resulting in an increase in uric acid synthesis or a decrease in its excretion. Currently, there is no cure for it. The current treatment still focuses on controlling and reducing blood uric acid levels to prevent urate deposition, damage to joints and kidneys. Besides abstaining from alcohol, reducing purine intake and emphasizing regular meals, medication remains the main treatment approach. At present, Western medicine mainly uses drugs such as benzbromarone and allopurinol for treatment, but it is highly prone to adverse reactions such as gastrointestinal reactions, liver damage and bone marrow suppression. However, the treatment of hyperuricemia with traditional Chinese medicine has the advantages of low cost, easy availability and few adverse reactions. Therefore, it has become one of the current research hotspots and trends. Patients with hyperuricemia may develop a series

of joint diseases such as gouty arthritis, interstitial nephritis and tophi. With the in-depth research on the integration of traditional Chinese and Western medicine in the treatment of gouty arthritis, people have gradually begun to realize the importance of traditional Chinese medicine in the treatment of gouty arthritis. Therefore, it is of great practical significance to explore a traditional Chinese medicine with definite therapeutic effect, safety and effectiveness for the treatment of hyperuricemia [4-6]. *Ginkgo biloba*, also known as ginkgo seeds, are the fruits of the ginkgo tree. As a traditional Chinese medicinal material, they have a long history of application in China. *Ginkgo biloba* are rich in various chemical components, such as flavonoids, terpenoids, phenols, etc., and possess multiple biological activities including antioxidation, anti-inflammation, and antibacterial properties. With the wide application of bioinformatics, in this paper, network pharmacology and molecular docking methods were adopted to explore the network mechanism by which various active components in *ginkgo biloba* reduce uric acid through multi-target and multi-pathway synergistic effects. The relevant results were verified using molecular docking technology, aiming to find the potential molecular basis of the uric acid-lowering effect. To provide certain assistance for the subsequent treatment of traditional Chinese medicine and the research and development of new drugs, with the expectation of expanding to the research on the mechanism of action of more diseases.

CHAPTER I
LITERATURE REVIEW
1.1 RESEARCH STATUS OF HYPERURICEMIA

Hyperuricemia (HUA) can be classified as a type of metabolic disease. The main cause is purine metabolism disorder, and the influencing factors mainly include genetic and environmental aspects [7]. The basis for its judgment is that under the conventional purine diet, when the serum uric acid content is detected on an empty stomach on two different days, it is defined as hyperuricemia in men and women when it is higher than 0.7 mg/L (420 μmol/L) and 0.6 mg/L (357 μmol/L, respectively [8]. The core pathology is that the serum uric acid level exceeds the saturation concentration (approximately 6.8 mg/dL at 37℃, that is, 404 μmol/L), resulting in the deposition of urate crystals. It has been found in clinical research that it is closely related to many different types of chronic diseases such as gout, hypertension and diabetes. The "White Paper on the Trends of Hyperuricemia and Gout in China" (2021) indicates that the number of patients with hyperuricemia in China has been increasing year by year, and at the same time, the age of patients shows a trend of getting younger [9]. At present, there are approximately 77 million patients with hyperuricemia in China, accounting for about 13.3% of the total population. Among them, the corresponding proportions of patients aged 18-25, 26-35, and 36-45 are 22%, 38%, and 6% respectively, seriously threatening public health in society [10]. At present, although commonly used uric acid-lowering drugs in clinical practice, such as allopurinol and benzbromarone, have certain therapeutic effects, they have side effects such as hepatotoxicity, allergic reactions and drug interactions. Plant-based active ingredients have shown unique advantages in regulating uric acid metabolism due to their multi-target action characteristics and high biocompatibility. Therefore, seeking active ingredients for lowering uric acid with fewer side effects from natural products has become a current research hotspot.

1.2 RESEARCH AND APPLICATION OF NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TECHNOLOGY

Natural plants have shown unique advantages in the treatment of metabolic diseases due to their rich bioactive components and low toxicity. *Ginkgo biloba*, as one of the medicinal materials, are rich in various chemical components, such as flavonoids, polyphenols, *Ginkgo biloba* terpene lactones and other bioactive substances. They have multiple functions such as protecting the cardiovascular and cerebrovascular system, delaying aging, anti-cancer, anti-inflammatory and antioxidant [11]. In the field of lowering uric acid to treat hyperuricemia, studies have shown that the flavonoids in them inhibit the activity of uric acid-producing enzymes, Lower the level of blood uric acid, thereby reducing the accumulation of uric acid in the body [12]. There are numerous targets for traditional Chinese medicines that are both food and medicine, and the data volume is vast. At present, the scientific field urgently needs to conduct rapid and precise screening of the active ingredients of drugs for the treatment of hyperuricemia. Network pharmacology breaks through the limitations of traditional disciplines by using bioinformatics methods. It mainly involves three aspects: grid construction, network analysis, and network verification, and is an innovative discipline [13]. The ultimate goal of network construction is to facilitate the interaction between active chemical substances and target proteins, as well as among different target proteins. The search and verification of key target proteins are accomplished through network analysis and network validation, mainly including the screening of drug active substances, the discovery of target proteins, the evaluation of drug toxicity, and the study of the mechanism of action. The prominent advantages of network pharmacology mainly lie in the extremely extensive biological theoretical system it possesses, the comprehensiveness of the network analysis of biological systems, and the realization of multi-target design of drug molecules [14]. Network pharmacology can explore different signaling pathways of drugs through multiple different paths. It can not only understand

the main efficacy of drugs, but also effectively eliminate the toxic and side effects of certain drugs, thereby reducing the capital cost of new drug research and development and greatly increasing the probability of successful research and development [15].

1.3 STUDY PURPOSE AND SIGNIFICANCE

This article focuses on the screening and functional analysis of the active components for lowering uric acid in gelled *ginkgo biloba*. It is found that isorhamnetin, β -sitosterol, anthocyanin and (-) -epigallocatechin-3-gallic acid esters have a stronger matching degree with the target proteins of the related pathways involved in the disease. It is expected that based on the concept of food and medicine sharing the same origin [16], By applying bioinformatics analysis methods such as network pharmacology and molecular docking techniques, it is extended to the research on the mechanism of action of more diseases.

Summary of the chapter I

1. Hyperuricemia is a metabolic disorder caused by abnormal purine metabolism, influenced by genetic and environmental factors.
2. Diagnostic criteria for hyperuricemia: >420 μmol/L for men, >357 μmol/L for women (fasting serum uric acid).
3. Core pathology of hyperuricemia: deposition of urate crystals, related to gout, hypertension, diabetes, etc.
4. Current situation in China: There are approximately 177 million patients (13.3% of the population) with hyperuricemia, and the trend of younger age is significant (with a high proportion among those aged 18-35).
5. Current treatment limitations: Common drugs (such as allopurinol, benzbromarone) have side effects such as liver toxicity and allergies. Plant-derived active components have become a research hotspot due to their multi-targeting and low toxicity.

6. *Ginkgo biloba* contains components such as flavonoids and polyphenols, which have anti-inflammatory, antioxidant, and uric acid-lowering effects. Flavonoids can reduce blood uric acid levels by inhibiting uric acid-producing enzymes.

7. Network pharmacology application: Through bioinformatics methods, drug components are rapidly screened and the multi-targeting mechanism is analyzed. Advantages: Wide coverage, low cost, can avoid side effects, and accelerate the research process.

8. Research objective: To screen active components for uric acid-lowering in *Ginkgo biloba* (such as isoquercitrin, β-sitosterol, etc.). Combined with network pharmacology and molecular docking technology, explore its mechanism of action and application as food and medicine.

Chapter II
OBJECT, PURPOSE, AND METHODS OF THE STUDY

2.1 INTRODUCTION

In the treatment of hyperuricemia, *Ginkgo biloba*, as a traditional Chinese medicine with both food and medicine properties, are widely used due to their advantages such as low price, wide availability, and good safety. However, research on their active ingredients and mechanisms of action is still lacking, which limits basic research and clinical application [17]. Therefore, this paper takes *ginkgo biloba* as the object, uses network pharmacology to explore their active components, studies the mechanism of action in the treatment of hyperuricemia, and verifies it by molecular docking technology. Research has found that the uric acid reduction of *ginkgo biloba* is attributed to components such as isorhamnetin, which provides some inspiration for the development of new drugs and the treatment of traditional Chinese medicine.

In terms of the research process, the common target genes of diseases and drugs are screened first and presented using Venn diagrams. Then, a PPI network is constructed to clarify the protein interactions and screen the key targets [18]. Subsequently, enrichment analysis of target genes was conducted, pathways with many genes were screened for in-depth exploration, and the component-target-pathway network diagram was drawn through bioinformatics software [19]. Finally, the binding of drug active ingredients to disease targets is verified by molecular docking technology, and the results are presented in visual images to provide theoretical support for the synthesis of new drugs.

2.2 RESEARCH METHODS AND APPROACHES

2.2.1 RETRIEVAL OF DRUG ACTIVE COMPONENTS AND TARGETS

The medicinal value of *ginkgo biloba* was discovered by the ancients very early on. The Compendium of Materia Medica records that *ginkgo biloba*, when cooked, warm the lungs, benefit qi, relieve asthma and cough, reduce constipation, and stop white turbidity. "Eat raw, reduce phlegm, relieve alcohol intoxication, disinfect and kill insects." [20] According to traditional Chinese medicine, *ginkgo biloba* are neutral in nature, sweet, bitter, astringent in taste, slightly toxic, and belong to the lung and kidney meridians. They have the effects of consolidating the lungs, relieving asthma, stopping vaginal discharge and reducing urine. They have unique effects in treating coughs, asthma, spermatorrhea and enuresis [21]. In the treatment of hyperuricemia, *ginkgo biloba* are important traditional Chinese medicines that are both food and medicine, with many obvious advantages, such as low price, wide availability, easy and simple acquisition, and extremely prominent safety. They have a relatively long history of use in the field of traditional Chinese medicine.

Ginkgo biloba input to the Chinese medicine pharmacology system analysis platform database (TCMSP, https://www.tcmsp-e.com) [222324], to find and screening of the active components of target drug and target name, for all kinds of effective components of *ginkgo biloba* absorption, distribution, metabolism and excretion, such as data, According to the ADME principle [25], the screening criteria included oral bioavailability (OB) and drug-likeness (DL), and the screening conditions were set as follows: Drug similarity (DL) ≥0.18, oral bioavailability (OB) ≥30%, obtain the active ingredients of the core drugs, and understand their matching action targets. The active ingredients were retrieved through the TCMSP database, and the associated target proteins were sorted. Then, the protein database UniProt (https://www.uniprot.org/) [26] was used for targeted retrieval to obtain the protein ID of each target protein. Select "Homo Sapiens" as the analytical species, and match the target gene names (gene ids) with each target protein for subsequent analysis. On this basis, the names of the target genes are merged, the duplicate genes that appear are deleted, and the unique items are retained. This result can be regarded as the predicted target of the active ingredient.

2.2.2 ACQUISITION OF COMMON TARGET GENES OF DISEASE AND DRUG AND CONSTRUCTION OF PPI NETWORK

The purpose of screening the common target genes of diseases and drugs is to identify the relevant target proteins in the active ingredients of traditional Chinese medicine that can treat diseases, that is, the target proteins where drugs can exert their effects. Therefore, it is necessary to first obtain the common target genes of diseases and drugs and visually reveal the common genes through Venn diagrams. Subsequently, the protein-protein interaction network (PPI network) was utilized to clarify the possible potential interaction mechanisms among proteins. The aim was to describe the interrelationships between genes or proteins, thereby obtaining the proteins with the greatest influence in the entire network, screening and obtaining key targets, and providing a strong basis for the in-depth mining of genes in the next step [27].

With keyword "Hyperuricemia" in the human genome database (GeneCards) [28,29] (https://www.genecards.org/), human online Mendelian inheritance platform (OMIM) [30,31] (https://omim.org/) Retrieval was conducted to ultimately obtain the related genes of hyperuricemia. The obtained related genes were de-duplicated and combined, the disease targets were effectively integrated, and then paired with the active component action targets of *ginkgo biloba*. In microscopic letter website [32] (https://www.bioinformatics.com.cn/) import UniProt database of high uric acid hematic disease target genes and target genes, *ginkgo biloba* complete Wayne figure drawing, obtain high uric acid hematic disease - *ginkgo biloba* common target genes. Subsequently, a protein-protein interaction (PPI) network of key targets was constructed. The disease-drug common target genes obtained above were entered into the STRING web site [33,34] (https://cn.string-db.org/), and the selected species was identified as "Homo sapiens". Further obtain the interactions existing among the target proteins. The key targets were screened according to the degree values, the protein

interaction network files were exported, and finally the graphic optimization was carried out through Cytoscape software [35,36].

2.2.3 GENE ENRICHMENT ANALYSIS AND COMPONENT-TARGET-PATHWAY NETWORK DIAGRAM

In order to further obtain the abundance of target genes that exert therapeutic effects on the relevant disease pathways, it is necessary to conduct enrichment analysis on the target genes, screen out the pathways with a larger total number of genes, and then further deeply explore the genes of the obtained pathways, in order to more efficiently exert the active ingredients in the drug and more specifically find disease treatment methods. After completing the gene enrichment analysis and obtaining the disease-related pathways, a series of visualization operations need to be carried out using bioinformatics software to obtain the component-target-pathway network diagram, so as to reveal the relationship among the three more intuitively and provide a strong basis for disease treatment.

Within David database [37] import disease - drug common genes, species selection, identified as "Homo sapiens", implement the GO enrichment analysis [38], KEGG enrichment analysis [39,40], and to get and high uric acid hematic disease has the close relation of signal access path graph. In "micro letter" website (https://www.bioinformatics.com.cn/) into the above results, and the results are visible operation, drawing histogram GO enrichment and KEGG bubble chart, intuitive draw gene which has the most number of genes, or where the path of enrichment of genes to achieve, Obtain the key pathways of the disease to lay the foundation for subsequent research. At present, the genes corresponding to each target protein of the active ingredient and the genes corresponding to the disease-related pathways have been obtained. In order to more clearly show the relationship among the drug - target gene - disease pathway, the Cytoscape software was used to draw the network diagram of the active ingredient - target - signaling pathway of *ginkgo biloba*. The number of edges in

the diagram represents the connection with other nodes. The role played by the nodes in the network graph is closely related to the number of edges of the nodes, and the two are directly proportional.

2.2.4 MOLECULAR DOCKING VERIFICATION

Molecular docking is an important part of drug development, which can reveal the interaction between drug molecules and biological macromolecules, and can also be used for the discovery and optimization of lead compounds. The aim is to find the optimal binding position between drug molecules and disease-related target protein macromolecules, and ultimately discover suitable small molecules as ligands from the drug molecule database. It mainly uses the bioinformatics software CB-DOCK2 and Discovery Studio [41] to verify whether the drug active component target can closely dock with the disease target, thereby exploring the potential therapeutic mechanism and presenting the experimental results in the form of 2D and 3D visualized images. This provides strong theoretical support for exploring disease treatment methods and guiding new drug synthesis.

First, obtain the 3D structure of the drug active component, download the 3D structures of 29 effective components in *ginkgo biloba* from the PubChem database [42,43] (https://pubchem.ncbi.nlm.nih.gov/), save them in "sdf" format, and use them as small molecule ligand molecules for molecular docking. Then, prepare the receptor molecule, select the top six core protein targets based on the degree value, query these 6 core protein targets in Uniprot, obtain the corresponding gene names, and for target protein proteins with more conformations, select the peptide chain of the target gene as much as possible to reduce the error in the docking process. Finally, download the 3D structure of the protein from RCSBPDB (https://www.rcsb.org/) and save it in "pdb" format, as the large molecule receptor molecule. After preparing the ligand and receptor, use the CB-DOCK2 database (https://cadd.labshare.cn/) for molecular docking verification, obtain the 3D diagram, and these results visually show the binding posture of the

receptor and ligand in space, including the position of the binding site, the distance and angle between molecules, and other important information. However, for some detailed analysis, such as the display of hydrogen bonds, hydrophobic interactions, etc., it is not intuitive enough. To analyze the results of molecular docking from different angles, import the 3D molecular docking results into Discovery Studio for processing, obtain intuitive and detailed 2D docking results, observe the matching degree and binding degree, and determine the effectiveness of the active component of the drug. The chemical bonds shown in the picture, such as hydrogen bonds, covalent bonds, and ionic bonds, can reflect the force between groups, thereby being able to determine the drug active component with the best therapeutic effect.

Summary of chapter II

1. Research Background: *Ginkgo biloba* is a medicinal and edible herb with low cost, wide availability, and good safety. However, the mechanism of its uric acid-lowering effect is still unclear.
2. Research Methods: This study combines network pharmacology and molecular docking technology to explore the active components (such as isorhamnetin) of *ginkgo biloba* and their mechanisms of action.
3. Target Selection: Disease-drug common target genes are obtained through Venn diagrams.
4. PPI Network Construction: Analyze protein interactions and screen key targets.
5. Enrichment Analysis: Identify key pathways (GO, KEGG).
6. Network Diagram Drawing: Construct the "component-target-pathway" network.
7. Molecular Docking Verification: Predict the binding ability of active components to targets.
8. Key Tools: TCMSP, STRING, Cytoscape, DAVID, CB-DOCK2, Discovery Studio.
9. Objective: To clarify the mechanism of the active components (such as isorhamnetin) of *ginkgo biloba* in uric acid-lowering, providing a basis for new drug development.

Chapter III
EXPERIMENTAL PART
3.1 INTRODUCTION

In the process of deeply exploring the therapeutic mechanism of *ginkgo biloba* on hyperuricemia, the research team utilized a series of advanced analytical techniques to conduct a comprehensive and detailed mining of the relevant data. Through a rigorous screening process, 21 active ingredients were successfully identified from *ginkgo biloba*, and 290 corresponding potential targets were simultaneously determined. In terms of hyperuricemia, researchers have identified as many as 1,391 disease-related targets.

Subsequently, through precise comparative analysis, the research team discovered 91 identical targets between *ginkgo biloba* and hyperuricemia. To further reveal the potential molecular mechanism of *ginkgo biloba* in treating hyperuricemia, researchers carefully selected several key targets such as TP53, TNF, IL6, PPARG, IL1B and CASP3 from these 91 targets and conducted molecular docking experiments on them.

The results of the molecular docking experiment indicated that the four key targets, TP53, TNF, PPARG and CASP3, exhibited good binding activities with the active components such as isorhamnetin, β -sitosterol, anthocyanidin and (-) -epigallocatechin-3-gallic acid ester in *ginkgo biloba*. Based on this experimental result, researchers predict that TP53, TNF, PPARG and CASP3 may be the core key targets for treating hyperuricemia with *ginkgo biloba*.

Furthermore, through KEGG pathway enrichment analysis, researchers found that *ginkgo biloba* may exert therapeutic effects on hyperuricemia through multiple important signaling pathways, including the TNF signaling pathway, the cancer signaling pathway, and the AGE-RAGE signaling pathway in diabetic complications, etc. These findings provide important clues for a deeper understanding of the molecular mechanism of *ginkgo biloba* in treating hyperuricemia, and also lay a solid theoretical

foundation for the subsequent research and development and clinical application of related drugs.

3.2 RESULTS AND ANALYSIS

3.2.1 SEARCH FOR THE ACTIVE INGREDIENTS AND TARGETS OF THE DRUG

A total of 80 active components of *ginkgo biloba* were retrieved through the TCMSP database. Then, they were screened under the filtration conditions of OB≥30% and DL≥0.18, and it was found that there were a total of 21 active components. Including isorhamnetin, beta-sitosterol, formononetin, (-) -epigallocatechin-3-gallate, etc. The basic information is shown in Table 3-1. Then, the target corresponding to each active ingredient was input into the UniProt database respectively to obtain the name of the target gene. In this experiment, the Uniprot KB knowledge base was mainly used to merge and de-duplicate the target genes of the compounds predicted by the above approach, and establish the "Active Ingredient - Target Database of *Ginkgo Biloba*". Twenty-one active ingredients and 290 related target genes were obtained.

Table 3-1 Active Ingredients of GInkgo biloba

Chinese medicine name	ID	Molecule Name	OB	DL
Ginkgo biloba	MOL011042	18alpha-Hydroglycyrrhetic acid	38.93	0.71
	MOL011059	Ginkgolid B	42.84	0.73
	MOL011061	Ginkgolide B	46.14	0.73
	MOL011063	heneicosadienoic acid	35.61	0.23
	MOL011072	Quinicine	75.44	0.33
	MOL011073	Scillaren A	56.12	0.21
	MOL011074	Scillaren A_qt	57.67	0.78
	MOL011075	Shikodonin	78.16	0.56
	MOL001771	poriferast-5-en-3beta-ol	36.91	0.75
	MOL002773	beta-carotene	37.18	0.58
	MOL000449	Stigmasterol	43.83	0.76
	MOL000354	isorhamnetin	49.6	0.31
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000392	formononetin	69.67	0.21
	MOL000422	kaempferol	41.88	0.24
	MOL004350	Ruvoside_qt	36.12	0.76
	MOL000492	(+)-catechin	54.83	0.24
	MOL005236	gibberellin	81.59	0.53
	MOL006821	(-)-epigallocatechin-3-gallate	55.09	0.77
	MOL008691	alpha-Carotene/ beta,epsilon-Carotene	34.51	0.58
	MOL000098	quercetin	46.43	0.28

3.2.2 ACQUISITION OF COMMON TARGET GENES FOR DISEASES AND DRUGS AND CONSTRUCTION OF PPI NETWORK

(1) Acquisition of disease genes: Disease genes were obtained from GeneCards and OMIM. After sorting and removing duplicates, 1,391 effective genes were obtained.

(2) Acquisition of common target genes for diseases and drugs: 1,391 disease effective target points and 290 drug effective active component target points were imported into MicroBio, and a Venn diagram was drawn as shown in Figure 3-1. A total of 91 intersection genes were found.

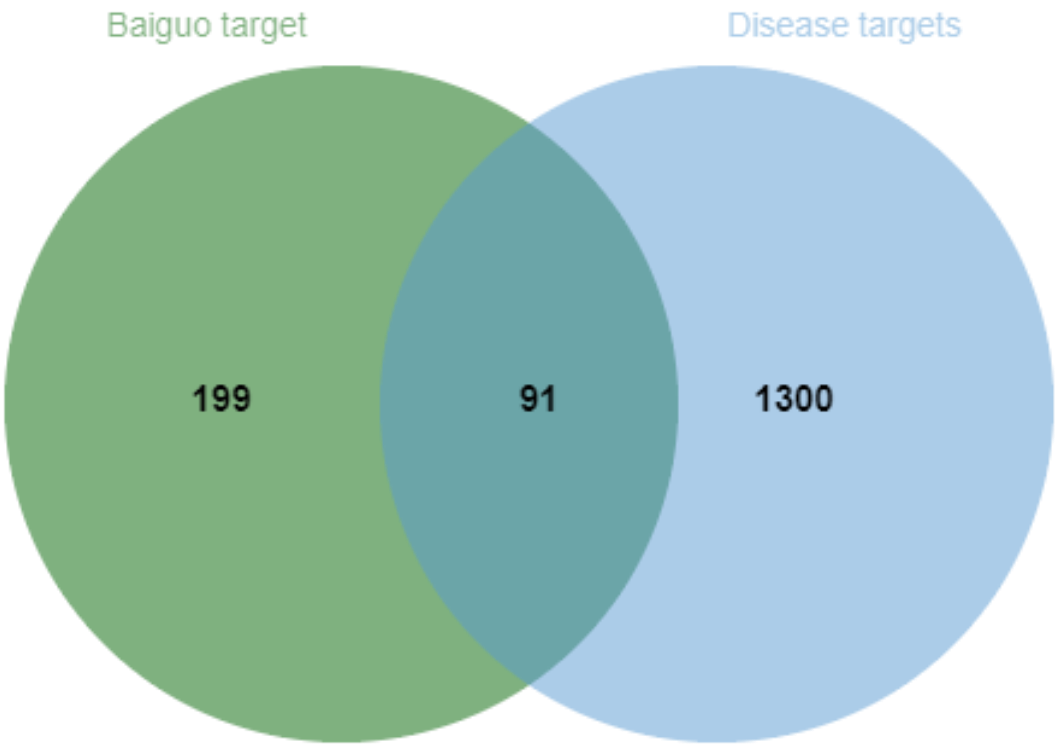


Fig. 3-1 Venn Diagram of disease-drug intersection genes

(3) Construction of the PPI network of key targets: Input the above common genes into the STRING database, as shown in Figure 3-2, to form a PPI network diagram of key targets, and store the PPI network in TSV format. Use Cytoscape software for data processing, sort the core genes by degree value, and the top ten genes are: TP53, TNF, IL6, PPARG, IL1B, CASP3, PTGS2, ESR1, BCL2, MYC, with degree values corresponding to 74, 74, 72, 66, 65, 65, 64, 64, 64, 64 respectively. Targets in the PPI network are displayed as nodes and connected by edges. Key targets have relatively dense edges, indicating that they play a more important role in the PPI network, from which it can be determined which target is more effective.

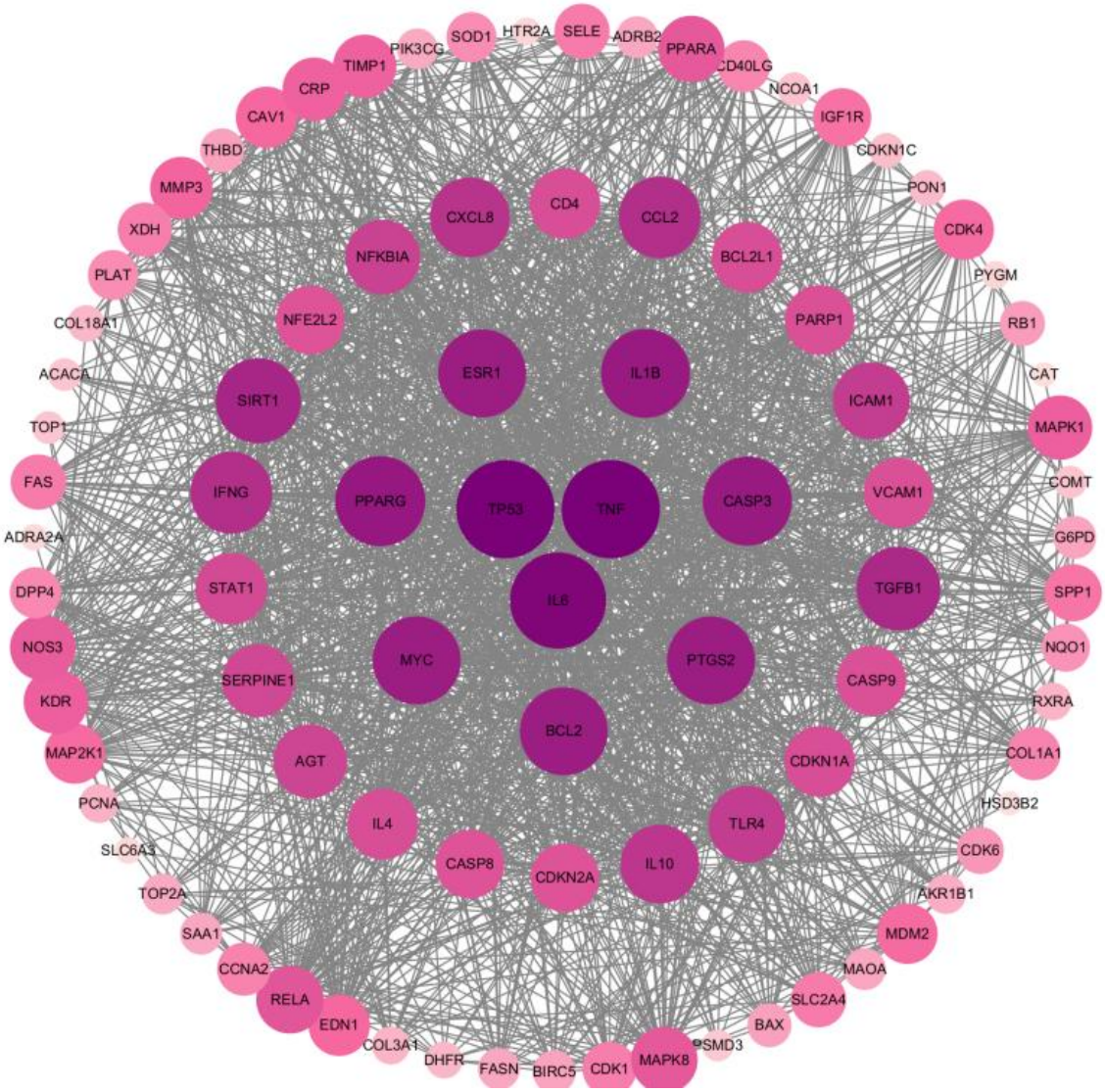


Fig. 3-2 PPI network diagram of disease-drug intersection genes

3.2.3 GENE ENRICHMENT ANALYSIS AND COMPONENT-TARGET-PATHWAY NETWORK DIAGRAM

(1) GO Enrichment: The 91 common target genes of disease and drug obtained in 3.2.2 were imported into the David database to conduct GO enrichment analysis. The bar charts for biological process (BP), cellular component (CC), and molecular function (MF) were created using the "MicroBioInfo" website. For details, see Figure 3-3. The

longer the length of each rectangle in the bar chart, the more genes there are under that process and the more significant the enrichment effect. BP is generally used to describe the biological process that a certain protein needs to complete; CC is used to describe the location where the protein functions, that is, the expression site; MF mainly involves protein functions, such as catalytic ability, transport ability, etc. Through GO enrichment analysis, a large number of target protein genes are classified into different ontology categories based on functional similarity, thereby more efficiently screening the effective component genes of drugs.

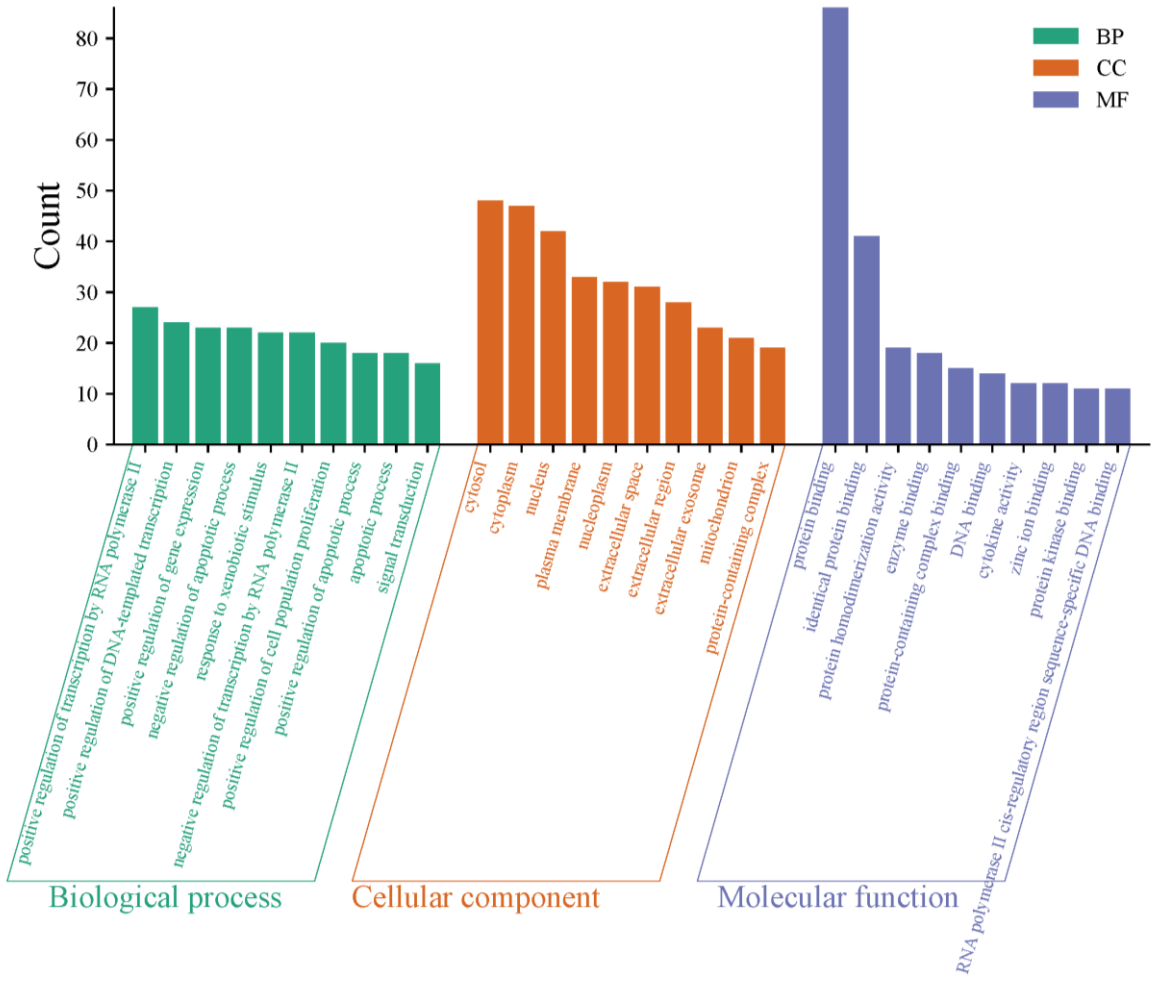


Fig. 3-3 GO enrichment analysis results

(2) KEGG Enrichment: KEGG enrichment analysis revealed that the pathways involved in hyperuricemia mainly include AGE-RAGE signaling pathway in diabetic

complications, Pathways in cancer, Lipid and atherosclerosis, Hepatitis B, Kaposi sarcoma-associated herpesvirus infection, Human cytomegalovirus infection, Fluid shear stress and atherosclerosis, Epstein-Barr virus infection, Pancreatic cancer, Hepatitis C, TNF signaling pathway, Influenza A, Toxoplasmosis, p53 signaling pathway, Chronic myeloid leukemia, Malaria, Chagas disease, Cellular senescence, Small cell lung cancer, Platinum drug resistance, etc. See Figures 3-4. By analyzing the KEGG enrichment map, we can know that the larger the circle, the more genes are enriched in this pathway. Therefore, the most genes are enriched in cancer-related pathways. The smaller the p-value, the less accidental it is, that is, the more likely the genes are enriched in the related pathways, which provides an efficient and powerful basis for guiding us on how to treat diseases. In addition, in the David database, the pathways closely related to hyperuricemia, Pathways in cancer and Lipid and atherosclerosis, were searched. See Figures 3-5 and 3-6.

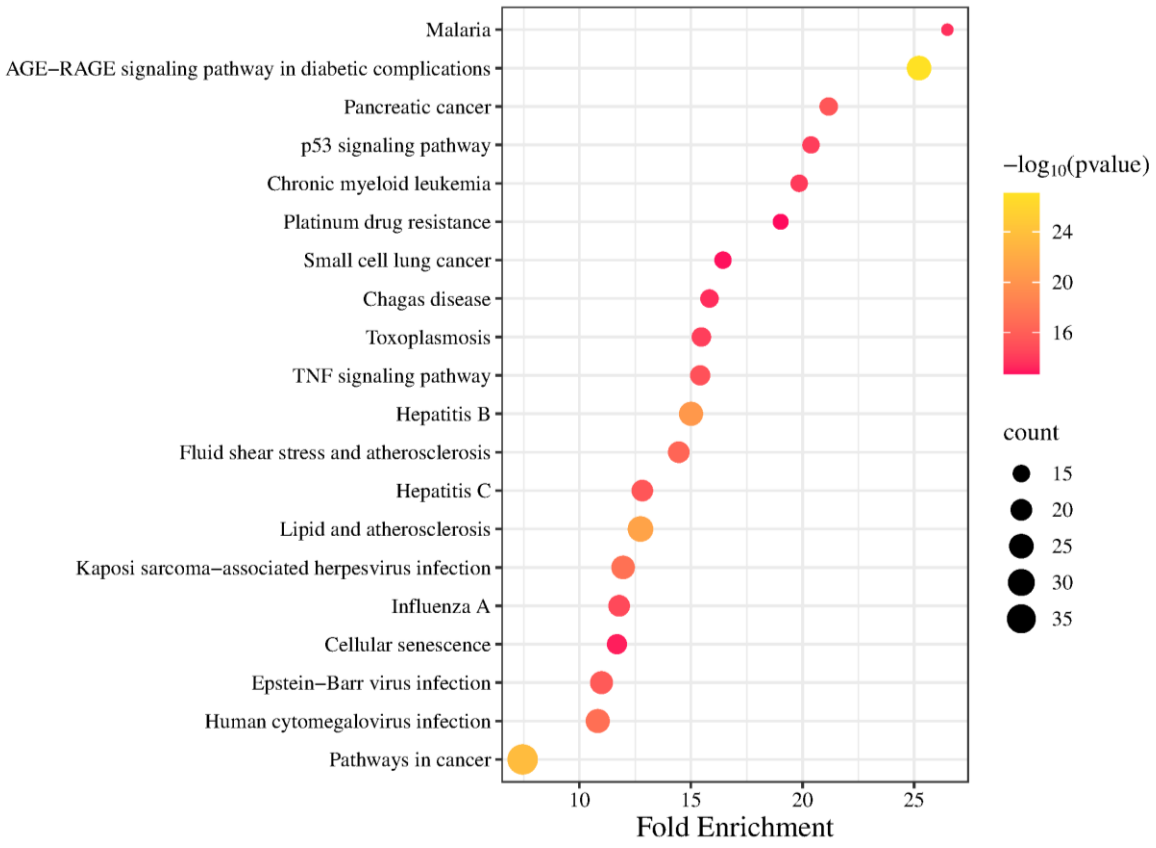


Fig. 3-4 KEGG enrichment analysis results

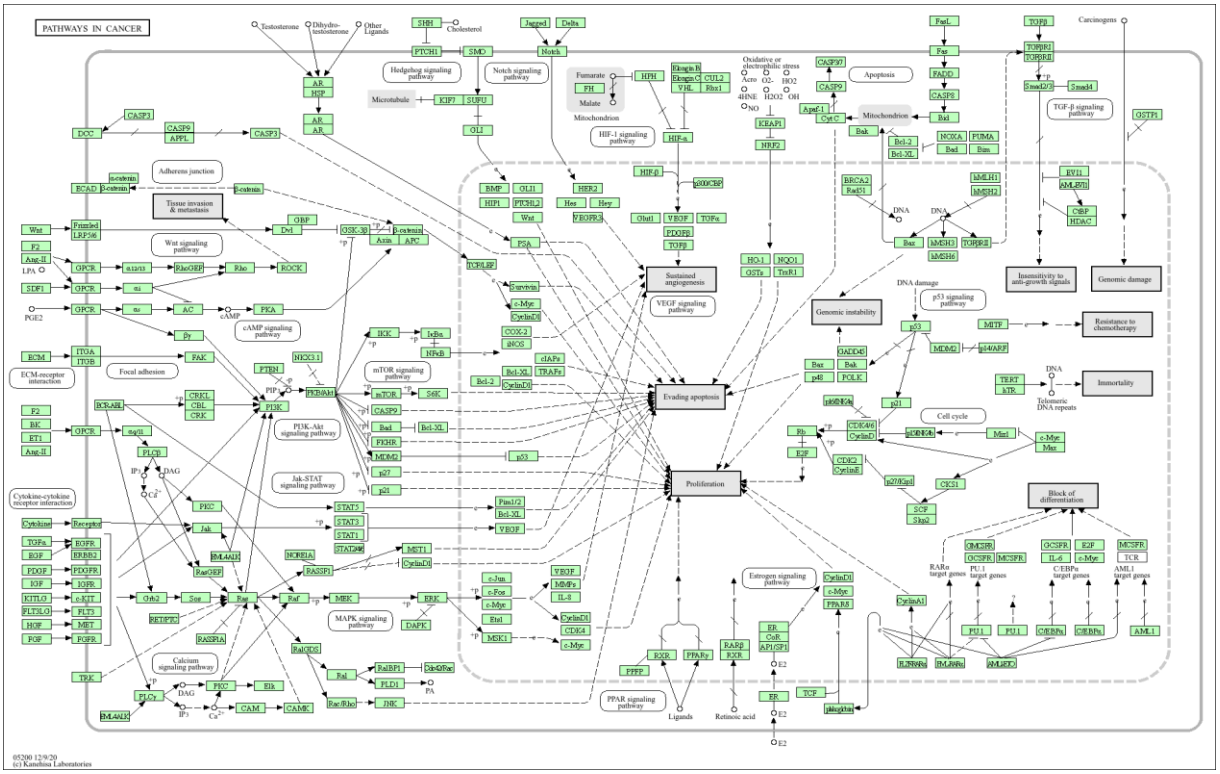


Fig. 3-5 Pathways in cancer signaling pathway map

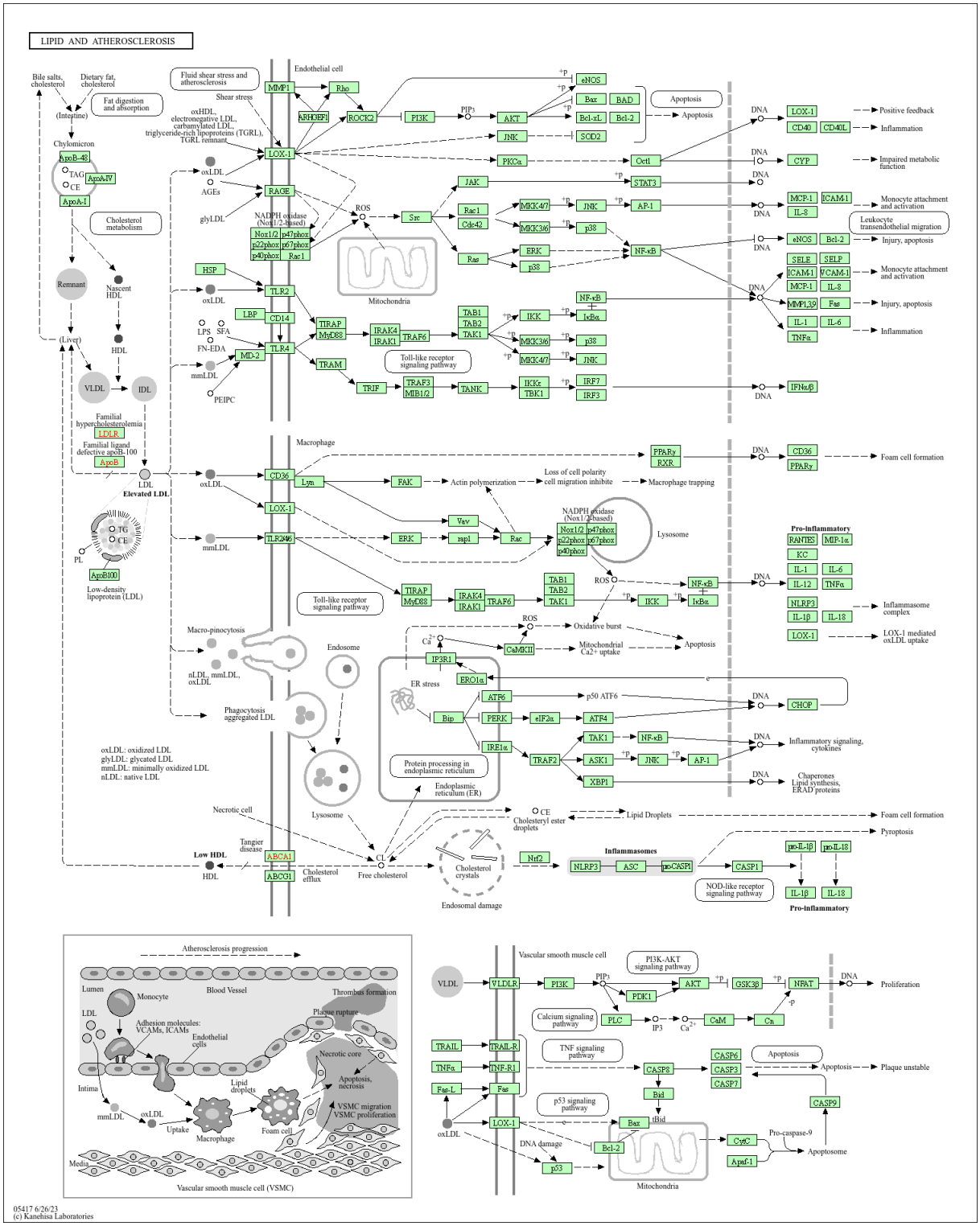


Fig. 3-6 Lipid and atherosclerosis signaling pathway diagram

(3) Analysis of the active ingredients, target sites, and signaling pathway network of *ginkgo biloba*: Import the obtained data on *ginkgo biloba* into Cytoscape software,

including effective active ingredients and corresponding protein targets, to complete the construction of the "drug active ingredient-target site-disease pathway" network, as shown in Figures 3-7. The information presented in the network diagram clearly demonstrates that the therapeutic effects of *ginkgo biloba* on hyperuricemia are achieved through the coordinated action of multiple components, multiple targets, and multiple pathways. Green oval nodes represent drug active ingredients, purple octagonal nodes represent disease-related pathway signals, and blue square nodes represent target gene sites. Edges indicate connections between nodes; the more edges, the closer the connection to other nodes, and the greater the role played in the entire network.

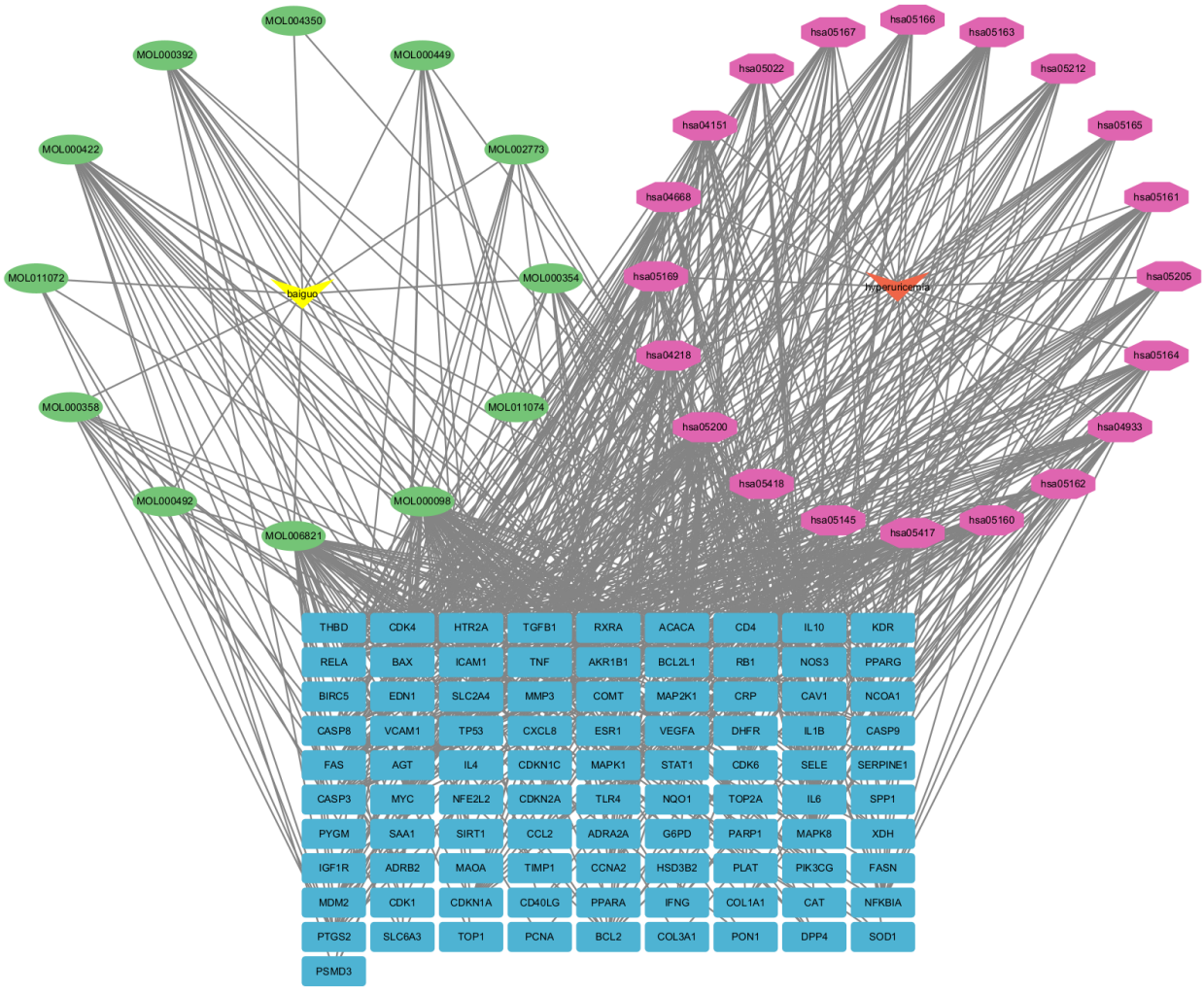
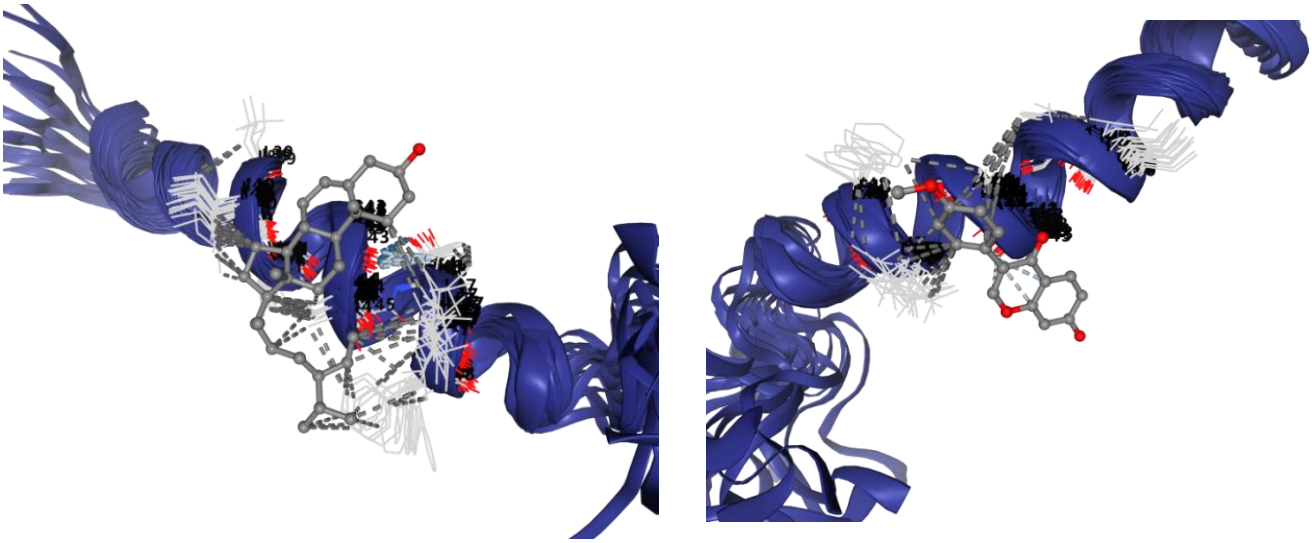


Fig. 3-7 Diagram of active components - target sites - signaling pathways of *ginkgo biloba*

3.2.4 MOLECULAR DOCKING VERIFICATION

Molecular docking verification was conducted using the CB-DOCK2 database. The resulting 3D diagrams visually presented the binding postures of the receptor and ligand in space, including the positions of the binding sites, the distances and angles between molecules, and other important information. To more comprehensively and deeply analyze the results of molecular docking, the 3D molecular docking results were imported into Discovery Studio for processing, obtaining intuitive and detailed 2D docking results. By observing the matching degree and binding extent, the degree of action of the active components was determined. The obtained results were screened and ranked. The results indicated that isorhamnetin, β-sitosterol, formononetin, and (-)-epigallocatechin-3-gallate had higher binding affinities with tumor protein p53 and tumor necrosis factor, providing strong evidence for proving the mechanism of action of the effective active components. The 3D interaction diagrams of ligand-receptor are shown in Figure 3-8, and the 2D stereograms are shown in Figure 3-9.

A B



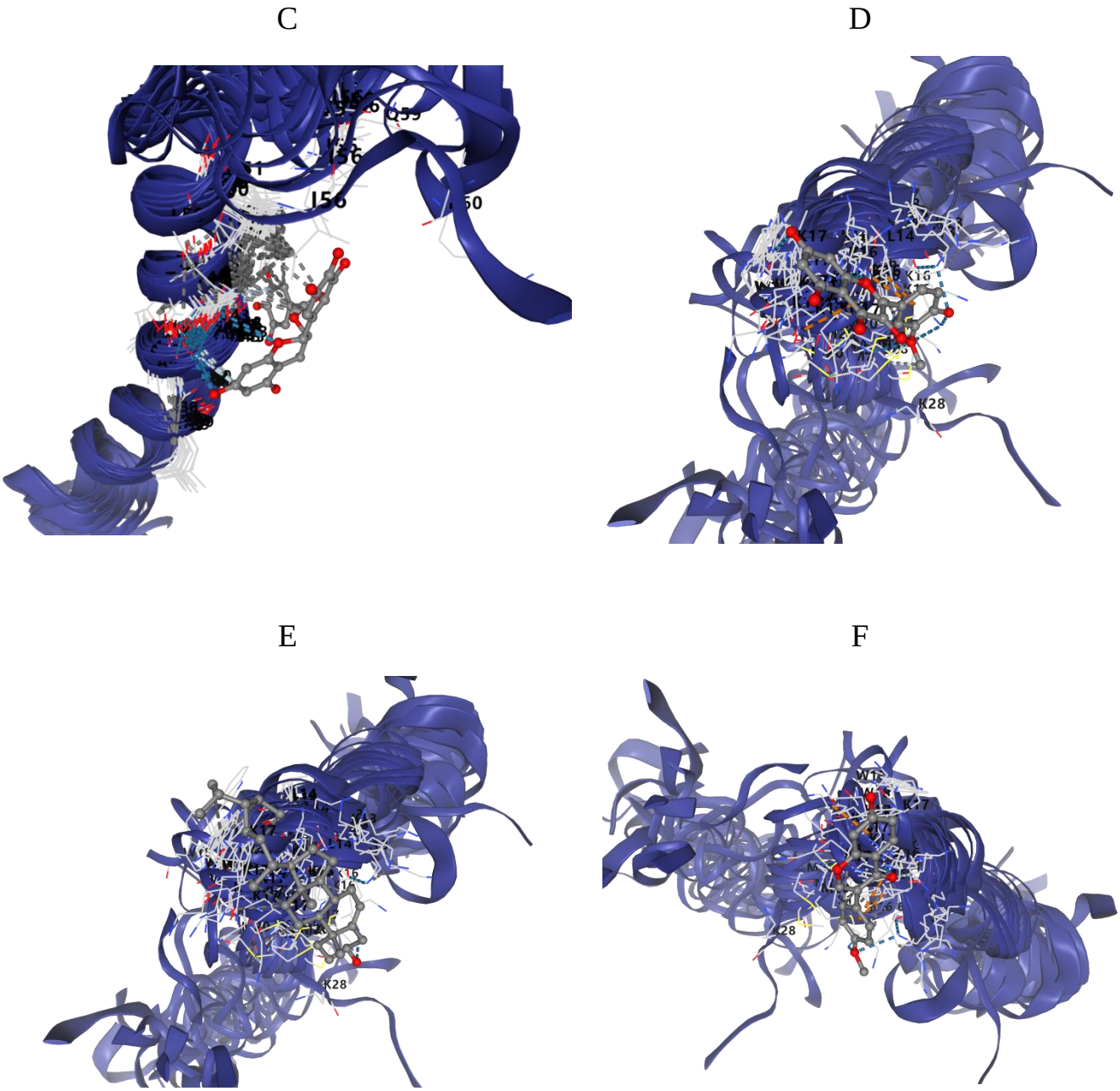
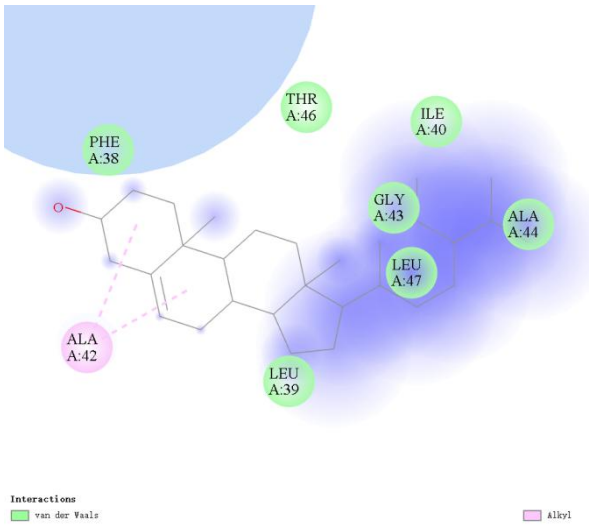


Fig. 3-8 Three-dimensional planar diagram of ligand-receptor interaction

Note: (A).TNF binding to β-glucosinolate; (B).TNF binding to sulfolan; (C).TNF binding to (-)-epigallocatechin-3-gallate; (D).TP53 binding to isorhamnetin; (E).TP53 binding to β-glucosinolate; (F).TP53 binding to sulfolan

A


THR
A:46
ILE
A:40
PHE
A:38
GLY
A:43
ALA
A:44
LEU
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ALA
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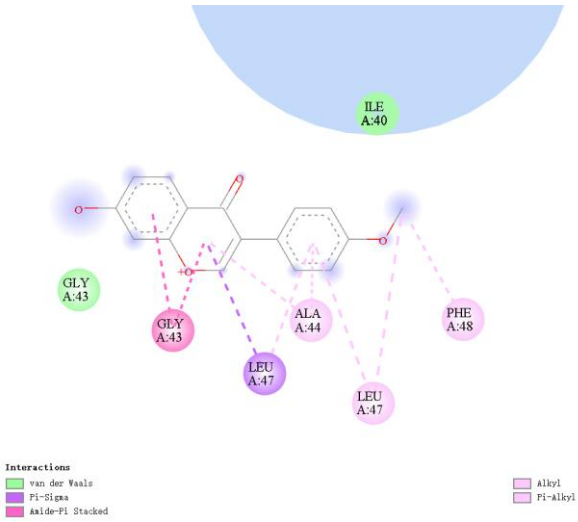
LEU
A:39
Interactions
van der Waals
Alkyl

B


ILE
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GLY
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GLY
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ALA
A:44
PHE
A:48
LEU
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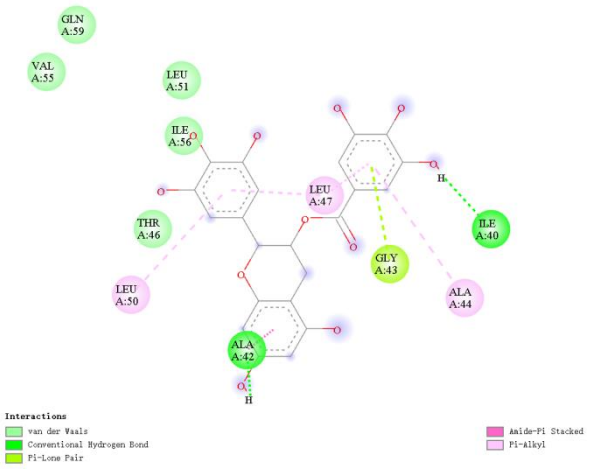
A:47
Interactions
van der Waals
Pi-Sigma
Amide-Pi Stacked
Alkyl
Pi-Alkyl

C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VAL
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LEU
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ILE
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LEU
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THR
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ILE
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GLY
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LEU
A:50
ALA
A:44
ALA
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H
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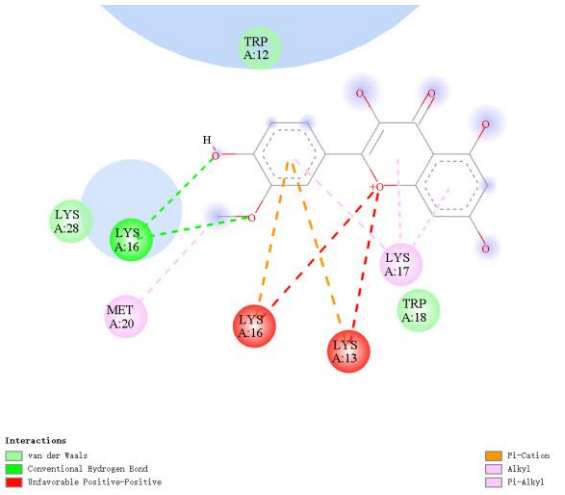
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Lone Pair
Amide-Pi Stacked
Pi-Alkyl

D


TRP
A:12
H
LYS
A:28
LYS
A:16
LYS
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MET
A:20
LYS
A:16
TRP
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LYS
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Interactions
van der Waals
Conventional Hydrogen Bond
Unfavorable Positive-Positive
Pi-Cation
Alkyl
Pi-Alkyl

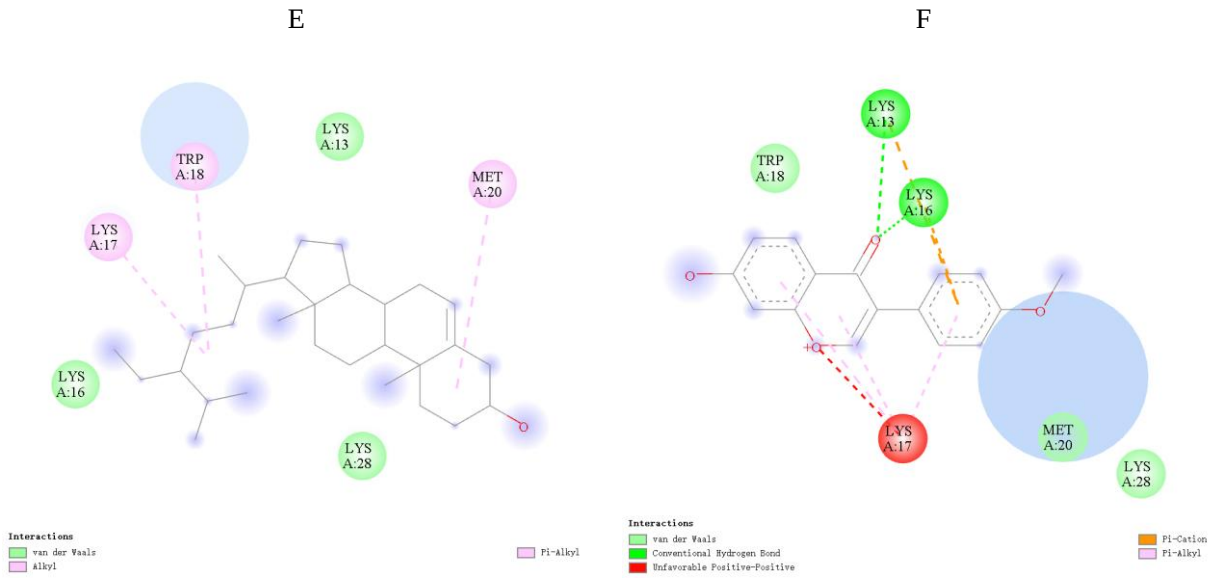

Fig. 3-9 Two-dimensional planar diagram of ligand-receptor interaction

Note: (A).TNF binding to β-glucosinolate; (B).TNF binding to sulfolan; (C).TNF binding to (-)-epigallocatechin-3-gallate; (D).TP53 binding to isorhamnetin; (E).TP53 binding to β-glucosinolate; (F).TP53 binding to sulfolan

Summary of chapter III

1. Screening results of active components from *ginkgo biloba*: 80 components of *ginkgo biloba* were obtained from the TCMSP database. By setting the criteria of OB ≥ 30% and DL ≥ 0.18, 21 active components were finally retained. Through UniProt matching, 290 related target genes were obtained.

2. Disease-drug common target analysis: 1391 genes related to hyperuricemia were obtained from GeneCards and OMIM. Through Venn diagram analysis, 91 common targets of drugs and diseases were identified.

3. PPI network and key targets: The key targets ranked by degree values were TP53, TNF, IL6, PPARG, IL1B, etc. The more edges in the PPI network diagram, the more crucial the target is in the network.

4. Gene enrichment analysis: (1) GO enrichment analysis (biological process, cellular component, molecular function) BP (biological process): The gene enrichment was the most significant (such as inflammatory response, metabolic regulation). CC (cellular component): The targets were mostly located in the cell membrane, nucleus, etc. MF (molecular function): Involved in protein binding, enzyme activity, etc. (2) KEGG pathway enrichment: Main pathways: AGE-RAGE (diabetic complications), lipid and atherosclerosis, TNF signaling pathway, p53 signaling pathway, etc. Cancer-related pathways: Enriched genes were the most (such as Pathways in cancer). Significance: The smaller the p-value, the stronger the association between the pathway and the disease.

5. Molecular docking verification results and the best binding component: Isorhamnetin, β-sitosterol, etc. had tight binding with TP53, TNF. Interaction forces: hydrogen bonds, hydrophobic interactions, etc. (displayed in 2D/3D diagrams).

CONCLUSION

Hyperuricemia is a disease characterized by an increase in the level of uric acid in the blood due to excessive uric acid production in the body or reduced uric acid excretion [44]. It is a key cause for the development of gout and many other diseases such as cardiovascular diseases, kidney diseases, hypertension, and metabolic syndrome. Uric acid is the final product of the breakdown of purine nucleotides [45], and xanthine oxidase in the liver is the key enzyme for uric acid decomposition, while urate transporter proteins in the kidneys are the main transport proteins for eliminating uric acid [46]. With the improvement of people's living standards, dietary structure has undergone significant changes, characterized by a significant increase in the intake of high-energy and high-purine foods, leading to an increasing incidence of hyperuricemia and gout, and a trend of younger onset [47]. Uric acid and its crystalline products can induce inflammatory responses in the vascular wall, stimulate the production of IL-6 and TNF by monocytes [48]. The active components in *ginkgo biloba*, such as isorhamnetin, β-sitosterol, and isorhamnetin-3-O-glucoside, can inhibit the production and expression of inflammatory cytokines such as tumor necrosis factor, effectively controlling the increase in IL-6 and TNF caused by uric acid, thereby enhancing the immune response of the human body, reducing the inflammatory response of the body, and achieving the purpose of reducing blood uric acid levels while achieving anti-inflammatory effects. The mechanism of *ginkgo biloba* in treating gouty arthritis involves TNF signaling pathways, AGE-RAGE signaling pathways in diabetic complications, cancer signaling pathways, etc., and these reactions are also closely related to the immune inflammatory response of the human body. The results show that the AGE-RAGE pathway is closely related to the occurrence of inflammatory responses, it can upregulate the phosphorylation level of MAPK, promote the expression of inflammatory factors, including IL-1, tumor necrosis factor, IL-6, etc. [49].

Therefore, *ginkgo biloba* mainly functions in inhibiting inflammation and immune regulation, by acting on multiple components, multiple targets, and multiple pathways to regulate inflammatory factors in the blood, adjust the immune function of the human body, and simultaneously inhibit the inflammatory response of the body, thereby achieving the therapeutic effect of gouty arthritis.

According to modern pharmacological research results, *ginkgo biloba* has good effects in anti-bone damage and regulating cell apoptosis, and can achieve the effect of protecting bone joints and alleviating bone joint damage. In the process of maintaining joint cartilage function and matrix secretion, chondrocytes play a crucial role and are indispensable components. Studies have shown that in the development of gouty arthritis, joint cartilage is often damaged, and the apoptosis of chondrocytes is closely related to the reduction of cartilage matrix secretion 50. *Ginkgo biloba* lactone inhibits IL-17-induced ATDC5 cell inflammatory damage through JNK and NF-κB signaling pathways, has a protective effect on chondrocytes, and can also inhibit the expression of inflammatory mediators such as IL-1β-induced ATDC5 chondrocytes and inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) in the rat osteoarthritis model through AMPK/SIRT1/mTOR pathways, thereby exerting anti-inflammatory effects [51]. In terms of regulatory pathways, *ginkgo biloba* mainly regulates the TNF signaling pathway, cancer signaling pathways, and the signaling pathway of AGE-RAGE in diabetic complications to regulate chondrocyte proliferation, differentiation, and apoptosis. Therefore, *ginkgo biloba* can alleviate the destruction of joint cartilage in patients with gouty arthritis, further alleviate the inflammatory response of gouty arthritis, and significantly improve the clinical symptoms.

In conclusion, this paper, through the method of network pharmacology, breaks through the single-target research model and provides great convenience for the research of traditional Chinese medicine. It explores the network mechanism by which various active components in Platycladus orientalis act synergistically through multiple components, multiple targets, and multiple pathways on hyperuricemia. Through molecular docking technology, it verifies the interaction between the active ingredients

of the drugs and the disease targets. It is found that the isorhamnetin, β-sitosterol, and strobilin in Platycladus orientalis can effectively alleviate the clinical symptoms of hyperuricemia by means of anti-inflammatory, analgesic, and reducing uric acid levels, and sometimes can also achieve the effect of protecting the kidneys. Compared with Western medicine, it has the advantages of less toxic side effects, safety and reliability, and long-term application. However, due to the complex and variable structure of traditional Chinese medicine and the numerous target points, the mechanism of action is difficult to be clarified. Currently, the research on traditional Chinese medicine in the treatment of hyperuricemia still has certain limitations. Most studies only focus on the validation of efficacy, and the sample size of the test population is limited or the selection criteria are not rigorous enough, which to some extent affects the reliability and scientificity of the experimental results. Through literature analysis, it can be found that the existing traditional Chinese medicine intervention schemes can play a certain role in alleviating the symptoms of gout caused by hyperuricemia, but there are still obvious deficiencies in blocking the disease progression and achieving clinical cure. Therefore, we should work harder to study, and expect more reliable and practical traditional Chinese medicine to be applied to clinical practice, bringing benefits to our patients, and promoting the development of our traditional Chinese medicine culture [52].

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