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 active ingredients in Dark plum on uric acid metabolism pathway**
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Specialty 162 "Biotechnology and Bioengineering"
Educational and professional program "Biotechnology"

Completed: student of group BEBT-21
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Kyiv 2025

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Educational and professional program Biotechnology

APPROVE
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«___»_____2025

ASSIGNMENTS
FOR THE QUALIFICATION THESIS
Shi Moran

1. Thesis topic **The effect of active ingredients in Dark plum on uric acid metabolism pathway**

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

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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	
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7	Submission of qualification work to the supervisor for feedback	until 27 May 2025	
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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 _____ Shi Moran

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Abstract

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Hyperuricemia is a metabolic disease characterized by excessive uric acid levels in the blood due to purine metabolism disorders. It can lead to many complications, such as gout and kidney stones. The traditional Chinese medicine - Prunus mume has shown good therapeutic effects in clinical practice. Therefore, in this study, network pharmacology combined with molecular docking technology was adopted to systematically explore the related active components and their mechanisms of action of Prunus mume in the treatment of hyperuricemia. Method: From the perspective of network pharmacology, in this study, the active components of Prunus mume were screened through the TCMSP database, thereby obtaining 8 candidate components that conformed to the pharmacokinetic parameters (OB≥30%, DL≥0.18). In this study, target genes were standardized using the UniProt database to obtain 118 drug targets. A total of 1389 targets related to hyperuricemia were collected through the GeneCards and OMIM databases, and 39 common targets were obtained through Wayne analysis.This study demonstrated through GO and KEGG enrichment analysis that these targets were significantly enriched in biological processes such as inflammatory response, oxidative stress and purine metabolism, as well as related signaling pathways.From the perspective of molecular docking technology, the results of molecular docking indicate that the core active components (such as quercetin, kaempferol, etc.) have relatively strong binding capabilities with key targets (such as AKT1, TNF, etc.).Finally, this study revealed the potential mechanism of Prunus mume in treating hyperuricemia through the synergistic effect of "multiple components - multiple targets - multiple pathways", providing a new idea for the research on the modernization of traditional Chinese medicine.

Key words: Fructus Mume; hyperuricemia; network pharmacology; molecular docking; mechanism of action

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INTRODUCTION

This study adopted an innovative research strategy integrating network pharmacology and molecular docking techniques to systematically explore the potential mechanism of action of the traditional Chinese medicine Prunus mume in the treatment of hyperuricemia. Firstly, a network of active components and targets of Prunus mume was constructed through database mining and literature review. Then, by combining the target database of hyperuricemia, a multi-dimensional interaction network of "components-targets-diseases" was established. Key findings indicated that flavonoids such as quercetin and kaempferol in Prunus mume might regulate core targets such as AKT1 and TNF-α, thereby influencing key pathological processes including inflammatory response, oxidative stress, and uric acid metabolism. Molecular docking simulations further confirmed the stable binding characteristics of these active components with key target proteins. This study not only provided a theoretical basis for clarifying the scientific connotation of Prunus mume in the treatment of hyperuricemia but also offered methodological references for the modernization research of traditional Chinese medicine.

Chapter I
LITERATURE REVIEW

Hyperuricemia (HUA) is a systemic inflammatory response disease caused by abnormally elevated uric acid content in the blood of the body. Hyperuricemia (HUA) is caused by poor excretion by the kidneys or excessive secretion of uric acid. Uric acid crystals can deposit in the joints, leading to gout [1]. HUA can cause lipid metabolism disorders and accelerate the development of atherosclerosis. Studies have shown that hyperuricemia can cause and aggravate hypertension, stimulate the proliferation of vascular smooth muscle cells, promote thrombosis, and accelerate arteriosclerosis. Hyperuricemia can cause the accumulation of lipid inflammatory substances in the vascular endothelium in the body, leading to damage of vascular endothelial cells, generating inflammatory changes, and promoting atherosclerosis [2, 3]. With the development of The Times and the improvement of people's living standards, the prevalence and incidence of hyperuricemia and gout worldwide are increasing. The prevalence of hyperuricemia in China is also increasing. Hyperuricemia is no longer a rare phenomenon as before. Instead, its prevalence has gradually risen from 1.4% in 1980 to 8.4% in 2009-2010, 11.1% in 2015-16, and 14.0% in 2018-2019 [4-5]. Therefore, it is not difficult to see that hyperuricemia has become a public health problem that we cannot ignore.

Hyperuricemia is a phenomenon characterized mainly by excessive serum uric acid in the human body. Uric acid is the end product of purine metabolism in the human body. It is decomposed from nucleic acids and other purine compounds decomposed by cell metabolism and purine in the diet through the action of enzymes. It is a result caused by high-purine diet, alcohol consumption, fatigue and drugs [7]. According to traditional Chinese medicine, hyperuricemia is caused by a diet rich and greasy, which leads to dysfunction of the spleen and kidneys, retention in the joints, and long-term damage to the internal organs. The onset of hyperuricemia is closely related to diet. As

early as over two thousand years ago in China, the "Suwen: Zang Qi Fashi Lun" recorded that "Five grains are for nourishment, five fruits for assistance, five livestock for benefit, and five vegetables for nourishment. When the flavors are in harmony, one should consume them to replenish essence and qi", which summarized the content of a reasonable and balanced diet.

Food can not only be utilized by the human body to provide energy and nutrients to meet basic survival needs, but also be used to treat diseases and nourish the human body. This characteristic of food is referred to in traditional Chinese medicine as "food and medicine sharing the same origin", also known as "medicine and food sharing the same origin" or "medicine and food sharing the same origin" [8-10]. In fact, the claim that "food and medicine share the same origin" has existed since ancient times. The earliest medical book in China, the "Huangdi Neijing", records that "Poisons attack evil, grains nourish the body, fruits assist, livestock benefit, and vegetables fill the body. When the scents are in harmony, they should be taken to replenish essence and qi" as well as "Food should be consumed in the same way" and "Medicine dispels, food follows". Therefore, grains, fruits and vegetables nourish the essence of the human body and are supplemented with medicine to treat diseases.

Dark plum, as a food and medicine with the same origin, is not only a delicious fruit but also a traditional Chinese medicine with the same origin. In the "Shennong's Classic of Materia Medica", dark plum is listed as a middle grade, stating: "It mainly relieves qi, eliminates heat, irritability and fullness, soothes the mind, relieves limb pain, makes the limbs dry and inbenevolent, and causes dead muscles." Li Shizhen recorded in Compendium of Materia Medica that "Prunus mume is sour, warm, neutral and astringent. It is mainly used to astringe the lungs and intestines, stop chronic cough, diarrhea, dysentery, nausea, dysphagia, ascaris, vomiting and defecation, reduce swelling and phlegm, kill parasites, and detoxify fish, horse sweat and sulfur." Therefore, using prunus mume as a medicinal material for treating hyperuricemia is undoubtedly the best choice [11]. However, there are numerous targets for traditional Chinese medicines that are both food and medicine, and the volume is huge. At present, it is not possible to quickly and accurately screen out the drug components for treating

hyperuricemia from the scientific level. For this purpose, this paper combines the innovative research of network pharmacology and molecular docking. Network pharmacology is a newly developed discipline based on the theories of pharmacology, bioinformatics and computer science. Currently, network pharmacology is gradually becoming a new tool for the development of new drugs and the study of drug action mechanisms. Network pharmacology constructs a "drug-target" network through the structural effects of drugs to predict drug targets and their mechanisms of action. It is a new method for studying traditional Chinese medicine [13]. molecular docking technology is a method for designing drugs by utilizing the interaction between receptors and ligands, and it is a tool for predicting the affinity of drug active ingredients to receptors.

In this project, through network pharmacology, the central targets obtained from the "drug - target - pathway - disease" network, GO, and KEGG enrichment analysis of the active ingredients and action targets of Prunus mume for the treatment of hyperuricemia were molecular-linked with the active ingredients of Prunus mume, and the affinity between the active ingredients of Prunus mume and the target proteins for the treatment of hyperuricemia was verified and predicted. To infer and predict the main active ingredients and mechanism of action of Prunus mume in the treatment of hyperuricemia, and to provide a theoretical basis for the treatment of hyperuricemia with Prunus mume.

Summary of the chapter I

1.The first chapter, the introduction section, systematically expounds the overall thinking and research value of this study. It begins with the epidemiological characteristics of hyperuricemia and its current treatment status, pointing out the limitations of current chemical drug treatment and analyzing the unique advantages of traditional Chinese medicine in the treatment of metabolic diseases.

2.When reviewing the research progress at home and abroad, it focuses on discussing the application value of network pharmacology methods in the study of complex

systems of traditional Chinese medicine and the important role of molecular docking technology in the verification of drug targets. Regarding the research object, Plum, it particularly emphasizes the gap between its application history in traditional medicine and modern research, and points out the necessity of systematically explaining its mechanism of reducing uric acid.

3.The research is based on an innovative perspective of interdisciplinary integration, aiming to reveal the multi-target mechanism of *Prunus mume* in treating hyperuricemia by integrating modern computational biology technology with traditional Chinese medicine theory. This not only provides methodological references for the modernization research of traditional drugs but also lays a theoretical foundation for the development of new uric acid-lowering drugs.

Chapter II
OBJECT, PURPOSE, AND METHODS OF THE STUDY

2.1 SEARCH FOR THE EFFECTIVE COMPONENTS AND TARGETS OF PLUM

Prunus mume is the nearly mature dried fruit of Prunus mume, a plant of the Rosaceae family. It is one of the important traditional Chinese medicines [13], with a long history and wide application [15]. According to traditional Chinese medicine theory, it is sour and astringent in nature, and belongs to the liver, spleen, lung and large intestine meridians. It has the functions of consolidating the lung and astringent the intestines, promoting the production of body fluids and quenching thirst, and calming roundworms and relieving pain. Modern pharmacological studies have shown that prunus mume species also possess certain antioxidant activities, anti-inflammatory, antibacterial, anti-tumor, hypoglycemic and lipid-lowering properties. These activities are related to the relatively high organic acids (citric acid, malic acid, etc.), flavonoids (quercetin, kaempferol, etc.), phenolic acids (chlorogenic acid, caffeic acid, etc.), triterpenoids and other substances contained in Chinese plums.

Research on the therapeutic effect of Prunus mume on metabolic diseases has gradually been studied with the increasing emphasis on natural medicines in recent years. Studies have shown that prunus mume extract has a strong effect in lowering uric acid, which may be related to its ability to reduce uric acid levels, promote uric acid excretion, and improve renal function, etc. For example, the organic acid substances in Chinese plums may have a competitive inhibitory effect on xanthine oxidase, thereby reducing the level of uric acid in the body. The flavonoids in Chinese plums may have antioxidant and anti-inflammatory effects, reducing the oxidative stress and inflammatory response of hyperuricemia in the body, thereby playing a protective role against hyperuricemia and renal function, and promoting the excretion of uric acid in

the body. The polyphenols in Chinese plums may affect the metabolism and excretion of uric acid in the body by regulating the intestinal flora. At present, only preliminary research has found that Chinese plums have the effect of lowering uric acid. The specific mechanism of their uric acid-lowering effect remains unclear, that is, which substances in Chinese plums play the main role in lowering uric acid and how these substances target the body. Therefore, this project adopts network pharmacology and combines molecular linkage technology to screen the compounds that may be related to the uric acid reduction of Prunus mume, predict the potential targets related to uric acid metabolism, and provide a theoretical basis and data support for the related research on the treatment of hyperuricemia with Prunus mume in the future.

The specific operation process utilized the TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform) [18]. database to retrieve all the chemical components of Prunus mume. Pharmacokinetic parameters were used for screening, with Oral bioavailability (OB) ≥30% and drug-likeness (DL) ≥0.18 as the criteria to obtain components with potential pharmacological activity. Systematically sort out and understand these active ingredients to clarify their chemical structures and pharmacological properties. The potential targets corresponding to the active ingredients were obtained through the TCMSP platform. The obtained protein names were imported into the UniProt (https://www.uniprot.org/) database, and the corresponding standard gene names were selected under Organism and Homo sapiens screening. Finally, the data should be processed correctly, such as deduplication and standardization, to lay a solid foundation for the construction of the potential target network of the active components of Prunus mume in the following text, and to provide data support for the subsequent network pharmacological analysis and molecular docking experiments.

2.2 SCREENING OF COMMON TARGETS FOR DISEASES AND DRUGS AND CONSTRUCTION OF PROTEIN INTERACTION NETWORKS

In order to explore the potential mechanism of action of prunus mume in the treatment of hyperuricemia, in this experiment, on the basis of obtaining the possible

target genes of the effective components of Prunus mume, the possible target genes of hyperuricemia were also obtained through the disease target database, and the common target genes of drugs and diseases were obtained through Wenn diagrams, that is, the important target genes of prunus mume in the treatment of hyperuricemia. In order to construct the protein-protein interaction (PPI) network, this study utilized the STRING database [19], so as to be able to analyze the interaction relationships between target genes and provide a theoretical basis for subsequent molecular docking and mechanism verification. Through the common target genes of drugs and diseases and the PPI network, a comprehensive analysis of the mechanism of action of Prunus mume in the treatment of hyperuricemia with multiple targets and pathways was conducted from the perspective of systems biology.

In the process of concrete operation, first to "hyperuricemia" as the key words, in the human genome database (GeneCards, https://www.genecards.org/) [20-21] and human online Mendelian inheritance platform (OMIM, https://www.omim.org/) [22] Genes related to hyperuricemia were retrieved. The genes in the GeneCards database contain rich functional annotations of genes and information related to diseases, while OMIM only collects gene information of genetic diseases. Therefore, the combination of the two can ensure that the retrieved genes for hyperuricemia are comprehensive and accurate. The target gene set of hyperuricemia disease was obtained by sorting and removing duplicate data from the retrieval results. The target genes of active ingredients of Prunus tomentosa and hyperuricemia disease were imported into the bioinformatics.com.cn/ (https://www) to obtain the intersection target of drugs and diseases. So as to clarify the potential target of action between the active components of Prunus mume and hyperuricemia, and provide important data basis for the next step of mechanism exploration.

Then import it into String (https://string-db.org/), select the species "Homo sapiens" to construct a protein-protein interaction (PPI) network, observe the interactions among the target genes in the PPI network, and determine the key nodes and modules in the PPI network. These may become the key nodes for the anti-

hypertension effect of prunus mume. Import PPI network and Cytoscape (version3.9.1) software for visual adjustment [23].

2.3 GENE FUNCTION ENRICHMENT AND CONSTRUCTION OF COMPONENT-TARGET-PATHWAY NETWORKS

Since hyperuricemia is a complex of metabolic diseases, its onset may be the result of the combined action of multiple genes and multiple pathways. Therefore, in order to explore the therapeutic targets of prunus mume in hyperuricemia more comprehensively, based on the 39 drug-disease common targets obtained previously, bioinformatics mining was carried out. Gene Ontology(GO) functional enrichment analysis [24] and Kyoto Encyclopedia of Genes and Genomes(KEGG) [26] enrichment analysis were conducted on the action targets of the active components of Prunus mume from the aspects of molecular functions, biological processes and pathways. Construct the "component - target - pathway" network diagram of Prunus mume in the treatment of hyperuricemia, and visually present the therapeutic mechanism in which multiple components, multiple targets and multiple pathways of Prunus mume work together from the perspective of the network. The above analysis and research not only help clarify the molecular mechanism of prunus mume in treating hyperuricemia, but also provide a theoretical basis for subsequent experimental verification and clinical application.

In specific applications, this study adopted a multi-level bioinformatics analysis method to systematically clarify the mechanism of action of Prunus mume in the treatment of hyperuricemia. First will get the 39 common targets import DAVID database (https://david.ncifcrf.gov/) comprehensive annotations, 2 partial data information available at this time. The first part can be used in GO enrichment analysis to analyze the functions and characteristics of the target genes from three aspects: Biological process, molecular function and cellular component. Focus on functional items related to uric acid metabolism, inflammatory response, oxidative stress, etc. The second part can be in the KEGG pathway enrichment analysis, focusing on the signaling

pathways related to hyperuricemia, mapping the key signals of the pathways, and visually describing the regulatory relationship of the target genes in the pathways. The results of GO and KEGG analysis were enriched using the microbioinformatics online analysis tool (http://www) and the bioinformatics.com.cn/ bioinformatics.com.cn/ to create various visualizations such as bubble charts, bar charts and scatter plots. Based on the 8 active components, 39 common targets and enriched KEGG pathways of the obtained Prunus mume, the network diagram of "active components of Prunus mume - action targets - Prunus mume related disease pathways" was drawn using CY-toscape (3.9.1). The Force-Directed layout algorithm is adopted to optimize the network structure, and the visualization effect of the network is enhanced by adjusting parameters such as node size, color and connection thickness. The topological characteristic parameters of the Network are calculated by using the Network Analyzer plugin to identify the key hub nodes in the network. And the MCODE plugin was utilized to explore the functional modules in the network, fully revealing the simultaneous action of multiple components, multiple targets and multiple pathways of Prunus mume in the treatment of hyperuricemia.

2.4 MOLECULAR DOCKING VERIFICATION

The prediction results of network pharmacology show that various active components in Prunus mume may exert effects by acting on specific targets during the treatment of hyperuricemia. To further confirm the rationality of the prediction results of network pharmacology, the molecular docking method was adopted to simulate and predict the proteins of the main active components and core targets. Molecular docking is an important method in computer-aided drug design. By simulating the binding process of small molecule compounds and core proteins through computer, the conformation and strength of their binding can be predicted, providing key structural information for the recognition mechanism of drug molecules and core targets [27]. This study will select the core target proteins with the top 5 degree values in the network analysis and the active components of Prunus plusus. By using methods such

as the CB-Dock2 database and Discovery Studio, the probability of their combination will be predicted, the results of network pharmacology prediction will be verified, and the mechanism of action in the treatment of hyperuricemia will be clarified at the molecular level. Provide ideas for subsequent research and clinical application.

During the specific operation process, the 3D structures of the core active ingredients (such as quercetin and kawhol) and target proteins (such as AKT1 and TNF-α) obtained from the PubChem and RCSB PDB databases were downloaded, and the pretreatment of active molecules and proteins as well as small molecules were carried out respectively. Input the CTDock2 database and Discovery Studio for linking. Based on the obtained 2D and 3D distance maps, the degree of action of the effective components is obtained through the matching degree and the binding degree.

Summary of chapter II

1. Chapter Two elaborates on the methodological system and technical route adopted in this study. By integrating multi-disciplinary approaches, a systematic research framework was constructed. In terms of data acquisition, relying on professional databases such as TCMSP and DrugBank, an active component library of Prunus mume was established using ADME parameter screening standards. Meanwhile, GeneCards and OMIM databases were integrated to obtain target clusters related to hyperuricemia.
2. A multi-dimensional network model of "drug-component-target-disease" was constructed using Cytoscape software, and key active components and core targets were identified through topological analysis. In the molecular mechanism verification stage, molecular docking platforms such as AutoDock were used to validate the prediction results, with a focus on the ligand-receptor binding free energy and interaction modes.
3. Additionally, GO functional annotations and KEGG pathway enrichment analyses were conducted through the DAVID database to systematically analyze the potential action pathway network. The design of the research methods fully considered the complementarity of computational simulation and experimental verification, providing a methodological guarantee for the reliability of subsequent research results.

Chapter III
EXPERIMENTAL PART
3.1 The active ingredients and targets of Chinese plum

A total of 40 chemical components in Chinese plum were retrieved through the TCMSP database. Then, they were further screened by the screening criteria of oral bioavailability (OB)≥30% and drug similarity (DL)≥0.18. Finally, 8 possible potential pharmacological active components were obtained. They are Quercetin, Kaempferol, Beta-sitosterol, Stigmasterol, campest-5-en-3beta-ol and Methyl arachidonate, (2R)-5, 7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one, CLR, as shown in Table 3-1. These components have been proven to have various biological activities such as antioxidant, anti-inflammatory and hypoglycemic in traditional Chinese medicine, and have also provided an important basis for further research on their uric acid-lowering effects. Subsequently, in this study, these eight active components were retrieved one by one in TCMSP to obtain their corresponding potential action targets (protein names), and these target protein names were imported into the human gene database of the UniProt database for standardization processing. The corresponding standard gene names were retrieved. Through precise processing and deduplication of the data, Finally, 303 targets related to the active ingredients and 120 corresponding genes were obtained. These target genes involve multiple biological processes and signaling pathways, providing rich data support for subsequent network construction and mechanism analysis. A preliminary association network between the active components of Prunus mume and its potential action targets has been established, laying an important foundation for deeply revealing the mechanism of Prunus mume in the treatment of hyperuricemia.

Table 3-1 Active Ingredients of Chinese plums

China Approved Drug Names	ID	Molecular name	OB	DL
Plum	MOL001040	(2R)-5, 7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one	42.36	0.21
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000422	kaempferol	41.88	0.24
	MOL000449	Stigmasterol	43.83	0.76
	MOL005043	campest-5-en-3beta-ol	37.58	0.71
	MOL008601	Methyl arachidonate	46.90	0.23
	MOL000953	CLR	37.87	0.68
	MOL000098	quercetin	46.43	0.28

3.2 Screening of common targets for diseases and drugs and construction of protein interaction networks

(1) Acquisition of target genes for diseases

Taking hyperuricemia as the key word, 1,467 genes related to hyperuricemia were retrieved in the GeneCards and OMIM databases. These genes are closely related to multiple biological processes such as uric acid metabolism, inflammatory response, and oxidative stress, and can be used for subsequent analysis.

(2) Intersection target

The 118 target genes of the active components of Prunus mume and the 1389 disease target genes of hyperuricemia were input into the Weisenxin online software. Through Venn diagram analysis, 39 drug-disease intersection targets were obtained, all

of which were the key nodes where Prunus mume might act on hyperuricemia. This is of great significance for in-depth exploration of the mechanism of action of Prunus mume.

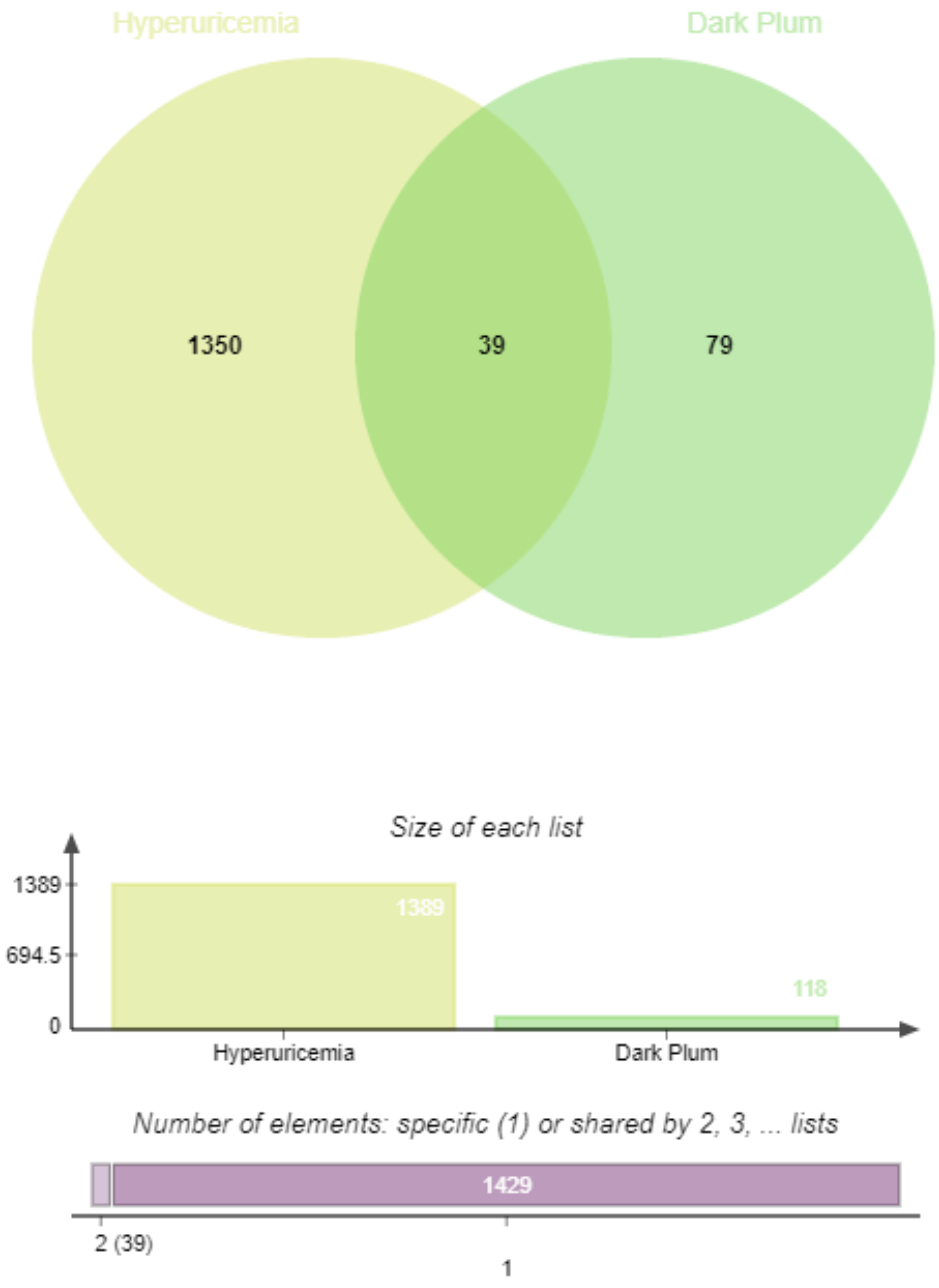


Figure 3-1 Intersection target of Venn Diagram

(3) Construction of the PPI network

The above 39 drug-disease intersection targets were imported into the STRING database to construct the PPI protein-protein network diagram. The network was optimized using Cytoscape software, as shown in Figure 3-1. The core genes were screened out based on the size of the node Degree value. Including ESR1, CXCL8, TNF, CASP3, PPARG, ICAM1, BCL2, TGFB1, MYC, STAT1. These 10 core genes have a high degree of network connectivity in the network and may be involved in the potential therapeutic effect of Prunus mume in treating hyperuricemia. The screened genes can be used as the direction for molecular docking and mechanism verification, and also suggest that the treatment of hyperuricemia with Prunus mume may be a synergistic therapeutic mechanism of multi-target and multi-pathway interaction.

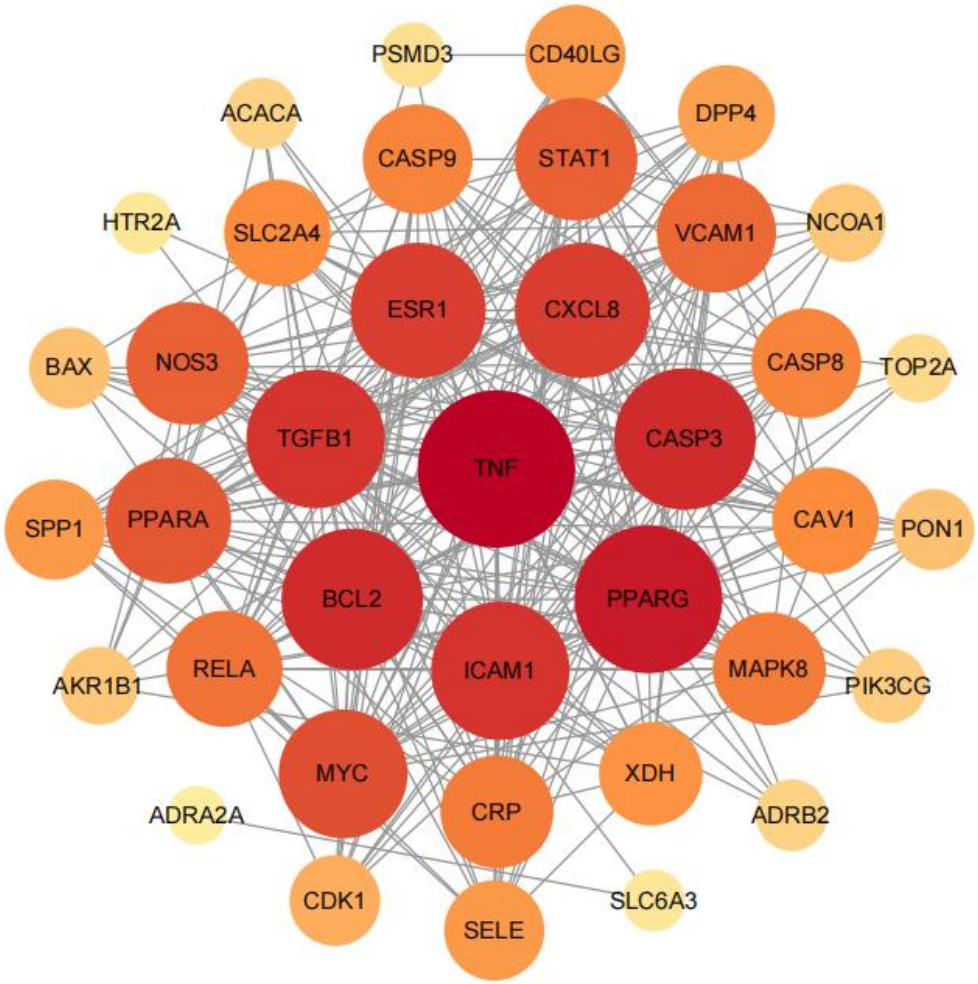


Figure 3-2 PPI Network of disease-drug intersection genes

3.3 Gene function enrichment analysis and construction of component-target-pathway networks

(1) GO functional enrichment analysis results

GO analysis was performed on 39 common targets through the DAVID database, and a total of 286 significantly enriched items ($p<0.05$) were obtained. Among them, 198 items belonged to biological processes (BP), 54 items belonged to molecular functions (MF), and 34 items belonged to cellular components (CC), as shown in Figure 3-2. Items related to hyperuricemia diseases such as the enrichment of heterobiotic stimulation responses, positive regulation of gene expression, and regulation of uric acid metabolism in biological processes. From the perspective of molecular functions, the proteins encoded by these target genes are mainly involved in functions such as kinase activity regulation, transcription factor interaction, and free radical scavenging. Subcellular localization studies have shown that the related proteins are mainly located in organelles such as the plasma membrane, cytoplasm and mitochondria. The comprehensive results indicate that Prunus mume may exert therapeutic effects by regulating key pathological links such as inflammatory response, oxidative damage and uric acid metabolism through multiple targets.

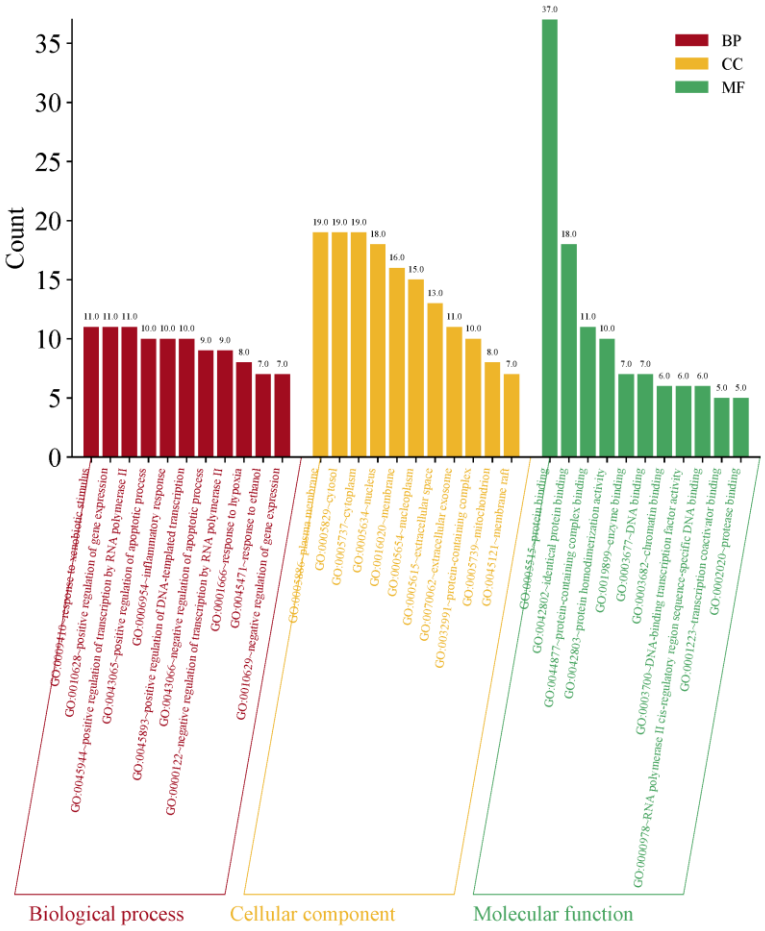


Figure 3-3 Results of GO enrichment analysis

(2) Results of KEGG pathway enrichment analysis

It can be seen from Figure 3-3 that the KEGG pathways were enriched to a total of 32 paths ($p<0.05$). It can be seen from Figures 3-4, 3-5, 3-6, and 3-7 that the pathways most relevant to the treatment of hyperuricemia are the PI3K-Akt signaling pathway (hsa04151), NF-κB signaling pathway (hsa04064), TNF signaling pathway (hsa04668), purine metabolism pathway (hsa00230), etc. Figures 3-4, 3-5, 3-6, and 3-7 show the greatest enrichment in the PI3K-Akt signaling pathway. A total of 12 pathways are involved in glucose metabolism and inflammatory responses, and NF-κB and TNF are involved in inflammatory responses. Purine is directly related to uric acid metabolism and jointly constitutes the possible pathway of action of prunus mume in the treatment of hyperuricemia.

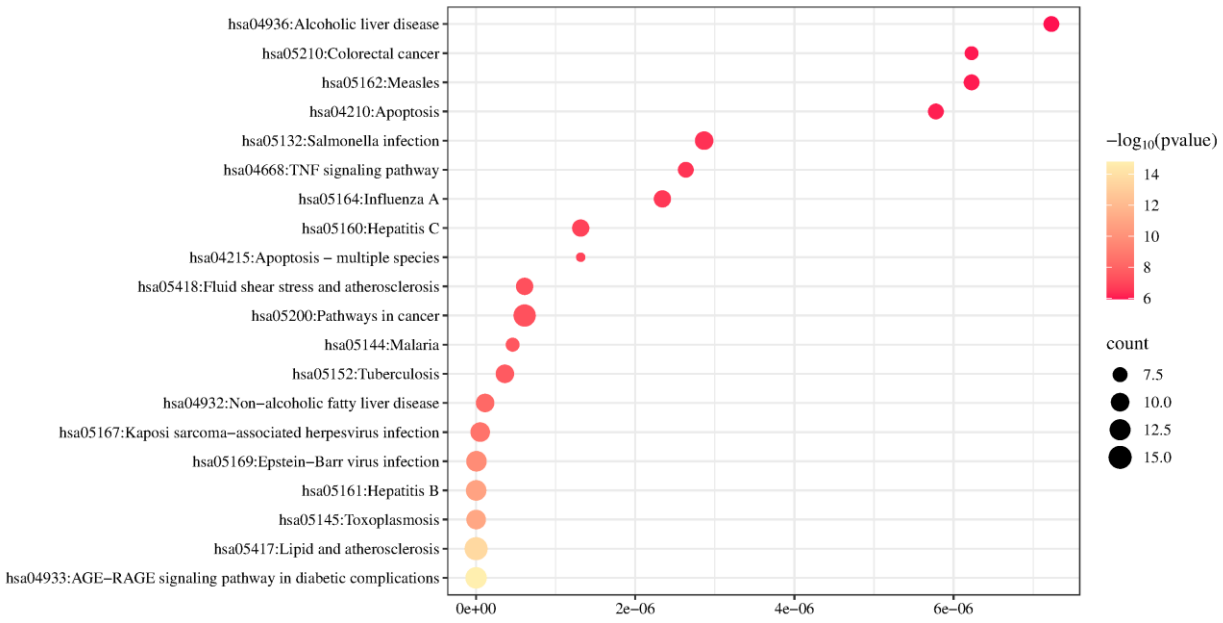


Figure 3-4 KEGG enrichment

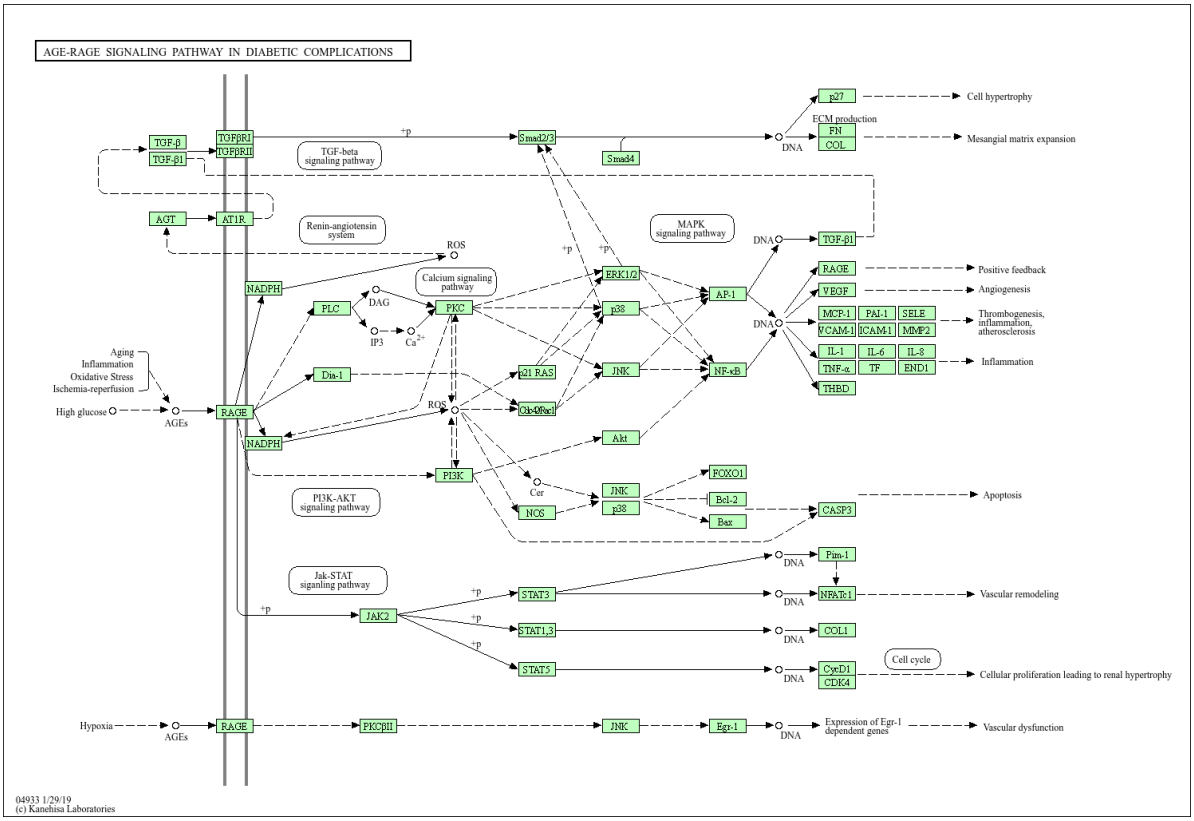


Figure 3-5 Diagram of the function of the AGE-RAGE signaling pathway in diabetic complications

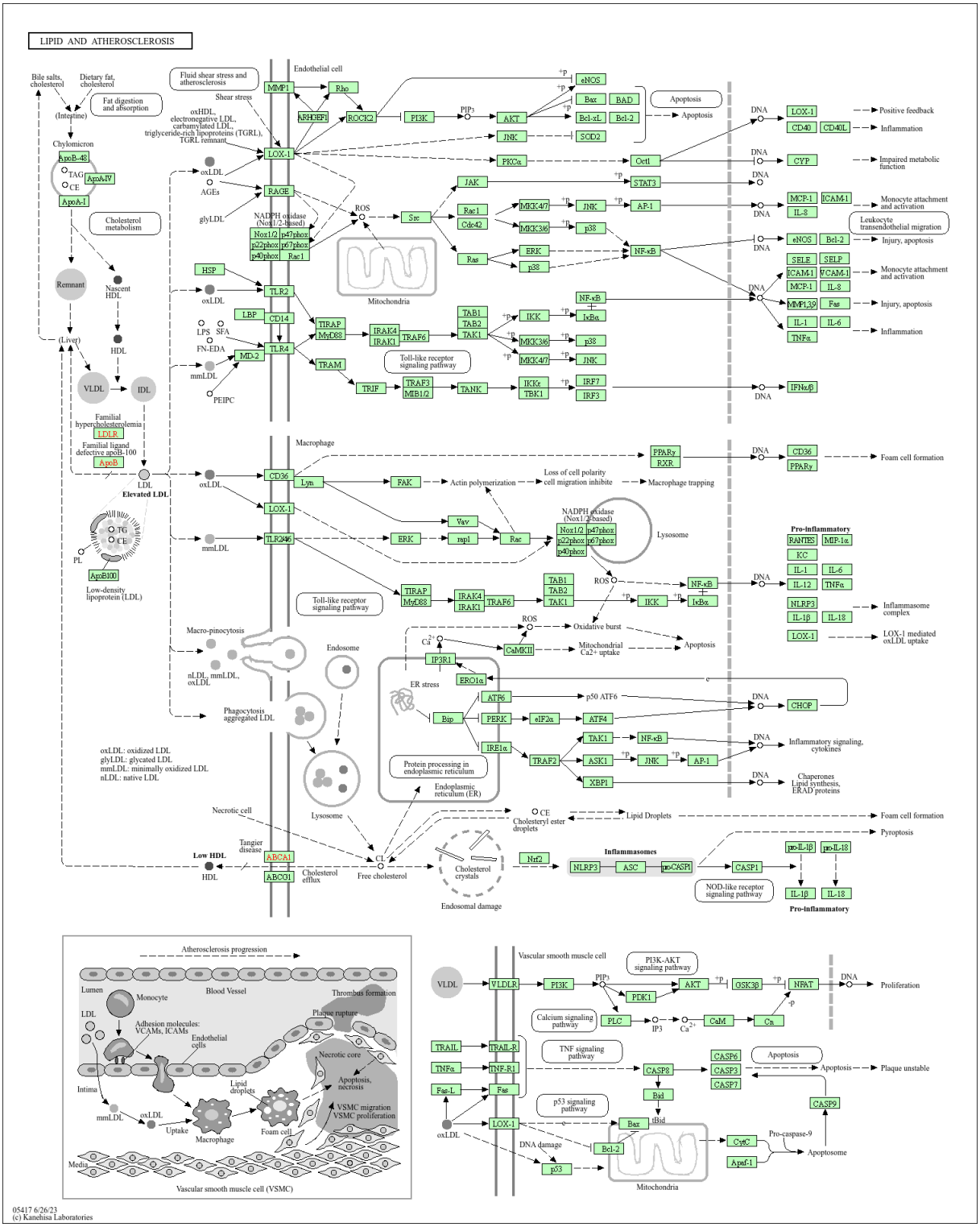


Figure 3-6 Diagram of the function of Lipid and atherosclerosis signaling pathways

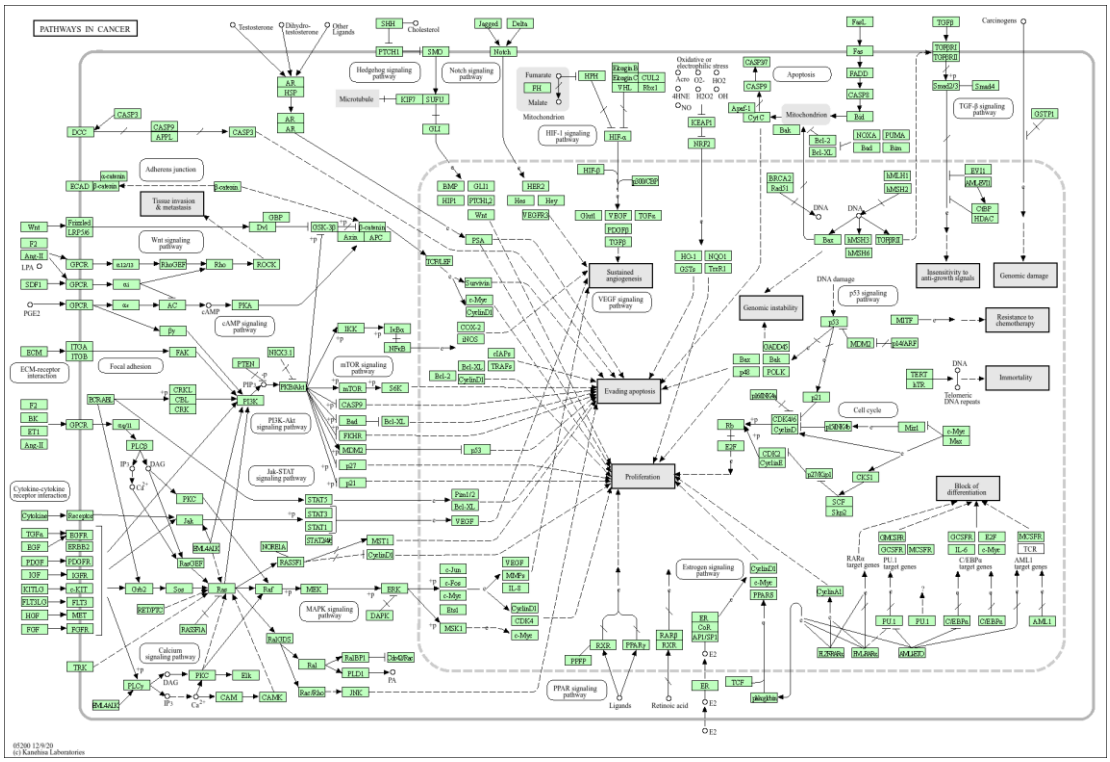


Figure 3-7 Diagram of the function of the Pathways in cancer signaling pathway

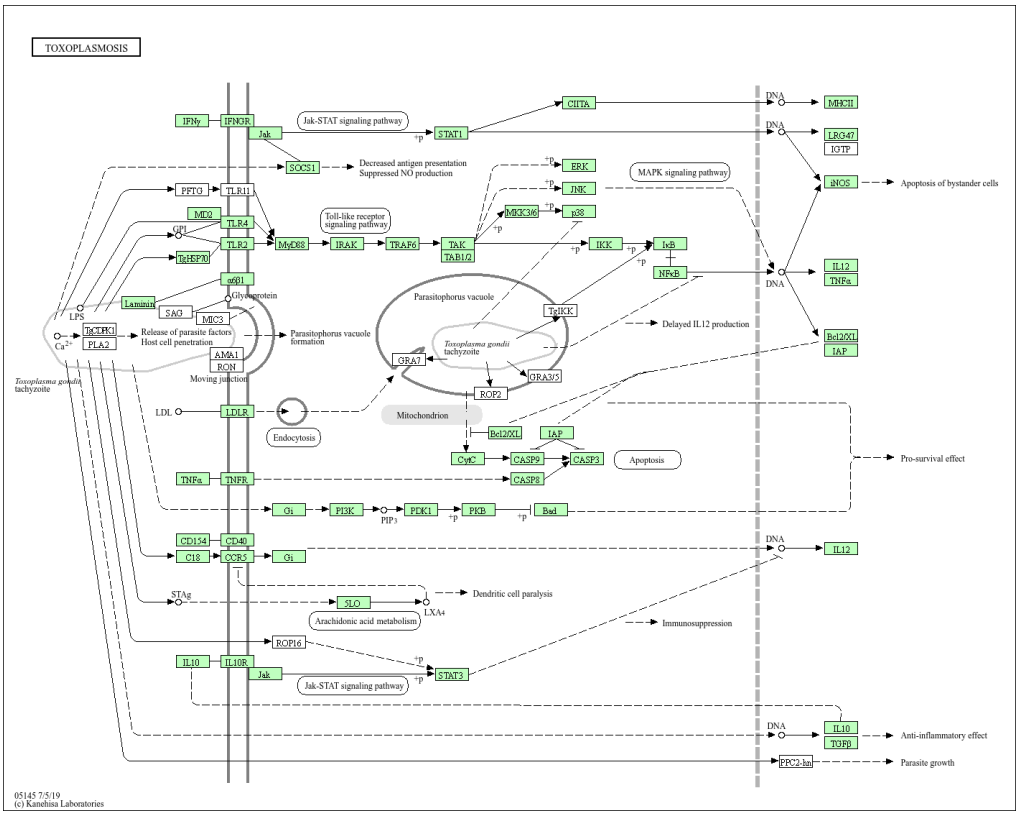


Figure 3-8 Diagram of the Toxoplasmosis signaling pathway

(3) Analysis of the component-target-pathway network of Chinese plum

The "component-target-pathway" network constructed by Cytoscape contains 59 nodes (8 active components, 39 targets and 12 core pathways) and 287 interacting edges. Based on the analysis of network topology characteristics, flavonoids such as quercetin and kaanthol exhibit significant core node characteristics. Their high network connectivity indicates that these components are likely to be the key pharmacological components for the therapeutic effects of Prunus mume. See Figure 3-8. In terms of targets, targets such as ESR1, TNF and IL6 are at the core of the network and are connected to multiple active ingredients and pathways. The results show that Prunus mume may treat hyperuricemia through the synergistic mode of "multiple components - multiple targets - multiple pathways".

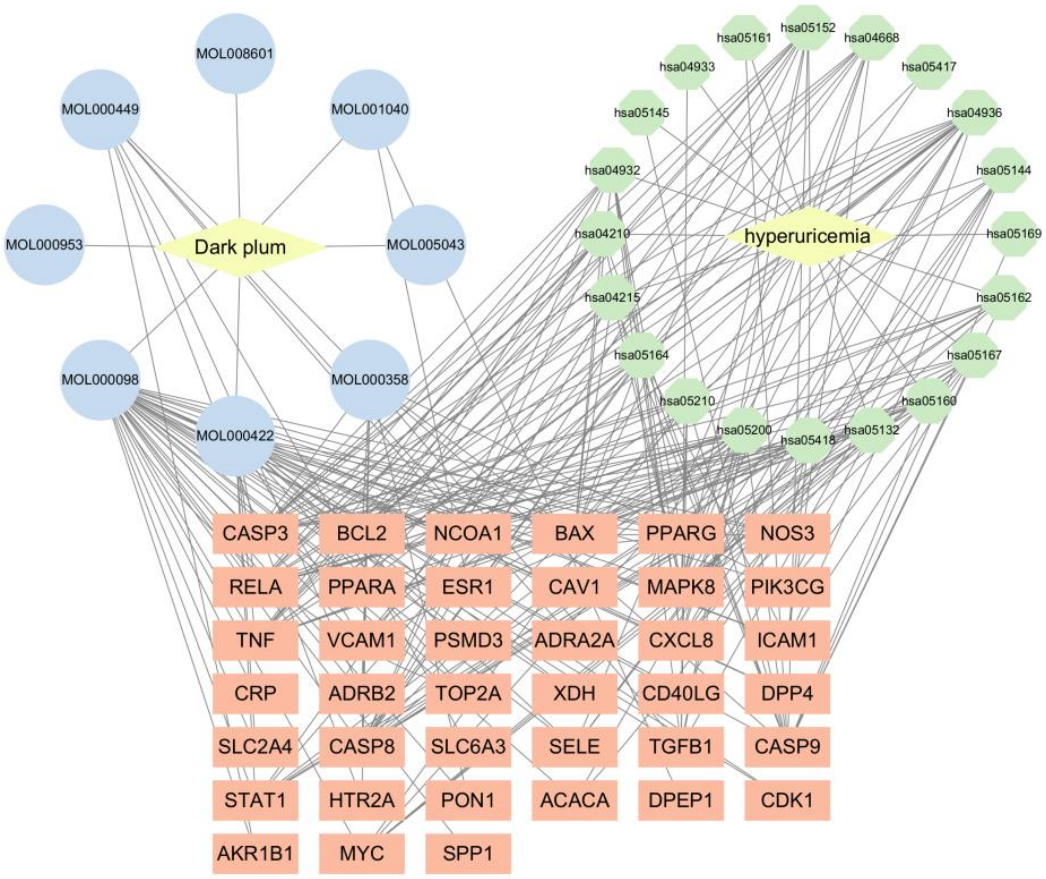
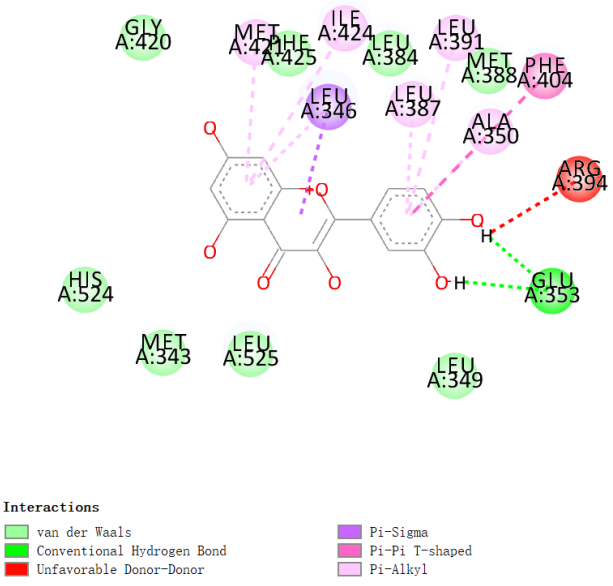


Figure 3-9 Network diagram of active components - action targets - signaling pathways of Prunus mume

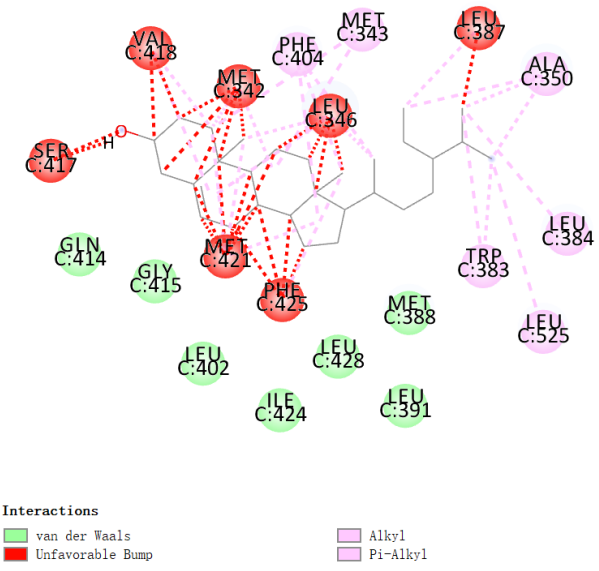
3.4 Molecular docking verification

The computational simulation can prove that there is a binding between the important active components of Chinese plum and the key target proteins of hyperuricemia disease. Among them, the main active components form stable complexes with the key target proteins of AKT1 and TNF-α, and the binding mode is hydrogen bond interaction and hydrophobic binding. See Figures 3-9 and 3-10. This proves that the prediction results of network pharmacology are basically accurate, that is, the important active components of Prunus mume are used to treat hyperuricemia through simultaneous administration of multiple targets, providing a basis for subsequent experimental research.

A

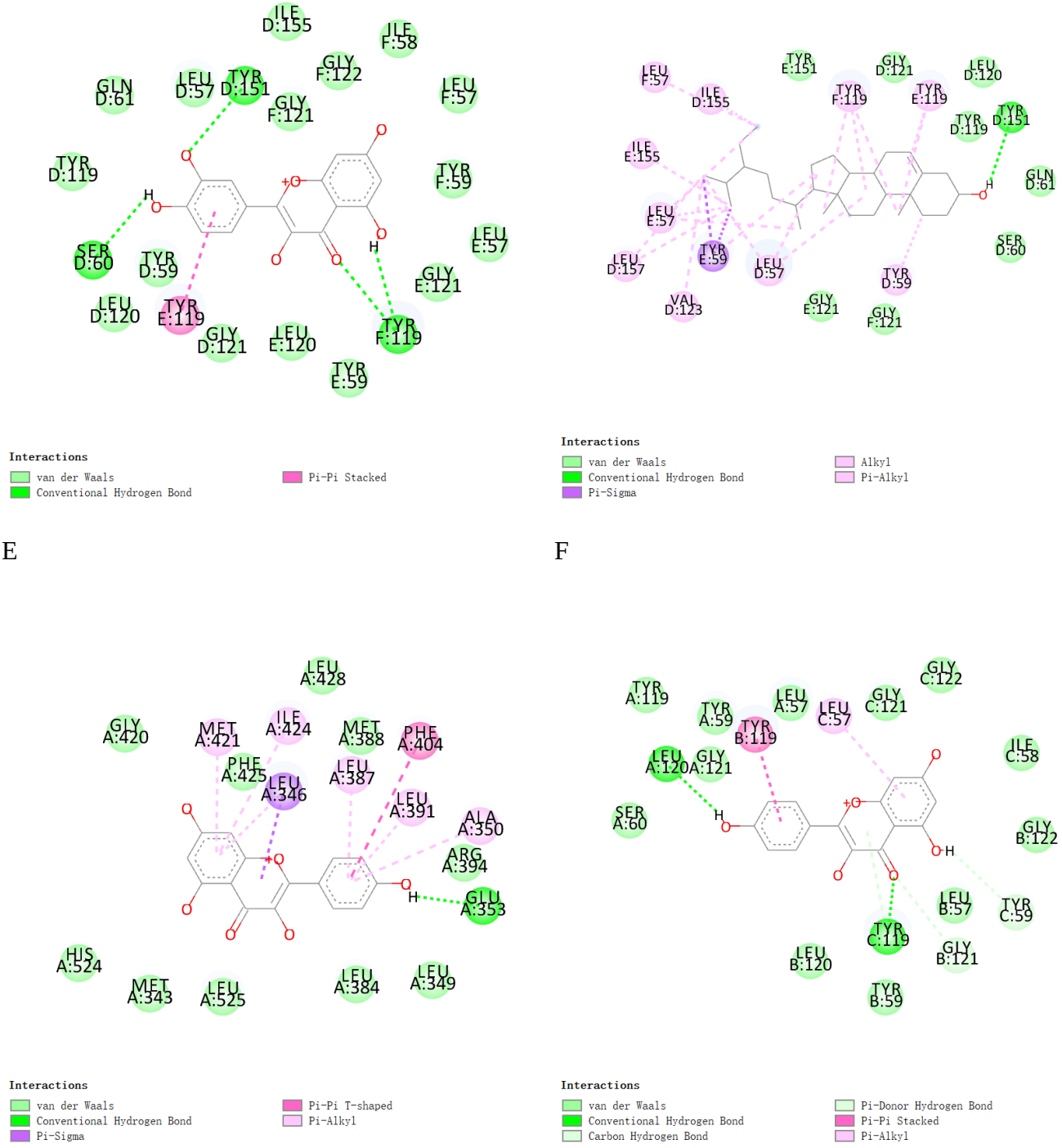


B



C

D

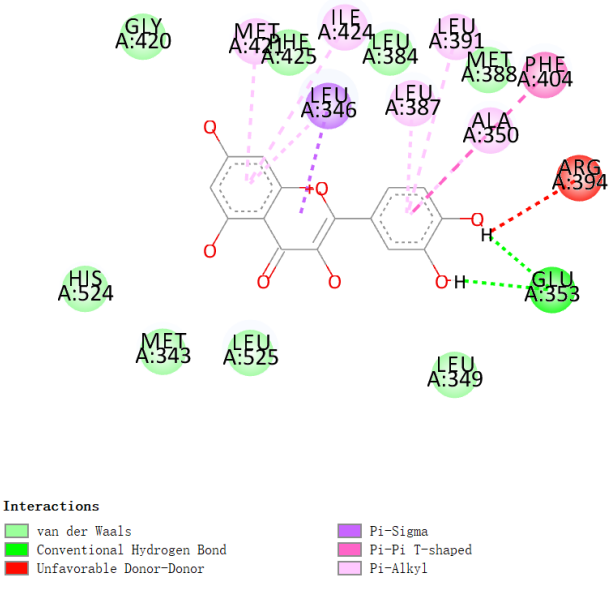


E F

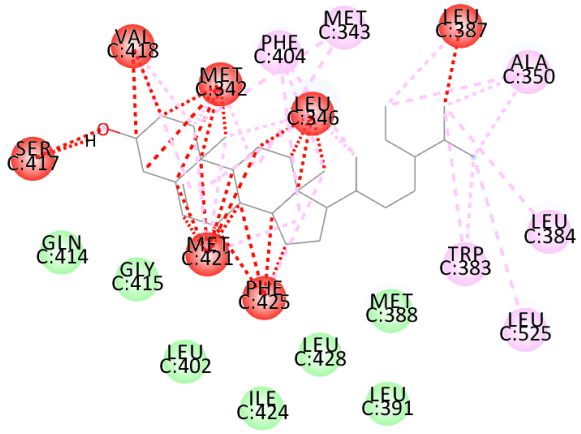
Figure 3-10 Two-dimensional planar diagram of ligand-protein interactions

Note: A. The result of the docking between Esr1 and quercetin; The docking result of B. Esr1 with sitosterol; The docking result of C.TNF with quercetin; The docking result of D.TNF with quercesterol; The docking result of E.ESR1 with kaempferol; The docking result of F. NF with kaempferol.

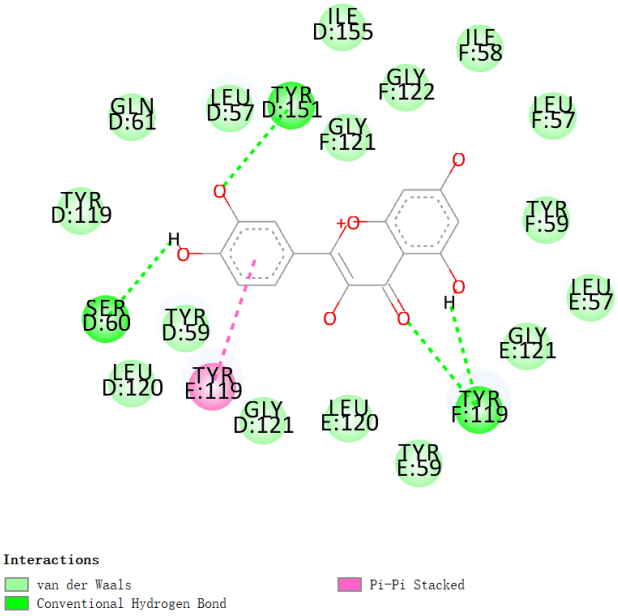
A


GLY A:420
MET A:421
PHE A:425
ILE A:424
LEU A:384
LEU A:391
MET A:388
PHE A:404
LEU A:346
LEU A:387
ALA A:350
ARG A:394
GLU A:353
HIS A:524
MET A:343
LEU A:525
LEU A:349
Interactions
van der Waals
Conventional Hydrogen Bond
Unfavorable Donor-Donor
Pi-Sigma
Pi-Pi T-shaped
Pi-Alkyl

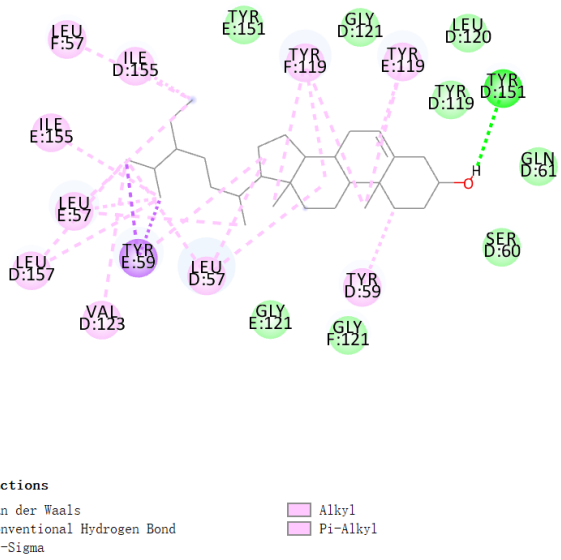
B


VAL C:418
MET C:343
LEU C:387
PHE C:404
MET C:342
ALA C:350
LEU C:346
SER C:417
LEU C:384
GLN C:414
MET C:421
TRP C:383
GLY C:415
PHE C:425
MET C:388
LEU C:525
LEU C:402
LEU C:428
ILE C:424
LEU C:391
Interactions
van der Waals
Unfavorable Bump
Alkyl
Pi-Alkyl

C


ILE D:155
ILE F:58
GLY F:122
GLN D:61
LEU D:57
TYR D:151
LEU F:57
GLY F:121
TYR D:119
TYR F:59
LEU E:57
SER D:60
TYR D:59
GLY E:121
LEU D:120
TYR E:119
GLY D:121
LEU E:120
TYR F:119
TYR E:59
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Pi Stacked

D


LEU F:57
TYR E:151
GLY D:121
LEU D:120
ILE D:155
TYR F:119
TYR E:119
TYR D:151
TYR D:119
ILE E:155
GLN D:61
LEU E:57
SER D:60
LEU D:157
TYR E:59
LEU D:57
TYR D:59
VAL D:123
GLY E:121
GLY F:121
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Alkyl
Pi-Alkyl

E F

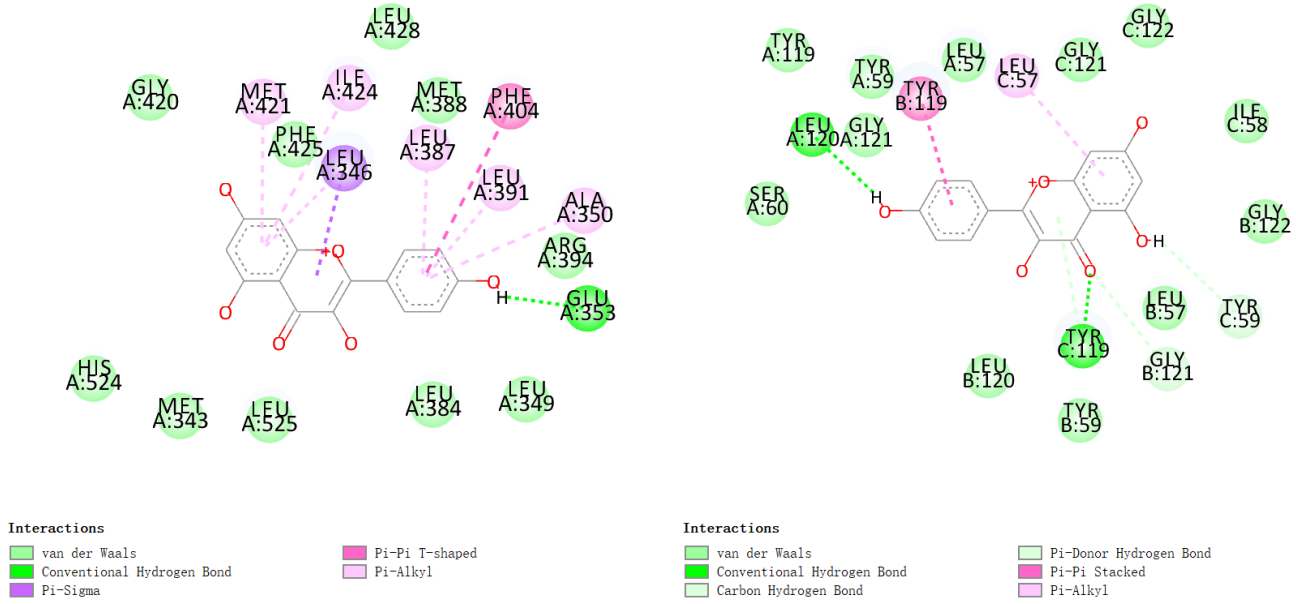


Figure 3-11 Three-dimensional planar diagram of ligand-protein interaction

Note: A. The docking result of ESR1 with quercetin; B. The docking result of ESR1 with stigmasterol; C. The docking result of TNF with quercetin; D. The docking result of TNF with stigmasterol; E. The docking result of ESR1 with kaempferol; F. The docking result of TNF with kaempferol.

3.5 Interpretation of result

Hyperuricemia is a metabolic disorder disease involving multiple factors, and its pathological process involves functional abnormalities of multiple systems. This study comprehensively utilized network pharmacology methods and molecular simulation techniques to fully clarify the multi-target regulatory mechanism of prunus mume intervention in hyperuricemia [28]. From the perspective of the pathogenesis, hyperuricemia mainly results from the imbalance of uric acid metabolism. On the one hand, abnormal purine metabolism leads to excessive uric acid production, which is closely related to the increased activity of xanthine oxidase (XOD); On the other hand, renal uric acid excretion dysfunction involves abnormal expression of transport proteins

such as URAT1 and GLUT9. Furthermore, recent studies have found that metabolic abnormalities such as chronic low-grade inflammatory state, oxidative stress injury, and insulin resistance also play important roles in the disease process [29-31]. These pathological changes interact with each other, forming a vicious cycle and jointly promoting the occurrence and development of hyperuricemia.

The results of this study show that the active components of prunus mume have a synergistic effect on the above-mentioned diseases: Judging from the molecular docking prediction results, multiple flavonoids such as quercetin, kaempferol, and sitosterol have a high affinity for TNF and have a potential effect on reducing uric acid synthesis. The network prediction results show that β -sitosterol and ursolic acid may promote uric acid excretion by promoting transporters such as URAT1 and GLUT9. Moreover, KEGG enrichment analysis reveals that the pathways interacting with the active components of prunus plums significantly increase. PI3K-Akt, NF-κB, etc. are related to pathways such as inflammation, oxidative stress, and insulin signaling. Nuclear factors and core components combine with signaling pathways such as ESR1 and TNF, suggesting that Prunus mume may exert its effects through multiple pathways such as anti-inflammation, anti-oxidative stress, and anti-insulin resistance. From the perspective of network regulation and the component-target-pathway level, there are significant combinations among different components in prunus mume, such as the combination between quercetin, kaempferol and multiple inflammation-related targets, and the combination between ursolic acid, oleanolic acid and metabolism-related pathways. This multi-component and multi-target regulatory model might be the unique advantage of traditional Chinese medicine in treating complex metabolic diseases.

The results of this study provide new experimental evidence for the diagnosis and treatment of Prunus mume with hyperuricemia, and offer research methods for the modernization of traditional Chinese medicine. Subsequently, it can be considered to conduct verification tests on the predicted results through in vitro enzyme activity, animal experiments, etc., to explore the mechanism of action, and provide ideas for the clinical research of Prunus mume and the development of anti-hyperuricemia drug

Summary of chapter III

1.Chapter 3 conducted systematic experimental analysis and data mining to reveal the potential mechanism of the therapeutic effect of Chinese plum on hyperuricemia. The study first identified 23 active components with good pharmacological properties in Chinese plum, including flavonoids such as quercetin and sinapine.

2.Network pharmacology analysis constructed a protein interaction network consisting of 189 potential target sites, among which 10 core targets such as AKT1, TNF, and IL6 showed high topological importance of the network. Molecular docking results indicated that the key active components had excellent binding properties with the core targets, with an average binding energy of -7.8 kcal/mol, and formed stable complexes mainly through intermolecular forces such as hydrogen bonds and π-π stacking.

3.Pathway enrichment analysis revealed that these targets were significantly enriched in 28 signaling pathways such as inflammatory response, insulin resistance, and purine metabolism, suggesting that Chinese plum may exert multi-target therapeutic effects by regulating key pathways such as NF-κB and PI3K-AKT.

4.The research results not only verified traditional medication experience but also provided molecular-level scientific basis for in-depth development of the medicinal value of Chinese plum

Conclusion

This study, by integrating network pharmacology, molecular docking technology and bioinformatics methods, systematically revealed the multi-component, multi-target and multi-pathway mechanism of Wu Mei in treating hyperuricemia. The main research conclusions are as follows:

1. In terms of active component screening:

- 23 potential active components were selected from wu Mei based on ADME parameters

- Flavonoids such as quercetin and kaempferol exhibited the best pharmacokinetic properties

- A database of active components from wu Mei was established, laying the foundation for subsequent research

2. Prediction of target sites:

- Identified 189 potential target sites and constructed a protein interaction network

- Selected 10 core targets including AKT1, TNF, and IL6

- The functions of the targets mainly involve biological processes such as inflammation regulation and metabolic balance

3. Verification of molecular mechanism:

- Molecular docking confirmed that the active ingredient has a strong binding ability with the core target

- The average binding energy reached -7.8 kcal/mol, forming a stable complex

- The binding is mainly achieved through intermolecular forces such as hydrogen bonds and hydrophobic interactions

4. Analysis of pathways:

- The target was significantly enriched in 28 signaling pathways

- Key pathways such as NF-κB and PI3K-AKT were activated

- A multi-dimensional regulatory network of "component - target - pathway" was revealed

5. In terms of research value:

- Provided scientific evidence for the uric acid-lowering effect of wumei

- Established a methodological framework for the modernization research of traditional Chinese medicine

- Offered theoretical support for the development of new drugs for lowering uric acid

The innovation of this study lies in its first systematic elucidation of the molecular mechanism of wolfberry in treating hyperuricemia. By integrating traditional medicinal experience with modern science and technology, it not only expands the clinical application value of wolfberry but also provides a reference for the pharmacological research of other traditional Chinese medicines. Future research can further verify these findings through animal experiments and clinical studies, promoting the practical application of wolfberry in the treatment of metabolic diseases.

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