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Exploration on Molecular Mechanism of Lonicerae Japonicae Flos-Forsythiae Fructus Herbal Pair in Traeting Acne Vulgaris Based on Network Pharmacology and Molecular Docking Technology

Jing Gan[1], Can Wu[1], Wenbin Li[2,*], Yong Liu[2], Meihong Li[2]

[1]Shaanxi University of Chinese Medicine, Shaanxi 712046, China
[2]Shaanxi Hospital of Traditional Chinese Medicine, Shaanxi 710000, China
**Corresponding author*

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Abstract: Objective: this study aim to explore main active components and possible molecular mechanism of "Lonicerae Japonicae Flos-Forsythiae Fructus" (JYH-LQ) herbal pair in treating acne vulgaris disease by network pharmacology and molecular docking technology. Method: The active components and related targets of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair were obtained from TCMSP Database platform, correcting the official gene symbol names of the targets of the herbal pair from UniProt database. The GeenCards, OMIM and DisGeNET databases were used to find the targets related to acne vulgaris disease. Taking the intersection targets of active components and disease and inputting them into the String database for protein-protein interaction (PPI) network prediction. Then using Cytoscape sofeware to render "effective active components - intersection targets" network prediction. GO annotation and KEGG pathway enrichment analysis for the intersection targets of “Lonicerae Japonicae Flos-Forsythiae Fructus “herbal pair- acne vulgaris disease were performed with DAVID database. Molecular docking between the active components and the key targets was carried out by Autodock. Result: The effective active components of lonicerae japonicae flos-forsythiae fructus herbal Pair in traeting acne vulgaris are quercetin, luteolin, kaempferol. the core targets including TNF, IL-6, TP53. The GO enrichment analysis indicated that the main functions JYH-LQ herbal pair included the response to drug, positive regulation of gene expressionand, positive regulation of nitric oxide biosynthetic process and so on. The main pathways involved in the KEGG pathway analysis were FoxO, Cytokine-cytokine receptor interaction, T cell receptor signaling pathway and so on. Molecular docking showed that the main active components of the herbal pair had stable binding activity with the core targets of the disease. Finally, “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair can be through multi-components, multi-targets and multi-pathways applie to acne vulgaris, providing ideas for clinical diagnosis and treatment of traditional Chinese medicine.

1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicle, affecting up to 85% of adolescents and adults, in which sebaceous gland production is increased, changes in the process of keratinization lead to the formation of comedones, the presence of Propionibacterium acnes settles in hair follicles,and inflammatory mediators around the pilosebaceous unit are common influencing factors. In addition, multiple loci were also found to be associated with acne[1]. It is the eighth most common disease in the world, and many studies have found that acne can affect the mental health and quality of life of patients. A survey found that the duration of acne in patients with acne was directly and positively correlated with higher Perceived Stress Scale scores and Appearance Anxiety Scale scores[2]. Many acne patients also have a certain degree of scarring, which is caused by the abnormal production and degradation of collagen during the healing process of acne.Among them, atrophic scars are the most common type of acne scars[3],and no matter what kind of scars,they will cause thepatient's facial beauty affects.

Traditional Chinese medicine has been widely used in the clinical treatment of acne vulgaris. By exploring its medication rules, it is found that heat-clearing drugs are one of the commonly used drugs, and honeysuckle and forsythia are frequently appearing drugs in heat-clearing drugs[4]. "Shennong's classic of Materia Medica" contains "Honeysuckle has the effect of clearing away heat and detoxification, cooling blood and removing blood stasis, and mainly treats exogenous wind-heat...sore boils, redness, swelling, heat and pain and so on". "Forsythia governs cold and heat, rat fistulas, scrofula, carbuncles... Fever and so on" Honeysuckle and Forsythia both have heat-clearing and detoxifying effects and can be used for the treatment of acne. Modern pharmacological studies have also confirmed that the two have anti-inflammatory, bactericidal, antiviral and other effects. The flavonoids they share can inhibit inflammation. In addition, iridoids in honeysuckle and lignans in forsythia can also inhibit inflammation[5,6]. As an inflammatory skin disease of acne vulgaris, honeysuckle and forsythia are commonly used drug combinations, and their effects may be related to the inhibition of inflammation.

Network pharmacology is a new subject that includes pharmacology, bioinformatics, and systems biology. It can analyze the mechanism of action between drugs and the body from an overall perspective by building a "drug-gene-disease" network[7]. In this study, the main active components and potential mechanism of action of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair in the treatment of acne vulgaris were explored through the research methods of traditional Chinese medicine network pharmacology and molecular docking.

2. Materials and methods

2.1. Screening of active ingredients and targets of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair

Through the TCMSP (https://tcmsp-e.com/) database, honeysuckle and forsythia were retrieved respectively, and oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 were used as the screening conditions to collect and screen. Identify the active ingredients of the drug and the targets of the related effects of the active ingredients of the drug. Use the Uni Prot (https://www.uniprot.org/) database to obtain drug targets and corresponding gene names. A "drug-active ingredient-target" network graph was constructed in Cytoscape.

2.2. Acne vulgaris disease target collection

A median screen was performed through the Human Mendelian Inheritance Database(OMIM,

https://omim.org/), Genecards database (https://www.genecards.org/) for a median screen, the DisGeNET database (https://www.disgenet .org/) to screen the data, enter the keyword "acne vulgaris" to obtain the disease targets related to acne vulgaris, the data obtained from various databases are merged and deduplicated, and the UniProt database (https://www.uniprot.org /)was used to process the data to obtain the correct standardized gene names.

2.3. Disease-active ingredient common target screening

Withthe help of the online mapping tool Weishengxin platform (http://www.bioinformatics.com.cn/), a Venn diagram was drawn to obtain the intersection targets of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair on the active ingredient target and the target of acne vulgaris disease.

2.4. Intersection gene protein-protein interactions

In the STRING database (https://cn.string-db.org/), enter the intersection targets of active pharmaceutical ingredients and acne vulgaris, the gene species is limited to "Homo sapiens", and the interaction threshold is set to " medium confidence (0.400)", remove a single free target protein, output the data in tsv format, import the data into Cytoscape 3.9.0, and construct a PPI network diagram.

2.5. Construct a network diagram of "effective active ingredients-intersection targets"

The effective active ingredients mapped from the intersection targets were integrated, and Cytoscape 3.9.0 was used to construct the "effective active ingredients-intersection targets" relationship diagram. Degree analysis was performed using the Network Analyzer to obtain the main chemical components in the treatment of acne vulgaris in the network graph.

2.6. Enrichment analysis

GO function and KEGG pathway enrichment analysis was performed on the intersection genes through the David database (https://david.ncifcrf.gov/), with $P<0.05$ as the condition, using the online mapping platform Weishengxin (http://www.bioinformatics.com.cn/) to draw a histogram for the top 10 GO enrichment analysis results, and a bubble chart for the top 20 KEGG enrichment analysis results.

2.7. Molecular docking verification of main active ingredients and targets

Theactiveingredients with the highest degree value in the "effective active ingredients-intersection targets" network and the core genes in the PPI network of potential targetswere selected for molecular docking. Obtain the molecular structure of the main active components of the “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair from the TCMSP database and download it in mol2 format, download the key target protein structure from the PDB (http://www.rcsb.org/) database, and apply AutoDock 1.5 .7 software for molecular docking. Molecular docking visualization analysis was performed between the compounds with higher docking scores and the target protein by Pymol 2.4.0 software.

3. Results

3.1. Screening results of active and active ingredients of drugs and target screening

Table 1List of active ingredients of Lonicerae Japonicae Flos-Forsythiae Fructus Herbal Pair, in which A, B, C, and D belong to the two common active ingredients, / are the corresponding targets that have not been found

medicinal herbs	MOLID	Ingredient name	OB	DL	Numbering
honeysuckle	MOL001494	Mannitol	42	0.19	JYH1
honeysuckle	MOL001495	Ethyl linoleate	46.1	0.2	JYH2
honeysuckle	MOL002707	Phytofluoride	43.18	0.5	/
honeysuckle	MOL002914	eriodictyol (flavanone)	41.35	0.24	JYH3
honeysuckle	MOL003006	(-)-(3R,8S,9R,9aS,10aS)-9-vinyl-8 -(-D-glucopyranosyloxy)-2,3,9,9a, 10,10a-hexahydro- 5-oxo-5H, 8H-pyrano[4,3-d]oxazolo[3,2-a] pyridine-3-carboxylic acid-qt	87.47	0.23	JYH4
honeysuckle	MOL003014	secologanic dibutyl acetal_qt	53.65	0.29	JYH5
honeysuckle	MOL002773	beta-carotene	37.18	0.58	JYH6
honeysuckle	MOL003036	Zinc 03978781	43.83	0.76	JYH7
honeysuckle	MOL003044	Emodin	35.85	0.27	JYH8
honeysuckle	MOL003059	Krypton flavin	47.25	0.57	/
honeysuckle	MOL003062	4,5'-Retro-.beta.,.beta.-Carotene -3,3'-dione, 4',5'-didehydro-	31.22	0.55	/
honeysuckle	MOL003095	5-Hydroxy-7-methoxy-2-(3,4,5- trimethoxyphenyl)chromone	51.96	0.41	JYH9
honeysuckle	MOL003101	7-epi-vogloside	46.13	0.58	/
honeysuckle	MOL003108	Apigenin C	55.64	0.73	/
honeysuckle	MOL003111	Centauroside_qt	55.79	0.5	JYH10
honeysuckle	MOL003117	Ionic Acetal B_qt	61.19	0.19	JYH11
honeysuckle	MOL003124	Xyloside	43.17	0.64	/
honeysuckle	MOL003128	diethyl glucosinolate	48.46	0.48	JYH12
Honeysuckle Forsythia	MOL000358	beta-carotene	36.91	0.75	A
Honeysuckle Forsythia	MOL000422	Kaempferol	41.88	0.24	B
honeysuckle	MOL000449	stigmasterol	43.83	0.76	JYH15
Honeysuckle Forsythia	MOL000006	Luteolin	36.16	0.25	C
Honeysuckle Forsythia	MOL000098	Quercetin	46.43	0.28	D
Forsythia	MOL000173	Scutellaria baicalensis	30.68	0.23	LQ1
Forsythia	MOL003281	20(S)-dammar-24-ene-3β,20-diol-3 -acetate	40.23	0.82	/
Forsythia	MOL003283	(2R,3R,4S)-4-(4-Hydroxy-3-methoxy -phenyl)-7-methoxy-2,3-dimethylol -tetrahydronaphthalene-6-ol	66.51	0.39	LQ2
Forsythia	MOL003290	(3R,4R)-3,4-bis[(3,4- dimethoxyphenyl)methyl]oxolan -2-one	52.3	0.48	LQ3
Forsythia	MOL003295	(+)-Pinoresinol monomethyl ether	53.08	0.57	LQ4
Forsythia	MOL003305	Phililine	36.4	0.86	LQ5
Forsythia	MOL003306	ACon1_001697	85.12	0.57	LQ6
Forsythia	MOL003308	(+)-Pinoresinol monomethyl ether -4-D-β-glucoside_qt	61.2	0.57	LQ7
Forsythia	MOL003315	3beta-Acetyl-20,25-epoxydammarane -24alpha-ol	33.07	0.79	LQ8
Forsythia	MOL000211	Merlin	55.38	0.78	LQ9
Forsythia	MOL003322	Forsythol	81.25	0.57	LQ10
Forsythia	MOL003330	(-)-Phillygenin	95.04	0.57	LQ11
Forsythia	MOL003344	β –Sitosterol	42.06	0.74	/
Forsythia	MOL003347	Hypericin	44.03	0.6	LQ12
Forsythia	MOL003348	epinephrine	44.03	0.61	/
Forsythia	MOL003365	Lactosterol	40.99	0.85	/
Forsythia	MOL003370	Angianthrone I	79.16	0.3	LQ13
Forsythia	MOL000522	burdock	34.45	0.84	LQ14
Forsythia	MOL000791	Bicuculline	69.67	0.88	LQ15

In the TCMSP database, the active ingredients of honeysuckle and forsythia were searched, with oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 as the screening conditions, a total of 46 active ingredients were screened, and a total of 4 ingredients were screened. Among them, there are 23 active ingredients of honeysuckle and 23 active ingredients of forsythia. The results are shown in Table (1). A total of 229 targets related to active pharmaceutical ingredients were retrieved after deduplication. The "drug-active ingredient-target" network graph was constructed in Cytoscape 3.9.0, and the result is shown in Figure (1), with a total of 263 nodes and 956 edges.

3.2. Disease target screening results

Searching the Human Mendelian Inheritance Database (OMIM), 18 disease targets were obtained after deduplication, 173 disease targets were obtained from the Genecards database after a median processing, and the DisGeNET database was screened on the condition of score≥0.8, and 776 disease targets were obtained after deduplication. A total of 924 disease targets were obtained after merging the disease target information of each database and deduplication again.

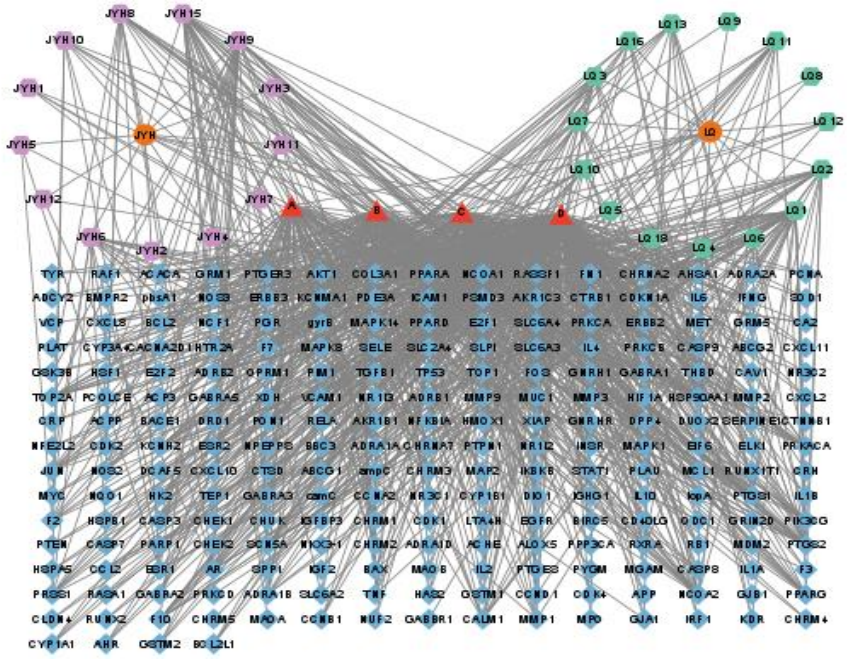

Figure 1: "Drug-active ingredient-target" network diagram

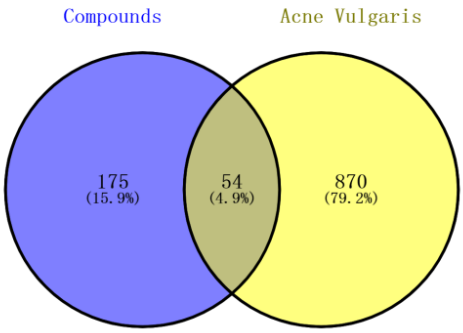

Figure 2: Venn diagram of drug-disease target intersection

3.3. Disease-active ingredient common target screening

The Venn diagram was drawn with the help of the online mapping tool Weshengxin platform to obtain a total of 54 intersection genes of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair on active ingredient targets and acne vulgaris disease targets, as shown in Figure (2).

3.4. PPI network analysis of intersection genes

The PPT network graph (3) of the intersection targets of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair and acne vulgaris disease was constructed through string database and Cytoscape 3.9.0 software, involving a total of 53 nodes and 555 edges.The cytohubba plug-in is used to sort the targets according to the degree value as shown in Figure (4). The deeper the color, the greater the value, and the results indicate that TNF, IL-6, TP53, IL1B, ESR1, PPARG, EGFR, CXCL8, CCL2, CTNNB1, etc. play an important role in the PPI network.

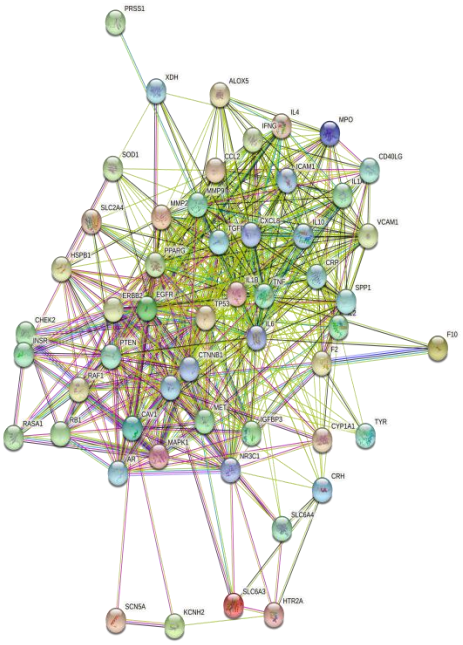

Figure 3: PPI network diagram of intersection targets

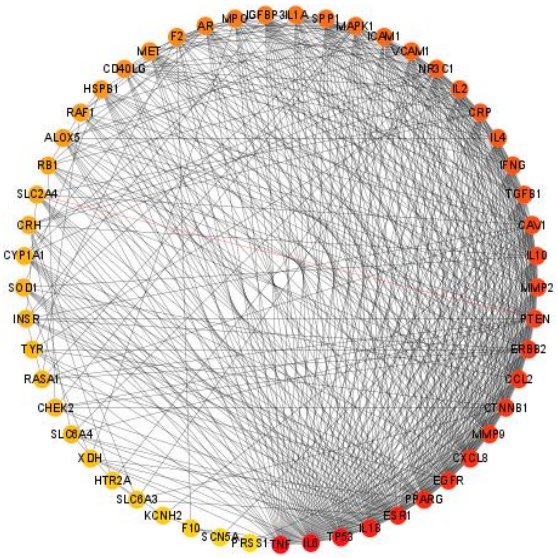

Figure 4: PPI network diagram construction of intersection targets

3.5. "Effective active ingredients-intersection targets" Network Diagram

The effective active ingredients mapped by the intersection targets were integrated, and Cytoscape 3.9.0 was used to construct the "effective active ingredients-intersection targets" network graph. The results are shown in Figure (5), with a total of 81 nodes and 275 edges, and the yellow represents the active ingredients related to forsythia, the purple represents the active ingredients related to honeysuckle, the red triangles represent the active ingredients shared by the “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair, and the green represents the intersection target gene.Use the Network Analyzer in Cytoscape 3.9.0 to analyze the degree value (Degree) of the effective active ingredients of related drugs, and sort them according to the degree value. The main active ingredients in the top ranking are quercetin, kaempferol, luteolin, β –Sitosterol.

3.6. KEGG and GO enrichment analysis

GO function and KEGG pathway enrichment analysis was carried out by importing “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair and acne vulgaris disease intersection genes into David database, limiting the species to human, and taking P<0.05 as the condition, the number of enriched genes was carried out from small to large. Sort and screen out the top 10 biological processes and pathways.Use the WeChat website to draw a histogram of GO information (6),It can be seen from the figure that the top biological processes (BP) are response to drug, positive regulation of gene expression, and response to ethanol, positive regulation of nitric oxide biosynthetic process, etc.; Cellular component (CC) includes extracellular space, extracellular region, External side of plasma membrane, cell surface, etc. Molecular function (MF) mainly includes cytokine activity, enzyme binding, identical protein binding, protein phosphatase binding, protein binding, etc.

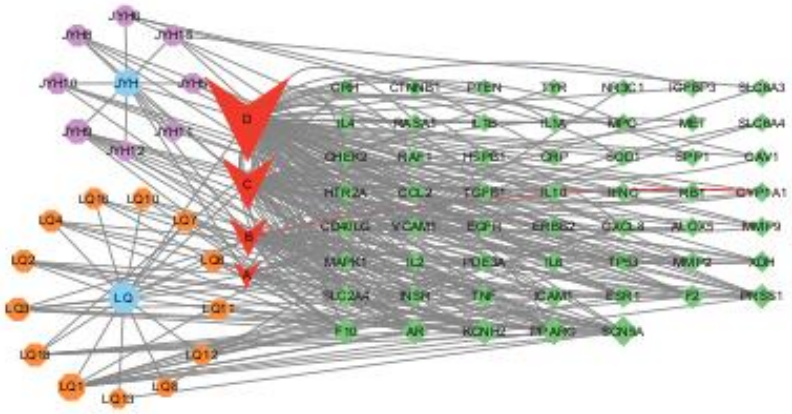

Figure 5: Network diagram of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair and acne vulgaris "effective active ingredients-intersection targets

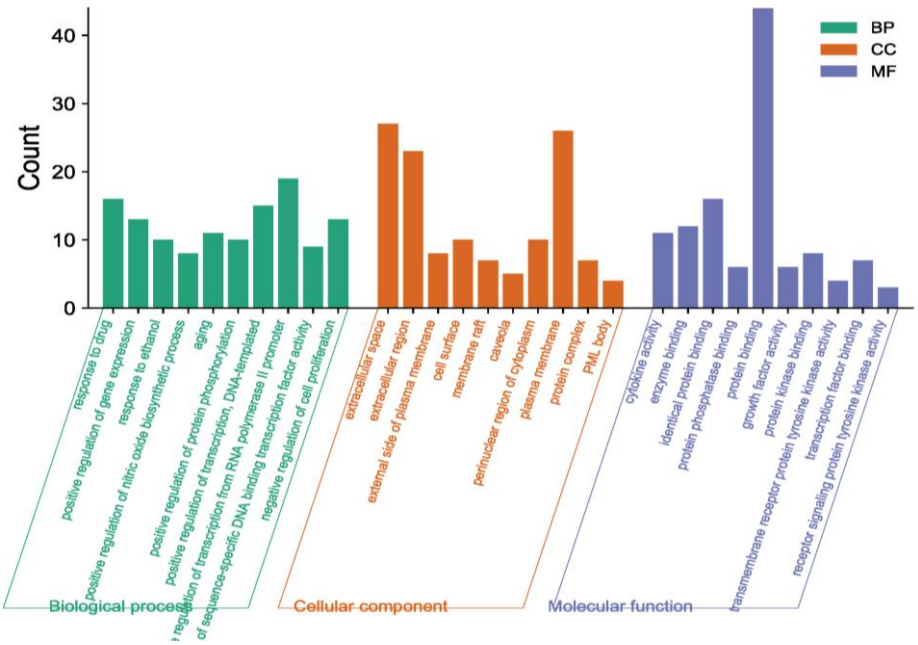

Figure 6: GO functional enrichment analysis of intersection genes

After KEGG enrichment analysis, the top 20 items were selected in descending order of P value from small to large, and a bubble *Figure* (7) was drawn. The results showed that the intersection targets of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair and acne vulgaris were mainly enriched in Pathways in cancer, Proteoglycans in cancer, Cytokine-cytokine receptor interaction, Malaria, Influenza A, Hepatitis B, Chagas disease (American trypanosomiasis), FoxO signaling pathway, T cell receptor signaling pathway, Rheumatoid arthritisand other signaling pathways.

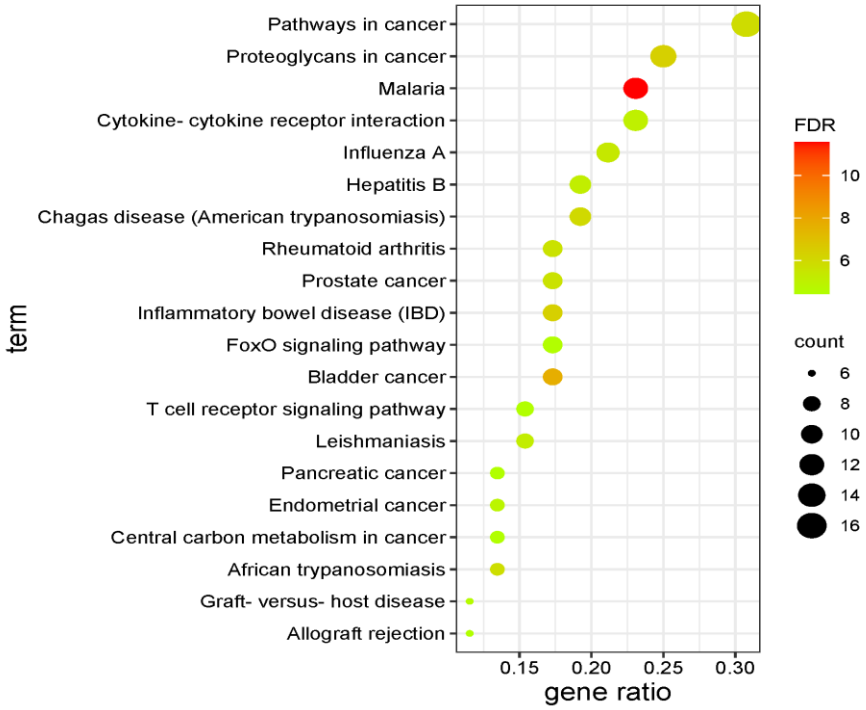

Figure 7: KEGG pathway enrichment analysis of intersection genes

3.7. Molecular docking verification

The active ingredients quercetin, luteolin, kaempferol and honeysuckle-forsythia in the treatment of acne vulgaris from the protein interaction network diagram of the active ingredients with the highest degree value of "effective active ingredients-intersection targets". The top targets TNF and IL-6 were used as core targets for molecular docking, and the results are shown in Figure (8).

4. Discussion

Honeysuckle and Forsythia are a combination of medicines that are often used together. The combination of the two can enhance the power of clearing away heat and detoxification. Modern pharmacological studies have shown that Honeysuckle and Forsythia have antiviral, antibacterial, antipyretic and anti-inflammatory effects, and can be used for many treatment of diseases[8].In the clinical prescriptions for acne vulgaris, many physicians applied honeysuckle-forsythia, and achieved good curative effects[9,10,11].Therefore, this study explored the mechanism of action of honeysuckle-forsythia in the treatment of acne vulgaris through network pharmacology method and molecular docking technology, and provided data basis for further research.

Through the database, the targets of “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair on the effective active ingredients and the targets of acne vulgaris were screened, and the targets were intersected, and the data visualization software was used to draw the results. The results

showed that the main active ingredients of honeysuckle-forsythia on acne vulgaris are mainly quercetin, luteolin, kaempferol and β-sitosterol, which were common to both. The key targets for screening are TNF, IL-6, TP53 and so on. Quercetin, luteolin, and kaempferol all belong to flavonoids, which are considered antioxidants, antibacterials, anti-inflammatory and anti-allergic agents[12]. Quercetin, a flavonoid, inhibits the production of proinflammatory cytokines in HaCaT, THP-1 and RAW 264.7 cells stimulated by Propionibacterium acnes[13]. Luteolin has antioxidant and anti-inflammatory activities on keratinocytes, fibroblasts and some immune cells, it can inhibit the pro-inflammatory mediators IL-6, TNF-α and modulate various signaling pathways that regulate many inflammatory processes in the skin[14], the two inflammatory mediators contain IL-6 and TNF-α are related to the occurrence of acne[18,20],It can be concluded that luteolin may regulate the occurrence of acne by inhibiting inflammatory mediators. Acne is also affected by dietary factors, mainly regulating the PI3kAkt-mTORC1 signaling pathway through insulin and insulin-like growth factor. Insulin can promote androgen synthesis and affect the signal transduction of its receptors, increasing dihydrotestosteron, and further promoting lipid synthesisand inflammatory cytokine production[15], Kaempferol interferes with androgen receptor-mediated androgen signaling, and it inhibits DHT-induced androgen receptor transcriptional activity, suggesting that kaempferol is a potential androgen receptor antagonist, but when the environment lacks androgen, it will combine with androgen receptor to produce androgen effect, which has two-way regulating effect on androgen[16].β –Sitosterol belongs to one of the phytosterols, and many studies have found that it has anti-inflammatory, antioxidant, antibacterial, lipid-lowering, and immune system-regulating effects[17]. The above shows that the “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair can play a role in treating acne vulgaris through these effective active ingredients.

Screening of key targets include TNF, IL-6, TP53 and so on. TNF can be divided into TNF-α and TNF-β. TNF-α is a primary inflammatory cytokine. The elevated level of this cytokine will activate secondary inflammatory cytokines and lead to inflammation. Some studies have found that Increased expression of TNF -α was positively associated with acne severity, with the TNF-α-863C/A polymorphism associated with acne vulgaris and in women and men with heterozygous genotypes at the TNF-α-863C/A locus Patients are at risk of developing acne[18]. IL-6 is an important inflammatory factor in the course of acne vulgaris, and the IL-6 gene promoter polymorphism is associated with susceptibility to acne vulgaris[19]. Foreign reports have found that IL-6-572 G/C polymorphism is associated with Pakistani population. It is significantly related to acne vulgaris[20], and studies have found that IL-6 can stimulate lipid synthesis in SZ95 cells in vitro, and the occurrence of acne vulgaris and other related diseases may be related to this process[21]. In addition, Propionibacterium acnesis one of the main factors in the occurrence of acne, the production of TNF-α and IL-6 is also related to Propionibacterium acnes, which can stimulate Langerhans cells, funnel-shaped cells and sebocytesthrough Toll-like receptor 2, resulting in the production of IL-12, IL-8, IL-6, IFN-γ and TNF-α, and then the formation of papules, pustules and other inflammatory lesions[22]. The “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair acts on acne vulgaris through these targets.

Enrichment analysis shows that “Lonicerae Japonicae Flos-Forsythiae Fructus” herbal pair can intervene in acne vulgaris through multi-component, multi-channel and multi-channel. KEGG enrichment analysis showed that FoxO, Cytokine-cytokine receptor interaction and T cell receptor signaling pathway were the main pathways.FoxO1, a member of the class O subfamily of FoxO transcription factors, regulates the activity of the most important target genes involved in acne pathogenesis[23].It has been hypothesized that the increase in IGF-1and insulin associated with a hyperglycemic diet may reduce the nuclear localization of the FoxO1 transcription factor by activating the phosphatidylinositol-3 kinase (PI3K)/Akt pathway. In order to promote the occurrence of acne, it was studied by stimulating SZ95 sebocytes with different concentrations of

IGF-1 and insulin, and the results proved that in the pathological state of acne, FoxO1 may affect sebaceous gland production and inflammation mainly by participating in the regulation of growth factor stimulation[24]. Cheng Biao et al. found that Cytokine-cytokine receptor interaction is one of the important pathways in the pathogenesis of acne by exploring candidate genes and related signaling pathways in inflammatory acne. In the results of molecular docking, the main active ingredients quercetin, luteolin and kaempferol were docked with key targets TNF and IL-6 to form a stable complex, which further proved that "Lonicerae Japonicae Flos-Forsythiae Fructus" herbal pair has a therapeutic effect on acne vulgaris effect.

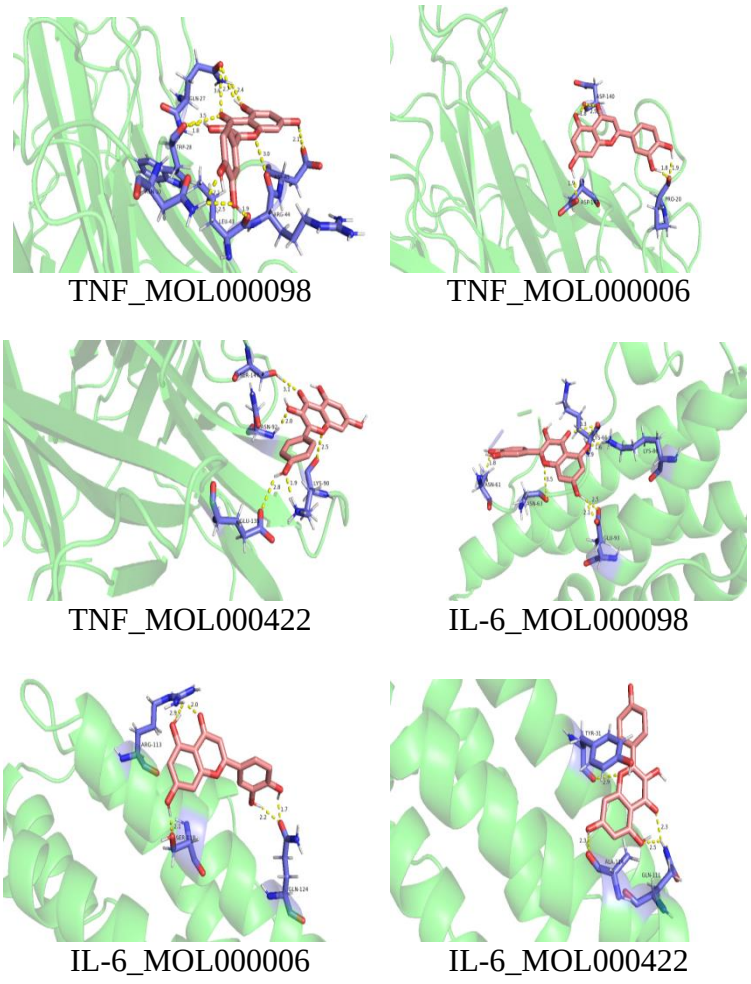

Figure 8: Molecular docking results of main active ingredients and core targets of "Lonicerae Japonicae Flos-Forsythiae Fructus" herbal pair in the treatment of acne vulgaris

In this study, through network pharmacology and molecular docking technology, the "Lonicerae Japonicae Flos-Forsythiae Fructus" herbal pair was discussed to act on acne vulgaris through multi-component, multi-target and multi-pathway, so as to provide directions and ideas for future clinical diagnosis and treatment of traditional Chinese medicine.

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