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Simiao Yongan Decoction in Treating Herpes Zoster: A Network Pharmacology- Based study

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ABSTRACT

Background Herpes zoster (HZ) is an infectious disease, which impacts on patients' quality of life. Herein, we employed the network pharmacological methods to predict the target of bioactive components in Simiao Yongan Decoction (SYD) in the treatment of HZ.

Method We utilized the TCMSP and GenneCards databases to screen for the bioactive components of SYD, their targets, and HZ related targets. The bioactive component-target network of "SYD" was constructed by Cytoscape. Also, we constructed a PPI (protein-protein interaction) network using the Search Tool for the Retrieval of Interacting Genes Database (STRING) to identify the potential SYD targets for the treatment of HZ. "ClusterProfiler" in R-project was used for Gene Ontology (GO) analysis and KEGG pathway enrichment analysis. The SYD hub genes were screened by component-target network topological parameters, and the findings confirmed by molecular docking.

Results We selected 126 bioactive components and 235 targets. By assessing the topological parameters of degree network, we identified five hub genes related to SYD based therapy against HZ, that is, CDK2, CASP3, JUN, AKT1, and MAPK1. According to the results of enrichment analysis, the treatment of HZ with SYD mainly involved toll-like receptor signaling, C-type lectin receptor, MAPK, PI3K-Akt, and other signal pathways. The results of molecular docking analysis showed that the binding energy between SYD bioactive compounds and hub targets was good.

Conclusion The results showed that SYD is effective in the treatment of HZ through multi-target and multi-pathway. It provides certain theoretical support for SYD treatment of HZ and a new direction for the treatment of HZ by traditional Chinese medicine.

Keywords： Herpes zoster, Simiao Yongan Decoction, Network pharmacological, Molecular docking

1. Introduction

Herpes zoster (HZ) is a localized infection that transpires in the dorsal root ganglia of the spinal/ cranial nerves and spreads like a rash over the corresponding dermatome. It is in most cases by varicella-zoster virus [1], which seriously impact on patients' quality of life. In recent years, some countries have reported an increased incidence of HZ. In the United States, the incidence of HZ is 3.2/1 000~4.2/1 000 person-years in most populations [2]. Oral antiviral drugs are the most important basis for the treatment of HZ. Currently, three oral based antiviral medications have been approved for HZ treatment, and these include famciclovir, acyclovir, and its derivative valacyclovir. Studies based on meta-analyses have revealed that oral acyclovir substantially decreases HZ-associated symptoms, including intensity, duration, and frequency of zoster-mediated pain. But, this drug does not affect postherpetic neuralgia (PNH)[3], acyclovir might produce neurological side effects[4] . At present, there is no ideal drug therapy for the treatment of HZ.

Simiao Yongan Decoction (SYD) is a classic prescription in traditional Chinese medicine (TCM,) listed in the "Yan Fang Xin Pian". SYD is composed of four single Chinese herbs, including Jinyinhua, Xuanshen, Gancao and Danggui. The clinical studies in China suggest that SYD is beneficial for treating patients with HZ, and has no significant side-effects [5]. Other research shows that SYD exhibits certain efficacy for PNH [6]. However, Chinese herbs contain more active ingredients and have various pharmacological effects, so it is difficult to clarify its mechanism.

Network pharmacology is a scientific field that involves the construction and analysis of biological networks to study disease pathogenesis [7]. Now, Network pharmacology has been widely used in exploring the pharmacological mechanism of Chinese herbs. In this study, we applied network pharmacology and molecular docking to reveal the core target and main active substance, and possible relationship between them, provide theoretical support for PAP HZ treatment by SYD.

2. Material and Methods

2.1 Screening and identification of SYD compounds

The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)(http://tcmspw.com/tcmsp.php) is a platform based on systems pharmacology and exclusively focuses on Chinese herbal medicine. It shows the interactions between drugs, targets, and diseases[8]. Given this, TCMSP was used to identify the main active components of SYD herbs. The screening parameters were OB (Oral bioavailability) and DL (drug-like). The two parameters are the frequently applied approaches for screening the chemical composition of TCM. OB value indicates a relative amount of the drug that gets into the bloodstream following extravascular administration. DL indicates how the compound is similar to a known drug and shows the likelihood of the compound to become a drug[9]. In this study, we chose the compounds with OB$\geqslant$30% and DL$\geqslant$0.18.

2.2 Target Prediction

The targets of effective components of SYD was collected by using TCMSP. These targets were verified by the Uniprot protein sequence resource(http://www.Uniprot.org). We removed the bioactive compounds that lacked potential target information. The ”Herpes zoster” was used as a keyword to collect disease targets by using GenneCards database(https://www.genecards.org/)[10].Finally,we matched these targets of SYD and HZ, and then selected 31 overlapping targets as related targets of SYD in treating HZ by drawing a Venn diagram, which performed using the R-project version 3.6.3 with the "VennDiagram" package.

2.3 Protein-Protein interaction(PPI) Construction and Hub gene analysis

The targets as related targets of SYD in treating HZ were input to the STRING (http://stringdb.org) [11] for PPI analysis, with the species selected “Homo sapiens”, and drew the network map of PPI. Then we downloaded the data of PPI analysis from the STRING website for further research. Furthermore, we imported the data downloaded from STRING into the Cytoscape software V3.72[12] to perform topological attribute analysis. The “CytoNCA” was performed for calculating Degree (DC). DC indicates the number of connections between one nod and the other. Finally, the top 3 genes of DC values are considered Hub genes.

2.4 GO and KEGG analysis

The GO (Gene Ontology), as a bioinformatics project, provides crucial information regarding gene functions [13]. The KEGG (Kyoto Encyclopedia of Genes and Genomes) database provides information that aids in the understanding of the functions and utilities of the biological system, which includes the cell, the organism, and the ecosystem. It contains molecular information, particularly large-scale molecular datasets obtained via genome sequencing or highly automated technologies [14]. In this work,"clusterProfiler", "DOSE", "org.Hs.eg.db" and "enrichplot" packages were used for GO and KEGG analysis. We set PvalueCutoff=0.05, qvalueCutoff=0.05 in R-project. And the Bubble Chart was plotted using "ggplot2" package.

2.5 Molecular Docking

At last, we performed molecular docking by using AutoDock Vina software, which is an

open-source program for doing molecular docking [15]. In this work, we selected compounds and targets with top 3 degree values in the compounds-targets network to dock stimulation. All compounds structures were downloaded from TCMSP and the 3D structures of the targets were retrieved from PBD (http://www.rcsb.org/).

3. Results

3.1 bioactive compounds in SYD

We obtained 126 bioactive compounds of SYD from TCMSP. Among these compounds, there were 2 species of Danggui,92 species of Gancao,23 species of Jinyinhua, and 9 species of Xuanshen**.** The bioactive compounds of SYD were listed in (Table 1).

Table1 Bioactive compounds and ADME(absorption,distribution,metabolism,excretion) parameters of SYD

MOL ID	Molecule Name	OB (%)	DL	Herb
MOL000358	beta-sitosterol	36. 91	0. 75	Danggui
MOL000449	Stigmasterol	43. 83	0. 76	Danggui
MOL001484	Inermine	75. 18	0. 54	Gancao
MOL001792	DFV	32. 76	0. 18	Gancao
MOL000211	Mairin	55. 38	0. 78	Gancao
MOL002311	Glycyrol	90. 78	0. 67	Gancao
MOL000239	Jaranol	50. 83	0. 29	Gancao
MOL002565	Medicarpin	49. 22	0. 34	Gancao
MOL000354	isorhamnetin	49. 6	0. 31	Gancao
MOL000359	sitosterol	36. 91	0. 75	Gancao
MOL003656	Lupiwighteone	51. 64	0. 37	Gancao
MOL003896	7-Methoxy-2-methyl isoflavone	42. 56	0. 2	Gancao
MOL000392	formononetin	69. 67	0. 21	Gancao
MOL000417	Calycosin	47. 75	0. 24	Gancao
MOL000422	kaempferol	41. 88	0. 24	Gancao

MOL004328	naringenin	59. 29	0. 21	Gancao
MOL004805	(2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl) phenyl]-8, 8-dimethyl-2, 3-dihydropyrano[2, 3-f]chromen-4-one	31. 79	0. 72	Gancao
MOL004806	euchrenone	30. 29	0. 57	Gancao
MOL004808	glyasperin B	65. 22	0. 44	Gancao
MOL004810	glyasperin F	75. 84	0. 54	Gancao
MOL004811	Glyasperin C	45. 56	0. 4	Gancao
MOL004814	Isotrifoliol	31. 94	0. 42	Gancao
MOL004815	(E)-1-(2, 4-dihydroxyphenyl)-3-(2, 2-dimethylchromen-6-yl) prop-2-en-1-one	39. 62	0. 35	Gancao
MOL004820	kanzonols W	50. 48	0. 52	Gancao
MOL004824	(2S)-6-(2, 4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2, 3-dihydrofuro[3, 2-g]chromen-7-one	60. 25	0. 63	Gancao
MOL004827	Semilicoisoflavone B	48. 78	0. 55	Gancao
MOL004828	Glepidotin A	44. 72	0. 35	Gancao
MOL004829	Glepidotin B	64. 46	0. 34	Gancao
MOL004833	Phaseolinisoflavan	32. 01	0. 45	Gancao
MOL004835	Glypallichalcone	61. 6	0. 19	Gancao
MOL004838	8-(6-hydroxy-2-benzofuranyl)-2, 2-dimethyl-5-chromenol	58. 44	0. 38	Gancao
MOL004841	Licochalcone B	76. 76	0. 19	Gancao
MOL004848	licochalcone G	49. 25	0. 32	Gancao
MOL004849	3-(2, 4-dihydroxyphenyl)-8-(1, 1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin	59. 62	0. 43	Gancao
MOL004855	Licoricone	63. 58	0. 47	Gancao
MOL004856	Gancaonin A	51. 08	0. 4	Gancao
MOL004857	Gancaonin B	48. 79	0. 45	Gancao
MOL004860	licorice glycoside E	32. 89	0. 27	Gancao
MOL004863	3-(3, 4-dihydroxyphenyl)-5, 7-dihydroxy-8-(3-methylbut-2-enyl) chromone	66. 37	0. 41	Gancao
MOL004864	5, 7-dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl) chromone	30. 49	0. 41	Gancao
MOL004866	2-(3, 4-dihydroxyphenyl)-5, 7-dihydroxy-6-(3-meth	44. 15	0. 41	Gancao

	ylbut-2-enyl) chromone			
MOL004879	Glycyrin	52.61	0.47	Gancao
MOL004882	Licocoumarone	33.21	0.36	Gancao
MOL004883	Licoisoflavone	41.61	0.42	Gancao
MOL004884	Licoisoflavone B	38.93	0.55	Gancao
MOL004885	licoisoflavanone	52.47	0.54	Gancao
MOL004891	shinpterocarpin	80.3	0.73	Gancao
MOL004898	(E)-3-[3, 4-dihydroxy-5-(3-methylbut-2-enyl) phenyl]-1-(2, 4-dihydroxyphenyl) prop-2-en-1-one	46.27	0.31	Gancao
MOL004903	liquiritin	65.69	0.74	Gancao
MOL004904	licopyranocoumarin	80.36	0.65	Gancao
MOL004905	3, 22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid	34.32	0.55	Gancao
MOL004907	Glyzaglabrin	61.07	0.35	Gancao
MOL004908	Glabridin	53.25	0.47	Gancao
MOL004910	Glabranin	52.9	0.31	Gancao
MOL004911	Glabrene	46.27	0.44	Gancao
MOL004912	Glabrone	52.51	0.5	Gancao
MOL004913	1, 3-dihydroxy-9-methoxy-6-benzofurano[3, 2-c]chromenone	48.14	0.43	Gancao
MOL004914	1, 3-dihydroxy-8, 9-dimethoxy-6-benzofurano[3, 2-c]chromenone	62.9	0.53	Gancao
MOL004915	Eurycarpin A	43.28	0.37	Gancao
MOL004917	glycyroside	37.25	0.79	Gancao
MOL004924	(-)-Medicocarpin	40.99	0.95	Gancao
MOL004935	Sigmoidin-B	34.88	0.41	Gancao
MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl) chroman-4-one	71.12	0.18	Gancao
MOL004945	(2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl) chroman-4-one	36.57	0.32	Gancao
MOL004948	Isoglycyrol	44.7	0.84	Gancao
MOL004949	Isolicoflavonol	45.17	0.42	Gancao
MOL004957	HMO	38.37	0.21	Gancao

MOL004959	1-Methoxyphaseollidin	69. 98	0. 64	Gancao
MOL004961	Quercetin der.	46. 45	0. 33	Gancao
MOL004966	3'-Hydroxy-4'-O-Methylglabridin	43. 71	0. 57	Gancao
MOL000497	licochalcone a	40. 79	0. 29	Gancao
MOL004974	3'-Methoxyglabridin	46. 16	0. 57	Gancao
MOL004978	2-[(3R)-8, 8-dimethyl-3, 4-dihydro-2H-pyrano[6, 5-f]chromen-3-yl]-5-methoxyphenol	36. 21	0. 52	Gancao
MOL004980	Inflacoumarin A	39. 71	0. 33	Gancao
MOL004985	icos-5-enoic acid	30. 7	0. 2	Gancao
MOL004988	Kanzonol F	32. 47	0. 89	Gancao
MOL004989	6-prenylated eriodictyol	39. 22	0. 41	Gancao
MOL004990	7, 2', 4'-trihydroxy-5-methoxy-3-arylcoumarin	83. 71	0. 27	Gancao
MOL004991	7-Acetoxy-2-methylisoflavone	38. 92	0. 26	Gancao
MOL004993	8-prenylated eriodictyol	53. 79	0. 4	Gancao
MOL004996	gadelaidic acid	30. 7	0. 2	Gancao
MOL000500	Vestitol	74. 66	0. 21	Gancao
MOL005000	Gancaonin G	60. 44	0. 39	Gancao
MOL005001	Gancaonin H	50. 1	0. 78	Gancao
MOL005003	Licoagrocarpin	58. 81	0. 58	Gancao
MOL005007	Glyasperins M	72. 67	0. 59	Gancao
MOL005008	Glycyrrhiza flavonol A	41. 28	0. 6	Gancao
MOL005012	Licoagroisoflavone	57. 28	0. 49	Gancao
MOL005013	18α-hydroxyglycyrrhetic acid	41. 16	0. 71	Gancao
MOL005016	Odoratin	49. 95	0. 3	Gancao
MOL005017	Phaseol	78. 77	0. 58	Gancao
MOL005018	Xambioona	54. 85	0. 87	Gancao
MOL005020	dehydroglyasperins C	53. 82	0. 37	Gancao
MOL000098	quercetin	46. 43	0. 28	Gancao
MOL003117	Ioniceracetalides B_qt	61. 19	0. 19	Jinyinhua
MOL001494	Mandenol	42	0. 19	Jinyinhua

MOL001495	Ethyl linolenate	46. 1	0. 2	Jinyinhua
MOL003006	(−)-(3R, 8S, 9R, 9aS, 10aS)-9-ethenyl-8-(beta-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	Jinyinhua
MOL000422	kaempferol	41. 88	0. 24	Jinyinhua
MOL002914	Eriodyctiol (flavanone)	41. 35	0. 24	Jinyinhua
MOL000006	luteolin	36. 16	0. 25	Jinyinhua
MOL003044	Chryseriol	35. 85	0. 27	Jinyinhua
MOL000098	quercetin	46. 43	0. 28	Jinyinhua
MOL003014	secologanic dibutylacetal_qt	53. 65	0. 29	Jinyinhua
MOL003095	5-hydroxy-7-methoxy-2-(3, 4, 5-trimethoxyphenyl)chromone	51. 96	0. 41	Jinyinhua
MOL003128	dinethylsecologanoside	48. 46	0. 48	Jinyinhua
MOL002707	phytofluene	43. 18	0. 5	Jinyinhua
MOL003111	Centauroside_qt	55. 79	0. 5	Jinyinhua
MOL003062	4, 5'-Retro-. beta. , . beta. -Carotene-3, 3'-dione, 4', 5'-didehydro-	31. 22	0. 55	Jinyinhua
MOL003059	kryptoxanthin	47. 25	0. 57	Jinyinhua
MOL003101	7-epi-Vogeloside	46. 13	0. 58	Jinyinhua
MOL002773	beta-carotene	37. 18	0. 58	Jinyinhua
MOL003124	XYLOSTOSIDINE	43. 17	0. 64	Jinyinhua
MOL003108	Caeruloside C	55. 64	0. 73	Jinyinhua
MOL000358	beta-sitosterol	36. 91	0. 75	Jinyinhua
MOL003036	ZINC03978781	43. 83	0. 76	Jinyinhua
MOL000449	Stigmasterol	43. 83	0. 76	Jinyinhua
MOL002222	sugiol	36. 11	0. 28	Xuanshen
MOL007662	harpagoside_qt	122. 87	0. 32	Xuanshen
MOL001925	paeoniflorin_qt	68. 18	0. 4	Xuanshen
MOL007659	scropolioside D	36. 62	0. 4	Xuanshen
MOL007658	14-deoxy-12(R)-sulfoandrographolide	62. 57	0. 42	Xuanshen
MOL000359	sitosterol	36. 91	0. 75	Xuanshen

MOL000358	beta-sitosterol	36. 91	0. 75	Xuanshen
MOL007657	scropolioside A_qt	38. 63	0. 77	Xuanshen
MOL007660	scropolioside D_qt	33. 17	0. 82	Xuanshen

3.2 Identifying HZ Related Targets in SYD

We were screened 2056 targets related to the bioactive compounds of SYD from TCMSP. Among these targets, there were 55 targets related to Danggui, 1543 to Gancao,402 targets to Jinyinhua, and 56 to Xuanshen, removing duplicate targets. We were also screened 328 targets corresponding to HZ. Finally, 235 targets were identified, interacting with 126 bioactive compounds of SYD, and 31 targets related with HZ (Fig.1).

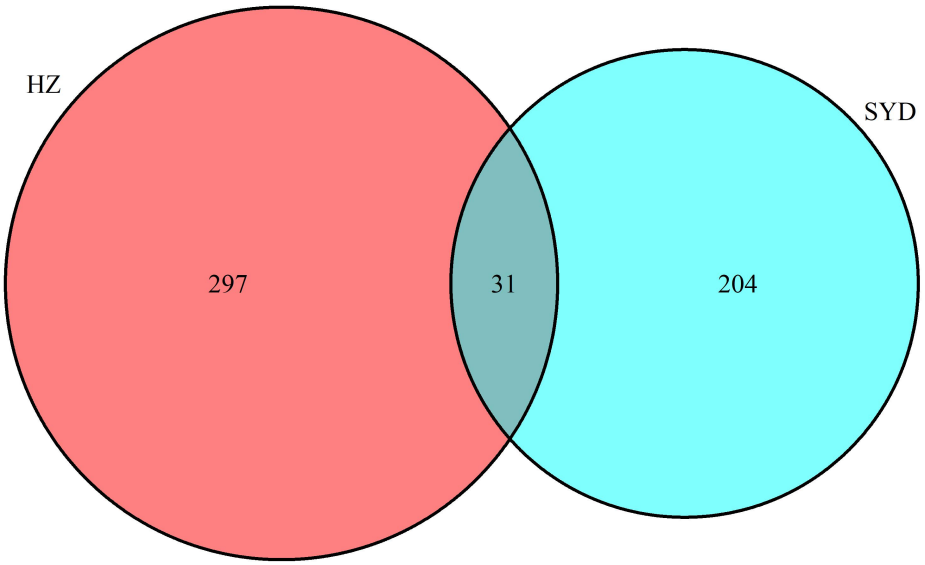

Fig.1 Screening of targets for HZ treated by SYD

3.3 Compound-Target Network

The compound-target network established by Cytoscape, with 98 nodes and 122 edges (Fig.2). The degree value indicates the link between the targets and bioactive compounds. The degree value of the targets and bioactive compounds were shown in Table 2. As the Table 2 shown, MOL000098 (quercetin, degree=21), MOL000006 (luteolin, degree=13), and MOL000422 (Kaempferol, degree=11) have lots of potential targets.

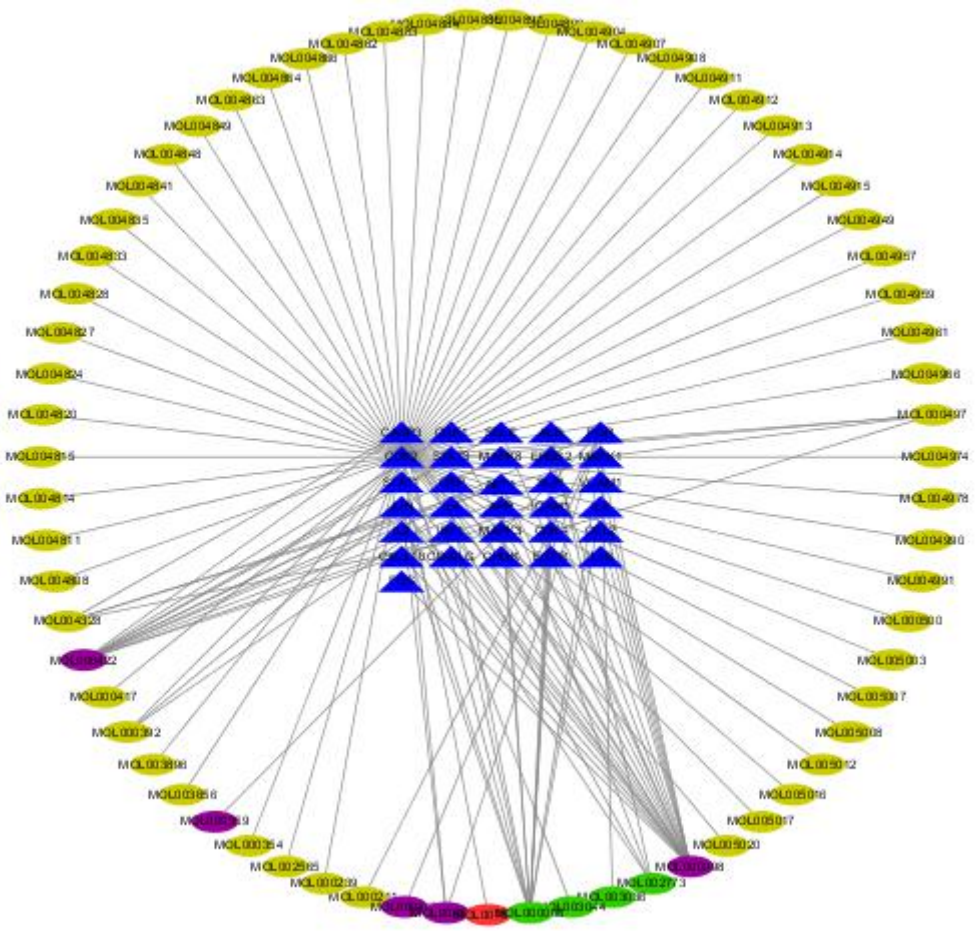

Fig.2 Compound-target network (The triangle node represents the targets,the ellipse node represents the compounds).

Table2 Targets and bioactive compounds

Target name	Degree	Compound	Degree
CDK2	57	MOL000098	21
CASP3	58	MOL000006	13
JUN	59	MOL000422	11
PGR	60	MOL002773	4
AKT1	5	MOL000497	4
MAPK1	4	MOL004328	4
ICAM1	3	MOL000392	3
CD40LG	2	MOL000358	3
IL2	2	MOL007662	1

ERBB2	2	MOL003044	1
IL6	2	MOL003036	1
EGFR	2	MOL005020	1
CDK4	2	MOL005017	1
VCAM1	2	MOL005016	1
SELE	2	MOL005012	1
CDK1	2	MOL005008	1
STAT1	2	MOL005007	1
IL4	2	MOL005003	1
APP	1	MOL000500	1
ALB	1	MOL004991	1
IRF1	1	MOL004990	1
CHUK	1	MOL004978	1
CXCL10	1	MOL004974	1
CRP	1	MOL004966	1
CCL2	1	MOL004961	1
IL1B	1	MOL004959	1
FOS	1	MOL004957	1
STAT3	1	MOL004949	1
		MOL004915	1
		MOL004914	1
		MOL004913	1
		MOL004912	1
		MOL004911	1
		MOL004908	1
		MOL004907	1
		MOL004904	1
		MOL004898	1
		MOL004891	1
		MOL004885	1

	MOL004884	1
	MOL004883	1
	MOL004882	1
	MOL004866	1
	MOL004864	1
	MOL004863	1
	MOL004849	1
	MOL004848	1
	MOL004841	1
	MOL004835	1
	MOL004833	1
	MOL004828	1
	MOL004827	1
	MOL004824	1
	MOL004820	1
	MOL004815	1
	MOL004814	1
	MOL004811	1
	MOL004808	1

3.4 Protein-Protein interaction(PPI)

In PPI network analysis (medium confidence $\geqslant$ 0.4), we obtained 31 nodes and 318 interactions (Fig. 3). PPI analysis shows the average node degree of PPI network was 20.5 and the local clustering coefficient was 0.848. Based on this analysis, the three nods with the highest degree value were considered Hub genes, and included CDK2, CASP3, and JUN. These target proteins might be significant in the SYD treating HZ process.

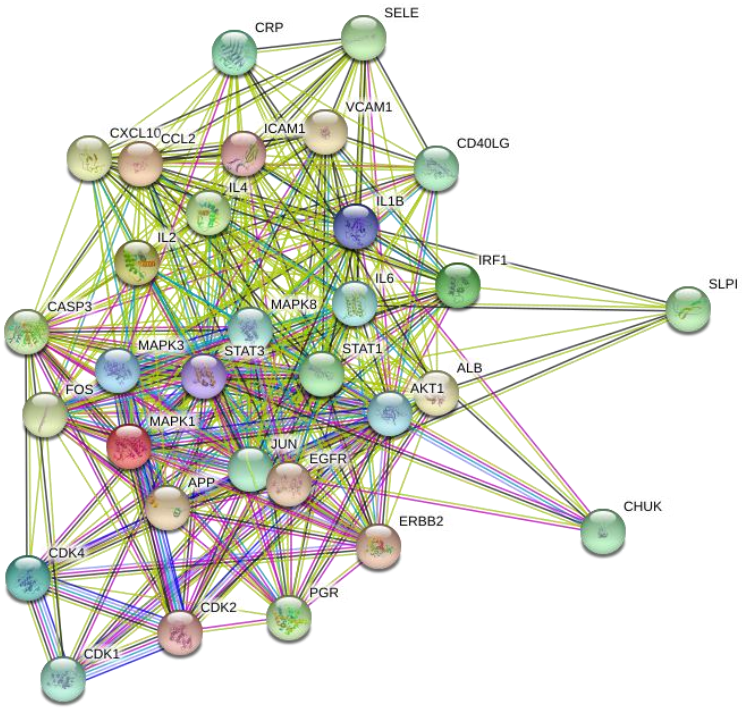

Fig.3 PPI network

3.5 GO and KEGG Pathway Enrichment Analysis

We used R-project for GO_BP enrichment analysis. The top 20 ranked entries are shown as a Bubble Chart (Fig 4 A). The PPI network targets were mostly involved in response to lipopolysaccharide, molecules of bacterial origin, and reactive oxygen species, as well as leukocyte cell−cell adhesion, modulation of DNA−binding transcription factor activity, T cell activation, and other molecular functions.

Then we also used R-project for KEGG pathway enrichment analysis. The top 20 ranked entries are shown as a Bubble Chart (Fig 4 B). The enrichment analysis indicated the targets were mostly associated with Toll-like receptor signaling pathway, C-type lectin receptor signaling pathway, Endocrine resistance, Osteoclast differentiation, FoxO signaling pathway, and MAPK signaling pathway. Toll-like receptor signaling pathway is more significant, so we mapped the pathway (Fig 5). Both GO functional and KEGG pathway enrichment analysis suggested multiple targets of SYD could act on multiple biological processes to treat HZ.

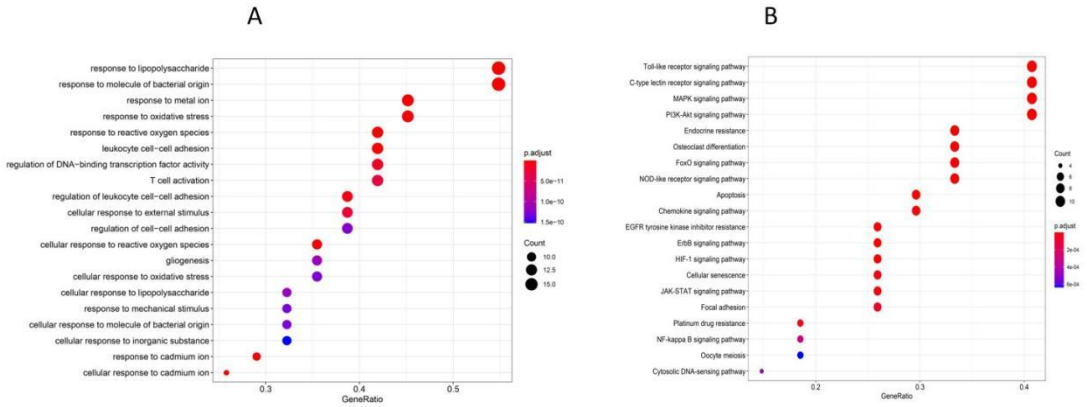

Fig.4 GO and KEGG enrichment analysis.(A.The top 20 significant enriched terms in GO_BP. B..The top 20 significant enriched terms in KEGG.

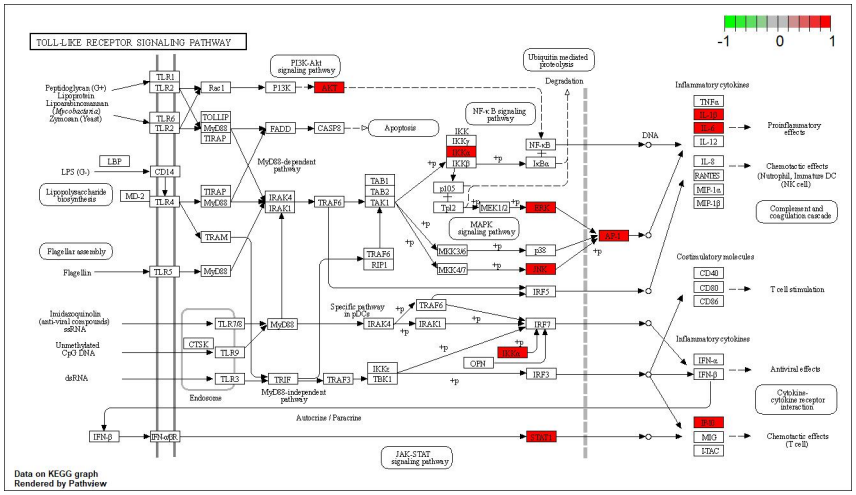

Fig.5 The PI3K Akt signaling pathway

3.6 Molecular Docking Analysis

We selected compounds and targets with top 3 degree values in the compounds-targets network to dock stimulation (Table 3). The lower the energy of ligand-receptor is, the better the binding activity between ligand and receptor is. Partial molecular docking processes were shown in (Fig 6).

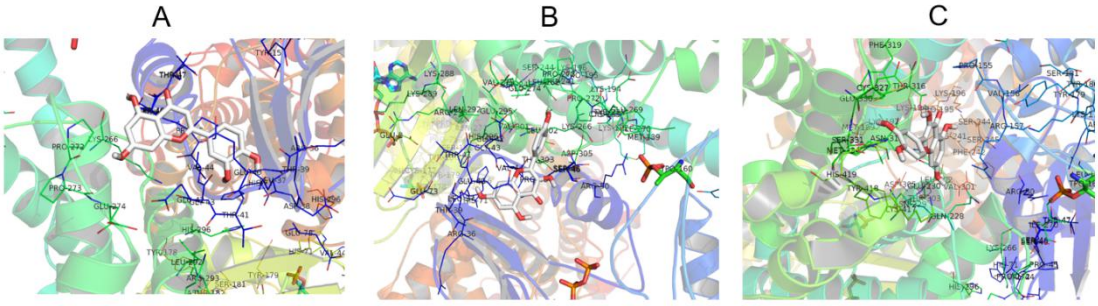

Fig.6 Bioactive compound-hub genes doching combination. A.Quercetin-CKD2 B. Luteolin-CKD2 C. kaempferol-CKD2.

Table 3 Molecular docking results

Target name	PDB ID	Compound	Energy (kcal/mol)
CKD2	2cch	MOL000098	−8. 6
CKD2	2cch	MOL000006	−8. 5
CKD2	2cch	MOL000422	−8. 1
PGR	2c7a	MOL000098	−7. 2
PGR	2c7a	MOL000006	−7. 4
PGR	2c7a	MOL000422	−7. 5
JUN	1s9k	MOL000098	−7. 7
JUN	1s9k	MOL000006	−7. 8
JUN	1s9k	MOL000422	−7. 6

4. Discussion

Herpes zoster(HZ) is an infectious disease of viral etiology. According to traditional Chinese medicine, HZ belongs to “Snake sore” and “girdling fire cinnabar”. Simiao Yongan Decoction (SYD) is a famous prescription in TCM. Several clinical trials have shown the effectiveness of SYD in patients with HZ and postherpetic neuralgia (PNH)[5 6]. Therefore, we use TCM network pharmacology approaches to unveil these mechanisms.

The findings of this study showed that the major bioactive compounds of SYD are quercetin, luteolin, and kaempferol, etc. Quercetin is a bioflavonoid compound that is found in various vegetables and fruits. The compound has been shown to possess potent antioxidant and anti-inflammatory activities [16] [17]. A study demonstrated that quercetin could relieve pain in animal models of inflammatory-induced pain [18] and neuroprotective effect [19]. Luteolin exerts multiple bioactive effects, including nervous system protection [20], and anti-inflammatory [21] effects as well as antioxidant [22]. Kaempferol is a flavonoid that exhibits many health benefits, particularly against inflammatory diseases [23]. Kaempferol has been demonstrated to attenuate inflammation pathway by modulating NF- κ B [24]. The PPI network analysis showed CDK2, CASP3, JUN, AKT1, and MAPK1 have the largest degree value. CDK2 participate in cell cycle regulation [provided by RefSeq, Aug 2020]. The CASP3 participates in apoptosis, inflammation, and necrosis related signaling pathways. [provided by RefSeq, Aug 2017]. AKT1plays a vital role in the regulation of cell survival, angiogenesis, tumor formation, and insulin signaling. The JUN plays a role in growth and differentiation[25].MAPK1 plays an essential function in neuropathic pain and inflammatory reaction[26] [27].These suggest that the bioactive compounds of SYD and the targets of these compounds played a crucial function in the treatment of HZ and PNH.

Based on the KEGG pathway enrichment analysis, it was mostly enriched in the Toll-like receptor signaling pathway, C-type lectin receptor signaling pathway, MAPK signaling pathway, PI3K-Akt signaling pathway, and other signaling pathways. Toll-like receptors perceive conserved microbial structures, like bacterial lipopolysaccharide or viral double-stranded RNA. Upon perception, they induce various signaling pathways related to immune responses against microbial infections [28].C-type lectin receptor is mainly expressed on myeloid cells and are involved in antifungal immunity. MAPK signaling pathway is vital in the mediation of multiple cellular processes, which include proliferation, stress response, differentiation, motility, survival, growth, and death[29]. The PI3K – Akt signaling pathway plays a vital role in mediating survival signals in different types of neuronal cells. Recently, it was suggested that it could suppress cell death by regulating the cytoplasmic cell death machinery, as well as the expression of genes that facilitate cell death and survival [30].

Therefore, we think that SYD might clear HZ virus through Toll-like receptor signaling pathway, amplifies Immunity through C-type lectin receptor signaling pathway, and regulating cell apoptosis by MAPK signaling pathway and PI3K/Akt pathway.

At last, according to molecular docking analysis results, the binding energy between SYD bioactive compounds and hub targets was good, suggesting that our study has high reference value.

5. Conclusion

In conclusion, this study analyzed the mechanism of Simiao Yongan Decoction (SYD) in the treatment of herpes zoster (HZ) using network pharmacology. Our findings revealed that SYD is effective against HZ through multi-target and multi-pathway. It provides certain theoretical support for the treatment of HZ and a new direction for the treatment of HZ by traditional Chinese medicine. However, the results of our study need to be verified by experimental research.

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