Network Pharmacology-based Study of Simiao Yongan Decoction for Treatment of Herpes Zoster Infection

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Research

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Abstract

Background: Herpes zoster (HZ) is a virus that causes infectious diseases that impact the quality of life of patients. Herein, we applied network pharmacological methods to predict the target of bioactive components in Simiao Yongan Decoction (SYD) that could treat HZ.

Methods: We developed a Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMP) and GenneCards databases for screening of bioactive components of SYD, their targets, and HZ related targets. A bioactive component-target network of SYD was constructed using Cytoscape. We also constructed a protein-protein interaction (PPI) network using the Search Tool for the Retrieval of Interacting Genes Database (STRING) to identify potential SYD targets for the treatment of HZ. "ClusterProfiler" in R-project was used for Gene Ontology (GO) and KEGG pathway enrichment analyses. We screened SYD hub genes based on component-target network topological parameters and confirmed the findings by molecular docking. We selected 126 bioactive components and 235 targets.

Results: By assessing the topological parameters of the degree network, we identified that CDK2, CASP3, JUN, AKT1, and MAPK1 were hub genes related to SYD-based therapy against HZ. The findings showed that treatment of HZ with SYD mainly involved toll-like receptor, C-type lectin receptor, MAPK, PI3K-Akt, and other signaling pathways. The molecular docking results revealed good binding energy between the SYD bioactive compounds and hub targets.

Conclusion: We showed that SYD could effectively treat HZ via multiple targets and pathways. Our results provide theoretical support for treatment of HZ with SYD and a new direction for such treatment using traditional Chinese medicine.

Background

Herpes zoster (HZ) causes a localized infection of the dorsal root ganglia of the spinal/cranial nerves that spreads like a rash over the corresponding dermatome. It is usually caused specifically by the varicella-zoster virus [1], which seriously impacts the quality of life of patients. The incidence of HZ is increasing; for example, in the United States, the incidence of HZ infection is 3.2–4.2 per 1 000 person-years [2]. Oral antiviral drugs are the most important basis for treatment of HZ. The oral-based antiviral medications that are approved for HZ treatment include famciclovir, acyclovir, and its derivative, valacyclovir. Meta-analyses have revealed that oral acyclovir substantially decreases HZ-associated symptoms, including intensity, duration, and frequency of zoster-mediated pain. However, this drug does not affect postherpetic neuralgia (PNH) [3], and acyclovir may produce neurological side effects [4]. An ideal agent for treatment of HZ has not been identified thus far.

Simiao Yongan Decoction (SYD) is a classic traditional Chinese medicine (TCM) prescription listed in the “Yan Fang Xin Pian”. It includes the Chinese herbs, Jinyinhua, Xuanshen, Gancao, and Danggui. Clinical studies in China have suggested that SYD can treat HZ without causing significant side-effects [5]. Others have shown that SYD is effective for treatment of PNH [6]. However, Chinese herbs contain many active
ingredients with various pharmacological effects; hence, mechanisms of action should be elucidated for appropriate clarification.

Network pharmacology involves the construction and analysis of biological networks to study disease pathogenesis [7]. Network pharmacology has been widely utilized to explore the pharmacological mechanisms of Chinese herbs. In the present study, we applied network pharmacology and molecular docking to reveal the core target and main active agents, and possible relationships among them, to provide theoretical support for (PAP) HZ treatment by SYD.

**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 that exclusively focuses on Chinese herbal medicine. It shows interactions between drugs, targets, and diseases [8]. We therefore used the TCMSP to identify the main active components of SYD herbs. The screening parameters were OB (oral bioavailability) and DL (drug-like). These parameters are popular approaches for screening of the chemical composition of TCM. The OB is defined as the relative amount of a drug that enters the bloodstream after extravascular administration, and DL indicates the extent of similarity of a compound with a known drug and the likelihood of the compound to be used as a pharmaceutical agent [9]. Herein, we analyzed compounds with OB \( \geq 30\% \) and DL \( \geq 0.18 \).

2.2 Target prediction

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

2.3 Protein-protein interaction (PPI) network construction and Hub gene analysis

Data on the possible related targets of SYD for treatment of HZ were used as input for STRING (http://stringdb.org) [11] for PPI analysis, with the selected species, Homo sapiens, and a network map of PPI was constructed. We then downloaded PPI data from STRING for further investigation. We also imported data from STRING into the Cytoscape software V3.72 [12] to analyze topological attributes. Degrees (DC) calculated using CytoNCA indicate numbers of connections between nodes. Finally, we considered genes with the top three DC values as Hub genes.

2.4 GO and KEGG analyses
The GO (Gene Ontology) project provides crucial information regarding gene functions [13]. The Kyoto Encyclopedia of Genes and Genomes (KEGG) database provides information that facilitates understanding of the functions and roles of biological systems, namely cells, organisms, and ecosystems. It contains large-scale molecular datasets obtained via genome sequencing or highly automated technologies [14]. Here, we used the clusterProfiler, DOSE, org.Hs.eg.db, and enrichplot packages for GO and KEGG analysis. We set PvalueCutoff = 0.05 and qvalueCutoff = 0.05 in R-project. A Bubble Chart was plotted using the ggplot2 package.

### 2.5 Molecular docking

We performed molecular docking using the open-source software, AutoDock Vina [15]. We selected compounds and targets with the top three degree values in the compounds-targets network for dock stimulation. All compound structures were downloaded from TCMSP and the 3D structures of the targets were retrieved from PBD (http://www.rcsb.org/).

## Results

### 3.1 Bioactive compounds in SYD

We obtained information on 126 bioactive compounds of SYD from TCMSP; data on the following species were obtained: Danggui (n = 2), Gancao (n = 92), Jinyinhua (n = 23), and Xuanshen (n = 9). Table 1 lists the bioactive compounds 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 |
| MOL ID    | Molecule Name                                                                 | OB(%) | DL  | Herb   |
|-----------|-------------------------------------------------------------------------------|-------|-----|--------|
| 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 | Phaseolinisoflanan                                                            | 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-methylbut-2-enyl)chromone          | 44.15 | 0.41| Gancao |
| 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 | licoisoflanavone                                                              | 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 |
| MOL ID     | Molecule Name                                                                 | OB(%) | DL   | Herb  |
|------------|-------------------------------------------------------------------------------|-------|------|-------|
| 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  | Isolicoavonol                                                                 | 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|
| MOL004974  | 3'-Methoxyglabridin                                                           | 46.16 | 0.57 | Gancao|
| MOL004978  | 2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyran0[6,5-f]chromen-3-yl]-5-methoxyphenol| 36.21 | 0.52 | Gancao|
| MOL004980  | Inacoumarin A                                                                 | 39.71 | 0.33 | Gancao|
| MOL004985  | icos-5-enolic acid                                                            | 30.7  | 0.2  | Gancao|
| MOL ID     | Molecule Name                                                                 | OB(%) | DL   | Herb     |
|------------|-------------------------------------------------------------------------------|-------|------|----------|
| 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   |
| MOL005000  | 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)-2,3,9a,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|
| MOL ID     | Molecule Name                                                                 | OB(%) | DL  | Herb       |
|------------|-------------------------------------------------------------------------------|-------|-----|------------|
| 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  | Centaurosine\_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 Identification of HZ-related targets in SYD
After removing duplicate targets, we screened 2,056 targets related to the bioactive compounds of SYD from TCMSP. Among these 55, 1,543, 402, and 56 targets were related to Danggui, Gancao, Jinyinhua, and Xuanshen, respectively. We also screened 328 targets corresponding to HZ. Finally, 235 targets were identified that interacted with 126 bioactive compounds of SYD, and 31 targets that were associated with HZ (Fig. 1).

### 3.3 Compound-target network

The compound-target network established by Cytoscape had 98 nodes and 122 edges (Fig. 2). The degree value indicates links between the targets and bioactive compounds. Table 2 shows the following degree values of potential targets and bioactive compounds: MOL000098 (quercetin, degree = 21), MOL000006 (luteolin, degree = 13), and MOL000422 (Kaempferol, degree = 11)
| 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      |
| Target name | Degree | Compound       | Degree |
|-------------|--------|----------------|--------|
| 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      |
3.4 Protein-protein interaction

We obtained 31 nodes and 318 interactions from the PPI network analysis (medium confidence ≥ 0.4; Fig. 3). The average node degree of the PPI network was 20.5 and the local clustering coefficient was 0.848. Based on these findings, the three nodes with the highest degree were considered as Hub genes, and included CDK2, CASP3, and JUN. These target proteins might be significant in the SYD-based treatment of HZ.

3.5 GO and KEGG pathway enrichment analyses

We applied R-project for GO_BP enrichment analysis. The bubble chart shown in Fig. 4A shows the top 20 ranked entries. The PPI network targets were mostly involved in response to lipopolysaccharides, 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.

We also applied R-project for KEGG pathway enrichment analysis. The bubble chart shown in Fig. 4B shows the top 20 ranked entries. The findings indicated targets that were mostly associated with the Toll-like receptor signaling pathway, C-type lectin receptor signaling pathway, Endocrine resistance, Osteoclast differentiation, and the FoxO, and MAPK signaling pathways. The Toll-like receptor signaling pathway was more significant, and thus we mapped the pathway (Fig. 5). Both GO functional and KEGG pathway enrichment analyses suggested that multiple targets of SYD could act on multiple biological processes for treatment of HZ.

3.6 Molecular docking

We selected compounds and targets with the top three degrees in the compound-target network to dock stimulation (Table 3). Lower energy of binding of a ligand-receptor indicates better binding activity between them. Figure 6 shows partial molecular docking processes.
Table 3
Molecular docking results

| Target name | PDB ID | Compound  | Energy (kcal/mol) |
|-------------|--------|-----------|-------------------|
| CKD2        | 2cch   | MOL000098 | -8.6              |
| CKD2        | 2cch   | MOL00006  | -8.5              |
| CKD2        | 2cch   | MOL000422 | -8.1              |
| PGR         | 2c7a   | MOL000098 | -7.2              |
| PGR         | 2c7a   | MOL00006  | -7.4              |
| PGR         | 2c7a   | MOL000422 | -7.5              |
| JUN         | 1s9k   | MOL000098 | -7.7              |
| JUN         | 1s9k   | MOL00006  | -7.8              |
| JUN         | 1s9k   | MOL000422 | -7.6              |

Discussion

The virus Herpes zoster (HZ) causes infections like chicken pox and shingles, and it is classified under “Snake sore” and “girdling fire cinnabar” in traditional Chinese medicine (TCM). Simiao Yongan Decoction is a famous TCM prescription. Several clinical trials have shown that SYD is effective in patients with HZ infection and PNH\(^5\)\(^6\). Therefore, we applied TCM network pharmacological approaches to elucidate these mechanisms.

The present findings showed that the major bioactive compounds of SYD were quercetin, luteolin, and kaempferol. Quercetin is a bioflavonoid with potent antioxidant and anti-inflammatory activities that is found in various vegetables and fruits [16, 17]. Quercetin can relieve inflammatory-induced pain in animal models [18] and it exerts neuroprotective effects [19]. Luteolin protects the nervous system [20] and exerts anti-inflammatory [21], and antioxidant [22] effects. Kaempferol is a flavonoid with many health benefits, particularly against inflammatory diseases [23]. Kaempferol attenuates inflammatory pathways by modulating NF-κB [24]. The PPI network analysis showed that CDK2, CASP3, JUN, AKT1, and MAPK1 had the highest degree values; CDK2 participates in cell cycle regulation (RefSeq, Aug 2020); CASP3 participates in apoptosis, inflammation, and necrosis-related signaling pathways (RefSeq, Aug 2017); AKT1 plays a vital role in the regulation of cell survival, angiogenesis, tumor formation, and insulin signaling; JUN functions in growth and differentiation [25], and MAPK1 plays essential roles in neuropathic pain and inflammatory reactions [26, 27]. All these suggest that the bioactive compounds of SYD and the targets of these compounds play crucial roles in the treatment of HZ and PNH.

Toll-like receptor, C-type lectin receptor, MAPK, PI3K-Akt signaling pathway, and other KEGG signaling pathways were enriched. Toll-like receptors perceive conserved microbial structures, such as 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 receptors are expressed mainly on myeloid cells and are involved in antifungal immunity. The 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. The PI3K-Akt signaling pathway may suppress cell death by regulating cytoplasmic cell death machinery, as well as the expression of genes that facilitate cell death and survival [30]. Therefore, we postulate that SYD clears HZ through the Toll-like receptor signaling pathway, amplifies immunity through the C-type lectin receptor signaling pathway, and regulates cell apoptosis via the MAPK and PI3K-Akt signaling pathways. The molecular docking results showed good binding energy between SYD bioactive compounds and hub targets, suggesting that our findings demonstrated high reference value.

Conclusion

We found that SYD was effective against HZ via multiple targets and pathways. Our results provide theoretical support for the treatment of HZ and a new direction for such treatment by TCM. However, experimental validation is warranted before SYD can be realized as a viable pharmaceutical treatment for HZ infection.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Please contact author for data requests.

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Competing interests

The authors declare that they have no competing interests.

Authors’ contributions
Guanyan Chen and Zhenhai Wu provided Chinese medicines. Yixian Li is a consultant dermatologist. Hongtao Liu and Qiuqin Tang analyzed the results and prepared the manuscript. All authors read and approved the final version of the manuscript.

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