Prediction the Molecular Mechanism of Shengmai Injection in Acute Treatment of COVID-19 Based on Network Pharmacology

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Abstract

Objective: To predict the mechanism of Shengmai Injection (SMI) in the acute treatment of COVID-19 by network pharmacology and molecular docking. Methods: Search the compounds in the Traditional Chinese Medicine Systems Pharmacology (TCMSP), and screen them by Drug-like properties (DL) and Oral bioavailability (OB); Using PharmMapper database and GeneCards database to collect compounds targets and COVID-19 targets, and using UniProt database to standardize the names of target genes; Using DAVID database for KEGG pathway annotation and GO bioinformatics analysis; Using Cytoscape 3.8.2 software and STRING 10.5 database to construct “Component-Target-Pathway” network and Protein-Protein Interaction network (PPI); Using molecular docking to predict the binding ability of key compounds and key proteins. Results: A total of 34 active components, 38 core targets and 180 signaling pathways were screened out. The results of molecular docking showed that Schisantherin A and Moupinamide have strong binding with EGFR and MAPK1. Conclusion: The key active compounds of SMI in the treatment of COVID-19 may be Schisantherin A and Moupinamide, and the molecular mechanism may be related to key targets such as EGFR and MAPK1, and may be involved in the PI3K-Akt signaling pathway and MAPK signaling pathway.

Keywords

network pharmacology, shengmai injection, COVID-19, molecular docking, mechanism of action, acute treatment

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Introduction

Corona Virus Disease 2019 (COVID-19), which broke out in Wuhan, China, is a kind of super virus pneumonia with fast infection speed, wide infection range and strong mutation ability. COVID-19 with fever, dry cough, fatigue as the main manifestations, a small number of patients with stuffy nose, runny nose, diarrhea and other upper respiratory and digestive tract symptoms. As of Dec. 24, 2021, there have been a total of 276,753,278 confirmed cases and 5,376,631 deaths of COVID-19 worldwide, and there are 970,349 new confirmed cases and 6844 new deaths worldwide in a single day. Therefore, it is urgent to control the crazy spread of COVID-19 in time and protect human beings from it.

In recent years, the clinical application value of traditional Chinese medicine and its’ component prescription has been studied extensively and deeply by many scholars all over the world. Traditional Chinese medicine has been inherited in China for 5000 years because of it’s effectiveness, security and other characteristics, and it has been gradually accepted by the authoritative medicine worldwide. According to the characteristics of the disease, different ways of administration and flexible dosage according to the symptoms have significant characteristics and advantages for the treatment of COVID-19. Shengmai Injection (SMI) is a proprietary Chinese medicine composed of Talinum paniculatum (Jacq.) Gaertn. (Hongshen), Ophiopogon japonicus (Linn. f) Ker-Gawl. (Maidong) and Schisandra chinensis (Turcz.) Baill. (Wuweizi). SMI can immediately activate the cardiovascular system, improve the retraction of the heart and accelerate the heart-beat, increase the cardiac output strip, and increase the heart rate. In clinical medicine, it is used for mild to moderate cardiogenic shock,
Figure 1. Flow chart of network pharmacology analysis.
SMI is analyzed and explained. High-throughput molecular biology, through multi-platform, multi-software, multi-way analysis and exploration of drugs and diseases, the treatment of traditional Chinese medicine or auxiliary treatment of diseases. If the target proteins of the disease could be identified and drugs could act on them, the drugs can treat the disease. The obtained 3D structures were imported into SwissTargetPrediction (http://www.swisstargetprediction.ch/), and all the potential target genes of SMI were obtained by $P > 0.8$. After entering the keywords “COVID-19” and “Corona Virus Disease 2019” in GeneCards (https://www.genecards.org/), all the target genes related to the disease were obtained. The intersection targets of disease and drug can be represented by Venn diagram, and these intersection targets can be regarded as potential targets for SMI in the acute treatment of COVID-19.

Materials and Methods

Collection and Screening of Active Components
We searched all the chemical components related to Talinum paniculatum (Jacq.) Gaertn., Ophiopogon japonicus (Linn. f.) Ker-Gawl. and Schisandra chinensis (Turcz.) Baill. on Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://old.tcmsp-e.com/tcmsp.php), and screened all the active components by Oral Bioavailability (OB) ≥ 30% and Drug-Like (DL) ≥ 0.18. For the integrity of the obtained data, we have integrated some components retrieved from other databases to supplement the components obtained from TCMSP, such as TCMID (http://www.megabionet.org/tcmid/), TCM@Taiwan (http://tcn.cmu.edu.tw/zh-tw/). After that, these active components were retrieved and verified by PubChem (https://pubchem.ncbi.nlm.nih.gov/), and their 3D structures were obtained.

Screening of Intersection Target Genes
Traditional Chinese medicine, including many components, to treat disease by acting on certain targets and regulating pathways. Through the combination of drug molecules and target proteins, the drugs can achieve the effect of curing diseases. If the target proteins of the disease could be identified and drugs could act on them, then the drugs can treat the disease. The obtained 3D structures were imported into SwissTargetPrediction (http://www.swisstargetprediction.ch/), and all the potential target genes of SMI were obtained by $P > 0.8$. After entering the keywords “COVID-19” and “Corona Virus Disease 2019” in GeneCards (https://www.genecards.org/), all the target genes related to the disease were obtained. The intersection targets of disease and drug can be represented by Venn diagram, and these intersection targets can be regarded as potential targets for SMI in the acute treatment of COVID-19.

GO Function and KEGG Pathway Enrichment Analysis
The Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/) v6.8 comprises a full Knowledgebase update to the sixth version of our original web-accessible programs. Therefore, we used the DAVID database to annotate the Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes pathway (KEGG) of the potential targets. GO function includes three indicators, namely Biological Process (BP), Cellular Component (CC) and Molecular Function (MF). Through GO function enrichment analysis, combined with biological problems and functional annotations of genes, we can judge whether the changes of these intersection target genes have

### Table 1. Abbreviations List

| Abbreviation | Official Name |
|--------------|--------------|
| 3CL-Mpro     | SARS-cov-23CL hydrolase |
| ACE2         | Angiotensin-converting enzyme 2 |
| AKT1         | RAC-alpha serine/threonine-protein kinase |
| AR           | Androgen receptor |
| BP           | Biological Process |
| BRAF         | Serine/threonine-protein kinase B-raf |
| CASP3        | Caspase-3 |
| CASP8        | Caspase-8 |
| CC           | Cellular Component |
| COVID-19     | Corona Virus Disease 2019 |
| C-T-P        | Component-Target-Pathway |
| DAVID        | Database for Annotation, Visualization and Integrated Discovery |
| D-C          | Drug-Component |
| DL           | Drug-Like |
| EGFR         | Epidermal growth factor receptor |
| GO           | Gene Ontology |
| HCV          | hepatitis C virus |
| IL6          | Interleukin-6 |
| JAK2         | Tyrosine-protein kinase JAK2 |
| JAK3         | Tyrosine-protein kinase JAK3 |
| KEGG         | Kyoto Encyclopedia of Genes and Genomes pathway |
| MAPK1        | Mitogen-activated protein kinase 1 |
| MF           | Molecular Function |
| MTOR         | Serine/threonine-protein kinase mTOR |
| NOS2         | Nitric oxide synthase, inducible |
| OB           | Oral Bioavailability |
| PDB          | Protein Data Bank |
| PPI          | Protein-Protein Interaction |
| SMI          | Shengmai Injection |
| STAT3        | Signal transducer and activator of transcription 3 |
| TCMSF        | Traditional Chinese Medicine Systems Pharmacology |
| TNF          | Tumor necrosis factor |
| VEGFA        | Vascular endothelial growth factor A |
| physical overdraft and low blood pressure 3. In China, SMI is also a proprietary Chinese medicine for critically ill COVID-19 patients in Guidelines on the Novel Coronavirus-Infected Pneumonia Diagnosis and Treatment, and some studies have shown that ShengMai is effective in the treatment of convalescent cases of COVID-19 3. As a result, SMI is an effective treatment for patients with severe illness. Although SMI has a definite therapeutic effect in patients with COVID-19 in the early stages of severe disease, the mechanism of action is obscure, so the active components and mechanism of SMI in the acute treatment of COVID-19 need long-term study.

Network pharmacology is based on the theory of systems biology, through multi-platform, multi-software, multi-way analysis and exploration of drugs and diseases, the treatment of traditional Chinese medicine or auxiliary treatment of diseases of multi-component, multi-target, multi-pathway mechanism is analyzed and explained. High-throughput molecular docking technique is used to simulate the interaction between small molecular ligands and protein receptors to predict the active sites of drugs and the binding mode and affinity between ligands and receptors. The purpose of this study is to explore the potential active components and mechanism of SMI in the acute treatment of COVID-19 by means of network pharmacology and molecular docking.

Abbreviation Of...
biological significance. Through KEGG pathway enrichment analysis, we could predict which signaling pathways these intersection target genes are involved in and regulate.

**Protein-Protein Interaction Network**

Analysis of Protein-Protein Interaction (PPI) network helps to study the molecular mechanism of disease from the perspective of the system and discover new drug targets. Then we imported the screened potential targets into STRING (https://www.string-db.org/) to obtain the connections or potential connections between protein and protein interactions, so as to find the potential target genes that interact most closely, and which are most likely to be needed.\textsuperscript{12}

**Network Construction**

In order to visualize all the screened data to analyze them, potential components, potential targets and signaling pathways were imported into cytoscape3.8.2 software to construct a “Component-Target-Pathway” (“C-T-P”) and “Drug-Component” (“D-C”) network diagram.\textsuperscript{13} Then the core components and core targets were screened by analyzing these network diagrams.
Molecular Docking

Through the analysis of PPI and network diagram, the core components and core targets were obtained. Retrieved these core targets in RCSB PDB (http://www1.rcsb.org/) to obtain their protein structures which are closely related to COVID-19. Then we docked these protein structures with the chemical structures obtained in step 2.1 by the Discovery Studio 2019 Client software. It is generally believed that the LibDockScore ≥ 90 indicates that the small molecular ligand has stronger affinity with the receptor and binds more easily.

Results

Collection and Screening of Active Components

By searching Talinum paniculatum (Jacq.) Gaertn., Ophiopogon japonicus (Linn. f.) Ker-Gawl., and Schisandra chinensis (Turcz.) Baill. in TCMSP and other special databases of traditional Chinese medicine, a total of 28 active components in SMI were obtained by setting threshold OB ≥ 30% and DL ≥ 0.18. Through the reports of Ophiopogon japonicus (Linn. f.) Ker-Gawl. and Schisandra chinensis (Turcz.) Baill. in the published literature, we confirmed that although their OB or DL did not reach the threshold, they were still active components. And then 34 active components were finally obtained, including 4 from Talinum paniculatum (Jacq.) Gaertn., 9 from Ophiopogon japonicus (Linn. f.) Ker-Gawl. and 21 from Schisandra chinensis (Turcz.) Baill. Information about these chemical components is listed in Table 2.

Screening of Intersection Target Genes

By searching the active ingredients obtained in 3.1, 698 target genes were obtained from 34 active components and 178 target genes of COVID-19 were obtained from GeneCards. The active component target genes and disease target genes
were analyzed and compared by Veen diagram, as shown in Figure 2. The intersection genes of active component target genes and disease target genes can be regarded as potential targets for SMI in the acute treatment of COVID-19. These targets are shown in Table 3.

**GO Function and KEGG Pathway Enrichment Analysis**

The intersection target genes were imported into the DAVID database, then the GO function and KEGG pathway can be analyzed by these intersection target genes. The results are shown in Figure 3 and Figure 4. Through the GO function enrichment analysis, 346 items were finally obtained. In Figure 3, it is clear that these target proteins are involved in biological functions such as biological regulation, cellular process, metabolic process and more.

Finally, according to statistical data, the smaller the P value, the pathway is related to the disease, and the top 20 signaling pathways were obtained. In Figure 4, these target proteins can be analyzed to participate in the regulation of cancer, immune correlation, and infectious diseases pathways. Among them, AGE-RAGE signaling pathway in diabetic complications involves 10 genes, like MAPK1, IL6, VEGFA, AKT1. PI3K-Akt signaling pathway involves 15 genes, like MAPK1, EGFR, IL6, VEGFA, AKT1. Jak-STAT signaling pathway involves 11 genes, like AKT1, EGFR, IL6, STAT3. MAPK signaling pathway involves 11 genes, like MAPK1, EGFR, VEGFA, AKT1. According to the results, we speculated that SMI may act on key genes such as EGFR, MAPK1, IL6, VEGFA, AKT1, participate in the regulation of some cancer and immune-related pathways, and thus play a role in the acute treatment of COVID-19.

**Protein-Protein Interaction Network**

Imported the potential targets into the STRING database, generated an interactive network diagram, and analyzed it by Cytoscape3.8.2 software, as shown in Figure 5A. Obviously, these proteins have high scores in PPI network, such as EGFR, IL6, MAPK1, VEGFA and AKT1. We also analyzed the top 15 target genes with high scores in the PPI network diagram (Figure 5B), and further found that target genes such as EGFR and MAPK1 occupied the core position in the “C-T-P” topology and PPI network. Therefore, we predicted that the mechanism of SMI in the acute treatment of COVID-19 may be related to the regulation of key targets and related co-expression genes.

**Network Construction**

34 active components, 38 potential targets and the top 20 signaling pathways were imported into cytoscape3.8.2 software to construct “C-T-P” and “D-C” network diagram, as shown in Figure 6A and Figure 6B. In Figure 6A, there are 92 nodes, including 34 green active component nodes, 38 blue potential target nodes, 20 red signal pathway nodes, with 396 edges. In Figure 6B, there are 37 nodes, including 3 yellow drug nodes, 34 purple active ingredient nodes, with 34 edges. The network diagram showed the interaction between edges. The higher the correlation is, the more concentrated the convergence of these edges will be, meanwhile the greater the...
Degree score of the node will be. At the same time, different components interact with the same gene, which is very similar to the mechanism of multi-gene interaction of multi-component of traditional Chinese medicine. According to the critical degree between the components and the genes, the top 15 key genes were screened, which were EGFR, MAPK1, AR, MTOR, AKT1, JAK2, STAT3, BRAF, NOS2, IL6, JAK3, VEGFA, TNF, CASP8, CASP3. The top 15 components and genes are shown in Table 4. As can be seen from the network diagram, SMI acts on multi-gene through multi-components, coordinates and regulates through multi-pathway, and has the characteristics of restorative treating diseases.

**Molecular Docking**

It is generally believed that the lower binding between the small molecule ligands and the receptors is, the higher the LibDock score, the larger the interaction, the stronger the potential activity of the component. According to PPI and network analysis results, we chose three components with higher scores Schisantherin A, Gomisin-a, moupinamide, and two currently recognized targets 3CL and ACE2 related to COVID-19 for molecular docking. Then we let these three components dock with core gene EGFR, MAPK1. The docking results were analyzed as a screening criterion in LibDock score, and showed that the LibDock score of the selected target genes and components were greater than the threshold 90, showing good binding activity. This means that these three components play an important role in the process of SMI in the acute treatment of COVID-19. The docking results are shown in Table 5 and Figure 7A, 7B, 7C, 7D.

**Discussion**

In more than 5000 years of application, traditional Chinese medicine has fully proved its effectiveness and security. Since 2003, traditional Chinese medicine has played an important role in the prevention and control of major epidemic such as...
Table 4. The Top 15 Active Components and Core Targets.

| Component       | Degree | Gene | ENSG ID                  | Degree |
|-----------------|--------|------|--------------------------|--------|
| neokadsuranin   | 11     | EGFR | ENSG00000146648          | 27     |
| Kadsulignan C   | 11     | MAPK1| ENSG00000100030          | 27     |
| Schisantherin A | 10     | AR   | ENSG00000169083          | 24     |
| Schisandrin C   | 10     | MTOR | ENSG00000198793          | 24     |
| Schizandrer B   | 10     | AKT1 | ENSG00000142208          | 22     |
| Angeloylgomisin O | 10   | JAK2 | ENSG00000096968          | 18     |
| Interiotherin B | 10     | STAT3| ENSG00000168610          | 16     |
| Schisandrol G   | 9      | BRAF | ENSG00000157764          | 15     |
| Gomisin-A       | 9      | NOS2 | ENSG00000071717          | 15     |
| Deoxyharringtonine | 9    | IL6  | ENSG00000136244          | 14     |
| guanosine       | 7      | JAK3 | ENSG00000105639          | 14     |
| p-Coumaroyltyramine | 6    | VEGFA| ENSG00000112715          | 12     |
| Adenosine       | 6      | TNF  | ENSG00000232810          | 12     |
| changnanic acid | 6      | CASP8| ENSG00000064012          | 11     |
| Moupinamide     | 5      | CASP3| ENSG00000164305          | 11     |

Table 5. Results of Molecular Docking.

| Component       | Source           | LibDock score | 3CL(6lu7) | ACE2(1r42) | EGFR(6di9) | MAPK1(4zzn) |
|-----------------|-----------------|---------------|-----------|------------|------------|-------------|
| Schisantherin A | Schisandra      |               | 116.367   | 99.028     | 112.891    | 103.013     |
| Gomisin-A       | Schisandra      |               | 114.871   | 94.7242    | 109.247    | 100.198     |
| Moupinamide     | Ophiopogon japonicus |           | 126.928   | 117.485    | 113.348    | 109.374     |

Figure 7. Results of moupinamide molecular docking. A: 3CL-Moupinamide. B: ACE2-Moupinamide. C: EGFR-Moupinamide. D: MAPK1-Moupinamide.
SARS, H1N1. The clinical treatment of COVID-19 proves that traditional Chinese medicine still plays an irreplaceable role\textsuperscript{16–18}. Therefore, screening the effective compound of anti-COVID-19 based on clinical practice is of great significance for the prevention and treatment of the epidemic situation.

SMI is a traditional Chinese patent medicine composed of Talinum paniculatum (Jacq.) Gaertn., Ophiopogon japonicus (Linn. f.) Ker-Gawl. and Schisandra chinensis (Turcz.) Baill. It is an effective drug for the treatment of acute diseases such as septic shock and heart failure\textsuperscript{19–21}. Based on the theory of systems biology, this study constructed “C-T-P” and “D-C” topology networks through network pharmacology to explore the active components, potential targets and signaling pathways of COVID-19 in the acute treatment of SMI, in order to predict the mechanism of action.

Through data screening and analysis, we obtained 34 active components, 38 potential targets and 20 signaling pathways that may be the information for SMI in the acute treatment of COVID-19. Through the analysis of “C-T-P” and “D-C” topology network, we found that Schisantherin A, Gomisin-A, Moupinamide occupy the core position in the network diagram. There are findings indicated that Schisantherin A exerted potent anti-inflammatory properties in LPS-induced mouse ARDS, possibly through blocking the activation of NF-κB and mitogen activated protein kinases (MAPKs) signaling pathways\textsuperscript{22}. Gomisin-A may exert neuroprotective effects by attenuating the microglia-mediated neuroinflammatory response via inhibiting the TLR4-mediated NF-κB and MAPKs signaling pathways\textsuperscript{23}. Schisantherin A may be involved in the PI3K-Akt signaling pathway and MAPK signaling pathway. This study provides a valuable scientific basis for further acute treatment of COVID-19 with SMI and lays a theoretical foundation for follow-up clinical trials.

Through the analysis of PPI and “C-T-P”, we found that the potential target Epidermal growth factor receptor (EGFR), Mitogen-activated protein kinase 1 (MAPK1) not only has a high Degree score, but also has a correlation with COVID-19. EGFR Acts as a receptor for hepatitis C virus (HCV) in hepatocytes and facilitates cell entry. Mediates HCV entry by promoting the formation of the CD81-CLDN1 receptor complexes that are essential for HCV entry and by enhancing membrane fusion of cells expressing HCV envelope glycoproteins\textsuperscript{25}. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements\textsuperscript{26}.

According to the results of enrichment analysis of GO function and KEGG signaling pathway, most of the 38 potential targets are involved in biological regulation, cellular process, metabolic process and other biological processes. The above core targets are closely related to AGE-RAGE signaling pathway in diabetic complications, PI3K-Akt signaling pathway and MAPK signaling pathway, and these pathways are related to oxidative stress, cell growth, transcription, translation, cell proliferation, cell movement and glycogen metabolism\textsuperscript{27,28}.

To sum up, based on the results of network pharmacology and molecular docking, we speculated that Schisantherin A, Gomisin-A and Moupinamide in SMI may act on 3CL, ACE2, EGFR, MAPK1 and other targets through AGE-RAGE signaling pathway in diabetic complications, PI3K-Akt signaling pathway, MAPK signaling pathway and other pathways, so as to exert the effects of anti-inflammation, anti-shock, immune regulation and more. Therefore, SMI through the multi-component, multi-gene, multi-pathway of the joint action of acute treatment of COVID-19.

**Conclusion**

In summary, in this study, through network pharmacology, molecular docking and previous literature research, the key active compounds of SMI in the treatment of COVID-19 may be Schisantherin A and Moupinamide, and the molecular mechanism may be related to key targets such as EGFR and MAPK1, and may be involved in the PI3K-Akt signaling pathway and MAPK signaling pathway. This study provides a valuable scientific basis for further acute treatment of COVID-19 with SMI and lays a theoretical foundation for follow-up clinical trials.

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**Data Availability**

For reasonable requirements, the data related to this study can be requested from the corresponding author.

**Ethical Approval**

Ethical Approval is not applicable for this article.

**Statement of Human and Animal Rights**

This article does not contain any studies with human or animal subjects.

**Statement of Informed Consent**

There are no human subjects in this article and informed consent is not applicable.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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