*American Journal of Health Research*
2025, Vol. 13, No. 3, pp. 186-194
https://doi.org/10.11648/j.ajhr.20251303.18

Research Article

# Active Ingredients Research of SYF Based on Network Pharmacology, Molecular Docking and SPR

**Changqiong Xu[1, 2, †], Xuehui Li[3, †], Liqiong Xia[4], Shaojie Li[5], Ran Li[2, 6 *]**

[1]Medical college, Shaoguan University, Shaoguan, China

[2]Research Institute, Hunan Yueyang Maternal & Child Health-Care Hospital, Yueyang, China

[3]Anorectal Department, Caidian District People's Hospital, Wuhan, China

[4]Pharmacy Department, Loudi Central Hospital, Loudi, China

[5]Department of Respiratory Medicine, Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine, Zhuhai, China

[6]Clinical Medical College, Yichun University, Yichun China

## Abstract

Objective: To study the active ingredients of SYF in the prevention and treatment of COVID-19 using network pharmacology and molecular docking technology. Methods: The active components and targets of SYF for prevention and treatment of COVID-19 were screened by network pharmacology. The SARS-CoV-2 Spike protein was interacted with the screened core molecules by MOE software. Surface plasmon resonance (SPR) was used to determine the intermolecular forces of SYF and selected active ingredients. Results: Through network pharmacological analysis, 185 intersection targets of TCM and disease were obtained. Twenty core active ingredients were obtained, including Indigo, Forsythiaside, Phillyrin, Rutin, etc. Further molecular matchmaking of the core active ingredients showed that Forsythoside B, Forsythoside A, Phillyrin, rutin and other active ingredients with strong affinity compared to the positive compound Molnupiravir were found. SPR assay showed that SYF had A strong affinity with 2019-nCoV Spike, and the active ingredient Forsythoside A had a higher affinity with 2019-nCoV Spike than Molnupiravir, a positive compound already on the market. Conclusions: SYF compound has A strong affinity with 2019-nCoV Spike, and its core components, Forsythoside A and Rutin, have shown strong affinity with 2019-nCoV Spike in molecular docking and SPR experiments, and are guiding ingredients for the study of SYF for the prevention and treatment of COVID-19.

## Keywords

SYF, COVID-19, SPR, Network Pharmacolog, Molecular Docking

*Corresponding author: wwwlr@163.com (Ran Li)

† Changqiong Xu and Xuehui Li are co-first authors.

**Received:** 23 April 2025; **Accepted:** 16 June 2025; **Published:** 22 June 2025

# 1. Introduction

The novel coronavirus-induced epidemic has widely affected global public health security. Since the outbreak of COVID-19, traditional Chinese medicine has played an important role in prevention and treatment. The "Diagnosis and Treatment Plan for Pneumonia Caused by Novel Coronavirus" has added content related to traditional Chinese medicine (TCM) starting from the 3rd edition. It requires actively exerting the role of traditional Chinese medicine in prevention and treatment measures and integrating the full participation of traditional Chinese medicine in the prevention and treatment of COVID-19.

In the COVID-19 prevention and control efforts in Hunan Province, the participation rate of traditional Chinese medicine (TCM) was high and the cure and discharge rate was also high. The competent authorities organized several renowned TCM masters and experts to conduct repeated analyses and deliberations, and successively formulated the No. 1 TCM prescription for resuming work and epidemic prevention, the No. 1 TCM prescription for prevention, and the No. 2 TCM prescription for prevention, etc. They coordinated with the Provincial Health Commission, the Provincial Drug Administration, and the Provincial Medical Insurance Bureau to open an emergency green channel for the emergency filing of TCM preparations in medical institutions. They conducted emergency approval and filing for 13 reference prescriptions and 57 varieties, and included 24 in-hospital TCM preparations of medical institutions in the medical insurance directory. The prevention and control plans have shown significant effects in terms of preventing infection, controlling the development of the disease, alleviating symptoms, and improving the quality of life [1–4]. In 2022, in response to the severe and complex epidemic prevention and control situation, the Hunan Provincial Administration of Traditional Chinese Medicine organized an expert team of renowned masters of traditional Chinese medicine to research and formulate an anti-epidemic prevention formula (SYF, composed of 10 grams of honeysuckle, 10 grams of fructus forsythiae, 6 grams of mint, 10 grams of isatis root, 10 grams of radices sileris, 6 grams of agastache rugosus, 6 grams of acorus gramineus, 6 grams of licorice, etc.), which was applied for the prevention of novel coronavirus pneumonia. Among them, honeysuckle and fructus forsythiae can not only dispel wind-heat and clear heat-toxicity, but also eliminate foul odors and purify turbid substances; mint can dispel wind-heat in the upper part of the body and clear the orifices and the head; isatis root can clear heat-toxicity, cool blood and relieve pharyngitis; radices sileris can dispel wind, relieve exterior symptoms and relieve dampness; agastache rugosus can promote perspiration and transform dampness; acorus gramineus is good at transforming dampness and turbidity; licorice can harmonize various herbs. The whole prescription jointly achieves the functions of dispelling wind-heat and detoxifying, transforming turbidity and clearing heat-toxicity, and clearing and promoting lung qi.

Although traditional Chinese medicine has played an important role in the fight against the epidemic, there are still deficiencies in the mechanism of trust between Chinese and Western medicine and in the research on the combination of Chinese and Western medicine for the prevention and treatment of diseases [5]. Since SYF was independently developed, no one has conducted relevant research work on it. This study elucidates the active ingredients and targets of SYF's preventive and therapeutic effects on COVID-19 through network pharmacology, molecular docking and Spike protein affinity determination, and preliminarily explores its mechanism of action.

# 2. Materials and Methods

## 2.1. Acquisition of Components and Prediction of SYF

The chemical components of SYF were obtained by jointly using the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database and the HERB (http://herb.ac.cn/) database. The potential active components in the compound formula were screened using the ADMET lab3.0 (https://admetlab3.scbdd.com/) drug absorption, distribution, metabolism, excretion, and toxicity prediction tool. The screening conditions were that they should comply with the five rules of the Lipinski's class of drugs and have a low plasma protein binding rate (PPB less than 90%).

## 2.2. Acquisition of Components of SYF and Relevant Targets of COVID-19 Disease

The Swiss Target Prediction platform (http://www.swisstargetprediction.ch) was used to predict the relevant targets of potential active ingredients. The targets of COVID-19 disease were obtained from the Genecards database (https://www.genecards.org/) and OMIM database (https://omim.org/) for further network analysis. The intersection of SYF and the relevant targets of COVID-19 disease was analyzed using Origin 2023 Academic Edition software to obtain the potential targets of SYF for preventing and treating COVID-19.

## 2.3. Construction of PPI Protein Interaction Network and "Chinese Medicine - Component - Target - Disease" Network

The STRING database was used to conduct protein interaction network analysis on the intersecting targets. The Organisms setting was set as Homo sapiens, and the minimum required interaction score was set at 0.700. The PPI protein

interaction network file was obtained. The PPI protein interaction network diagram and the "Chinese Medicine - Component - Target - Disease" network diagram were drawn using Cytoscape 3.9.0 software. Core components were obtained by sorting according to the Degree values in the "Chinese Medicine - Component - Target - Disease" network.

### 2.4. Molecular Docking

The smiles structures were obtained from the database based on the CAS number of the compounds, and the structures were prepared through the MOE software. The compound structures and 3D conformations were selected through MOE software and hydrogen atoms were added. The gradient RMS of the structure energy optimization was set at 0.1 kcal/mol/A. Molecular docking was performed with the SARS-CoV-2 Spike protein. The Triangle Match algorithm was used to generate the initial docking mode of the complex, and the London δG scoring function was used to calculate the affinity of each initial docking mode. The GBVI/WAS scoring function was used for evaluation, and 5 conformations were output for manual selection.

### 2.5. Drug Preparation

SYF was soaked for 30 minutes, then extracted three times with pure water, the combined extracts were concentrated under reduced pressure and freeze-dried. PBS was used to prepare a series of drug solutions at concentrations of 10, 5, 2, 0.8, and 0.2 mg/mL for future use.

For the configuration of TCM Monomers, the TCM Monomers were dissolved in DMSO to make a 100 mM stock solution. Then, the stock solution was diluted with PBS to prepare series solutions at concentrations of 60 μM, 24 μM, 9.6 μM, 3.84 μM, and 1.54 μM for future use.

### 2.6. Molecular Interactions (SPR) Test

Install the COOH chip in accordance with the standard operating procedure of the SPR (KA0001 P4PRO, Affinite Instruments, Canada) instrument. Click Prime, reach the signal baseline, flush the sample ring with buffer solution, and empty it with air. Stable baseline: within 10 minutes, the response is <35 Ru. Adjust the buffer flow rate to 25 μL/min; activate the chip by loading 250 μL of EDC/NHS (800 mM/200 mM, 1:1) solution in two channels; run for 4 minutes with 200 μL of ligand (S protein, 50 μg/mL) diluted in Immobilization Buffer (200 mM ethanolamine hydrochloride 41 mL, 200 mM sodium acetate 9 mL, 450 mL H2O, pH=4.0) to run the chip; after the signal is stable, load 200 μL of Blocking buffer (ethanolamine hydrochloride, 1 M, pH=8.5) solution and seal the chip. Rinse the sample ring with PBS and empty it with air. Stable baseline for 5 minutes, run the sample.

### 2.7. Data Processing of Molecular Interactions (SPR)

Using the TraceDrawer 1.8.1 (Affinite Instruments, Canada) analysis software, the data collected from the corresponding channels were imported. For each concentration, the blank chip curve was selected as the reference curve and non-specific results were deducted. Further, the curve obtained from the injection of PBS was used as the reference curve and the baseline was deducted. Affinity and kinetics evaluations were conducted.

## 3. Results

### 3.1. Acquisition of Traditional Chinese Medicine Components and Prediction of Active Components

A total of 357 chemical components of isatis root, 362 chemical components of mint, 101 chemical components of radices sileris, 445 chemical components of licorice, 171 chemical components of agastache rugosus, 227 chemical components of fructus forsythiae, 260 chemical components of acorus gramineus, and 379 chemical components of honeysuckle were obtained from PubChem and HERB databases. Through the ADMET lab3.0 prediction, 572 potential active ingredients that meet the five rules of Lipinski's class of drugs and have a low plasma protein binding rate (PPB less than 90%) were obtained.

### 3.2. Analysis of Target Points Related to TCM Components, Disease-related Target Points and Their Correlation

1294 potential active component-related targets in SYF (with Probability > 0) were obtained using the Swiss Target Prediction database. 1578 COVID-19-related targets were obtained using the Genecards database and OMIM database. After intersection, a total of 185 common targets of traditional Chinese medicine and diseases were obtained (Figure 1A). The STRING protein-protein interaction analysis platform was used to construct a PPI protein-protein interaction network for 185 common targets (Figure 1B). The "Chinese medicine - component - target - disease" network was constructed using Cytoscape software, where red represents disease names, blue represents Chinese medicine names, green represents disease gene targets, orange represents effective components of Chinese medicines, and yellow represents core components of Chinese medicines (Figure 1C).

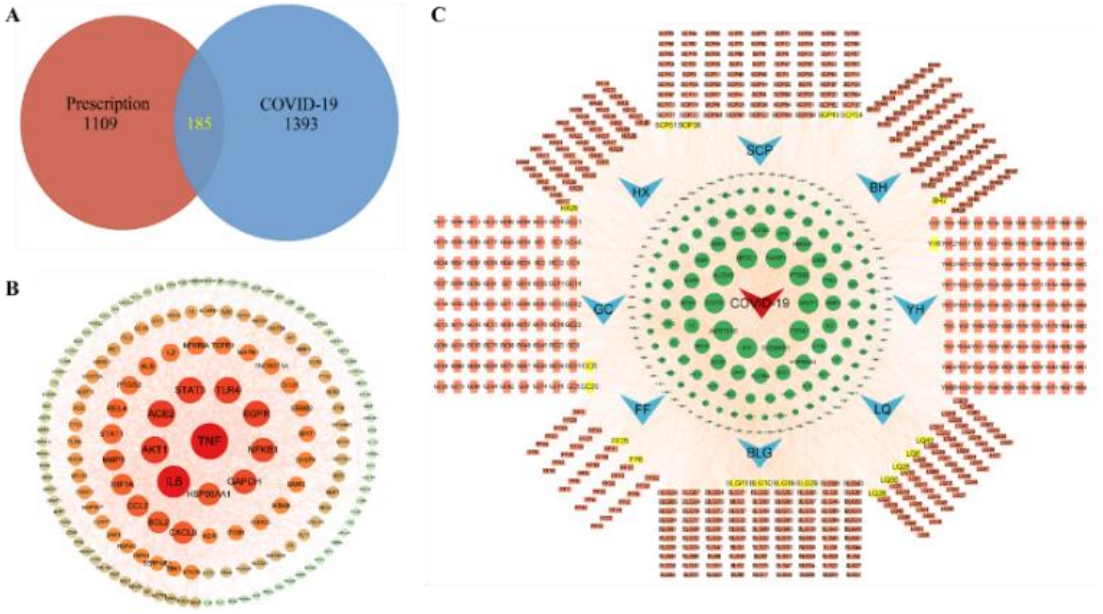


***Figure 1.*** *A. Intersection target Venn diagram of A.SYF and COVID-19; B. PPI protein interaction network; C. "Traditional Chinese Medicine - Components - Targets - Diseases" network.*

Based on the Degree values, 20 core active ingredients were selected. Relevant information (Table 1) and molecular structures (Figure 2) were provided.

***Table 1.*** *Information on Core Components.*

| Compounds name | Degree | Closeness centrality | Betweenness centrality | PubChem CID |
|---|---|---|---|---|
| Indigo | 41 | 0.389399 | 0.007755 | 10215 |
| Forsythiaside | 41 | 0.40552 | 0.007953 | 5281773 |
| Phillyrin | 40 | 0.400419 | 0.006361 | 101712 |
| Rutin | 40 | 0.404233 | 0.00633 | 5280805 |
| Calceolarioside C | 40 | 0.404661 | 0.007629 | 45360240 |
| Indirubin | 39 | 0.370874 | 0.005857 | 10177 |
| sec-o-Glucosylhamaudol | 39 | 0.390593 | 0.007166 | 10478277 |
| Isoschaftoside | 39 | 0.401682 | 0.006937 | 3084995 |
| l-Menthol | 38 | 0.400419 | 0.008912 | 16666 |
| Enoxolone | 38 | 0.4 | 0.009029 | 10114 |
| Nodakenetin | 37 | 0.390993 | 0.006966 | 26305 |
| Adoxosidic acid | 37 | 0.399164 | 0.005694 | 13892717 |
| Esculetin | 36 | 0.357343 | 0.003994 | 5281416 |
| Dihydrodehydrodiconiferyl alcohol | 36 | 0.391393 | 0.007177 | 384679 |
| Isocalamendiol | 36 | 0.400839 | 0.00694 | 12302240 |
| Pinoresinol | 35 | 0.380478 | 0.005739 | 73399 |
| Epipinoresinol | 35 | 0.397503 | 0.00897 | 637584 |
| Glycyrrhizinate Dipotassium | 34 | 0.371957 | 0.005687 | 656852 |

| Compounds name | Degree | Closeness centrality | Betweenness centrality | PubChem CID |
|---|---|---|---|---|
| Cedrol | 31 | 0.389399 | 0.004948 | 65575 |
| alpha-Hederin | 31 | 0.381238 | 0.008714 | 73296 |

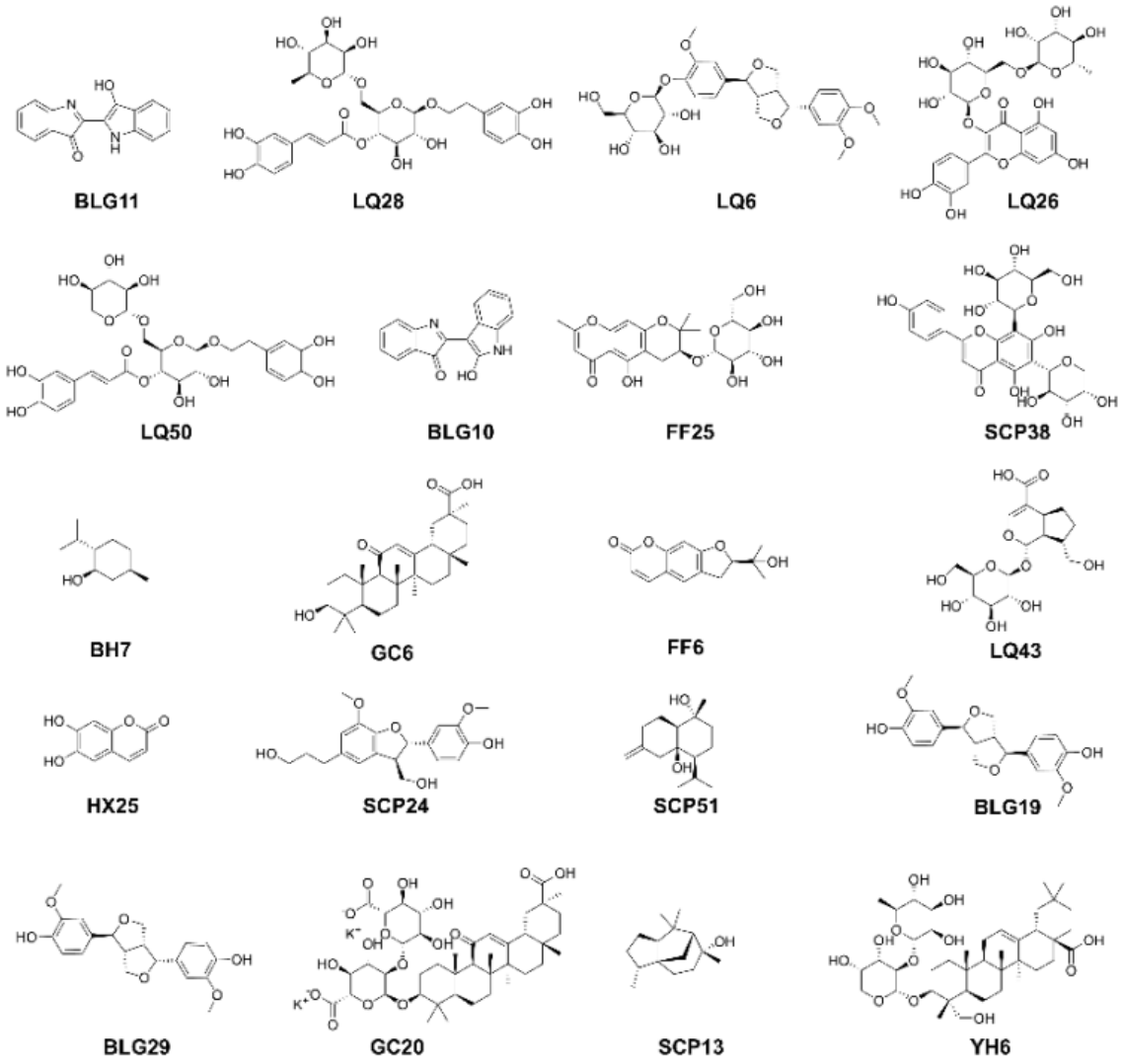


***Figure 2.*** *The molecular structure of the core active ingredient.*

## 3.3. Molecular Docking Results

The docking scoring results of SARS-CoV-2 Spike protein molecule with the selected part of the active compounds from the above screening are shown in Table 2. Here, Pose represents the compound docking conformation number, E_Conf is the potential energy of the compound conformation in the docking mode, E_Place is the conformational energy of molecular docking, E_Score1 is the London δG scoring value, E_Score2 is the GBVI/WAS scoring value, E_refine is the total sum of van der Waals forces, electrostatic interactions, and solvent effects generated during the docking process of the complex, and the interaction energy score value between the protein and the compound in each complex is represented by S value. The smaller the value, the stronger the affinity. After visual selection, the scoring values of Forsythoside B are -7.37 kcal/mol, Forsythoside A are -6.75 kcal/mol, Phillyrin are -6.44 kcal/mol, Rutin are -5.34 kcal/mol, all of which are higher than the scoring value of the positive compound Molnupiravir -5.34 kcal/mol (Figure 3).

*Table 2. The molecular docking results of SARS-CoV-2 Spike protein molecule with some active compounds.*

| name | CAS | S | rmsd_refine | E_conf | E_place | E_score1 | E_refine | E_score2 |
|---|---|---|---|---|---|---|---|---|
| Forsythoside B | 81525-13-5 | -7.37 | 4.36 | 155.96 | -55.36 | -8.71 | -45.96 | -7.37 |
| Forsythoside A | 79916-77-1 | -6.75 | 5.21 | 98.51 | -63.09 | -9.02 | -42.78 | -6.75 |
| Phillyrin | 487-41-2 | -6.44 | 1.60 | 119.00 | -58.08 | -13.71 | -37.48 | -6.44 |
| Rutin | 153-18-4 | -6.08 | 1.86 | 131.49 | -52.59 | -9.37 | -36.20 | -6.08 |
| Molnupiravir* | 2349386-89-4 | -5.34 | 1.24 | -54.56 | -43.98 | -7.01 | -26.29 | -5.34 |
| Glycyrrhetinic acid | 471-53-4 | -5.20 | 3.62 | 41.83 | -31.70 | -6.72 | -27.28 | -5.20 |
| Indigo | 482-89-3 | -4.37 | 1.65 | 109.78 | -37.35 | -7.54 | -16.98 | -4.37 |

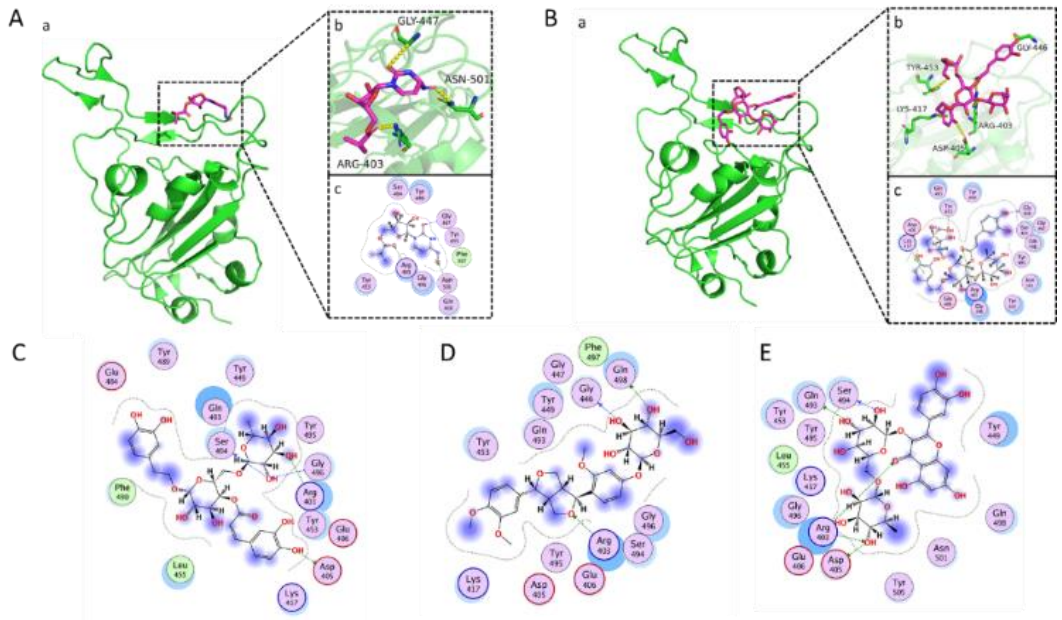


*Figure 3. Positive compound Molnupiravir and the molecular docking binding mode of the main active ingredients screened by network pharmacology. A. Molnupiravir; B. Forsythoside B; C. Forsythoside A; D. Phillyrin; E. Rutin.*

## 3.4. SPR Detection Results

The SPR signal is usually expressed in Resonance Units (RU), which reflects the change in the molecular mass of the molecules bound to the chip surface. An increase in RU usually corresponds to an increase in the binding of the analyte to the ligand. The strong affinity of SYF for 2019-nCoV Spike was verified by SPR technology (Figure 4A). Affinity determinations were conducted for some monomers, and the smaller dissociation constant (KD) value indicates a stronger molecular binding. The KD values for the binding of Forsythoside A, Rutin, and 2019-nCoV Spike were 13.4 μM and 102.0 μM, respectively (Figure 4B-C), and Forsythoside A had a higher affinity than the marketed positive compound Molnupiravir (KD value of 18.1 μM, Figure 4D).

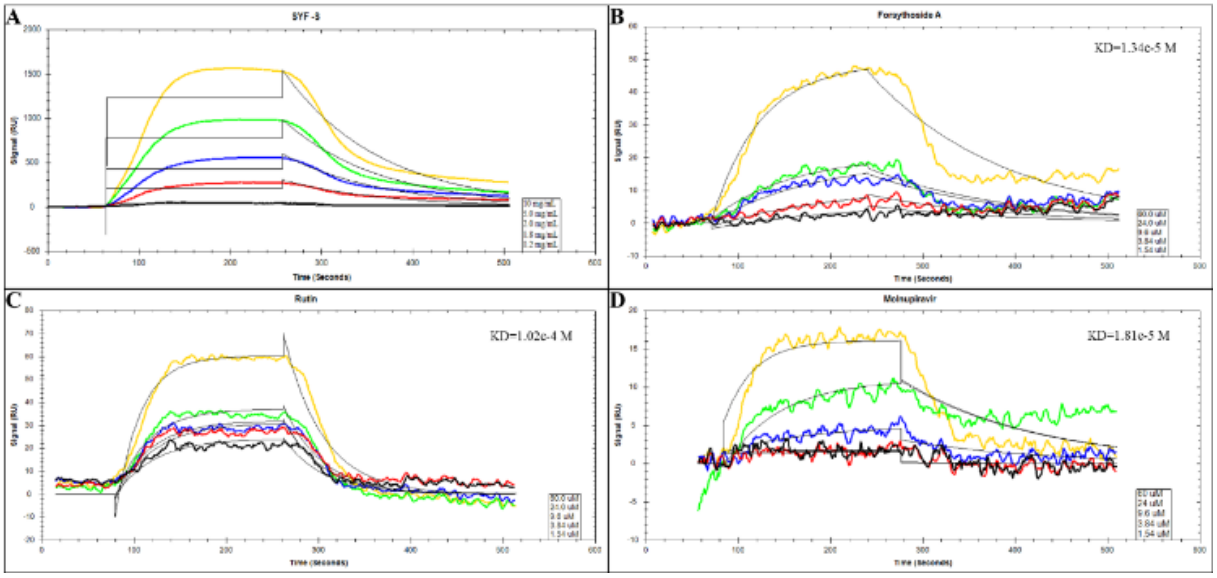


***Figure 4.*** *Binding affinities of SPR for SYF and some active monomers and 2019-nCoV Spike protein. A. SYF extract; B. Forsythoside A; C. Rutin; D. Molnupiravir.*

## 4. Discussion

Traditional Chinese Medicine is a treasure of the Chinese nation and an important experience accumulated during the process of its people's reproduction and development. Since the Shang Dynasty, there have been written records about epidemics. Over the past 3,600 years, there have been hundreds of major and minor epidemics. In historical records and medical literature of all dynasties, TCM has made outstanding contributions to combating epidemics [6]. The pneumonia caused by COVID-19 falls under the category of "epidemic diseases", and its essence is external pathogenic toxins. Traditional Chinese Medicine has played an important role throughout the outbreak of COVID-19. SYF was developed by the Hunan Provincial Administration of Traditional Chinese Medicine in collaboration with an expert team of renowned TCM masters. It has the efficacy of dispelling pathogenic toxins with a cool and soothing nature, eliminating turbidity and detoxifying, and clearing and promoting lung qi. The research on the active ingredients, target points and mechanism of action of SYF for prevention and treatment has significant historical significance for the fight against the epidemic in Hunan Province. Network pharmacology and molecular docking have certain guiding significance for the prediction of target points and mechanism of action of TCM compound prescriptions.

Based on the PubChem and HERB databases, through the ADMET lab3.0 prediction, it was discovered that there are 572 potential active ingredients in SYF that comply with the five rules of Lipinski's class drugs and have a low plasma protein binding rate. There are 1294 active ingredient-related targets, and the intersection with the targets related to COVID-19 is 185. SARS-CoV-2 achieves the invasion and infection of host cells by interacting with the ACE2 expressed by the host cells through its RBD region of the S protein [7, 8]. After SARS-CoV-2 invades the human body, it will trigger an excessive immune hypersensitivity reaction mediated by inflammatory mediators, eventually leading to an "inflammatory storm". However, after the body is infected by microorganisms, various cytokines such as interleukin IL-1, IL-6, IL-8, tumor necrosis factor TNF-α, interferon-α, interferon-β, interferon-γ, and monocyte chemoattractant protein MCP-1 will be rapidly and abundantly produced in the body fluids, which is also an important cause of acute respiratory distress syndrome and multiple organ dysfunction syndrome [9]. The predicted targets in network pharmacology include 20 core targets such as TNF, IL6, AKT1, ACE2, TLR4, NFKB1, etc. and are closely related to inflammation and immune regulation [10, 11].

The SARS-CoV-2 Spike protein is sensitive to the ACE2 receptor [8, 12, 13]. The receptor-binding domain (RBD) of the Spike protein of SARS-CoV and the amino acids that bind to the human ACE2 receptor are 14 in total, namely T402, R426, Y436, Y440, Y442, L472, N473, Y475, N479, Y484, T486, T487, G488, and Y491. Among them, 8 amino acids are completely conserved in the SARS-CoV-2 RBD, and 6 amino acids have mutated: R426SARS-CoV-2, N439SARS-CoV-2, Y442SARS-CoV-2, L472SARS-CoV-2, N479SARS-CoV-2, Y484SARS-CoV-2, and T487SARS-CoV-2 [14].

In our research, we conducted molecular docking between the Spike protein molecule of SARS-CoV-2 and some core active ingredients. Among them, Molnupiravir was set as a positive compound in the molecular docking stage. It is the first oral nucleoside analog anti-COVID-19 drug developed by Merck Sharp & Dohme Ltd. [15, 16].

The main sources of Forsythoside B, Forsythoside A, Phillyrin, rutin, Glycyrrhetinic acid and Indigo are Chinese

medicinal herbs such as fructus forsythiae, licorice and isatis root. In the SPR experiment, the SYF compound signal RU reflects that there are many substances that can bind to the 2019-nCoV Spike on the chip surface through SYF. It has the characteristics of multi-target components. Among them, in the molecular docking and SPR detection, Molnupiravir, Forsythoside, and Rutin all indicate strong affinity. The KD value of Forsythoside A binding to 2019-nCoV Spike is 13.4 μM, which is higher than that of the positive compounds on the market. In the future, we will further demonstrate the competitive blocking effect of SYF on the binding of ACE2 and 2019-nCoV Spike, analyze the components of SYF entering the bloodstream, and verify the intermolecular forces to provide more research support data for the application of traditional Chinese medicine in epidemic prevention and control.

## 5. Conclusions

Based on the network pharmacology techniques such as PubChem, HERB database, and ADMET lab3.0 prediction, this study identified 572 potential active components in SYF. The intersection with COVID-19-related targets was selected, and more than 300 compounds were used for molecular docking with the SARS-CoV-2 Spike protein. The results of molecular docking scoring showed that Forsythoside B, Forsythoside A, Phillyrin, rutin, Glycyrrhetinic acid, Indigo, etc. had much stronger binding forces with SARS-CoV-2 Spike than the individual monomers measured, suggesting that SYF contains multiple active components that can bind to 2019-nCoV Spike, and the active components have synergistic and enhancing effects. Besides small molecules, polysaccharides and supramolecules may play important roles. This study has promising prospects for further research.

## Abbreviations

| | |
|---|---|
| TCM | Traditional Chinese Medicine |
| SYF | Anti-epidemic Prevention Formula |
| SPR | Surface Plasmon Resonance |
| COVID-19 | Novel Coronavirus Pneumonia |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| ACE2 | Angiotensin-converting Enzyme 2 |

## Author Contributions

**Changqiong Xu:** Conceptualization, Writing original draft, Funding acquisition, Writing review & editing.

**Xuehui Li:** Data curation, Formal Analysis, Software, Writing review & editing.

**Liqiong Xia:** Data curation, Formal Analysis, Investigation, Funding acquisition, Writing review & editing.

**Shaojie Li:** Investigation, Supervision, Funding acquisition, Resources.

**Ran Li:** Conceptualization, Methodology, Data curation, Formal Analysis, Supervision, Funding acquisition, Resources, Writing review & editing.

## Funding

This work is supported by Hunan Province Key Field Research and Development Program Special Project on Combating COVID-19 (2022SK2126) Key Project of Hunan Provincial Administration of Traditional Chinese Medicine (A2023054) Doctoral Research Start-up Fund of Shaoguan University (9900064704/032) Zhuhai Science and Technology Plan Project in the Field of Social Development (2320004000279)Natural Science Foundation of Hunan province (2022JJ40460, 2022JJ80098).

## Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest.

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