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Exploring the Mechanism of "Fangyifang" in the Prevention of COVID-19 based on Network Pharmacology and Molecular Docking

Wu Tao[1,2]; Qu Mengrou[1,2]; Chen Xianmei[1,2]; Wang Jieqiong[2,3]*; Qiao Mingqi[2]*

[1]College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China.

[2]College of Traditional Chinese Medicine, Research and Innovation Team of Emotional Diseases and Syndrome Research, Shandong University of Traditional Chinese Medicine, Jinan, China.

[3]Department of Science and Technology, Shandong University of Traditional Chinese Medicine, Jinan, China.

Abstract

Objective: To investigate the mechanism of "FangyiFang" in preventing novel coronavirus pneumonia (COVID-19) using network pharmacology and molecular docking technology.

Methods: In accordance with the pharmacopoeia of Traditional Chinese Medicine (TCM), the characteristics and main efficacy of herbal medicine in the "FangyiFang" were obtained. TCMSP database was searched to obtain the ingredients of herbal medicine. The action targets of herbal ingredients were obtained via the "Swiss Target Prediction" platform. The disease targets were obtained using GENECARD database. The Protein-Protein Interaction (PPI) network was built using STRING database, and the visual analysis was conducted using cytoscape 3.7.1 software. Go analysis and KEGG analysis were conducted using Metascape database.

Result: A total of 1004 drug targets, 1039 disease targets, and 176 intersection targets were acquired. A total of 10 key targets were screened (TNF, AKT1, IL-6, GAPDH, ALB, VEGFA, STAT3, MAPK3, HSP90AA1, and EGFR) in accordance with the PPI network. A total of 1891 biological process entries (BP), 69 molecular function entries (MF), and 123 cell composition entries (CC) were yielded through Go enrichment. According to the top 10 KEGG pathways, 10 active ingredients were screened, including 14 acetyl coripotoacyl-8-trans atractylol, bicuculline and secological dibutylacetal, etc. 100 molecular docking results suggest that all docking binding energies are less than 0, and most of them are less than -5.

Conclusion: To sum up, the TCM compound "FangyiFang" exhibits the characteristics of "multi-component and multi-target". This study explored the mechanism of "FangyiFang" in preventing novel coronavirus through network pharmacology, providing a research basis for its subsequent social promotion.

Keywords: COVID-19; TCM; Network pharmacology; Chinese herbal compound.

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Correspondance: *Wang Jieqiong & Qiao Mingqi, College of Traditional Chinese Medicine, Research and Innovation Team of Emotional Diseases and Syndrome Research, Shandong University of Traditional Chinese Medicine, Jinan, China.*

Emails: jieqiong2016@126.com & qmingqi@163.com

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Introduction

The novel coronavirus pneumonia (COVID-19) outbreak at the end of 2019 has continuously raged all around the world. Existing research has suggested that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) comprises single stranded positive strand RNA 1, which is easy to invade the respiratory and digestive systems of the body, thus causing several disease symptoms. More asymptomatic infections were identified with the deepening of research and the further optimization of detection technology 2. As of 2022, over 6 million people have died worldwide. SARS-COV-2 has exerted significant adverse effects on social and economic development and the lives of residents due to its high infectivity and pathogenicity.

COVID-19 falls into the category of "Yibing" in TCM, also known as "plague"3, and TCM shows great advantages in treating this disease4-7. Due to the continuous spread of the pandemic, Shandong Province officially released the TCM compound, "Fangyifang", for the prevention of COVID-19 in March 2022 (https://sd.ifeng.com/c/8ENYvTJXsKw), which has played a major role in preventing COVID-19. Fangyifang comprises Hedysarum Multijugum Maxim 12 g, Atractylodes Macrocephala Koidz 9 g, Saposhnikoviae Radix 6 g, Lonicerae Japonicae Flos 9 g, Forsythiae Fructus 9 g, Mori Follum 6 g, Fructus Arctii 6 g, Phragmitis Rhizoma 9 g, as well as licorice 3 g. It is capable of nourishing qi and strengthening the surface, clearing heat, and detoxifying poisonous substances. In this study, the mechanism of action of "FangyiFang" in the intervention of COVID-19 was explored using network pharmacology technology to provide theoretical support for its social promotion.

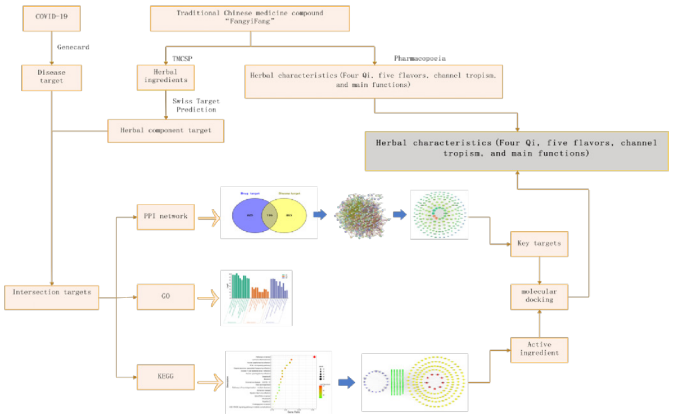

Figure 1: The flow chart of this study.

Methods and tools

Characteristics of "FangyiFang"

The four properties, five tastes, channel tropism, and main effects of the drug are obtained by consulting the pharmacopoeia of TCM (http://yaobw.cn/yaobw/).

Collection of components and component targets of herbal medicines in "FangyiFang"

The active ingredients of Hedysarum Multijugum Maxim, Atractylodes Macrocephala Koidz, Saposhnikoviae Radix, LonicerаeJaponicae Flos, Forsythiae Fructus, Mori Follum, Fructus Arctii, Phragmitis Rhizoma and licorice were searched through the TCMSP database (https://old.tcmsp-e.com/tcmsp.php), with the oral availability (OB)≥30% and drug-likeness properties (DL) ≥ 0.18 as the screening conditions [8]. Subsequently, Pubchem (https://pubchem.ncbi.nlm.nih.gov) was adopted to search the corresponding "Canonical SMILES" of each component, or use another method—download the structural formula of the component compound from the TCMSP database. Next, the structural formula was imported into open Babel GUI software to obtain "Canonical SMILES". Lastly, the target was predicted on the platform of "Swiss Target Prediction", input the "Canonical SMILES", set the species as "Homo sapiens", the Excel format was downloaded, and the target information with possibility=0 was deleted in the Excel table.

Obtaining disease targets

With "new coronavirus pneumonia" 9 as the keyword, the targets related to COVID19 were collected through the Genecard database (https://www.genecards.org) search.

Obtain the intersection target of "herbal ingredients-diseases"

The "TCM ingredient-disease" intersection target was obtained intuitively. The WENN Y2.1 online tool (https://bioinfogp.cnb.csic.es/tools/venny/), input disease targets and d rug targets were employed, respectively, and Venn diagrams were drawn to obtain disease-component intersection targets.

Protein-Protein Interaction network (PPI) network construction and network pharmacology analysis

To more effectively observe the interconnection between the intersection targets and show the vital targets that work. The acquired intersection targets were submitted to the STRING11.0 database [10] (https://string-db.org), the biological species was set to "Homo sapiens", the rest of the options was set as default settings, and unconnected targets were removed. Lastly, the TSV format file was downloaded and imported into Cytoscape 3.7.1 software for visual network topology analysis.

Bioinformatics-GO and KEGG enrichment analysis

Input intersection targets into "Metascape" platform (https://metascape.org/gp/index). Subsequently, its main biological process (BP), molecular function (MF), cellular component (CC) and KEGG pathway were analyzed. Lastly, the main BP, MF, CC were integrated, and metabolic pathway results were plotted into the bubble charts for visualization.

Construct an "active ingredient-target-KEGG pathway" network to screen the key active ingredients of "FangyiFang"

TCM exhibits the characteristics of multiple components acting on multiple targets, which is in part to screen out the key active ingredients in this herbal compound. The top 20 pathways and the targets on the pathway were selected, and the "active ingredient-target-KEGG pathway" network diagram was constructed by CytoScape 3.7.2 software. Next, the key active ingredients that play a role were screened out according to the network topology parameters Degree, Betweenness and Closeness.

Molecular docking of active ingredients and vital targets

To better demonstrate the binding ability of the drug and the target, the active in gredients and vital targets were screened from the above steps for molecular docking verification. First, the crystal structure of the core target (receptor) was downloaded from the PDB database [11,12], and the structural formula of the active ingredient of the small molecule (ligand) were downloaded from the TCMSP database. Next, molecular docking experiments were performed by importing into "Schrödinger Maestro" software [13]. Before docking, the ligands were processed by the "LIGPEP" program. If the downloaded receptor has a ligand structure, molecular docking was performed at the receptor site. If there is no ligand structure, the "Binding Site Detect" program will be select ted to predict the binding site. Finally, the two were docked by the "Receptor Grid Generation" procedure, and the binding energy was recorded.

Table 1: Characteristics and main efficacy of traditional Chinese medicine of "FangyiFang".

Drug name	Four properties and five tastes	Meridians	Main efficacy
Hedysarum Mul tijugum Maxim	Lukewarm, sweet	Lung, spleen	Invigorate Qi and Yang, strength hen the exterior and stop sweating, etc.
Atractylodes M acrocephala Koidz	Warm, bitter and sweet	Spleen, Stomach	Strengthening the spleen and replenishing qi, etc.
Saposhnikoviae Radix	lukewarm, pungent and sweet	Bladder, Liver and Spleen	Expelling wind to relieve superficies, removing dampness to relieve pain
Lonicerae Japo nicae Flos	cold, sweet	lung, heart and stomach	Clearing away heat and toxin, evacuating wind heat
Forsythiae Fructus	micro cold, bitter	Lung, heart an d Small Intestine	Heat clearing and detoxification, detumescence and dissipation, and evacuation of wind heat
Mori Follum	Cold, bitter and sweet	Lung and liver	Evacuate wind heat, clear lung and moisten dryness
Fructus Arctii	Cold, bitter and pungent,	Lung and stomach	Evacuate wind-heat, detoxify et c.
Phragmitis Rhizoma	Cold and sweet	Lung and stomach	Clearing heat and purging fire, generating saliva and quenching thirst, etc.
licorice	Peaceful, sweet	Heart, lung, spleen and stomach	Invigorate the spleen and stomach, etc.

Results

Drug characteristics in "FangyiFang"

The characteristics and main effects of nine Chinese herbal medicines were obtained through the review of the Chinese pharmacopoeia. The characteristics of herbal medicines contain four properties (including cold, cool, warm, and hot), five tastes (including sour, bitter, sweet, pungent, and salty) and meridians to which they belong, and the above characteristics determine their efficacy and clinical application, as listed in table 1.

Herbal component targets and disease targets

Through the TCMSP database, 20 components of Hedysarum Multijugum Maxim, 7 components of Atractylodes Macrocephala Koidz, 17 components of Saposhnikoviae Radix, 23 components of LoniceraeJaponicae Flos, 23 components of Forsythiae Fructus, 29 components of Mori Follum, 8 components of Fructus Arctii, 11 components of Phragmitis Rhizoma and 92 components of licorice (Figure 2) were obtained, including 4 components that did not predict the target (MOL003111, MOL011753, MOL011730, MOL004829). After summarizing and removing duplicate drug targets, 1004 drug targets were obtained (Table 2). A total of 1039 disease targets were obtained. Drugs and diseases share 176 targets (Figure 3).

Table 2: The number of ingredients and the target number of ingredients in each herb.

Chinese name	English latin name		Number active ingredients	Number of targets
黄芪	Hedysarum Huangqi Multijugum Maxim		20	1149
白术	Atractylodes Baizhu Macrocephala Koidz		7	400
防风	Saposhnikoviae Radix Fangfeng		17	913
金银花	Lonicerae Japonicae Flos	Jinyinhua	23	1321
连翘	Forsythiae Fructus	Lianqiao	23	11263
桑叶	Mori Follum	Sangye	29	1503
牛蒡子	Fructus Arctii	Niubangzi	8	341
芦根	Phragmitis Rhizoma	Lugen	1	42
甘草	licorice	Gancao	92	3293

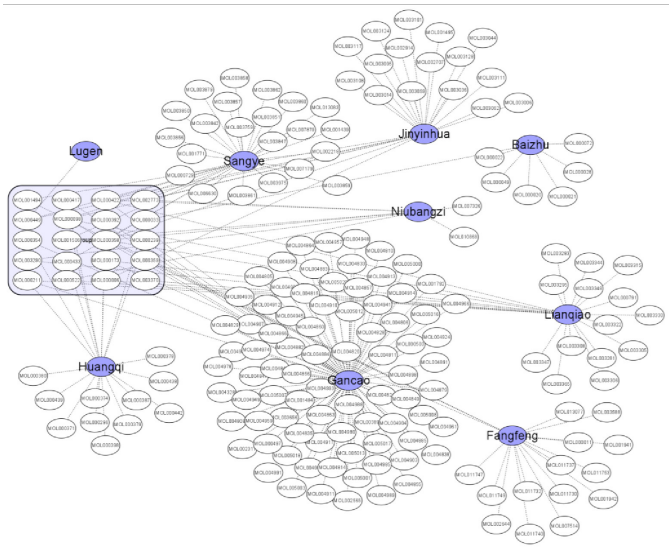

Figure 2: "Herbal-Herbal Ingredient" network diagram. The MOL number is the number of the herbal ingredient in the TCMSP database, ⬭ is herbal, ⬭ is herbal in gradient contains ingredients that exist in at least two herbal medicines.

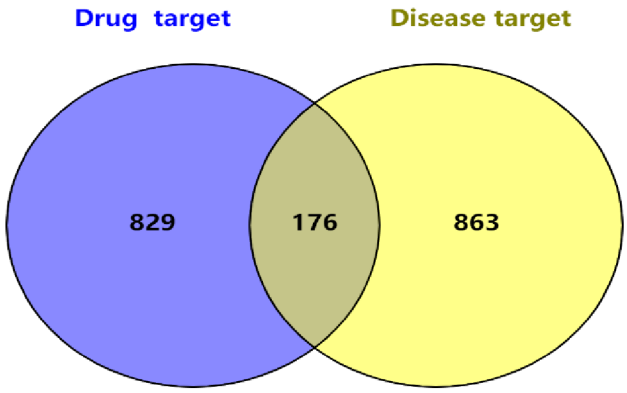

Figure 3: Venn diagram of the intersection target of "herbal component-disease". Obtained 176 intersection targets.

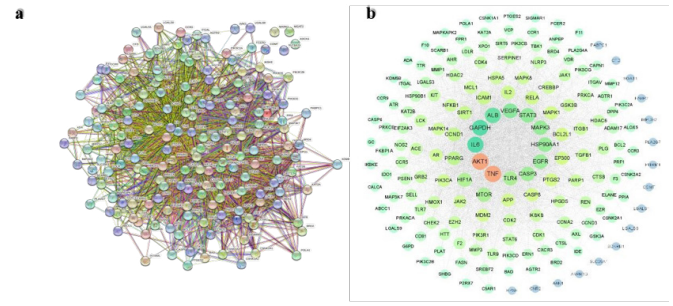

Figure 4: (a) PPI initial network. (b) PPI optimized network. The size of a node is related to the Degree of its node in the network (the larger the Degree value, the larger the node).

PPI Network

The 176 intersection targets entered STRINGT database to obtain the initial PPI network (Figure 4a), in which there were four independent targets (MARK1, MGAT2, ADCK4 and SLC6A15). After the four free targets were removed, the initial network was down loaded and imported into Cytoscape 3.7.1 software to optimize the visual view, such that a PPI network graph with 172 nodes and 2729 edges (Figure 4b) was obtained. Th e top 10 (≥86) targets in the PPI network were selected as the vital targets (Table 3).

Table 3: Top ten gene targets in PPI network and pharmacological parameters of gene target network.

Gene name	Degree	Betweenness centrality	Closeness centrality
TNF	123	0.086296115	0.780821918
AKT1	123	0.088332264	0.780821918
IL6	112	0.063460802	0.743478261
GAPDH	111	0.045357392	0.737068966
ALB	105	0.053842489	0.721518987
VEGFA	92	0.021565811	0.678571429
STAT3	88	0.017621213	0.66023166
MAPK3	87	0.022613706	0.66536965
HSP90AA1	87	0.024370702	0.657692308
EGFR	86	0.026471547	0.662790698

Enrichment of Go and KEGG pathways at intersection targets

GO enrichment analysis was conducted on 176 intersection targets. A total of 1902 biological process entries (BP), 184 molecular function entries (MF) and 122 cellular composition entries (CC) were obtained. BP primarily comprises protein phosphorylation, cellular response to nitrogen compound, inflammatory response, cellular response to organonitrogen compound, cell activation, response to hormone, positive regulation of cytokine production, positive regulation of response to external stimulus, positive regulation of cell migration and positive regulation of cell motility, etc. MF involves kinase activity, phosphotransferase activity, alcohol group as acceptor, protein kinase activity, protein serine/threonine/tyrosine kinase activity, kinase binding, protein serine/threonine kinase activity, protein kinase binding, protein serine kinase activity, lipid binding and protein domain specific binding, etc. CC covers side of membrane, external side of plasma membrane, membrane raft, membrane, microdomain, peripheral region of cytoplasm, lytic vacuole, lysosome, vesicle lumen, cytoplasmic vesicle lumen and nuclear envelope, etc. The top 10 were selected for drawing respectively (Figure 5). Furthermore, it is speculated that the "FangyiFang" to prevent COVID-19 may be correlated with the above biological processes.

Likewise, 176 intersection targets were subjected to KEGG enrichment analysis. A tot al of 198 pathways were obtained, and the top 20 signaling pathways were selected to make KEGG bubble charts for view analysis (Figure 6). The results suggest that besid es the cancer pathway ranking first, the above pathways are more correlated with viral infection (e.g., human tumor virus infection, Kaposi's sarcoma-associated herpes virus infection, hepatitis B, human T-cell leukemia virus 1 infection, and Human cytomegal ovirus infection), of which the COVID-19 pathway ranks 10th.

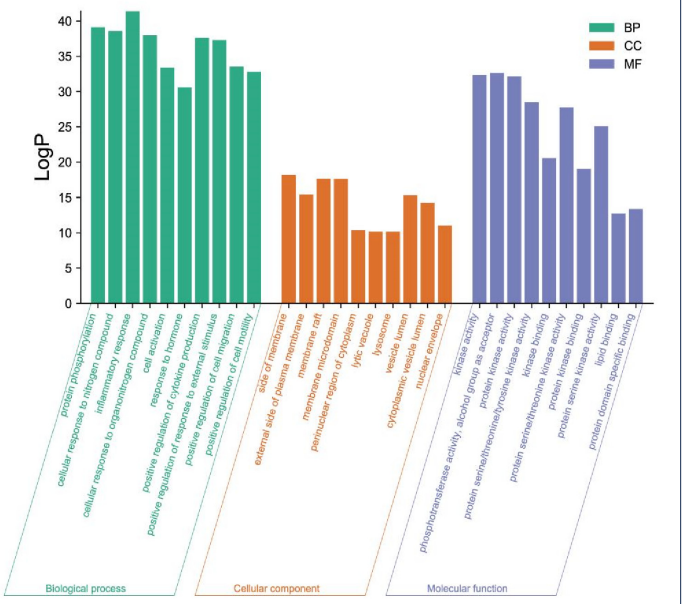

Figure 5: Go enrichment. Select the top ten for drawing. The x-axis is the three functional groups (BP, CC, and MF) and the y-axis is the LOP value for the number of genes.

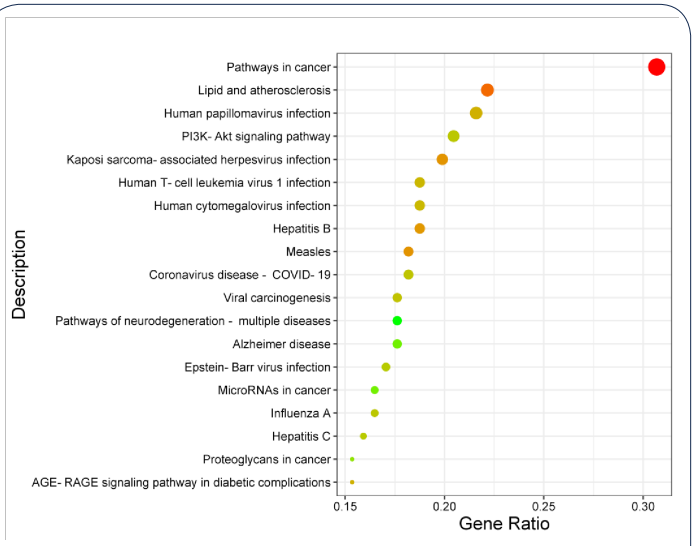

Figure 6: Top 20 KEGG pathway analysis. The x-axis is the number ratio of genes. The y-axis is the pathway name. More about the pathways of viral infection, including human tumor virus infection, Kaposi's sarcoma-associated herpesvirus infection, etc. The coronavirus COVID-19 pathway ranks 10th.

Table 4: Network node characteristic parameters of active ingredients for preventing COVID-19 in "FangyiFang".

MOL	Name	Degree	Betweenness	Closeness	Source
MOL000021	14-acetyl-12senecioyl-2E,8 E,10E-atractyl entriol	27	0.013471	0.433846	Atractylodes Mac rocephala Koidz
MOL004905	3,22-Dihydrox y-11-oxo-delt a (12)-oleane ne-27-alphamethoxycarbo nyl-29-oic acid	26	0.017478	0.444795	licorice
MOL000791	bicuculline	26	0.008636	0.435185	Forsythiae Fructus
MOL003014	secologanic di butylacetal_qt	25	0.011171	0.431193	Lonicerae Japoni cae Flos
MOL000438	(3R)-3-(2-hyd roxy-3,4-dime thoxyphenyl) chroman-7-ol	24	0.005712	0.420896	Hedysarum Multi jugum Maxim
MOL003370	Onjixanthonel	24	0.00682	0.439252	Forsythiae Fructus
MOL004820	Kanzonols W	23	0.012377	0.429878	licorice
MOL000371	3,9-di-O-methylnissolin	22	0.008715	0.414706	Hedysarum Multi jugum Maxim
MOL004891	shinpterocarpin	22	0.005478	0.435185	licorice
MOL000020	12-senecioyl2E,8E,10E-atra ctylentriol	22	0.010159	0.433846	Atractylodes Mac rocephala Koidz

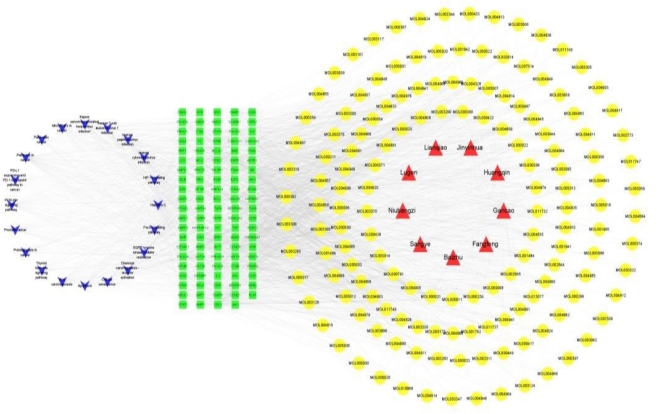

Figure 7: "Pathway- target-herbal ingredients-herbal" network. ▼ represents the pathway, ▬ represents the gene target, ⬭ represents the pathway her bal ingredients and the MOL number can find the corresponding compound in the TCMSP database.

Construction of "drug ingredient-target-pathway" network and screening of active ingredients in "FangyiFang"

We selected the top 20 KEGG pathways and reversely screened the active ingredients in the "FangyiFang" for the prevention of COVID-19 according to the targets on the pathway. The Cytoscape 3.8.2 software view shows that the network has 283 nodes and 2325 edges (Figure 7), which are sorted according to the numerical values of Degree, Betweenness, and Closeness to obtain active components (Table 2).

Molecular docking results of active ingredients and vital target

We conduct molecular docking between the active ingredients and vital targets of the "FangyiFang", and calculate the binding energy between the two to predict their binding activity. It is generally believed that the binding energy < 0 kcal·mol^{-1} indicates that the two molecules can spontaneously bind, and the binding energy <-5.0 kcal·mol^{-1} indicates a good binding effect.

As depicted in Figure 8, all molecular docking results in this experiment were less than 0 kcal·mol^{-1}, and most of the 100 docking results had binding energies less than -5.0 kcal·mol^{1}, suggesting that some active ingredients and vital targets can be well combined. Furthermore, it indicates the scientific nature of the "FangyiFang" to prevent COVID-19. According to the molecular docking value, the top three molecular docking views are displayed (Figure 9).

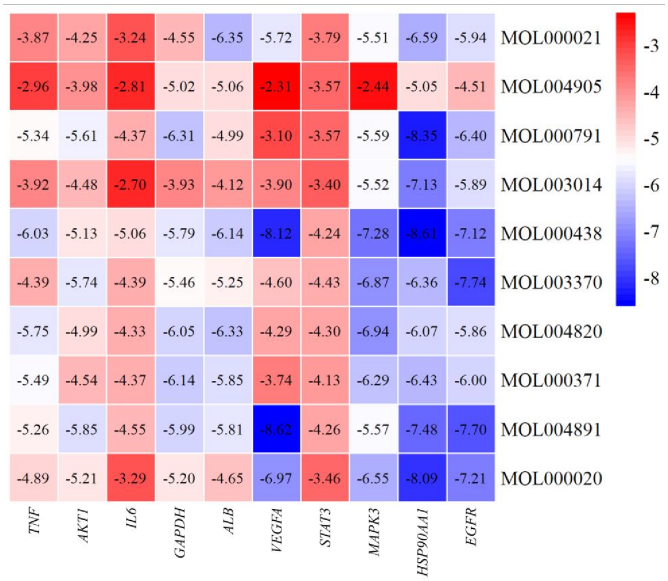

Figure 8: Molecular docking heat map. The smaller the value, the better the docking activity will be. Among the 100 docking results, all docking results were less than 0 kcal·mol^{-1}, and most of them were less than -5 kcal·mol^{-1}.

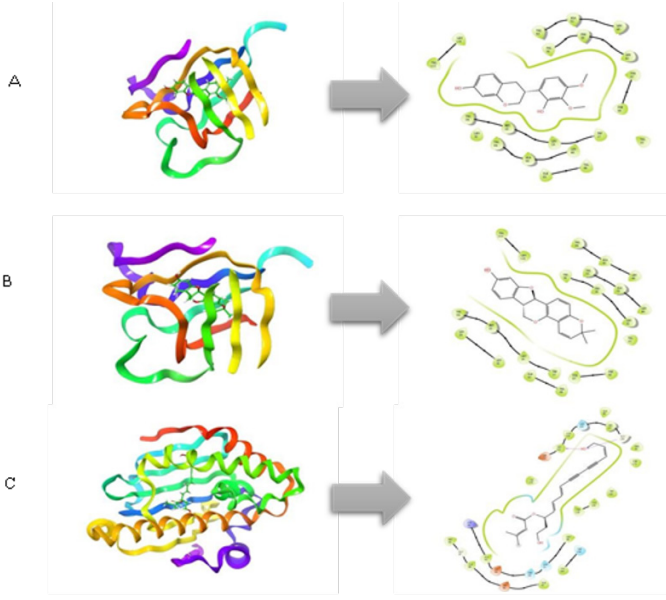

Figure 9: 2D and 3D interaction diagrams. (A) Molecular docking view of VEGFA (PDB ID 4QAF) and MOL000438 [(3R)-3-(2-hydroxy-3,4-dimethoxyphenyl) chroman-7ol]. (B) Molecular docking view of VEGFA (PDB ID 4QAF) and MOL004891 [shinpterocarpin], (C) Molecular docking view of HS90AA1(PDB ID 5H22) and MOL000020 [12-senecioyl-2E,8E,10E-atractylentriol].

Discussion

The COVID-19 pandemic has raged for over two years, and there have been mutations (e.g., Omicron and delta) recently [14]. Although COVID-19 is a class B infectious disease, it is still prevented and controlled as a Class A infectious disease in China15. In this study, the mechanism of action of "FangyiFang" in the intervention of COVID-19 was explored using network pharmacology and molecular docking technology.

Prescription analysis of "FangyiFang"

In accordance with existing literature reports, patients with COVID-19 mostly had respiratory symptoms (e.g., fever and cough), and some also developed gastrointestinal symptoms (e.g., anorexia, nausea and vomiting, as well as diarrhea). More asymptomatic infections have been found over the past few years. The pathogenesis theory of TCM suggests that "the righteousness is in the body, and the evil cannot do it" [16,17], and "the lack of the righteousness is the fundamental cause of the disease of the body". Most of the herbs in the "FangyiFang" are "sweet and warm" in four properties and five tastes (e.g., Hedysarum Multijugum Maxim). The above are designed to nourish the body's righteousness. Second are herbs with "bitter and cold" in four properties and five tastes (e.g., Forsythiae Fructus and Lonicerae Japonicae Flos), which are designed to clear away heat and detoxify poisonous substances since patients with COVID-19 have fever. Furthermore, dampness is the critical factor causing the pathogenesis of COVID-19 18, so Phragmitis Rhizoma is given to treat dampness and heat toxicity

Vital targets

SARS-CoV-2 invades the adjacent deep lung stroma and binds with ACE2 on the alveoli, thus inducing the activation of inflammatory cytokines and causing damage to the epithelial cells of the alveolar wall. The result achieved under CT microscope has i ndicated that the COVID-19 patient's lungs show glassy shadows [19].

In the PPI network of this study, TNF, AKT1, IL-6, GAPDH, ALB, VEGFA, STAT3, MA PK3, HSP90aa1 and EGFR were selected as the vital targets to take effect in accordance with the topological parameter values of degree and other networks. It is speculated that the above targets may be the vital target genes for the "FangyiFang" to prevent COVID-19. STAT3 takes on a critical significance in regulating the expression of inflammatory factors 20, which can be activated by different cytokines and growth factor s (e.g., IL-6 and TNF). IL-6 is an endogenous pyrogen of which the function is correlated with various inflammation related diseases and can cause high fever in people with autoimmune diseases or virus infection. Existing research has suggested that 21 C OVID-19 can be effectively prevented by down-regulating the expression of IL-6 in serum. SARS-CoV-2 can induce human macrophages and dendritic cells to release proinflammatory cytokines (e.g., TNF- α). Furthermore, too much TNF can result in lung tissue damage.

AKT1 is one of the three members of Akt serine threonine protein kinase family. It is capable of regulating numerous processes (e.g., metabolism, proliferation, cell survival, growth, and angiogenesis). In addition, AKT1 can regulate the development and function of innate immune cells (neutrophils, macrophages, and dendritic cells) [22]. Forced AKT1 signal transduction can lead to

the proliferation of airway smooth muscle and the occurrence of asthma [23,24]. AKT1 is confirmed as a potential target for COVID-19 treatment and prevention [25].

GAPDH exhibits the activities of glyceraldehyde-3-phosphate dehydrogenase and nitrosylase, which play a role in glycolysis and nuclear function respectively. Recent studies have shown that inhibition of GAPDH in individuals with deteriorating cellular innate immune response (e.g., the elderly) may be beneficial to treat COVID-19 and other viral diseases [26]. ALB is capable of regulating plasma colloidal osmotic pressure, and it takes on a critical significance in maintaining human nutrition as a carrier protein of various endogenous molecules (e.g., hormones, fatty acids, and metabolites) and exogenous drugs. Recent studies have suggested that elderly patients with COVID-19 have a significantly high prevalence of malnutrition, and malnutrition will increase the mortality of SARS-CoV-2 [27].

Go enrichment and KEGG pathway analysis

In this study, GO enrichment analysis of 176 intersecting targets was conducted on the Metascape platform. The results suggest that the intersecting targets are primarily mainly enriched in biological processes (e.g., inflammation, protein phosphorylation, positive regulation of cell migration, and positive regulation of cell movement). Molecular function items include the activities of a series of enzymes (e.g., phosphoprotein serine/threonine/tyrosine kinases), and most of the above enzymes are correlated with protein phosphorylation. Protein phosphorylation is one of the most investigated and well-understood protein post-translational modifications, and it plays a role in almost all biological processes [28]. It is speculated that "FangyiFang" may affect the regulation of inflammatory factors by affecting the process of protein phosphorylation, thus inhibiting the "cytokine storm" and avoiding the occurrence of COVID-19. The result of KEGG pathway analysis suggests that most of the pathways are correlated with viral infect ion, among which the COVID-19 pathway ranks 10th.

In brief, based on the concept of "prevention treatment of disease" in TCM, "FangyiFang" acts on the main pathways of human papillomavirus, Kaposi's sarcoma associated herpesvirus, cytomegalovirus, and COVID-19 through vital targets (e.g., TNF, AKT1, I L6, and STAT3), inhibits the occurrence of inflammatory reaction by affecting the level of protein phosphorylation, and plays a certain role in COVID-19 prevention.

In this study, we confirmed the multi-component, multi-target, and multi-channel mechanism of the TCM compound "FangyiFang" through network pharmacology and molecular docking technology. For reverse screening of active components through the main channels, 14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol,3,22-Dihydroxy-11-oxo-delta (12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid, bicuculline and other active ingredients (Table 4). It is necessary to conduct in-depth experimental verification for the specific inhibitory effect of the above active ingredients on SARS-CoV-2.

Declarations

Data availability: Data will be made available on request.

Funding sources: This study was supported by the Jinan"20 Items in Universities" Funded Project (NO. 2020GXRC002).

Author contributions: Wu Tao is responsible for the overall writing and typesetting design of the paper. Qu mengrou and Chen XianMei are responsible for querying and collecting the target s of Chinese herbal ingredients and sorting them out. Yu Xufeng provided very valuable opinions for this study and also provided technical support for molecular docking. Professors Qiao Mingqi and Wang Jieqiong checked the overall design of the study, and revised and reviewed the manuscript.

Declaration of competing interest: The authors declare no conflicts of interest.

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