Mechanism of Huo-Xiang-Zheng-Qi in Preventing and Treating COVID-19: A Study Based on Network Pharmacology and Molecular Docking Techniques

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Abstract

Objective: The Chinese herbal formula Huo-Xiang-Zheng-Qi (HXZQ) is effective in preventing and treating coronavirus disease 19 (COVID-19) infection; however, its mechanism remains unclear. This study used network pharmacology and molecular docking techniques to investigate the mechanism of action of HXZQ in preventing and treating COVID-19. Methods: The Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) was used to search for the active ingredients and targets of the 10 traditional Chinese medicines (TCMs) of HXZQ prescription (HXZQP). GeneCards, Online Mendelian Inheritance in Man (OMIM), Pharmacogenomics Knowledge Base (PharmGKB), Therapeutic Target Database (TTD), and DrugBank databases were used to screen COVID-19-related genes and intersect them with the targets of HXZQP to obtain the drug efficacy targets. Cytoscape 3.8 software was used to construct the drug-active ingredient–target interaction network of HXZQP and perform protein–protein interaction (PPI) network construction and topology analysis. R software was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Finally, AutoDock Vina was utilized for molecular docking of the active ingredients of TCM and drug target proteins. Results: A total of 151 active ingredients and 250 HXZQP targets were identified. Among these, 136 active ingredients and 67 targets of HXZQP were found to be involved in the prevention and treatment of COVID-19. The core proteins identified in the PPI network were MAPK1, MAPK3, MAPK8, MAPK14, STAT3, and PTGS2. Using GO and KEGG pathway enrichment analysis, HXZQP was found to primarily participate in biological processes such as defense response to a virus, cellular response to biotic stimulus, response to lipopolysaccharide, PI3K-Akt signaling pathway, Th17 cell differentiation, HIF-1 signaling pathway, and other signaling pathways closely related to COVID-19. Molecular docking results reflected that the active ingredients of HXZQP have a reliable affinity toward EGFR, MAPK1, MAPK3, MAPK8, and STAT3 proteins. Conclusion: Our study elucidated the main targets and pathways of HXZQP in the prevention and treatment of COVID-19. The study findings provide a basis for further investigation of the pharmacological effects of HXZQP.

Keywords

network pharmacology, COVID-19, SARS-COV-2, mechanism, Huo Xiang Zheng Qi

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-associated symptoms and infectious respiratory illness are designated as coronavirus disease 19 (COVID-19). According to the World Health Organization (WHO) statistics, as of February 25, 2021, there have been nearly 112 million confirmed cases of COVID-19 and 2.49 million deaths worldwide. This has brought severe menace to the lives and health of people worldwide and has become a vital global public health emergency. 1,2 SARS-CoV-2 is a novel coronavirus with respiratory droplet transmission as the main route of transmission. It can also be
transmitted through contact. It has the features of fast and widespread transmission, high infectivity, and common susceptibility to all kinds of individuals. Patients with mild COVID-19 have symptoms such as fever, weakness, and tussiculation. Patients with severe infection may have symptoms such as respiratory distress syndrome, dyspnea, or septic shock. At present, there is no specific medicine for COVID-19 treatment. To facilitate early detection, reporting, isolation, and treatment of the disease, and to increase the cure rate and reduce the mortality rate, the General Office of the National Health and Wellness Commission of the People’s Republic of China and the Office of the State Administration of Traditional Chinese Medicine of the People’s Republic of China recommended the use of traditional Chinese medicine (TCM) in the treatment of novel coronavirus pneumonia (Trial Version 7-9).

A Venn diagram of disease-related genes was obtained. The UniProt database was used to find the disease-related genes. A Venn diagram of disease-related genes was obtained. The UniProt database was used to find the disease-related genes.

**Results**

**Prediction of Active Ingredients and Targets of HXZQP**

Using the TCMSP database, the targets of the active ingredients of HXZQP were identified. The UniProt database was used to obtain all the official gene symbols corresponding to the target information. Finally, we obtained HXZQP with 151 active ingredients that met the 2 screening conditions of oral bioavailability (OB) value ≥30% and drug-likeness (DL) value ≥0.18. The results show that Huoxiang has 8 active ingredients and 157 targets, Zisu has 13 active ingredients and 90 targets, Gancao has 4 active ingredients and 52 targets, Chenpi has 5 active ingredients and 61 targets, Houpu has 2 active ingredients and 23 targets, Baizhi has 20 active ingredients and 49 targets, Fuling has 6 active ingredients and 18 targets, Dafupi has 2 active ingredients and 10 targets, Banxia has 11 active ingredients and 88 targets, and Gancao has 92 active ingredients and 210 targets. In total, 250 targets were identified.

**Mining Disease Targets of COVID-19**

Using GeneCards, Online Mendelian Inheritance in Man (OMIM), Pharmacogenomics Knowledge Base (PharmGKB), Therapeutic Target Database (TTD), and DrugBank databases, with “2019-nCoV,” “COVID-19,” and “SARS-CoV-2” as keywords, COVID-19 human disease-related genes were identified. A total of 749 related genes were screened, including 657 GeneCard-related genes, 1 OMIM-related gene, 15 PharmGKB-related genes, 128 TTD-related genes, and 1 DrugBank-related gene. A Venn diagram of disease-related genes is shown in Figure 1.

**Drug-Active Ingredient–Target Interaction Network Construction of HXZQP**

For the 749 COVID-19-related targets, we took the intersection with 250 HXZQP action targets to obtain 67 intersection targets (Figure 2). The drug-active ingredient–target interaction network of HXZQP for the prevention of COVID-19 is shown in Figure 3.
Protein–Protein Interaction (PPI) Network Construction and Topological Analysis of HXZQP for the Prevention and Treatment of COVID-19

The 67 intersection genes of HXZQP and COVID-19 were entered into STRING online software to construct a PPI network, and the protein interaction network (.tsv) files and pictures were downloaded (Figure 4). The files were imported into Cytoscape 3.8 software, and 6 topological features of Betweenness Centrality (BC), Closeness Centrality (CC), Degree Centrality (DC), (Eigenvector Centrality) EC, (network centrality) NC, and (local average connectivity) LAC were selected using CytoNCA. The first circle candidate targets showed BC values > 20.978, CC > 0.625, DC > 26.5, EC > 0.112, LAC > 20.419, and NC > 22.691; whereas the second circle candidate targets showed BC values > 3.314, CC > 0.912, DC > 28, EC > 0.179, LAC > 24.571, and NC > 26.661 (see Figure 5). We identified 13 PPI network core proteins: MAPK1, MAPK3, MAPK8, MAPK14, STAT3, PTGS2, CXCL8, CASP3, CCL2, TP53, EGFR, VEGFA, and FOS.

Gene Ontology (GO) Enrichment Analysis of the Targets of HXZQP for the Prevention and Treatment of COVID-19

GO enrichment analysis was performed using R software and colorspace, stringi, ggplot2, DOSE, clusterProfiler, and enrichplot packages for GO enrichment analysis, including 3 parts: biological process (BP), molecular function (MF), and cell component (CC). Considering $P < .05$, $q < .05$, the result of the targets was related to 2103 items for BP, 46 items for CC, and 129 items for MF. Each category was sorted according to the number of enriched genes, and the top 10 items were displayed in the form of a bar plot and a bubble chart, as shown in Figure 6 and Figure 7. The results show that, in terms of the enrichment results of biological processes, the targets of HXZQP are mainly involved in defense response to the virus, modulation of host cellular process by the virus, regulation of defense response to virus by the host, cellular response to biotic stimulus, response to lipopolysaccharide, response to oxidative stress, response to molecule of bacterial origin, and cellular response to chemical stress. From the results of
Figure 2. Venn diagram of the intersection of HXZQP and COVID-19 disease-related genes.

Figure 3. The drug-active ingredient–target interaction network of HXZQP for the prevention and treatment of COVID-19.
molecular function enrichment, HXZQP is mainly reflected in virus receptor activity, membrane raft, RNA polymerase II transcription regulator complex, protein kinase complex, plasma membrane raft, serine/threonine protein kinase complex, caveola, cyclin-dependent protein kinase holoenzyme complex, transcription regulator complex, membrane region, and membrane microdomain. From the results of the enrichment results of cellular components, the targets of HXZQP in the prevention and treatment of COVID-19 were identified to be mainly involved in cytokine receptor binding, protein serine/threonine kinase activity, death domain binding, BH domain binding, DNA-binding transcription factor binding, chemokine receptor binding, cytokine activity, RNA polymerase II-specific DNA-binding transcription factor binding, protein phosphatase binding, and phosphatase binding.

**Kyoto Encyclopedia of Genes and Genomes (KEGG)**

Enrichment Analysis of the Targets of HXZQP in the Prevention and Care of COVID-19

Using R software and colorspace, stringi, ggplot2, DOSE, clusterProfiler, enrichplot, and pathview packages for KEGG enrichment analysis of the targets of HXZQP in the prevention...
and treatment of COVID-19, screening rules were set at $P < .05$, $q < .05$. The top 30 terms were visually displayed through bar plots and bubble charts (Figure 8 and Figure 9), and a total of 170 signaling pathways were screened. The main pathways of HXZQP in preventing COVID-19 include COVID-19, human papillomavirus infection, VEGF signaling pathway, PI3K-Akt signaling pathway, Epstein-Barr virus infection, human T-cell leukemia virus 1 infection, Th17 cell differentiation, influenza A, HIF-1 signaling pathway, TNF signaling pathway, IL-17 signaling pathway, apoptosis, toxoplasmosis, hepatitis C, measles, hepatitis B, human cytomegalovirus infection, and Kaposi sarcoma–associated herpesvirus infection. The COVID-19 pathway map was selected to draw the pathway map; the part marked in red is the target of HXZQP on this pathway with a total of 17 targets (Figure 10).

Analysis of the Molecular Docking Results of Some Active Ingredients of HXZQP and Target Protein

The key target proteins involved in the COVID-19 treatment pathway were selected, namely, EGFR (PDB ID: 2M0B), MAPK1 (PDB ID: 4FV5), MAPK3 (PDB ID: 2ZOQ),
Figure 7. The bubble chart of gene ontology enrichment analysis.

Figure 8. The bar plot of Kyoto Encyclopedia of Genes and Genomes enrichment analysis.
MAPK8 (PDB ID: 3ELJ), and STAT3 (PDB ID: 6TLC), to analyze the molecular docking results of the target protein and chemical components of HXZQP. The low energy stable conformation between the ligand and receptor suggests a large likelihood of interaction between them. In this study, AutoDock Vina (v4.2) docking software was used to perform molecular docking of the effective components of HXZQP (small-molecule ligands) and drug target proteins (receptors). The smaller the docking score, the stronger the binding affinity. The conformation with the highest score (the lowest affinity value) was selected as the docking conformation, and PyMol was used to visually analyze the docking conformation. Among the several binding conformations of the docking results for every active ingredient, we selected the conformation with the lowest binding energy. The smaller the binding energy, the higher the affinity between the receptor ligands (see Table 1). The molecular docking model of the representative core active ingredients of HXZQP and the key target proteins involved in the COVID-19 treatment are shown in Figure 11.

Discussion

According to the National Health Commission of the People’s Republic of China, as of February 25, 2021, 101 778 patients with COVID-19 have been confirmed, and 96 361 patients have been cured and discharged in China. TCM has shown distinctive advantages in epidemic prevention and control. The number of confirmed cases treated by TCM in China has exceeded 90%. HXZQP and other Chinese patented medicines have been recommended by the state and have played a positive role in the front line of the epidemic. However, owing to its complexity, the specific active components and pharmacological effects of HXZQP cannot be accurately clarified. Network pharmacology studies interactions among drugs, targets, and diseases from the standpoint of biomolecular networks. The interactions among drugs, active ingredients, targets, and related diseases are abstracted as a network model. The topological parameters of each node in the network are obtained. These parameters are used to appraise the significance of the nodes in the entire network.

In this study, with the aid of TCMSP, the OB and DL values for screening conditions were used to collect the targets of the active ingredients of all the drugs of HXZQP, and the UniProt database was used to obtain all official gene symbols of correspondence target information and 151 active ingredients of HXZQP. The results reflected that the most active ingredients in HXZQP were Glycyrrhizae Radix et Rhizoma, Angelicae Dahuricae Radix, Perillae Folium, Pinelliae Rhizoma, and with COVID-19 have been confirmed, and 96 361 patients have been cured and discharged in China. TCM has shown distinctive advantages in epidemic prevention and control. The number of confirmed cases treated by TCM in China has exceeded 90%. HXZQP and other Chinese patented medicines have been recommended by the state and have played a positive role in the front line of the epidemic. However, owing to its complexity, the specific active components and pharmacological effects of HXZQP cannot be accurately clarified. Network pharmacology studies interactions among drugs, targets, and diseases from the standpoint of biomolecular networks. The interactions among drugs, active ingredients, targets, and related diseases are abstracted as a network model. The topological parameters of each node in the network are obtained. These parameters are used to appraise the significance of the nodes in the entire network.

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Figure 10. Target annotation mapping of active components of HXZQP in COVID-19 treatment.
Table 1. Binding Energy of Representative Core Active Ingredients of HXZQP With Key Target Protein Molecules Involved in COVID-19 Treatment.

| MOL ID   | Active ingredient | Target | Source | Affinity (kJ/mol) |
|----------|------------------|--------|--------|-------------------|
| MOL000098 | Quercetin        | EGFR   | Huoxiang, Gancao | −6.5 |
| MOL000006 | Luteolin         | EGFR   | Zisu   | −6.5 |
| MOL004328 | Naringenin       | MAPK1  | Zisu   | −9.0 |
| MOL00497  | Licochalcone A   | MAPK1  | Huoxiang, Gancao | −8.4 |
| MOL00497  | Licochalcone A   | MAPK1  | Huoxiang, Gancao | −8.9 |

Pogostemonis Herba, Poria, Citri Reticulatae Pericarpium, Atractylolis Rhizoma, Magnolii Officinalis Cortex, and Arecae Pericarpium. Thereafter, we explored the potential biological mechanisms of HXZQP in the prevention and treatment of COVID-19. We used GeneCards, OMIM, PharmGKB, TTD, and DrugBank databases and obtained 749 COVID-19-related targets and 67 intersection targets through the intersection with HXZQP targets. By constructing a PPI network with 67 intersection targets, we discovered that there were complicated connections between these proteins and not a single-line action. The proteins MAPK1, MAPK3, MAPK8, MAPK14, STAT3, PTGS2, CXCL8, CASP3, CCL2, TP53, EGFR, VEGFA, and FOS in the PPI core network could be the major direct targets of HXZQP in the prevention and treatment of COVID-19. Among them, MAPK1, MAPK3, MAPK8, and MAPK14 are members of the mitogen-activated protein kinase (MAPK) family, which plays a critical role in many cell multiplication-related signaling pathways. It is a key signaling pathway that participates in the physiological control of cell differentiation, growth, survival, apoptosis, and migration. Research has shown that the MAPK pathway is activated by many viral infections and is indispensable for viral proliferation. Studies have confirmed that SARS-CoV-2 is transmitted through the respiratory system, and the virus enters the circulatory system, causing an immune response in the blood and activating the MAPK signaling pathway to resist the virus. STAT3 mediates the expression of multiple genes involved in cytokinesis; therefore, it plays a critical role in many cellular processes, such as cell multiplication and apoptosis. In SARS-CoV-2-infected cells, a positive feedback loop established between STAT3 and plasminogen activator inhibitor-1 (PAI-1) may lead to an escalating cycle of activation, similar to the interdependent signaling networks affected in COVID-19. Cytokine release syndrome is a manifestation of excessive activation of the immune system. Compared with other respiratory viral infections such as influenza, the main pathogenic mechanism involved in the severe clinical features of COVID-19 is an abnormal host immune response, which causes the excessive release of cytokines and chemokines, called “cytokine release syndrome (CRS).” Although the pathophysiological mechanism of CRS is not yet clear, many studies have shown that the pathogenesis of CRS is closely related to the disorder of the interaction and regulation of various cytokines between cells and the imbalance between pro-inflammatory and anti-inflammatory responses. The results of the PPI core network in this study showed that targets belonging to the pro-inflammatory cytokines PTGS2 and CXCL8 are closely related to CRS. Cyclooxygenase-2 (COX-2) catalyzes the production of prostaglandin E2 (PGE2), which is widely involved in the inflammatory response in multiple tissues and organs and plays a very important role in the body’s inflammatory response. CXCL8, also known as interleukin-8 (IL-8), is a glutamate (leucine) CXC chemokine. Studies have found that COVID-19 patients have higher levels of CXCL8, VEGFA, and VEGF in the peripheral blood than healthy individuals. CASP3 is the main virus-induced apoptotic effector and an important mediator of p53-induced apoptosis. CCL2 is considered one of the earliest chemokines significantly upregulated in SARS-CoV-infected pulmonary epithelial cells, and its serum level correlated positively with the severity of SARS infection.

In addition, GO and KEGG enrichment analysis of the signaling pathways of 67 proteins revealed that the targets of HXZQP are involved in defense response to the virus, modulation of host cellular process by the virus, regulation of defense response to virus by the host, virus receptor activity, and other virus-related regulation. The main actions of HXZQP to prevent and cure COVID-19 include COVID-19, human papillomavirus infection, VEGF signaling pathway, PI3K-Akt signaling pathway, Epstein-Barr virus infection, human T-cell leukemia virus 1 infection, Th17 cell differentiation, influenza A, HIF-1 signaling pathway, TNF signaling pathway, IL-17 signaling pathway, apoptosis, toxoplasmosis, hepatitis C, measles, hepatitis B, human cytomegalovirus infection, Kaposi sarcoma–associated herpesvirus infection, and other signaling pathways that are closely related to COVID-19. In the COVID-19 pathway, SARS-CoV-2 infects alveolar epithelial cells (mainly alveolar epithelial type 2 (AEC2) cells) via angiotensin-converting enzyme 2 (ACE2) receptors. When ACE2 is occupied by SARS-CoV-2, the level of serum-free angiotensin II (Ang II) increases due to a decrease in ACE2-mediated degradation, which promotes the activation of the NF-κB pathway through Ang II type 1 receptor (AT1R), and then produces interleukin-6 (IL-6). SARS-CoV-2 activates the innate immune system. Macrophage stimulation causes excessive production of pro-inflammatory cytokines (including IL-6) and cytokine storm," leading to systemic inflammatory response syndrome and multiple organ failure. The synthetic effects of endothelial injury, neutrophil
imbalance, complement activation, and a hypercoagulable state seem to be intertwined, leading to serious features of COVID-19. Targeting the IL-17 signaling pathway axis can be used as a new strategy for the treatment of lung injury. Targeting the TH17 type reaction participates in the cytokine storm in viral lung infections, including SARS-CoV-2, causing tissue damage and possibly promoting pulmonary edema. Targeting the TH17 pathway may benefit patients with dominant TH17 immunity. The PI3K-Akt signaling pathway plays a major role in cell differentiation, proliferation, oxidative stress, and apoptosis. It inhibits autophagy in lung fibroblasts and reduces the formation of lung fibrosis.

There are 17 targets of HXZQP related to COVID-19 treatment: PRKCA, RELA, FOS, MAPK14, IL6R, CCL2, CXCL8, MAPK3, MAPK1, MAPK8, IKBKB, STAT1, STAT3, EGFR, IL1B, PRKCB, and CXCL10. Among these, EGFR, MAPK1, MAPK3, MAPK8, and STAT3 were the core targets. The core active components of EGFR, MAPK1, MAPK3,
Materials and Methods

Mining and Screening of Active Ingredients and Targets of HXZQP

The Huoxiang, Zisu, Cangzhu, Chenpi, Houpu, Baizhi, Fuling, Dafupi, Banxia, and Gancao in HXZQP were input into the TCMSP database (http://tcmspw.com/tcmsp.php) to search and obtain their respective active ingredients by screening and meeting the 2 conditions of OB value ≥30% and DL value ≥0.18. Thereafter, the targets of the active ingredients of all the drugs of HXZQP in the TCMSP database were identified using the UniProt database (https://www.uniprot.org/) to obtain all the official gene symbols corresponding to the target information, and this section of the information was applied for follow-up network pharmacology data analysis.

Mining Disease Targets of COVID-19

We used GeneCards (https://www.genecards.org/), OMIM (https://omim.org/), PharmGKB (https://www.pharmgkb.org/), TTD (http://db.idrblab.net/ttd/), and DrugBank (https://www.drugbank.ca/) database to identify disease targets of COVID-19 using “2019-nCoV,” “COVID-19,” and “SARS-CoV-2” as keywords to filter and merge COVID-19 human disease–related genes.

Drug–Active Ingredient–Target Interaction Network

Construction of HXZQP to Prevent and Treat COVID-19

Using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/index.html) online software, we considered the intersection of HXZQP action targets and COVID-19 disease targets, and the intersection targets were considered the core targets of HXZQP to prevent and treat COVID-19. We used Cytoscape 3.8 software to construct a drug-active ingredient–target interaction network for HXZQP in the prevention and treatment of COVID-19.

PPI Construction and Topological Analysis of HXZQP to Prevent and Treat COVID-19

The online software STRING: functional protein association networks (https://www.string-db.org/), select multiple proteins, protein name: input the intersection gene of front HXZQP and COVID-19; Organism: Select Homo sapiens to build a protein-protein interaction (PPI) network. We used Cytoscape 3.8 software to obtain the core protein of the PPI network.
GO and KEGG Pathway Enrichment Analysis for the Targets of HXZQP

R software was used to carry out GO and KEGG pathway enrichment analysis for the prevention and treatment of COVID-19 by HXZQP. To elucidate the molecular mechanism of HXZQP in preventing COVID-19, we need to begin with 2 aspects of gene function and pathway analysis.

Component-Target Molecular Docking

The PPI network core protein was used as an example to analyze the molecular docking results of the target proteins and chemical components. First, we downloaded the 2D structure SDF format file of the small-molecule ligand (the active ingredient of Huoxiang Zhengqi Chengfang) from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and used ChemOffice software to convert its 2D structure into a 3D structure. The 3D structure PDB format file of the PPI network core protein was downloaded from the RSCB PDB database (https://www.rcsb.org/), and the PyMol software removed the water molecules and small-molecule ligands in the target protein and then saved it as a PDB format file. AutoDockTools software was used to convert the SDF format files into PDBQT format files and to determine the active pockets. Finally, AutoDock Vina was used for molecular docking of the active ingredients of traditional Chinese medicine (small-molecule ligands) and drug target proteins (receptors).

Supporting Information

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Declaration of Conflicting Interests

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