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Research Article

Bicuculline from Corydalis Species as a Natural Anti-COVID-19 Drug

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Abstract

Objective: To perform molecular docking of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) 3CL hydrolytic enzyme (3CL^{pro}) and Angiotensin-Converting Enzyme Ⅱ (ACE2) receptors, and to seek potential natural anti-COVID-19 drugs using computer virtual screening technology.

Methods: In this study, the Autodock Vina software was first used to achieve the molecular docking of the targets, namely, sars-cov-2 3CL hydrolase and ACE2. Then, the herbals acting on 3CL^{pro} and ACE2 receptors were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), and the active ingredients were also selected. After that, the chemical-target network was constructed based on the network pharmacology, and the functional enrichment analysis of Gene Ontology (GO) and the pathway enrichment analysis of Kyoto Gene and Genome Encyclopedia (KEGG) were carried out by DAVID to speculate about the mechanism of action of the core drug.

Results: A total of six potential anti-COVID-19 active ingredients were selected from natural herbs. They were evaluated by the "ADME" and "Lipinski" rules and their content in the natural herbs were determined by the literature mining method. Finally, Bicuculline was selected as the anti-covid-19 candidate drug.

Conclusion: Bicuculline has a stronger ability to combine with 3CL^{pro} and ACE2 than chemical drugs recommended in the clinical practice. Internet pharmacological analysis confirms that Bicuculline can effectively resist COVID-19 pneumonia through multiple pathways.

Keywords: Angiotensin-Converting Enzyme Ⅱ (ACE2); Bicuculline; COVID-19; Molecular docking; Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) 3CL hydrolytic enzyme (3CL^{pro})

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Introduction

Coronavirus Disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, characterized by rapid and extensive spread, strong infectivity and general susceptibility of the population. Currently, there is no specific drug for it. The new coronavirus was officially designated as SARS-CoV-2 (formerly known as 2019-ncov) by the International Commission on the Classification of Viruses (ICTV) on February 11, 2020. On the same day, the World Health Organization (WHO) named the disease caused by this virus as 2019 Corona Virus Disease (covid-19). As of March 25, 2020, WHO announced 375498 confirmed cases and 16362 deaths, involving 196 countries, areas and territories? As the WHO Director-General said, "The pandemic is spreading with an accelerating pace. It took 67 days from the first reported case to the first 100,000 cases, 11 days from the first to the second 100,000 cases and just 4 days from the second to the third 100,000 cases". However, there are still no specific vaccines or treatments for COVID-19 now. At present, the homology of bat sars-like coronavirus (bat-sl-covzc45) is more than 85%. The s-protein expressed by sars-cov-2 virus binds to angiotensin-converting enzyme II (ACE2) in the human body, thereby infecting cells, invading the body and causing disease [1]. The human coronavirus 229E replicase gene encodes two overlapping polyproteins pp1a and pp1ab that mediate all the functions required for viral replication and transcription. Expression of the C-proximal portion of pp1ab requires (-1) ribosomal frame shifting. The functional polypeptides are released from the polyproteins by extensive proteolytic processing and that is primarily achieved by 3C-Like Proteinase (3CLpro) [2]. On January 26th, professors Rao ZH and Yang HT's research team from Shanghai University of Science and Technology has obtained a high-resolution crystal structure of 2019-nCoV coronavirus 3CL hydrolase (Mpro), which is considered to be an effective target of the COVID-19 virus [3]. These studies have brought hope for the seeking of effective clinical drugs to treat covid-19, and may help us to develop a more effective way to fight against covid-19.

One of the important ways to develop new drugs is to study the active ingredients of natural medicine. Scientists have been focused on searching for antiviral active ingredients with low toxicity and high curative effect from natural plants in recent years. Natural active substances have the characteristics of novel structure, high activity, and few side effects. There is a growing trend to explore plants for pharmacologically active compounds and nutraceutical supplements.

Molecular docking is a method of designing drugs based on the characteristics of the receptor and the way the receptor interacts with the drug molecule. As an emerging research method combining

the physical and chemical principles with scientific calculation algorithm, it provides a feasible strategy for exploring the basis and mechanism of the pharmacodynamic substances of natural medicine and promotes the modern research process of natural medicine [4]. In this study, with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) 3CL hydrolytic enzyme ($3CL^{pro}$) and Angiotensin-Converting Enzyme Ⅱ (ACE2) as the receptors, molecular docking of the two was performed to select potential effective anti-COVID-19 ingredients, which can promote the rapid and accurate search of antiviral chemical components and provide reference for the clinical application of existing natural drugs.

Materials and Methods

Database and software

Data used in this study were extracted from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (http://tcmspw.com/tcmsp.php), Protein Databank (PDB) (https://www.rcsb.org/); Swiss Target Prediction database (http://www.swisstargetprediction.ch/), STRING online database (https://string-db.org/), and Biological information annotation database DAVID (https:// DAVID. Ncifcrf. Gov/summary. The JSP, Version 6.8). The software used included AutoDockTools1.5.6 software, AutoDockVina software (http://vina.scripps.edu/), biological information analysis tools Cytoscape v3.8.1, data analysis tools R 3.6.2, protein molecules and visualization software PyMOL.

Molecular docking

Three-dimensional structures of 12541 compounds in MOL2 format were downloaded from the TCMSP database, and a virtual screening small molecule database for molecular docking was established. The 3D structure of ACE2 (PDB ID: 1R42) protein (PDB format) was downloaded from PDB data (https://www.rcsb.org/). Sars-cov-2 is determined to be a high-resolution crystal structure (PDB ID: 6LU7) of sars-cov-2 3CL hydrolase (Mpro) by Rao Zihe/Yang Haitao's research group from Shanghai University of Science and Technology. PyMOL software was used for water removing, hydrogenation and other operations, and high-throughput molecular docking was carried out by Autodock Vina and R. According to the optimal binding energy (affinity) of each compound to 3CL hydrolase and ACE2 converting enzyme, a small molecule database of anti-covid-19 Chinese medicine was established.

Assessment based on "ADME" and lipinski's rules

"ADME" refers to the absorption, distribution, metabolism and the excretion process of exogenous chemicals in the body, and screening ADME properties of drugs based on the criteria of oral availability (OB) ≥30% and class drug resistance (DL) ≥0.18 is an important means of development of candidate drugs [5], "Lipinski" are the basic rules proposed by Christopher a. Lipinski in 1997 for selecting drug-like molecules, specifically including relative molecular weight (MW) < 500, ClogP < 5, number of hydrogen bond donors (Hdon) < 5, number of hydrogen bond receptors (Hacc) < 10, number of keys (RBN) ≤10. Compounds that conform to Lipinski's rules will have better pharmacokinetic properties and higher bioavailability in the metabolic process in vivo, and are therefore more likely to be made into oral drugs. In this study, the active ingredients were further chosen from the small molecule database, which helped to find compounds with good pharmacokinetic properties and high bioavailability in a more efficiency way. Based on the above screening results, we speculated the anti-covid-19 herbs from the TCMSP database.

Network pharmacology predicts the molecular mechanisms of the core drug

In this study, SARS and viral pneumonia were used as references to search for potential targets of anti-covid-19 core drug. Swiss Target Prediction server was used to predict the potential targets, STRING database was employed to the analysis of the relationship between drug targets, and then the visual analysis was carried out with Cytoscape software. After that, the potential targets of the screened active components were submitted to the bioinformatics database DAVID 6.8 for functional annotation of GO gene and enrichment analysis of KEGG and REACTOME pathways, in order to further understand the functions of the targets and their role in the signaling pathway, thereby exploring and predicting the potential molecular mechanism of the core drug.

Results

Anti-COVID-19 molecule database

It is generally believed that the lower the stabilization energy of ligand binding to the receptor, the greater the possibility of action. In order to minimize the probability of false-positive results, the optimal binding energy of small molecule compounds in herbs was compared with that of the currently recommended clinical chemical drugs in this study, and the binding energy in screening criteria was changed to ≤−5.0kcal/mol (-20 kJ/mol). The partial results are shown in table 1.

Molecule	Formula	MW	$3CL^{pro}$	ACE2	DL	OB (%)	Lipinski
Puerarin	$C_{21}H_{20}O_{10}$	432.38	-33.47	-38.07	0.69	24.03	Yes
Bicuculline	$C_{20}H_{17}NO_6$	367.4	-26.78	-41.42	0.88	69.67	Yes
Luteolin	$C_{15}H_{10}O_6$	286.24	-26.78	-36.82	0.25	36.16	Yes
Quercetin	$C_{15}H_{10}O_7$	302.24	-26.36	-36.40	0.28	46.43	Yes
Isorhamnetin	$C_{16}H_{12}O_7$	316.27	-25.95	-35.15	0.31	49.6	Yes
Irisolidone	$C_{17}H_{14}O_6$	314.29	-25.53	-38.49	0.3	37.78	Yes
Lopinavir	$C_{37}H_{48}N_4O_5$	628.8	-22.59	-37.24			
Ritonavir	$C_{37}H_{48}N_6O_5S_2$	720.94	-24.69	-36.40			
Remdesivir	$C_{27}H_{35}N_6O_8P$	602.58	-25.94	-36.40			
Arbidol	$C_{22}H_{25}BrN_2O_3S$	531.89	-28.03	-30.54			
Chloroquine	$C_{18}H_{26}C_1N_3$	319.87	-24.3	-27.20			
Ribavirin	$C_{37}H_{48}N_6O_5S_2$	720.96	-25.52	-32.22			
Nitazoxanide	$C_{12}H_9N_3O_5S$	307.28	-23.85	-34.73			

Table 1: Binding energy (kJ/mol) of representative components and clinically recommended chemical drugs with sars-cov-2 3CL and ACE2.

A total of six potential anti-covid-19 active ingredients were picked out from plant, and Bicuculline was selected as the core drug in this study because of its high oral utilization and low binding energy with both two target proteins. Bicuculline was originally identified in plant alkaloid extracts in 1932 and has been isolated from *Dicentra cucullaria*, *Adlumia fungosa*, *Fumariaceae* and several *Corydalis species*.

Content of bicuculline in herbs

Bicuculline is a phthalide isoquinoline alkaloid first isolated from the plant Dicentra cucullaria and subsequently from a variety of *Corydalis*, *Dicentra* and *Adlumia* species. According to a literature review, a Chinese study showed that the amount of Bicuculline was as high as 1.1025 g/kg in *Co*rydalis Decumbens (Thunb.) Pers [6] and 0.203.5 g/kg in *Corydalis conspersa Mazim* [7] Four kinds of traditional Chinese medicine containing Bicuculline were found by searching TCMSP, namely, *Corydalis Bungeanae Herba*, *Forsythiae Fructus*, *Corydalis Rhizoma* and Corydalis *Decumbens (Thunb.)* Pers. The results are shown in table 2.

Chinese name	Latin name	channel tropism
Kudiding	*Corydalis Bungeanae Herba*	Heart, spleen
Lianqiao	*Forsythiae Fructus*	Lungs, heart, small intestine
Xiatianwu	*Corydalis Decumbens(Thunb.)Pers.*	Liver, kidney
Yanhusuo	*Corydalis Rhizoma*	Liver, spleen, heart

Table 2: Plant containing Bicuculline.

Network pharmacologic analysis of bicuculline

The potential targets of the Bicuculline and the disease targets were input into the R platform for the determination of the intersection of 3 types of targets. The Venn diagram shows that 16 of the 40 targets of Bicuculline intersect with other targets (Figure 1).

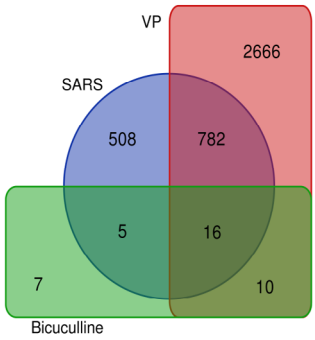

Figure 1: Venn diagram of intersected targets.

The topological analysis of the protein interaction network of Bicuculline targets is shown in figure 2 (degree value ≥30). The analysis of network topology properties by the Network Analyzer suggested that the protein interaction network consisted of 38 nodes and 57 edges, in which nodes represent proteins and edges stand for protein-protein interactions. The larger the target is, the stronger the correlation degree is. The average node degree is 3.

To illustrate the mechanism underlying the effects of Bicuculline on COVID-19 more comprehensively and specifically, we performed GO enrichment analysis of the 16 targets intersecting with others in the ingredient-disease target network. 167 GO-terms significantly enriched in Biological Process, 27 in Molecular Function and 18 in Cellular Component. The smallest P-adjusted value showed in synaptic transmission, cholinergic, protein kinase activity, exogenous drug catabolic process and cyclin-dependent protein kinase holoenzyme complex.

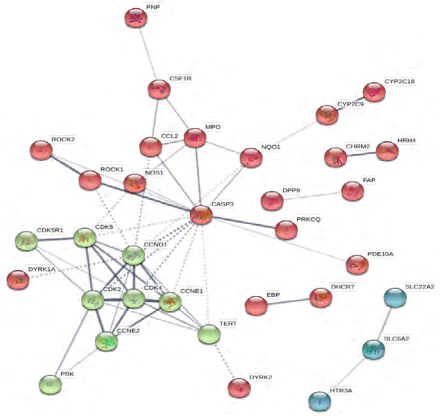

Figure 2: The network of targets of Bicuculline.

The enrichment analysis of the KEGG and Reactome pathways was carried out to elucidate the critical pathways of the 16 potential targets that related to Bicuculline's anti-COVID-19 effect. It was found that 50 pathways significantly enriched in KEGG and 24 in Reactome. After removing the duplicates, the results were compared with the super pathways of SARS and viral pneumonia and seven overlapping potential pathways were selected ultimately (Figure 3).

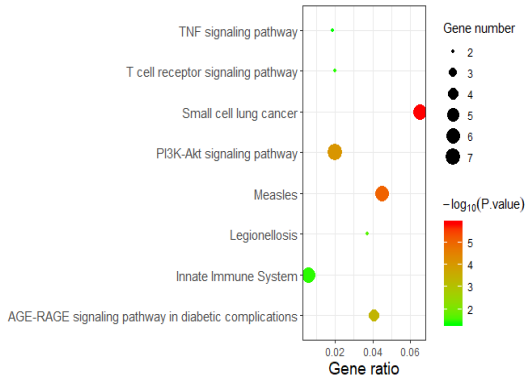

Figure 3: Seven selected overlapping potential pathways.

Discussion

In this study, six active ingredients were firstly chosen from natural herbs with low binding energy to receptors through molecular docking. Then, based on the ADME and Lipinski rules, Bicuculline was selected as a natural anti-COVID-19 ingredient with an oral absorption rate several times higher than that of other candidate drugs.

Subsequently, Bicuculline was found to be present in a variety of natural herbs in the literature review. Four plant were found to contain Bicuculline, and they were Corydalis *Bungeanae Herba, Forsythiae Fructus, Corydalis Rhizoma and Corydalis Decumbens (Thunb.) Pers* and its content was up to 1.1025g/kg in *Corydalis Decumbens (Thunb.) Pers*.

These findings indicated that Bicuculline was a potential natural anti-COVID-19 drug. One study suggested that the GABA (A) R could aggravate the inflammatory response syndrome and oxidative stress in the lungs and played an essential role in LPS-induced acute lung injury [8]. Bicuculline is a GABA receptor antagonist, which

may play an important role in acute lung injury. An earlier study confirmed that benzodiazepine augmented γ-amino-butyric acid signaling increases mortality from pneumonia in mice, and found that the increases in mortality and bacterial load were reversed by bicuculline [9]. The Upregulation of α-Smooth Muscle Actin (α-SMA) in fibroblasts by Transforming Growth Factor-β1 (TGF-β1) is an important step in the process of lung fibrosis. In an experiment on asthmatic mice, bicuculline was shown to inhibit the expression of alpha-SMA and alpha-SMA mRNA [10]. Data from previous coronavirus infections such as severe acute respiratory syndrome and Middle East respiratory syndrome, as well as emerging data from the COVID-19 pandemic, suggest there could be substantial fibrotic consequences following SARS-CoV-2 infection. Antifibrotic therapy is recommended for mitigate severe COVID-19 [5].

To further check the anti-COVID-19 mechanism of Bicuculline, the network pharmacology tool was used to analyze its targets, the cell signal transduction pathways that may be involved in the regulation, and the potential pharmacological mechanism.

Of Bicuculline's 40 targets, 16 intersected with those of SARS and viral pneumonia, indicating that Bicuculline might play its therapeutic role against COVID-19 in 8 overlapping pathways (PI3K-Akt signaling pathway, Small cell lung cancer, Innate Immune System, Measles, AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, T cell receptor signaling pathway and Legionellosis). First of all, the small-cell lung cancer pathway and the Innate Immune System pathway are known to be able to effectively resist COVID-19 pneumonia. The enrichment of Bicuculline's targets in these two pathways greatly increases its reliability as a potential drug. It has been found in many studies that drugs can suppress the inflammatory response through the PI3K-Akt signaling pathway [11-13]. TNF drives the release of itself and other proinflammatory cytokines (e.g., IL-1β and IL-6) [14,15], participates in the systemic inflammatory response, and is one of the cytokines that contribute to the acute phase response. A study revealed that spatial heterogeneity of the T cell receptor repertoire reflected the mutational landscape in lung cancer [16] and T cell-targeted immunotherapy has been increasingly applied to the treatment of non-small cell lung cancer [17]. The enrichment of these pathways from network pharmacology confirmed the hypothesis that Bicuculline was a natural and effective anti-COVID-19 drug.

Given the limitations of the virtual screening results, further in vitro and in vivo experiments are needed to verify the results of this study if possible, so as to provide the experimental basis for the development of natural antiviral drugs.

Conclusion

As a natural active substance with the characteristics of novel structure, high activity, and few side effects, Bicuculline has been proved to have low binding energy with two COVID-19 targets in this study. Besides, its high content in natural herbs and high oral utilization rate make it a potential natural antiviral drug against COVID-19. Through the analysis of its antiviral mechanism by Internet pharmacological tools, several key pathways have been found, which theoretically confirms the hypothesis that Bicuculline is a natural anti-COVID-19 drug.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Author Contributions Statement

All authors contributed to the study conception and design. Material preparation, data collection performed by PHL and SDC, and analysis were performed by JX and LQG .The first draft of the manuscript was written by JX and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Contribution to the Field Statement

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. However, there are still no specific vaccines or treatments for COVID-19 at present. Based on the molecular docking of receptors Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) 3CL hydrolytic enzyme ($3CL^{pro}$) and Angiotensin-Converting Enzyme Ⅱ (ACE2), potential natural anti-COVID-19 drugs are found using computer virtual screening technology. Bicuculline from Corydalis species is selected as a natural Anti-COVID-19 drug from tens of thousands of natural compounds due to its low binding energy to the two target enzymes and high oral availability. We hope that this discovery will facilitate the application of natural medicines in the prevention of COVID-19 viral infections and reducing the side effects of chemicals.

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