# The Key Mechanism of Radix Isatidis in the therapy of coronavirus disease 2019 based on network pharmacology and molecular docking

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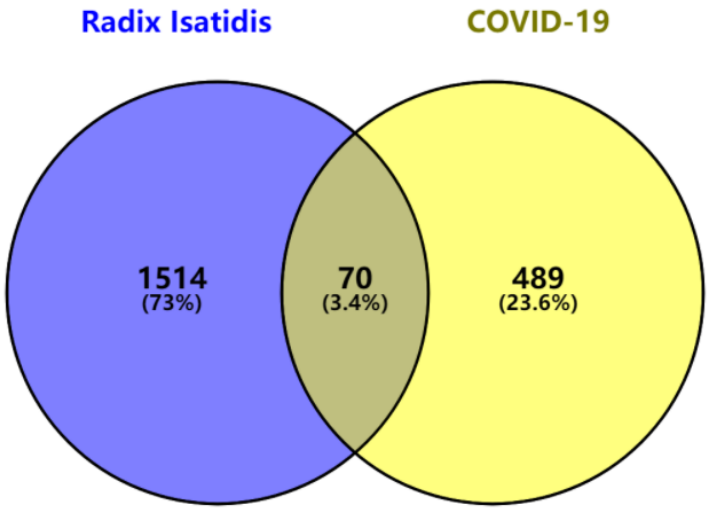
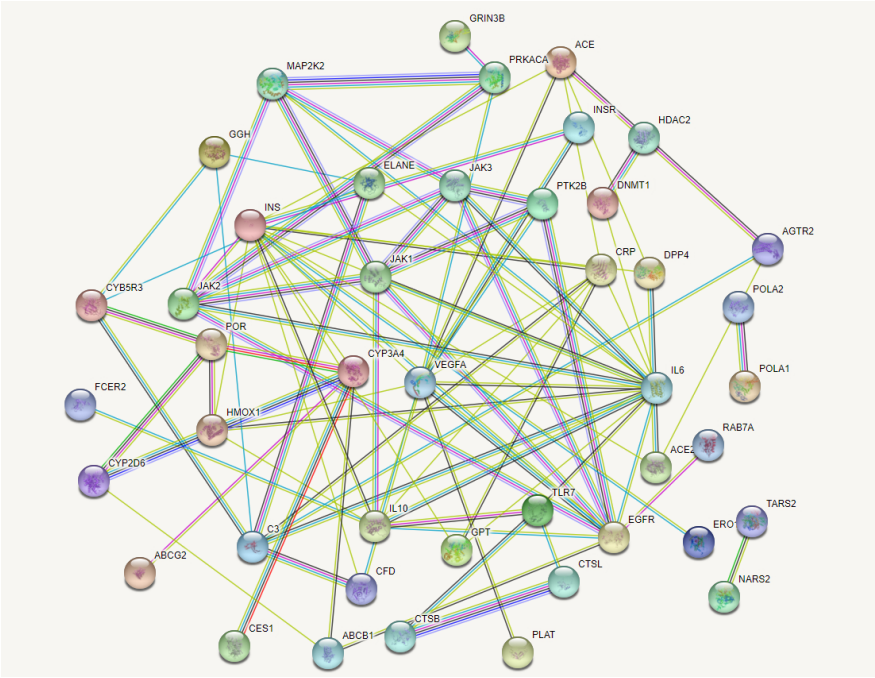
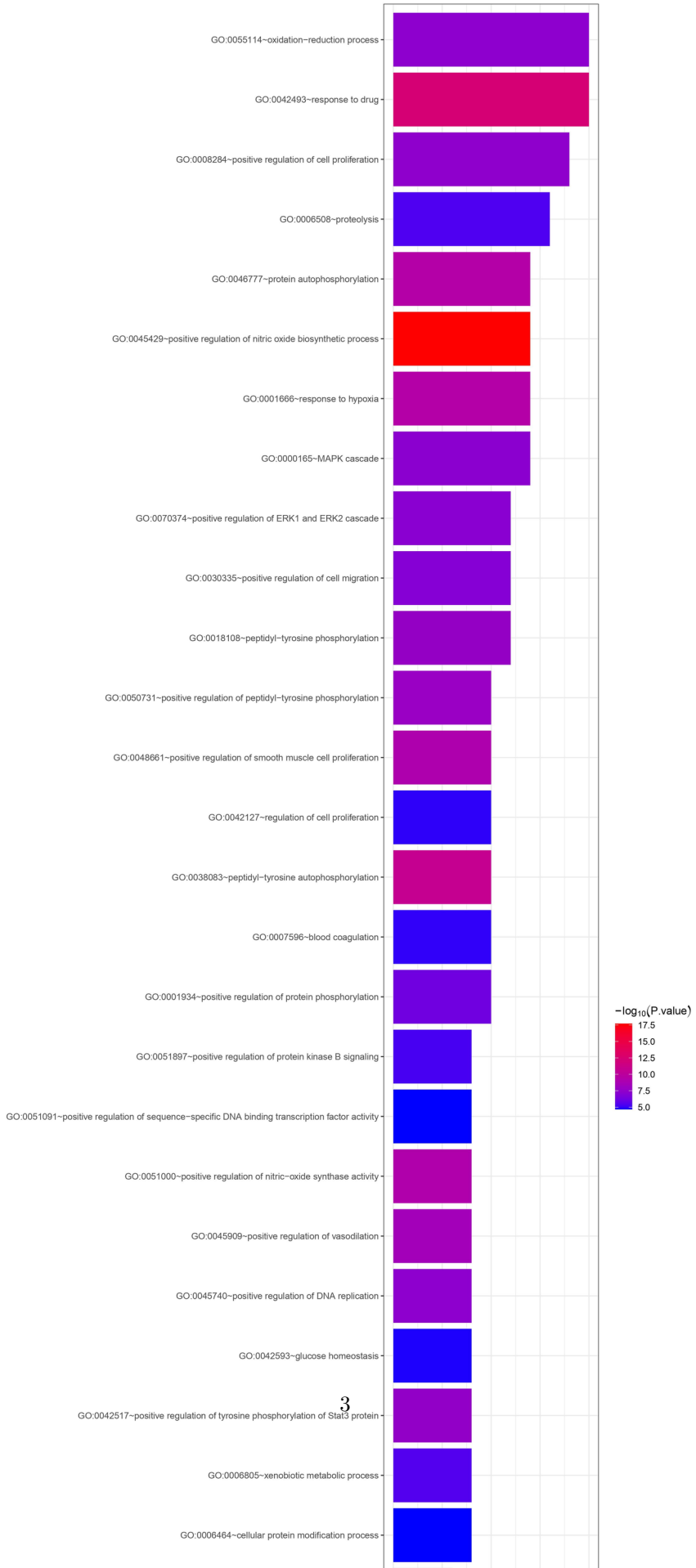
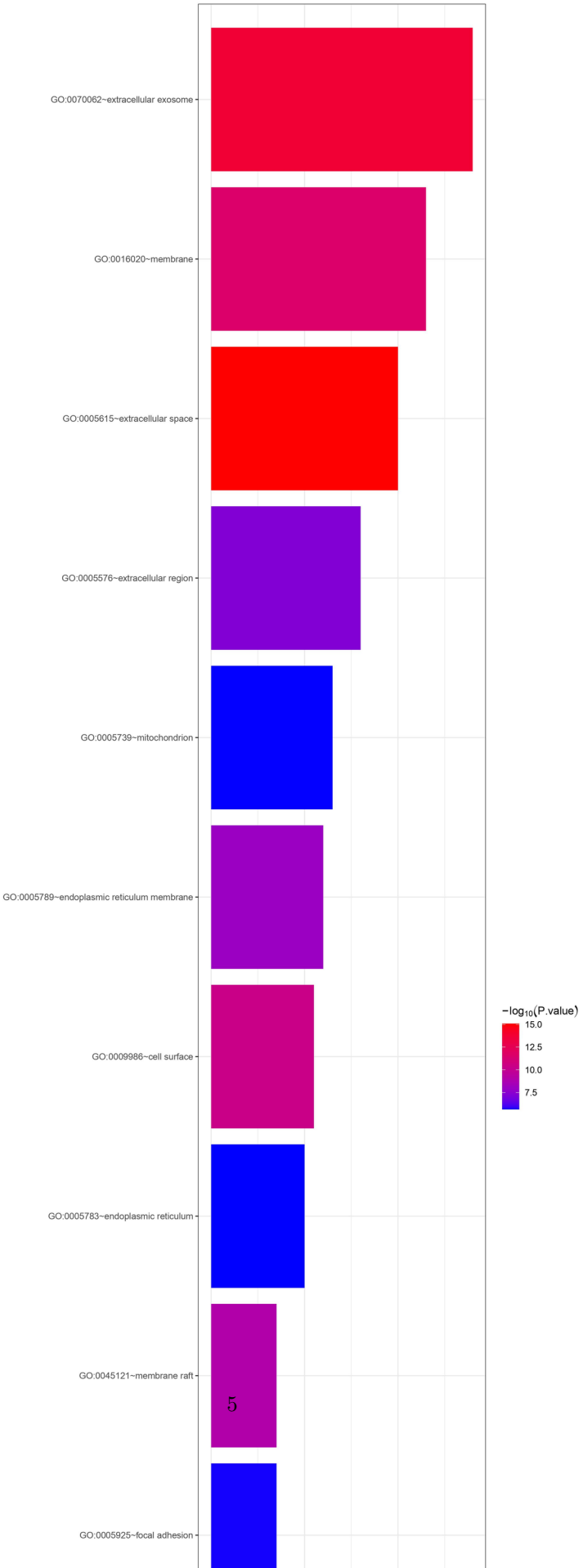
**Abstract**

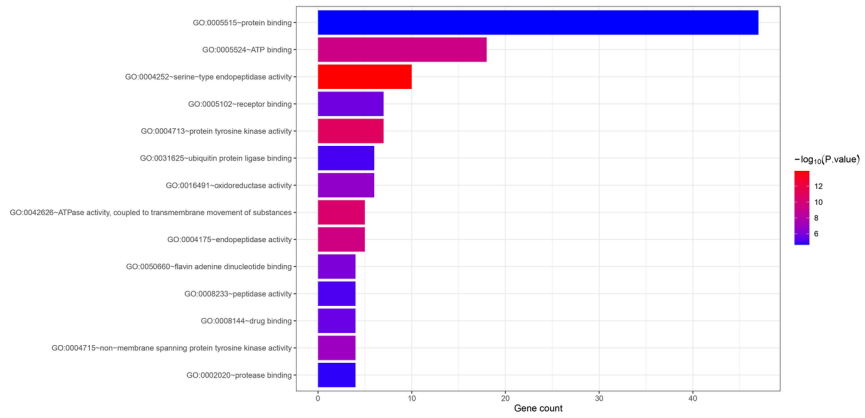
Background Using network pharmacology,systematicly reveals the Mechanisms of Radix Isatidis in the therapy of coronavirus disease 2019 (COVID-2019). Methods The active components and targets of Radix Isatidis were obtained by searching the Batman, TCMSP, and SwissTargetPrediction databases, and COVID-19 related targets were searched through Genecards, Drugbank, and Malacards database. After that, we used String database to establish protein-protein interaction, using David database to conduct enrichment analysis of gene ontology and pathway enrichment analysis based on the Kyoto encyclopedia of genes and genomes. The molecular docking was performed using ChemOffice, PyMOL, and Auto Dock software. Result A total of 73 active ingredients and 1584 related gene targets of Radix Isatidis were screened from kinds of databases while 559 gene targets of COVID-19 were picked out. Among them, there are 70 of the same targets. According to the GO enrichment analysis(P[?]0.01), 35 of them belong to biological process, 13 of them belong to cell component, and 14 of them belong to molecular function. And for KEGG analysis, 22 pathways were obtained(P[?]0.01), including PI3K - Akt signaling pathway andHIF - 1 signaling pathway. Conclusions Radix Isatidis may act on the PI3K - Akt signaling pathway and HIF-1 signaling pathway Through direct or indirect regulation of the above goals and ways to play role in the therapy of COVID-19

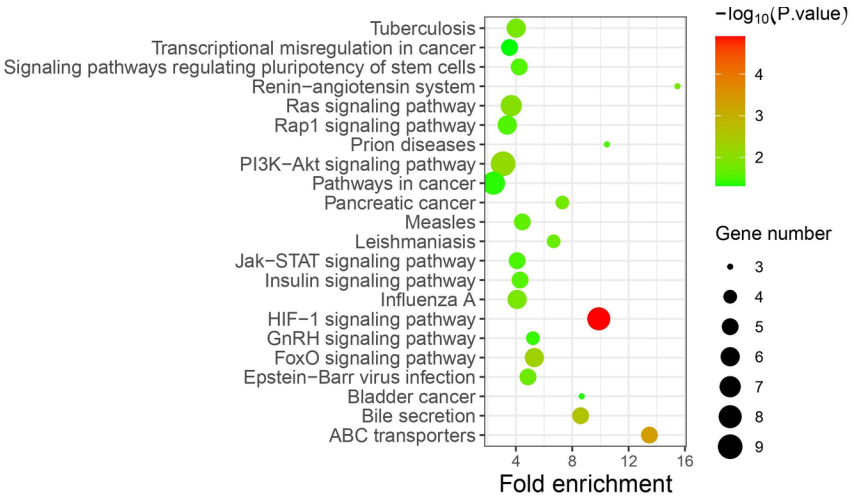


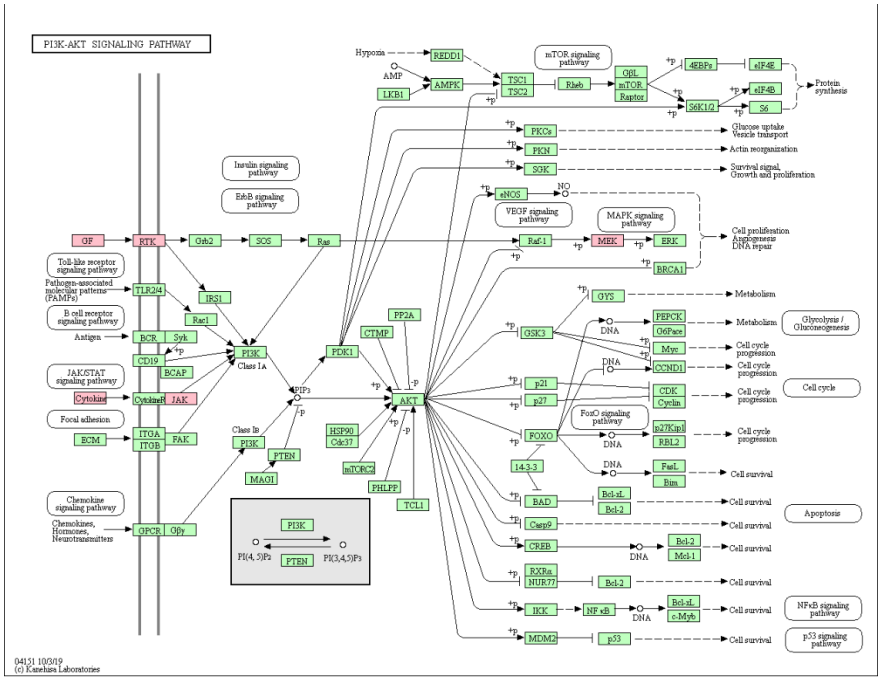



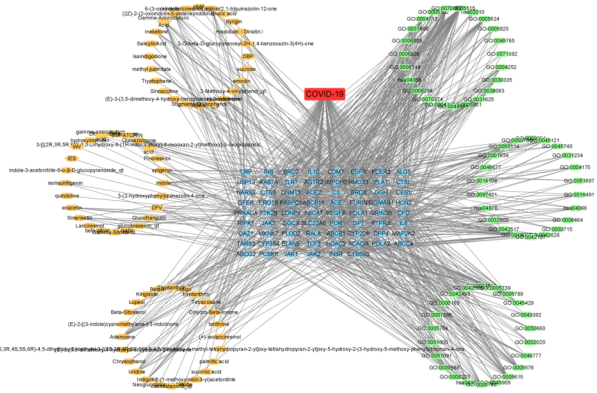


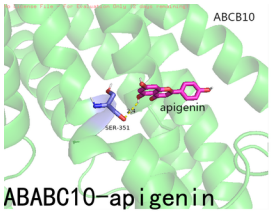




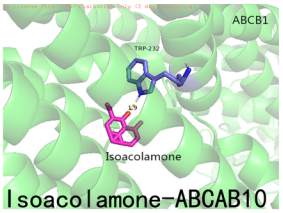








ABABC10-apigenin

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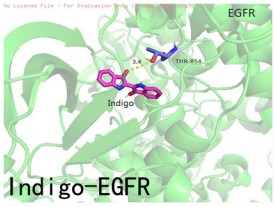


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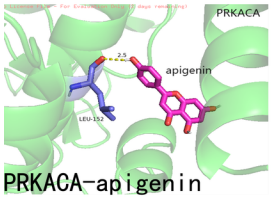


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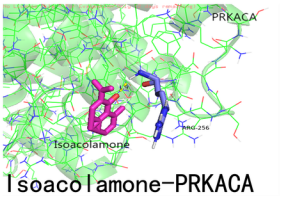


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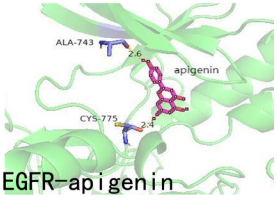


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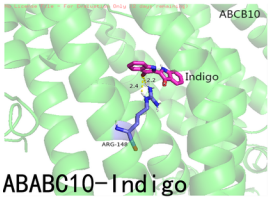


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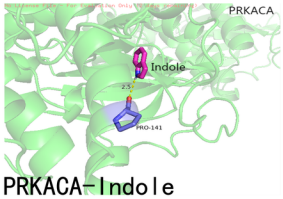
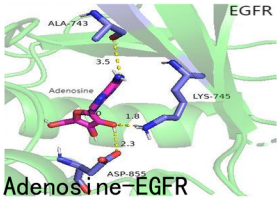



PRKACA-Indole

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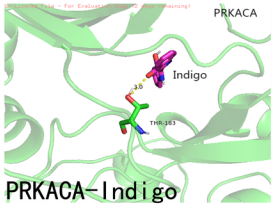


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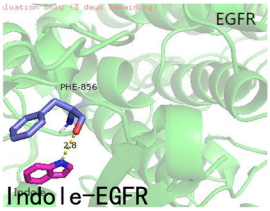


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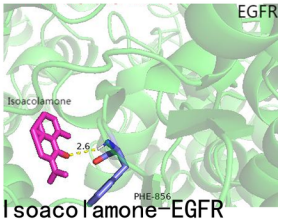


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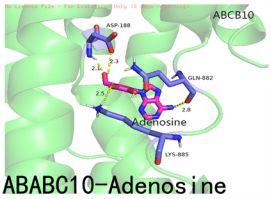
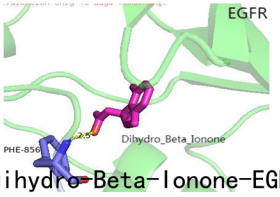
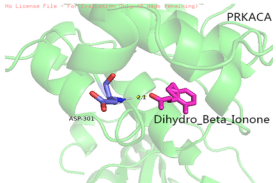


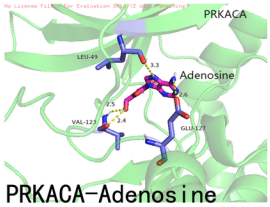

ABABC10-Adenosine



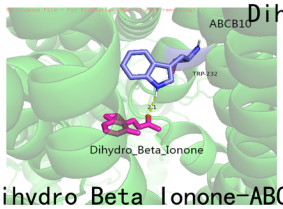

Dihydro-Beta-Ionone-EGFR




Dihydro_Beta_Ionone-PRKACA




PRKACA-Adenosine




Dihydro_Beta_Ionone-ABCAB10

| Molecule ID | Name | Molecular Formula | Molecular Weight | CAS | Binding protein | Binding energy/(kJ/mol) |
|---|---|---|---|---|---|---|
| MOL000008 | apigenin | C15H1005 | 270.24 | 520-36-5 | PRKACA | -6.5 |
| | | | | | ABCB1 | -5.49 |
| | | | | | EGFR | -7.12 |
| MOL001781 | indigo | C16H10N202 | 262.26 | 68651-46-7 | PRKACA | -6.84 |
| | | | | | ABCB1 | -6.71 |
| | | | | | EGFR | -8.12 |
| MOL011099 | adenosine | C10H13N504 | 267.24 | 58-61-7 | PRKACA | -3.2 |
| | | | | | ABCB1 | -3.28 |
| | | | | | EGFR | -4.27 |
| MOL001775 | isoacolamone | C15H240 | 220.35 | 39012-15-2 | PRKACA | -7.41 |
| | | | | | ABCB1 | -7.12 |
| | | | | | EGFR | -8.6 |
| MOL001773 | indole | C8H7N | 117.15 | 120-72-9 | PRKACA | -5.12 |
| | | | | | ABCB1 | N/A |
| | | | | | EGFR | -5.4 |
| MOL001772 | dihydro-beta-ionone | C13H220 | 194.31 | 17283-81-7 | PRKACA | -5.99 |
| | | | | | ABCB1 | -5.63 |
| | | | | | EGFR | -7.05 |

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## Abstract

### Background

Using network pharmacology，systematicly reveal the Mechanisms of Radix Isatidis in the therapy of coronavirus disease 2019 （COVID-2019）.

### Methods

The active components and targets of Radix Isatidis were obtained by searching the Batman, TCMSP, and SwissTargetPrediction databases, and COVID-19 related targets were searched through Genecards, Drugbank, and Malacards database. After that, we used String database to establish protein-protein interaction, using David database to conduct enrichment analysis of gene ontology and pathway enrichment analysis based on the Kyoto encyclopedia of genes and genomes. The molecular docking was performed using ChemOffice, PyMOL, and Auto Dock software.

### Result

A total of 73 active ingredients and 1584 related gene targets of Radix Isatidis were screened from kinds of databases while 559 gene targets of COVID-19 were picked out. Among them, there are 70 of the same targets. According to the GO enrichment analysis(P≤0.01), 35 of them belong to biological process, 13 of them belong to cell component, and 14 of them belong to molecular function. And for KEGG analysis, 22 pathways were obtained(P≤0.01), including PI3K − Akt signaling pathway andHIF − 1 signaling pathway.

## Conclusions

Radix Isatidis may act on the PI3K − Akt signaling pathway and HIF−1 signaling pathway Through direct or indirect regulation of the above goals and ways to play role in the therapy of COVID-19

**Keywords**: SARS-CoV-2; COVID-19; network pharmacology; molecular docking; Radix Isatidis; Target spot

# Introduction

An unfamiliar coronavirus, which can cause grim respiratory disease, has emerged out of Wuhan city of China in December 2019. Recently, the COVID-19 pandemic has resulted in the worst global crisis in public health. The novel coronavirus has been formally named "SARS-CoV-2", and at the same time, the disease-associated has been accordingly named coronavirus disease 2019 (COVID-19) by the World Health Organization[1]. After SARS-CoV-2 infection, the patients presented significant respiratory symptoms, it is usually manifested as cough, fever, and dyspnea, and draws out inflammatory reactions, particularly in the lungs, leading to pneumonia. Besides, for the responsive people, viruses are able to produce massive inflammatory reactions, recognized as "cytokine storm", bringing great difficulties to clinical treatment. [2]At present, there is no effective drug for COVID-19, and it will take a certain time to develop an effective SARS-CoV-2 vaccine.[3]

At present, the epidemic of COVID-19 has broken out in many countries around the world. How to form a rapid and effective epidemic prevention and control program is a major problem. However, the drugs currently used for the treatment of diseases that originated from SARS-CoV-2 cannot completely cure the etiology radically[4-5], and there is evidence that many patients will have sequelae[6]. Traditional Chinese medicine is used for disease intervention and the cure of patients with sequelae, which may be an effective method for virus-related sequelae. Based on comparison with western medicine, traditional Chinese medicine is endowed with the characteristics of dialectical treatment entirely, and the efficacy is mild, which helps the patients recover better. According to the prevention prescriptions of various provinces and municipalities issued by the People's Republic of China, the Administration of Traditional Chinese Medicine (SATCHM), as well as the hospitals practicing TCM, it is found that the core drugs' efficacy is mainly to tonify and clear heat. Radix isatidis is a kind of heat-clearing and detoxifying drug which has similar efficacy as the core drug[7], also, China's provinces and cities often use methods of

adding drugs based on the core drug when preventing and treating COVID-19[8-9].
Studies have shown that Radix Isatidis has the pharmacological effect of anti-influenza virus[10] However, its mechanism is not clear, so it is necessary to conduct an in-depth study.
In the past, the investigation into the mechanism of the reaction of traditional Chinese medicine mostly used animal experiments, cell experiments, and other methods to study a certain mechanism of action, so it is difficult to obtain the overall appearance of the network of the workings of action of the time-honored Chinese medicine.[11]
Network pharmacology is recognized as the amalgamation of bioinformatics and multidirectional pharmacology. [12]It is a comprehensive research method that can reflect the interaction between multiple components and numerous targets of traditional Chinese medicine.[13] It is consistent with the holistic notion of traditional Chinese medicine and the basic principle of treatment according to syndrome differentiation. This study intends to analyze the network pharmacology of Radix Isatidis, explore the antiviral mechanism of active ingredients of COVID-19, and offer a theoretical foundation for further exploring some material basis of its antiviral effect.

# Materials and Methods

## *Chemical Compounds in Radix Isatidis*

Traditional Chinese Medicine（TCM）is a complicated platform consisting of many components，therefore not all components can enter the body to exert their action. Considering the prediction of the drug property in vivo, we screened the major active compounds of this herb through Traditional Chinese Medicine Systems Pharmacology Database(TCMSP, https://tcmspw.com/) on the basis of two pharmacokinetic parameters: ALogP<5 and drug-likeness (DL) ⩾ 0.18. [14] At the same time in batman-tcm（ http://bionet.ncpsb.org/batman-tcm ）database, major components of Radix Isatidis were screened with screening conditions set as score cut-off= 20 and Adjusted P_value cut-off= 0.05.[15]

## *Compound Targets for Radix Isatidis*

Tcmsp database was searched to obtain the target of the predicted active molecules of Radix Isatidis. In addition, the corresponding target genes were obtained through UniProt (http: / / www.uniprot. Org /) and UniProtKB database in UniProt, with the search formula of "organization:" homo sapiens "and reviewed: Yes". The active components of Yupingfeng powder were screened from PubChem, and the corresponding smile number was found, which was saved as an SDF file and uploaded to SwissTargetPrediction database （ http://www. swisstargetprediction.ch/ ）. [16] Based on the principle of reverse molecular docking, target prediction was carried out according to the 2D / 3D structure of components, and the predicted target of Radix Isatidis was obtained. Besides, when we screened the active components of Radix Isatidis in batman-tcm database, we not

only got the active ingredients, but also the corresponding genes.[17]

***COVID-2019 potential targets***

To gather disease-related targets, we used three key websites,GeneCards （ http://www.genecards.org/ ） 、 DrugBank （ http://www.drugbank.ca/)[18] 、 MalaCards（http://www.malacards.org/) with key words'COVID-19' or'Sars-Cov2'

## *Common targets of Radix Isatidis and COVID-19*

The corresponding genes of the active ingredient of Radix Isatidis selected in "2.2" and the COVID-19 potential targets selected in "1.2" were uploaded to the online Venn diagram (http://bioinfogp.cnb.csic.es/tools/ venny/ index.html) to match and draw a common target Venn diagram.

## *The protein-protein interaction network data*

The common targets of Radix Isatidis and COVID-19 were imported into Search Tool for the Retrieval of Interacting Genes database (String,https://string-db.org/) with the species set as "Homo sapiens", aiming to obtain all protein-protein interaction (PPI) interaction to construct Protein-protein interaction networks (PPI).[19]

## *Functions and pathway enrichment analysis*

To perform KEGG pathway and GO analysis, we input key targets into David （ https://david. ncifcrf.gov/ ） and "Homo sapiens" were selected as species. The key targets were analyzed by go bioaccumulation and KEGG metabolic pathway

## *Ingredient-Target & Function-Pathway Network construction and Hub gene extraction*

We used the data obtained from DAVID database to analyze the pharmacological mechanisms. First, genes related to the pathways were collated. After sequencing was done on category, we set a limit as 'P-value ≤0.01' and we got the pathways and pathway-related genes. Next, the main active components-target and target-pathway were sorted out. Finally, Cytoscape software was used to visualize the Ingredient-Target & Function-Pathway network and analyze it from a perspective of topology. The double median of node degree is selected as the screening criteria, and the median of "Betweenness" and "closeness" is used as the screening basis to extract the hub network.[20]

## *Molecular docking*

The PDB format file of 3D structure of the target is downloaded from RCSB PDB （ https://www.rcsb.org/ ）. The protein was dehydrated and hydrogenated by PyMOL software. Finally, molecular docking was conducting using auto dock software.[21]

# Result

## *Common targets of Radix Isatidis and COVID-19*

Through TCMSP and Batman-TCM database, 73 kinds of effective components of Radix Isatidis were obtained by specific screening conditions. Besides, through the approach of reverse docking in SwissTargetPrediction database and the method of obtaining directly in Batman-TCM database, 1584 related targets were collected. Meanwhile, Genecards, Drugbank, and Malacards database were used to search for potential targets related to COVID-19. Finally, 559 relevant targets of COVID-19 were screened after deleting duplicate values. Among the targets of both, 70 targets have been shared(Fig.1).

## *Construction of PPI network with common targets*

To analyze protein–protein interactions and visualize them, a total of 70 target genes were imported into the STRING database. In the construction of the PPI network, we set a limit as 'minimum required interaction score $\geqslant$ 0.7' to ensure the obtained interaction was high-confidence. Afterward, we acquired the PPI network with 70 notes, 92edges, and an average node degree of 2.63, which means the network has significantly more interactions. (Fig 2)

## *GO Enrichment Analysis*

To elucidate the function of Radix Isatidis in various biological processes, GO analysis was conducted for 70 targets. GO analysis consists of three parts, including biological process (BP), cell component (CC), and molecular function (MF). The pathway value was limited to P $\leqslant$ 0.01 and a total of 62 pathways were obtained, among that 35 of them belong to biological process(Fig.3a), 13 of them belong to cell component(Fig.3b), and 14 of them belong to molecular function(Fig.3c). Being ordered by the gene count, the enriched BP ontologies were dominated by oxidation–reduction process, response to drug and positive regulation of cell proliferation, the enriched CC ontologies were dominated by extracellular exosome, membrane and extracellular space, The enriched MF ontologies were dominated by protein binding, ATP binding and serine–type endopeptidase activity.

## *KEGG Enrichment Analysis*

To analyze revealed several enriched pathways, KEGG analysis was conducted based on 70 common gene targets. After the P value was set to Less than or equal to 0.01, 22 pathways were obtained. They were mainly involved in ABC transporters(hsa02010), Bile secretion(hsa04976), FoxO signaling pathway(hsa04068), GnRH signaling pathway, HIF－1 signaling pathway(hsa04066), and PI3K－Akt signaling pathway(hsa04151). The specific details are listed in Fig.4. Among them, P13K-AKT signaling pathway has the most gene numbers, which were considered as a fundamental pathway, and HIF–1 signaling pathway gains the highest P-value. For further analysis, the specific pathway of P13K-AKT signaling pathway, including identified targets were displayed in Fig.5.

## *Establishment of Ingredient-Target & Function-Pathway Network and*

### *Hub gene extraction*

The main active components-target and target-pathway were imported into Cytoscape software and an Ingredient-Target & Function-Pathway Network with 210 notes and 823 edges were obtained. (Fig.6) The targets with a high degree, betweenness, and closeness were chosen as the hub genes, which are ABCB1, PRKACA, and EGFR. Besides, the main active compounds were analyzed by using the same method.

### *Analysis of molecular docking results*

First, we chose the most active genes, PRKACA, ABCB1, and EGFR, of COVID-19 from PPI analysis as the receptor and the top six active compounds, which is apigenin, indigo, adenosine, isoacolamone, indole, and dihydro_beta_iononecompounds, of Radix Isatidis from "hub gene extraction" as the ligand. After conducting the molecular docking between the receptor and compounds, we obtain the binding energy of molecular docking. According to the identified studies, when the ligand binds to the receptor, the lower the energy is, the more stable the conformation is, which brings more possibilities to interact between them, and it is considered that a binding affinity with less than −5kcal/mol indicates that these compounds possess the good binding capacity to these target proteins. Commonly, the binding between the ligand and receptor has more than one binding method which means we would obtain various b According to relevant literatures, we would first pay attention to the binding energy and choose the highest. If there is no hydrogen bond for this bond, we would select the next one in descending order until there is a hydrogen bond. The specific data is listed in Table.1. The visualization results are shown in Figure 5.

## Discussion

Since modern times, traditional Chinese medicine has played a significant part in the prevention and control of Japanese encephalitis, SARS, H1N1 influenza, and other major epidemics. It has verified and established a series of effective diagnosis and treatment programs, which are still in use today [22]. In the case of relative lag in vaccine development and lack of specific drugs, traditional Chinese medicine has gradually changed from a participant in the past epidemic prevention and control to the main force of epidemic treatment. [23] COVID-19 has belonged to the sort of "epidemic disease" in traditional Chinese medicine, and its etiology is mainly attributed to "dampness or dampness heat evil", and its core pathogenesis is concentrated in syndrome elements such as "cold, dampness, heat, blood stasis, closure and deficiency" [24] Radix Isatidis tastes bitter and cold, can clear away heat and detoxify cool blood and throat, and has the effect of treating pestilence toxin, so it can play the role of detoxification against COVID-19 [25].

In this research, the network pharmacology and molecular docking methods were used to detect the potential active components in Radix Isatidis, and the core components and targets were obtained by topological analysis of the network. The core components and targets were connected to detect the probable mechanism of

action. Analyzing the PPI network, three active targets were mainly involved in cell proliferation. A catalytic subunit of protein kinase A is encoded by the PREAKA gene, which exists as a tetrameric holoenzyme in its inactive form with two regulatory subunits and two catalytic subunits. The inactive holase dissociated into a regulatory subunit dimer under the action of cAMP, which can bound to four cAMP and two free monomeric catalytic subunits. cAMP-dependent phosphorylation of proteins by PKA is significant to numerous cellular processes, including differentiation, proliferation, and apoptosis. As a member of the epidermal growth factor receptor family, signal transduction of EGFR is closely related to cell survival, proliferation, and differentiation. Studies have shown that EGFR overexpression exists in non-small cell lung cancer [33], and cell apoptosis is inhibited. In addition, after SARS CoV infection, the host over response to lung injury mediated by EGFR signal can induce pulmonary fibrosis symptoms [34]. This suggests that inhibition of EGFR signaling can be used as one of the ideas for diagnosing and treating COVID-19.

Go enrichment analysis results mainly include protein binding, ATP binding, protein tyrosine kinase activity, oxidoreductase activity, ATPase activity, coupled to transmembrane movement of substances, oxidation-reduction process, protein analysis, MAPK cascade, response to hypoxia, etc. It was showed by KEGG pathway enrichment analysis that HIF − 1 signaling pathway and PI3K − Akt signaling pathway played a key role. Further analysis shows that the target can affect ATP binding by affecting ATPase activity, and redox reaction by affecting oxidoreductase activity, especially in hypoxia. HIF-1 signaling pathway is very important in the body's response to hypoxia concentration or hypoxia. The protein encoded by HIF-1 target gene can enhance O2 supply and mediate adaptive response to O2 depletion. Moreover, studies have shown that reactive oxygen species can lead to the activation of HIF-1 α, and a large number of reactive oxygen species are produced during HIV replication, indicating that HIF-1 signaling pathway plays a significant role in RNA virus replication [24,25]. PI3K − Akt signaling pathway has participated in cell proliferation, which requires a large amount of ATP and redox reaction. ATPase related to substance transmembrane exchange may affect the intracellular and extracellular concentration difference by affecting the sodium-potassium exchange pump, thus affecting the intracellular glucose utilization. The activation of PI3K − Akt signaling pathway requires many growth factors. The specific mechanism is as follows: growth factors and their tyrosine kinase receptors help to activate signaling pathways. This pathway can be activated by regulating protein tyrosine kinase activity. By regulating MAPK cascade can not only regulate MAPK signaling pathway, which is an essential pathway in the inflammatory response but also participate in cell proliferation of PI3K − Akt signaling pathway. Therefore, Radix Isatidis can accomplish the intention of treating COVID-19 by regulating hypoxic response, reducing inflammation, and participating in cell recovery after injury.

According to the result of molecular docking, most bindings have a good binding affinity.

## Conclusions

Comprehensive analysis, Radix Isatidis may act on the PI3K − Akt signaling pathway and HIF−1 signaling pathway Through direct or indirect regulation of the above goals and ways to play role in the treatment of COVID-19.

## Tables' and Figures' Legends

Table 1.Binding energies of core compound molecules in Radix Isatidis.
Figure 1. Venny diagram of Radix Isatidis and COVID-19
Figure 2 Protein-protein interaction (PPI) network of Radix Isatidis and COVID-19. The connection between nodes represents the interaction between two proteins, and different colors represent different types of interaction
Figure 3.
a Column chart of BP from GO functional enrichment analysis. Colors reflect P value.
b Column chart of CC from GO functional enrichment analysis. Colors reflect P value.
c Column chart of MF from GO functional enrichment analysis. Colors reflect P value.
Figure 4.Bubble chart of top 22 signaling pathways. Bubble size represented gene number and colors reflect P value.
Figure 5.Detailed signaling pathway of PI3K − Akt Targets identified from the 70 common targets were highlighted in red.
Figure 6.Network of Ingredient-Target & Function-Pathway
Figure 7.Molecular docking diagram of PRKACA, ABCB1, and EGFR with core compounds of Radix Isatidis.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Author Contribution*

Xu-Guang Guo conceived and designed the experiments. Zi-Yuan Yu, Sheng-Chen Hu, Bo-Yuan Chen, Dong-Mei Liao and Zheng-Yi Zhou analyzed the data and made the tables. Zi-Yuan Yu, Sheng-Chen Hu, Bo-Yuan Chen, Dong-Mei Liao and Zheng-Yi Zhou participated in the writing, reading, and revising of the manuscript and approved the final version of the manuscript.

### *Competing Interests*

The authors declare that there are no competing interests associated with the

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