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Pharmacology Discovery 2024;4(1):3. https://doi.org/10.53388/PD202404003

The basic core traditional Chinese medicine for the prevention and treatment of COVID-19 and its active mechanisms

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Author contributions
Zhe Xu and Hui-Fang Zhou designed the study, collected the data and wrote the manuscript. Zi-Xin Li, Zi-Yao Geng and Rong-Li Shu collected and analyzed the data. Hui-Fang Zhou and Yu-Hong Bian drafted the manuscript. Yu-Hong Bian provided guidance and funding support. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This work was supported by the National Key R & D Program of China (2018YFC1706506 and 2021YFE0200300) and the Tianjin Municipal Education Commission Science and Technology Plan Project (2021KJ137).

Peer review information
Pharmacology Discovery thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations
CNIPA, China National Intellectual Property Administration; TCM, traditional Chinese medicines; BC-TCM, basic core traditional Chinese medicines; OB, oral bioavailability; DL, drug-like index; BP, biological process; CC, cellular component; MF, molecular function.

Citation
Xu Z, Li ZX, Geng ZY, Shu RL, Zhou HF, Bian YH. The basic core traditional chinese medicine for the prevention and treatment of COVID-19 and its active mechanisms. *Pharmacol Discov.* 2024;4(1):3. doi: 10.53388/PD202404003.

Executive editor: Ting Yu.
Received: 22 August 2023; **Accepted:** 01 March 2024; **Available online:** 05 March 2024.

Abstract
Background: COVID-19 has had a dramatic impact on human health, economies, societies, and livelihoods around the world. Traditional Chinese medicine (TCM) formulae have played an important role in the prevention and treatment of COVID-19. WHO evaluated the role of TCM in treating of COVID-19 and encouraged other countries to promote the use of TCM formulae. However, the key is to find the basic core traditional Chinese medicine (BC-TCM) among those formulae. **Methods:** For the first time, we mined the data of TCM formulae in CNIPA and analyzed herb characteristics and association rules. We then determined the BC-TCM and screened main compounds and therapeutic targets. Finally, the potential molecular mechanisms were explored by using enrichment analyses and molecular docking. **Results:** This study screened 123 patented TCM formulae, including 312 herbs. According to frequency statistics and association rules, nine herbs (Gan Cao, Jin Yinhua, Guang Huoxiang, Fu Ling, Huang Qi, Jie Geng, Lian Qiao, Cang Zhu, Ku Xingren) were selected as the BC-TCM. The BC-TCM involved 166 main compounds and 48 therapeutic targets. The active compounds Hederagenin, Spinasterol, Beta-sitosterol, and Liquiritin had high binding activity to the COVID-19 targets 3CL, ACE2, and core targets RELA, HSP90AA1, STAT3, MAPK3, and TP53 according to molecular docking results. Interestingly, Hederagenin might be a potential compound for the prevention and treatment of COVID-19. **Conclusion:** Our research predicted and confirmed the preventive therapeutic effect of BC-TCM on COVID-19. This has the potential to broaden the scope of TCM, guide people in using clinical formulae, and provide valuable insights for future TCM discovery research.

Keywords: COVID-19; traditional Chinese medicine; China national intellectual property administration; data mining; network pharmacology

Introduction

COVID-19 is an emerging acute respiratory infection that is now a major global public health event [1]. Since its outbreak in December 2019, COVID-19 has had a dramatic impact on human health, economies, societies, and livelihoods worldwide. SARS-CoV-2 invades cells in various organs of the body mainly by binding the surface stinger protein S to the ACE-2. Infection can lead to multi-system diseases such as respiratory, liver, neurological, and gastrointestinal problems [2–6].

Last year, the WHO assessed TCM's usefulness in treating COVID-19 and encouraged other countries to boost the usage of TCM formulae. Several clinical practice experiences in provinces and cities in China have also shown that TCM formulae have an essential role in the prevention and treatment of COVID-19 [7–9]. Numerous TCM formulae such as *Xuanfei Baidu* Decoction and *Fu-zheng-jiu-fei* have been proven in studies to be effective against COVID-19 and have been granted national patents [10–12].

Therefore, it is imperative to apply modern research methods to investigate patented formulae and search for basic core traditional Chinese medicine (BC-TCM). Our study first mined the data of TCM formulae for COVID-19 in CNIPA, analyzed herb characteristics and association rules, determined the BC-TCM, then applied network pharmacology and molecular docking methods, and screened the main compounds and therapeutic targets. We explored and elaborated on the underlying molecular mechanisms of BC-TCM and provided references for clinical extension. Figure 1 depicts the whole research concept.

Materials and methods

Data availability

The datasets used for the current study are available from the corresponding author upon request.

Tcm formulae data sources

The website of "State Intellectual Property Office-CNIPA" was used, entering "Advanced Search" and checking both "Invention Publication" and "Invention Grant". The search was carried out by entering "COVID-19 AND Traditional Chinese Medicine", "SARS-CoV-2 AND Traditional Chinese Medicine" and "Pneumonia AND Traditional Chinese Medicine" as "name" items, and the results were aggregated and filtered to generate the final data. The search period spanned from the database's inception until May 7, 2023.

Inclusion of TCM formulae and data standardization

The patents for all TCM formulas and TCM extracts were included. Patents with the same composition but various dosages might be included repeatedly, and patents with the same composition and dosage only once. Patents for external usage and non-TCM medical products were excluded. The COVID-19 TCM formulae patent database was established, and the results were itemized. In the *2020 edition of Chinese Pharmacopoeia* and *Chinese Materia Medica*, the names were standardized based on herb names. The *Chinese Pharmacopoeia* was used to standardize herb efficacy categories.

Data association rules

The IBM SPSS Modeler 18.0 software was utilized to examine the association rules based on the Apriori algorithm for the included TCM formulae, setting the herb pairs that simultaneously met support ≥ 0.5, confidence ≥ 0.5, and lift ≥ 1 as the core herbs for COVID-19 [13].

Mining the main compounds and targets of BC-TCM

The main compounds of the BC-TCM were mined through the TCMSP and screened by setting the OB at ≥ 30% and the BL at ≥ 0.18 [14]. In addition, the reported compounds of BC-TCM were compiled by reviewing the literature. The target names were standardized using the Uniprot database [15].

Screening potential targets of COVID-19

The keywords "Corona Virus Disease", "COVID-19", "SARS-CoV-2", and "2019-nCoV" were searched in the GeneCards and UniProt database [16].

Construction of the PPI network and screening therapeutic targets

By comparing the targets of BC-TCM with the potential targets of COVID-19, duplicated targets were screened. To construct PPI network, the String Version 11.5 platform was imported with the duplicate targets [17]. High confidence intervals with scores > 0.9 were selected from String and the therapeutic targets were screened out according to the degree [17].

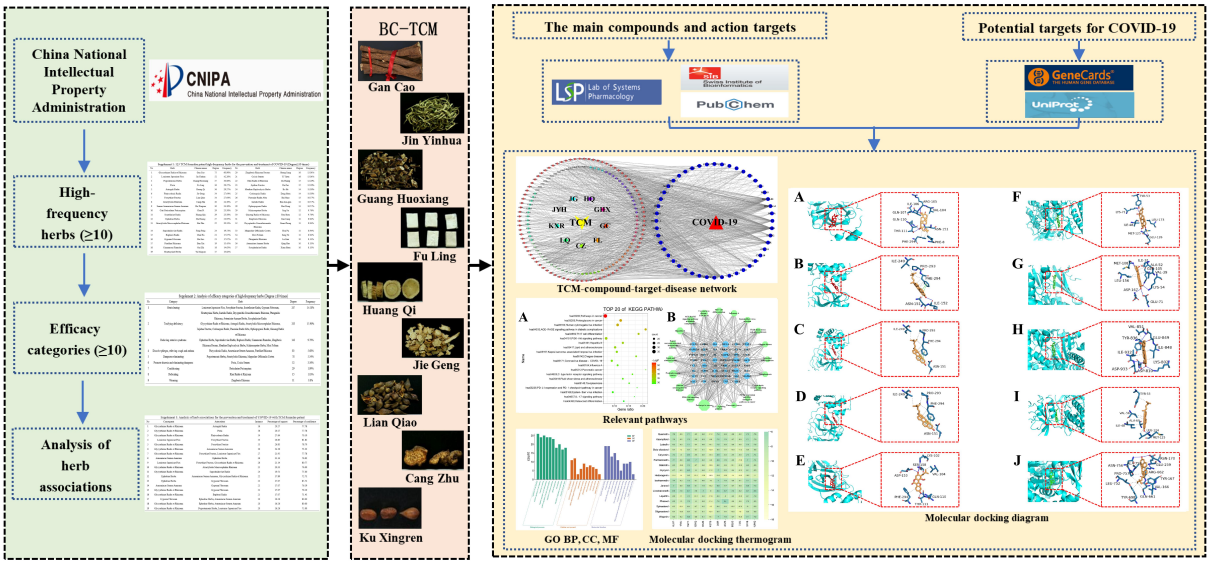

Figure 1 The whole research concept. CNIPA, China national intellectual property administration; TCM, traditional Chinese medicines; BC-TCM, basic core traditional Chinese medicines; Gan Cao, GC, *Glycyrrhizae Radix et Rhizoma*; Jin Yinhua, JYH, *Lonicerae Japonicae Flos*; Guang Huoxiang, GHX, *Herba pogostemonis*; Fu Ling, FL, *Poria*; Huang Qi, HQ, *Radix astragali*; Jie Geng, JG, *Radix platycodonis*; Lian Qiao, LQ, *Fructus forsythia*; Cang Zhu, CZ, *Rhizoma atractylodis*; KuXingren, KXR, *Semen armeniacae amarum*; BP, biological process; CC, cellular component; MF, molecular function.

Construction of the TCM-compound-target-disease network

The BC-TCM, main compounds, therapeutic targets, and disease were imported into Cytoscape 3.8.0 software to construct the TCM-compound-target-disease networks [18].

Analysis of KEGG pathway and GO function enrichment

By entering the therapeutic targets into the Metascape platform, a comprehensive analysis was carried out to further investigate the role of BC-TCM [19]. Using the bioinformatics online service, the top 20 results of enrichment were represented as bubble plots [20]. Cytoscape software was used to map the key pathway-target information network [18].

Validation of molecular docking

The active compounds of BC-TCM with more targets, such as Quercetin, Kaempferol, Luteolin, Beta-sitosterol, Calycosin, Formononetin, Glabridin, Glycyrol, Hederagenin, Isorhamnetin, Jaranol, LicochalconeB, Liquiritin, Phaseol, Spinasterol, Stigmasterol, and Wogonin, were chosen for initial molecular docking validation with core targets. The Autodock vina1.1.2 software was used to calculate molecular docking binding energy using the Config file [21–23]. Additionally, PLIP Web conducted a visual analysis [24].

Results

Analysis of patent search

By retrieving the national patent database, 286 patents were obtained and, after removing the same elements, 123 patents were included. With 123 patents including 312 plants, a total frequency of pharmaceutical usage of 1460 times, the largest number of formulas contained in the Chinese herb was 37, and the least number was 2. Additionally, 37 herbs were used ten or more times, making up 56.23% of all pharmaceutical usage (Table 1). Gan Cao (*Glycyrrhizae Radix et Rhizoma*), Jin Yinhua (*Lonicerae Japonicae Flos*), Guang Huoxiang (*Herba pogostemonis*), Fu Ling (*Poria*), Huang Qi (*Radix astragali*), Jie Geng (*Radix platycodonis*), Lian Qiao (*Fructus Forsythia*), Cang Zhu (*Rhizoma atractylodis*), Ku Xingren (*Semen armeniacae amarum*), and Chen Pi were the top 10 herbs in terms of usage and frequency. Analyzing efficacy and category of herbs used more than 10 times, the top three categories in terms of frequency of use were utilized for heat-clearing herbs, tonifying deficiency herbs, and relieving exterior syndrome herbs, as shown in Supplementary Table 1. The therapeutic effects were, mostly, clearing away heat and dispelling pathogens, dissipating dampness and detoxification, strengthening immunity and removing pathogens, and dispelling filth and turbidity.

Table 1 123 TCM formulae patent high-frequency herbs (Degree ≥ 10 times)

No.	Herb	Chinese name	Degree	Frequency	No.	Herb	Chinese name	Degree	Frequency
1	*Glycyrrhizae Radix et Rhizoma*	Gan Cao	75	60.98%	20	*Zingiberis Rhizoma Recens*	Sheng Jiang	16	13.01%
2	*Lonicerae Japonicae Flos*	Jin Yinhua	52	42.28%	21	*Coicis Semen*	Yi Yiren	16	13.01%
3	*Pogostemonis Herba*	Guang Huoxiang	37	30.08%	22	*Rhei Radix et Rhizoma*	Da Huang	15	12.20%
4	*Poria*	Fu Ling	36	29.27%	23	*Jujubae Fructus*	Da Zao	15	12.20%
5	*Astragali Radix*	Huang Qi	36	29.27%	24	*Menthae Haplocalycis Herba*	Bo He	14	11.38%
6	*Platycodonis Radix*	Jie Geng	34	27.64%	25	*Codonopsis Radix*	Dang Shen	14	11.38%
7	*Forsythiae Fructus*	Lian Qiao	34	27.64%	26	*Paeoniae Radix Alba*	Bai Shao	13	10.57%
8	*Atractylodis Rhizoma*	Cang Zhu	30	24.39%	27	*Isatidis Radix*	Ban Langen	13	10.57%
9	*Semen Armeniacae Semen Amarum*	Ku Xingren	30	24.39%	28	*Ophiopogonis Radix*	Mai Dong	13	10.57%
10	*Citri Reticulatae Pericarpium*	Chen Pi	29	23.58%	29	*Schizonepetae Herba*	Jing Jie	12	9.76%
11	*Scutellariae Radix*	Huang Qin	29	23.58%	30	*Ginseng Radix et Rhizoma*	Ren Shen	12	9.76%
12	*Ephedrae Herba*	Ma Huang	27	21.95%	31	*Zingiberis Rhizoma*	Gan Jiang	11	8.94%
13	*Atractylodis Macrocephalae Rhizoma*	Bai Zhu	25	20.33%	32	*Dryopteridis Crassirhizomatis Rhizoma*	Guan Zhong	11	8.94%
14	*Saposhnikoviae Radix*	Fang Feng	24	19.51%	33	*Magnoliae Officinalis Cortex*	Hou Pu	11	8.94%
15	*Bupleuri Radix*	Chai Hu	21	17.07%	34	*Mori Folium*	Sang Ye	11	8.94%
16	*Gypsum Fibrosum*	Shi Gao	21	17.07%	35	*Phragmitis Rhizoma*	Lu Gen	10	8.13%
17	*Pinelliae Rhizoma*	Ban Xia	19	15.45%	36	*Artemisiae Annuae Herba*	Qing Hao	10	8.13%
18	*Cinnamomi Ramulus*	Gui Zhi	18	14.63%	37	*Scrophulariae Radix*	Xuan Shen	10	8.13%
19	*Houttuyniae Herba*	Yu Xingcao	17	13.82%					

Analysis of association rules

The association rules were analyzed by importing 37 herbs into IBM SPSS Modeler 18.0 software. Setting the maximum number of antecedents to 2, an analysis was performed. 154 association rules were obtained, and the number of examples ≥ 20 was selected for display (Table 2). The results showed that the highest support among the second-order association rules was for "Gan Cao-Huang Qi", with a support percentage of 29.27 and a confidence percentage of 77.78. The third-order was for "Gan Cao-Lian Qiao, Jin Yinhua".

Compounds and targets of BC-TCM

According to frequency statistics and association rules, nine herbs (Gan Cao, Jin Yinhua, Guang Huoxiang, Fu Ling, Huang Qi, Jie Geng, Lian Qiao, Cang Zhu, Ku Xingren) were selected as BC-TCM. Based on literature and results collected from the search and screening, 166 main compounds with 1020 related targets were obtained.

Potential targets for COVID-19

The GeneCards database search yielded 321 disease-related targets for Gene card Corona Virus Disease, 3329 for COVID-19, 2322 for SARS-CoV-2, and 36 for 2019-nCoV. 204 COVID-19 related targets were screened by UniProt. 3689 disease targets were found by aggregating and removing duplicate genes.

Construction of PPI network and screening of therapeutic targets

313 duplicate targets were discovered when 1020 BC-TCM targets and 3689 COVID-19 targets were intersected (Figure 2A). And 313 duplicate targets were imported into the STRING platform for PPI visualization (Figure 2B). The degree of freedom was used to determine the 48 therapeutic targets.

Construction of TCM-compound-target-disease network

Nine herbs, 166 main compounds, 48 therapeutic targets, and one COVID-19 disease information were integrated into Cytoscape 3.8.0 software to create the TCM-compound-target-disease network. The network involves 228 nodes and 1230 edges (Figure 3).

Analysis of KEGG pathway and GO function enrichment

184 KEGG pathways were obtained by introducing 48 therapeutic targets into the Metascape platform for KEGG pathway enrichment analysis. The top-ranked pathways comprise, mainly, Human cytomegalovirus infection, PI3K-Akt, Coronavirus disease-COVID-19, Influenza A, IL-17 signaling pathway, and so on. The top 20 pathways were displayed and the bubble diagram for enrichment analysis was shown in Figure 4A. The top 20 key pathways and 48 therapeutic targets were loaded into the Cytoscape software to map the key pathway-target information network. The network involves 67 nodes and 409 edges (Figure 4B).

Table 2 Analysis of herb associations

No.	Consequent	Antecedent	Instance	Percentage of support	Percentage of confidence
1	Gan Cao	Huang Qi	36	29.27	77.78
2	Gan Cao	Fu Ling	36	29.27	77.78
3	Gan Cao	Jie Geng	34	27.64	70.59
4	Jin Yinhua	Lian Qiao	33	26.83	81.82
5	Gan Cao	Lian Qiao	33	26.83	78.79
6	Gan Cao	Ku Xingren	30	24.39	73.33
7	Gan Cao	Lian Qiao, Jin Yinhua	27	21.95	77.78
8	Ku Xingren	Ma Huang	26	21.14	76.92
9	Jin Yinhua	Lian Qiao, Gan Cao	26	21.14	80.77
10	Gan Cao	Bai Zhu	25	20.33	76.00
11	Gan Cao	Fang Feng	24	19.51	75.00
12	Ma Huang	Ku Xingren, Gan Cao	22	17.89	72.73
13	Ma Huang	Shi Gao	21	17.07	85.71
14	Ku Xingren	Shi Gao	21	17.07	76.19
15	Gan Cao	Shi Gao	21	17.07	76.19
16	Gan Cao	Chai Hu	21	17.07	71.43
17	Shi Gao	Ma Huang, Ku Xingren	20	16.26	80.00
18	Gan Cao	Ma Huang, Ku Xingren	20	16.26	80.00
19	Gan Cao	Guang Huoxiang, Jin Yinhua	20	16.26	75.00

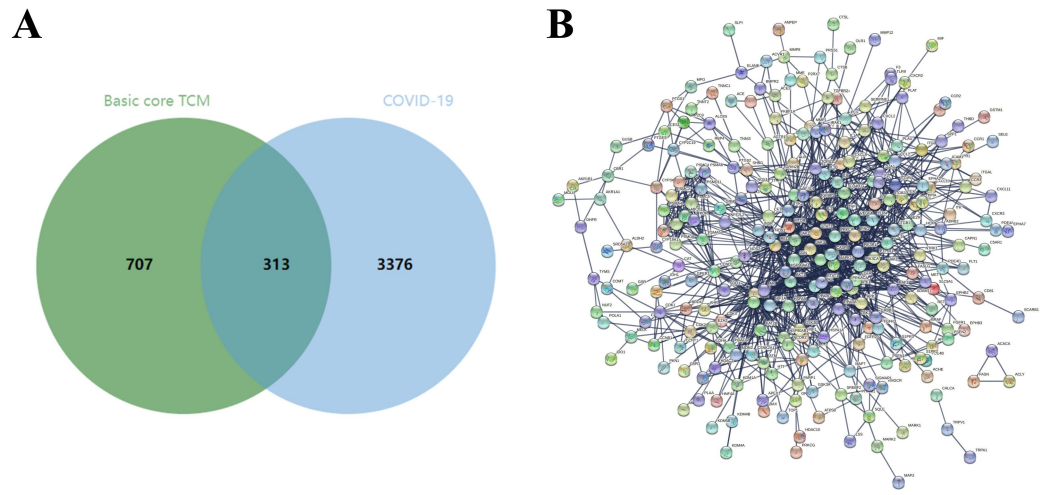

Figure 2 Analysis of BC-TCM. (A) Intersection of targets. (B) PPI network.

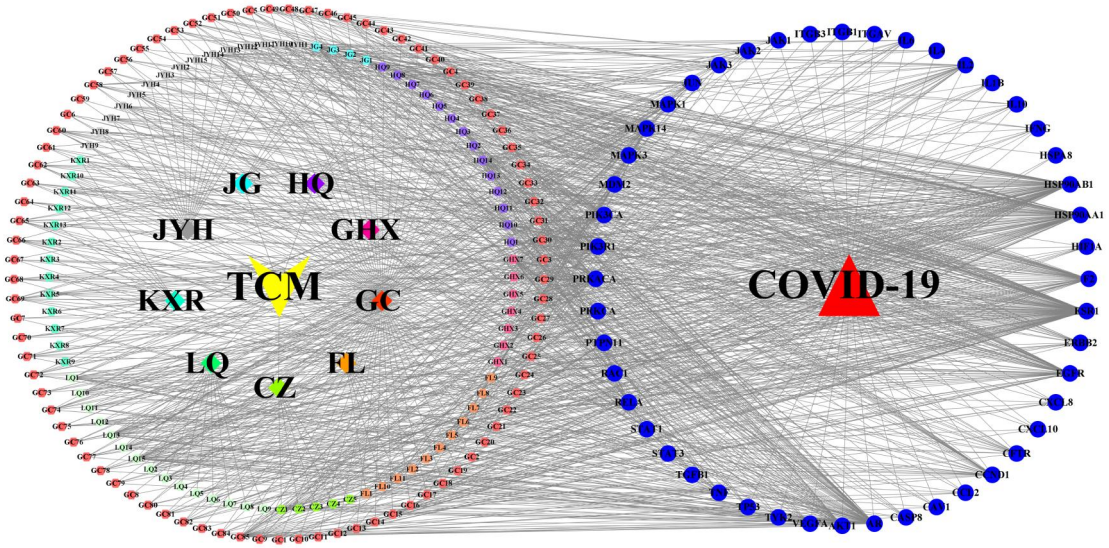

Figure 3 TCM-compound-target-disease network. The V-shaped node represents TCM, the diamond-shaped node single BC-TCM, the hexagonal node main compounds, the circular node therapeutic targets, and the triangle COVID-19 disease.

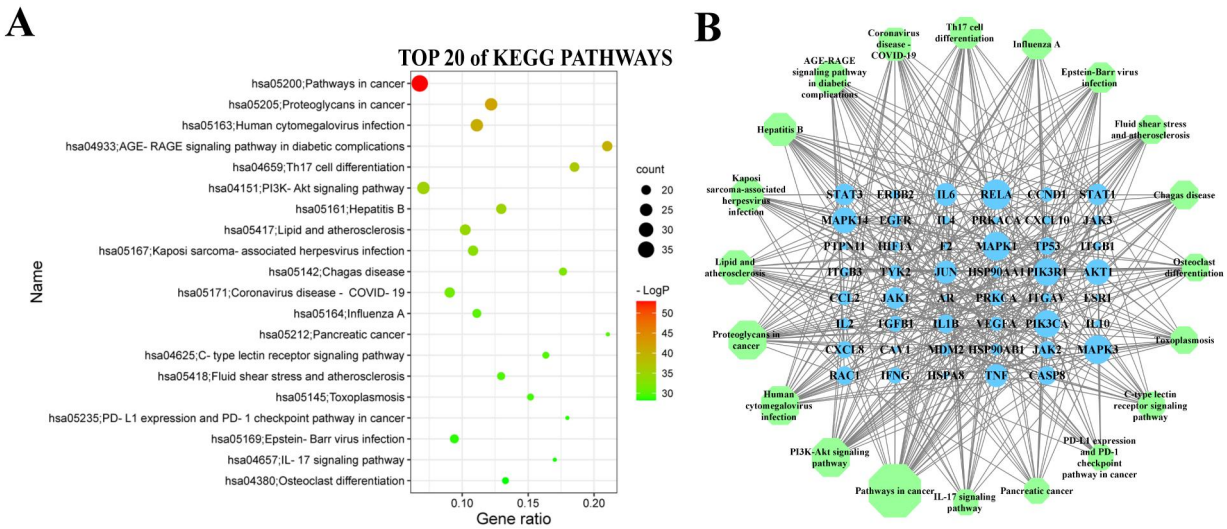

Figure 4 KEGG pathway enrichment analysis of BC-TCM. (A) Bubble diagram. (B) Network of key pathways-therapeutic targets.

Forty-eight therapeutic targets were also imported into the Metascape platform for GO BP, CC, and MF enrichment analysis. 1223 BP entries, 67 CC entries, and 100 MF entries were obtained. The top 10 molecular function entries for GO BP, CC, and MF were selected for enrichment analysis histograms (Figure 5). The results showed that BP was mainly related to cell adhesion regulation, regulation of T cell activation, etc. CC mainly included the focal adhesion, perinuclear region of cytoplasm, platelet alpha granule, etc. MF mainly included cytokine receptor binding, kinase binding, C-X3-C chemokine binding, etc.

Validation of molecular docking

Quercetin, Kaempferol, Luteolin, Beta-sitosterol, Calycosin, Formononetin, Glabridin, Glycyrol, Hederagenin, Isorhamnetin, Jaranol, LicochalconeB, Liquiritin, Phaseol, Spinasterol, Stigmasterol and Wogonin, the active compounds of BC-TCM, were molecularly docked and combined with the COVID-19 target 3CL(6LU7), ACE2(1R4L) and the core targets RELA(1MY7), HSP90AA1(1BYQ), STAT3(6NJS), MAPK3(4QTB), PIK3R1(3I5R), TP53(4CZ5), MAPK1(6SLG), PIK3CA(7JIU), JUN(5FV8), AKT1(1UNQ) [25, 26]. The results of this study showed that all 17 active compounds of BC-TCM bound well to the core targets. Hederagenin, Spinasterol, Stigmasterol, Beta-sitosterol, and Glycyrol were the five compounds with the lowest binding energies to SARS-COV-2 3Cl-Pro, while Hederagenin, Spinasterol, Beta-sitosterol, Liquiritin, and Glabridin were the five compounds with the lowest binding energies to ACE2 [27]. Interestingly, Hederagenin is an intriguing molecule that exhibits the best molecular docking with all of the core targets. The results were shown in Supplementary Table 2. Figures 6 and Figure 7 depict the molecular docking diagram and the molecular docking thermogram, respectively.

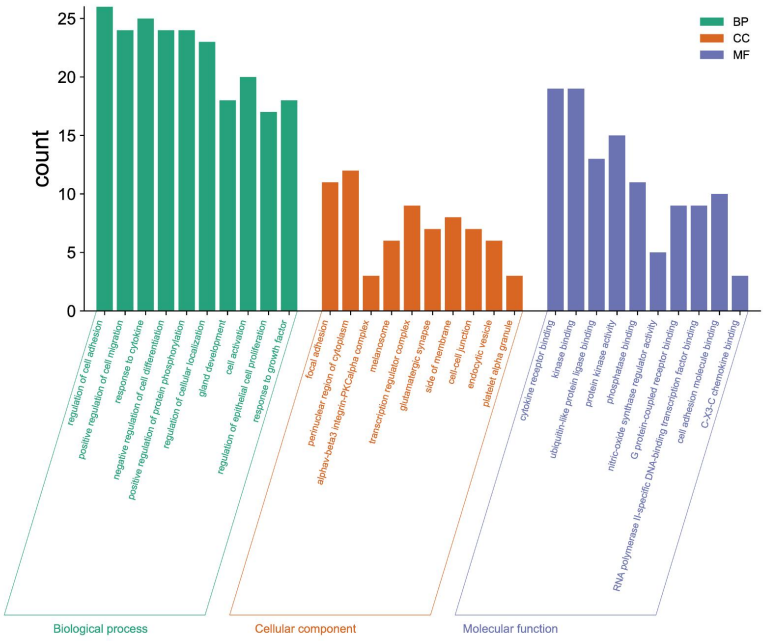

Figure 5 Enrichment analysis histogram for GO BP, CC, and MF

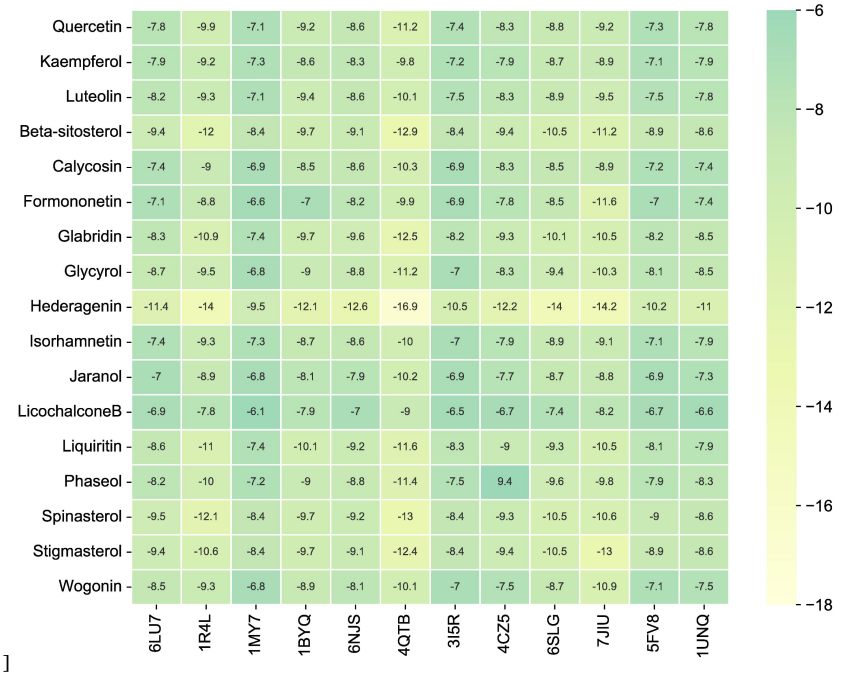

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Figure 6 The molecular docking thermogram

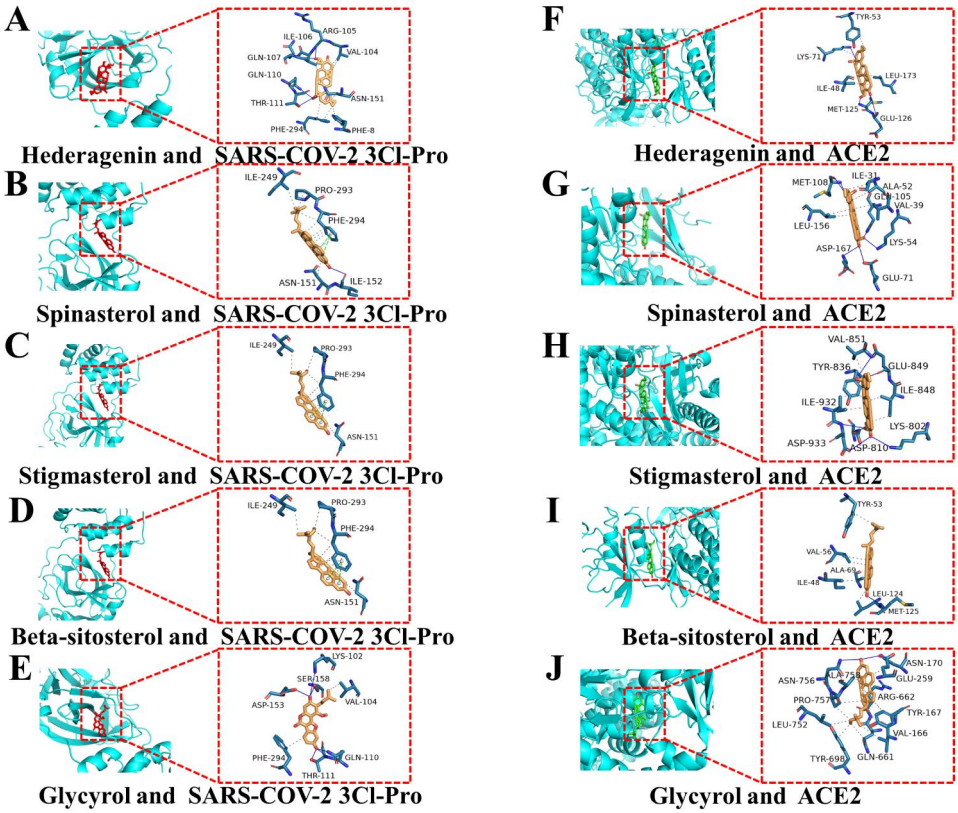

Figure 7 The molecular docking diagram

Discussion

COVID-19 belongs to the "plague" in traditional theory and the basic pathogenesis of the disease is "invasion of epidemic toxins, pathogenic factors in the lungs, and deficiency of immunity". The recommended prescriptions in "Diagnosis and Treatment Protocol for COVID-19" include BC-TCM, such as Huoxiang Zhengqi Capsule (including *Radix glycyrrhizae, Herba pogostemonis, Poria, Radix platycodonis*), Jinhua Qinggan Granule (including *Radix glycyrrhizae, Rlos lonicerae, Radix platycodonis*， *Semen armeniacae amarum*), Qingfei Paidu Decoction (including *Radix glycyrrhizae, Herba pogostemonis, Poria, Semen armeniacae amarum*), Xuanfei Baidu Decoction (including *Radix glycyrrhizae, Herba pogostemonis, Rhizoma atractylodis, Semen armeniacae amarum*), Huashi Baidu Formula (including *Radix glycyrrhizae, Herba pogostemonis, Poria, Radix astragali, Rhizoma atractylodis, Semen armeniacae amarum*), etc [28]. We, therefore, believe that the BC-TCM has an essential role.

123 patents were included, including 312 herbs and 37 high-frequency herbs. It was clear to find that in the patented formulae, the mainstay was often a heat-clearing agent, supplemented by a tonifying deficiency herb and a relieving exterior syndrome herb. "Gan Cao, Jin Yinhua, Guang Huoxiang, Fu Ling, Huang Qi, Jie Geng, Lian Qiao, Cang Zhu, Ku Xingren" were determined as BC-TCM.

166 main compounds, 313 duplicated targets, and 48 therapeutic targets were screened using network pharmacology. Analysis of PPI network revealed that RELA, HSP90AA1, STAT3, MAPK3, PIK3R1, TP53, MAPK1, PIK3CA, JUN, AKT1, and other proteins are the core targets of BC-TCM. NF-κB is a principal compound in treating various common respiratory ailments, including asthma, lung cancer, pulmonary fibrosis, COPD, and infectious diseases such as pneumonia, tuberculosis, and COVID-19 [29]. During the early stages of infection, HSP90AA1, a cell surface protein of avian influenza virus-binding receptors, causes autophagy [30]. Following virus recognition, a direct link between HSP90AA1 and the AKT-MTOR pathway triggers autophagy, a critical step in the control of infection [31]. STAT3 mediates signal transduction and transcriptional activation in response to growth factors, and together with IL6 and JAK2, regulates immune and inflammatory responses. Studies have shown that JAK inhibitors such as Baricitinib have been shown to effectively reduce cytokine storm by inhibiting the JAK-STAT signaling pathway and can reduce viral replication and abnormal host inflammatory responses [32, 33]. The MAPK family is involved in cellular proliferation, differentiation, apoptosis, oxidative stress, inflammation, and immune responses [34]. MAPK1 has an essential role in treating various inflammatory diseases and is also an important regulator of acute lung injury and LPS-induced cell injury [35, 36]. Li found that the inflammatory gene PIK3R1 was highly expressed in critically ill/critically ill COVID-19 patients [37]. The p53 protein encoded by it is related to the regulation of the cell cycle, apoptosis, and senescence. Xiong discovered that SARS-CoV-2 infection may promote lymphocyte apoptosis by increasing TP53 activation to control the immune inflammatory response [38]. ACE2 affects TP53 expression in lung endothelial cells, and deletion of the TP53 binding site leads to increased promoter activity of ACE2 [39]. It is obvious that core targets have a role in processes like as autophagy, apoptosis, immunological modulation, and inflammatory responses.

Seventeen active compounds, Quercetin, Kaempferol, Luteolin, Beta-sitosterol, Calycosin, Formononetin, Glabridin, Glycyrol, Hederagenin, Isorhamnetin, Jaranol LicochalconeB, Liquiritin, Phaseol, Spinasterol, Stigmasterol, and Wogonin were screened out as the main active compounds. Quercetin has strong virucidal activity, preventing or curing human cytomegalovirus, murine coronavirus, and influenza A virus as well as inhibiting virus synthesis, delaying virus replication, improving survival, and enhancing cellular defense. It can also play a modulating, biphasic, and regulatory action on inflammation and immunity [40–44]. Kaempferol has significant antiviral activity, in addition to inhibiting viral latency, impairing viral protein and DNA synthesis, and inhibiting virus-induced autophagy and replication [45–47]. Luteolin is effective in clearing the influenza A virus, inhibiting influenza virus replication, lowering lung index, and reducing inflammatory factors [43, 48].

Beta-sitosterol, Calycosin, Stigmasterol, and Wogonin have anti-inflammatory and immunomodulatory activity and can significantly improve the inflammatory response and acute lung injury caused by the influenza virus, and bind stably to AEC2 and 3CL proteins [49–56]. Formononetin, Glabridin, Licochalcone B, Glycyrol, and Spinasterol are good anti-inflammatory, immunomodulatory compounds that improve the inflammatory response and immune disorders in the organism [57–61]. The antiviral, antidiabetic, and immunomodulatory activities of Hederagenin have been extensively investigated and Sakshi found that Hederagenin bound best to the anti-SARS-CoV-2 major protease, RNA-dependent RNA polymerase, spike protein, angiotensin-converting enzyme receptor, and dipeptidyl peptidase receptor by predicting the comorbidity-associated proteins of SARS-CoV-2 infection [62, 63]. This is consistent with the findings of our research, where Hederagenin showed the best docking activity with the COVID-19 targets 3CL pro (6LU7), ACE2 (1R4L), and the core targets. Isorhamnetin is considered by many scientists to be a potential candidate compound in treating COVID-19, which could interfere with the attachment of the SARS-CoV-2 stinger protein to ACE2 and prevent viral infection [64, 65]. Liquiritin has a variety of pharmacological effects including anti-inflammatory, detoxification, and immunomodulation, and may prevent and cure COVID-19 by mimicking type I interferon [66]. Gao showed that DC-SIGN is closely associated with systemic infections and cytokine storms and that Liquiritin is an antagonist of DC-SIGN that has a former pathway [67]. We can conclude that these active compounds are mainly involved in processes like viral synthesis, viral replication, resistance to inflammation, and immunomodulation.

Furthermore, we investigated the binding ability using molecular docking technology, which offered a theoretical foundation. The results of this study showed that all 17 active compounds of BC-TCM bound well to the core targets. Interestingly, the molecular docking findings indicated that Hederagenin might be a potential compound. KEGG pathway and GO functional enrichment analysis suggested that BC-TCM may act through Human cytomegalovirus infection, PI3K-Akt, Coronavirus disease-COVID-19, Influenza A, IL-17 signaling pathway, which is involved in cellular proliferation, differentiation and apoptosis, virus synthesis and replication. The core targets are involved in processes such as cell adhesion regulation, positive regulation of cytokine production, perinuclear region of cytoplasm, cytokine receptor binding, kinase binding, ubiquitin-like protein ligase binding, thus influencing the development of COVID-19 and acting as a therapeutic agent for COVID-19.

However, our research has several limitations. The characteristics of TCM diagnosis and treatment were not adequately considered in data mining. Furthermore, in vivo and in vitro investigations are required to validate the correctness of our predictions.

Conclusion

Our research offered the first evidence that "Gan Cao, Jin Yinhua, Guang Huoxiang, Fu Ling, Huang Qi, Jie Geng, Lian Qiao, Cang Zhu, Ku Xingren" were determined as the BC-TCM for the prevention and treatment of COVID-19 in the CNIPA by data mining. This may provide a certain reference basis for clinicians to use formulae, and also provide predictive ideas for fundamental research of TCM.

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