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Original Article

Network pharmacology-based analysis reveals the putative action mechanism of *polygonum cuspidatum* against COVID-19

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Abstract: Background: To evaluate the potential pharmacological activity of *polygonum cuspidatum,* a popular Chinese herb medicine (CHM), against COVID-19. Methods: The TCMSP database was utilized to screen the active ingredients and potential drug-targets of *polygonum cuspidatum*. Then GO/KEGG enrichment analysis of these common targets was performed, followed with the protein-protein interaction (PPI) network construction and core target extraction by Cytoscape and MCODE plugin, respectively. The molecular docking analysis was conducted by using CB-Dock. Furthermore, a newly developed TCMATCOV platform was employed to predict therapeutic effects of *polygonum cuspidatum* for COVID-19. Results: Fifteen key ingredients and 62 common targets were obtained from the above screening. The GO/KEGG enrichment analyses of these common targets and the core targets extracted from the PPI network suggested that *polygonum cuspidatum* had antiviral and immunoregulatory activities. Further molecular docking analysis showed that two key ingredients, physciondiglucoside and chrysophanol, had good binding affinities with the core targets, suggesting an important role for them in mediating the pharmacological activity of *polygonum cuspidatum*. The therapeutic effect of *polygonum cuspidatum* for COVID-19 was further validated by using the TCMATCOV platform. Conclusion: These results based on network pharmacology and bioinformatics analysis suggest *polygonum cuspidatum* is a promising CHM candidate against COVID-19.

Keywords: COVID-19, traditional Chinese medicine (CHM), *polygonum cuspidatum* (Hu Zhang), network pharmacology, immunomodulation, antiviral

Introduction

The recent COVID-19 pandemic is considered a global health emergency. At present, the number of COVID-19 patients continues to rise. COVID-19 is similar to Severe Acute Respiratory Syndrome (SARS) in term of pathogenicity, clinical spectrum, and epidemiology [1, 2]. To date, no effective treatment for COVID-19 has been found, and the current therapeutic strategy is basically symptomatic treatment, such as respiratory support, corticosteriod support and antiviral therapy [3].

CHM has a long history in the prevention and treatment of infectious diseases in China. In fact, many CHMs have significant antiviral activity, and some CHM extracts have been widely used against viral infection [4, 5]. In 2003, the intervention of CHM has achieved remarkable therapeutic effect on the SARS epidemic. More recently, the results of some clinical trials have shown that CHM can effectively improve symptoms and shorten the course of COVID-19, providing a bright perspective for disease control [6-10].

As a popular CHM, *Polygonum cuspidatum* has been widely used in the treatment of various diseases, such as atherosclerosis, hypertension and carcinoma [11]. In recent years, a number of studies have shown that *polygonum*

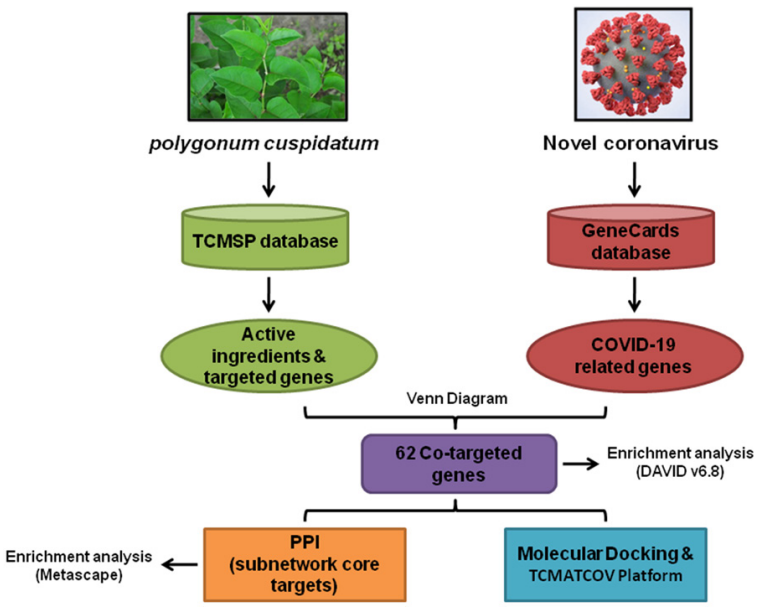


Figure 1. The workflow chart of our study.

cuspidatum extracts exhibited inhibitory activities against hepatitis B virus, EBV virus and influenza A (H1N1) virus [12-14]. However, the potential therapeutic effect of *polygonum cuspidatum* on COVID-19 remains to be evaluated. Thus, the aim of this study is to identify the active ingredients of *polygonum cuspidatum* by using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) online platform, and to explore the effectiveness and potential action mechanism of *polygonum cuspidatum* against COVID-19 (See workflow chart in **Figure 1**).

Materials and methods

Collection of active ingredients

The potential active ingredients of *polygonum cuspidatum* were obtained from Traditional Chinese Medicine Systems Pharmacology (TCMSP) Database (http://lsp.nwu.edu.cn/tcmsp.php), and the parameters for selection were set as oral bioavailability (OB) ≥30% and drug-likeness (DL) ≥0.18 as standards [15, 16]. Furthermore, literature-mining methods (www.CNKI.net) were also used to search the key ingredients, which failed to meet the above parameters, but have been previously characterized as the main component of *polygonum cuspidatum*, for further analysis.

Enrichment analysis

Functional and pathway enrichment analyses of the related targets were performed using The Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8 (https://david.ncifcrf.gov/) and Metascape online tools (http://www.omicshare.com/tools), [17, 18]. A value of $P<0.05$ was considered as statistically significant.

PPI network construction and excavation of core targets

A protein-protein interaction (PPI) analysis was performed by using the Search Tool of Retrieval of Interacting Genes (STRING, version 11.0, https://string db.org) online database [19]. The proteins with a combined score >0.7 were selected for further PPI analysis. The PPI systematic network was constructed using Cytoscape software 3.2.1. The Cytoscape plugin, Molecular Complex Detection (MCODE), was used to screen the modules of this PPI network. The top modules were defined as having Degree cutoff >5 and K-core >5. The core subnetwork extraction from the parent PPI network was performed using the MCODE plugin with the same parameter settings as the above. The average shortest path length and closeness centrality, another two key topological parameters, were calculated by NetworkAnalyzer [20]. The R-value was determined as previously described [21].

Molecular docking

CB-Dock (http://cao.labshare.cn/cb-dock/) was employed to predict the binding activities of proteins to compounds and calculate the center and size of the binding cavity [22]. PDB formats of core protein targets and ligand files in SDF formats were input to CB-Dock to evaluate the binding activities. The style of ligand and receptor were set as “spacefill” and “cartoon”. The color of ligand and receptor were chosen by “element” and “chain”.

Results

Screening of the potential active ingredients

Firstly, we combined OB screening with DL evaluation to identify the active ingredients in *polygonum cuspidatum* (**Figure 2A**). A total of 10 potential ingredients with appropriate val-

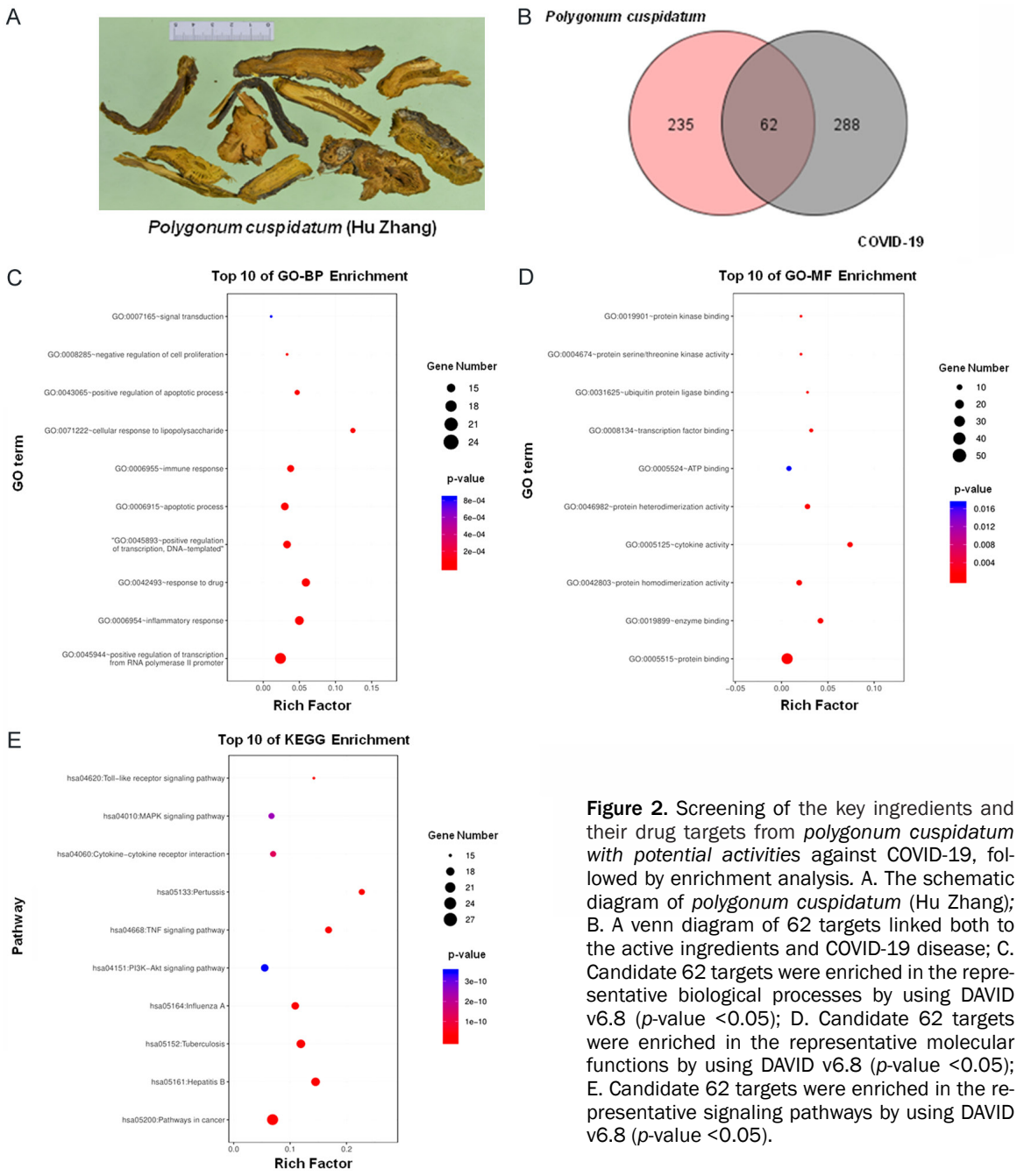


Figure 2. Screening of the key ingredients and their drug targets from *polygonum cuspidatum with potential activities* against COVID-19, followed by enrichment analysis. A. The schematic diagram of *polygonum cuspidatum* (Hu Zhang); B. A venn diagram of 62 targets linked both to the active ingredients and COVID-19 disease; C. Candidate 62 targets were enriched in the representative biological processes by using DAVID v6.8 (*p*-value <0.05); D. Candidate 62 targets were enriched in the representative molecular functions by using DAVID v6.8 (*p*-value <0.05); E. Candidate 62 targets were enriched in the representative signaling pathways by using DAVID v6.8 (*p*-value <0.05).

ues for the above two parameters were obtained from *polygonum cuspidatum*. Furthermore, other 5 ingredients with OB <30% or DL <0.18 that were characterized as the key ingredients and exhibited extensive pharmacological activities by literature mining were also collected for subsequent analysis. These 15 potential active ingredients of *polygonum cuspidatum* were listed in **Table 1**.

Identification and enrichment analysis of the drug targets of polygonum cuspidatum against COVID-19

A systematic drug targeting approach was employed to identify potential targets for the medicinal composition of *polygonum cuspidatum*. The potential drug targets were obtained from the TCMSP database (see Supplementary

Table 1. Pharmacological and molecular parameters of *Polygonum cuspidatum*

MOL_ID	Name	MW	AlogP	Hdon	Hacc	OB (%)	Caco-2	BBB	DL	TPSA	RBN
MOL013287	Physovenine	262.34	2.08	1	5	106.21	0.51	0.2	0.19	50.8	2
MOL002268	Rhein	284.23	1.88	3	6	47.07	-0.2	-0.99	0.28	111.9	1
MOL000492	(+)-catechin	290.29	1.92	5	6	54.83	-0.03	-0.73	0.24	110.38	1
MOL000098	Quercetin	302.25	1.5	5	7	46.43	0.05	-0.77	0.28	131.36	1
MOL000358	beta-sitosterol	414.79	8.08	1	1	36.91	1.32	0.87	0.75	20.23	6
MOL013288	Picralinal	366.45	1.8	1	6	58.01	0.23	-0.21	0.75	67.87	3
MOL002259	Physciondiglucoside	608.6	-0.91	8	15	41.65	-2.64	-3.43	0.63	242.13	7
MOL002280	torachrysone-8-O-beta-D-(6'-oxayl)-glucoside	480.46	0.64	5	12	43.02	-1.23	-1.84	0.74	189.28	8
MOL000006	Luteolin	286.25	2.07	4	6	36.16	0.19	-0.84	0.25	111.13	1
MOL013281	6,8-Dihydroxy-7-methoxyxanthone	258.24	2.41	2	5	35.83	0.68	0.1	0.21	79.9	1
MOL000472	Emodin	270.25	2.49	3	5	24.4	0.22	-0.66	0.24	94.83	0
MOL001729	Chrysophanol	254.25	2.76	2	4	18.64	0.62	-0.2	0.21	74.6	0
MOL012744	Resveratrol	228.26	3.01	3	3	19.07	0.8	-0.01	0.11	60.69	2
MOL013289	Polydatin	390.42	1.11	6	8	21.44	-0.9	-1.81	0.5	139.84	5
MOL000008	Apigenin	270.25	2.33	3	5	23.06	0.43	-0.61	0.21	90.9	1

Table 1 for details), and COVID-19 disease targeted genes were acquired by using the GeneCards database (http://www.genecards.org/) [23]. "Novel Coronavirus" were used as keywords for searching. The obtained drug and disease targets/genes were then combined and the overlapped ones were removed (see Supplementary Table 2 for details). Thus, a total of 62 targets linked to both drug active ingredients and COVID-19 disease were identified (see Supplementary Table 3 for details). A Venn diagram was created to visualize the above results (**Figure 2B**). Next, we performed enrichment analysis for these 62 candidate targets of *polygonum cuspidatum* using DAVID v6.8 online tools. The analysis for these potential targets was divided into GO biological process (GO-BP), GO molecular function (GO-MF) and KEGG signaling pathway, respectively. Our results showed that the related biological processes included transcription, inflammatory response, response to drug, apoptotic process and immune response, while the main affected molecular functions were protein binding, enzyme binding, protein homodimerization activity, cytokine activity and protein heterodimerization activity (**Figure 2C** and **2D**). Meanwhile, the affected signaling pathways included pathways in cancer, Hepatitis B, Tuberculosis, Influenza A, TNF signaling pathway and Cytokine-cytokine interaction (**Figure 2E**). These results support a view that *polygonum cuspidatum* exerts its therapeutic effect on COVID-19 by regulating the major signaling pathways involved in antiviral reaction and immunoregulation.

Construction of the PPI network and enrichment analysis of the core targets

The 62 obtained targets were further analyzed using the STRING online software with a combined score >0.7, which resulted in the construction of the PPI network containing 61 nodes and 497 connections. Then, the key modules of the PPI network were screened out by MCODE plugin of Cytoscape 3.2.1 (see Supplementary Table 4 for details). The top core subnetwork with the highest MCODE score, containing a total of 21 nodes and 168 connections, was thus extracted from the parental PPI network (**Figure 3A**). Next, we further performed the systematic enrichment analysis for the identified 21 potential core targets of *polygonum cuspidatum* using Metascape online tools. Consistently, we found that *polygonum cuspidatum* had a great impact on host immunoregulation via immune-related signaling pathways, such as signaling by interleukins, IL-17 signaling pathway, IL-4 and IL-13 signaling pathways, cytokine-mediated signaling pathway and IL-10 signaling pathway (**Figure 3B-D**).

Molecular docking analysis was performed to evaluate the bind activities between the key ingredients and the core targets

Because the number of the putative core targets (21 nodes) and the connections (168 edges) among the above subnetwork were still high and complicated, we further performed a topological analysis for the PPI network, and obtained 2 groups of the top 10 targets according to the R value and the MCODE scores, respectively. Ultimately, four overlapped between the both groups, namely IL6, TNF, MAPK1 and CXCL8, which were chosen as the core targets for further docking analysis (**Table 2**). The top 5 Vina scores were gained from CB-Dock software, and the lowest binding energy (Vina score) was selected as the group representative. A spacefill and a cartoon chain represented an ingredient ligand and a protein target, respectively. Our molecular docking results revealed that the potential active ingredients of *polygonum cuspidatum* had good general binding activities to the core targets (**Table 3**). Moreover, the docking results showed that the Vina scores between physciondiglucoside (MOL002259) and IL6, TNF, MAPK1 and chrysophanol (MOL001729) and CXCL8 were higher than that between others, suggesting important roles of these two ingredients in mediating antiviral and immunomodulation effects of *polygonum cuspidatum* (**Figure 4A-D**).

Therapeutic effect prediction of polygonum cuspidatum against COVID-19 by using TCMATCOV

The influence of the drug target on the topological characteristics of a disease target network can be used to evaluate the intervention effect of the drug on the disease. TCM Anti COVID-19 (TCMATCOV, http://tcmatcov.bbtcml.com), established using SARS transcriptome data, is a recently developed platform utilizing a quantitative evaluation algorithm to analyze the dis-

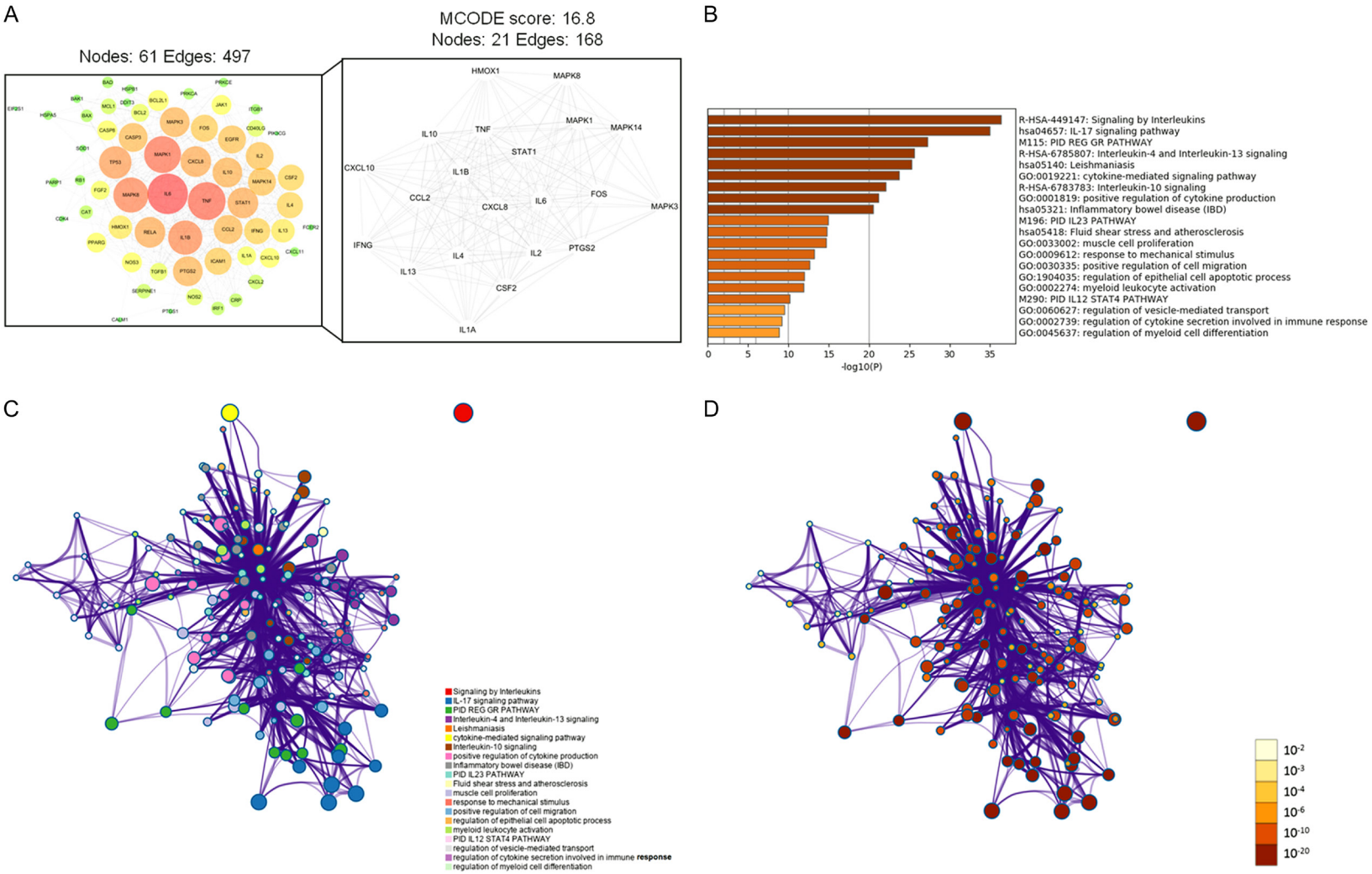


Figure 3. PPI network construction, core targets excavation and systematic *enrichment analysis*. A. PPI network construction with 61 nodes, and subnetwork construction with 21 nodes. PPI, protein-protein interaction; B. Bar graph of enriched terms across input 21 targets by using Metascape online software (*p*-value <0.01); C. Network of enriched terms colored by cluster ID, where nodes that share the same cluster ID are typically close to each other; D. Network of enriched terms colored by *p*-value, where terms containing more genes tend to have a more significant *p*-value.

Table 2. The four key targets of *Polygonum cuspidatum* with topological analysis

Protein code	Genes	Description	Average shortest path length	Closeness centrality	R	MCODE score
P05231	IL6	Interleukin-6, IL-6	1.36667	0.73171	0.00000	10.90580
P01375	TNF	Tumor necrosis factor	1.41667	0.70588	0.03864	10.90580
P28482	MAPK1	Mitogen-activated protein kinase 1, MAP kinase 1, MAPK 1	1.45000	0.68966	0.06439	11.02339
P10145	CXCL8	Interleukin-8, IL-8	1.58333	0.63158	0.16742	10.58571

Table 3. Vina scores of compound-target molecular docking

ID number	IL6 (4CNI)	TNF (2AZ5)	MAPK1 (2OJG)	CXCL8 (5D14)
MOL000006	-8.3	-8.9	-9.2	-6.0
MOL000008	-8.3	-8.3	-8.9	-6.3
MOL000098	-8.0	-7.7	-9.2	-6.3
MOL000358	-7.7	-7.9	-8.5	-6.8
MOL000472	-8.6	-7.9	-9.7	-6.8
MOL000492	-7.7	-8.5	-9.1	-5.7
MOL001729	-8.4	-7.9	-9.6	-7.0
MOL002259	-10.1	-9.0	-11.1	-6.8
MOL002268	-8.3	-8.1	-9.8	-6.6
MOL002280	-8.1	-7.8	-8.4	-6.6
MOL012744	-7.7	-7.6	-8.1	-5.8
MOL013281	-7.7	-8.2	-8.4	-5.9
MOL013287	-7.9	-7.1	-8.0	-5.8
MOL013288	-8.1	-5.9	-6.4	-6.1
MOL013289	-8.6	-8.3	-8.6	-6.4

turbance of an imitating COVID-19 disease network upon a candidate CHM attacking. Thus, to predict the potential therapeutic effect of *polygonum cuspidatum* against COVID-19, we employed TCMATCOV to calculate the disturbance score of *polygonum cuspidatum* [24]. The cutoff of the PPI confidence score was 0.4. Our result showed that *polygonum cuspidatum* has a high disturbance score, comparable to that of the positive control herbs (Hong Hua and Ban Lan Gen), which have been reported to be effective in clinical treatment for COVID-19. Please see **Table 4** for details.

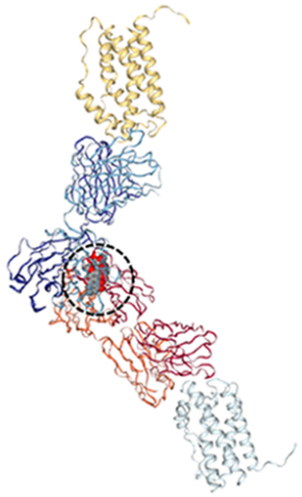
Discussion

As a popular CHM, *polygonum cuspidatum*, is widely used in China to treat various types of inflammation, infection, jaundice, skin burns, hyperlipemia and other symptoms and diseases [25]. Over 100 CHM prescriptions contain *polygonum cuspidatum*, and its multifactor pharmacological activities include antiviral, anti-inflammatory, antioxidant, anti-cancerous, antibacterial, lipid regulating and anti-shock effects have been well documented [26-28]. In this study, taking advantage of the recent advances in network pharmacology and computational methods, we screened out 15 potential active ingredients in *polygonum cuspidatum,* and obtained 62 targets related both to the drug active ingredients and COVID-19 disease. The results of subsequent enrichment analysis suggested that these targets were closely related to antiviral reactions and immunoregulation.

Since signal transduction exists between different signaling pathways and targets, the therapeutic effects of a drug is not merely resulted from its direct drug targets, but more commonly involved in a complex regulatory network composed of both its direct and indirect drug targets [29]. In this context, the construction of PPI networks can greatly facilitate the in-depth understanding of the complex interactions between the targets. Thus, to further explore the action mechanism of *polygonum cuspidatum* against COVID-19, we constructed a drug-COVID-19 co-target protein PPI network and performed core subnetwork extractions, followed with the core target enrichment analysis by using Metascape systematic online tool. Intriguingly, a cluster of hub targets from the extracted subnetwork was mainly composed of various cytokines and molecules involved in immunoregulation and inflammation, such as TNF, IL10, IL6. In fact, associated with pro-inflammatory cytokines such as IL-6, Acute Respiratory Distress Syndrome (ARDS) is a common consequence of 'cytokine storms', a lethal systemic complication mainly caused by virus-induced abnormal immune activation [30, 31]. Recent laboratory examination and pathological findings have provided evidence for the existence of ARDS and immune injury in patients with COVID-19, demonstrating that a 'cytokine storm' is a crucial factor related to the severity and mortality of COVID-19 patients [20, 32]. Indeed, abnormal levels of cytokines have been found in many COVID-19 patients, such as TNF-α, IL-1β and IL-6 [33, 34], suggesting that *polygonum cuspidatum* may exert its therapeutic effects against COVID-19 though immunomodulation.

To further explore the underlying mechanisms of *polygonum cuspidatum* against COVID-19 at the molecular level, we next performed molecular docking analysis. The results showed that the 15 active ingredients of *polygonum cuspidatum* had an overall good binding activity with multiple core targets, such as IL6, TNF, MAPK1 and CXCL8, showing a "multi-ingredient and multi-target" pharmacological characteristic of *polygonum cuspidatum*.

A



MOL002259 and IL6
(Binding Modes)

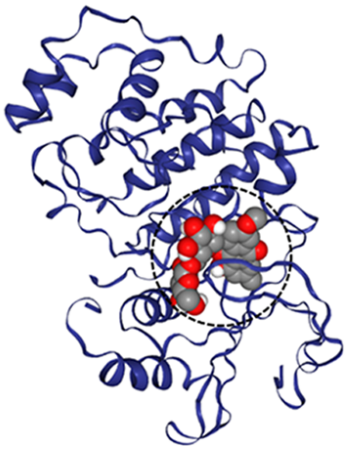
Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-10.1	3316	110	-22	-17	27	34	35
-9.2	751	103	2	-25	27	27	35
-8.4	372	61	-60	2	27	27	27
-7.4	410	79	-67	-1	27	27	27
-6.9	421	98	33	-33	27	27	27

B

MOL002259 and TNF
(Binding Modes)

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-9	345	7	67	12	27	27	27
-8.8	508	-6	82	27	27	27	27
-7.5	248	-11	71	1	27	27	27
-6.9	245	-15	74	52	27	27	27
-6.7	115	-35	64	32	27	27	27

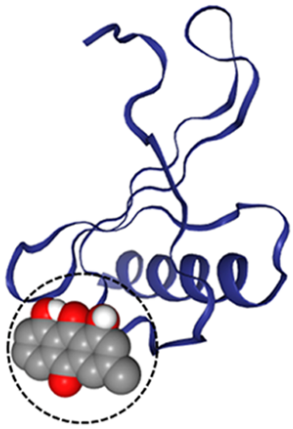
C



MOL002259 and MAPK1
(Binding Modes)

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-11.1	1098	-9	15	38	27	27	27
-9.8	224	-8	18	54	27	27	27
-7.7	696	9	0	55	27	27	27
-7.4	395	6	2	37	27	27	27
-7.3	272	-13	12	67	27	27	27

D



MOL001729 and CXCL8
(Binding Modes)

Vina score	Cavity size	Center			Size		
		x	y	z	x	y	z
-7	147	1	21	-14	19	19	19
-6.3	166	0	26	-5	19	19	19
-5.9	145	-3	22	3	19	19	19
-5.5	92	9	21	-3	19	19	19
-5.4	92	9	24	7	19	19	19

Figure 4. Molecular docking analysis between the key ingredients of *polygonum cuspidatum* and the core targets. A. Compound MOL002259 docking with IL6; B. Compound MOL002259 docking with TNF; C. Compound MOL002259 docking with MAPK1; D. Compound MOL001729 docking with CXCL8.

Table 4. *Polygonum cuspidatum* (herb: Hu Zhang) and related TCM prescriptions or herbs validation results by TCMATCOV platform

TCM herbs	Sum score	Average Degree	Average shortest path	Degree centrality	Closeness centrality
BXTM (Negative Control)	12.59	-1.84	3.53	-0.76	-6.46
LWDH (Negative Control)	15.43	-2.42	5.48	-1.22	-6.31
Ban Lan Gen (Positive Control)	18.04	-4.81	5.94	-1.09	-6.21
Hong Hua (Positive Control)	17.90	-4.03	8.45	-0.84	-4.58
Hu Zhang	16.36	-4.65	2.87	-4.89	-3.95

SARS-CoV-2 virus-related *in vitro* experiments are required to be performed in biosafety labs at the P4 level. Unfortunately, we do not have the access to such facility, which led to a main limitation of our study. Nevertheless, the ingredients of *polygonum cuspidatum* mentioned in the present study, such as quercetin, luteolin and resveratrol, have been recently reported to be somewhat effective in COVID-19 treatment [35-37]. Moreover, mounting evidence has shown that *polygonum cuspidatum* holds antiviral and immune-regulatory activities. For instance, a previous study showed that the extracts or active ingredients isolated from *polygonum cuspidatum* were potential drug candidates for vesicular stomatitis virus (VSV), types 1 and 2 herpes simplex virus (HSV), parainfluenza virus (PV) and vaccinia virus (VV) after being determined by a direct pre-infection incubation assay [38, 39]. Also, a recent study found that after treating with the extracts from *polygonum cuspidatum* at a dose of 200 mg/day for 6 weeks, the mRNA expressions of TNF-α, IL-6 and NF-κB were significantly decreased in healthy human subjects [40]. Thus, the above results suggest that *polygonum cuspidatum* has a great potential against COVID-19 via its "multi-ingredient, multi-targeted and multi-functional" pharmacological activities.

Conclusions

We set about to screen the active ingredients and their potential targets by using the TCMSP database, which resulted in 15 key ingredients and 62 co-targets related both to the key ingredients of *polygonum cuspidatum* and COVID-19 disease. Subsequent enrichment analysis revealed that *polygonum cuspidatum* has antiviral and immunoregulatory activities. In addition, we used the TCMATCOV platform to evaluate the pharmacological activity of *polygonum cuspidatum*, which validated our results of network pharmacology and bioinformatics analysis. Thus, our results show that *polygonum cuspidatum* is a promising candidate CHM against COVID-19.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

TCM, Traditional Chinese medicine; CHM, Chinese herb medicine; PPI, Protein-protein interaction; SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus 2; OB, Oral bioavailability; DL, Drug-likeness; ARDS, Acute Respiratory Distress Syndrome.

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Supplementary Table 4. The core targets extraction from PPI network by using MCODE plugin

Targets	MCODE scores
IFNG	11.73626374
IL10	11.25146199
MAPK1	11.02339181
FOS	11.02339181
CCL2	11.01578947
TNF	10.9057971
IL6	10.9057971
CXCL10	10.63736264
CSF2	10.58823529
CXCL8	10.58571429
STAT1	10.53684211
IL1B	10.52380952
MAPK8	10.5
MAPK14	10.19607843
MAPK3	10.15384615
IL13	10.08333333
IL2	10.07114625
IL4	10.04210526
IL1A	9.991666667
HMOX1	9.487179487
PTGS2	9.485714286