wjpmr, 2023, 9(11), 38-46

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

NETWORK PHARMACOLOGY-BASED EXPLORATION OF ACTIVE COMPONENTS AND TARGETS OF ACTION OF LICORICE-DRIED GINGER SOUP AGAINST NOVEL CORONAVIRUSES

Chen Wei[1], Hongge Zhang[2], Huihui Fang[1], Yangjie Zuo[3], Yubing Shi [1] and Jing Dong[1,2*]

[1]Second Clinical College of Medicine, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi Province, China.
[2]Department of Cardiology, the Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi Province, China.
[3]School of Medical Technology, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi Province, China.

***Corresponding Author: Jing Dong**

Second Clinical College of Medicine, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi Province, China.

Article Received on 14/09/2023 **Article Revised on 04/10/2023** **Article Accepted on 25/10/2023**

ABSTRACT

Objective: In clinical practice, Licorice ginger soup has been utilized to treat new coronavirus pneumonia, and this study looked into the potential targets and mechanisms of action of licorice ginger soup from the perspective of network pharmacology. Methods: To begin, the chemical makeup and target of action of licorice dried ginger were obtained using the TCMSP database. Next, COVID-19 targets were retrieved in the Genecards database, common targets for drugs and diseases were retrieved using Venny, intersecting targets were constructed using String to build a PPI network, and a drug-component-disease-target network was constructed using Cytoscape software. Finally, GO function and KEGG pathway enrichment were analyzed for the action target. Results: With 324 important GO biological processes and 56 KEGG signaling pathways, which were mostly involved in inflammation, immunity, and transcription, 56 prospective targets were discovered for the therapy of COVID-19 with licorice-dried ginger soup. Conclusion: licorice ginger soup may treat COVID-19 by interacting with various targets, including STAT3, RELA, IL6, and others.

KEYWORDS: lycyrrhiza glabra; Dried ginger; Novel coronavirus pneumonia; Network pharmacology; Target; Signaling pathway.

INTRODUCTION

Novel coronavirus pneumonia (COVID-19) is a highly infectious and morbid condition brought on by a novel single-stranded RNA-coronavirus with high mutation and genetic recombination rates that can spread between species to infect humans.[1] The transmission and virulence of its mutant strains differs as well[2], making the new crown challenging to avoid and cure. This research examines the possible targets and mechanism of action of licorice and dried ginger soup for the treatment of neocoronavirus from the perspective of network pharmacology. Licorice and dried ginger soup has been utilized to prevent and control new coronavirus pneumonia in clinical studies. First, the chemical makeup and action targets of licorice stem ginger were obtained using the TCMSP database. Next, COVID-19 targets were retrieved from the Genecards database, common targets for drugs and diseases were retrieved using Venny, intersecting targets were created using String to create a PPI network, and a drug-component-disease-target network was created using the Cytoscape software. Finally, the action targets were further analyzed by GO function and KEGG. targets were further examined for KEGG pathway enrichment and GO function. With the use of licorice-ginger broth, we were able to identify 56 possible COVID-19 therapy targets, including 324 GO biological processes and 56 KEGG signaling pathways that were primarily involved in inflammation, immunology, and transcription. Therefore, licorice ginger soup may cure COVID-19 by acting on STAT3, RELA, IL6, and other targets through a variety of mechanisms.

The Treatise on Typhoid Fever and The Essentials of the Golden Chamber both provide recipes for Licorice and Dried Ginger Soup[3], which combine these two ingredients. A traditional remedy for lung impotence, Licorice and Ginger Soup is found in Zhang's Treatise on Typhoid Fever from the Han Dynasty.[3] Chen stated: "Licorice and Ginger Soup is a formula for warming the spleen and the earth and generating yin and fluids." Glycyrrhizin flavonoids, glycyrrhizic acid, triterpenoids,

glycyrrhizin, and other chemical components found in licorice[4] have anti-inflammatory, antioxidant, immunological modulating, detoxifying, and anticancer effects.[5] Glycyrrhiza glabra is a common single herb prescribed in Chinese medicine, and it can be combined with a wide range of medications to fight the epidemic.[6] Ginger[7] Volatile oil, curcumin, and other chemicals are the primary chemical active components. Its pharmacological effects range from antipyretic to analgesic to anti-inflammatory to antioxidant to anti-bacterial to increasing blood circulation to anti-tumor. Glycyrrhiza glabra is utilized in this formulation as a cancer preventative. Licorice is employed in this formula to warm the fluid and help the middle qi, while dried ginger warms the spleen and lungs. Licorice and dry ginger have the ability to cultivate the earth, produce gold, and warm the lungs in the spleen[3]; this ability is directly related to the etiology of COVID-19[8], and it has a great therapeutic impact when administered in the clinic. Modern pharmacological research has universally acknowledged the usefulness of licorice in suppressing cough and expectorant, which is why it is frequently used with cough-relieving and expectorant medications in clinical use. The basic components of Er Chen Tang, which comes from "Taiping Huimin Hekebao prescription (TCM)" and can be used to "treat phlegm and drink" are glycyrrhiza glabra and dried ginger. It has recently been a hot issue in the study of respiratory diseases.[9] It was rumored that licorice-ginger soup may be prepared during the outbreak to treat and prevent neoguan. Licorice-ginger soup's target in relation to COVID-19 and the signaling pathway were examined from the perspective of cyber-pharmacology in order to determine whether it has the ability to treat and prevent neoguan.

1. MATERIALS AND METHODS

1.1 Chemical Composition and Targets of Licorice and Ginger Soup

When the drug name was entered, the TCMSP database was searched for the pertinent chemical components and the corresponding targets. The compliant chemical components and their corresponding targets of action were then screened on the basis of OB (Oral Bioavailability) ≥ 30 and DL (Drug-Like-Likeness) ≥0.18.

1.2 Screening of licorice-ginger broth and COVID-19-related targets

Lookup COVID-19 disease-related targets in the Gamecards database. Utilize Venny to look for potential therapeutic targets for the COVID-19 treatment with licorice ginger soup by looking for drug-disease common targets.[10]

1.3 Protein Interaction Analysis and Network Construction

String was used to build the PPI network, "Homo sapiens "was chosen as the species, and a confidence level as high as 0.9[10] were all chosen. Using the cytoscape program, the network was built and the primary targets were acquired.

1.4 GO and KEGG enrichment analysis

The GO and KEGG pathway enrichment of Homo sapiens was examined using the DAVID database and GO functional enrichment and KEGG pathway enrichment maps were produced, respectively.

2. RESULTS

2.1 Composition and targets of licorice and dried ginger

In the TCMID database, 280 different types of licorice drug components were searched, yielding a total of 2506 action targets; 92 different types of licorice drug components were searched with bioavailability OB≥30 and drug-like property DL ≥0.18, The main components of licorice are shown in table 1.While each component has multiple drug targets, as shown in table 2 of the targets of component Glycyrol with Mol ID of MOL002311, yielding a total of 1,764 drug targets, of which 235 remained after removing duplicate targets.

Table 1: The main components of licorice.

Medicine	Mol ID	Molecule Name	OB (%)	DL
licorice	MOL002311	Glycyrol	90.78	0.67
	MOL004990	7,2',4'-trihydroxy－5-methoxy-3－arylcoumarin	83.71	0.27
	MOL004904	licopyranocoumarin	80.36	0.65
	MOL004891	shinpterocarpin	80.3	0.73
	MOL005017	Phaseol	78.77	0.58
	MOL004841	Licochalcone B	76.76	0.19
	MOL004810	glyasperin F	75.84	0.54
	MOL001484	Inermine	75.18	0.54
	MOL000500	Vestitol	74.66	0.21
	MOL005007	Glyasperins M	72.67	0.59
	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	71.12	0.18
	MOL004959	1-Methoxyphaseollidin	69.98	0.64
	MOL000392	formononetin	69.67	0.21
	MOL004863	3-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-	66.37	0.41

		2-enyl)chromone		
	MOL004903	liquiritin	65.69	0.74
	MOL004808	glyasperin B	65.22	0.44
	MOL004829	Glepidotin B	64.46	0.34
	MOL004855	Licoricone	63.58	0.47
	MOL004914	1,3-dihydroxy-8,9-dimethoxy-6-benzofurano[3,2-c]chromenone	62.9	0.53

Table.2: The targets of component glycyrol.

Mol ID	Molecule name	Target name
MOL002311	Glycyrol	Nitric oxide synthase, inducible
MOL002311	Glycyrol	Estrogen receptor
MOL002311	Glycyrol	Peroxisome proliferator activated receptor gamma
MOL002311	Glycyrol	Prostaglandin G/H synthase 2
MOL002311	Glycyrol	Vascular endothelial growth factor receptor 2
MOL002311	Glycyrol	Mitogen-activated protein kinase 14
MOL002311	Glycyrol	Glycogen synthase kinase-3 beta
MOL002311	Glycyrol	Serine/threonine-protein kinase Chk1
MOL002311	Glycyrol	Proto-oncogene serine/threonine-protein kinase Pim-1
MOL002311	Glycyrol	Cyclin-A2
MOL002311	Glycyrol	Thrombin

There were 148 different types of dry ginger drug components and 995 different action targets. 5 different types of dry ginger drug components with bioavailability OB ≥30 and drug-like property DL≥ 0.18 were searched. 48 drug targets based on the five main dry ginger components were found, and 43 targets remained after removing the duplicate targets. The main components of ginger are shown in table 3. After conversion to gene name by uniprot, 230 common targets of licorice and stem ginger were screened by Venny diagram.

Table.3: The main components of ginger.

Medicine	Mol ID	Molecule Name	OB (%)	DL
Ginger	MOL002464	1-Monolinolein	37.18	**0.3**
	MOL002501	X-2,2-dimethylcyclopropane-1-carboxylate	62.52	**0.31**
	MOL002514	Sexangularetin	62.86	**0.3**
	MOL000358	beta-sitosterol	36.91	**0.75**
	MOL000359	sitosterol	36.91	**0.75**

2.2 Screening of chemical composition and disease-related targets

A total of 5337 COVID-19 illness targets were analyzed by GeneCards; 745 targets remained after eliminating those with scores below 1.2. The 56-point Venny diagram was used to screen the co-interacting targets of licorice, dried ginger, and COVID19, as shown in fig4.

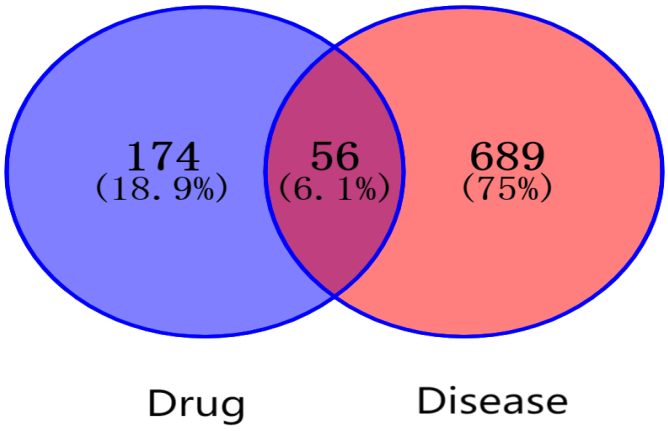


Fig.4 Drug-disease co-targeting.

2.3 Compound target network diagram construction

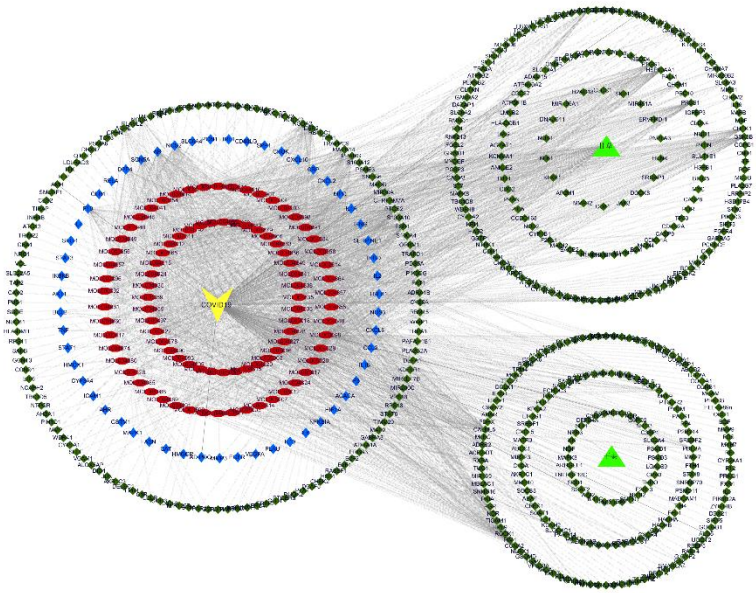


Fig.5: Drug-component-target-disease network.

Using the cytoscape software, the drug-component-target-disease relationship network was created, as shown in the figure 5. Green represents the drug, yellow represents the disease, red represents the drug's chemically active component, blue represents the drug's potential therapeutic target for treating COVID-19, and dark green represents the target of the drug's active ingredient. The phenomena of distinct compounds acting on the same target can be noticed in addition to the same compound and multi-target interaction, which illustrates the integrated and connected character of the drug multi-component and multi-target interaction.[11] According to degree, quercetin, 7-methoxy-2-methylisoflavone, kaempferol, -glutosterol, etc. are the key ingredients of the sorted medications. Important gene targets include PTGS2, ESR1, CALML5, AR, and NOS2,as shown in table 6.

Table.6 Degree sorting key chemicals and targets.

Ingredient	Degree	Betweenness	gene name	Degree2	Betweenness3
MOL000098	145	0	PTGS2	82	0
MOL000422	57	0	ESR1	77	20.301632
MOL003896	38	0	CALML5	70	453.9848
MOL000358	37	0	AR	67	2059.197
MOL004328	36	0	NOS2	66	0
MOL000392	33	0	HSP90AA1	62	0
MOL000354	32	0	ALOX5AP	2	15741.959
MOL000497	31	0	ACACA	2	9209.118
MOL002565	31	0	F10	53	4958.378
MOL004978	29	0	ESR2	54	4958.378

2.4 Relevant target PPI network diagram construction

With a high confidence level of 0.9[12], String was used to build the PPI network,as shown in fig7, and the molecular target protein network's overall characterisation revealed that: 56 nodes, 165 edges, an average node degree of 5.89, an average local clustering coefficient of 0.534, and a PPI enrichment p-value of 1.0e-16 make up this network. To identify the primary targets and create the network diagram, the cytoscape software was used to assess the network topology parameters, an shown in fig8.There were a total of 43 nodes, each of which represented a protein. Lines connecting the nodes showed the interactions between the proteins. Nodes are used to represent proteins; lines connecting the nodes show how the proteins interact; the more lines, the greater the correlation; the larger the node, the darker the color, the more significant the target; each edge shows how the proteins interact; the thicker the edge, the closer the relationship. The gene with the highest Betweenness Centrality (BC) value in the network is STAT3 (BC=324.75), followed by RELA (BC=272.97), IL6 (BC=199.92), and the remaining genes with more than BC=100 are TNF (BC=324.75), IL4 (BC=272.97), EGFR (BC=272.97), MMP3, AKT1, and IL10, which were critically linked in the PPI network.

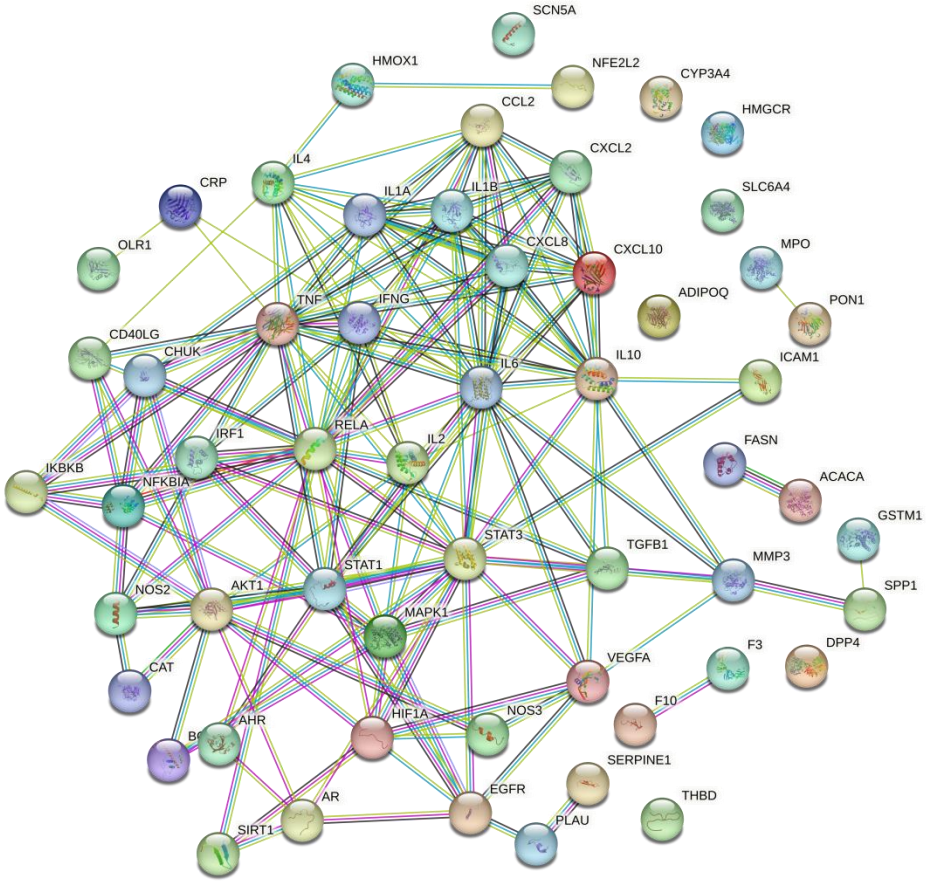


Fig.7: Protein interactions map.

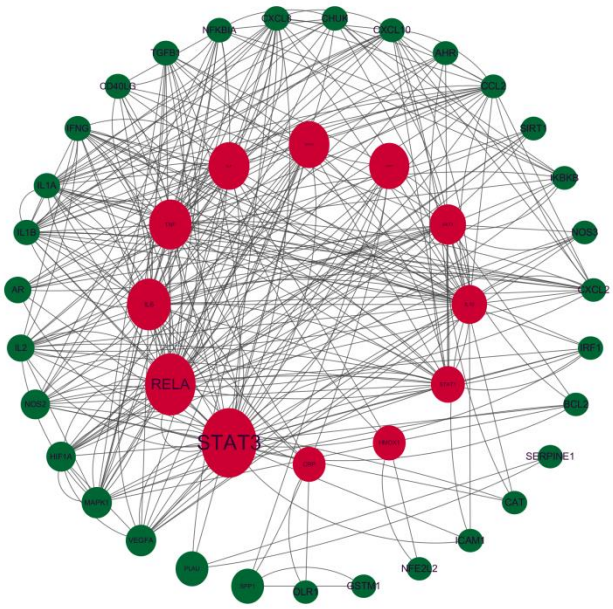
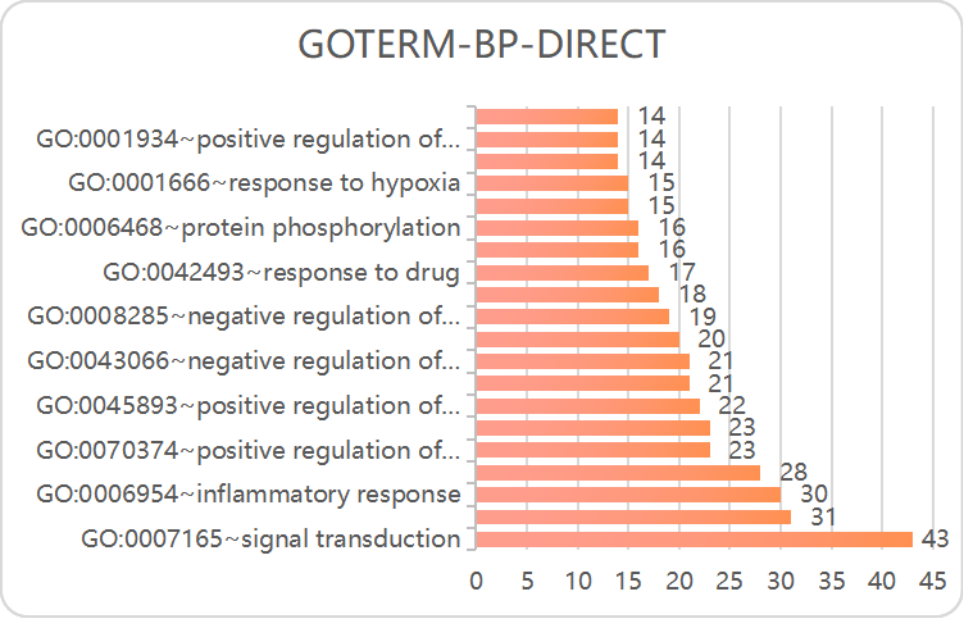


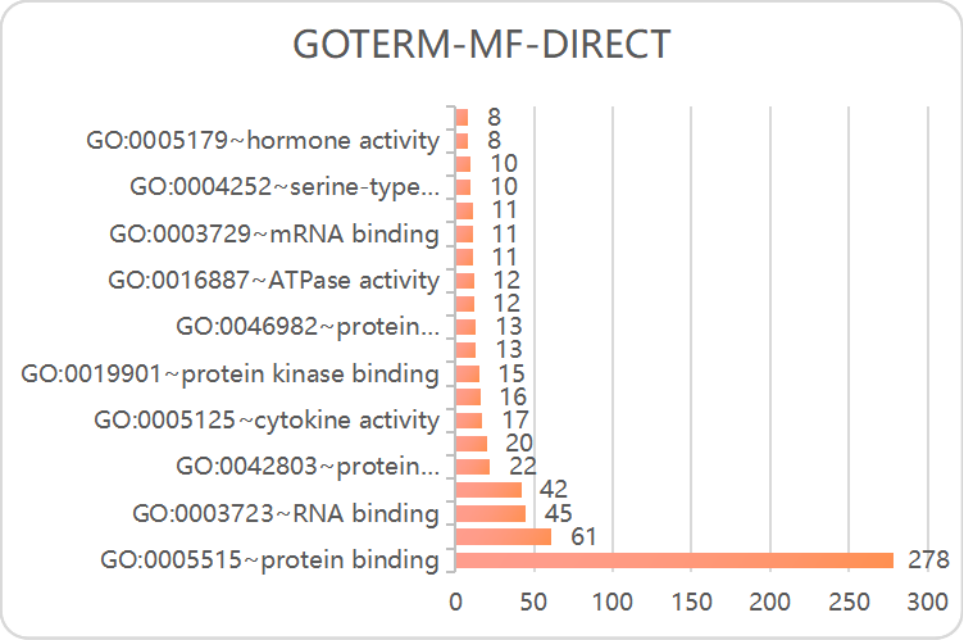
Fig.8: Core target protein networks.

2.5 GO analysis and KGEE analysis of drug-related targets.

When $P < 0.05$ was used to perform GO enrichment analysis on intersecting targets[13], the results were filtered to produce BP (218 items), CC (67 items), and MF (39 items), and the top 20 were selected based on the count value, as shown in Fig 9. The GO analysis's

findings revealed that biological processes such as signaling, intrinsic immune response, inflammation, immune response, positive regulation of ERK1 and ERK2 cascades, positive regulation of cellular proliferation, positive regulation of template DNA transcription, and other processes were primarily involved. Proliferation is positively regulated, as is the transcription of template DNA. Cytoplasmic lysate, cytoplasm, the cell membrane, and cellular exosomes are where most cellular functions take place. Protein binding, protein homodimer activation, RNA binding, ATP binding, calcium binding, and other molecular processes receive the majority of attention. With regard to cytokine receptor interactions, cancer, amyotrophic lateral sclerosis, PI3K-Akt signaling pathway, JAK-STAT signaling pathway, cancer MicroRNAs, influenza A, coronavirus, Alzheimer's disease, EBV infection, lipid, and atherosclerosis, KEGG pathway analysis[14] produced 56 enriched results, and there are 10 pathways with gene numbers >15.





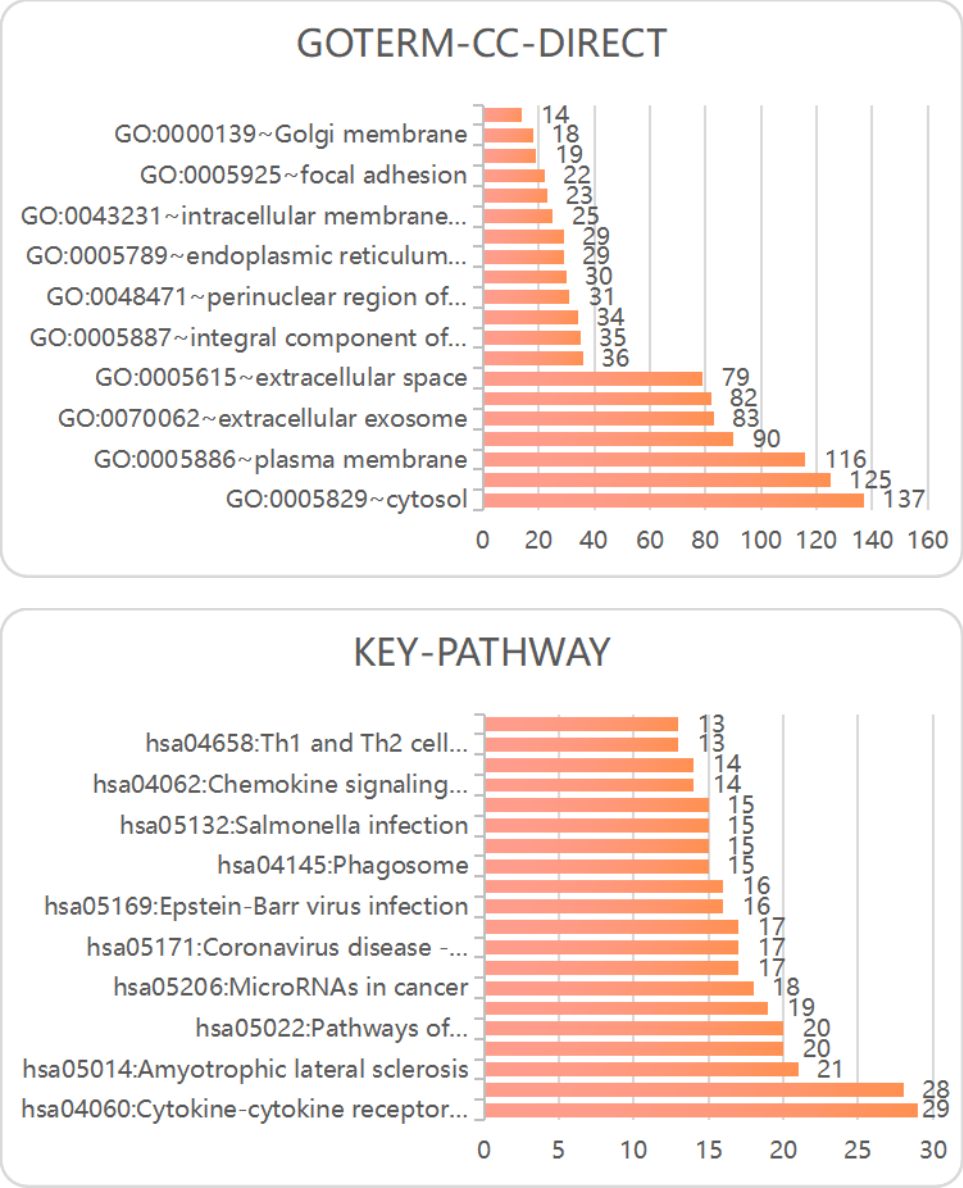


Fig.9: GO enrichment and KEGG pathway analysis.

3. DISCUSSION

Since 2020, the new crown epidemic has swept the world, and at present the mutated strains of the new crown have exceeded more than 1000 strains[15], the new crown virus belongs to RNA viruses, mainly six kinds of omicron[16], gamma, alpha, beta, delta, ramda, because of its rapid spread, strong infectiousness, rapid morbidity process, etc.[17], which has caused great loss of medical resources, human resources and people's lives and security in our country. Among them, Chinese medicine plays an important role in the prevention, control and treatment of the epidemic in China. Among these, Chinese medicine is crucial for the treatment, containment, and prevention of the pandemic in China. According to clinical research, the Omicron variant virus is classified as "cold and dampness" in Chinese medicine[18] and is a cold and damp epidemic virus.[19] It may be more easily contracted by those who have qi and yang deficiencies, and it is more likely to cause a serious illness after infection and be difficult to recover from.[20,21] Additionally, licorice is used to supplement deficient[22] symptoms, as stated in the "Materia Medica": "Spleen deficiency is appropriate for this tonic.[23]" As stated in Shennong's Herbal Classics: "The main five viscera and six internal organs of cold and heat evil qi[24]", licorice is also used to refill the five viscera and eliminate the evil qi of the internal organs. From the perspective of traditional Chinese medicine, licorice and dried ginger soup is helpful for the prevention and treatment of novel coronavirus pneumonia by tightening the COVID-19 illness mechanism. Through the retrospective analysis of clinical cases, Xia[25] et al. confirmed that treating COVID-19 with Chinese medicine in addition to Western medicine can lessen clinical symptoms, shorten the course of the disease, and significantly increase the clinical cure rate. As a result, it is worthwhile to encourage the use of this combination.

In this study, a PPI network was created using network pharmacology, and 56 core targets of licorice root ginger soup were analyzed and gathered for COVID-19 treatment. These targets were primarily involved in signal transduction, intrinsic immune response, inflammatory response, immune response, ERK1 and ERK2 cascade positive regulation, positive regulation of cell proliferation, positive regulation of template DNA transcription, etc., and the target genes were mainly located in these areas. signal transduction, intrinsic immune response, inflammatory reaction, immune response, etc., indicating that the treatment of COVID-19 with licorice and dried ginger soup is probably connected to its effects on transcriptional regulation, anti-inflammatory effects, and immunity control. This article, which is based on network pharmacology, investigates the active ingredients, targets, and related signaling pathways of licorice ginger soup against novel coronaviruses and confirms that the remedy has an undeniable role in preventing novel coronavirus pneumonia. Additionally, it shows that the medication is affordable, practical, and simple to obtain, making it suitable for both small- and large-scale prophylaxis against novel coronaviruses.

SUMMARY

In summary, licorice and dried ginger soup has the potential to treat novel coronavirus pneumonia through a variety of targets and pathways; however, it is not guaranteed that all of the drug's components will be fully incorporated into the soup due to the potential for herb composition to change after high-temperature decoction. Additionally, because a number of chemical components and some targets were neglected during the study, the efficacy of these neglected components is unknown. It is impossible to rule out the validity of these overlooked substances and targets, thus clinical work needs to be improved upon and verified.[26]

Funding details
This research received no external funding.

Disclosure statement
The authors report there are no competing interests to declare.

Data availability statement
Not applicable.

Authors' contributions
CW performed the literature search and selection, extracted and analyzed the data, and drafted the manuscript, YS, HZ, HF and YZ revised the manuscript. JD designed and supervised the study, analyzed the data, and revised the manuscript. All authors granted the final approval for submission.

REFERENCE

1. Min R, Liu M, Dai Z, Sun J. Progress in the pathogenesis and clinical study of novel coronavirus pneumonia. Chinese Journal of Hospital Infection, 2020; 30: 1171–1176.
2. Wu N, Liu M. Study of the incubation period of COVID-19 infected by different novel coronavirus variants. Chinese General Medicine, 2022; 25: 1309-1313+1319.
3. Li F, Xu J, Yuan H. Discussion on the application of liquorice and dried ginger soup in the treatment of rheumatoid arthritis-associated interstitial lung disease. Journal of Shaanxi University of Traditional Chinese Medicine, 2022; 45: 71–76.
4. Zhou J. Basic research on the regulation of medicinal properties of Radix et Rhizoma Pinelliae with Radix et Rhizoma Glycyrrhizae, Rhizoma Dahuang and Radix et Rhizoma Ginger. doctoral. Chengdu University of Chinese Medicine, 2009.
5. Li X, Li Y. Progress of pharmacological effects of active components of liquorice extracts. Jiangsu Traditional Chinese Medicine, 2019; 51: 81–86.
6. Tao H, Peng X, Fan J, Yuan Z. A preliminary study on the characteristics of Professor Shu Lan's traditional Chinese medicine for patients with persistent positive or re-positive nucleic acid in neocoronitis pneumoniae. Journal of Hunan University of Traditional Chinese Medicine, 2021; 41: 887–892.
7. Yuan, Zhang Y. Progress of chemical and pharmacological studies on dried ginger. Shandong Chemical Industry, 2018; 47: 41–52.
8. Ren P, Li Z, Zhu H, Wang P. Discussion on the Chinese medicine treatment pattern of new coronavirus pneumonia based on the theory of warm epidemic. Journal of Jinan University (Natural Science and Medicine Edition), 2020; 41: 144-150+162.
9. Bao Y, Xie W, Wang J. Progress in the study of Er Chen Tang. Chinese Journal of Experimental Formulary, 2019; 25: 9–18.
10. Lin S, Lin S, Shen Y, Huang G. Study on the mechanism of diammonium glycyrrhizinate in the treatment of influenza based on network pharmacology. Mass Technology, 2022; 24: 102–107.
11. Deng Y, Liu B, He Z, Liu T. Exploration of active compounds of Huo Xiang Zheng Qi Oral Liquid against novel coronavirus pneumonia (COVID-19) based on network pharmacology and molecular docking approach. Chinese Herbal Medicine, 2020; 51: 1113–1122.
12. Zhao J, Tian S, Yang J, Liu J. Cyberpharmacological investigation of the mechanism of lung-clearing and detoxification soup for the treatment of novel coronavirus pneumonia. Chinese Herbal Medicine, 2020; 51: 829–835.
13. Zong Y, Ding M, Jia K, Ma S. Network pharmacology and molecular docking based approach to explore the active compounds of

Darwon drink for the treatment of novel coronavirus pneumonia (COVID-19). Chinese Herbal Medicine, 2020; 51: 836–844.
14. Wang T, Liu W, Zhang P, Wang Y. Exploring the active components and targets of Zhongyan Yi Lung Detoxification Tang against novel coronavirus pneumonia (COVID-19) based on network pharmacology and molecular docking. Journal of Shaanxi University of Traditional Chinese Medicine, 2023; 46: 1–8.
15. Update on the novel coronavirus pneumonia outbreak as at 2400 hours on 23 December n.d. http: //www.nhc.gov.cn/xcs/yqtb/202212/cb666dbd11864 171b6586887c964791c.shtml.
16. Shi C, Ao X, Shao B, Yang W. Characterisation of cases testing positive for novel coronavirus nucleic acid at the centralised quarantine points for incoming persons. Preventive Medicine, 2022; 34: 325–329.
17. Lin W, Jia X. Updated Interpretation of Chinese Medicine Treatment in the "Diagnostic and Treatment Plan for New Coronavirus Pneumonia (Trial Implementation of the Ninth Version). Journal of Shandong University of Traditional Chinese Medicine, 2023; 47: 38–42.
18. Fu J, Mao X, Jiang L. Correlative survey and physical analysis of patients with persistent positivity for neoguan omijon. Emergency Chinese Medicine, 2022; 31: 1800–1803.
19. Zheng R, Chen Q, Huang M. Identifying and treating new coronavirus pneumonia from "cold-dampness-epidemiological toxin." China Journal of Traditional Chinese Medicine Information, 2020; 27: 18–20.
20. Yang J, Su W, Qiao J, Cai R. Analysis of Chinese medicine symptoms and constitution of 90 patients with common type novel coronavirus pneumonia. Journal of Chinese Medicine, 2020; 61: 645–649.
21. Hu R, Dong H. Prevention and early intervention of novel coronavirus pneumonia analysed from the doctrine of constitution in Chinese medicine. Henan Traditional Chinese Medicine, 2020; 40: 1316–1318.
22. Song H. Literature study of liquorice. doctoral. Shandong University of Chinese Medicine, 2015.
23. Xue Y. Introduction to the Materia Medica (Chinese materia medica). vol. 26. Beijing: Huaxia Publishing House, 1999.
24. Wu J, Sun X, Shi X. Shennong's Herbal Classics. Shenyang: Liaoning Science and Technology Press, 1997.
25. Xia W, An C, Deng C. Clinical study on 34 cases of novel coronavirus pneumonia treated with combination of Chinese and Western medicine. Journal of Chinese Medicine, 2020; 61: 375–382.
26. Luo Y, Zhang Y, Ge F, Zhou R. Molecular mechanism of antimigraine in Paeonia lactiflora and Glycyrrhiza glabra broth based on network pharmacology study. World Journal of Integrative Medicine, 2022; 17: 425-438+446.