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Research Article

Construction of network pharmacology-based approach and potential mechanism from major components of *Coriander sativum* L. against COVID-19

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Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Despite the fact that various therapeutic compounds have shown potential prevention or treatment, no specific medicine has been developed for the COVID-19 pandemic. Natural products have recently been suggested as a possible treatment option for COVID-19 prevention and treatment. This study focused on the potential of *Coriander sativum* L. (CSL) against COVID-19 based on network pharmacology approach. Interested candidates of CSL were identified by searching accessible databases for protein–protein interactions with the COVID-19. An additional GO and KEGG pathway analysis was carried out in order to identify the related mechanism of action. In the end, 51 targets were obtained through network pharmacology analysis with EGFR, AR, JAK2, PARP1, and CTSB become the core target. CSL may have favorable effects on COVID-19 through a number of important pathways, according to GO and KEGG pathway analyses. These findings suggest that CSL may prevent and inhibit the several processes related to COVID-19.

Keywords

Network pharmacology, COVID-19, *Coriander sativum* L., Protein interaction

Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and transmitted from person to person by interaction or respiratory droplet transmission (Chavda et al. 2022). The first reported incidence was discovered in the Chinese city of Wuhan in December of 2019 and the virus had spread fast throughout the world in less than six months. It had infected more than 40 million individuals over the world by March 1, 2022, resulting in more than 6 million deaths and the World Health Organization (WHO) declaring

it a global pandemic (Krumm et al. 2021; Tanase et al. 2022). COVID-19 is currently untreatable with any antiviral treatment that has been approved by the FDA. There is presently no recognized antiviral drug that can treat COVID-19. If the patient is in critical condition, a combination of antipyretic medications, oxygen therapy, and antibiotic therapy, may be used to better meet the individual needs of each patient (Majumder and Minko 2021; Chavda et al. 2022).

Currently, there are already 8 drugs authorized by European Medicines Agency (EMA) for COVID-19 (for example: tixagevimab, anakinra, paxlovid, regdanvimab, tocilizumab, casirivimab, sotrovimab and remdesivir) and two more drugs with awaiting marketing authorization (molnupiravir and baricitinib) (EMA 2022). Although there are various treatment options, more effective and less toxic COVID-19 therapies are urgently necessary. Because of this, more effective and less toxic COVID-19 therapies are urgently necessary. Following the outbreak, numerous clinical professionals investigated a wide range of traditional medicines from many nations in order to achieve beneficial clinical outcomes for their patients (Chakravarti et al. 2021). A growing body of research suggests that traditional medicines can be useful resources for the discovery of innovative pharmaceuticals (Ren et al. 2020; Lee et al. 2021). One example of traditional medicine from plants is *Coriander sativum* L. (CSL) which has been used widely in every country. Modern pharmacological researchers have discovered that Apiaceae-family member (CSL) has numerous pharmacological actions including anticancer, antibacterial, antidiabetic, antioxidant, anti-inflammatory, and high cholesterol inhibition (Silva et al. 2011; Sreelatha and Inbavalli 2012; Sahib et al. 2013; Yu et al. 2015; Aelenei et al. 2019; Sinaga et al. 2019; Mechchate et al. 2021; Mahleyuddin et al. 2022). According to International Organization of Standards (1998) and Guring et al. (2020), CSL contain several essential oil such as linalool, limonene, α-pinene, geraniol, and α-terpineol. All of these active compounds from CSL have shown abundant health benefits (Gurning et al. 2020).

Recent years have seen a significant increase in the acceptance of traditional medicine as a complementary therapies medicine with low toxicity and side effects and higher efficacy (Zhang et al. 2015; Iksen et al. 2021). While traditional medicine has a pharmacological mechanism that is vague, traditional medicine has many components, many targets, and many pathways, which makes it difficult to develop and improve (Wang et al. 2012). Pharmacological networks allow for systematic investigation of interactions between drugs, protein targets, diseases, genes and other factors. This is in line with the basic concept of conventional medicine treatment. A network pharmacology approach to the study of traditional medicine is scientifically solid and essential, as a result (Hopkins 2008; Ye et al. 2016). At the moment, many academics are increasingly turning to the study of traditional medicine's material basis and mechanism of action using network pharmacology. The use of network pharmacology has been presented as a possible tool for understanding natural products and predicting potential novel medications or targets for the specific disorders under investigation. The active components and potential mechanisms of action of CSL against COVID-19 were examined using network pharmacology in this study.

Materials and methods

Establishment of compounds information

For several compounds information, we used the Chinese herbal medicines platform database (TCMSP; http://lsp.nwu.edu.cn/tcmsp.php) and PubChem database. Compounds standard names, SMILES, and specific structures of the active candidate compounds was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and use ChemDraw 15.0 to draw the structures.

Establishment of target

The Swiss Target Prediction database (http://www.swisstargetprediction.ch/) provided information on candidate drugs target proteins, which was used to identify compounds that might be potential targets (Daina et al. 2019). COVID-19-related therapeutic targets were searched for and repetitive targets were eliminated using GeneCards (www.genecards.org/). The resulting target set for the disease was then constructed. In the end, Venny Diagram tool version 2.1 was used to perform and visualize the two groups of overlapping proteins between compounds and COVID-19 proteins (https://bioinfogp.cnb.csic.es/tools/venny/).

PPI network between components and COVID-19 targeted proteins

The protein–protein interaction network (PPI) between active compounds from CSL and COVID-19 proteins were analyzed by STRING database (https://string-db.org/) and Cytoscape 3.9.1 software.

GO and KEGG enrichment analysis

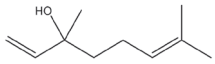
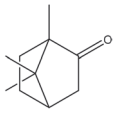
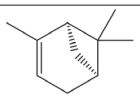
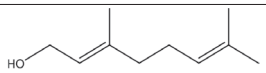
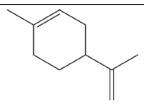
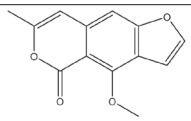
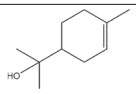
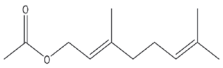
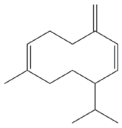
Analysis of GO and KEGG pathway enrichment was carried out using R software, which was used to upload the combined target library's protein targets. The biological process, molecular function, and cellular component are all considered as part of the GO enrichment study. The pathway related to CSL-COVID-19 could have a molecular mechanism explained by KEGG enrichment, and a R language tool created a bubble diagram showing the GO and KEGG pathway's significance.

Results

Investigation of potential targets

As a result of our earlier investigation and literature searching, we were able to identify a total of nine major chemicals in CSL (Table 1) (Gurning et al. 2020; Satyal and Setzer 2020). The GeneCards database was searched for targets linked to COVID-19, and the results revealed that there were 4,585 targets connected to COVID-19 and a total of 195 possible targets of 9 active compounds of CSL. As shown in Venn diagram in Fig. 1, a total of 51 potential anti-COVID19 targets were obtained through the interception of common targets.

Table 1. The main compounds information from *Coriander sativum* L.

Compounds	Chemical structures	Molecular weight	Log P
Linalool (C1)		154.25	2.6698
Camphor (C2)		152.23	2.4017
α-Pinene (C3)		136.23	2.9987
Geraniol (C4)		154.25	2.6714
Limonene (C5)		136.23	3.3089
Coriandrin (C6)		230.22	2.8562
α-Terpineol (C7)		154.25	2.5037
Geranyl acetate (C8)		196.29	3.2422
Germacrene D (C9)		204.35	4.8913

Protein-protein interaction of CSL against Covid-19

String predictions and Cytoscape were used to create a visualization of protein interaction using the Cytoscape software. The interaction between proteins was represented by 51 nodes and 104 edges, with an average node degree of 4.08 and an average local clustering coefficient of 0.5 (Fig. 2). The top 20 hub genes were screened out according to the degree of nodes, including EGFR, AR, JAK2, PARP1, CTSB, GSK3B, MMP1, PTPN1, HMOX1, MPO, CDK2, PRKDC, PLAU, IKBKB, BRD4, F2, TRPV1, CTSL, ELANE, and TYK2. The interaction between these genes is shown in Fig. 3 which explained that these targets are the key targets of the PPI network from CSL against COVID-19. Among these genes, EGFR, AR, JAK2, PARP1, and CTSB have the highest node degrees, which are 18, 9, 9, 8, and 8, respectively (Table 2). The higher the degree, the closer the node is to the center of the network. Apart from the degree parameter to determine the key targets, other parameters such as shortest path length, betweenness centrality, closeness central, and clustering coefficient might also have the role in the determination of key targets in the network. It is suggested that EGFR, AR, JAK2, PARP1, and CTSB may be five key targets for anti-COVID-19 activity of CSL.

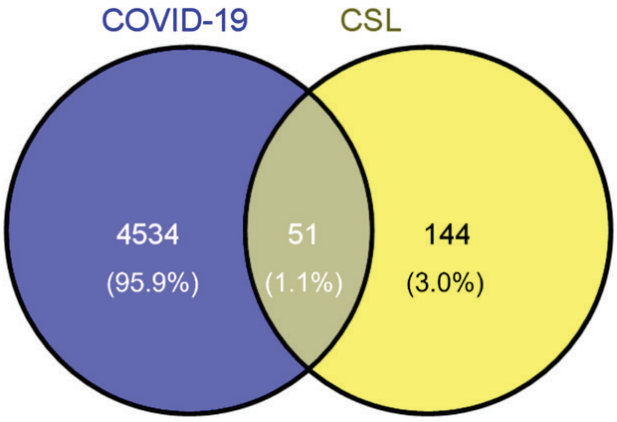


Figure 1. Venn diagram of the potential anti-COVID-19 targets.

Active compounds target network interaction

Cytoscape created a total of data pairs containing active compounds and disease target genes, and the interaction between active compounds and disease target genes was constructed as shown in Fig. 3. Fig. 4 showed the interaction between 9 active compounds with the intercept proteins with GeneCards database. In this network, the blue circle is the protein target, and the yellow circle is the compounds. The compounds-target relationship suggested that the targets may be potential therapeutic efficacy against COVID-19.

GO and KEGG enrichment analysis

To further evaluate better the molecular mechanism of the compounds-targets on COVID-19, GO and KEGG pathway enrichment analyses was conducted with the help of Cytoscape and RStudio. There were three different types of GO functional enrichment assessments carried out on these possible target genes, and the biological process (BP), molecular function (MF), and cellular component (CC) were included. The GO biological processes (Fig. 5A) were mainly involved in response to organic substance, response to chemical, inflammatory

Table 2. The top 20 targets of CSL related to COVID-19.

Target	Degree	Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Clustering Coefficient
EGFR	18	1.125	0.556039	0.888889	0.065359
AR	9	1.72	0	0.581395	0.180556
JAK2	9	1.333333	0.141063	0.75	0.125
PARP1	8	1	0.016184	1	0.160714
CTSB	8	1.666667	0	0.6	0.196429
GSK3B	7	1.75	0.301449	0.571429	0.095238
MMP1	7	1.333333	0.188325	0.75	0.214286
PTPN1	7	1	0.221498	1	0.166667
HMOX1	6	1.9	0.388889	0.526316	0.066667
MPO	6	0	0	0	0.133333
CDK2	6	2.142857	0.064493	0.466667	0.2
PRKDC	6	0	0	0	0.266667
PLAU	6	1	0.100483	1	0.233333
IKBKB	6	1.333333	0.336473	0.75	0.033333
BRD4	5	1.944444	0.150725	0.514286	0.25
F2	5	1.333333	0.047987	0.75	0.15
TRPV1	5	0	0	0	0.1
CTSL	5	1.5	0	0.666667	0.3
ELANE	5	1.6	0.032045	0.625	0.3
TYK2	5	0	0	0	0.35

response, response to stress, and response to external stimulus. GO molecular function (Fig. 5B) revealed that catalytic activity, protein binding, identical protein binding, small molecule binding, and nucleotide binding is the main activities related to the targets. Cellular component (Fig. 5C) showed that the targets mainly distributed in the plasma membrane, vesicle, side of membrane, membrane, and endomembrane system. According to the KEGG pathway analysis (Fig. 5D), the signaling pathways were mainly focused on the Hepatitis C, prostate cancer, Kaposi sarcoma-associated herpesvirus infection, pathways in cancer, metabolic pathways, and other immune system related pathway such as chemokine signaling pathway, Th1 and Th2 cell differentiation, PD-L1 expression and PD-1 checkpoint pathway in cancer, and Th17 cell differentiation.

Discussions

It has been proven that the COVID-19 virus is spreading and that it poses a hazard to human health since the

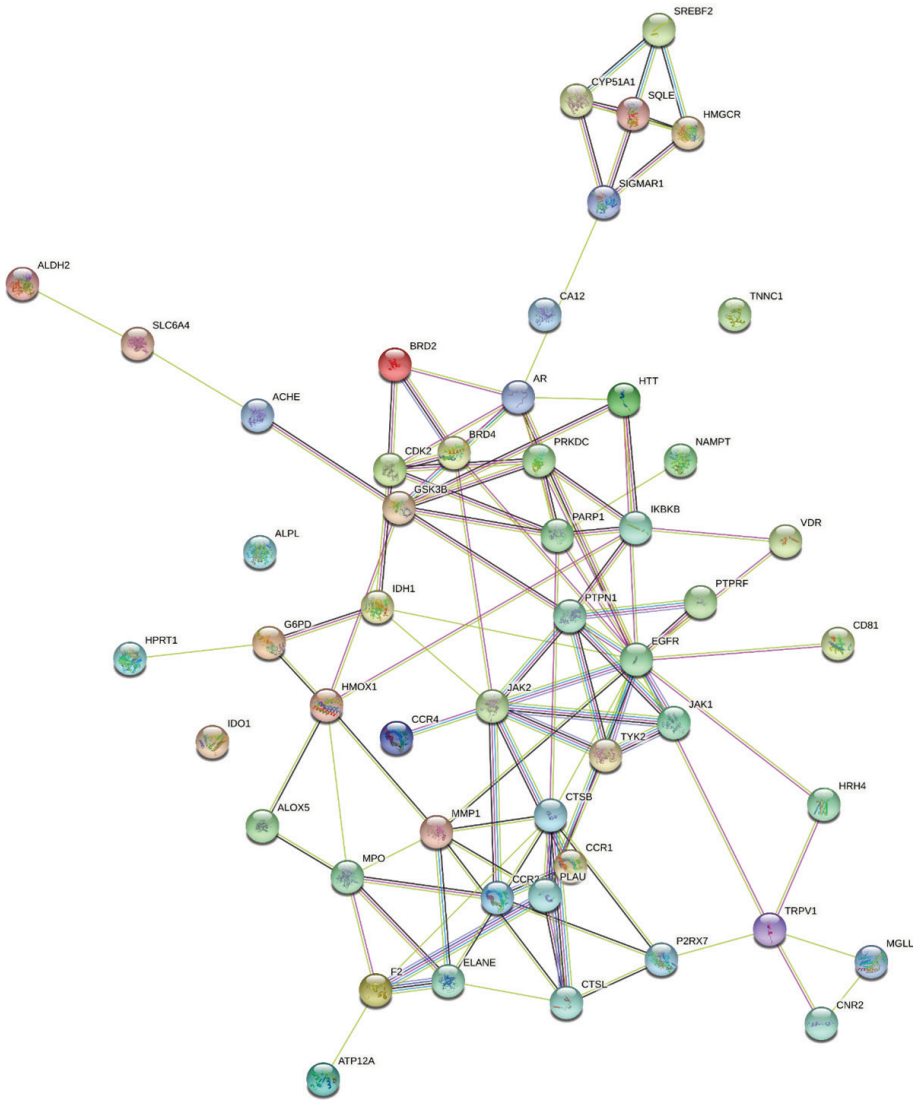


Figure 2. Protein-protein interaction (PPI) and hub genes of CSL against COVID-19.

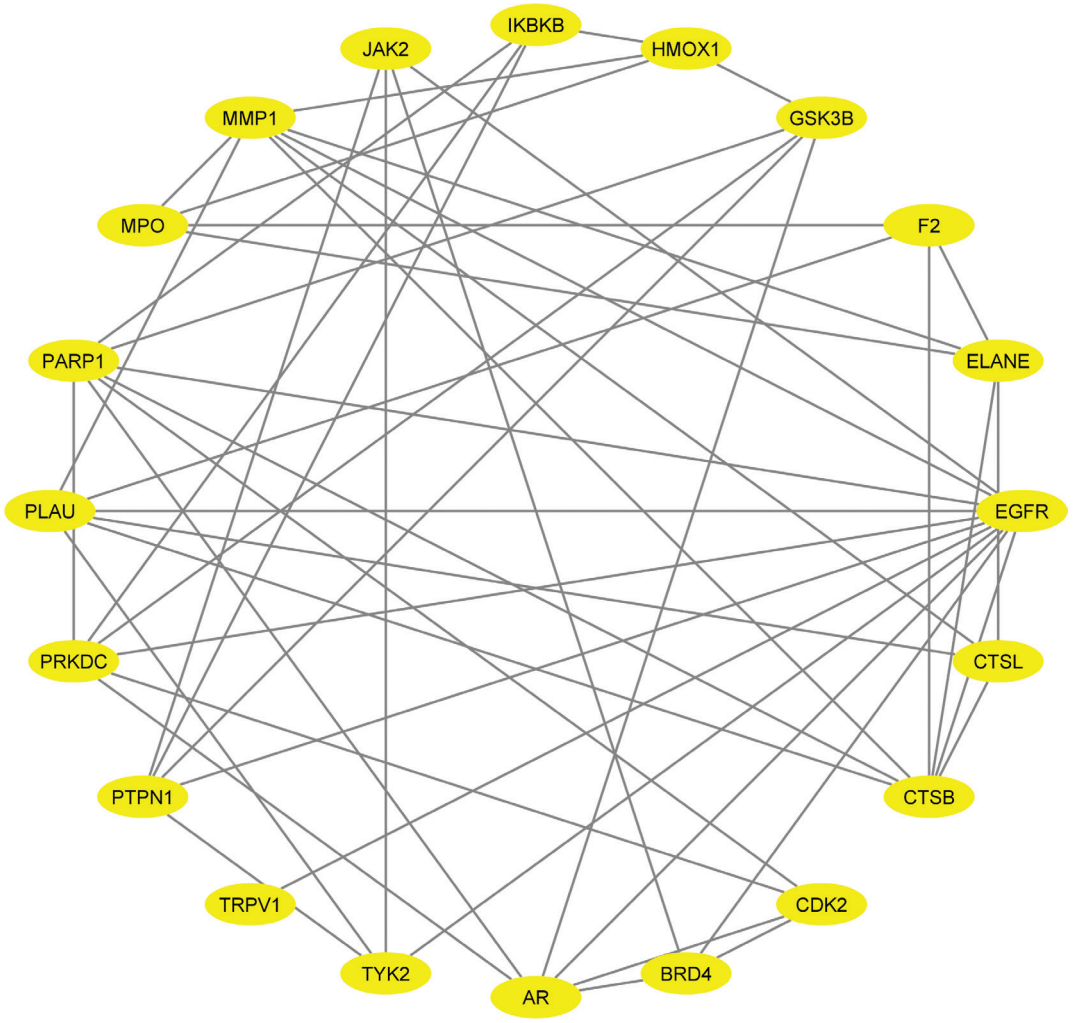


Figure 3. The PPI interaction between top 20 targets of CSL in COVID-19.

virus's outbreak at the end of 2019 was discovered (Harrison et al. 2020). The pandemic is still not ended, and all health scientist from all around the world have committed their time and resources to combating the disease. Even though there is currently no medicine or successful treatment plan for COVID-19, a variety of drugs are being repurposed (Gavriatopoulou et al. 2021). The fact that traditional medicine may be utilized to prevent or treat a variety of complicated disorders is undeniable, and it also represents a viable source for the discovery of further candidate medications for treating COVID-19 (An et al. 2021; Li et al. 2021; Lyu et al. 2021). The developing field of network pharmacology provides a novel technique and a great tool for determining the biological basis of traditional medication (Hopkins 2007), which is particularly useful in the treatment of COVID-19. A significant number of resources and time would be required to investigate the effects and mechanisms of traditional medicine and its pharmacological activities due to the characteristics of multi-components, multi-targets, and multi-pathways, which represents a significant barrier to widespread acceptance and use of traditional medicine in clinical settings (Hopkins 2007; Yang et al. 2021).

One example of widely used traditional medicines is CSL. As common traditional medicine, CSL is a plant that is used to treat disorders of the upper respiratory tract and lung related disease (Yang et al. 2021). Following the screening of nine key compounds in CSL, we discovered that these nine compounds occurred in the compound-target interaction, indicating that CSL's anti-COVID-19 activities are likely to be closely related to the nine compounds described in the previous section. Compound-disease networking analysis demonstrated that the therapeutic effect of CSL against COVID-19 was directly related 51 targets.

Degree screening showed that EGFR, AR, JAK2, PARP1, and CTSB might become the most important target of CSL in the treatment of COVID-19. EGFR, which is one common type of growth factor receptor in the membrane cell, plays a crucial role in the attachment and internalization of viral (Hondermarck et al. 2020). Apart from the internalization of viral, EGFR overactivation might decreases Interferon regulatory factor 1 (IRF-1) and, consequently, suppressed the host's immune response (Ueki et al. 2013). AR is one of steroid hormone receptors are ligand-activated transcription factors that regulate eukaryotic gene expression and

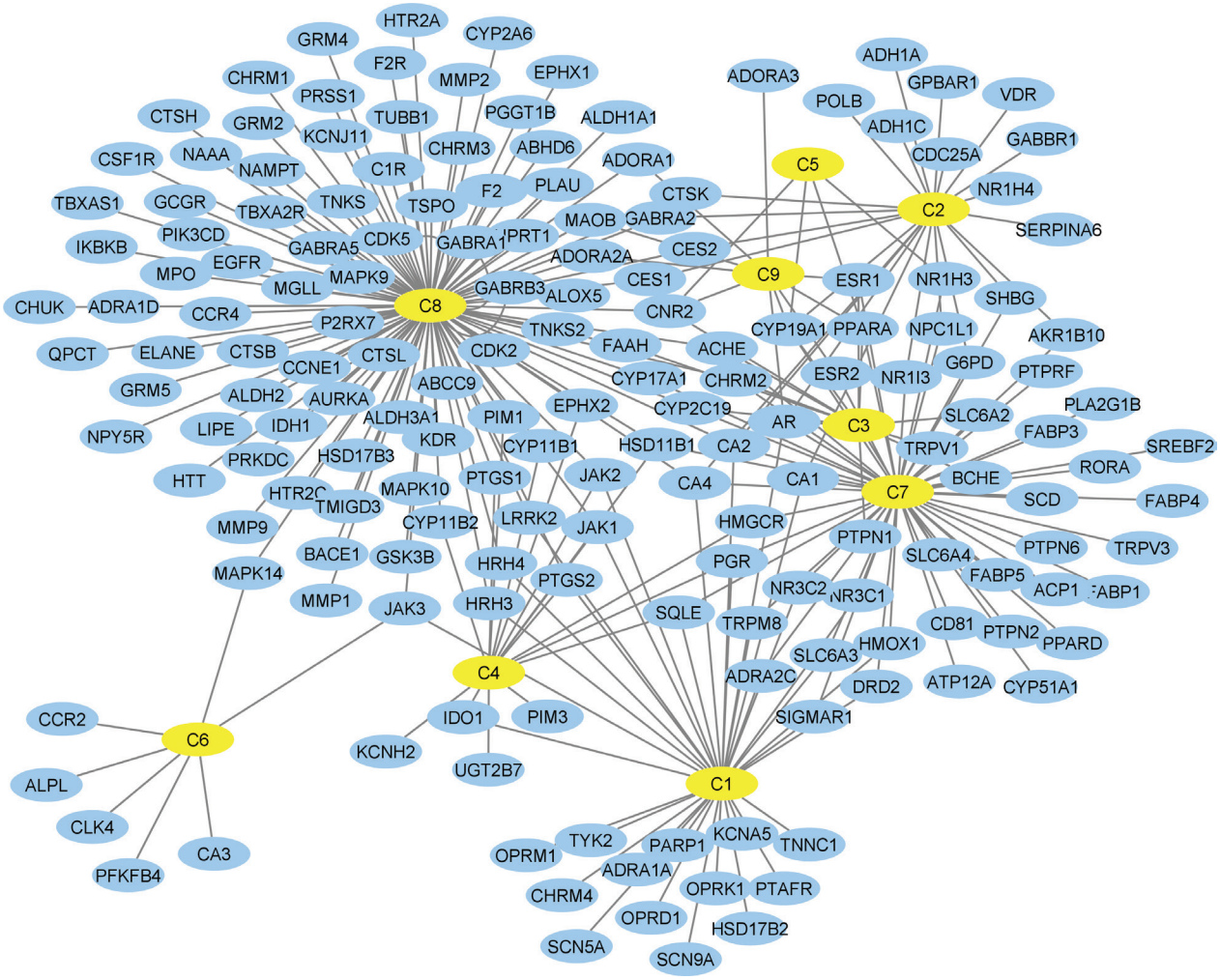


Figure 4. The network interaction between 9 compounds from CSL with targets from COVID-19.

affect cellular proliferation and differentiation in target tissues (Baratchian et al. 2021). Activated AR induces immunomodulatory responses and capable of affecting the function of most immune cell populations (Vom Steeg et al. 2020). Several cytokine receptors have been shown to signal through the JAK2 signaling pathway (Yang et al. 2017; Heidel and Hochhaus 2020). PARP1 is one of the internal regulator of cell death in cells and regulator of cytokine production. Suppression of PARP1 has been shown to reduce the production of inflammatory cytokines in the body (Rajawat and Chandra 2021). CTSB is a lysosomal proteases that plays an important role in physiological processes such as energy metabolism, intracellular protein degradation, and immune responses. Apart from the normal regulator system, CTSB is required for COVID-19 to infect cells (Yadati et al. 2020; Hashimoto et al. 2021).

Even though several researches have been done on COVID-19, and some linked susceptibility genes have been reported, the possible mechanism for its initiation is still unknown. Because of PPI, susceptibility genes may influence an individual's vulnerability to COVID-19. We used GO and KEGG analysis to look for potential critical pathways which may be inhibited by CSL. Collectively, for the GO analysis, it revealed that the related biological process for anti-COVID-19 activity related to CSL is inflammatory response, response to stress, response to external stimulus, and etc. Molecular functions are associated with several protein binding such as ion binding, small molecule binding, nucleotide binding, chemokine interaction, and etc. Related target cell components showed that several components inside the cells might involve mostly in the region of plasma membrane and cell surface. Moreover, KEGG enrichment analysis revealed CSL could involve in several pathways especially in the immune regulation related pathway such as Th1 and Th2 cell differentiation, PD-L1 -PD-1 checkpoint pathway, and Th17 cell differentiation. Several recent studies have suggested that the PD-1/PD-L1 pathway may have a key role in the control of the host immune response (Sabbatino et al. 2021). Apart from immune regulation pathway, several virus, cancer, growth factor, and insulin resistance related pathway might be involved. Based on our network pharmacology studies, it has been suggested that CSL may have an anti-COVID19 effect; however, more research is needed to understand the exact mechanisms by which CSL acts. Because of the genetic, ethnic,

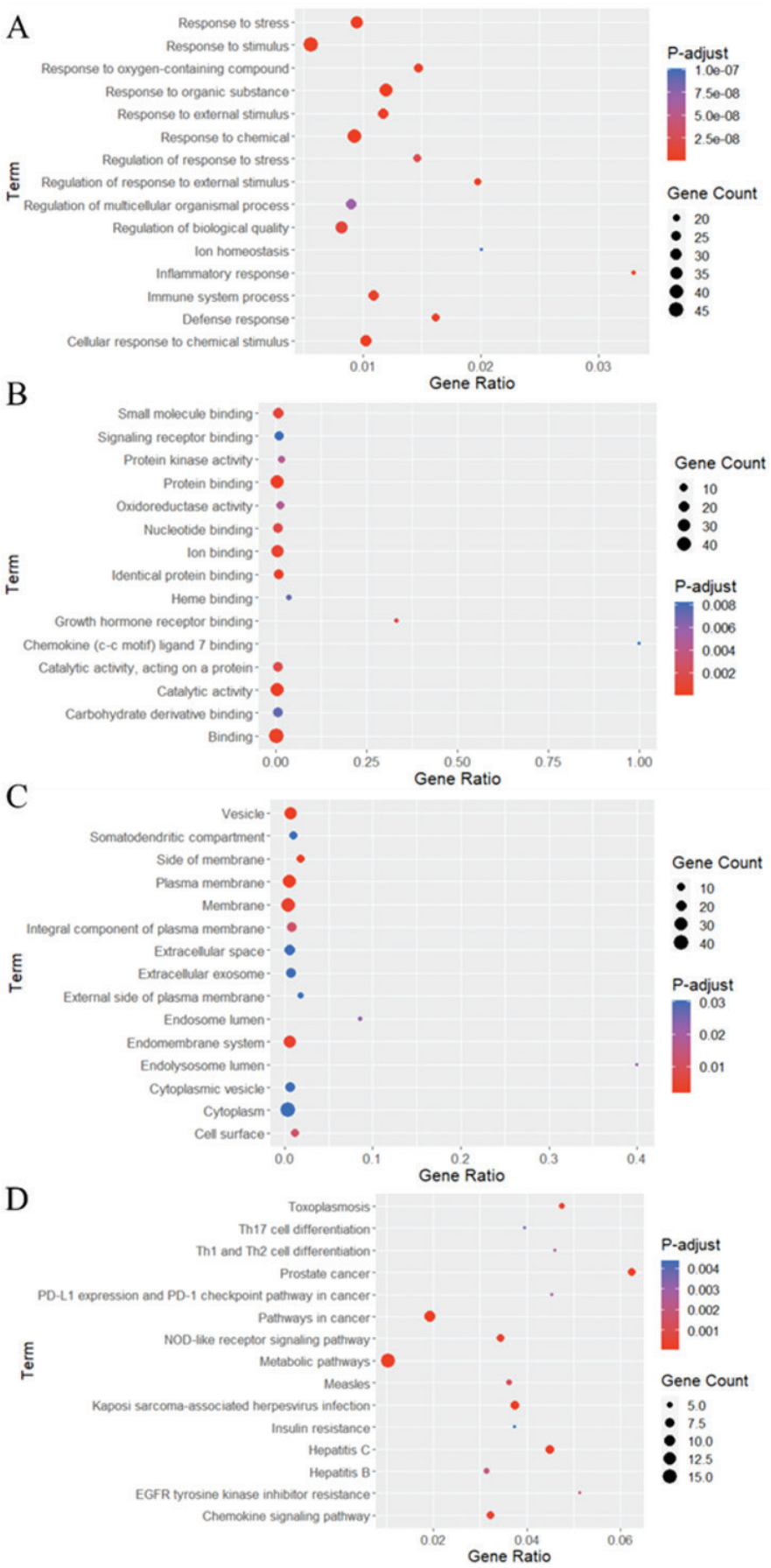


Figure 5. GO and KEGG pathway enrichment analysis. **A.** Biological process; **B.** Molecular function; **C.** Cellular component; **D.** KEGG pathways.

and underlying diseases linked with COVID-19, the study of CSL against COVID-19 may be relevant for clinical application, primarily based on the genetic, ethnic, and underlying diseases related with the therapeutic technique.

Conclusions

This study showed that 9 active ingredients in CSL had potential anti-COVID-19 activity, involving 51 target genes related to COVID-19. EGFR, AR, JAK2, PARP1, and CTSB are the hub target in treatment of COVID-19. The obtained results revealed that CSL may exert multiple functions in regulating immune response and inhibiting viral infections, hereby indicating the potential of CSL against COVID-19.

Conflict of interests

The authors declare that there is no conflict of interest.

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