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Network Pharmacology-Based Analysis and Exploration of Potential Mechanisms of Key Coriandrum sativum L. Components Against COVID-19

Maximilian Meyer[1], Clara Fischer[1]*, Elias Neumann[1]

[1]Department of Drug Discovery, University of Düsseldorf, Düsseldorf, Germany.

***E-mail** ✉ clara.fischer@yahoo.com

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by the SARS-CoV-2 virus and represents a significant global health challenge. Although several therapeutic agents have shown promise for prevention or treatment, no specific drug has been definitively developed for COVID-19. Recently, natural products have emerged as potential candidates for COVID-19 management. This study investigated the potential effects of Coriandrum sativum L. (CSL) against COVID-19 using a network pharmacology approach. Active compounds from CSL were identified through database searches, followed by analysis of protein–protein interactions relevant to COVID-19. Furthermore, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were conducted to elucidate the possible mechanisms of action. Network pharmacology analysis revealed 51 potential targets, with EGFR, AR, JAK2, PARP1, and CTSB identified as key hub targets. GO and KEGG analyses suggested that CSL may exert protective effects against COVID-19 by modulating multiple critical biological pathways. Overall, these results indicate that CSL could potentially contribute to the prevention and inhibition of various processes involved in COVID-19 pathogenesis.

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

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Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spreads primarily through person-to-person contact and respiratory droplets [1]. The first cases were reported in Wuhan, China, in December 2019, and within six months, the virus had rapidly disseminated worldwide. By March 1, 2022, COVID-19 had affected over 40 million people globally, leading to more than six million deaths, prompting the World Health Organization (WHO) to declare it a pandemic [2, 3]. To date, there is no FDA-approved antiviral treatment specifically for COVID-19. Critically ill patients are typically managed with supportive therapies, including antipyretics, oxygen supplementation, and antibiotics, tailored to individual clinical needs [1, 4].

Currently, the European Medicines Agency (EMA) has authorized eight drugs for COVID-19 treatment (including tixagevimab, anakinra, paxlovid, regdanvimab, tocilizumab, casirivimab, sotrovimab, and remdesivir), with two additional drugs (molnupiravir and baricitinib) pending approval [5]. Despite these options, there remains an urgent need for safer and more effective therapies. In response, clinicians worldwide have investigated traditional medicines to improve patient outcomes [6]. Accumulating evidence suggests that traditional remedies can serve as valuable sources for developing new pharmacological agents [7, 8].

One widely used medicinal plant is Coriandrum sativum L. (CSL), a member of the Apiaceae family. Research has demonstrated that CSL possesses multiple pharmacological properties, including anticancer, antibacterial, antidiabetic, antioxidant, anti-inflammatory, and cholesterol-lowering effects [9-16]. According to the International Organization of Standards (1998) and Gurning *et al*. (2020) [17], CSL contains several essential oils,

such as linalool, limonene, α-pinene, geraniol, and α-terpineol, all of which have demonstrated notable health benefits.

In recent years, there has been growing acceptance of traditional medicine as a complementary therapy, valued for its low toxicity, minimal side effects, and potential efficacy [18, 19]. However, traditional remedies are complex, often containing multiple active compounds that interact with numerous targets and pathways, making it challenging to fully elucidate their mechanisms [20]. Network pharmacology provides a systematic approach to analyze interactions among drugs, protein targets, diseases, and genes, aligning with the principles of modern medicine. Consequently, applying network pharmacology to study traditional medicine is both scientifically robust and essential [21, 22]. Currently, many researchers employ network pharmacology to investigate the material basis and mechanisms of traditional medicines. This approach can help identify active components and predict potential therapeutic targets for specific diseases. In this study, network pharmacology was used to explore the active compounds and possible mechanisms of CSL in combating COVID-19.

Materials and Methods

Compound information collection

Information on CSL compounds was obtained from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP; http://lsp.nwu.edu.cn/tcmsp.php) and the PubChem database. Standardized compound names, SMILES notations, and chemical structures of candidate compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and drawn using ChemDraw 15.0.

Target identification

Candidate compound target proteins were predicted using the SwissTargetPrediction database (http://www.swisstargetprediction.ch/) [23]. COVID-19-related therapeutic targets were identified via GeneCards (www.genecards.org/), and duplicate entries were removed. The resulting dataset was used to construct the disease-target library. Overlapping proteins between CSL compounds and COVID-19-related targets were visualized using Venny Diagram Tool version 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/).

PPI network construction

Protein–protein interaction (PPI) networks between CSL active compounds and COVID-19-related proteins were analyzed using the STRING database (https://string-db.org/) and visualized with Cytoscape 3.9.1 software.

GO and KEGG enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed in R software. The combined target library was used to investigate biological processes, molecular functions, and cellular components. KEGG analysis provided insights into molecular mechanisms by identifying relevant pathways, and bubble diagrams were generated to depict the significance of GO terms and KEGG pathways.

Results and Discussion

Identification of potential targets

Through literature review and database searches, nine major bioactive compounds were identified in CSL **(Table 1)** [17, 24]. Searching the GeneCards database for COVID-19-associated targets revealed 4,585 disease-related proteins, while 195 potential targets were identified for the nine CSL compounds. As shown in the Venn diagram **(Figure 1)**, 51 overlapping targets were identified, representing potential anti-COVID-19 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

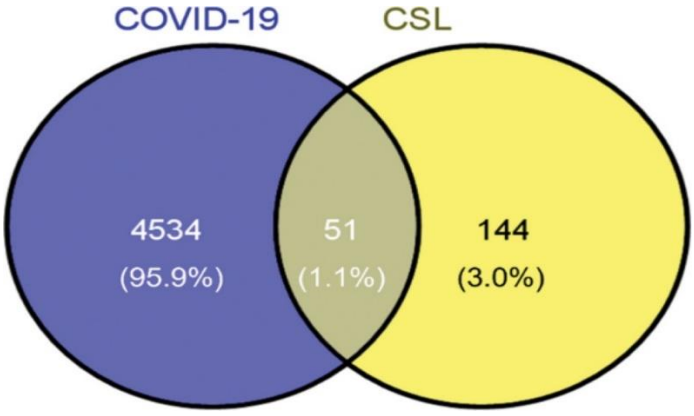


Figure 1. Venn diagram of the potential anti-COVID-19 targets

Protein–protein interaction analysis of CSL against COVID-19

The protein–protein interaction (PPI) network for CSL's active compounds against COVID-19 was constructed using STRING and visualized with Cytoscape. The network included 51 nodes connected by 104 edges, showing an average node degree of 4.08 and a local clustering coefficient of 0.5 **(Figure 2)**. Using node degree as a criterion, the top 20 hub genes were identified: EGFR, AR, JAK2, PARP1, CTSB, GSK3B, MMP1, PTPN1, HMOX1, MPO, CDK2, PRKDC, PLAU, IKBKB, BRD4, F2, TRPV1, CTSL, ELANE, and TYK2. **Figure 3** illustrates the interactions among these key genes, demonstrating their central positions within the PPI network of CSL against COVID-19.

Among the hub genes, EGFR, AR, JAK2, PARP1, and CTSB had the highest connectivity, with node degrees of 18, 9, 9, 8, and 8, respectively **(Table 2)**. Nodes with greater connectivity are generally more influential in network signaling. Beyond node degree, other network metrics such as betweenness centrality, closeness centrality, shortest path length, and clustering coefficient can further inform target significance. Based on these analyses, EGFR, AR, JAK2, PARP1, and CTSB are likely to be the most critical targets mediating CSL's potential anti-COVID-19 activity.

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

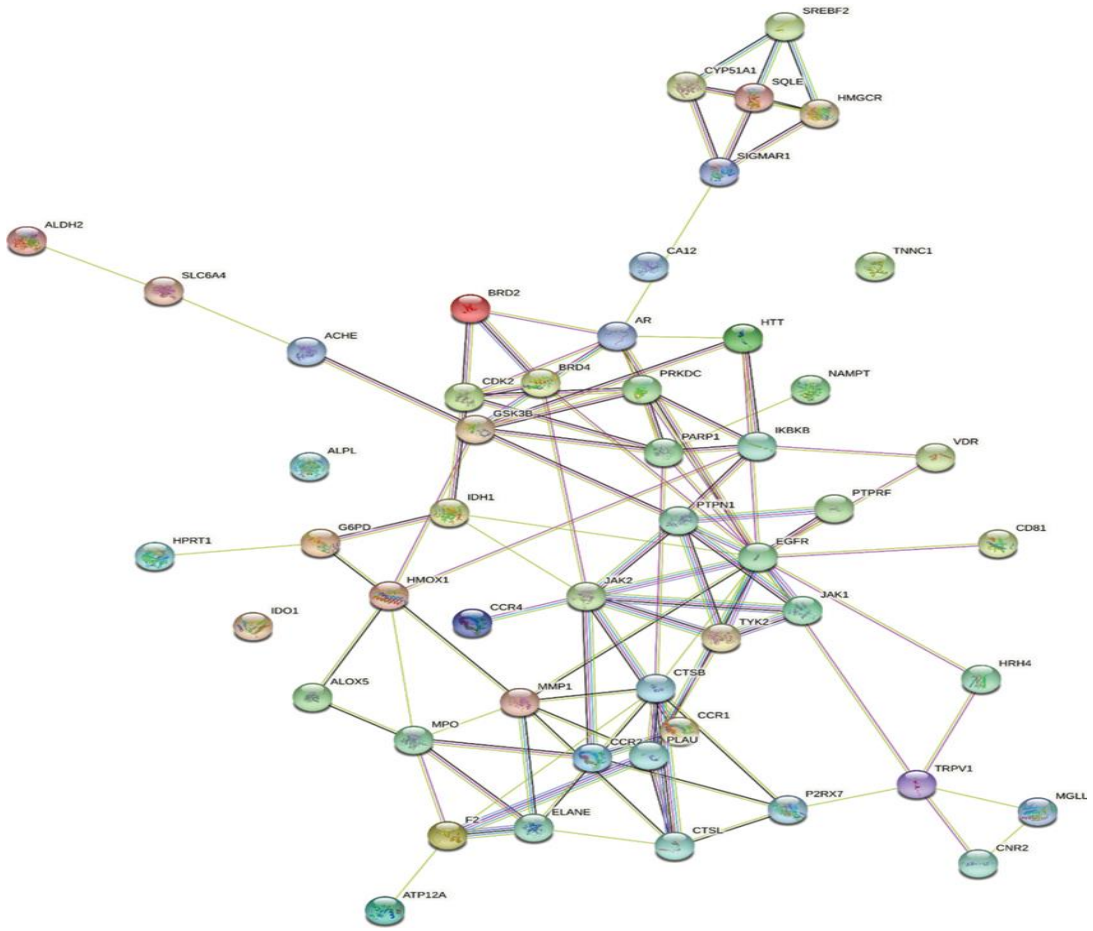


Figure 2. Protein-protein interaction (PPI) and hub genes of CSL against COVID-19.

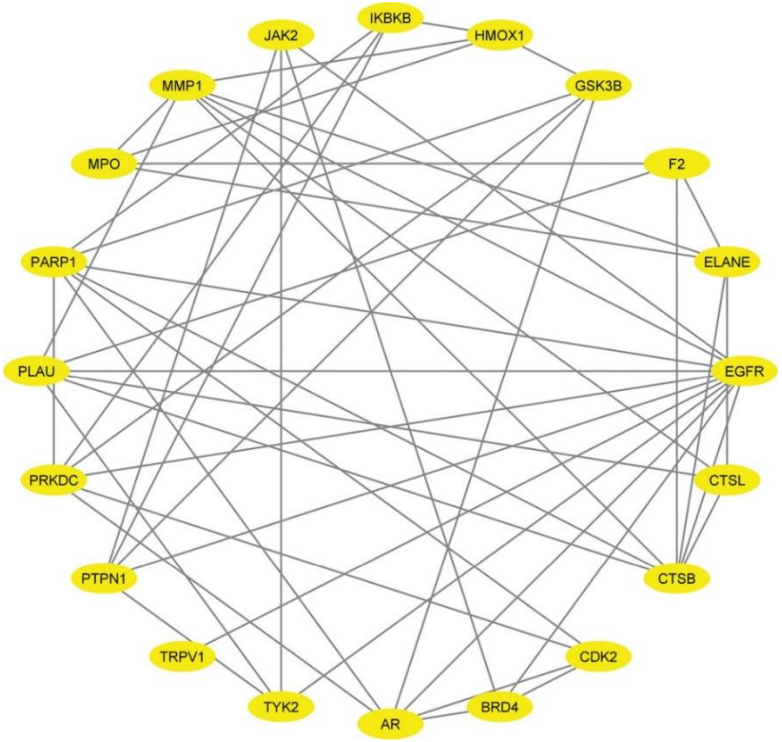


Figure 3. The PPI interaction between top 20 targets of CSL in COVID-19.

Active compounds–target network analysis

Using Cytoscape, a network comprising active compounds and their corresponding disease-related target genes was constructed **(Figure 3)**. **Figure 4** illustrates the interactions between the nine identified active compounds and the intersecting proteins obtained from the GeneCards database. In this network, protein targets are represented by blue nodes, while the compounds are shown as yellow nodes. The relationships depicted in this network indicate that these targets could serve as potential mediators of CSL's therapeutic effects against COVID-19.

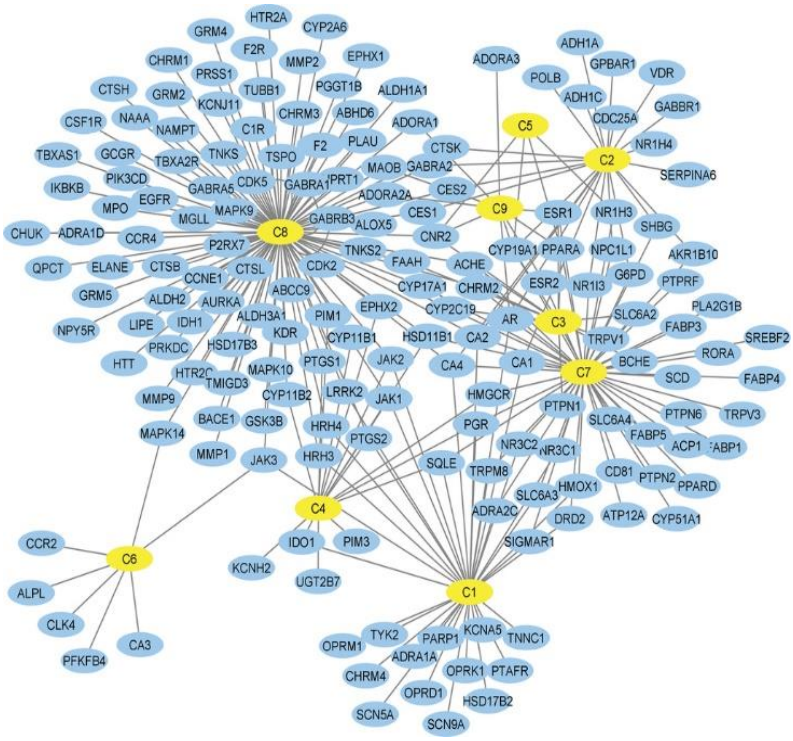


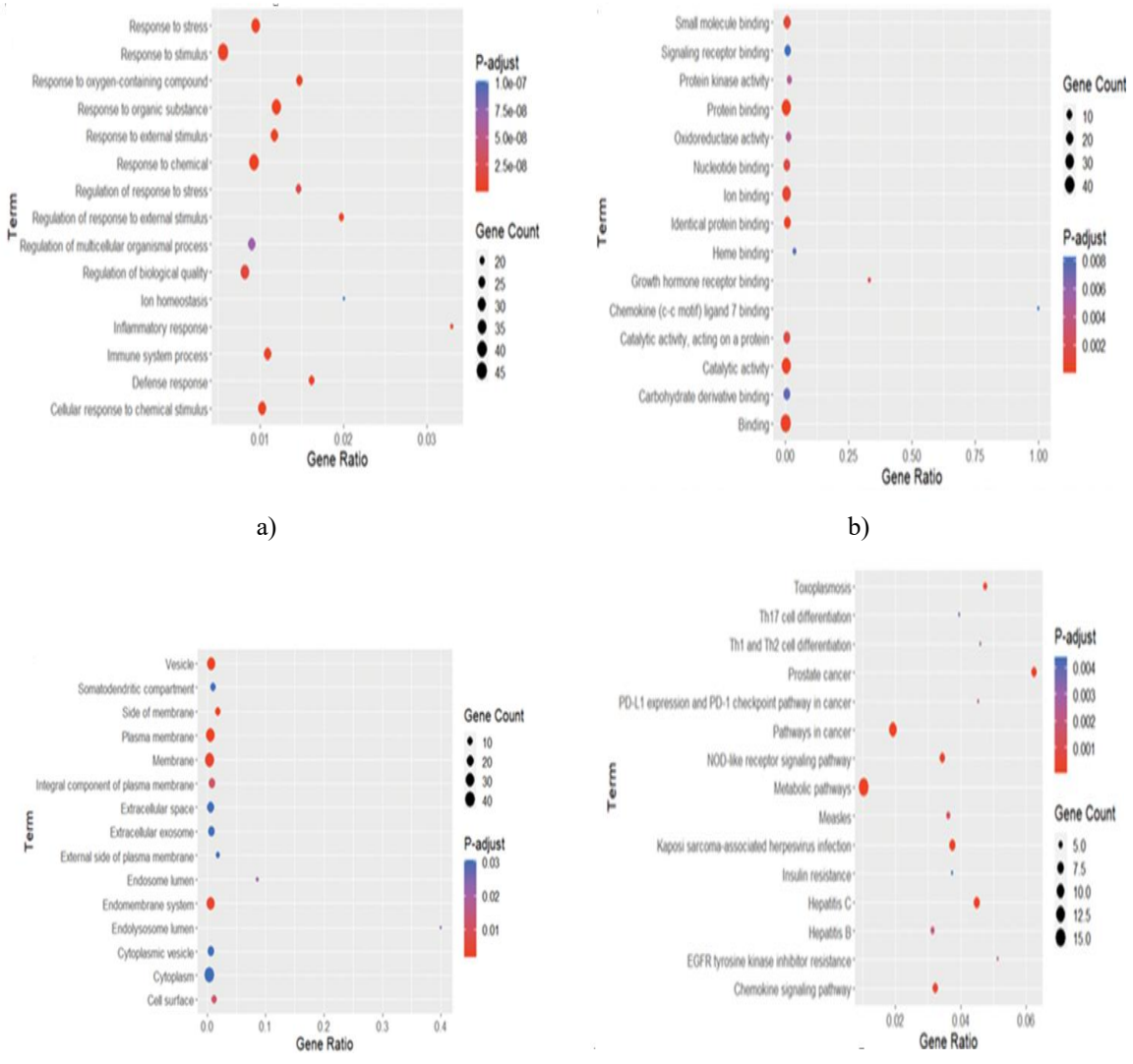
Figure 4. The network interaction between 9 compounds from CSL with targets from COVID-19.

GO and KEGG pathway analysis

To clarify the potential molecular mechanisms by which CSL compounds may act against COVID-19, we performed enrichment analyses using Gene Ontology (GO) and KEGG pathways via Cytoscape and RStudio. GO analysis was divided into three categories: biological process (BP), molecular function (MF), and cellular component (CC).

For biological processes **(Figure 5a)**, the targets were primarily associated with responses to chemical and organic stimuli, inflammatory regulation, stress adaptation, and reactions to external environmental factors. The molecular function analysis **(Figure 5b)** indicated that the targets were predominantly involved in catalytic activities, binding to proteins or identical proteins, small molecule interactions, and nucleotide interactions. Cellular component analysis **(Figure 5c)** suggested that these proteins were largely located in the plasma membrane, vesicular structures, membrane surfaces, general membrane areas, and the endomembrane system.

KEGG enrichment results **(Figure 5d)** revealed that the targets were enriched in pathways related to viral infections (e.g., Hepatitis C, Kaposi's sarcoma-associated herpesvirus), cancer pathways (prostate cancer, general oncogenic pathways), metabolic processes, and key immune system pathways. Specifically, pathways involved in chemokine signaling, differentiation of Th1, Th2, and Th17 cells, and PD-1/PD-L1 immune checkpoint regulation were prominent.



a) b)

c) d)

Figure 5. GO and KEGG pathway enrichment analysis. a). Biological process; b). Molecular function; c). Cellular component; d). KEGG pathways.

Since its emergence in late 2019, COVID-19 has demonstrated rapid transmission and a serious threat to global health [25]. The pandemic continues to persist, prompting scientists worldwide to dedicate significant resources to combating the disease. Although no definitive treatment or approved antiviral exists for COVID-19, a variety of existing drugs are being repurposed for potential therapeutic use. Traditional medicines, known for their capacity to prevent or treat complex disorders, also offer a promising source for identifying new therapeutic candidates against COVID-19 [26-28]. Network pharmacology has emerged as a powerful approach to elucidate the biological mechanisms of traditional remedies [29], providing an efficient strategy to study multi-component, multi-target, and multi-pathway interventions. However, the inherent complexity of traditional medicines poses challenges for their clinical evaluation and acceptance [29, 30].

Coriandrum sativum L. (CSL) is one widely used traditional remedy, particularly for respiratory and lung-related disorders [30]. In this study, nine key bioactive compounds in CSL were identified and found to participate in compound-target interactions, suggesting that these compounds are likely responsible for its anti-COVID-19 activity. Network analysis revealed 51 potential targets associated with these compounds, with EGFR, AR, JAK2, PARP1, and CTSB emerging as the most significant hub targets.

EGFR, a cell membrane growth factor receptor, is critical for viral attachment and internalization. Overactivation of EGFR can reduce Interferon Regulatory Factor 1 (IRF-1) levels, thereby suppressing host immune responses [31, 32]. AR, a steroid hormone receptor, regulates gene expression and affects cellular proliferation and differentiation, also modulating immune cell functions [33, 34]. JAK2 mediates signaling of several cytokine receptors [35, 36], while PARP1 regulates cell death and cytokine production, with its inhibition reducing inflammatory cytokine levels [37]. CTSB, a lysosomal protease, is involved in energy metabolism, protein degradation, and immune responses, and is also required for SARS-CoV-2 cell entry [38, 39].

Despite extensive research on COVID-19, the molecular mechanisms underlying its pathogenesis remain incompletely understood. PPI analysis suggests that susceptibility genes may influence individual vulnerability to infection. GO enrichment analysis in this study highlighted that CSL targets are mainly involved in inflammatory responses, stress responses, and reactions to external stimuli. Molecular function analysis indicated significant roles in protein, ion, nucleotide, and chemokine binding, while cellular component analysis showed that most targets are associated with the plasma membrane and cell surface. KEGG pathway enrichment suggested that CSL may modulate several immune-related pathways, including Th1, Th2, and Th17 cell differentiation and PD-1/PD-L1 checkpoint regulation, which are critical for controlling host immune responses [40]. Additionally, pathways related to viral infections, cancer, growth factors, and insulin resistance were implicated. Overall, these network pharmacology results indicate that CSL could exert multi-target effects against COVID-19, though further experimental studies are necessary to confirm the precise mechanisms. Clinical relevance may also depend on genetic, ethnic, and comorbidity factors associated with COVID-19 patients.

Conclusion

This study identified nine active compounds in CSL with potential anti-COVID-19 activity, acting through 51 related target genes. EGFR, AR, JAK2, PARP1, and CTSB were recognized as hub targets in mediating therapeutic effects. The findings suggest that CSL may modulate immune responses and inhibit viral infection through multiple pathways, highlighting its potential as a complementary treatment option against COVID-19.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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