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Bioinformatics analysis of radix *Angelica dahurica*, *Chuanxiong* rhizoma, and *Cyperi* rhizoma for COVID-19 treatment

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Abstract

Background: The COVID-19 pandemic, which has unfolded over the past years, poses significant threats to global public health and socioeconomic well-being. Three herbs (radix *Angelica dahurica, Chuanxiong* rhizoma, and *Cyperi* rhizoma) have been long utilized in combination for treating common colds and flu.

Objective: To analyze potential biotargets and explore possible effects of plant-derived compounds from 3 herbs towards COVID-19 treatment.

Method: Bioinformatics databases and network pharmacology were employed to identify bioactive compounds and their biotargets with integrated statistical calculation, followed by Gene Ontology enrichment. KEGG pathway analysis was performed to elucidate the involvement of selected bioactive compounds in COVID-19-related processes.

Results: Network pharmacology highlighted essential receptors, cytokines, and signaling proteins. Gene Ontology analysis revealed associations with signal transduction, RNA transcription enzymes, and crucial cellular components. Molecular function analysis emphasized interactions related to virus entry. KEGG analysis uncovered 32 potential targets across various pathways, elucidating their role in inflammation and cytokine storms.

Conclusion: This study provides new insight for the molecular mechanisms underlying the therapeutic potential of a combination of radix *Angelica dahurica, Chuanxiong* rhizoma, and *Cyperi* rhizoma against COVID-19. The identified targets and pathways offer new directions for further experimental validation, paving the way for potential therapeutic interventions for COVID-19.

Keywords: radix *Angelica dahurica, Cyperi* rhizome, *Chuanxiong* rhizome, COVID-19, bioinformatics

1. Introduction

In the context of the COVID-19 pandemic, the urgent need for effective treatments has prompted researchers to explore unconventional yet potentially impactful sources (Filip *et al*., 2022). Amid the COVID-19 pandemic, Traditional Chinese Medicine (TCM) has emerged as a potential therapeutic avenue (Ding *et al*., 2022). In China, TCM has shown efficacy in various conditions, including COVID-19 (Fan *et al*., 2020). TCM herbal formulas, based on specific combinations, have demonstrated effectiveness in alleviating respiratory symptoms and contributing to disease severity reduction (Fan *et al*., 2020). Despite differing perspectives between TCM and Western medicine on COVID-19, the scientific rationale of administration of TCM herbs in patients is evident (Ding *et al*., 2022).

Radix *Angelica dahurica, Chuanxiong* rhizoma, and *Cyperi* rhizoma, prominent constituents of traditional Vietnamese medicinal formulations, such as "Cam Xuyen Huong" (CXH) have long been recognized for their therapeutic efficacy in managing flu-like symptoms. This remedy aligns with traditional medicine principles for wind-cold invasion diseases, sharing symptoms with COVID-19 (Liu, 2010).

Pharmacological studies reveal that main herbal components of CXH possess antiviral, anti-inflammatory, anti-thrombotic, and immune-modulatory effects (Donkor *et al*., 2016), (Safa *et al.*, 2020), (Zhang *et al*., 2019), (Kamala *et al*., 2018), (Lee *et al*., 2020). Rich in essential oils and polyphenols, CXH shows promise as a potential agent for COVID-19 prevention and treatment (Solnier & Fladerer, 2020), (Asif *et al*., 2020). Notably, these traditional remedies have gained widespread acceptance for addressing common respiratory ailments, including colds and flu, with symptoms akin to those observed in most of mild or moderate COVID-19 patients. This raises a compelling question about the intentional or unintentional use of these traditional remedies for COVID-19 patients and underscores the need for a rigorous scientific investigation into their bioactive components and potential efficacy.

By employing advanced bioinformatics analysis and network pharmacology, our research aims to unravel the molecular underpinnings of radix *Angelica dahurica*, *Chuanxiong* rhizoma, and *Cyperi* rhizoma. Through the integration of computational methodologies, we seek to elucidate the potential therapeutic mechanisms of these traditional herbal compounds against COVID-19. This exploration is not only rooted in the rich tapestry of Vietnamese traditional medicine but also aligns with the pressing global imperative to identify safe and effective treatments for COVID-19. The significance of our research lies in bridging traditional wisdom with contemporary scientific methodologies, offering a unique perspective that could influence clinical considerations and public health strategies in the ongoing battle against the COVID-19 pandemic.

2. Method

Study was performed based on the methods previously described (Kang *et al*., 2024, Huang *et al*., 2021, Loganathan *et al*., 2024), with study design flow chart presented in **Figure 1**.

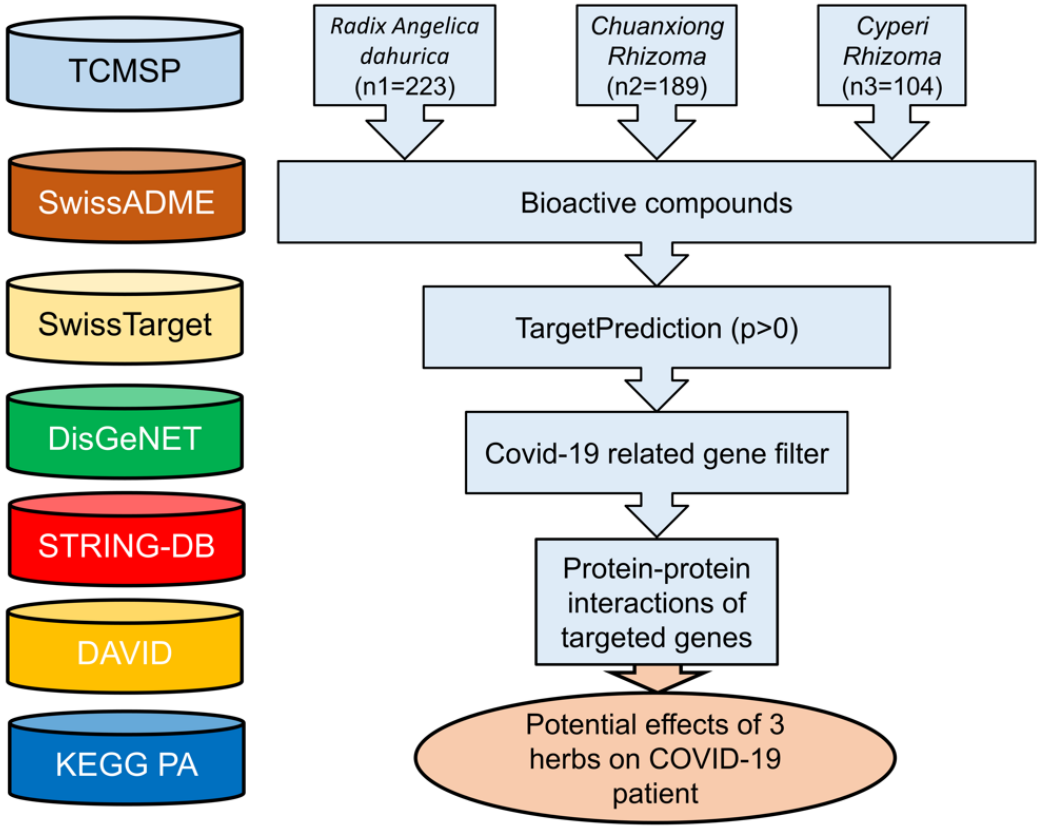

Figure 1: Flowchart of study design

2.1. Retrieval of bioactive compounds

The Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) (Ru *et al*., 2014), available at (https://tcmsp-e.com/tcmsp.php) was employed to retrieve a comprehensive list of bioactive compounds from radix *Angelica dahurica*, *Chuanxiong* rhizoma, and *Cyperi* rhizoma. This initial step aims to identify the chemical constituents present in these herbal sources. List of chemical identities were converted into SMILES (Simplified Molecular Input Line Entry System) as recorded in PUBCHEM database.

2.2. Drug-likeness assessment

SwissADME (Daina *et al.*, 2017) was utilized for assessing the drug-likeness properties of the identified bioactive compounds, using SMILES codes as input. The bioactive compounds were filtered based on their predicted physicochemical properties, following Lipinski's Rule of Five, to ensure their drug-likeness.

2.3. Biotarget prediction

SwissTargetPrediction (Gfeller *et al*., 2014) was employed to predict potential biotargets associated with the selected drug-like compounds. This computational approach helps in identifying the proteins or targets that may interact with the bioactive compounds, facilitating a deeper understanding of their pharmacological mechanisms. Compounds with a probability score greater than 0 in SwissTargetPrediction were retained, indicating a possible interaction with the selected targets. The higher probabilities indicate stronger predicted interactions.

2.4. Selection of target genes and network pharmacology analysis

Web-based DisGeNET tool (Pinero *et al*., 2017) was utilized to filter and prioritize target genes related to COVID-19. Subsequently, a network pharmacology analysis was conducted using STRING-DB web tool (Szklarczyk *et al*., 2021) to construct an interaction network between proteins under effect of bioactive compounds. The most interacting cluster was selected to display with high confidence value set to 0.7. This analysis provides insights into the potential synergistic effects at molecular interactions.

2.5. Functional GO analysis

DAVID bioinformatics tool (Sherman *et al*., 2022) was employed for functional Gene Ontology (GO) analysis. This step aims to categorize and annotate the identified target genes based on their biological processes, molecular functions, and cellular components, elucidating the functional implications of the selected bioactive compounds.

2.6. Pathway analysis

The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis (Kanehisa & Goto, 2000) was conducted to unravel the biological pathways associated with the identified target genes. This analysis will offer a systematic understanding of how the bioactive compounds from radix *Angelica dahurica*, *Chuanxiong* rhizoma, and *Cyperi* rhizoma may impact various cellular processes and signaling pathways relevant to COVID-19.

3. Result and discussion

3.1. Retrieval list of bioactive compounds and drug-likeness assessment

Using the TCMSP database, we can look up available compounds on the system for radix *Angelica dahurica* (223 compounds), *Chuanxiong* rhizoma (189 compounds), and *Cyperi* rhizoma (104 compounds). The SwissADME web tool was utilized for screening, eliminating compounds

violating Lipinski's rule of 5 (more than one of the criteria) in combination with the analysis of pharmacokinetic parameters (ADME). The screening process, led to the identification of 58 compounds with favorable drug-likeness and oral bioavailability (Data not shown). Notably, these compounds exhibited high permeability across Caco-2 cell membranes, emphasizing their potential for effective absorption and distribution via oral administration. For further screening of target proteins, a short list of bioactive compounds was selected. **Table 1** presented all selected compounds adhere to Lipinski rule and exhibit drug-likeness (DL) values greater than 0.2, along with oral bioavailability (OB) exceeding 20%. Additionally, these compounds display high permeability across Caco-2 cell membranes, all with values above 0.7 (log Papp in 10 cm/s), indicating their potential for effective absorption, distribution via oral administration, and there is a high possibility giving a therapeutic effect.

Table 1. Screening results based on the Lipinski rule and ADME parameters

No.	Compounds	*Caco-2* >0.7	Oral bioavailability %>=20	Drug-likeness >=0,2	Herbs (*)
1	Isoimperatorin	0.97	45.46	0.23	RAD
2	Prangenin	0.8	43.6	0.29	RAD
3	Byakangelicol	0.76	41.42	0.36	RAD
4	Phellopterin	0.98	40.19	0.28	RAD
5	Alloisoimperatorin	0.9	34.8	0.22	RAD
6	Ammidin	1.13	34.55	0.22	RAD
7	Cnidilin	1.03	32.69	0.28	RAD
8	9-[[(2R)-3,3-dimethyloxiran-2-yl]methoxy]furo[3,2-g]chromen-7-one	0.82	29.78	0.29	RAD
9	9-hydroxy-4-(3-methylbut-2-enoxy)furo[3,2-g]chromen-7-one	0.9	28.06	0.25	RAD
10	Oxypeucedanin	0.85	24.9	0.3	RAD
11	Perlolyrine	0.88	65.95	0.27	RLW
12	Senkyunone	1.15	47.66	0.24	RLW
13	Wallichilide	0.82	42.31	0.71	RLW
14	1,4-Epoxy-16-hydroxyheneicos-1,3,12,14,18-pentaene	1.28	45.1	0.24	RC
15	Isodalbergin	0.8	35.45	0.2	RC
16	Rosenonolactone	0.72	79.84	0.37	RC
17	Hyndarin	1	73.94	0.64	RC

(*) Radix *Angelica dahurica* (RAD), *Chuanxiong* rhizoma (RLW), *Cyperi* rhizoma (RC)

3.2. Selection of target genes and network pharmacology analysis

Among the 17 compounds screened, their respective SMILES codes were collected, and a target search was conducted using the online tool SwissTargetPrediction, identified 447 genes with a probability greater than 0. Subsequent comparison and categorization of genes associated with SARS-CoV-2-induced pneumonia were performed utilizing the DisGeNet database toolkit. The screening outcomes revealed 162 genes that overlapped with the initial set of 614 genes targeted by

03 herbs and COVID-19 related genes by database (**Figure 2A**). The list of overlapping genes (162) was used as input for STRING-DB to construct the Protein-Protein interaction network. The result is presented in **Figure 2B**. The network diagram shows the most important interactions with high possibilities between various nodes, including important receptors (**IGF1R, EGFR, INSR, EPOR, AR**, **ESR1, IL2RB**), cytokine (**IL2**), several central signal conductors (**AKT1, MAPK8, JAK1, JAK2, MDM2**).

The protein-protein interaction network analysis revealed critical interactions between receptors, cytokines, and signal transduction proteins, notably **IGF1R, EGFR, and IL2**. The bioactive compounds from radix *Angelica dahurica*, *Chuanxiong* rhizoma, and *Cyperi* rhizoma may collectively enhance the modulation of these targets. For instance, the combination of these herbs could result in synergistic effects on the inhibition of pro-inflammatory cytokines like **IL2**, thereby potentially reducing cytokine storm severity in COVID-19 patients. Further experimental validation is required to confirm these bioinformatic predictions.

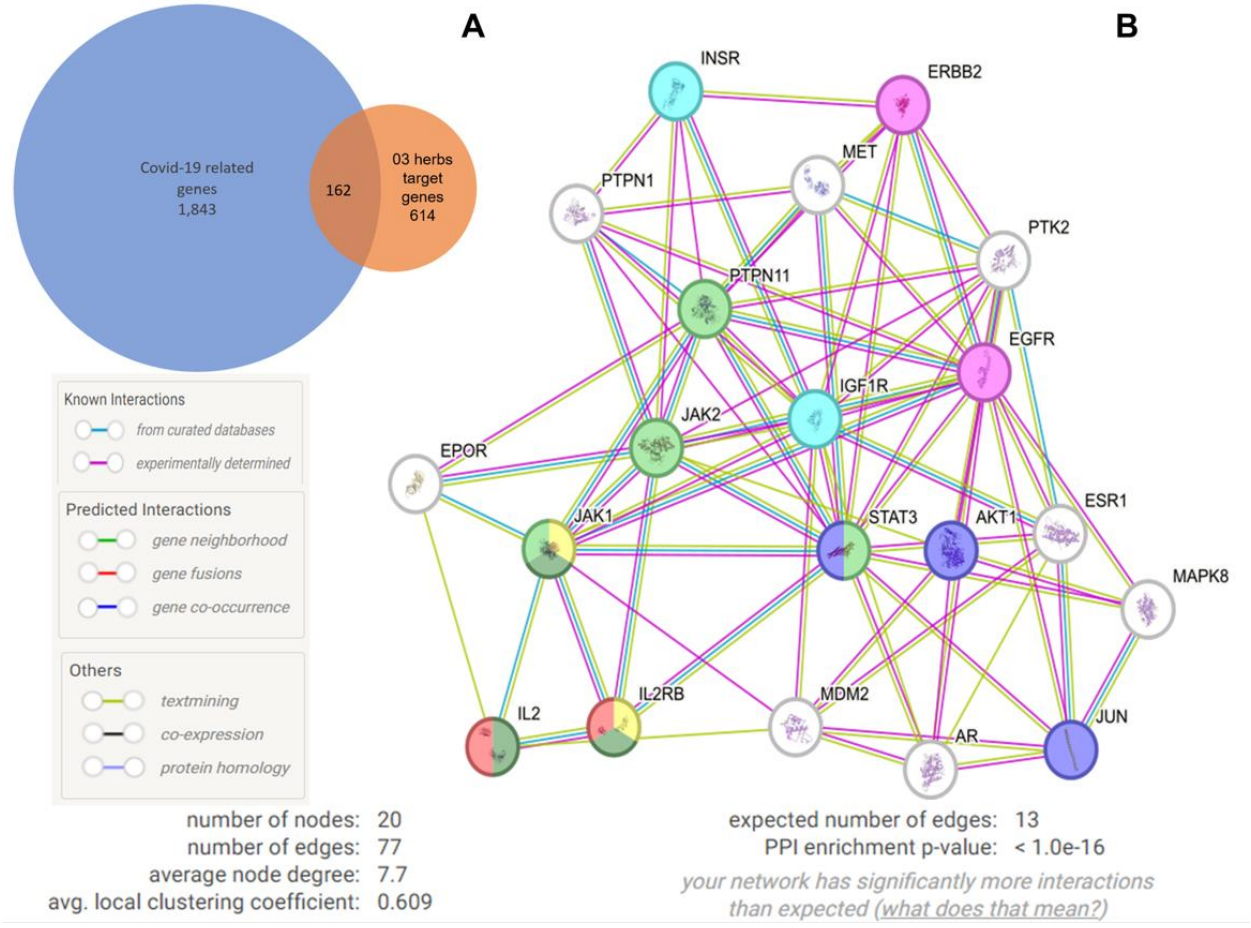

Figure 2: Analysis result of interfering target genes and protein-protein interaction network

3.3 Gene Ontology analysis

Analyzing 162 genes on the DAVID bioinformatics tool obtained Gene Ontology analysis. Functional GO analysis for biological process, results in **Figure 3** suggested that the mechanism of action of the compounds is strongly related to the signal transduction process, followed by the active coordination of the activities of the RNA transcription enzymes. Biological processes that are less affected include the response to drugs, downregulation of programmed cell death (apoptosis), and protein autophosphorylation. These processes hold significance in the context of COVID-19, as inflammation and cytokine storms are linked to multiple signal transduction pathways (Yang *et al*., 2021). Viral replication is strongly influenced by RNA transcription. Additionally, apoptotic cell death is also a previously reported phenomenon with CD4 and CD8 cells, related to the COVID-19 disease and strongly affecting disease prognosis (Choudhary *et al*., 2021, V'Kovski *et al*., 2021). The outcomes of the Gene Ontology (GO) analysis have offered insights into potential biological processes influenced by the investigated compounds and their relevance to COVID-19 pathology. Noteworthy information suggesting further experimental research on these compounds includes the activity of RNA transcription enzymes and the mechanism of programmed cell death of immune cells.

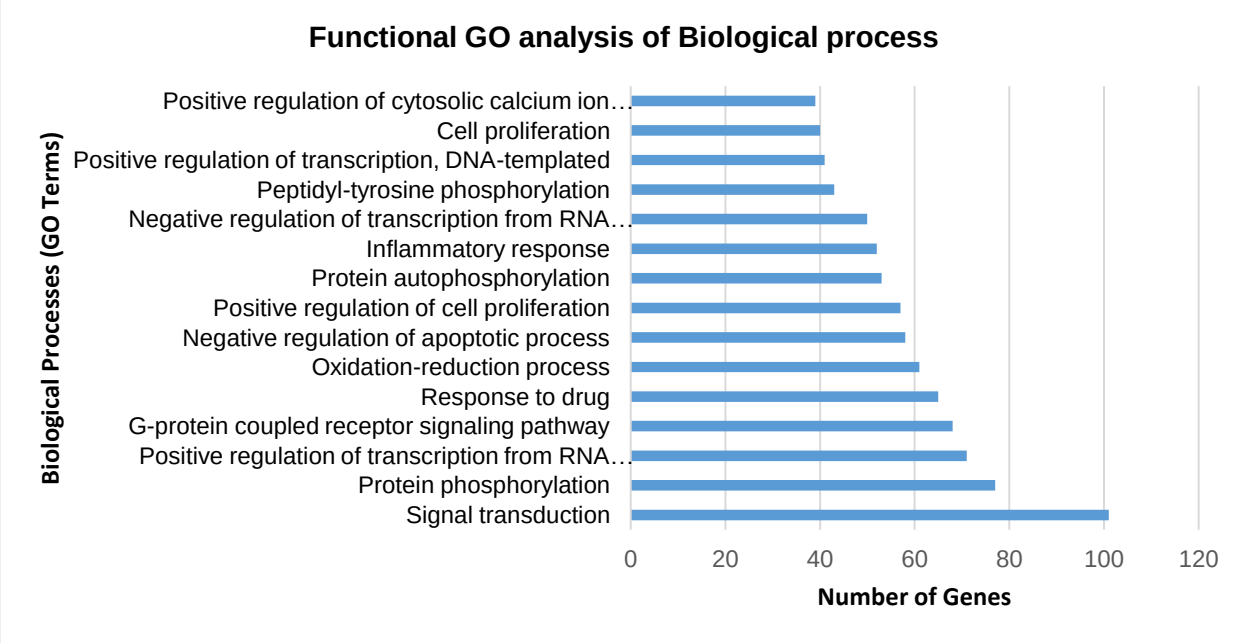

Figure 3: Gene Ontology analysis result of biological process

To further clarify the results of the biological process analysis, which demonstrated a relationship with the signal transduction process, GO of cellular component was analyzed. The results from **Figure 4** showed that the screened compounds may affect many different components of the cell, focusing on the plasma membrane, integral component of membrane and in the cytoplasm.

These results suggested a relationship between the biological effects of the compounds and the process of virus penetration through the host cell membrane, interaction with membrane receptor elements (integral component of membrane) and the entire membrane structure (plasma membrane), followed by the process of copying and multiplying viral RNA in the cytoplasm and nucleus (cytoplasm and nucleus). When SARS-CoV-2 approaches the cell membrane, the spike proteins (S proteins) of virus recognize and bind to the ACE2 receptor, and consequently transmit a signal to the serine protease TMPRSS2 on the cell surface to promote the viral invasion process, which in turn causes downregulation of ACE2 – this is also associated with inflammatory responses and cytokine storms. Therefore, the GO analysis results of cell components suggest that the 17 compounds screened above possibly produce biological activities through direct or indirect effects on the invasion process. Virus integration and replication require interaction with cellular components as abovementioned.

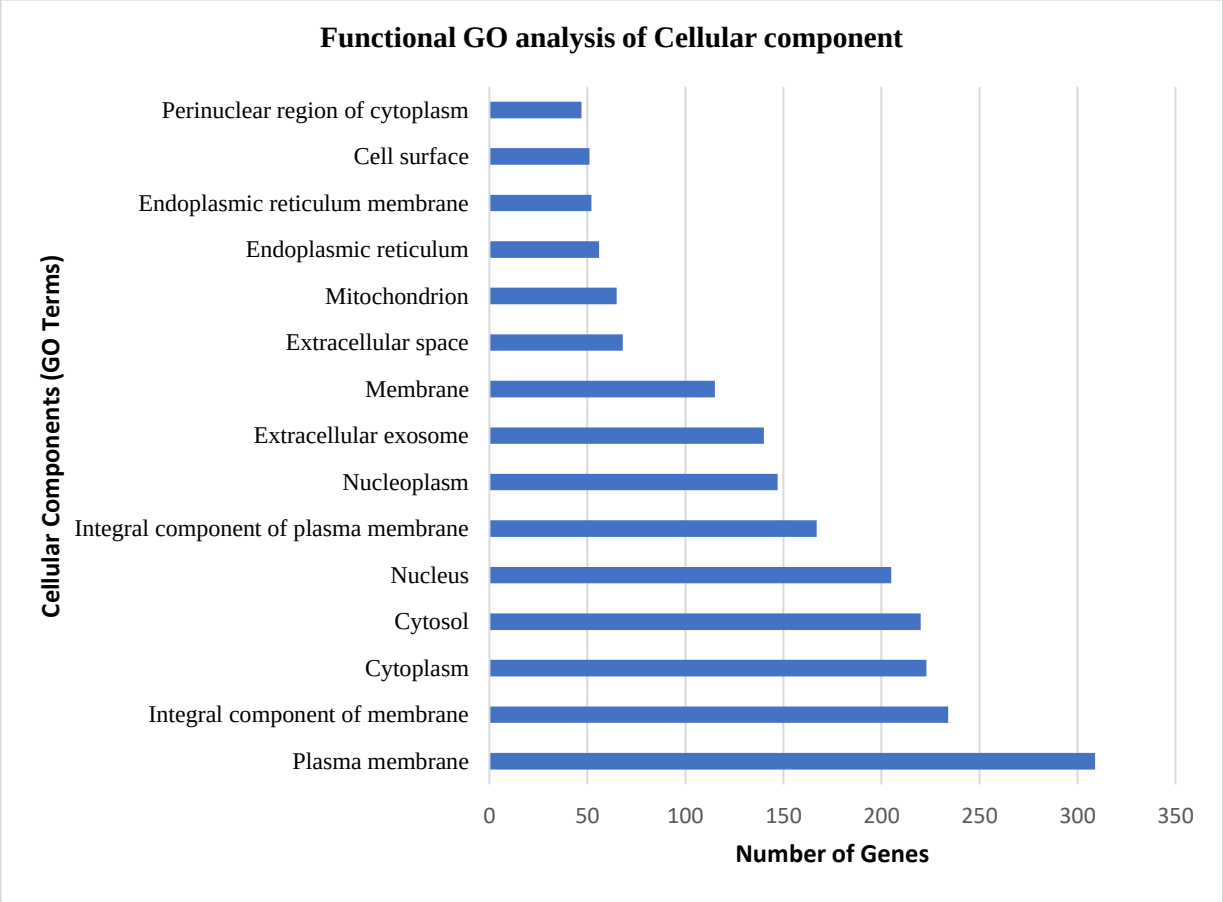

Figure 4. Gene Ontology analysis results of cell component

To further explore more possible activities of selected bioactive compounds at the molecular level, the functional GO analysis of the molecular function was conducted. **Figure 5** showed that the compounds with the highest biological interaction ability are concentrated in the protein binding

mechanism. Other biological interactions including ATP binding and metal ion binding also have a close relationship with the activity of proteins when it is necessary to mobilize energy from ATP and the mechanism that the activity of metalloproteins requires the presence of metals in the structure. These interactions help the SARS-CoV-2 virus enter cells by binding to proteins. Specifically, the protein binding interaction between the ACE2 receptor and the spike protein (S protein) of the SARS-CoV-2 virus is shown through the bridges between amino acids (Jiang *et al*., 2020, Gupta *et al*., 2020).

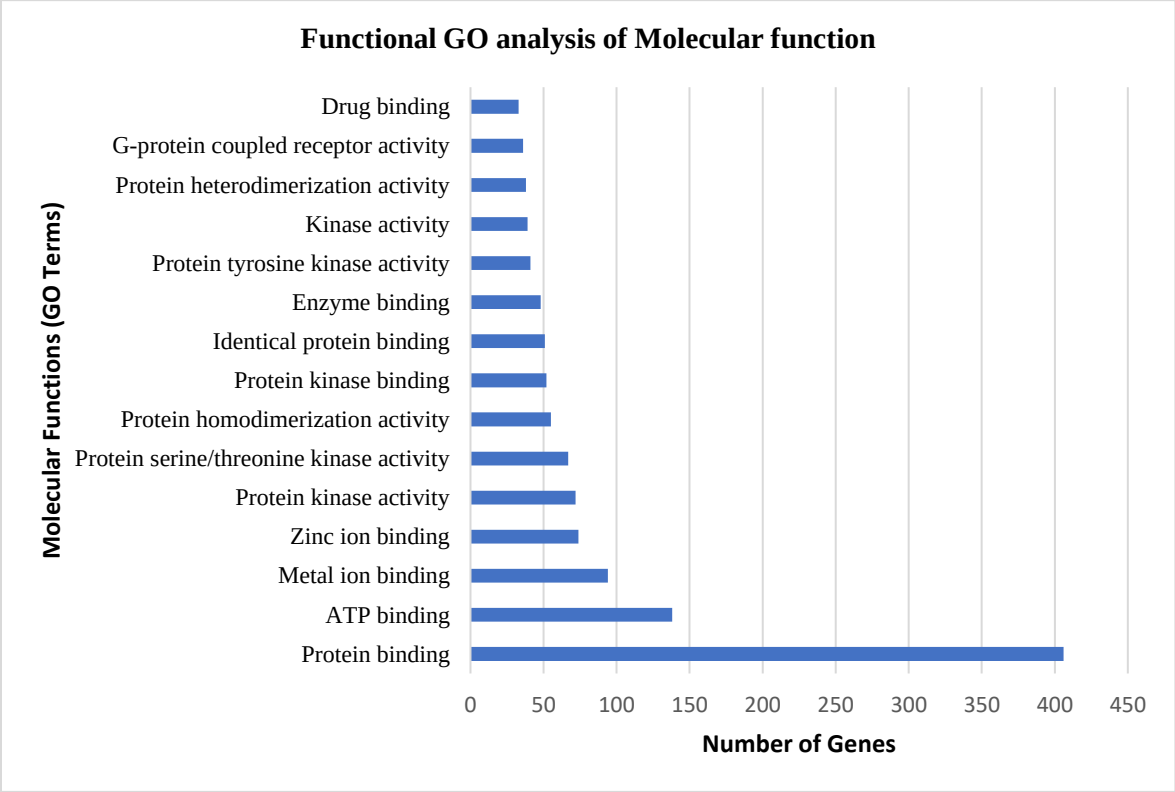

Figure 5. Gene Ontology analysis results of molecular function

3.3. KEGG signaling pathway analysis (pathway KEGG)

Table 2. Potential targets of 17 bioactive compounds at cellular level

Cell compartment	Target name
Extracellular	F2 (Thrombin); FXIII; FXIIIa; ACE; TNFα
Cell membrane	ATR1; ADAM17; TNFR; EGFR; TLR2/4; C3AR1
Intracellular	NFkB; MMP-3; IL-8; IL-2; IkB; Jak1; STAT3; SYK; PI3K; PLCγ; PKC; MAPK; TAK1; IKK; JNK; AP1; NLRP3; CASP1; TLR 7/8; TBK1; TNFα

The results of KEGG signaling pathway analysis showed that there are many diverse signaling pathways with 32 potential targets that have been highlighted (**Supplementary Figure S1**) that represent the mechanism of inflammation and cytokine storm in pneumonia caused by SARS-CoV-2. These targets are distributed not only extracellulary, but also at the cell membrane and in the

cytoplasm. Of these, there are 5 potential extracellular targets. These targets (**F2 (Thrombin); FXIII; FXIIIa; ACE; TNFα**) include factors related to blood clotting and signal information transmission, in which the ACE target is important in pathways related to the blood system, renin-angiotensin system through penetration and binding to the ACE2 receptor of the SARS-CoV-2 virus (Jiang *et al*., 2020, Gupta *et al*., 2020). There are 6 potential targets at the cell membrane (**ATR1; ADAM17; TNFR; EGFR; TLR2/4; C3AR1**) and the majority are also related to virus entry into cells and related to protein binding, which is consistent with the results of functional GO analysis of cellular components and molecular function (Yang *et al*., 2021, Palacios *et al*., 2021, Mikulicic *et al*., 2019). There are 21 potential targets that bearing the functions of activating inflammatory pathways and cytokine storms in the cytoplasm, demonstrating the diversity of cell death signaling pathways (**Table 2**). While bioinformatics analyses provide crucial insights into the potential therapeutic targets, the results must be validated through *in vitro* and *in vivo* studies to confirm the efficacy of these compounds against SARS-CoV-2.

4. Conclusion

In conclusion, the bioinformatics and network pharmacology analysis suggest that bioactive compounds from radix *Angelica dahurica*, *Chuanxiong* rhizoma, and *Cyperi* rhizoma may act synergistically against COVID-19 through interactions with key biological pathways and proteins associated with inflammation and viral entry. Future studies should focus on validating these findings experimentally to confirm the therapeutic potential of this herbal combination.

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