Research Article

Network pharmacology to uncover potential anti-inflammatory and immunomodulatory constituents in *Curcuma longa* rhizome as complementary treatment in COVID-19

Raden Bayu Indradi[1,2], Dian Ayu Eka Pitaloka[3,4], Suryani[5]

1 *Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Ir. Soekarno KM 21, Sumedang, Indonesia*

2 *Center of Herbal Study, Universitas Padjadjaran, Jl. Ir. Soekarno KM 21, Sumedang, Indonesia*

3 *Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jl. Ir. Soekarno KM 21, Sumedang, Indonesia*

4 *Center for Translational Biomarker Research, Universitas Padjadjaran, Jl. Ir. Soekarno KM 21, Sumedang*

5 *Department of Pharmacology and Toxicology, Faculty of Pharmacy, Universitas Jenderal Achmad Yani, Jl. Terusan Jend. Sudirman, Cimahi, Indonesia*

Corresponding author: Raden Bayu Indradi (bayu.indradi@unpad.ac.id)

Abstract

The immune status of patients plays an essential role in COVID-19. Herbal medicine with immunomodulatory and anti-inflammatory effect could have potential as a complementary therapeutic along with modern medicine. This study aims to investigate the anti-inflammatory and immunomodulatory constituents of *Curcuma longa* (*C. longa*) and its possible mechanisms in COVID-19. We systematically sorted the biochemical of *C. longa* rhizome from literature and repository. Next, we investigated targets related to COVID-19 in the selected active phytochemical constituents and analyzed the possible mechanisms against COVID-19 and performed molecular docking with four essential target proteins in COVID-19 for further verification. Ten active phytochemical constituents of *C. longa* were predicted to interact with four protein targets. The epidermal growth factor was the most interacted protein targeted by Calebin A, curcumin, cyclocurcumin, demethoxycurcumin, turmeronol a, turmeronol b, caffeic acid, and quercetin. Interferon-gamma was performed as the most critical protein targeted by 4-hydroxycinnamic acid. Curcumin was also predicted to interact with toll-like receptor 4 and Ar-turmerone with angiotensin II receptor type 2. We also reported four signaling pathways associated with target proteins-active phytochemical constituents against COVID-19: cytokine-cytokine receptor interaction, toll-like receptor signaling pathway, Jak-STAT signaling pathway, and PI3K-Akt signaling pathway. In conclusion, multi compounds in *C. longa* might act synergistically against COVID-19 by affecting the inflammatory and immune responses, and other pathological processes through multiple targets and pathways.

Keywords

PENSOFT.

Introduction

It has been highlighted that the emergence of coronavirus disease 2019 (COVID-19) pandemic in the world, including in Indonesia, posed a new challenge on the efforts to control this infectious disease. According to the latest data, the number of COVID-19 infection cases in Indonesia was estimated to be 6,088,460, total deaths of 156,737 per July 1, 2022 (Worldometer 2022), which significantly impacted the national healthcare system (Parikh et al. 2020). COVID-19 is caused by the SARS-CoV-2 virus that is highly contagious (Gorbalenya et al. 2020). Transmission of this virus is through droplets containing viruses, either directly or indirectly (Chan et al. 2020). Up to now, approximately 552 million positive cases of COVID-19 in all age groups have been recorded worldwide (Worldometer 2022).

The integrative treatment between modern and traditional medicines is useful for COVID-19 that currently has no specific treatment. Since the immune status of patients plays an essential role in COVID-19 infection, a herbal medicine, which has an immunomodulatory effect, could have the potential as a preventive measure and complementary therapeutic agent for patients with COVID-19 (Sharma et al. 2009; Zhang and Liu 2020). *Curcuma longa* (*C. longa*), widely known as turmeric, has been used traditionally by many countries and gained much interest in the scientific field (Kocaadam and Sanlier 2017). Curcumin as the medicinal part isolated from *C. longa* reported protecting from acute respiratory distress syndrome via targeting NF-κB, inflammasome, IL-6 trans signal, and HMGB1 pathways in COVID-19 patients (Thimmulappa et al. 2021). However, the synergistic mechanism as an anti-inflammatory and immunomodulator from multi-compound found in *C. longa* against COVID-19 is remain unclear.

Network pharmacology is based on high-throughput omics data analysis and network database retrieval, which combines systems biology with multidirectional pharmacology. It focuses on pattern changing from a single protein target and a single drug to multiple protein target and multiple drugs (Hopkins 2008). Currently, network pharmacology has been extensively utilized to explore multiple targets and unknown additional mechanisms against diverse diseases (Liang et al. 2016).

In this study, we applied a network pharmacology to investigate the active anti-inflammatory and immunomodulatory constituents of *C. longa* rhizome and their possible molecular mechanism & synergism effect of various compounds as complementary treatment against COVID-19. Firstly, we selected chemical compounds of *C. longa* rhizome via public websites and the COVID-19 related target proteins. Next, the extracted overlapping target proteins were discovered as target proteins for analyzing anti-COVID-19 properties. Finally, pathway enrichment analysis was performed to reveal the mechanisms of the most potent constituents against COVID-19. We also performed the molecular docking analysis to validate the interaction between the respective constituents and potential targets.

Materials and methods

Our protocol involved five main steps: (1) finding active phytochemical ingredients of *C. longa* rhizome from the literature database and public repository; (2) finding known targets and candidate genes related to COVID-19; (3) developing gene ontology and pathway analysis; (4) constructing different types of molecule-target networks and analyzing these networks; (5) performing molecular docking.

Active phytochemical components of *C. longa*

Phytochemical components of *C. longa* were collected from Dr. Duke's Phytochemical and Ethnobotanical Databases (U.S. Department of Agriculture 2021) (https://phytochem.nal.usda.gov/phytochem/search), and KNApSAcK Family (Afendi et al. 2012) (http://www.knapsackfamily.com/KNApSAcK_Family/). We focus on the rhizome part of *C. longa* which previously known to have biological activities and collected a total of 39 phytochemical components. We analyzed the Absorption, Distribution, Metabolism, and Extraction (ADME) of phytochemical components using SwissADME (Daina et al. 2017) (http://www.swissadme.ch/index.php) as SMILES chemical notation obtained from PubChem (Kim et al. 2021) (https://pubchem.ncbi.nlm.nih.gov/). These components were screened based on three following parameters: high gastrointestinal absorption, no Lipinski violation, and bioavailability ≥ 0.55 (Benet et al. 2016). We downloaded the 3D structure of selected phytochemical components in *C. longa* from PubChem (Kim et al. 2021) (one phytochemical component was excluded because of no 3D molecular structure provided at the website).

Potential targets of the herbal pair for COVID-19

We identified the potential target of selected phytochemical components using PharmMapper (Wang et al. 2017) (http://www.lilab-ecust.cn/pharmmapper/). We selected only human protein as target sets and chose the targets with normalized fit scores ≥ 0.8 to be considered potential targets for *C. longa* (Gordon et al. 2020). We also performed another analysis to uncover more potential targets using SwissTargetPrediction (Daina et al. 2019) (http://www.swisstargetprediction.ch/) (the criteria of probability ≥ 0.5) and BATMAN (Liu et al. 2016) (http://bionet.ncpsb.org.cn/batman-tcm/) (score cut off 80 and Adjusted P-value cut off 0.05).

COVID-19 related human gene annotations were downloaded from National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/gene/), and a total of 165 targets were obtained. We merged the selected phytochemical component targets of *C. longa* and COVID-19 related targets using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) to identify the targets of *C. longa* related to COVID-19. Overlapped targets were considered as *C. longa* targets related to COVID-19.

To identify the significant cluster of COVID-19 related targets, protein-protein interaction (PPI) data

from COVID-19 related targets were gained from STRING (Szklarczyk et al. 2021) (https://string-db.org/). The interaction was set with parameter limited to "Homo sapiens" and confidence score set to highest (>0.900) (Patel et al. 2014). The PPI data was generated and clustered using CytoCluster tools in Cytoscape v.3.8.2 (Shannon et al. 2003) (https://cytoscape.org/) with ClusterONE algorithm, the minimum size of 10, the minimum density of 0.5, and seeding method from every node. We chose the highest cluster (lowest p-values) as significant cluster of COVID-19 related targets (Nepusz et al. 2012).

Construction of "component-target-disease" network

Network constructions were visualized using Cytoscape v.3.8.2 for the following networks: 1) network between *C. longa* phytochemical components – common target and 2) network among *C. longa* common targets, COVID-19 related targets, and pathways. The nodes represent targets, compounds, and pathways, while edges represent interactions.

Enrichment analysis

We performed GO- and KEGG- enrichment analysis using The Database for Annotation, Visualization, and Integrated Discovery, DAVID v.6.8 (Jiao et al. 2012) (https://david.ncifcrf.gov/) to further investigate functional annotation and pathway involved in *C. longa* targets related to COVID-19. We used only significant cluster of COVID-19 targets listed to help pinpoint the significant pathways. The threshold was set on 10 (except 5 for molecular function) and p < 0.01 to be considered as significant (Reimand et al. 2019).

Molecular docking method

We performed molecular docking for each selected phytochemical constituent which was found potential against COVID-19 using AutoDock Vina (Trott and Olson 2010). All phytochemical structures were optimized by the molecular mechanic's optimization method based on the MMFF94 force field using AutoDockTools-1.5.6 (Morris et al. 2009) The X-ray crystal structures of 4 known targets were downloaded from Protein Data Bank (PDB) (https://www.rcsb.org/). These protein targets were EGFR (PDB ID: 5FED) (Lelais et al. 2016), TLR4 (PDB ID: 4G8A) (Ohto and Shimizu 2012), IFNG (PDB ID: 6E3K) (Jude et al. 2019), and AGTR2 (PDB ID: 5XJM) (Asada et al. 2018). Protein rigid used in the docking and water molecules were removed in preparation step before running, and exhaustiveness used were 16. This protocol used the docking score between native ligand and molecular protein complex and known targets proteins as the cutoff value. For all target proteins, the docking score of a phytochemical constituent and a target were compared to the native ligand (energy & amino acid residues), and when it gave a binding similarity, they were considered effective docking and could be regarded as nodes (Li et al. 2012). Their interaction could be further regarded as edges.

Results

The active phytochemical components of *C. longa*

We firstly acquired the phytochemical constituents and corresponding targets of the COVID-19-related *C. longa*. We collected a total of 39 phytochemical components of *C. longa* rhizome from two databases (Suppl. material 1: S1). We only focused on the rhizome part of *C. longa*, the most utilized in these herbs. ADME evaluation found that 25 phytochemical components of *C. longa* rhizome were met all the criteria (Suppl. material 1: S2). Using three different websites, identification of protein target for COVID-19 resulted in 253 different targets from 25 phytochemical components (280 nodes & 649 edges). These components predicted to interacts with several targets, except for 1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione and 1,7-Bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione compound which only predicted interact with one target (Suppl. material 1: S3).

"*C. longa* components common target" network

A total of 165 COVID-19 targets were obtained from NCBI (Suppl. material 1: S4) and six targets intersection of *C. longa* and COVID-19 were obtained by merging the phytochemical component targets with COVID-19 targets. The intersection of targets was regarded as the potential targets of *C. longa* against COVID-19 (Fig. 1). Then, the "*C. longa*-component-target-disease" network was constructed by Cytoscape, as depicted. The six overlapped targets were EGFR, F2, F3, TLR4, AGTR2, and IFNG from a total of 10 active ingredients. According to the degree value, the most critical ingredient of *C. longa* is curcumin which predicted to interact with EGFR, F3, and TLR4 targets of COVID-19, respectively (Fig. 2).
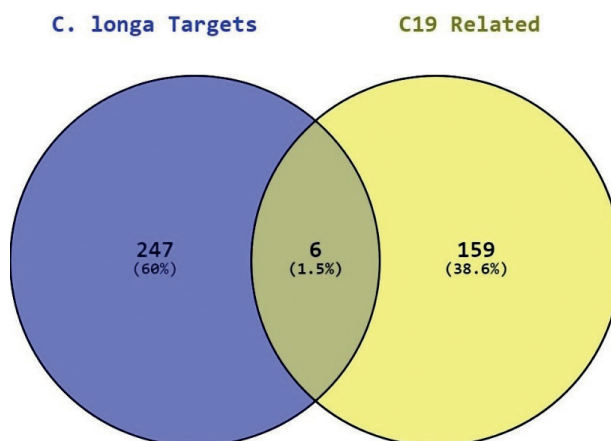

Figure 1. Venn diagram of *C. longa* phytochemical compound targets and COVID-19 related targets.
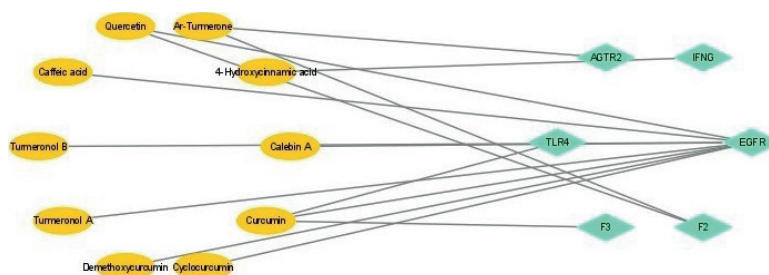
Figure 2. Compound – common target of *C. longa* and COVID-19 related network. Yellow ellipse represents *C. longa* compounds, blue diamond represents COVID-19 related protein targeted by *C. longa*.

PPI network of *C. longa* against COVID-19

PPI network has been widely used to identify many different interactions of the protein targets in the context of a complex disease. There was a total of 116 nodes and 429 interactions lines in the STRING PPI network. Due to the complexity of the original network obtained from the STRING database, we imported the PPI data into Cytoscape to explore the importance of potential targets in the protein networks and the main cluster in this network. We used ClusterONE to obtain the significant cluster. The highest cluster with lowest p-value contained 27 nodes (27 targets) and 181 edges (interactions) with a network density of 0,516 (Fig. 3), which were JAK1, TYJ2, IFNG, CCL2, CSF3, IL17A, CCL3, IL18, IL1A, IL2RA, CXCL2, IL4, CSF2, IL10, CXCL1, CXCL10, STAT 3, NFKB1, IL1B, IL6, JAK2, CXCL8, STAT1, TNF, CD4, CD8A, and IL2. We found that IFNG was among the proteins in significant cluster and also targeted directly by *C. longa* compound as in Fig. 2.

Enrichment of potential targets of *C. longa*

To further explore the underlying mechanisms of *C. longa* as a therapy against COVID-19, we performed GO-enrichment analysis with the 27 COVID-19 related targets from significant cluster identified by DAVID (Fig. 4). GO enrichment consists of three parts, biological process (BP), cellular component (CC), and molecular function (MF). There were 31 GO enrichment terms for BP. The top 5 enriched terms included immune response, defense response to the virus, type I interferon signaling pathway, inflammatory response, and innate immune response. Besides, a total of 11 CC items were obtained, and the most enriched terms included extracellular space, extracellular region, external side of the plasma membrane, and cell surface. There were 10 GO terms for MF enrichment, and the most enriched terms included cytokine activity, chemokine activity, double-stranded RNA binding, receptor binding, and growth factor activity.
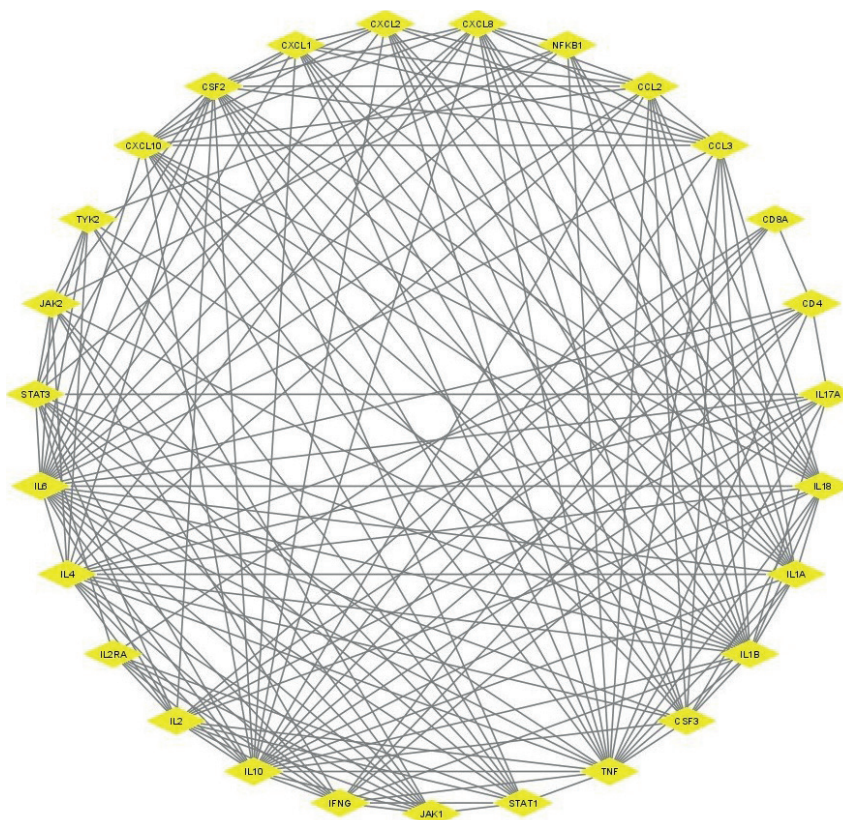

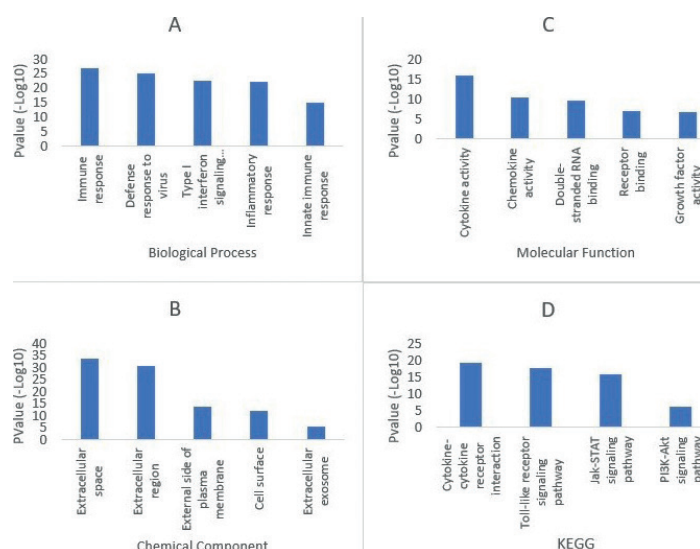**Figure 3.** Significant cluster of COVID-19 related targets.

Figure 4. Enrichment analysis of 27 COVID-19 related targets from significant cluster. **A** biological process; **B** chemical component; **C** molecular function; **D** KEGG.

From KEGG analysis, we obtained a total of 32 pathways which four of them were related to COVID-19: cytokine-cytokine receptor interaction, toll-like receptor signaling pathway, Jak-STAT signaling pathway, and PI3K-Akt signaling pathway. All this pathway showed a low p-value (<0.0001) and considered as an important pathway of *C. longa* anti-inflammatory and immunomodulatory activity against COVID-19.

"Common target-COVID-19 related target-pathway" network

We create network between *C. longa* target of COVID-19, other COVID-19 related target, and pathway to under-stand the interaction (Fig. 5). COVID-19 related targets involved in those 4 KEGG pathway were considered as interaction between them, resulting in 47 nodes and 100 edges in the network with 5 direct interactions between *C. longa* compounds common target with a pathway. The rest were considered as indirect interaction.

Molecular docking

The main active phytochemical constituents in *C. longa*, namely Quercetin, Ar-turmerone, 4-hydroxycinnamic acid, calebin A, curcumin, cyclocurcumin, demethoxycurcumin, turmeronol A, turmeronol B, and caffeic acid were used to dock with IFNG, AGTR2, EGFR, and TLR4 respec-
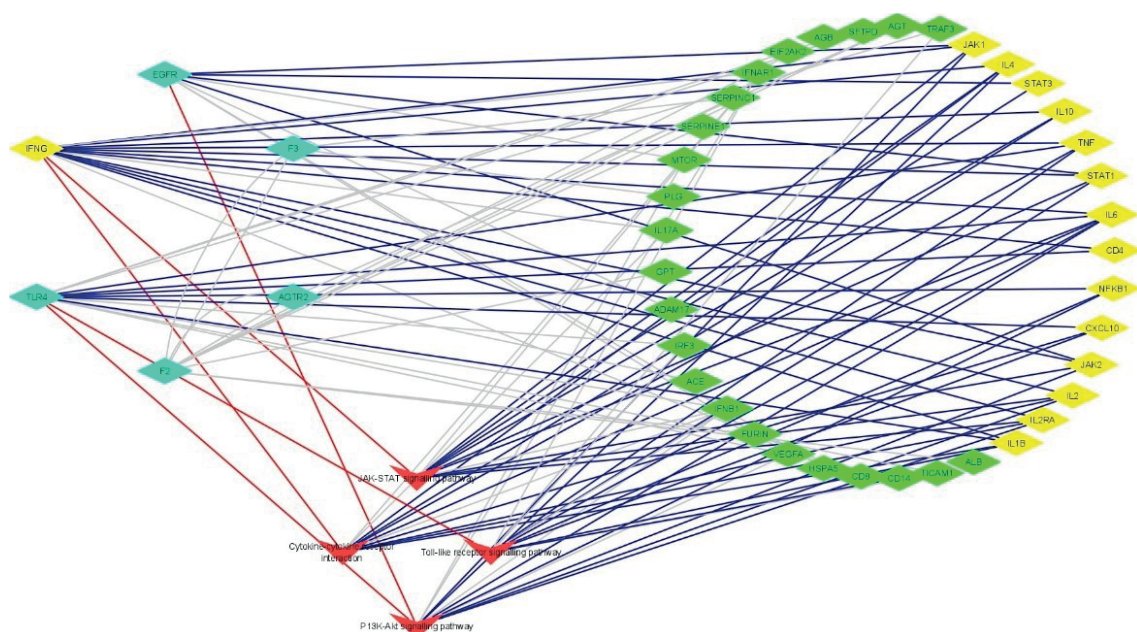

Figure 5. Network between *C. longa* common targets of COVID-19 (blue diamonds, upper left side) – other COVID-19 related targets (green diamonds, upper right side) – pathways (red arrows, down side). Yellow diamond depicts targets included in significant cluster for COVID-19. Red edges represent direct interaction while blue edges represent indirect interaction of *C. longa* COVID-19 related targets from significant cluster with pathways.

tively. Protein rigid used in the docking and water molecules were removed in preparation step before running. It is generally believed that the lower the binding energy of ligand and receptor, the more stable the conformation and the greater the possibility of action. The molecular docking results showed that the binding energies of the main phytochemical constituents in *C. longa* were predicted interact with COVID-19 related targets based on comparison to the native ligand (energy & amino acid residues) (Table 1). The interaction were visualized using Discovery Studio (Biovia 2021) could be seen in (Suppl. material 1: S9).

Table 1. Molecular docking result of found compound that predicted interact with COVID-19 targets.

Protein	Ligand	Binding Energy	Hydrogen Bond	Residue
EGFR	Native ligand	-8.8	4	LYS645, LYS745, CYS797, MET793
	Calebin A	-6.9	5	LYS745, THR790, THR854, ASP855, MET793
	Curcumin	-7.2	4	LYS745, MET793, ARG841, THR854
	Cyclocurcumin	-7.9	3	LYS745, MET793, THR854
	Demethoxycurcumin	-7.5	5	LYS745, MET793, THR854, ARG841, ASN842
	Turmeronol a	-6.7	4	LYS745, MET793, THR854, GLN791
	Turmeronol b	-6.7	4	LYS745, LYS745, THR854, GLN791
	Caffeic acid	-6.1	5	LYS745, MET793, THR854, MET793, MET793
	Quercetin	-7.9	6	LYS745, LYS745, LYS745, MET793, THR854, THR854
TLR4	Native ligand	-4.4	4	ASN173, GLU142, GLY147, HIS148
	Curcumin	-5.7	3	ASN173, GLU169, GLU142
AGTR2	Native ligand	-6.0	3	ARG2, ARG182, LYS215
	Ar-Turmerone	-6.4	1	ARG182
IFNG	Native ligand	-2.3	3	ASN69, SER71, ASP72
	4-Hydroxycinnamic acid	-1.5	1	ASN26

Discussion

Until now, people around the world are still actively fighting against COVID-19, and herbal medicine has played an important role in the complementary therapy of this disease. The result of our network analysis provides insights into the identification of active constituents of *C. longa* for COVID-19, identification of protein target related to COVID-19, active constituents-target interaction, and signaling pathway associated with target proteins of active constituents in *C. longa*.

Ten active constituents of *C. longa* rhizome were predicted to interact with six common protein targets of COVID-19. We found that among these active constituents, curcumin appears in two pairs of active constituents-target interaction as seen in the Fig. 5: EGFR and TLR4 protein. IFNG protein was also found as the most critical target

found in the PPI network. We reported four signaling pathways associated with target proteins of active constituents in *C. longa* rhizome against COVID-19: cytokine-cytokine receptor interaction, toll-like receptor signaling pathway, Jak-STAT signaling, and PI3K-Akt signaling pathway. The proposed mechanism of action are visualized in Fig. 6.

Numerous studies have been reported in curcumin as a potential treatment for COVID-19. Nanocurcumin was reported to modulate pro-inflammatory cytokines in patients with COVID-19. Patients showed high mRNA expression and secretion of IL-1β, IL-6, TNF-α, and IL-18 but showed a significant reduction in IL-6 and IL-1β after treatment with nano curcumin (Valizadeh et al. 2020). The previous study also demonstrated that the number of Th17 cells, gene expression, and serum Th17-mediated factors levels (IL-17, IL-21, IL-23, and GM-CSF) were significantly reduced in the group of patients with COVID-19 treated with nano curcumin (Tahmasebi et al. 2021).

IFNG played a vital role in COVID-19, although based on our result, it is only targeted by the 4-hydroxycinnamic acid of *C. longa*. A recent study reported that IFNG had driven differentiation of immature secretory cells into the largely ACE2+ ciliated cells in patients with COVID-19. ACE2 has upregulated in epithelial cells at least partially through IFNG signaling by immune cells in the patients with moderate COVID-19. Cytotoxic T lymphocytes displayed the characteristic transcriptional profile of high expression of IFNG and TNF together with genes encoding for cytotoxic receptors (KLRB1, KLRC1, and KLRD1) (Chua, et al., 2020). Upregulation of ACE2 in COVID-19 patients, which correlated to activation of IFNG signaling by 4-hydroxycinnamic acid of *C. longa*, might counteract viral infection, which is in line with the protective function of immune cells (Imai et al. 2005; Verdecchia et al. 2020).

Ar-turmerone, as one of the bioactive compounds in *C. longa* rhizome, was predicted to interact with AGTR2, and this result is in line with our previous idea. AGTR2 belongs to the G-protein coupled receptor one family and functions as a receptor for angiotensin II (Pubchem 2016). It is reported that infection of SARS-CoV-2 results in the down regulation of ACE2 and triggers severe inflammatory lesions in the lungs (Silhol et al. 2020). This inflammatory reaction also appears to be mediated by AGTR2 via activation of the ERK/MAPK signaling pathway, which was found upregulated in COVID-19 patients (Guo et al. 2020). AGTR2 is also found to promote activation of the PI3K-Akt signaling pathway via ADAM17 resulting in NF-κB activation (Sun et al. 2010). Inhibition of AGTR2 by Ar-turmerone might prevent these signaling activation, and inflammation can be minimized.

EGFR is the most interacted protein targeted by active constituents of *C. longa*. A total of 8/10 was predicted to interact with this target protein. EGFR is known to have a role in processing the membrane form of IL-6Rα into its soluble form sIL-6Rα. Complex sIL-6Rα-IL-6 leads to activation of the Jak-STAT signaling pathway via gp130, with it being important for complete activation of the NF-κB signaling pathway (Eguchi et al. 2018; Murakami et al. 2019). AGTR, as one of the protein targets from active constituents of
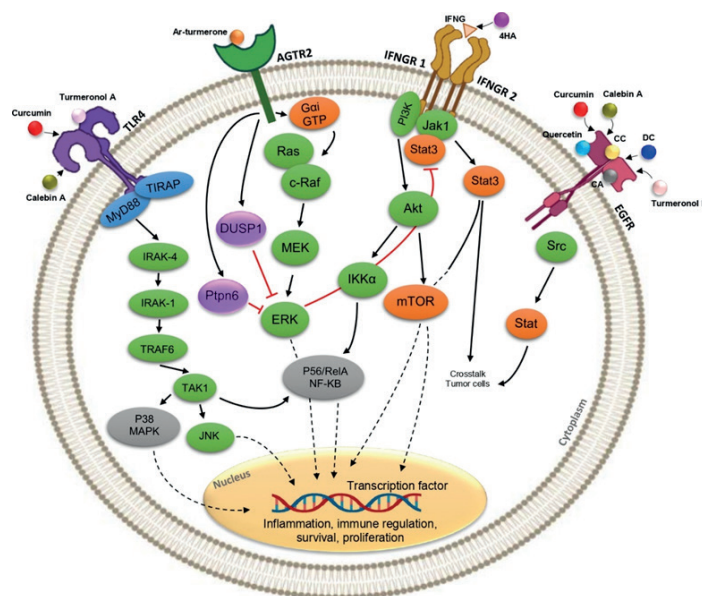
Figure 6. The proposed mechanism of action of multi compounds in *C. longa* rhizome on trans-signaling pathways (JAK/STAT, PI3K/Akt, and TLR) and their interaction with target proteins against COVID-19. JAK/STAT, The Janus kinase (JAK)/signal transducer and activator of transcription (STAT); PI3K, Phosphatidylinositol-3-kinase (PI3K); MAPK, Mitogen-activated protein kinase; NF-KB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; TLR, Toll-Like receptor; 4HA, 4-Hydroxycinnamic acid; CC, Cyclocurcumin; CA, Caffeic acid; DC, demetoxycurcumin. The figure was created using Biorender (https://biorender.com/).

C. longa, is also found to promote activation of the PI3K-Akt signaling pathway via ADAM17 resulting in NF-κB activation (Sun et al. 2010), preventing the NF-κB activation via EGFR and AGTR by active constituents of *C. longa* may prevent the release of pro-inflammatory cytokines leading to cytokine storm in COVID-19 patients.

Toll-like receptor (TLR) is also one of the signaling pathways regulated by active constituents of *C. longa*. As a component of innate immunity, it plays an important role in activating innate immunity, regulating cytokine expression, indirectly activating the adaptive immune system, and recognizing pathogen-associated molecular patterns (PAMPs) (Hedayat et al. 2011; Birra et al. 2020; Debnath et al. 2020). Khanmohammadi et al. (2021) reported that activation of TLR pathways leads to the secretion of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α, as well as type 1 interferon, which are potentially important in COVID-19 infection and its cytokine storms. Regulation of TLR signaling pathway by curcumin of *C. longa* could be a potential target in controlling infection against SARS-CoV-2.

Limitations

The network pharmacology analysis has identified ten candidates of bioactive compounds in *C. longa* against COVID-19 infection, this was obtained based on its binding to the six target proteins. The possible mechanism of bioactive compounds in *C. longa* against COVID-19 has been known in this study, that four pathways are targeted to control infection COVID-19. However, this study still has limitations, the effectiveness, and the mechanism of bioactive compounds in *C. longa* against COVID-19

needs to be re-validated through *in vitro* analysis, that is directly effect of bioactive compound to the virus which will support the result of the pathway analysis. The pharmacological effect in inhibiting the pathological process from COVID-19 by *C. longa* compound also could be validated through *in vivo* analysis. The *in vitro* and *in vivo* analysis could be the further research from this study.

Conclusions

The mechanism of multi compounds in *C. longa* rhizome were firstly investigated through network pharmacology. The finding of this research suggested 10 compounds (curcumin, turmeronol A, turmeronol B, cyclocurcumin, calebin A, 4-Hydroxycinnamic acid, ar-turmerone, caffeic acid, demetoxycurcumin, quercetin) were connected to 4 considered significant target proteins (EGFR, TLR4, IFNG, and AGTR2). The promising mechanism of *C. longa* rhizome against COVID-19 were connected to 4 pathways (cytokine-cytokine receptor interactions, PI3K/Akt, JAK/STAT, and TLR4 signaling pathways) and blocking the activation of these pathway. Overall, multi compounds in *C. longa* rhizome might act synergistically against COVID-19 by affecting the inflammatory and immune responses, cell apoptosis, and other pathological processes through multiple targets and pathways.

Supplementary data

The data underpinning the analysis reported in this paper are deposited at Figshare data repository at https://doi.org/10.6084/m9.figshare.21184429.v1.

References

Afendi FM, Okada T, Yamazaki M, Hirai-Morita A, Nakamura Y, Nakamura K, Ikeda S, Takahashi H, Altaf-Ul-Amin Md, Darusman LK, Saito K, Kanaya S (2012) KNApSAcK family databases: integrated metabolite-plant species databases for multifaceted plant research. Plant and Cell Physiology 53(2): e1. https://doi.org/10.1093/pcp/pcr165

Asada H, Horita S, Hirata K, Shiroishi M, Shiimura Y, Iwanari H, Hamakubo T, Shimamura T, Nomura N, Kusano-Arai O, Uemura T, Suno C, Kobayashi T, Iwata S (2018) Complex structure of angiotensin II type 2 receptor with Fab. Nature Structural & Molecular Biology 25: 570–576. https://doi.org/10.1038/s41594-018-0079-8

Benet LZ, Hosey CM, Ursu O, Oprea TI (2016) BDDCS, the Rule of 5 and drugability. Advanced Drug Delivery Reviews 101: 89–98. https://doi.org/10.1016/j.addr.2016.05.007

Biovia DS (2021) Discovery Studio 2021, Sab Diego: Dassault Systemes.

Birra D, Benucci M, Landolfi L, Merchionda A, Loi G, Amato P, Licata G, Quartuccio L, Triggiani M, Moscato P (2020) COVID 19: a clue from innate immunity. Immunologic Research 68: 161–168. https://doi.org/10.1007/s12026-020-09137-5

Chan KW, Wong VT, Tang SCW (2020) COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese-Western Medicine for the Management of 2019 Novel Coronavirus Disease. The American Journal of Chinese Medicine 48(3): 737–762. https://doi.org/10.1142/S0192415X20500378

Chua RL, Lukassen S, Trump S, Hennig BP, Wendisch D, Pott F, Debnath O, Thürmann L, Kurth F, Völker MT, Kazmierski J, Timmermann B, Twardziok S, Schneider S, Machleidt F, Müller-Redetzky H, Maier M, Krannich A, Schmidt S, Balzer F, Liebig J, Loske J, Suttorp N, Eils J, Ishaque N, Liebert UG, von Kalle C, Hocke A, Witzenrath M, Goffinet C, Drosten C, Laudi S, Lehmann I, Conrad C, Sander L-E, Eils R (2020) COVID-19 severity correlates with airway epithelium–immune cell interactions identified by single-cell analysis. Nature Biotechnology 38: 970–979. https://doi.org/10.1038/s41587-020-0602-4

Daina A, Michelin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports 7: 42717. https://doi.org/10.1038/srep42717

Daina A, Michielin O, Zoete V (2019) SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Research 47(W1): W357–W364. https://doi.org/10.1093/nar/gkz382

Debnath M, Banerjee M, Berk M (2020) Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. The FASEB Journal 34(7): 8787–8795. https://doi.org/10.1096/fj.202001115R

Eguchi S, Kawai T, Scalia R, Rizzo V (2018) Understanding Angiotensin II Type 1 Receptor Signaling in Vascular Pathophysiology. Hypertension 71(5): 804–810. https://doi.org/10.1161/HYPERTENSION-AHA.118.10266

Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, Haagmans BL, Lauber C, Leontovich AM, Neuman BW, Penzar D, Perlman S, Poon LLM, Samborskiy DV, Sidorov IA, Sola I, Ziebuh J (2020) The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology 5: 536–544. https://doi.org/10.1038/s41564-020-0695-z

Gordon DE, Jang GM, Bouhaddou M, et al. (2020) A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 583: 459–468. https://doi.org/10.1038/s41586-020-2286-9

Guo Y-J, Pan W-W, Liu S-B, Shen Z-F, Y Xu, Hu L-L (2020) ERK/MAPK signalling pathway and tumorigenesis. Experimental and Therapeutic Medicine 19(3): 1997–2007. https://doi.org/10.3892/etm.2020.8454

Hedayat M, Netea MG, Rezaei, N (2011) Targeting of Toll-like receptors: a decade of progress in combating infectious diseases. The Lancet Infectious Diseases 11(9): 702–7012. https://doi.org/10.1016/S1473-3099(11)70099-8

Hopkins AL (2008) Network pharmacology: the next paradigm in drug discovery. Nature Chemical Biology 4: 682–690. https://doi.org/10.1038/nchembio.118

Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui C-C, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436(7047): 112–116. https://doi.org/10.1038/nature03712

Jiao X, Sherman BT, Huang DW, Stephens R, Baseler MW, Lane HC, Lempicki RA (2012) DAVID-WS: a stateful web service to facilitate gene/protein list analysis. Bioinformatics 28(13): 1805–1806. https://doi.org/10.1093/bioinformatics/bts251

Jude K, Mendoza J, Garcia K (2019) Interferon gamma signalling complex with IFNGR1 and IFNGR2. Nature 567: 56–60. https://doi.org/10.2210/pdb6e3l/pdb

Khanmohammadi S, Rezaei N (2021) Role of Toll-like receptors in the pathogenesis of COVID-19. Journal of medical virology 93(5): 2735–2739. https://doi.org/10.1002/jmv.26826

Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE (2021) PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Research 49(D1): D1388–D1395. https://doi.org/10.1093/nar/gkaa971

Kocaadam B, Sanlier N (2017) Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. Critical reviews in food science and nutrition 57(13): 2889–2895. https://doi.org/10.1080/10408398.2015.1077195

Lelais G, Epple R, Marsilje TH, Long YO, McNeill M, Chen B, Lu W, Anumolu J, Badiger S, Bursulaya B, DiDonato M, Fong R, Juarez J, Li J, Manuia M, Mason DE, Gordon P, Groessl T, Johnson K, Jia Y, Kasibhatla S, Li C, Isbell J, Spraggon G, Bender S, Michellys P-Y (2016) Discovery of (R,E)-N-(7-Chloro-1-(1-[4-(dimethylamino) but-2-enoyl]azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (EGF816), a Novel, Potent, and WT Sparing Covalent Inhibitor of Oncogenic (L858R, ex19del) and Resistant (T790M) EGFR Mutants. Journal of Medicinal Chemistry 59(14): 6671–6689. https://doi.org/10.1021/acs.jmedchem.5b01985

Li B, Xu X, Wang X, Yu H, Li X, Tao W, Wang Y, Yang L (2012) A systems biology approach to understanding the mechanisms of action of chinese herbs for treatment of cardiovascular disease. International Journal of Molecular Sciences 13(10): 13501–13520. https://doi.org/10.3390/ijms131013501

Liang H, Ruyan H, Quyang Q, Lai L (2016) Herb-target interaction network analysis helps to disclose molecular mechanism of traditional Chinese medicine. Scientific Reports 6: 36767. https://doi.org/10.1038/srep36767

Liu Z, Guo F, Wang Y, Li C, Zhang X, Li H, Diao L, Gu J, Wang W, Li D, He F (2016) BATMAN-TCM: a Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine. Scientific Reports 6: 21146. https://doi.org/10.1038/srep21146

Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ (2009) Autodock4 and AutoDockTools4: automated docking with selective receptor flexibility. Journal of Computational Chemistry 30(16): 2785–2791. https://doi.org/10.1002/jcc.21256

Murakami M, Kamimura D, Hirano T (2019) Pleiotropy and Specificity: Insights from the Interleukin 6 Family of Cytokines. Immunity 50(4): 812–831. https://doi.org/10.1016/j.immuni.2019.03.027

Nepusz T, Yu H, Paccanaro A (2012) Detecting overlapping protein complexes in protein-protein interaction networks. Nature Methods 9: 471–472. https://doi.org/10.1038/nmeth.1938

Ohto U, Shimizu T (2012) Crystal structure of human TLR4 polymorphic variant D299G and T399I in complex with MD-2 and LPS. Journal of Biological Chemistry 287: 40611–40617. https://doi.org/10.1074/jbc.M112.404608

Parikh PA, Shah BV, Phatak AG, Vadnerkar AC, Uttekar S, Thacker N, Nimbalkar SM (2020) COVID-19 Pandemic: Knowledge and Perceptions of the Public and Healthcare Professionals. Cureus 12(5): e8144. https://doi.org/10.7759/cureus.8144

Patel DA, Patel AC, Nolan WC, Huang G, Romero AG, Charlton N, Agapov E, Zhang Y, Holtzman MJ (2014) High-throughput screening normalized to biological response: application to antiviral drug discovery. Journal of Biomolecular Screening 19(1): 119–130. https://doi.org/10.1177/1087057113496848

Pubchem (2016) AGTR2-angiotensin II receptor type 2 (human). [Online] https://pubchem.ncbi.nlm.nih.gov/gene/AGTR2/human [Accessed 22 02 2022]

Reimand J, Isserlin R, Voisin V, Kucera M, Tannus-Lopes C, Rostamianfar A, Wadi L, Meyer M, Wong J, Xu C, Merico D, Bader GD (2019) Pathway enrichment analysis and visualization of omics data using g:Profiler, GSEA, Cytoscape and EnrichmentMap. Nature Protocols 14: 482–517. https://doi.org/10.1038/s41596-018-0103-9

Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Research 13(11): 2498–2504. https://doi.org/10.1101/gr.1239303

Sharma M, Anderson SA, Schoop R, Hudson JB (2009) Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized *Echinacea*, a potent antiviral herbal extract. Antiviral research 83(2): 165–170. https://doi.org/10.1016/j.antiviral.2009.04.009

Silhol F, Sarlon G, Deharo J-C, Vaisse B (2020) Downregulation of ACE2 induces overstimulation of the renin-angiotensin system in COVID-19: should we block the renin-angiotensis system?. Hypertension Research 43: 854–856. https://doi.org/10.1038/s41440-020-0476-3

Sun Z-J, Chen G, Hu X, Zhang W, Liu Y, L-Zhu X, Zhou Q, Zhao Y-F (2010) Activation of PI3K/Akt/IKK-alpha/NF-kappaB signaling pathway is required for the apoptosis-evasion in human salivary adenoid cystic carcinoma: its inhibition by quercetin. Apoptosis 15(7): 850–863. https://doi.org/10.1007/s10495-010-0497-5

Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, N Doncheva T, Legeay M, Fang T, Bork P, Jensen LJ, von Mering C (2021) The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Research 49(D1): D605–D612. https://doi.org/10.1093/nar/gkaa1074

Tahmasebi S, El-Esawi MA, Mahmoud ZH, Timoshin A, Valizadeh H, Roshangar L, Varshoch M, Vaez A, Aslani S, Navashenaq JG, Aghebati-Maleki L, Ahmadi M (2021) Immunomodulatory effects of nanocurcumin on Th17 cell responses in mild and severe COVID-19 patients. Journal of Cellular Physiology 236(7): 5352–5338. https://doi.org/10.1002/jcp.30233

Thimmulappa RK, Mudnakudu-Nagaraju KK, Shivamallu C, Subramaniam KJT, Radhakrishnan A, Bhojraj S, Kuppusamy G (2021) Antiviral and immunomodulatory activity of curcumin: A case for prophylactic therapy for COVID-19. Heliyon 7(2): e06350. https://doi.org/10.1016/j.heliyon.2021.e06350

Trott O, Olson AJ (2010) AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. Journal of Computational Chemistry 31(2): 455–461. https://doi.org/10.1002/jcc.21334

U.S. Department of Agriculture (2021) U.S. Department of Agriculture. [Online] https://phytochem.nal.usda.gov/phytochem/search

Valizadehab H, Abdolmohammadi-vahidcd S, Danshinae S, Gencerf MZ, Ammarig A, Sadeghiab A, Roshangard L, Aslanih S, Esmaeilzadehi A, Ghaebii M, Valizadehb S, Ahmadi M (2020) Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. International Immunopharmacology 89: 107088. https://doi.org/10.1016/j.intimp.2020.107088

Verdecchia P, Cavallini C, Spanevello A, Angeli F (2020) The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. European Journal of Internal Medicine 76: 14–20. https://doi.org/10.1016/j.ejim.2020.04.037

Wang X, Shen Y, Wang S, Li S, Zhang W, Liu X, Lai L, Pei J, Li H (2017) PharmMapper 2017 update: a web server for potential drug target identification with a comprehensive target pharmacophore database. Nucleic Acids Research 45(W1): W356–W360. https://doi.org/10.1093/nar/gkx374

Worldometer (2022) Covid-19 Coronavirus Pandemic. [Online] https://www.worldometers.info/coronavirus/

Zhang L, Liu Y (2020) Potential interventions for novel coronavirus in China: A systematic review. Journal of Medical Virology 92(5): 479–490. https://doi.org/10.1002/jmv.25707

Supplementary material 1

Datasets of Network Pharmacology Process