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Network Pharmacology-Based Identification of Bioactive Compounds from Curcuma Longa Rhizome with Potential Anti-Inflammatory and Immunomodulatory Roles as Adjunct Therapy for COVID-19

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ABSTRACT

The immune condition of individuals is a key factor influencing the progression of COVID-19. Herbal remedies possessing immunomodulatory and anti-inflammatory properties may serve as effective complementary options alongside conventional treatments. This research aimed to identify and explore the immunomodulatory and anti-inflammatory components of Curcuma longa (C. longa) and elucidate their potential mechanisms of action in COVID-19. Biochemical constituents of C. longa rhizomes were systematically compiled from published studies and databases. Subsequently, targets associated with COVID-19 were identified for the selected bioactive phytochemicals, and their possible mechanisms of action were examined through network analysis and molecular docking against four major COVID-19-related proteins for validation. Ten active compounds from C. longa were predicted to interact with these protein targets. Among them, epidermal growth factor showed the highest level of interaction, being targeted by Calebin A, curcumin, cyclocurcumin, demethoxycurcumin, turmeronol A, turmeronol B, caffeic acid, and quercetin. Interferon-gamma emerged as another critical protein influenced by 4-hydroxycinnamic acid. Moreover, curcumin was predicted to interact with toll-like receptor 4, while Ar-turmerone targeted angiotensin II receptor type 2. Four signaling pathways—cytokine-cytokine receptor interaction, toll-like receptor signaling, Jak-STAT, and PI3K-Akt pathways—were identified as key mechanisms linking these phytochemicals to their targets against COVID-19. In summary, the diverse bioactive compounds in C. longa may exert synergistic effects against COVID-19 by modulating immune and inflammatory responses and influencing multiple molecular pathways involved in the disease.

Keywords: COVID-19, Anti-inflammatory, Immunomodulatory, Curcuma longa

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) worldwide, including in Indonesia, has posed a serious challenge to the management and control of infectious diseases. As of July 1, 2022, Indonesia recorded approximately 6,088,460 confirmed cases and 156,737 deaths [1], significantly straining the national healthcare system [2]. COVID-19 is caused by the highly transmissible SARS-CoV-2 virus [3], which spreads through droplets containing viral particles, either via direct person-to-person contact or indirectly through contaminated surfaces [4]. Globally, about 552 million confirmed cases have been reported across all age groups [1]

Since no specific therapy for COVID-19 currently exists, integrating traditional and modern medicine has become a promising approach for prevention and treatment. Given that the immune system plays a central role in the progression of COVID-19, herbal medicines with immunomodulatory properties may serve as both preventive and supportive therapies [5, 6]. Curcuma longa (C. longa), commonly known as turmeric, has been traditionally utilized in various countries and has drawn increasing scientific attention [7]. Curcumin, one of its primary active components, has been reported to protect against acute respiratory distress syndrome by targeting multiple

signaling pathways such as NF-κB, inflammasome, IL-6 trans-signal, and HMGB1 in COVID-19 patients [8]. However, the combined anti-inflammatory and immunomodulatory mechanisms of multiple compounds present in C. longa against COVID-19 remain largely unclear.

Network pharmacology, which integrates systems biology with multidirectional pharmacology using high-throughput omics data and network databases, has shifted the research paradigm from a "one drug–one target" approach to a "multi-compound–multi-target" perspective [9]. This approach has been extensively used to explore multi-target mechanisms and previously unknown therapeutic pathways in several diseases [10].

In the present study, we employed a network pharmacology approach to examine the active anti-inflammatory and immunomodulatory constituents of C. longa rhizome and to investigate their possible molecular mechanisms and synergistic effects as complementary treatments against COVID-19. First, chemical constituents of C. longa rhizome were retrieved from public databases and literature sources, and COVID-19-related target proteins were identified. Overlapping targets were then screened and used for anti-COVID-19 analysis. Finally, pathway enrichment and molecular docking analyses were performed to validate the interactions between the selected compounds and their potential protein targets.

Materials and Methods

Our methodological framework consisted of five major steps: (1) identification of active phytochemical components of C. longa rhizome from literature and online repositories; (2) identification of known and predicted targets related to COVID-19; (3) execution of gene ontology and pathway enrichment analysis; (4) construction and analysis of various molecule–target networks; and (5) molecular docking validation.

Active phytochemical components of c. longa

Phytochemical constituents of C. longa were collected from Dr. Duke's Phytochemical and Ethnobotanical Databases [11] (https://phytochem.nal.usda.gov/phytochem/search) and the KNApSAcK Family Database [12] (http://www.knapsackfamily.com/KNApSAcK_Family/). This study focused on the rhizome part of C. longa, which is known to exhibit multiple biological activities, and identified 39 phytochemical components. The Absorption, Distribution, Metabolism, and Excretion (ADME) profiles of these compounds were evaluated using SwissADME [13] (http://www.swissadme.ch/index.php), where the SMILES chemical notations were retrieved from PubChem [14] (https://pubchem.ncbi.nlm.nih.gov/). The compounds were filtered using three criteria: high gastrointestinal absorption, zero Lipinski's rule violations, and bioavailability score ≥ 0.55 [15]. The 3D structures of the selected phytochemical components were downloaded from PubChem [14] (https://pubchem.ncbi.nlm.nih.gov/), excluding one compound that lacked a 3D molecular structure.

Potential targets of c. longa constituents for COVID-19

Potential targets of the selected phytochemicals were identified using PharmMapper [16] (http://www.lilab-ecust.cn/pharmmapper/), with human proteins set as the target class and only targets with normalized fit scores ≥ 0.8 retained [17]. To complement this, SwissTargetPrediction [18] (http://www.swisstargetprediction.ch/) with a probability threshold ≥ 0.5 and BATMAN-TCM [19] (http://bionet.ncpsb.org.cn/batman-tcm/) with a score cutoff of 80 and adjusted p-value ≤ 0.05 were also used to uncover additional potential targets.

COVID-19-related human gene annotations were obtained from the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/gene/), yielding a total of 165 target genes. These were integrated with C. longa compound targets using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/) to identify overlapping targets, which were considered the C. longa-related COVID-19 targets.

To identify key protein clusters associated with COVID-19, protein–protein interaction (PPI) data were obtained from STRING [20] (https://string-db.org/), restricted to "Homo sapiens" and filtered by the highest confidence score (>0.900) [21]. The PPI network was then clustered using the CytoCluster plugin in Cytoscape v3.8.2 [22] (https://cytoscape.org/) with the ClusterONE algorithm, applying parameters of minimum cluster size = 10, minimum density = 0.5, and seeding from every node. The most significant cluster, determined by the lowest p-value, was selected as the primary COVID-19-related cluster [23].

Construction of the "component–target–disease" network

Visualization of the networks was performed using Cytoscape v3.8.2 [22] (https://cytoscape.org/). Two main networks were developed: (1) a network linking C. longa phytochemical constituents to their common targets, and (2) an integrated network connecting C. longa targets, COVID-19-related proteins, and signaling pathways. In these networks, nodes represented active compounds, target proteins, and pathways, while edges indicated their interactions.

Enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) version 6.8 [24] (https://david.ncifcrf.gov/) to explore the biological functions and pathways associated with Curcuma longa targets linked to COVID-19. Only significant clusters of COVID-19–related targets were selected to identify the most relevant pathways. The enrichment threshold was established at 10 (and 5 for molecular function), with a significance level set at $p < 0.01$ [25].

Molecular docking method

Molecular docking was carried out for each phytochemical constituent of C. longa with potential activity against COVID-19 using AutoDock Vina [26]. The molecular structures of the phytochemicals were optimized using the MMFF94 force field via AutoDockTools 1.5.6 [27]. The X-ray crystal structures of four target proteins were retrieved from the Protein Data Bank (https://www.rcsb.org/), including EGFR (PDB ID: 5FED) [28], TLR4 (PDB ID: 4G8A) [29], IFNG (PDB ID: 6E3K) [30], and AGTR2 (PDB ID: 5XJM) [31]. During docking preparation, water molecules were removed, proteins were kept rigid, and the exhaustiveness parameter was set to 16. Docking scores obtained from native ligand–protein complexes were used as reference cutoff values. Each phytochemical–protein interaction was compared to its native ligand based on binding energy and amino acid interactions. When comparable results were observed, the compound was considered to exhibit effective docking and designated as a node, with their interactions represented as edges [32].

Results and Discussion

Active phytochemical components of C. longa

Phytochemical constituents and their associated targets relevant to COVID-19 were initially retrieved for C. longa. In total, 39 phytochemicals from the rhizome were collected from two databases (Supplementary Material 1: S1), focusing exclusively on the rhizome due to its primary medicinal use. ADME screening identified 25 compounds meeting all inclusion criteria (Supplementary Material 1: S2). Target prediction across three online databases yielded 253 potential protein targets corresponding to these 25 compounds, forming a network of 280 nodes and 649 edges. Most phytochemicals interacted with multiple 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, each of which was predicted to bind only one target (Supplementary Material 1: S3).

"C. longa components–common target" network

A total of 165 COVID-19–related targets were retrieved from NCBI (Supplementary Material 1: S4). By integrating C. longa–derived targets with these COVID-19 targets, six overlapping targets were identified, representing potential therapeutic targets of C. longa against COVID-19 **(Figure 1)**. A "C. longa-component-target-disease" network was subsequently visualized using Cytoscape. The shared targets—EGFR, F2, F3, TLR4, AGTR2, and IFNG—were associated with ten active phytochemicals. Based on network degree analysis, curcumin emerged as the most influential compound, predicted to interact strongly with EGFR, F3, and TLR4, key COVID-19–related targets **(Figure 2).**

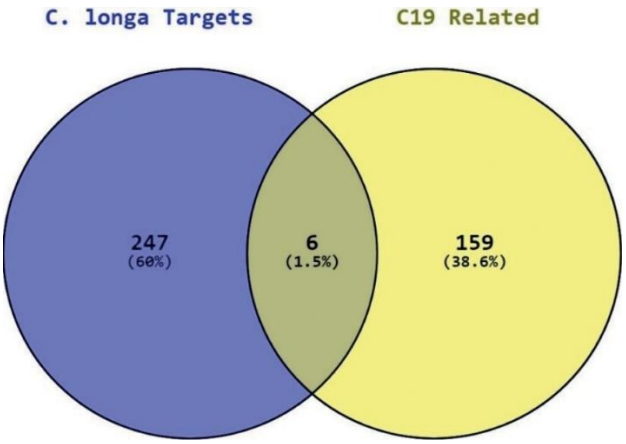


Figure 1. Venn diagram illustrating the overlap between C. longa phytochemical targets and COVID-19-associated protein targets.

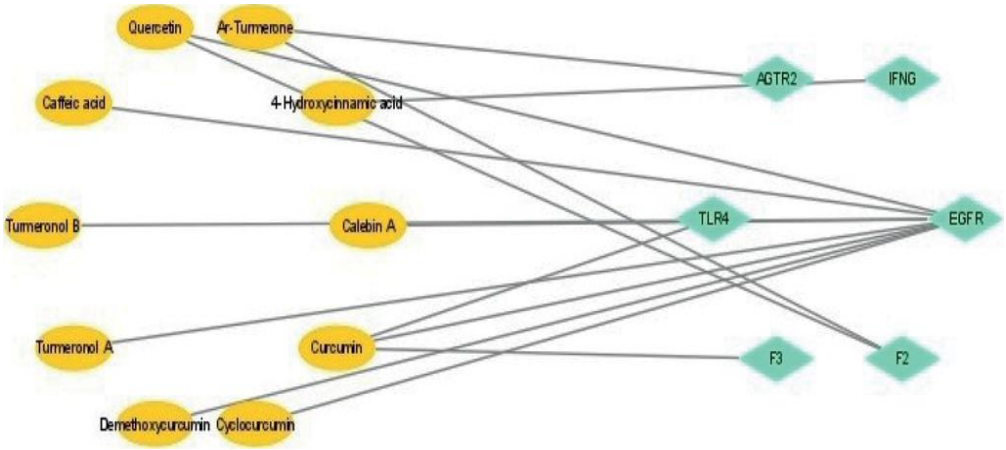


Figure 2. Network showing the relationships between C. longa phytochemical compounds and their shared COVID-19–related protein targets. Yellow ellipses denote C. longa compounds, while blue diamonds represent COVID-19–associated proteins targeted by these compounds.

PPI network of C. longa against COVID-19

Protein–protein interaction (PPI) network analysis is a valuable approach for revealing complex relationships among protein targets involved in multifactorial diseases. The STRING database generated a PPI network consisting of 116 nodes and 429 interaction links. Because of the intricate structure of this network, the data were imported into Cytoscape for further visualization and analysis of key targets and major clusters. Using the ClusterONE algorithm, a significant module was identified. The top-ranked cluster, characterized by the lowest p-value, included 27 nodes (targets) and 181 connecting edges, with a network density of 0.516 **(Figure 3).** The key proteins within this cluster were JAK1, TYK2, IFNG, CCL2, CSF3, IL17A, CCL3, IL18, IL1A, IL2RA, CXCL2, IL4, CSF2, IL10, CXCL1, CXCL10, STAT3, NFKB1, IL1B, IL6, JAK2, CXCL8, STAT1, TNF, CD4, CD8A, and IL2. Notably, IFNG appeared within this significant cluster and was also directly targeted by a C. longa phytochemical compound, as illustrated in **Figure 2**.

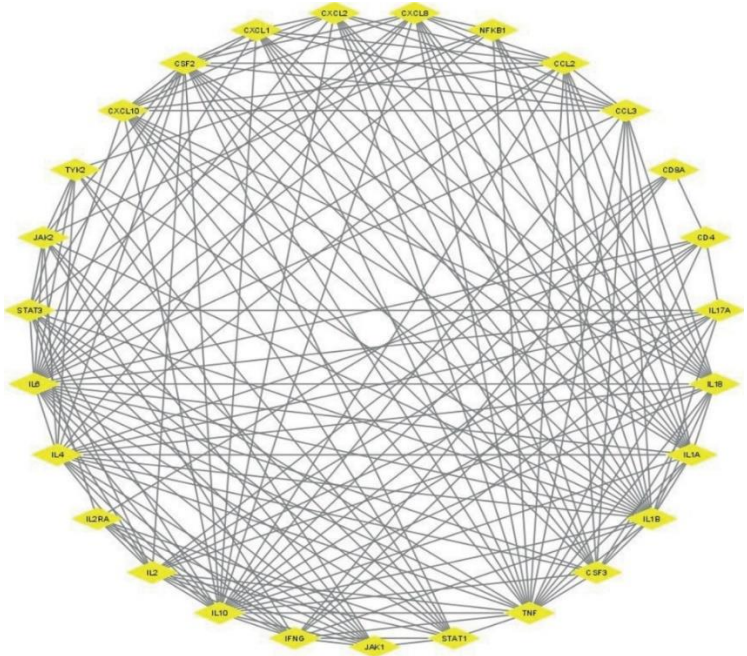
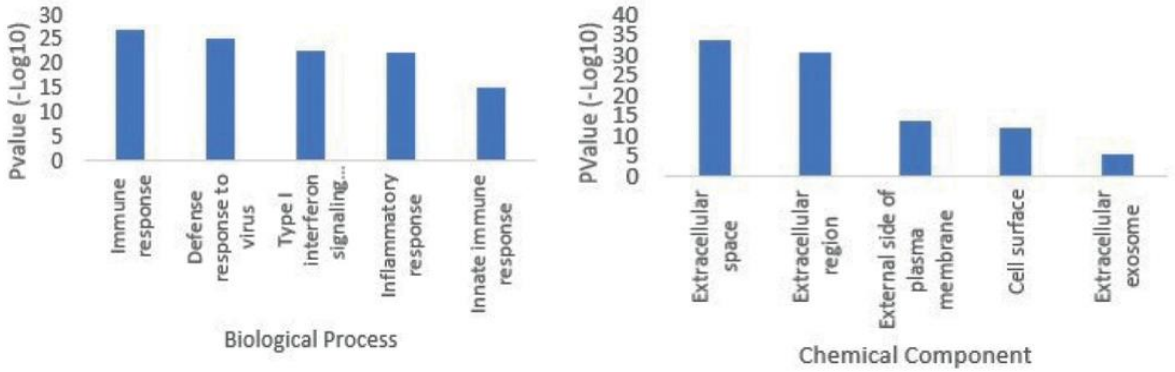


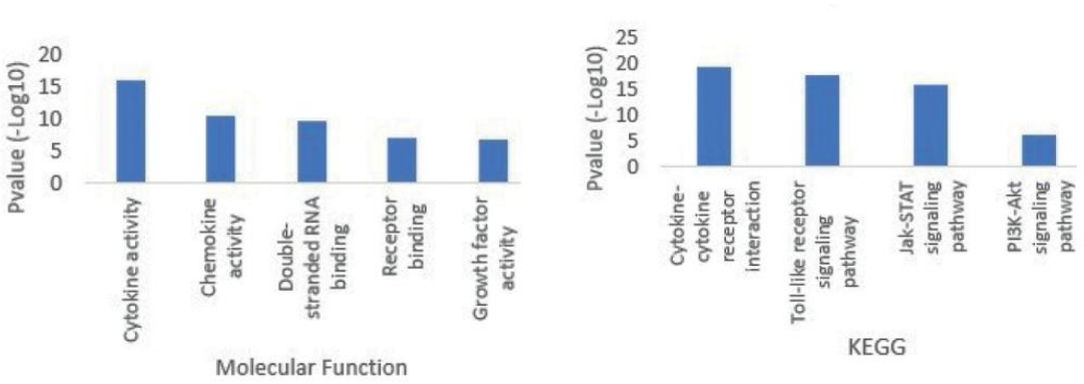
Figure 3. Core cluster of COVID-19–associated protein targets.

Functional enrichment of C. longa potential targets

To better elucidate how C. longa may exert therapeutic effects against COVID-19, a Gene Ontology (GO) enrichment analysis was carried out on the 27 COVID-19–related targets obtained from the key cluster using the DAVID database **(Figure 4).** The GO analysis encompassed three major categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). Within BP, 31 enrichment terms were identified, with the most prominent involving immune response regulation, antiviral defense mechanisms, activation of the type I interferon pathway, modulation of inflammation, and stimulation of innate immune activity. For CC, 11 enriched categories were recognized, predominantly associated with the extracellular environment, including the extracellular matrix, outer plasma membrane surface, and cell boundary structures. Regarding MF, 10 terms showed significant enrichment, mainly highlighting cytokine and chemokine signaling, receptor binding affinity, growth factor-related activity, and interactions with double-stranded RNA molecules.



a) b)



c) d)

Figure 4. Enrichment analysis of 27 COVID-19–associated targets identified from the key cluster: a) Biological Process, b) Cellular Component, c) Molecular Function, and d) KEGG pathways.

From the KEGG pathway analysis, 32 signaling pathways were identified, among which four—cytokine–cytokine receptor interaction, Toll-like receptor signaling, JAK–STAT signaling, and PI3K–Akt signaling—were directly associated with COVID-19. Each of these pathways exhibited highly significant enrichment ($p < 0.0001$) and was deemed crucial for the anti-inflammatory and immunomodulatory mechanisms of C. longa against COVID-19.

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

A network was constructed to visualize the interconnections among C. longa targets linked to COVID-19, additional COVID-19–related targets, and their corresponding pathways **(Figure 5).** The COVID-19–related proteins involved in the four KEGG pathways were used to map the interactions, forming a network consisting of 47 nodes and 100 connecting edges. Within this system, five direct associations were observed between C. longa common targets and specific pathways, while the remaining connections represented indirect interactions.

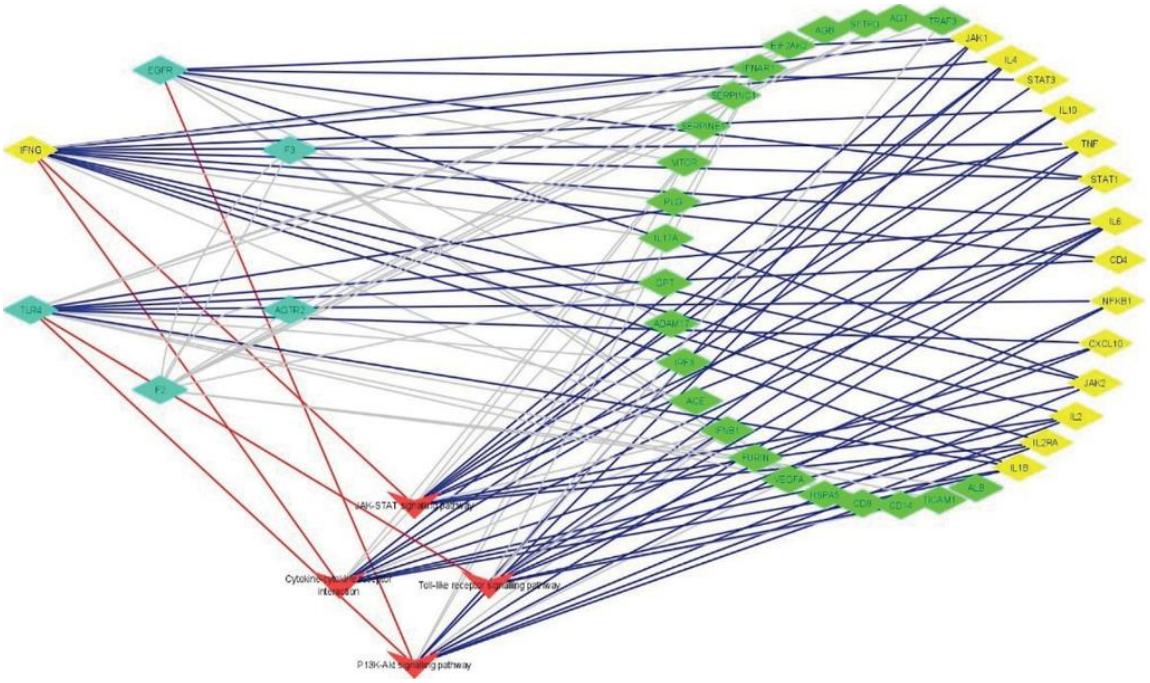


Figure 5. Network illustrating the relationships among C. longa common COVID-19 targets (blue diamonds, upper left), additional COVID-19–related targets (green diamonds, upper right), and corresponding pathways (red arrows, lower section). Yellow diamonds represent targets belonging to the significant COVID-19 cluster. Red edges indicate direct associations, while blue edges denote indirect connections between C. longa COVID-19–related targets from the significant cluster and their respective pathways.

Molecular docking

The principal bioactive compounds identified in C. longa—including quercetin, ar-turmerone, 4-hydroxycinnamic acid, calebin A, curcumin, cyclocurcumin, demethoxycurcumin, turmeronol A, turmeronol B, and caffeic acid—were subjected to molecular docking analysis with four target proteins: IFNG, AGTR2, EGFR, and TLR4. During docking preparation, the protein structures were treated as rigid, and all water molecules were excluded before simulation. In molecular docking, lower binding energy values indicate stronger ligand–receptor interactions and greater conformational stability. The docking simulations revealed that the major phytochemicals of C. longa demonstrated favorable binding affinities toward COVID-19–related targets, as determined by comparison with native ligand binding energies and interacting amino acid residues **(Table 1).** The resulting interactions were visualized using Discovery Studio software [33] and are presented in Supplementary 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

Despite global progress, the battle against COVID-19 continues, and herbal-based therapies have remained a valuable component of supportive treatment strategies. The findings from this network pharmacology analysis shed light on the bioactive compounds in C. longa, their potential protein targets related to COVID-19, the interactions between these compounds and targets, and the signaling pathways influenced by these interactions.

A total of ten active phytochemicals derived from C. longa rhizome were predicted to interact with six shared COVID-19–associated protein targets. Among these, curcumin stood out, forming two key compound–target interactions involving EGFR and TLR4, as shown in **Figure 5**. Within the protein–protein interaction (PPI) network, IFNG emerged as a central and highly connected node, indicating its pivotal role. Furthermore, four signaling pathways were identified as being associated with C. longa's target proteins in relation to COVID-19: cytokine–cytokine receptor interaction, Toll-like receptor signaling, JAK–STAT signaling, and PI3K–Akt signaling pathways. These pathways collectively suggest possible mechanisms underlying the anti-inflammatory and immunomodulatory effects of C. longa against COVID-19, illustrated in **Figure 6.**

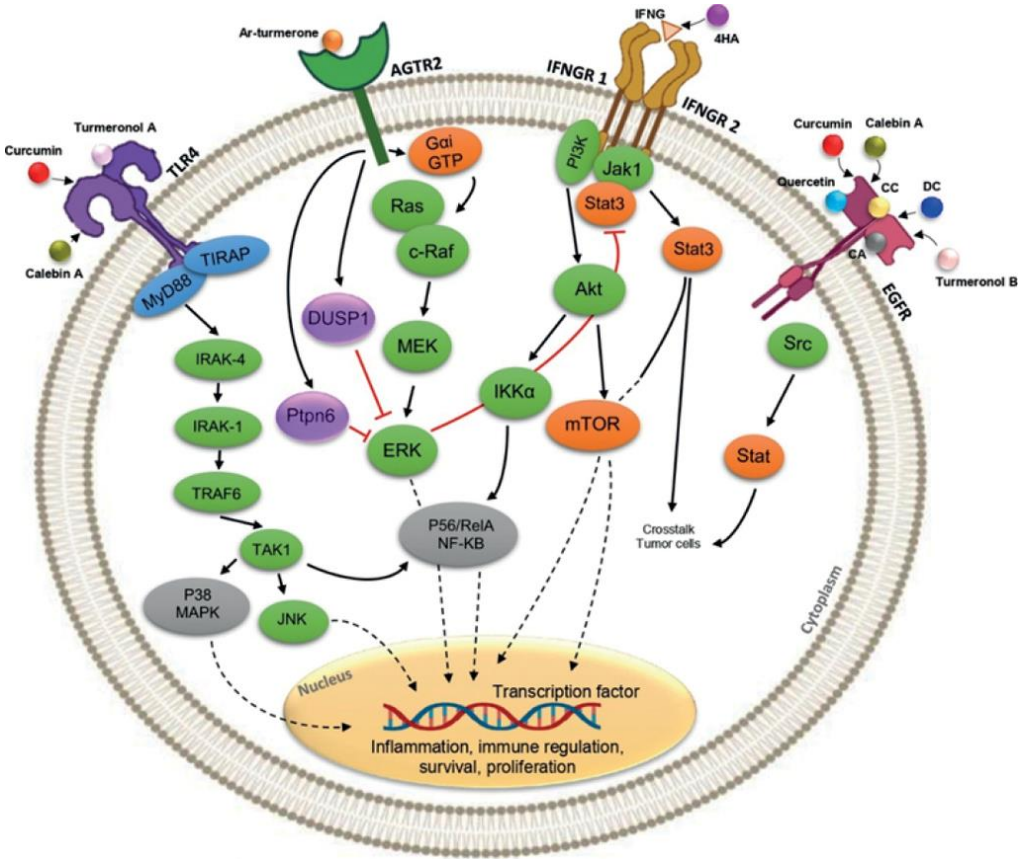


Figure 6. Proposed mechanism illustrating how multiple bioactive compounds from C. longa rhizome influence key trans-signaling pathways (JAK/STAT, PI3K/Akt, and TLR) and interact with target proteins involved in COVID-19 pathology. Abbreviations: JAK/STAT – Janus kinase/signal transducer and activator of transcription; PI3K – Phosphatidylinositol-3-kinase; MAPK – Mitogen-activated protein kinase; NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells; TLR – Toll-like receptor; 4HA – 4-hydroxycinnamic acid; CC – cyclocurcumin; CA – caffeic acid; DC – demethoxycurcumin. Figure created using BioRender (https://biorender.com/).

Numerous studies have highlighted curcumin as a promising therapeutic candidate against COVID-19. For instance, treatment with nanocurcumin was shown to modulate pro-inflammatory cytokine expression in infected patients, significantly lowering IL-6 and IL-1β levels that were initially elevated alongside IL-1β, IL-6, TNF-α, and IL-18 [34]. Another investigation demonstrated that nano-curcumin reduced the frequency of Th17 cells and downregulated Th17-associated cytokines (IL-17, IL-21, IL-23, and GM-CSF) in COVID-19 patients [35].

The IFNG protein, although targeted solely by 4-hydroxycinnamic acid from C. longa in this study, plays a pivotal role in COVID-19 pathology. Research indicates that IFNG drives the differentiation of immature secretory cells into ACE2-expressing ciliated cells in COVID-19 patients, with ACE2 expression being partially induced by IFNG signaling in epithelial tissues [36]. Cytotoxic T lymphocytes in these patients display high expression of IFNG and TNF, alongside genes encoding cytotoxic receptors such as KLRB1, KLRC1, and KLRD1. The observed ACE2 upregulation—mediated via IFNG activation by 4-hydroxycinnamic acid—may therefore help counter viral infection through immune system protection mechanisms [37, 38].

Ar-turmerone, another key constituent of C. longa, was predicted to bind AGTR2, supporting previous hypotheses. AGTR2, a member of the G-protein-coupled receptor family, acts as a receptor for angiotensin II [39]. SARS-CoV-2 infection has been shown to suppress ACE2 expression, provoking severe lung inflammation [40]. This response is believed to be driven by AGTR2 through activation of the ERK/MAPK pathway, which is upregulated in COVID-19 patients [41]. Additionally, AGTR2 stimulates the PI3K–Akt pathway via ADAM17, leading to NF-κB activation [42]. Thus, inhibition of AGTR2 by ar-turmerone could reduce these signaling cascades, minimizing inflammation.

EGFR emerged as the most frequently targeted protein, interacting with eight of the ten C. longa compounds. EGFR facilitates the conversion of membrane-bound IL-6Rα into its soluble form (sIL-6Rα), and the IL-6/sIL-6Rα complex activates the JAK–STAT pathway via gp130, which further contributes to full NF-κB pathway activation [43, 44]. Since AGTR also enhances PI3K–Akt signaling through ADAM17 and subsequent NF-κB activation [42], inhibition of both EGFR and AGTR by C. longa constituents may help block NF-κB activation, thereby reducing cytokine release and preventing cytokine storm in COVID-19 patients.

The Toll-like receptor (TLR) pathway, another target of C. longa constituents, is integral to innate immunity. It mediates recognition of pathogen-associated molecular patterns (PAMPs), regulates cytokine production, and bridges innate and adaptive immune responses [45-47]. Activation of TLR signaling induces the production of inflammatory mediators such as IL-1, IL-6, TNF-α, and type I interferons, all of which contribute to cytokine storms in severe COVID-19 [48]. Curcumin's ability to modulate TLR signaling may thus serve as a crucial mechanism for mitigating SARS-CoV-2–induced hyperinflammation.

Limitations

Although the current network pharmacology analysis identified ten potential bioactive compounds from C. longa interacting with six COVID-19–related targets and elucidated four key signaling pathways involved in its mechanism, the study remains computational in nature. Experimental validation is necessary to confirm these findings. In vitro studies assessing the direct antiviral and anti-inflammatory effects of these compounds, along with in vivo experiments to evaluate their pharmacological actions in disease models, are essential to substantiate the proposed mechanisms and therapeutic potential of C. longa.

Conclusion

This study represents the first systematic network pharmacology exploration of C. longa rhizome's multi-compound mechanisms against COVID-19. Ten phytochemicals—curcumin, turmeronol A, turmeronol B, cyclocurcumin, calebin A, 4-hydroxycinnamic acid, ar-turmerone, caffeic acid, demethoxycurcumin, and quercetin—were predicted to target four pivotal proteins: EGFR, TLR4, IFNG, and AGTR2. The major signaling pathways implicated were cytokine–cytokine receptor interaction, PI3K–Akt, JAK–STAT, and TLR4 pathways. By modulating these interconnected signaling routes, C. longa may exert synergistic effects that suppress inflammation, regulate immune responses, and prevent pathological progression in COVID-19 through multitarget, multipathway interactions.

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Conflict of Interest: None

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Ethics Statement: None

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