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Potential Mechanisms of Baicalin against Viral Pneumonia Revealed by Network Pharmacology and Molecular Docking

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ABSTRACT

While baicalin exhibits therapeutic potential against viral pneumonia, its systems-level mechanisms remain elusive. This study integrates network pharmacology, transcriptomic profiling, and molecular docking to decode these multi-target interactions. By mapping baicalin-associated genes against viral pneumonia profiles, we identified 223 shared targets. Subsequent network topology analysis prioritized core hub genes (e.g., AKT1, IL6, TP53, CTNNB1, and BCL2), whose clinical relevance was corroborated using a severe COVID-19 transcriptomic dataset (GSE171110). Specifically, the expression data revealed significant dysregulation in key inflammatory and apoptotic mediators, including the marked upregulation of MMP9, STAT3, and CASP3. Functional enrichment linked these networks primarily to PI3K-Akt signaling, MAPK cascades, and host antiviral immune responses. Furthermore, molecular docking confirmed high-affinity binding (–7.5 to –9.0 kcal/mol) between baicalin and the top five hub proteins. These findings delineate the specific kinase and cytokine networks mediating baicalin's protective effects, providing an empirically supported framework for future experimental validation.

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Introduction

Viral pneumonia remains a major challenge in the prevention and treatment of respiratory infections. The sustained circulation of SARS-CoV-2, influenza viruses, respiratory syncytial virus (RSV) and other respiratory viruses has shown that virus-induced pulmonary inflammation can cause acute respiratory symptoms and may progress to excessive inflammatory activation, alveolar epithelial injury, endothelial dysfunction, acute lung injury and acute respiratory distress syndrome (ARDS)[1-4]. Unlike pathology driven solely by pathogen replication, viral pneumonia typically involves coordinated host immune responses, cytokine release, oxidative stress, apoptosis and multiple inflammatory signaling pathways. A multi-target and multi-pathway perspective is therefore important for identifying molecules with immunomodulatory and anti-inflammatory potential[5-10].

Baicalin is one of the major flavonoid constituents of Scutellaria baicalensis Georgi and is the 7-O-glucuronide of baicalein. Pharmacological studies and reviews indicate that baicalin has anti-inflammatory, antioxidant, immunomodulatory and antiviral activities, with particular interest in inflammatory and lung diseases[11-13]. In respiratory-virus studies, baicalin has been reported to induce innate antiviral responses against RSV, inhibit SARS-CoV-2 RNA-dependent RNA polymerase in vitro, and show potential relevance to COVID-19 associated inflammatory states[14-20]. These observations provide experimental support for investigating baicalin in viral-pneumonia-associated host responses.

Nevertheless, viral pneumonia comprises a complex host molecular network, and it remains unclear whether baicalin connects inflammatory responses, antiviral defense and lung-tissue injury through specific hub targets. Previous studies often focused on a single virus, one pathway or isolated experimental phenomena. Recent systems--level work on Scutellaria baicalensis, baicalin-containing formulas and network pharmacology has reinforced the feasibility of integrating chemical profiles, targets, disease genes and docking to examine viral-pneumonia mechanisms[21-24]. In addition, lung-injury studies suggest that baicalin or related Scutellaria flavonoids can modulate NLRP3, NF-kB, metabolic and inflammatory injury modules[25-27].

Network pharmacology provides a suitable systems-biology framework for mechanism studies of natural products and active components of traditional medicine. It can integrate compound structure, disease-associated targets, PPI networks and enrichment analysis to reveal multi-target regulatory features. Combined with public transcriptomic validation and molecular docking, this approach can improve the biological plausibility of target prioritization

and provide directions for subsequent mechanistic experiments. In this study, we used baicalin as the research object, integrated drug-target prediction databases with viral-pneumonia disease-gene resources, screened intersecting targets, constructed a PPI network, identified hub targets, performed GO and KEGG enrichment, validated hub-gene expression in a public transcriptomic dataset, and evaluated the binding potential between baicalin and key proteins by molecular docking.

Materials and Methods

1. Study design

This study used an integrated network--pharmacology, transcriptomic validation and molecular-docking strategy to analyze the potential mechanism of baicalin against viral pneumonia. First, the chemical information of baicalin was obtained from PubChem, an updated chemical-information resource[28]. Potential baicalin targets were collected from multiple drug-target prediction and chemical-gene databases, and viral-pneumonia-related targets were retrieved from disease-related databases. The baicalin target set and viral-pneumonia target set were intersected to obtain candidate targets. A PPI network was then constructed, hub genes were screened, and GO/KEGG enrichment was conducted. Finally, public GEO transcriptomic data were used to evaluate hub-gene expression, and CB-Dock2-based molecular docking was used to estimate the binding potential of baicalin to selected hub proteins.

2. Chemical information of baicalin

Baicalin was searched in PubChem using the keyword 'Baicalin'. The PubChem CID, molecular formula, molecular weight, Canonical SMILES, Isomeric SMILES and two- or three-dimensional SDF structure files were recorded for target prediction and docking. PubChem lists baicalin as CID 64982 with the molecular formula $C21H_{18}O_{11}$. To avoid conceptual ambiguity, the compound studied here was baicalin rather than baicalein; baicalin is baicalein 7-O-glucuronide.

3. Prediction of baicalin-related targets

Potential baicalin targets were collected using SwissTargetPrediction, TargetNet and the Comparative Toxicogenomics Database (CTD). The SMILES structure or SDF file of baicalin was uploaded to the relevant platforms, and the species was restricted to Homo sapiens. SwissTargetPrediction targets with probability > 0 were retained, TargetNet targets with probability > 0.5 were retained, and CTD targets associated with baicalin were downloaded. Recent assessments of target-prediction tools support the use of multi-source predictions to improve coverage and reduce platform-specific bias[29,30]. Targets from different sources were merged, duplicates were removed, and UniProt was used to standardize protein names, UniProt IDs and aliases to official gene symbols. Targets that could not be

mapped to human gene symbols were excluded.

4. Collection of viral-pneumonia-related targets

Viral-pneumonia-related targets were retrieved from GeneCards, DrugBank and CTD. The search terms included 'viral pneumonia', 'pneumonia, viral', 'COVID-19 pneumonia', 'SARS-CoV-2 infection', 'influenza pneumonia', 'respiratory syncytial virus pneumonia' and 'acute lung injury'. In GeneCards, targets with a relevance score >= 1 were retained. DrugBank entries were screened using indications or disease-related targets associated with viral pneumonia, COVID-19, influenza pneumonia or respiratory viral infection. CTD entries were manually screened for links to viral infection, pulmonary inflammation, acute lung injury and immune regulation. Targets were merged, deduplicated and standardized to official gene symbols through UniProt.

5. Intersection analysis of baicalin and viral-pneumonia targets

The baicalin-related targets and viral--pneumonia-related targets were intersected using the R package venn, and a Venn diagram was generated to visualize the overlap. The overlapping genes were defined as candidate targets through which baicalin may act on viral pneumonia.

6. PPI network construction and hub-target screening

The intersecting targets were imported into the STRING database for PPI analysis. STRING is widely used to integrate known and predicted protein associations and functional networks[31]. The organism was restricted to Homo sapiens, and the minimum interaction confidence was set to high confidence (interaction score > 0.7). Isolated nodes were removed. The TSV network file was imported into Cytoscape for visualization. Hub targets were screened using the CytoHubba plugin with MCC, Degree, MNC, Closeness and Betweenness algorithms. The top 20 targets ranked by each algorithm were obtained, and targets present in the intersection of algorithms or consistently ranking highly were retained as candidate hub targets for GEO validation and docking.

7. External gene-expression validation

GEO was searched for gene-expression datasets related to viral pneumonia in Homo sapiens. After data retrieval, expression values for the hub genes were extracted from normal and viral-pneumonia-related samples. The selected validation dataset was GSE171110, a whole-blood RNA-seq dataset comprising severe COVID-19 patients and healthy donors. Because severe COVID-19 commonly involves viral pneumonia and systemic inflammation, this dataset was used as an independent source for hub-gene expression validation. Blood-transcriptome studies have shown that host-response signatures can stratify COVID-19 severity and reveal biologically relevant immune modules[36,37]. For each hub gene, two-group comparisons were performed using a

two-tailed Student's t-test, and results were displayed as box or bar plots with individual sample points.

8. GO and KEGG enrichment analysis

To explore biological functions, gene symbols for the baicalin-viral pneumonia intersecting targets were converted to Entrez IDs using the R package org.Hs.eg.db. GO functional enrichment and KEGG pathway enrichment were performed using clusterProfiler, enrichplot and ggplot2. clusterProfiler provides universal enrichment interfaces and visualization workflows for omics data interpretation[32,33]. Enrichment terms with P value < 0.05 and adjusted P value or q value < 0.05 were retained. The top GO terms and KEGG pathways ranked by q value were selected for visualizationand interpretation.

9. Molecular docking

Molecular docking was used to evaluate the interaction between baicalin and hub targets. The receptor proteins were hub targets identified by PPI analysis, and baicalin was used as the ligand. The baicalin structure was obtained from PubChem, and receptor structures were downloaded from the Protein Data Bank according to UniProt information. CB-Dock2 was used for ligand-receptor preprocessing and blind docking, including cavity detection, hydrogen addition, removal of water molecules, energy optimization and minimization[34,35]. The docking conformation with the lowest Vina score was selected as the optimal binding pose, the binding energy was recorded, and three-dimensional docking diagrams were generated.

Databases and online analytical platforms follows table 1.

Table 1. Data sources and access links

Database/platform	Access address
TargetNet	https://targetnet.scbdd.com/
SwissTargetPrediction	http://www.swisstargetprediction.ch/
CTD	https://ctdbase.org/
GeneCards	https://www.genecards.org/
OMIM	https://www.omim.org/
UniProt	https://www.uniprot.org/
STRING	https://string-db.org/
GEO	https://www.ncbi.nlm.nih.gov/gds
CB-Dock2	https://cadd.labshare.cn/cb-dock2/

Results

1. Screening of baicalin-and viral-pneumonia-related targets

To systematically identify the potential molecular basis of baicalin intervention in viral pneumonia, we first integrated multiple databases to construct baicalin-related and viral-pneumonia-related target sets. Baicalin targets were mainly obtained from TargetNet, CTD and SwissTargetPrediction, whereas viral-pneumonia targets were mainly obtained from CTD, OMIM and GeneCards. After deduplication, standardization and conversion to official gene symbols, all targets were used for subsequent analysis.

For baicalin target prediction, TargetNet yielded 495 candidate targets, CTD yielded 82 candidate targets, and Swiss Target Prediction yielded 94 candidate targets. Venn analysis of the three databases showed 429 TargetNet-specific targets, 55 CTD-specific targets and 38 Swiss TargetPrediction-specific targets. TargetNet and CTD shared 15 targets, TargetNet and Swiss Target Prediction shared 44 targets, CTD and SwissTargetPrediction shared 5 targets, and all three databases shared 7 targets (figure 1A).

These results indicate both complement--arity and stable overlap among target-prediction sources, supporting multi-database integration to improve target coverage and reliability. For viral-pneumonia disease targets, CTD, OMIM and GeneCards contributed distinct targets. Venn analysis showed 69 CTD-specific targets, 453 OMIM-specific targets and 800 GeneCards--specific targets. CTD and OMIM shared 12 targets, CTD and GeneCards shared 36 targets, OMIM and GeneCards shared 81 targets, and all three databases shared 15 targets (figure 1B). After integration and deduplication, 1,466 viral-pneumonia--related targets were obtained. This database heterogeneity is consistent with the complex host immune, inflammatory, antiviral and lung-injury networks involved in viral pneumonia.

Intersecting baicalin targets with viral-pneumonia targets identified 223 shared targets. In addition, 362 targets were specific to baicalin and 1,243 targets were specific to viral pneumonia (figure 1C). The 223 shared targets accounted for approximately 38.1% of all baicalin potential targets and 15.2% of viral-pneumonia disease targets, indicating substantial molecular overlap between the baicalin target spectrum and the disease network. These candidate targets were carried forward for baicalin-target-viral pneumonia network construction, PPI analysis, hub-target screening, enrichment analysis and docking validation.

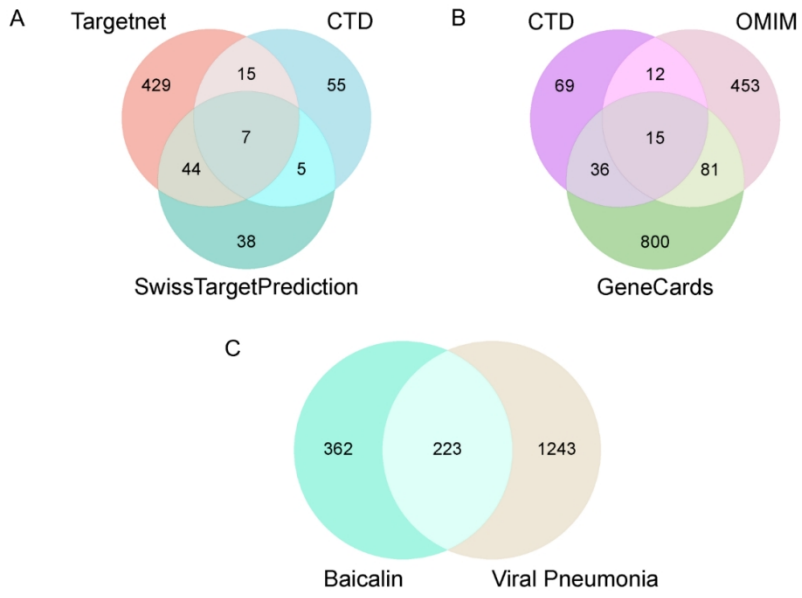

Figure 1: Screening and intersection analysis of baicalin- and viral-pneumonia-related targets

A, Venn diagram of baicalin potential targets from TargetNet, CTD and SwissTargetPrediction. B, Venn diagram of viral-pneumonia-related targets from CTD, OMIM and GeneCards. C, Intersection between baicalin potential targets and viral-pneumonia-related targets. The overlapping 223 targets were defined as candidate targets for baicalin intervention in viral pneumonia.

2. PPI network of shared genes and identification of hub targets

A PPI network was constructed for the 223 shared genes using STRING. After removal of isolated nodes, the network contained 206 nodes and 1,499 edges, with an average node degree of 7.63. The STRING-derived TSV file was imported into Cytoscape for network visualization and topological analysis. CytoHubba was used to prioritize hub genes. The MCC algorithm, which is widely used for robust hub-gene scoring, identified the top 20 hub genes: AKT1, IL6, TP53, CTNNB1, BCL2, MMP9, EGFR, STAT3, MAPK8, TNF, IL1B, CASP3, ESR1, SRC, CCND1, CASP8, RELA, MAPK3, TGFB1 and SIRT1 (figure 2). These nodes may occupy key positions in the network and represent potential targets through which baicalin could mitigate viral pneumonia.

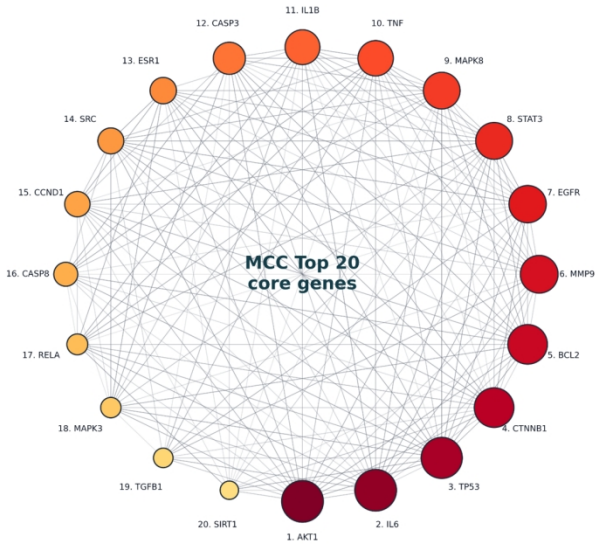

Figure 2: PPI network and hub genes identified using the MCC algorithm

The network displays interactions among the top 20 hub genes. Node size and color are proportional to the number or strength of interactions; larger and darker nodes indicate stronger network centrality. AKT1, IL6, TP53, CTNNB1 and BCL2 showed the highest MCC values and may be dominant nodes within the PPI network.

3. Expression validation of hub targets in an external dataset

To evaluate the expression characteristics of the PPI-derived hub targets in clinically relevant viral-pneumonia samples, we used the GEO dataset GSE171110 for external validation. GSE171110 is a Homo sapiens whole-blood RNA-seq dataset generated by high-throughput sequencing and designed to compare severe COVID-19 patients with healthy donors. It contains 44 severe COVID-19 samples and 10 healthy donor samples. Because severe COVID-19 patients commonly develop viral pneumonia and systemic inflammatory responses, this dataset was considered an independent data source for hub-gene validation.

Several of the 20 hub genes were significantly different between severe COVID-19 and healthy control samples. Compared with healthy donors, MMP9, STAT3, CASP3, ESR1, MAPK3 and TGFB1 were increased in the severe COVID-19 group, with MMP9 showing the most pronounced difference. In contrast, TP53, BCL2, MAPK8, CCND1 and SIRT1 were decreased in the severe COVID-19 group. Specifically, MMP9, TP53, BCL2, STAT3,

MAPK8, CASP3, CCND1, MAPK3, TGFB1 and SIRT1 showed strong statistical differences between groups, whereas ESR1 reached nominal significance but became borderline after multiple testing correction. AKT1, IL6, CTNNB1, EGFR, TNF, IL1B, SRC, CASP8 and RELA did not show significant between-group differences in this dataset (figure 3).

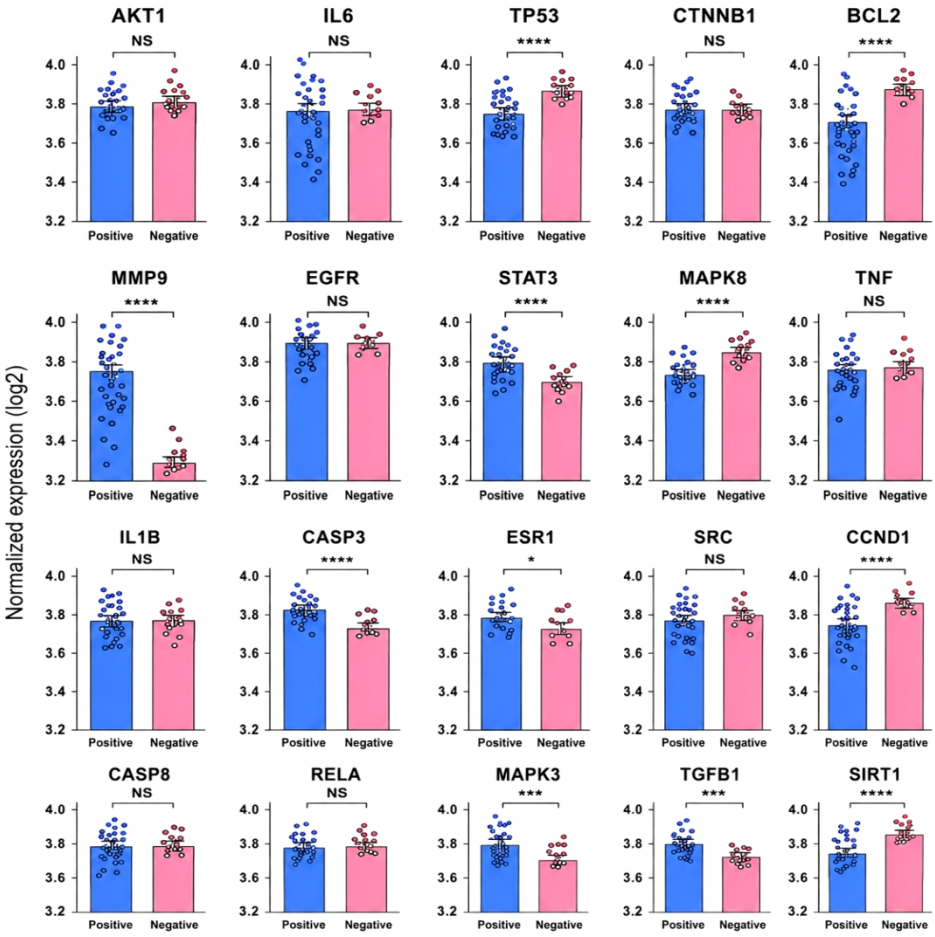

Figure3: Expression validation of hub targets in a viral-pneumonia-related external dataset

Normalized log2 expression levels of the 20 hub targets identified from the PPI network were compared between the Positive and Negative groups. Blue bars indicate the Positive group, and pink bars indicate the Negative group. Each dot represents an individual sample; bars represent mean expression, and error bars indicate the standard error of the mean. Statistical differences were assessed using a two-tailed Student's t-test. NS, not significant; *P < 0.05; ***P < 0.001; ****P < 0.0001.

4. GO and KEGG pathway enrichment analysis

To clarify the potential biological functions and signaling pathways of baicalin against viral pneumonia, we conducted GO and KEGG enrichment analyses for the 223 intersecting targets. GO analysis included Biological Process (BP), Cellular Component (CC) and Molecular Function (MF), whereas KEGG analysis was used to identify key signaling pathways (figures 4 and 5).

BP enrichment showed that intersecting targets were mainly associated with peptidyl-tyrosine phosphorylation, peptidyl-tyrosine modification, protein autophosphorylation, positive regulation of MAPK cascade, positive regulation of kinase activity, response to molecules of bacterial origin, positive regulation of cytokine production, positive regulation of response to external stimulus, regulation of inflammatory response and response to lipopolysaccharide. These biological processes indicate that the baicalin-viral pneumonia targets may participate in protein-kinase-mediated signal transduction, MAPK cascades, inflammatory regulation, cytokine production and pathogen-associated stimulus responses. CC enrichment indicated that the targets were predominantly located in membrane rafts, membrane microdomains, the external side of the plasma membrane, plasma membrane rafts, caveolae, focal adhesions, cell-substrate junctions, the apical part of the cell, vesicle lumen and apical plasma membrane. These regions are involved in receptor signaling, extracellular stimulus recognition, inflammatory factor responses and immune-cell adhesion or migration, suggesting that baicalin may influence viral-pneumonia pathology through membrane-receptor-mediated signaling networks. MF enrichment highlighted transmembrane receptor protein tyrosine kinase activity, transmembrane receptor protein kinase activity, protein tyrosine kinase activity, non-membrane--spanning protein tyrosine kinase activity, protein serine/threonine kinase activity, protein serine kinase activity, nuclear receptor activity, ligand-activated transcription-factor activity, endopeptidase activity and cytokine receptor binding. These molecular functions suggest that baicalin candidate targets have receptor kinase, protein kinase, nuclear receptor and cytokine-receptor-binding properties, supporting a potential connection with receptor tyrosine kinase signaling, nuclear receptor transcriptional regulation and cytokine signal transduction.

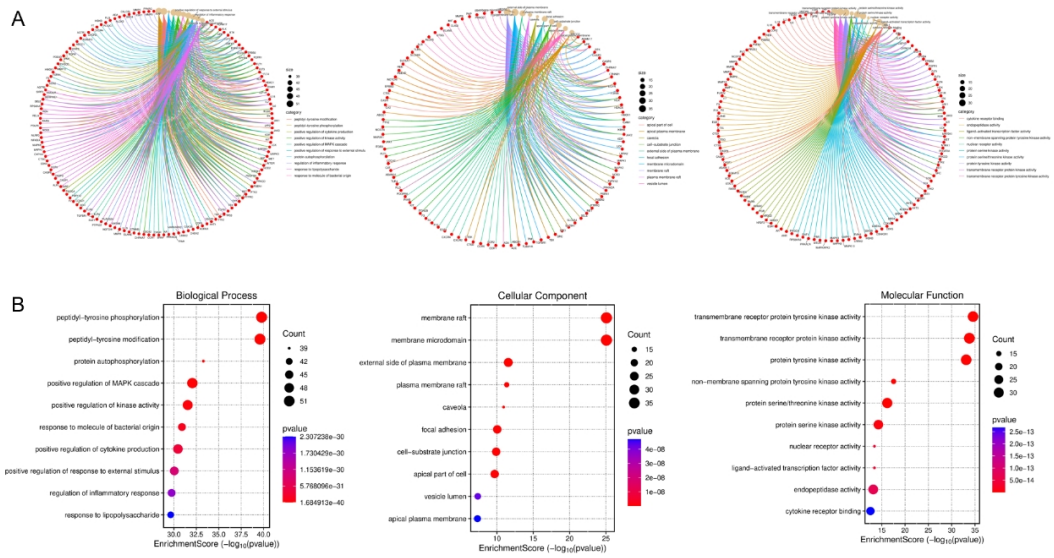

Figure4: GO functional enrichment of intersecting targets

A, GO chord plots showing many-to-many mapping between the top enriched GO terms and intersecting genes for Biological Process, Cellular Component and Molecular Function. B, GO dot plots showing representative enriched terms in Biological Process, Cellular Component and Molecular Function.

KEGG enrichment further showed that the baicalin-viral pneumonia targets were significantly enriched in inflammatory, metabolic, viral-infection and cell-signaling pathways. Top pathways included AGE-RAGE signaling pathway in diabetic complications, lipid and atherosclerosis, endocrine resistance, proteoglycans in cancer, pancreatic cancer, prostate cancer, PI3K-Akt signaling pathway, human cytomegalovirus infection, hepatitis B and EGFR tyrosine kinase inhibitor resistance. PI3K-Akt signaling and EGFR tyrosine kinase inhibitor resistance reflect links with receptor tyrosine kinases, cell survival, cell proliferation and inflammatory signaling. Human cytomegalovirus infection and hepatitis B suggest involvement in host antiviral responses, whereas AGE-RAGE signaling and lipid/atherosclerosis pathways are associated with oxidative stress, chronic inflammation and endothelial injury.

Some enriched pathways had tumor- or endocrine-resistance-related names, such as proteoglycans in cancer, pancreatic cancer, prostate cancer and endocrine resistance. This does not indicate that baicalin acts against viral pneumonia primarily through tumor-specific mechanisms. Instead, these terms reflect shared molecular modules,

including EGFR, PI3K-Akt, MAPK, cytokine signaling, apoptosis and extracellular-matrix remodeling. Taken together, the GO and KEGG analyses suggest that baicalin may act through coordinated regulation of receptor activation, kinase signaling, inflammatory responses, cytokine networks, oxidative stress and host antiviral responses.

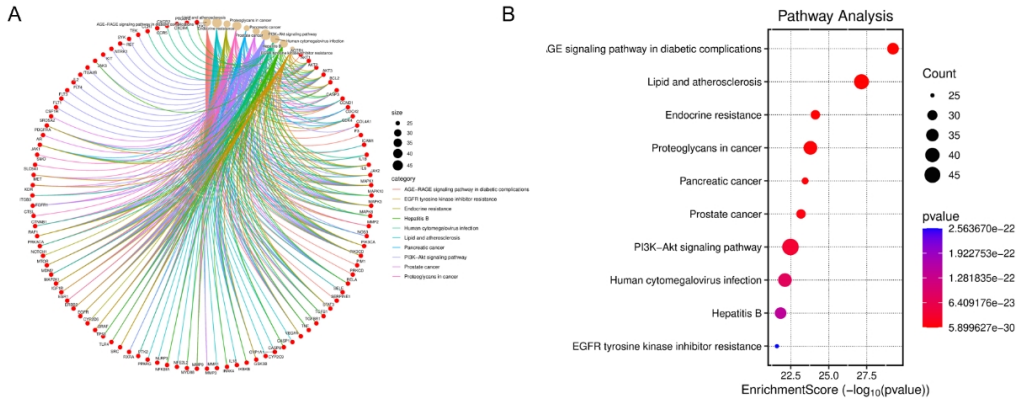

Figure 5. KEGG pathway enrichment analysis of intersecting targets

A, KEGG chord plot showing interactions between shared target genes and the top enriched pathways. B, KEGG dot plot showing representative pathways ranked by enrichment significance. The enrichment pattern suggests multi-target regulation of viral-pneumonia-related mechanisms by baicalin.

5. Molecular docking between baicalin and hub targets

To further evaluate the potential binding between baicalin and key hub targets, molecular docking was performed for the five top-ranked MCC targets: AKT1, IL6, TP53, CTNNB1 and BCL2. These proteins had high topological importance in the PPI network and were considered possible core regulatory targets of baicalin in viral pneumonia.

The docking results suggested that baicalin had favorable binding potential with all five core targets, with binding energies ranging from -7.5 to -9.0 kcal/mol (figures 6-10 and Table 2). The lowest binding energy was observed for BCL2 (-9.0 kcal/mol), indicating the most stable ligand-receptor conformation among the tested proteins. The binding energy for TP53 was -8.3 kcal/mol, whereas AKT1, CTNNB1 and IL6 showed binding energies of -7.9, -7.8 and -7.5 kcal/mol, respectively. Binding energy below zero indicates a spontaneous

binding tendency, and binding energy lower than -5.0 kcal/mol is commonly considered to suggest relatively strong binding activity. Thus, these docking results support stable interactions between baicalin and the selected hub proteins. Baicalin may bind to active pockets or potential binding regions through hydrogen bonds, hydrophobic interactions and van der Waals forces. However, docking provides only a structural hypothesis and requires validation by cell-based, animal or biophysical binding experiments.

Table 2. Molecular docking results

Target	PDB ID	Binding energy (kcal/mol)	Key interacting residues
AKT1	4EKL	-7.9	Thr21, Leu52
IL6	1ALU	-7.5	Thr740, Gln743
TP53	2OCJ	-8.3	His437, Val490
CTNNB1	1JDH	-7.8	Val77, His77
BCL2	4LVT	-9.0	Arg1746, Ser1749

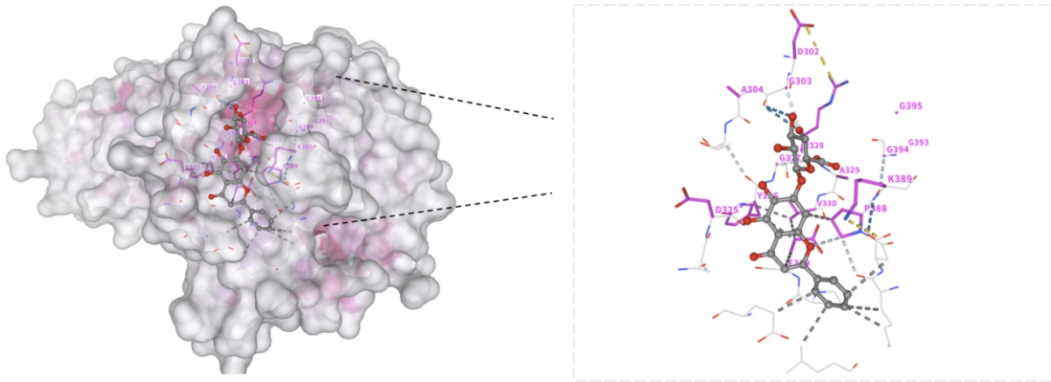

Figure 6. Molecular docking results of baicalin with AKT1

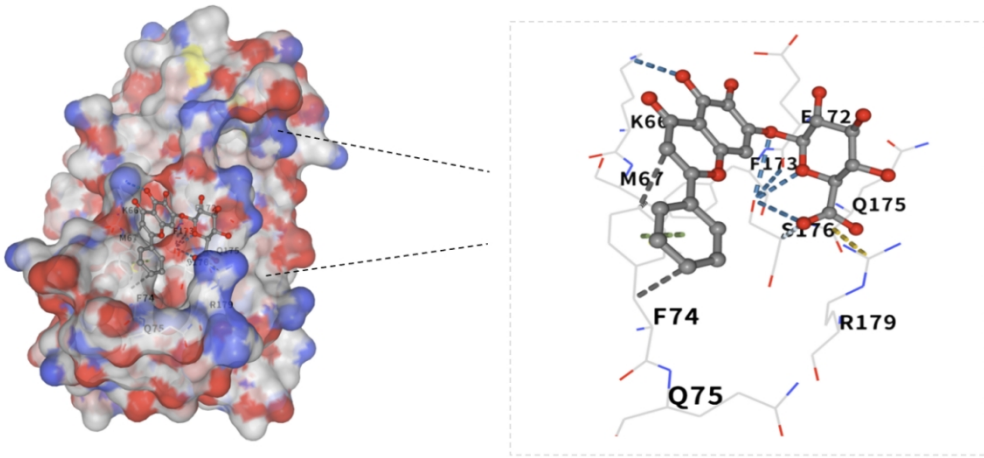

Figure 7. Molecular docking results of baicalin with IL6.

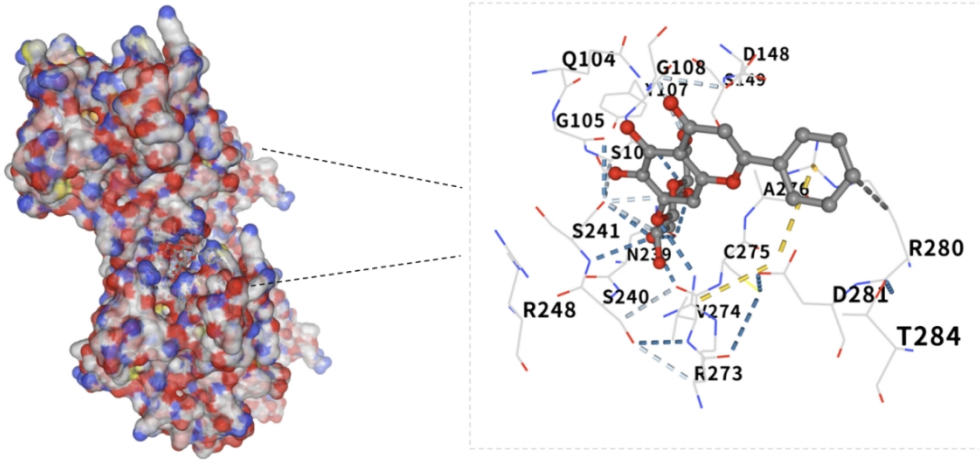

Figure 8. Molecular docking results of baicalin with TP53.

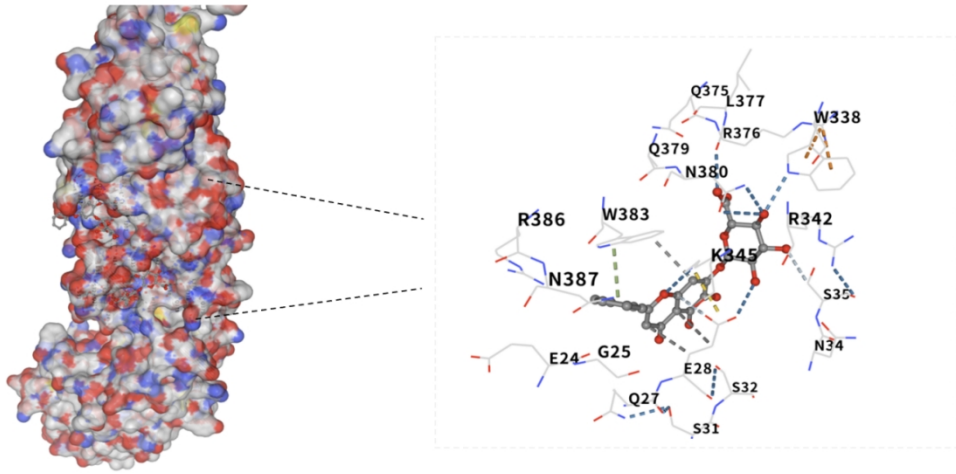

Figure 9. Molecular docking results of baicalin with CTNNB1.

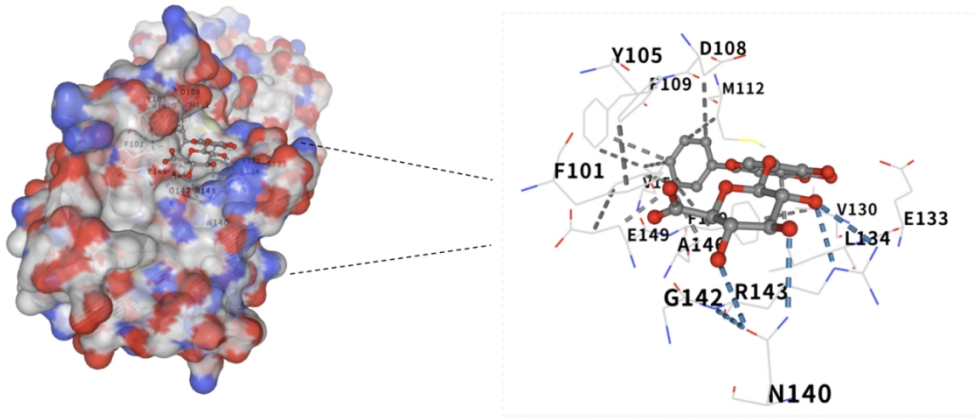

Figure 10. Molecular docking results of baicalin with BCL2.

Discussion

In this study, network pharmacology, public transcriptomic validation and molecular docking were integrated to investigate the potential molecular mechanisms by which baicalin may intervene in viral pneumonia. The results indicate substantial target overlap between baicalin and viral pneumonia, with potential effects converging on inflammatory regulation, protein kinase signaling, cytokine networks, apoptosis and host antiviral responses.

We first identified 223 candidate targets shared by baicalin and viral pneumonia. This result suggests that baicalin is unlikely to act through a single molecular target; instead, it may regulate complex disease networks through multi-target cooperation. Viral pneumonia involves virus replication, innate immune activation, inflammatory mediator release, alveolar epithelial injury, endothelial dysfunction and disordered tissue repair. The relatively high proportion of overlapping targets within the baicalin target spectrum indicates disease relevance. Previous studies on natural flavonoids and baicalin also support their multi-target and multi-pathway regulatory properties in inflammation, infection and immune imbalance[11-13].

PPI analysis identified AKT1, IL6, TP53, CTNNB1, BCL2, MMP9, EGFR, STAT3, MAPK8, TNF, IL1B, CASP3, RELA and SIRT1 as central genes. These genes are not isolated disease participants; rather, they connect inflammatory amplification, cell survival, apoptosis and tissue repair. IL6, TNF and IL1B are important inflammatory mediators after viral infection, and their dysregulation is associated with severe pneumonia, ARDS and cytokine storm[2,3,6,7]. AKT1, MAPK3, MAPK8 and EGFR reflect downstream kinase signaling after receptor activation, whereas TP53, BCL2 and CASP3 point to apoptosis and damage responses. STAT3, a central node of cytokine signaling, mediates IL6-related inflammation and participates in immune-cell differentiation and acute-phase responses[8,10]. These network features are consistent with the immuno-inflammatory imbalance, cell injury and tissue-remodeling characteristics of viral pneumonia.

The GSE171110 validation results provided expression-level support for the network analysis. Compared with healthy controls, severe COVID-19 samples showed increased MMP9, STAT3, CASP3, MAPK3 and TGFB1 and decreased TP53, BCL2, MAPK8, CCND1 and SIRT1. Elevated MMP9 may indicate enhanced matrix degradation, inflammatory-cell infiltration and pulmonary barrier disruption, as supported by clinical studies linking MMP9 to COVID-19 severity, mortality or persistent lung pathology[5,9]. Altered TGFB1 expression suggests post-inflammatory repair, fibrotic tendency

and tissue remodeling. STAT3 and CASP3 changes support the involvement of cytokine signaling and apoptosis. Reduced SIRT1 is biologically meaningful because SIRT1 is associated with antioxidant defense, mitochondrial homeostasis, autophagy and inflammatory suppression[20]. The absence of significant transcript-level differences for AKT1, IL6, TNF, IL1B, EGFR and RELA does not negate their network importance, because many cytokines and kinases are regulated through protein activation, phosphorylation, secretion or cell-type-specific expression rather than bulk whole-blood transcript abundance.

GO enrichment showed that the intersecting targets were mainly involved in tyrosine phosphorylation, protein autophosphorylation, MAPK cascades, regulation of cytokine production, inflammatory response and external stimulus response. Cellular-component enrichment concentrated in membrane rafts, membrane microdomains, the external plasma membrane, adhesion structures and vesicle lumens, suggesting that baicalin candidate targets may be associated with receptor recognition, immune-cell adhesion and inflammatory-signal initiation. Molecular-function enrichment highlighted receptor tyrosine kinase activity, protein kinase activity, nuclear receptor activity and cytokine receptor binding. These findings fit the process by which host cells detect viral or pathogen-associated stimuli through membrane receptors and transmit signals through intracellular kinase networks.

KEGG analysis further highlighted PI3K-Akt, EGFR-related signaling, viral-infection-related pathways, AGE-RAGE signaling and lipid/atherosclerosis pathways. PI3K-Akt and MAPK signaling have context-dependent functions in viral infection, cell survival, inflammation and barrier integrity: moderate activation may support survival and tissue protection, whereas persistent or dysregulated activation may amplify inflammation and tissue injury. AGE-RAGE signaling is associated with oxidative stress, endothelial injury and chronic inflammation, suggesting that baicalin may have potential value in modulating vascular inflammation and oxidative damage accompanying viral pneumonia. Pathways labelled as cancer or endocrine resistance should be interpreted as shared signaling modules rather than tumor-specific mechanisms in this context.

Molecular docking suggested that baicalin can bind AKT1, IL6, TP53, CTNNB1 and BCL2 with favorable predicted affinity. The lowest binding energies were observed for BCL2 and TP53, indicating relatively stable ligand-receptor conformations. These structural findings support potential interactions between baicalin and hub proteins. Together with existing reports that baicalin regulates

NF-kappaB, MAPK, NLRP3, interferon responses, metabolic inflammation and lung injury[14,20,25-27], the targets identified here converge on inflammatory control, antiviral response and cell-injury protection. However, docking cannot demonstrate activation or inhibition of target proteins; it should be regarded as a hypothesis--generating tool for subsequent biophysical and functional validation.

The significance of this study lies in the construction of a potential baicalin-hub target-viral pneumonia network from a systems-pharmacology perspective and the multi-layer validation of candidate targets using transcriptomic data and docking. Compared with studies focused on a single pathway, this approach better reflects the multi-target regulatory characteristics of baicalin as a natural small molecule in complex inflammatory disease. The results provide prioritized targets for future experiments, including MMP9/STAT3/ CASP3/TGFB1/SIRT1 expression changes and the protein activity, phosphorylation status and functional effects of AKT1, IL6, TP53, CTNNB1 and BCL2. From a translational perspective, these findings provide a theoretical basis for baicalin as a candidate adjunctive molecule for viral pneumonia, but clinical translation requires rigorous pharmacodynamic, safety and pharmacokinetic evidence.

This study has limitations. Target prediction depends on public databases that differ in coverage, evidence level and algorithmic models, which may introduce false positives or omit relevant targets. Viral pneumonia is a clinical syndrome caused by multiple viruses, whereas the expression--validation dataset primarily included severe COVID-19 whole-blood samples and therefore may not represent influenza-, RSV- or other virus-induced pneumonia. The sample size of GSE171110 is limited, and whole-blood transcriptomes are influenced by changes in immune-cell composition and may not directly reflect local processes in alveolar epithelial cells, alveolar macrophages or vascular endothelial cells. In addition, expression validation mainly used t-tests; future analyses could incorporate differential--expression modeling, multiple-testing correction, immune-cell deconvolution and multi-cohort validation. Although docking suggests binding potential, surface plasmon resonance, cellular thermal shift assays, protein activity assays, infected-cell models and animal models are required to verify causality.

In summary, baicalin appears to be involved in the pathogenesis of viral pneumonia by modulating inflammation, kinase signaling pathways, apoptosis, oxidative stress, and host antiviral mechanisms in a coordinated manner. Future research should integrate lung tissue or single-cell transcriptomic analyses with both in vitro and in vivo viral infection

models, alongside targeted perturbation experiments, to establish causal relationships and assess the translational applicability of these molecular networks.

Data availability

All data used in this study were obtained from publicly available databases, including PubChem, TargetNet, SwissTargetPrediction, CTD, GeneCards, OMIM, UniProt, STRING, GEO and the Protein Data Bank. The transcriptomic validation dataset was GSE171110.

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Ethics approval and consent to participate

Not applicable. This study used publicly available databases and did not involve newly recruited human participants or animals.

Competing interests

The authors declare no competing interests.

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