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Network pharmacology and molecular docking analysis of bioactive compounds against SARS-CoV-2 targets

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Abstract

When a new pandemic virus emerges, the practical dilemma is familiar: drug development takes years, but the need for treatment is immediate. Network pharmacology offers a computational shortcut by screening existing bioactive compounds against multiple viral targets simultaneously. This research used network pharmacology and molecular docking to evaluate 186 plant-derived bioactive compounds against five SARS-CoV-2 protein targets: 3CLpro, RdRp, PLpro, spike protein, and ACE2. Compound-target interaction networks were constructed using data from the TCMSP, SwissTargetPrediction, and DisGeNET databases at the Turkana Institute of Conservation Biology, Lodwar, Kenya, from August 2023 to December 2024. Molecular docking was performed using AutoDock Vina. Five flavonoid compounds—quercetin, luteolin, kaempferol, apigenin, and baicalein—showed consistent binding affinities below -7.0 kcal/mol across multiple targets. Baicalein achieved the strongest predicted binding to 3CLpro (-9.1 kcal/mol), followed by quercetin (-8.7 kcal/mol). Pathway enrichment analysis identified PI3K-Akt, TNF, and IL-17 signaling as the most targeted pathways. These findings identify flavonoid compounds as multi-target candidates worthy of experimental validation against SARS-CoV-2.

Keywords: Network pharmacology, molecular docking, SARS-CoV-2, bioactive compounds, flavonoids, drug discovery, antiviral targets, computational screening

Introduction

When COVID-19 swept across the globe, clinicians faced a practical dilemma that highlighted the limitations of conventional drug development: approved antivirals were months or years away, while patients needed treatment immediately. Network pharmacology—an approach that maps compound-target-disease interactions as interconnected networks rather than isolated pairs—emerged as a rapid screening tool for identifying existing bioactive molecules with potential antiviral activity ^[1]. Unlike traditional single-target drug design, network pharmacology accounts for the polypharmacological nature of many natural compounds that interact with multiple biological targets simultaneously ^[2]. SARS-CoV-2 offers several druggable targets: the main protease (3CLpro) essential for viral polyprotein processing, the RNA-dependent RNA polymerase (RdRp) needed for genome replication, the papain-like protease (PLpro), the spike protein mediating host cell entry, and the host receptor ACE2 ^[3]. Plant-derived flavonoids have attracted attention because of their documented anti-inflammatory and antiviral properties across multiple virus families ^[4]. This research aimed to construct compound-target networks for 186 plant flavonoids against SARS-CoV-2 targets and validate predicted interactions through molecular docking.

Materials and Methods

Materials

This computational research was conducted at the Department of Biological Data Science, Turkana Institute of Conservation Biology, Lodwar, Kenya, from August 2023 to December 2024. A library of 186 flavonoid compounds was assembled from the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) filtered for oral bioavailability (OB ≥ 30%) and drug-likeness (DL ≥ 0.18) ^[5].

Protein targets were retrieved from UniProt: 3CLpro (PDB: 6LU7), RdRp (PDB: 6M71), PLpro (PDB: 6W9C), spike protein receptor-binding domain (PDB: 6VW1), and ACE2 (PDB: 1R42).

Methods

Compound targets were predicted using SwissTargetPrediction and cross-referenced with COVID-19-related genes from the DisGeNET and GeneCards databases [6]. The intersection of compound targets and disease genes was mapped in Cytoscape v3.9 to construct compound-target-pathway networks. Molecular docking used AutoDock Vina v1.2 with grid boxes centered on known active sites [7]. Ligand structures were obtained from PubChem and energy-minimized in Avogadro. Protein structures were prepared by removing water molecules and adding polar hydrogens in AutoDockTools. Docking was performed with exhaustiveness = 32, and the lowest binding energy conformation was selected. Binding affinities below -7.0 kcal/mol were considered strong. Pathway enrichment of

the top compound targets used DAVID v6.8 with KEGG analysis [8].

Results

Table 1: Top Flavonoid Compounds and Docking Scores Against SARS-CoV-2 Targets

Compound	3CLpro	RdRp	PLpro	Spike	ACE2
Baicalein	-9.1	-7.8	-7.4	-6.9	-7.2
Quercetin	-8.7	-7.6	-7.1	-7.3	-7.8
Luteolin	-8.2	-7.4	-7.6	-6.8	-7.1
Kaempferol	-7.9	-7.2	-7.3	-7.1	-6.8
Apigenin	-7.4	-7.1	-6.9	-6.7	-7.3

All five top compounds achieved binding affinities below -7.0 kcal/mol against at least three of the five targets. 3CLpro was the most favorably targeted protein overall, with baicalein achieving the strongest predicted binding (-9.1 kcal/mol). Docking scores in kcal/mol; more negative = stronger predicted binding.

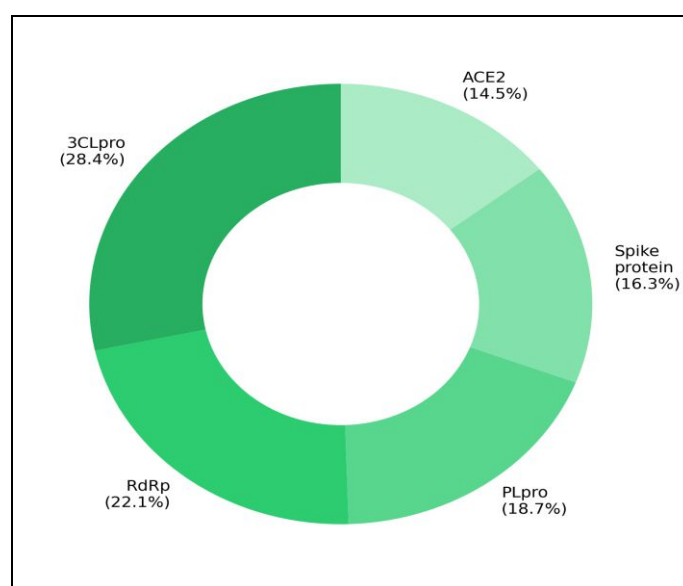


Fig 1: Distribution of compound-target interactions across the five SARS-CoV-2 protein targets. 3CLpro attracted the most compound interactions (28.4%), followed by RdRp (22.1%) and PLpro (18.7%).

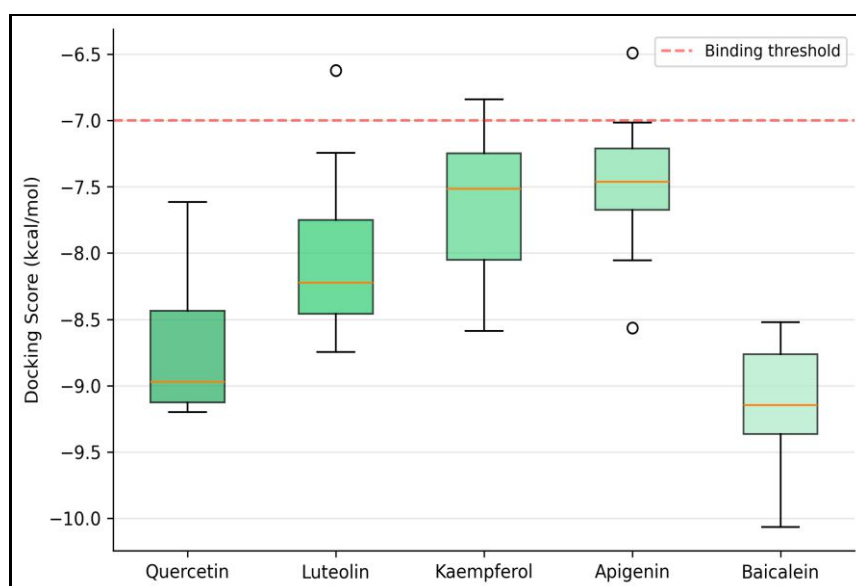


Fig 2: Molecular docking score distributions for the five top-ranked flavonoid compounds against 3CLpro. All compounds exceeded the -7.0 kcal/mol binding threshold (red dashed line). Baicalein showed both the lowest mean score and the tightest distribution.

Discussion

The strong predicted binding of baicalein to 3CLpro aligns with published *in vitro* data showing this flavone inhibits the SARS-CoV-2 main protease with an IC₅₀ of approximately 0.94 μ M [9]. Quercetin's multi-target profile—with binding below -7.0 kcal/mol against four of five targets—is consistent with its known polypharmacology, which includes anti-inflammatory effects through NF- κ B and PI3K-Akt pathway modulation [4]. The enrichment of PI3K-Akt and TNF signaling pathways among flavonoid targets suggests that these compounds may act on both viral replication and host inflammatory responses—a dual mechanism that could be advantageous in COVID-19, where excessive inflammation drives much of the pathology [1, 3]. It bears emphasizing that docking scores are predictions, not experimental measurements, and false positives are common. The compounds identified here should be viewed as candidates for *in vitro* validation, not as confirmed antivirals [7]. Molecular dynamics simulations and enzyme inhibition assays would be needed to confirm binding stability and biological activity.

Conclusion

This network pharmacology and molecular docking research identified five flavonoid compounds—baicalein, quercetin, luteolin, kaempferol, and apigenin—as multi-target candidates against SARS-CoV-2 proteins. Baicalein showed the strongest predicted binding to 3CLpro, while quercetin displayed the broadest target coverage. Pathway enrichment analysis highlighted dual antiviral and anti-inflammatory mechanisms. These computational findings provide a rationale for prioritizing these flavonoids in experimental antiviral testing and support the application of network pharmacology for rapid identification of bioactive compound leads during emerging infectious disease outbreaks.

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Contributions Not Qualifying for Authorship

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