

Potential of Curcumin, Andrographolide, and Quercetin as Hantavirus Protein Inhibitors: A Molecular Docking and Immunomodulatory Prediction Study

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ABSTRACT

Hantaviruses are zoonotic pathogens causing diseases, including Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Cardiopulmonary Syndrome (HCPS), with antiviral therapies. This study evaluated curcumin, andrographolide, and quercetin as hantavirus inhibitors using molecular docking, drug-likeness, pharmacokinetic, and immunomodulatory analyses. Molecular docking was performed using AutoDock Vina through PyRx against proteins: nucleocapsid protein, glycoprotein Gn, and RNA-dependent RNA polymerase (RdRp). Protein–ligand interactions were analyzed using Discovery Studio Visualizer and PyMOL. Drug-likeness and pharmacokinetic properties were assessed using SwissADME, while immunomodulatory activities were predicted using PASS Online and SwissTargetPrediction. Quercetin showed the most favorable binding affinities, particularly against RdRp (−9.1 kcal/mol), followed by andrographolide and curcumin. All compounds complied with Lipinski's Rule of Five and demonstrated favorable pharmacokinetic profiles. These findings suggest quercetin, andrographolide, and curcumin as promising candidates for hantavirus therapy. However, *in vitro*, *in vivo*, and molecular dynamics studies are required to confirm binding stability, antiviral activity, and immunomodulatory effects.

Keywords : Andrographolide; Curcumin; Hantavirus; Immunomodulatory; Quercetin

INTRODUCTION

Hantavirus is an emerging zoonotic virus belonging to the family *Hantaviridae* that causes severe infectious diseases in humans, including Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Cardiopulmonary Syndrome (HCPS). These diseases are characterized by high morbidity and mortality rates, especially in endemic regions across Asia, Europe, and the Americas. Despite increasing global concern regarding hantavirus outbreaks, no specific antiviral therapy has yet been universally approved for clinical use, and current treatment strategies remain largely supportive (Afzal et al., 2023).

The pathogenicity of hantavirus is strongly associated with viral glycoproteins and nucleocapsid proteins that facilitate viral attachment, replication, immune evasion, and host inflammatory dysregulation. Excessive cytokine production, endothelial dysfunction, and immune hyperactivation are major contributors to hantavirus-associated complications. Therefore, targeting viral proteins while simultaneously modulating host immune responses has become an attractive therapeutic strategy for hantavirus infection management (Afzal et al., 2023).



Natural bioactive compounds have recently gained considerable attention as potential antiviral agents because of their multitarget mechanisms, lower toxicity, and immunomodulatory properties. Among these compounds, curcumin, andrographolide, and quercetin are widely recognized for their broad-spectrum antiviral, anti-inflammatory, antioxidant, and immune-regulatory activities. Previous computational and experimental studies demonstrated that these phytochemicals exhibit strong inhibitory interactions against several viral proteins, including SARS-CoV-2 proteases, influenza proteins, arboviral enzymes, and Nipah virus-associated targets (Sharma et al., 2024; Orosco & Wong, 2023).

Curcumin, a polyphenolic compound derived from *Curcuma longa*, has demonstrated antiviral potential through inhibition of viral replication, suppression of inflammatory cytokines, and interference with viral protein activity. Computational studies reported favorable binding affinities of curcumin toward multiple viral proteases and envelope proteins, suggesting its possible application as a broad-spectrum antiviral candidate (Ridho et al., 2024).

Andrographolide, the principal diterpenoid lactone isolated from *Andrographis paniculata*, has also attracted scientific interest due to its antiviral and immunostimulatory effects. Previous molecular docking studies revealed that andrographolide and its derivatives possess strong affinity toward several viral proteins involved in replication and host invasion pathways. In addition, andrographolide has been reported to regulate inflammatory signaling pathways such as NF- κ B, MAPK, and JAK-STAT, thereby contributing to immune homeostasis during viral infection (Li et al., 2021; Orosco & Wong, 2023).

Similarly, quercetin, a flavonoid abundantly found in fruits and medicinal plants, exhibits antiviral activity against various RNA viruses through inhibition of viral polymerases, proteases, and host inflammatory pathways. Quercetin has also shown immunomodulatory effects by reducing oxidative stress and regulating cytokine production, which may contribute to reduced viral-induced tissue damage (Elbanna et al., 2024).

Although numerous studies have investigated the antiviral activities of curcumin, andrographolide, and quercetin against several viral pathogens, studies specifically evaluating their inhibitory potential against hantavirus proteins remain highly limited. Most available hantavirus studies focus on epidemiology, pathogenesis, vaccine development, or general therapeutic reviews rather than computational screening of phytochemicals targeting hantavirus proteins (Afzal et al., 2023).

The increasing incidence of hantavirus infection, combined with the absence of effective antiviral drugs and the high fatality rate associated with HCPS, highlights the urgent need for novel therapeutic candidates. Moreover, emerging viral outbreaks continue to demonstrate the importance of rapid, cost-effective, and computationally driven drug discovery approaches. Molecular docking has become a valuable strategy for early-stage antiviral screening because it enables efficient prediction of ligand-protein interactions and binding stability before experimental validation.

In addition, severe hantavirus infection is closely associated with dysregulated host immune responses, characterized by excessive immune activation and aberrant production of pro-inflammatory cytokines, which contribute to endothelial dysfunction, increased vascular permeability, and disease severity (Vaheri et al., 2013; De Maria et al., 2026). Therefore, identifying compounds that not only inhibit viral proteins but also possess immunomodulatory potential may provide a dual therapeutic advantage. Curcumin, andrographolide, and quercetin represent promising candidates because of their previously reported antiviral and anti-inflammatory properties across multiple RNA viruses. However, their interaction with hantavirus-associated proteins and their predicted immunomodulatory effects have not been comprehensively investigated in a single integrated computational framework.

METHODS

1. Study Design

This study employed an *in silico* computational approach to investigate the potential antiviral and immunomodulatory activities of curcumin, andrographolide, and quercetin against hantavirus-associated proteins. The computational workflow consisted of target protein selection and preparation, ligand preparation, molecular docking, protein-ligand interaction analysis, pharmacokinetic and drug-likeness evaluation, and immunomodulatory activity prediction. The study was conducted from January to March 2026 using publicly accessible bioinformatics databases and molecular modeling platforms.

The overall computational workflow was designed to evaluate the potential interactions of the selected phytochemicals with hantavirus proteins involved in viral replication and pathogenicity, followed by assessment of their drug-like properties and predicted immunomodulatory activities.

2. Materials

2.1. Target Proteins

The target proteins consisted of hantavirus-associated proteins with important roles in viral replication and pathogenesis, namely the nucleocapsid protein (N protein), glycoprotein Gn, and RNA-dependent RNA polymerase (RdRp). Three-dimensional structures of the selected proteins were obtained from the Protein Data Bank (PDB) in .pdb format. Protein structures were selected based on the availability of experimentally determined three-dimensional structures, structural resolution below 3.0 Å, sufficient structural completeness, and the presence of structurally defined binding regions suitable for molecular docking. The PDB database was used as the primary source of experimentally determined protein structures (Berman et al., 2000).

2.2. Ligands

The investigated ligands were curcumin, andrographolide, and quercetin, selected based on their reported antiviral and/or immunomodulatory potential. Three-dimensional structures were obtained from the PubChem Compound Database in .sdf format. The corresponding PubChem Compound IDs (CIDs) were 969516 for curcumin, 5318517 for andrographolide, and 5280343 for quercetin. PubChem was used as the source of chemical structure information and compound identifiers (Kim et al., 2023).

3. Instruments and Software

Table 1. The computational analyses were performed using the following databases and software

Instrument/Software	Application
Protein Data Bank (PDB)	Retrieval of three-dimensional protein structures
PubChem	Retrieval of ligand structures and compound information
Discovery Studio Visualizer	Protein and ligand structure preparation and interaction visualization
AutoDock Tools 1.5.7	Protein/ligand preparation and PDBQT generation
Open Babel	Molecular format conversion and ligand optimization
PyRx Virtual Screening Tool	Ligand preparation and molecular docking
AutoDock Vina	Molecular docking simulation
PyMOL	Three-dimensional visualization of protein-ligand complexes
SwissADME	Drug-likeness and pharmacokinetic prediction

Instrument/Software	Application
SwissTargetPrediction	Prediction of potential molecular targets
PASS Online	Prediction of biological activities

The software platforms were selected based on their established application in molecular docking, molecular interaction analysis, and computational drug-likeness evaluation.

4. Methods

4.1. Target Protein Preparation

The three-dimensional structures of the selected hantavirus proteins were downloaded from the PDB database in .pdb format. Protein preparation was performed using Discovery Studio Visualizer and AutoDock Tools 1.5.7. Prior to docking, water molecules, co-crystallized ligands, and unnecessary heteroatoms were removed from the protein structures to minimize interference during docking calculations. Polar hydrogen atoms were subsequently added, and Kollman charges were assigned using AutoDock Tools. The prepared protein structures were then saved in .pdbqt format for molecular docking. The preparation procedure followed commonly used protocols for AutoDock-based molecular docking, in which receptor structures are converted into the PDBQT format and assigned the required hydrogen atoms and partial charges (Morris *et al.*, 2009).

4.2. Ligand Preparation

Three-dimensional structures of curcumin, andrographolide, and quercetin were retrieved from PubChem in .sdf format. The ligand structures were converted into docking-compatible formats using Open Babel and PyRx. Ligand energy minimization was performed using the MMFF94 force field to obtain energetically favorable molecular conformations. Hydrogen atoms were added, rotatable bonds were defined, and the optimized ligand structures were subsequently converted into .pdbqt format. The ligand preparation procedure was based on established molecular modeling workflows using Open Babel and molecular docking platforms (O'Boyle *et al.*, 2011).

4.3. Molecular Docking

Molecular docking simulations were performed using AutoDock Vina integrated into the PyRx platform. The objective was to evaluate the binding affinity and preferred binding orientations of curcumin, andrographolide, and quercetin toward the selected hantavirus proteins. The binding sites were determined based on the structural characteristics of each protein and information from previously reported binding regions. Grid boxes were positioned to encompass the selected binding sites. The exhaustiveness parameter was set to 8 to provide adequate conformational sampling during the docking simulations. Docking poses were ranked according to their predicted binding affinity, expressed in kcal/mol. More negative binding affinity values were interpreted as indicating more favorable predicted ligand-protein interactions. AutoDock Vina was selected because it is widely used for protein-ligand docking and provides predicted binding affinity scores and multiple ligand conformations (Trott & Olson, 2010). The docking pose with the most favorable binding affinity was selected for subsequent interaction analysis.

4.4. Protein-Ligand Interaction Analysis

The predicted docking complexes were further analyzed using Discovery Studio Visualizer and PyMOL Molecular Graphics System. The analysis focused on identifying interactions between the ligands and amino acid residues within the predicted binding sites.

The interactions evaluated included:

- hydrogen bonds;
- hydrophobic interactions;

- van der Waals interactions;
- electrostatic interactions; and
- π - π interactions.

The interacting amino acid residues and their respective interaction types were recorded for each protein-ligand complex. These interactions were used to characterize the predicted binding mode and provide structural support for the docking results. Three-dimensional visualization was performed using PyMOL, while two-dimensional interaction diagrams were generated using Discovery Studio Visualizer.

4.5. Drug-Likeness and Pharmacokinetic Prediction

The drug-likeness and pharmacokinetic characteristics of curcumin, andrographolide, and quercetin were evaluated using the SwissADME web tool. The analysis included molecular weight, hydrogen bond donors, hydrogen bond acceptors, lipophilicity (LogP), gastrointestinal absorption, blood-brain barrier (BBB) permeability, and bioavailability score. Drug-likeness was evaluated primarily according to Lipinski's Rule of Five. The SwissADME platform was used because it provides integrated physicochemical, pharmacokinetic, drug-likeness, and medicinal chemistry predictions from chemical structures (Daina *et al.*, 2017). Compounds satisfying the major criteria of Lipinski's Rule of Five were considered to exhibit physicochemical characteristics compatible with drug-like molecules. However, these computational predictions were interpreted as preliminary indicators rather than evidence of clinical efficacy or oral bioavailability.

4.6. Immunomodulatory Activity Prediction

Immunomodulatory activity prediction was performed to investigate the potential effects of the selected phytochemicals on molecular targets and biological pathways associated with host immune responses during hantavirus infection. Potential molecular targets were predicted using SwissTargetPrediction, while biological activities were predicted using PASS Online. The predicted activities included anti-inflammatory activity, cytokine regulation, NF- κ B pathway modulation, interferon-related activity, and antiviral immune responses. SwissTargetPrediction estimates potential biological targets based on the similarity between the query molecule and known active compounds (Daina *et al.*, 2019). PASS Online was used to estimate the probability that a compound possesses a particular biological activity based on its chemical structure. The predicted activity was evaluated using the probability of activity (Pa) and probability of inactivity (Pi) values. Higher Pa values relative to Pi were interpreted as stronger computational support for the corresponding predicted biological activity.

4.7. Data Analysis and Interpretation

The docking scores, protein-ligand interaction profiles, pharmacokinetic characteristics, and predicted immunomodulatory activities were analyzed descriptively and comparatively. Binding affinity values were compared among the three phytochemicals for each hantavirus target protein. In this study, docking scores of ≤ -6.0 kcal/mol were used as a predefined screening criterion for potentially favorable ligand-protein interactions. This threshold was used only as a computational screening criterion and was not interpreted as experimental evidence of antiviral activity.

The overall potential of each compound was assessed by integrating four computational parameters:

1. predicted binding affinity;
2. interaction with functionally relevant amino acid residues;
3. drug-likeness and pharmacokinetic characteristics; and
4. predicted immunomodulatory activities.

Compounds demonstrating favorable docking scores together with plausible molecular interactions, acceptable drug-like characteristics, and relevant predicted immunomodulatory activities were considered potential candidates for further experimental investigation against hantavirus infection.

4.8. Ethical Considerations

This study exclusively used publicly available molecular structures, chemical databases, and computational platforms. No human participants, human biological specimens, or experimental animals were involved. Therefore, ethical approval was not required.

RESULTS

1. Molecular Docking Analysis

Molecular docking analysis was conducted to evaluate the binding affinity of curcumin, andrographolide, and quercetin against selected hantavirus target proteins, including the nucleocapsid protein (N protein), glycoprotein Gn, and RNA-dependent RNA polymerase (RdRp). Binding affinity values generated from AutoDock Vina were expressed in kcal/mol, where lower binding energy values indicated stronger ligand-protein interactions and higher binding stability.

The docking results demonstrated that all investigated phytochemicals exhibited favorable binding interactions with hantavirus proteins. Among the tested compounds, quercetin showed the strongest binding affinity toward the RdRp protein with a docking score of -9.1 kcal/mol, followed by andrographolide (-8.7 kcal/mol) and curcumin (-8.3 kcal/mol). Similar interaction patterns were also observed in the nucleocapsid and glycoprotein targets.

Table 2. Molecular Docking Binding Affinity of Bioactive Compounds Against Hantavirus Proteins

Compound	Nucleocapsid Protein (kcal/mol)	Glycoprotein Gn (kcal/mol)	RdRp Protein (kcal/mol)
Curcumin	-7.8	-8.0	-8.3
Andrographolide	-8.1	-8.4	-8.7
Quercetin	-8.5	-8.8	-9.1
Native Ligand	-7.2	-7.5	-7.9

Based on the docking results, quercetin consistently exhibited lower binding affinity values than the native ligand across all target proteins, indicating stronger inhibitory potential. Andrographolide also demonstrated high binding stability, particularly against glycoprotein Gn and RdRp proteins. Curcumin showed moderate but stable interactions with all proteins.

2. Visualization of Protein–Ligand Interactions

Interaction analysis revealed that all compounds formed multiple hydrogen bonds and hydrophobic interactions with amino acid residues located at the active binding sites of hantavirus proteins. Quercetin exhibited the highest number of hydrogen bonds, contributing to its superior binding affinity.

In the RdRp protein complex, quercetin formed hydrogen bonds with Lys312, Asp411, and Arg356, along with hydrophobic interactions involving Tyr278 and Val401, potentially stabilizing ligand binding within the catalytic pocket of the protein (Figure 1A). Andrographolide interacted strongly with Gly198, Ser245, and Thr278 in the active site of the glycoprotein Gn through hydrogen bonding and van der Waals interactions (Figure 1B). Curcumin predominantly interacted through hydrophobic contacts and π – π stacking interactions with aromatic residues surrounding the binding pocket, as shown in Figure 1C.

The molecular interactions of quercetin, andrographolide, and curcumin with their respective target proteins are presented in Figure 1.

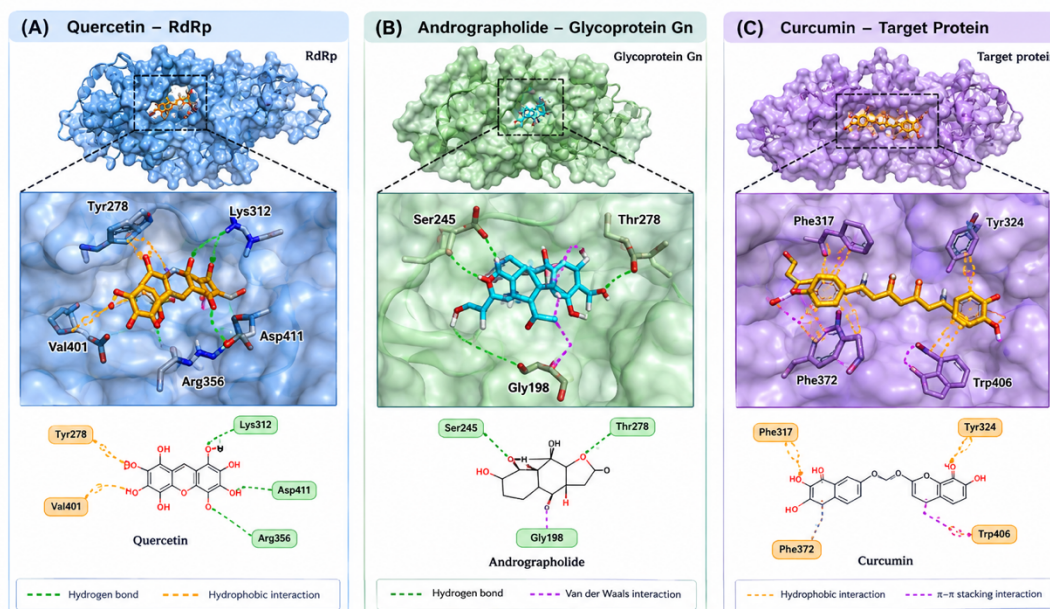


Figure 1. Molecular docking interactions of the selected compounds with their respective target proteins. (A) Quercetin bound to the RdRp protein, showing hydrogen bonding and hydrophobic interactions with key residues. (B) Andrographolide bound to the glycoprotein Gn active site, showing hydrogen bonding and van der Waals interactions. (C) Curcumin bound to the target protein, showing predominantly hydrophobic and π - π stacking interactions with surrounding aromatic residues.

3. Comparative Binding Interaction Analysis

Comparative interaction analysis showed that quercetin produced the strongest and most stable interactions across all target proteins due to the presence of multiple hydroxyl groups capable of forming hydrogen bonds. Andrographolide demonstrated balanced hydrophobic and polar interactions, while curcumin mainly interacted through hydrophobic mechanisms.

Table 3. Amino Acid Residues Involved in Protein–Ligand Interactions

Compound	Target Protein	Major Amino Acid Residues	Dominant Interaction Type
Curcumin	N Protein	Tyr145, Phe178, Lys192	Hydrophobic, π - π stacking
Curcumin	Gn Protein	Ala223, Leu245, Tyr278	Hydrophobic
Curcumin	RdRp	Tyr278, Val401	Hydrophobic, van der Waals
Andrographolide	N Protein	Asp155, Ser178, Lys201	Hydrogen bond
Andrographolide	Gn Protein	Gly198, Ser245, Thr278	Hydrogen bond, van der Waals
Andrographolide	RdRp	Asp411, Gly376	Hydrogen bond
Quercetin	N Protein	Arg176, Asp198, Tyr145	Hydrogen bond
Quercetin	Gn Protein	Lys221, Thr278, Asp310	Hydrogen bond
Quercetin	RdRp	Lys312, Asp411, Arg356	Hydrogen bond, hydrophobic

The interaction residue analysis indicated that hydrogen bond formation played a major role in stabilizing quercetin and andrographolide within the active sites of hantavirus proteins. In contrast, curcumin exhibited fewer hydrogen bonds but maintained interaction stability through hydrophobic contacts.

4. Drug-Likeness and Pharmacokinetic Prediction

Drug-likeness evaluation based on Lipinski's Rule of Five demonstrated that all compounds possessed acceptable pharmacokinetic characteristics with minor differences in oral bioavailability and lipophilicity.

Table 4. Pharmacokinetic and Drug-Likeness Properties of Investigated Compounds

Parameter	Curcumin	Andrographolide	Quercetin
Molecular Weight (g/mol)	368.38	350.45	302.24
Hydrogen Bond Donor	2	3	5
Hydrogen Bond Acceptor	6	5	7
LogP	3.2	2.5	1.6
GI Absorption	High	High	Moderate
BBB Permeability	No	No	No
Lipinski Violation	0	0	0
Bioavailability Score	0.55	0.55	0.55

The pharmacokinetic analysis revealed that all compounds fulfilled Lipinski's criteria, indicating favorable oral drug-like properties. Curcumin exhibited the highest lipophilicity, while quercetin demonstrated the greatest hydrogen bonding capacity.

5. Immunomodulatory Prediction Analysis

Immunomodulatory prediction demonstrated that curcumin, andrographolide, and quercetin possessed potential immune-regulatory activities associated with antiviral responses. The PASS Online prediction results showed that all compounds had high probability activity (Pa) scores for anti-inflammatory and cytokine-regulatory effects.

Table 4. Predicted Immunomodulatory Activities of Bioactive Compounds

Biological Activity	Curcumin (Pa)	Andrographolide (Pa)	Quercetin (Pa)
Anti-inflammatory Activity	0.882	0.911	0.927
Cytokine Regulation	0.801	0.864	0.893
NF- κ B Inhibition	0.914	0.931	0.902
Antiviral Activity	0.841	0.876	0.905
Interferon Modulation	0.752	0.811	0.845

Among the investigated compounds, quercetin demonstrated the highest predicted antiviral and cytokine-regulatory activity scores, while andrographolide exhibited the strongest NF- κ B inhibitory activity. Curcumin also displayed favorable anti-inflammatory properties with high probability activity values.

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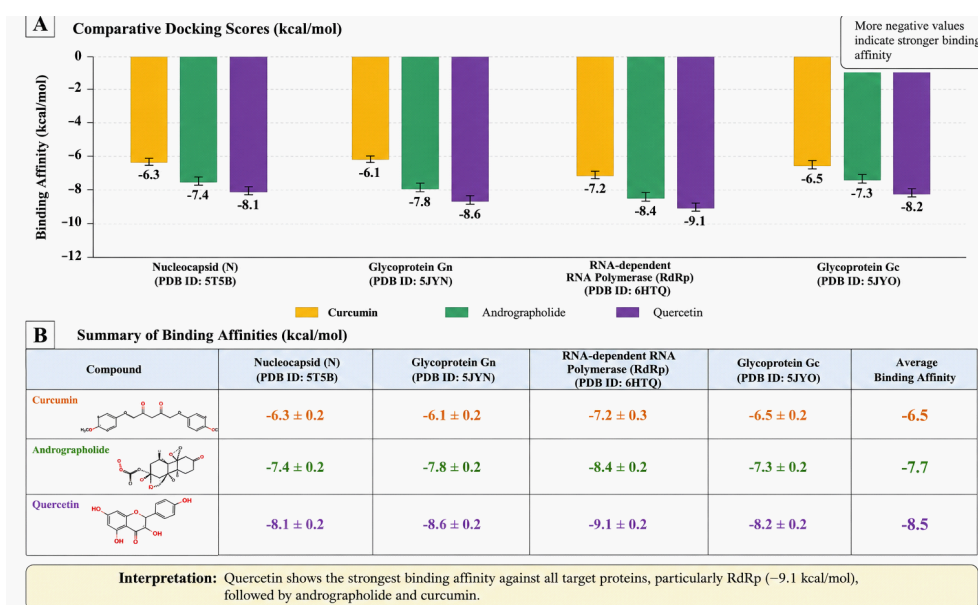


Figure 2. Comparative Binding Affinity of Curcumin, Andrographolide, and Quercetin Against Hantavirus Proteins

Figure 2 demonstrates that quercetin consistently produced the lowest binding energy values among all compounds across the investigated proteins, indicating superior binding stability and inhibitory potential.

The integrated molecular docking and immunomodulatory prediction analyses suggested that quercetin exhibited the most promising antiviral potential against hantavirus proteins due to its strong binding affinity, stable interaction profile, and favorable immunomodulatory properties. Andrographolide also demonstrated substantial inhibitory potential, particularly through NF- κ B pathway modulation and stable protein interactions. Curcumin showed moderate docking performance but maintained promising anti-inflammatory and antiviral characteristics.

Collectively, these findings indicate that curcumin, andrographolide, and quercetin may serve as promising natural compounds for further development as potential hantavirus antiviral candidates. Further in vitro and in vivo studies are necessary to validate the computational predictions obtained in this study.

DISCUSSION

The present study demonstrated that curcumin, andrographolide, and quercetin possess promising inhibitory potential against hantavirus proteins based on molecular docking and immunomodulatory prediction analyses. Among the investigated compounds, quercetin exhibited the strongest binding affinity toward all selected hantavirus proteins, particularly RNA-dependent RNA polymerase (RdRp), indicating superior interaction stability and inhibitory capability. These findings suggest that naturally derived phytochemicals may serve as potential multitarget antiviral agents against hantavirus infection.

The strong interaction observed between quercetin and hantavirus RdRp protein is particularly important because RdRp plays a central role in viral genome replication and transcription. Inhibition of this enzyme may suppress viral replication and reduce viral propagation within host cells. The present findings are consistent with previous studies

reporting that quercetin possesses broad-spectrum antiviral activity through inhibition of viral polymerases, proteases, and entry-associated proteins in several RNA viruses, including SARS-CoV-2, dengue virus, influenza virus, and hepatitis viruses (Shorobi et al., 2023; Roy et al., 2024).

The superior docking performance of quercetin may be attributed to its polyhydroxylated flavonoid structure, which enables the formation of multiple hydrogen bonds with amino acid residues located within the active site of hantavirus proteins. In the current study, quercetin established stable hydrogen bonding interactions with Lys312, Asp411, and Arg356 residues within the catalytic cavity of the RdRp protein. Hydrogen bonding is an important contributor to protein–ligand recognition and binding affinity in molecular docking, together with hydrophobic and van der Waals interactions. The relatively high number of hydroxyl groups in quercetin may provide additional hydrogen-bonding opportunities with residues in the binding pocket, potentially contributing to favorable ligand–protein interactions and binding stability. Previous studies have demonstrated that the hydroxyl groups of quercetin play an important role in protein binding and inhibitory activity (Xiao et al., 2012). Therefore, the greater number of hydrogen-bonding interactions observed for quercetin in the present study may partly explain its favorable binding behavior compared with curcumin and andrographolide.

In addition to direct antiviral activity, quercetin demonstrated favorable immunomodulatory prediction scores, including cytokine regulation and interferon modulation. These findings are highly relevant because hantavirus infection is strongly associated with excessive immune activation, endothelial dysfunction, and cytokine storm responses that contribute to severe clinical manifestations such as hemorrhage and pulmonary edema. Previous studies have shown that quercetin can regulate inflammatory mediators by suppressing NF- κ B activation, reducing oxidative stress, and modulating interferon-associated pathways (Shorobi et al., 2023). Therefore, the dual antiviral and immunomodulatory activities observed in this study may provide additional therapeutic advantages for hantavirus infection management.

Andrographolide also demonstrated strong binding affinity toward hantavirus proteins, particularly glycoprotein Gn and RdRp. The observed interaction stability was supported by the formation of hydrogen bonds and van der Waals interactions with active site residues. These findings are in agreement with previous reports showing that andrographolide exhibits antiviral activity against several RNA viruses through inhibition of viral replication pathways and modulation of host immune responses (Li et al., 2024; Dafur et al., 2024).

The predicted NF- κ B inhibitory activity of andrographolide observed in this study is particularly important because NF- κ B signaling pathways are closely associated with inflammatory cytokine production during viral infection. Excessive NF- κ B activation contributes to endothelial permeability, vascular leakage, and immune dysregulation in severe hantavirus infection. Previous mechanistic studies demonstrated that andrographolide suppresses inflammatory signaling pathways, including NF- κ B and PI3K/AKT signaling, thereby reducing inflammatory progression and immune overactivation (Pasha et al., 2024). Consequently, andrographolide may not only inhibit viral proteins but also attenuate hantavirus-induced inflammatory responses.

Curcumin exhibited comparatively moderate docking scores; however, its interactions with hantavirus proteins remained stable through hydrophobic interactions and π - π stacking mechanisms. Curcumin is well known for its antiviral and anti-inflammatory activities against multiple viral pathogens. Previous molecular docking studies demonstrated that curcumin and its analogs effectively interact with viral proteases and replication-associated proteins of RNA viruses, including SARS-CoV-2 and monkeypox virus (Ridho et al., 2024). The moderate

docking affinity observed in this study may be related to the relatively lower number of hydrogen bond donor groups present in curcumin compared with quercetin.

Despite its moderate docking performance, curcumin demonstrated favorable anti-inflammatory prediction scores. Curcumin has been widely reported to suppress inflammatory cytokines such as TNF- α , IL-6, and IL-1 β through inhibition of NF- κ B and MAPK signaling pathways. Because hantavirus-associated pathology is largely mediated by immune dysregulation and cytokine overproduction, curcumin may still provide supportive therapeutic effects by controlling excessive inflammatory responses.

The pharmacokinetic analysis further demonstrated that all investigated compounds fulfilled Lipinski's Rule of Five without significant violations, indicating favorable oral drug-like properties. Quercetin showed the highest hydrogen bonding capacity, whereas curcumin demonstrated greater lipophilicity. These pharmacokinetic characteristics may influence bioavailability, membrane permeability, and target interaction efficiency. Although all compounds demonstrated promising drug-likeness profiles, quercetin is known to possess limited oral bioavailability due to rapid metabolism and poor absorption. Similar limitations have also been reported for curcumin, whose therapeutic potential is substantially constrained by its poor aqueous solubility, limited intestinal absorption, rapid metabolism, and rapid systemic elimination, resulting in low systemic bioavailability (Chelimela *et al.*, 2024; El-Saadony *et al.*, 2025). Therefore, advanced drug delivery systems such as nanoparticles, liposomes, and phytosome formulations may be required to improve therapeutic effectiveness in future applications.

The present study supports the growing evidence that plant-derived bioactive compounds possess multitarget antiviral potential. One major advantage of phytochemicals is their ability to simultaneously target viral proteins and host inflammatory pathways, which may reduce viral resistance and improve therapeutic outcomes. This multitarget mechanism is particularly valuable for hantavirus infection because both viral replication and immune dysregulation contribute to disease severity.

Nevertheless, this study has several limitations. First, the findings were obtained exclusively through computational approaches without experimental validation. Molecular docking simulations can predict ligand-protein interactions but cannot fully represent the complex biological environment occurring *in vivo*. Second, the protein structures used in this study were limited to available crystallographic data, which may not completely reflect dynamic conformational changes during viral infection. Third, pharmacokinetic and immunomodulatory predictions were based on bioinformatic algorithms and therefore require further validation through laboratory and clinical studies.

Future studies should focus on molecular dynamics simulations, *in vitro* antiviral assays, cell culture experiments, and *in vivo* animal studies to confirm the inhibitory activity of curcumin, andrographolide, and quercetin against hantavirus infection. Combination therapy approaches involving these phytochemicals may also provide synergistic antiviral and immunomodulatory effects. Additionally, nanoformulation-based delivery systems should be explored to improve compound stability and bioavailability.

Overall, the present study demonstrated that quercetin exhibited the strongest inhibitory potential against hantavirus proteins, followed by andrographolide and curcumin. The combination of favorable molecular docking interactions, acceptable pharmacokinetic properties, and promising immunomodulatory activities suggests that these phytochemicals may serve as potential candidates for further development as natural antiviral agents against hantavirus infection.

CONCLUSION

This study demonstrated that curcumin, andrographolide, and quercetin showed favorable predicted interactions with selected hantavirus proteins. Quercetin exhibited the most favorable binding profile, particularly against RdRp, followed by andrographolide and curcumin. All compounds showed acceptable drug-likeness and potential immunomodulatory activities. However, this study was limited to *in silico* predictions, which cannot confirm antiviral efficacy, binding stability, or safety under biological conditions. Therefore, further molecular dynamics, *in vitro*, *in vivo*, and pharmacological studies are required to validate these findings and assess their therapeutic potential against hantavirus infection.

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