

Computational Evaluation of the Phytochemical Naringenin and Its Derivatives against Dengue Virus DENV2

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Abstract. Dengue, one of the most prevalent mosquito-borne viral infectious diseases of the twenty-first century, affects approximately 100–400 million individuals worldwide. The lack of definitive treatment has led to several *in vitro* and *in silico* investigations for potential antivirals. The RNA helicase of the dengue virus (DENV) is a vital protein that is important in viral replication. This study analyzed the antiviral activity of the flavanone naringenin and its derivatives through *in silico* and *in vitro* methods, targeting the DENV NS3 helicase enzyme. In this study, *in silico* screening based on molecular docking and ADMET properties of 20 derivatives of naringenin identified molecules, such as 6-fluoro naringenin, as the suitable compound. Further, comparative MD simulations and an MM-PBSA study for complexes as NS3-naringenin, NS3-6-fluoronaringenin, and NS3-ST-610 (standard inhibitor molecule) identified that naringenin was able to form a stable complex with the NS3 helicase enzyme of DENV2. These findings of the present study predict the promising anti-dengue nature of the compound naringenin as a replication inhibitor.

Key words: dengue virus, ns3 helicase, naringenin, molecular docking, molecular dynamics simulation, antiviral activity

INTRODUCTION

Dengue virus infection is one of the most prevalent mosquito-borne illnesses that can infect millions of people worldwide yearly in tropical and subtropical areas. As per the WHO report, the incidence of dengue has grown dramatically around the world in recent decades (505430 cases in 2000 to 5.2 million in 2019). However, the majority of cases are asymptomatic or mild hence creating difficulty in reporting the actual numbers of dengue cases. In 2023, more than 80 countries across all the regions of WHO recorded the highest number of dengue cases. Over 6.5 million cases and 7300 dengue-related deaths have been reported since the beginning of 2023 due to ongoing dengue transmission [1, 2]. The dengue virus commonly infects humans and monkeys. It is a member of the Flavivirus genus in the family Flaviviridae. A DENV infection causes several symptoms, including fever, rash, myalgia and joint pain, and severe headache. Dengue Shock Syndrome (DSS) and Dengue Hemorrhagic Fever (DHF) are more serious illnesses [3, 4]. Three structural proteins (Capsid protein C, Membrane protein M, and Envelope protein E) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) are encoded by the DENV genome. The 3' UTR region, ORF (open reading frame), and 5' UTR region constitute the three parts of the RNA genome. DENV is composed of 10,723 nucleotides (approximately 11 kb), which are used to encode larger polypeptide precursors containing ~3391 amino acid residues [5–7].

NS3, a multifunctional protein with adenosine triphosphatase (ATPase), helicase, protease, and RNA 5'-triphosphatase (RTPase) activity, is one of them and can be a good target for drugs. NS3 and the four DENV serotypes share 77 % amino acid sequence

similarity, while NS3 from ZIKV and YFV share 67 and 50 % identity, respectively. Serine protease, which cleaves the viral polyprotein, consists of 167 amino acids of N terminal region and membrane-associated central 40 amino acid region of NS2B cofactor. These Residues 172–618 of NS3 (NS3H) constitute the C-terminal domain, which has three subdomains and possesses RNA helicase/NTase/RTase activity. To unwind duplex RNA, NS3's helicase activity uses the chemical energy obtained from ATP hydrolysis [8–12]. So far, the specific therapeutic drug candidates for DENV infection are still unavailable. Similarly, effective vaccines against DENV are also having limited applications. The researchers have therefore made a great effort to develop antivirals that are effective against DENV [13, 14]. The majority of certified antiviral medications either directly or indirectly are linked to adverse effects, which ultimately shows the need for antiviral medications derived from natural phytochemicals. Due to their lower toxicity and less possibility of resistance, plant-derived antiviral medicines are becoming more and more popular worldwide. Traditionally, phytochemicals have been used to treat a wide range of disorders. They have also been shown to prevent the replication and transcription of viruses. The majority of them block the viruses either when they enter the host cell or when they replicate. Numerous phytochemicals found in plants, such as lignins, alkaloids, coumarins, terpenoids, and flavonoids, have antioxidant properties and aid in blocking the viral genome. Since medicinal plants have long been used in traditional medicine and have virucidal qualities, they are excellent substitutes for treating DENV infection. However, it's yet unclear how the plant components prevent the virus from replicating, which may be used to create synthetic medications with more potent effects and lower toxicity [15–18].

Among the several therapeutically important phytochemicals, the Naringenin ((2S)-5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one) is a flavonoid is widely distributed in fruits and vegetables, show the antiviral and anti-inflammatory and other health activities [19]. The antiviral effect of the compound has been studied in several viruses, however, the exact mode of the binding of the compounds with the different viral target proteins has not been studied yet [20–24]. Computer-aided drug design (CADD) has been used to find new antivirals against SARS-CoV-2 because it is fast, reliable, and enables the screening of compounds within a limited time in contrast to high throughput screening [25–28]. The computational analysis followed by *in vitro* analysis provides more insights to discover the potential nature of compounds against DENV [29–31].

The present study aims to evaluate the antiviral activity of the phytochemical Naringenin and its derived compounds on DENV, by using computational methods.

MATERIAL AND METHODS

Retrieval of target receptor and ligand molecules

The NS3 helicase enzyme (PDB ID:2BMF with resolution 2.41 Å) of DENV2 was selected as the receptor and the crystallographic structure was retrieved from the Protein Data Bank (www.rcsb.org). Chimera tool (www.cgl.ucsf.edu/chimera) was used for the removal of crystallographic water molecules, and heteroatoms, and only A chain was selected. Similarly, 20 naringenin derivatives with the wild-type naringenin phytochemical and the standard inhibitor molecules of NS3 helicase enzyme were selected as the ligands for the present study from the literature [32]. The required structural information and format conversion of the ligand was obtained from the PubChem Database (pubchem.ncbi.nlm.nih.gov) and by the Open Babel tool (openbabel.org).

Molecular docking study and screening of compounds

Molecular docking studies were conducted to predict the binding modes and affinities of selected ligands with target DENV NS3 helicase enzyme by using the MzDOCK tool (github.com/Muzatheking12/MzDOCK). MzDOCK is a new user-friendly docking program

that integrates several Python and batch scripts, including Smina (for docking), Open Babel (for file conversion), and PLIP (for interaction analysis). A specific set of scoring functions is used for both the ligand docking processes is implemented by Smina, which is based on a similar searching technique [33, 34]. As the selected receptor do not have any crystalized ligand, the validation of docking was performed by comparing the docking pose of standard inhibitor molecules with the test molecule. The screening process was based on the docking score, binding pose, and number of interacting residues to the domain of the NS3 helicase enzyme. The best-selected naringenin derivative-receptor complexes along with the wild-type naringenin and standard inhibitor were subjected to the MD simulation to compute the binding energy.

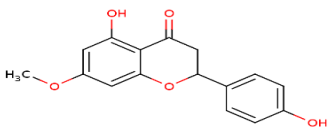
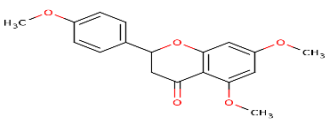
Molecular dynamics simulation study

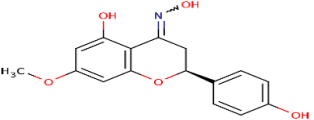
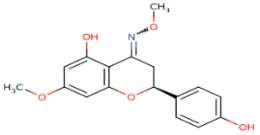
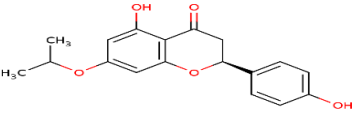
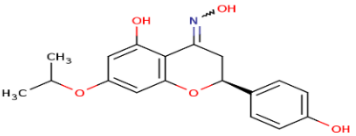
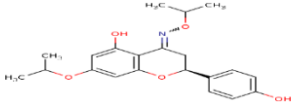
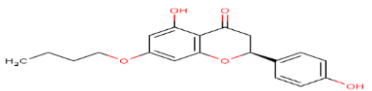
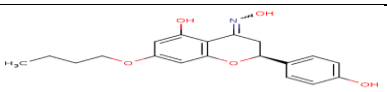
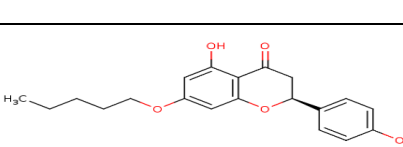
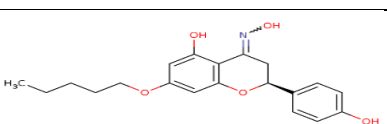
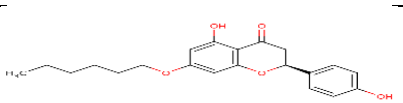
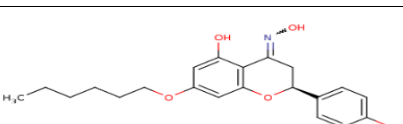
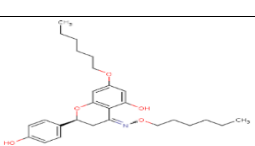
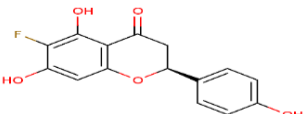
A 100 ns molecular dynamics simulation was performed for the compounds that formed the most energetically favourable and dynamically stable complexes with the NS3 helicase enzyme. The simulations were carried out using YASARA (Yet Another Scientific Artificial Reality Application) Structure software, version 23.12.24.W.64 (www.yasara.org) [35–37]. From the beginning of the simulation Ionic balance was maintained by choosing 0.9 % NaCl, from which excess of Na⁺ or Cl[−] ions to the ligand-receptor complex. Steepest descent energy minimization methods and simulated annealing techniques were applied to remove the interatomic clashes during the simulation. To compute parameters, AMBER14force fields were used for the protein and AM1BCC and GAFF2 were used for the ligands with the TIP3P water model. Several parameters such as Root Mean Square Deviation (RMSD), Root Mean Square Fluctuations (RMSF), Radius of Gyration (Rg), hydrogen bonding, ligand RMSD movement, and binding energy by MM-PBSA calculations were used to evaluate the stability of the receptor-ligand complex [38]. The molecular docking and dynamics simulation parameters used in this study are similar to those reported in our previous work [39, 40] and provided in the Appendix section.

RESULTS AND DISCUSSION

The selected 22 compounds including the parent molecule naringenin and its derivatives with the standard DENV NS3 inhibitor ST-610 molecules were considered for molecular docking by the MzDOCK tool. Further, the compounds were also tested for their theoretical enzyme inhibition activity (likelihood) obtained from Molinspiration program (www.molinspiration.com) output, and both results are represented in Table 1.

Table 1. Showing docking score and predicted enzyme inhibition activity of derivatives of naringenin with wild-type naringenin and NS3 standard inhibitor molecule

Sl No.	Compounds	Structure	Docking score (Kcal/mol)	Enzyme Inhibition activity (likelihood)
1	7-o-methylnaringenin		−8.2	0.54
2	Naringenin trimethyl ether		−8.3	0.31

Sl No.	Compounds	Structure	Docking score (Kcal/mol)	Enzyme Inhibition activity (likelihood)
3	7-O-methylnaringenin oxime		-9.5	0.54
4	7,4-di-O-methylnaringenin oxime		-7.6	0.53
5	7-O-isopropynaringenin		-8	0.44
6	7-O-isopropynaringenin oxime		-9.7	0.44
7	7,4-di-O-isopropynaringenin oxime		-8.4	0.42
8	7-O-butylnaringenin		-8.3	0.5
9	7-O-butylnaringenin oxime		-8.4	0.5
10	7-O-pentylnaringenin		-8.6	0.49
11	7-O-pentylnaringenin oxime		-8.6	0.49
12	7-O-hexylnaringenin		-7.6	0.47
13	7-O-hexylnaringenin oxime		-9.1	0.47
14	7,4-di-O-hexylnaringenin oxime		-7.6	0.45
15	6-fluoronaringenin		-8.7	0.66

Sl No.	Compounds	Structure	Docking score (Kcal/mol)	Enzyme Inhibition activity (likelihood)
16	6-chloronaringenin		-7.5	0.38
17	6-iodonaringenin		-7.4	0.53
18	6,8-difluoronaringenin		-9.6	0.46
19	6,8-dichloronaringenin		-7.4	0.19
20	6,8-diiodonaringenin		-7.1	0.34
21	Naringenin		-9.2	0.53
22	ST-610		-8.9	0.17

The Table 1 summarizes the molecular docking results of 22 compounds, including the wild-type naringenin, its derivatives, and the standard DENV NS3 inhibitor ST-610. Along with docking score by MzDOCK tool, theoretical enzyme inhibition activity was predicted using the Molinspiration program. The table lists each compound along with its chemical structure, docking score (in kcal/mol), and predicted enzyme inhibition activity. Lower docking scores indicate stronger predicted binding affinities, while higher inhibition activity values represent greater theoretical inhibitory potential against the NS3 protein. The compounds selected for further investigation are highlighted in bold.

The initial screening was performed based on the docking score, binding pose of the ligands with respect to the standard inhibitor molecule generated 5 potential molecules such as Naringenin trimethyl ether, 6-fluoronaringenin, 6-chloronaringenin and Naringenin, and the details of the binding poses are shown in Figure 1. In Figure 1, the NS3 helicase structure is shown in green cartoon form, while the ligands are represented as colored sticks for clarity. This figure illustrates the comparative binding orientations and spatial alignment of the selected phytochemicals and reference inhibitor at the active site of NS3 helicase.

A further round of screening was based on the number of amino acids interacting with the functional domain of the NS3 helicase enzyme, the docking score, and the theoretical enzyme inhibition value of the ligands. From the NCBI (www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=1494449) the domain positions were obtained and the interaction was mapped accordingly shown in Table 2. The Table 2 data categorizes interactions based on type (hydrophobic, hydrogen bond, π interactions, halogen) and maps them to three major conserved helicase domains: The “Total” column represents the sum of all interactions observed between each ligand and the combined helicase domains, indicating overall binding engagement strength.

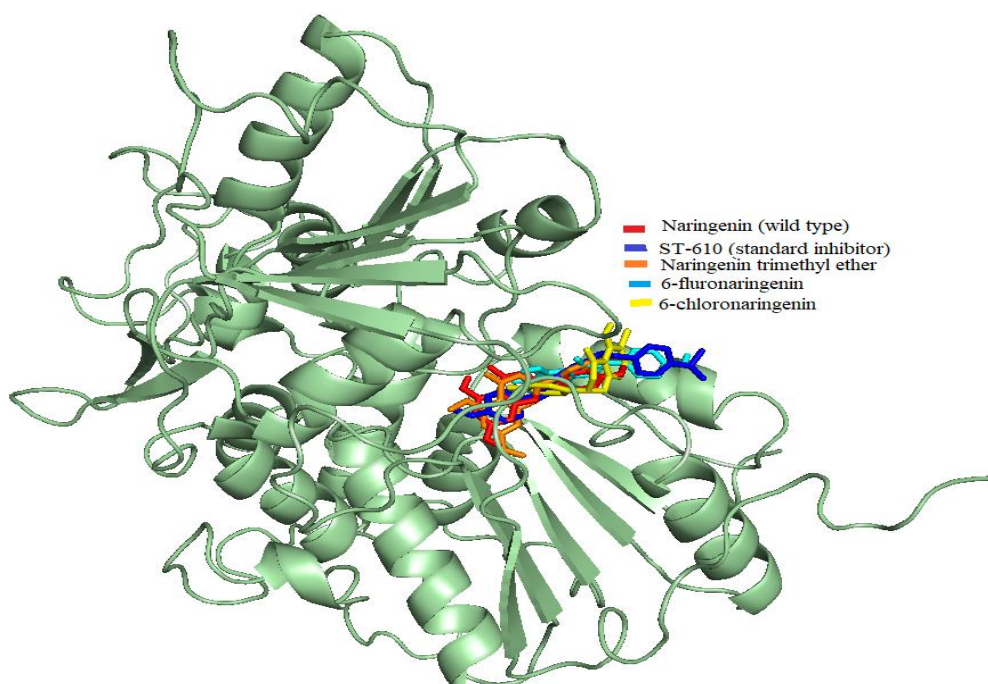


Fig. 1. Showing binding poses of the selected compounds (colored sticks) with NS3 helicase enzyme (Cartoon)

Table 2. Binding interaction of ligands to the domains of NS3-helicase enzyme

Complex Molecules	Interaction types	Functional helicase Domains and location			Total
		DEXDc; DEAD-like helicases superfamily Location: 182-325	Flavi_DEAD; Flavivirus DEAD domain Location:185-330	P-loop_NTPase; P-loop containing Nucleoside Triphosphate Hydrolases Location:355-464	
NS3-Naringenin trimethyl ether	Hydrophobic	3	0	0	5
	Hydrogen	0	0	2	
NS3-6-fluoronaringenin	Hydrophobic	4	0	0	10
	Hydrogen	2	0	2	
	Pie	0	1	0	
	Halogen	0	1	0	
NS3-Naringenin	Hydrophobic	2	2	0	11
	Hydrogen	2	0	5	
NS3-ST-610	Hydrophobic	7	7	0	16
	Hydrogen	1	1	0	
NS3-6-chloronaringenin	Hydrophobic	2	2	0	17
	Hydrogen	5	5	1	
	Pie	1	1	0	

Table 2 highlights how different ligands interact with the functional domains of NS3, revealing their potential binding stability and mechanisms. Among the complexes, NS3-ST-610 and NS3-6-chloronaringenin exhibit the highest interaction counts (16 and 17 respectively), dominated by hydrophobic and hydrogen bonds. The DEXDc domain (182–325) consistently supports the majority of hydrophobic interactions. The P-loop NTPase domain (355–464) does not show significant contributions in this analysis. Halogen and π -

interactions enhance the binding of specific ligands, such as NS3-6-fluoronaringenin and NS3-6-chloronaringenin, however, the halogen interactions observed only in NS3-6-fluoronaringenin, showing the role of the fluorine atom in enhancing ligand interaction through halogen bonding. The Flavi_DEAD domain (185–330) shows significant hydrogen bond interactions, particularly for NS3-Naringenin [41, 42]. The amino acid interaction of selected compounds has been shown in Figure 2, which illustrates the molecular docking interactions of three selected ligands Naringenin, ST-610, and 6-Fluoronaringenin within the active site of the 2BMF protein. For each ligand, the left panel shows the overall protein–ligand docking pose highlighting the binding pocket (yellow surface), while the right panel displays the 2D/3D interaction map depicting key intermolecular interactions with active-site residues.

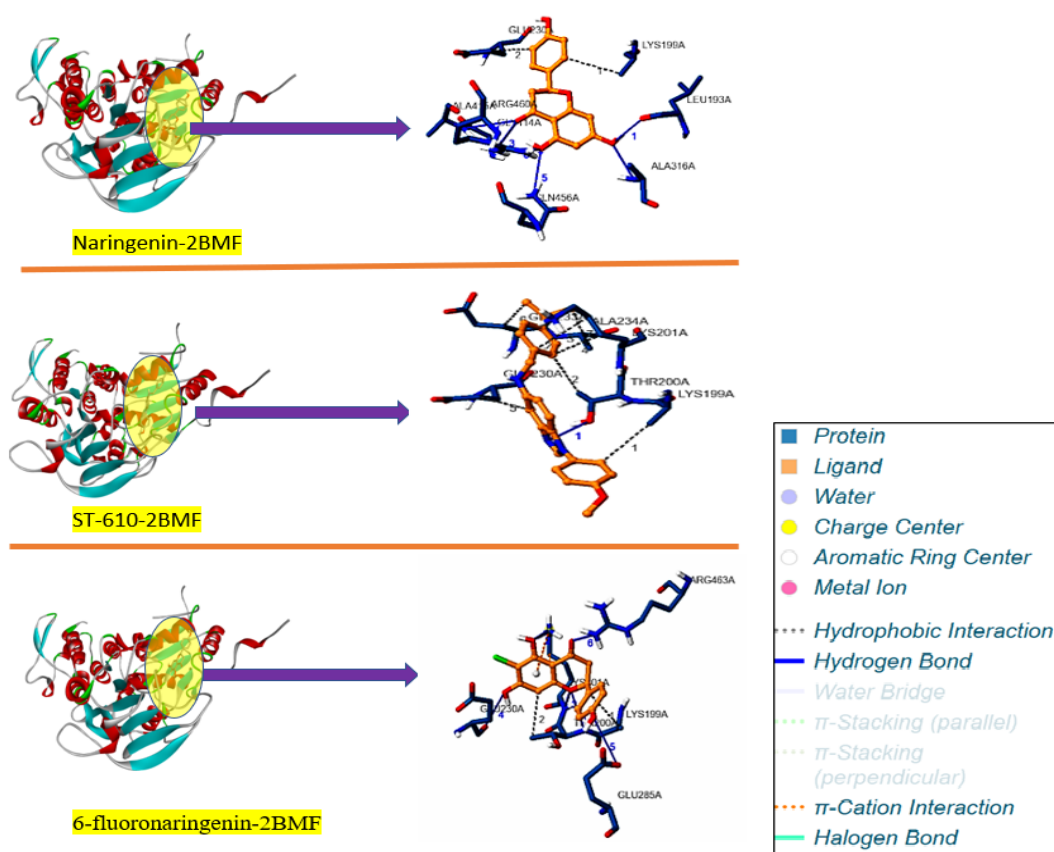


Fig. 2. Binding modes and key intermolecular interactions of naringenin derivatives within the target protein active site. [The full size image](#)

ADMET analysis shows all the compounds show high gastrointestinal absorption, suggesting good oral bioavailability potential. Only Naringenin Trimethyl Ether and ST-610 can cross the blood-brain barrier. Most compounds are easy to synthesize, with synthetic accessibility scores close to 3 (Table 3). The Table 3 contains the ADMET parameters, such as Molecular weight of the compound (MW); Topological polar surface area, indicating molecular polarity and permeability (TPSA); Predicted aqueous solubility based on the ESOL model (ESOL Solubility); Solubility classification derived from ESOL predictions (ESOL Class); Predicted gastrointestinal absorption level (GI absorption); Ability of the compound to penetrate the blood–brain barrier (BBB permeability); Predicted skin permeability coefficient (more negative values indicate lower permeability) (log Kp); Number of Lipinski's Rule of Five violations, indicating drug-likeness (Lipinski violations); Predicted oral bioavailability probability (default values: 0.11, 0.17, 0.55) (Bioavailability Score); Estimated ease of chemical synthesis (1 = very easy; 10 = very difficult) (Synthetic Accessibility).

Table 3. ADMET properties of the selected compounds

ADMET properties	Selected compounds				
	2	15	16	21	22
	Naringenin Trimethyl ether	6-fluoronaringenin	6-chloronaringenin	Naringenin	ST-610
MW	314.33	290.24	306.7	272.25	371.47
TPSA	53.99	86.99	86.99	86.99	39.08
ESOL Solubility (mg/ml)	$5.34 \cdot 10^{-2}$	$6.54 \cdot 10^{-2}$	$2.53 \cdot 10^{-2}$	$8.74 \cdot 10^{-2}$	$4.96 \cdot 10^{-4}$
ESOL Class	Soluble	Soluble	Moderately soluble	Soluble	Moderately soluble
GI absorption	High	High	High	High	High
BBB permeability	Yes	No	No	No	Yes
log Kp (cm/s)	-6.12	-6.21	-5.93	-6.17	-4.54
Lipinski violations	0	0	0	0	0
Bioavailability Score	0.55	0.55	0.55	0.55	0.55
Synthetic Accessibility	3.34	3.09	3.06	3.01	2.63

Results of MD simulation

MD simulation study was conducted for 100 nanoseconds by the YASARA structure tool (version 24.10.5) for three selected complexes, such as NS3-6-fluoronaringenin, NS3-Naringenin, and NS3-ST-610. The composition of the simulated system is given in the supplementary material section. The trajectories obtained after the simulation were analyzed to measure the RMSD, Rg, protein secondary structure dynamics, number of H-bonds made by the ligand molecule with the receptor, and the ligand movement. RMSD calculation concerning the binding site was calculated to interpret the stability of the structures during the simulation shown in Figure 3. Comparative molecular dynamics simulation results of the NS3–naringenin, NS3–ST-610, and NS3–6-fluoronaringenin complexes over the simulation period. Panels depict (from left to right): root mean square deviation (RMSD) of the solute relative to the starting structure, radius of gyration (Rg), protein secondary structure content, number of hydrogen bonds formed between the ligand and protein residues, and per-atom receptor interaction profiles of the ligand.

Figure 3 also displays the RMSD (Root Mean Square Deviation) of the solute (protein and ligand complex components) for three different complexes–NS3-Naringenin, NS3-ST-610, and NS3-6-Fluoronaringenin–relative to their starting structures during a 100-nanosecond (ns) period. For RMSD, the NS3-Naringenin complex shows the least deviation and remains highly stable throughout. The NS3-ST-610 complex displays moderate deviations, reflecting flexibility in its backbone and structure. The NS3-6-Fluoronaringenin complex shows larger RMSD values for the overall system, indicating reduced stability compared to the others. From the center of mass of the protein-ligand complexes, the radius of gyration is calculated.

In all cases, the compactness varied within a range of 1 Å, specifically from 22.8 Å to 23.8 Å, demonstrating dynamic compactness. In the case of naringenin and the standard complex, the radius of gyration showed a decreasing trend at the end of the 100 ns simulation, while the NS3-6 fulronaringenin complexes exhibited an increasing trend. Similarly, the secondary structure content was observed to be highly stable throughout the 100 ns simulation for all three complexes, indicating robust structural integrity. NS3-Naringenin Complex shows slightly higher consistency in helices compared to the other two complexes. The

overall secondary structure distribution is comparable among the complexes, reflecting similar folding patterns and stability. This highlights the adaptability of the protein in accommodating different ligands without significant conformational disruption [43].

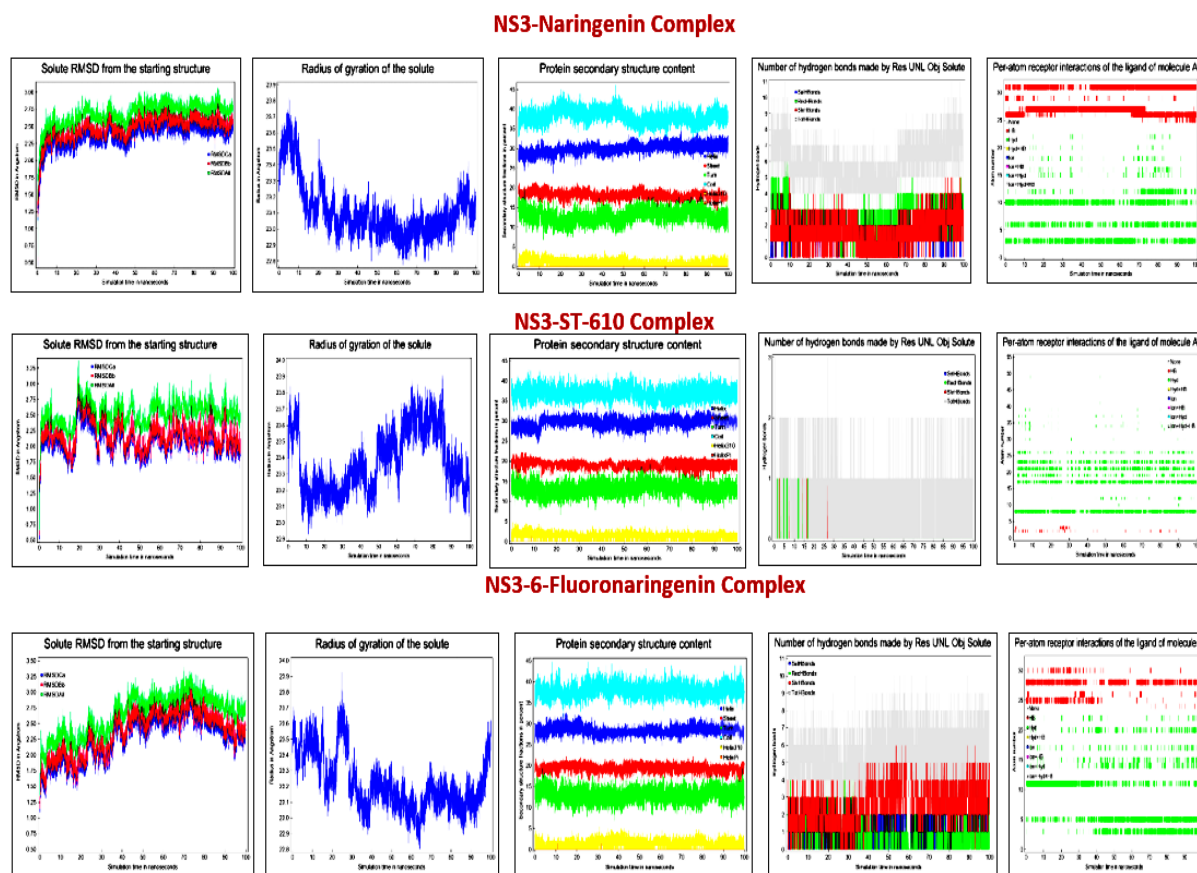


Fig. 3. Showing comparative MD simulation parameters for the selected complexes. [The full size image](#)

The hydrogen bond profiling shows three kinds of hydrogen bonds formed by atoms. The plot shows internal hydrogen bonds (blue), hydrogen bonds with the rest of the solute/protein molecule (green), hydrogen bonds with water (red), and the sum of all three in grey color. The plot shows internal hydrogen bonds of the ligand molecules in the case of NS3-naringenin were obtained during 0–10 ns and 70–80 ns and frequently found after 90 ns until the end of the simulation. However, no internal hydrogen was found in ST-610 and it was frequently found in 40–80 ns in the case of the NS3-6-fluoronaringenin complex [44, 45]. The per-atom receptor interactions of ligands within three different NS3 complexes during 100-nanosecond molecular dynamics (MD) simulations showed that the naringenin ligand shows stable receptor interactions primarily through hydrogen bonding and hydrophobic contacts. Consistency in interactions indicates satisfactory binding stability. This feature is also in agreement with the results obtained in hydrogen bond analysis. Similarly, the ST-610 ligand primarily relies on hydrophobic interactions, with fewer hydrogen bonds. This attribute reflects a moderate binding affinity, possibly explaining its flexibility observed earlier in the RMSD data. The 6-fluoronaringenin ligand maintains significant interaction through hydrogen bonds and hydrophobic contacts, with an initial period of instability during the ~35–50 ns period.

MM-PBSA analysis

The MM-PBSA analysis output for the three complexes was observed after MD simulation and is shown in Figure 4. NS3-6-Fluoronaringenin (cyan color) exhibits the most stable and favorable binding energy (B.E.) profile over the simulation period, suggesting that

the fluorinated derivative may have improved interaction and binding affinity toward the target with an average B.E. of -115.343 KJ/mol. Similarly, the complex NS3-ST-610 (red color) also shows strong interaction with the receptor but shows more fluctuations and has an average B.E. of -235.031 KJ/mol. Similarly, the NS3-Naringenin (yellow color) displays moderate stability with an average binding energy of -241.899 KJ/mol. The Figure 4 shows binding free energy variation of NS3 helicase complexes with naringenin, ST-610, and 6-fluoronaringenin calculated using the MM-PBSA method over a 100 ns molecular dynamics simulation. The plot shows the temporal fluctuations in binding free energy (ΔG_{bind}) for each ligand–protein complex (Y-axis), illustrating relative stability and interaction strength throughout the simulation trajectory.

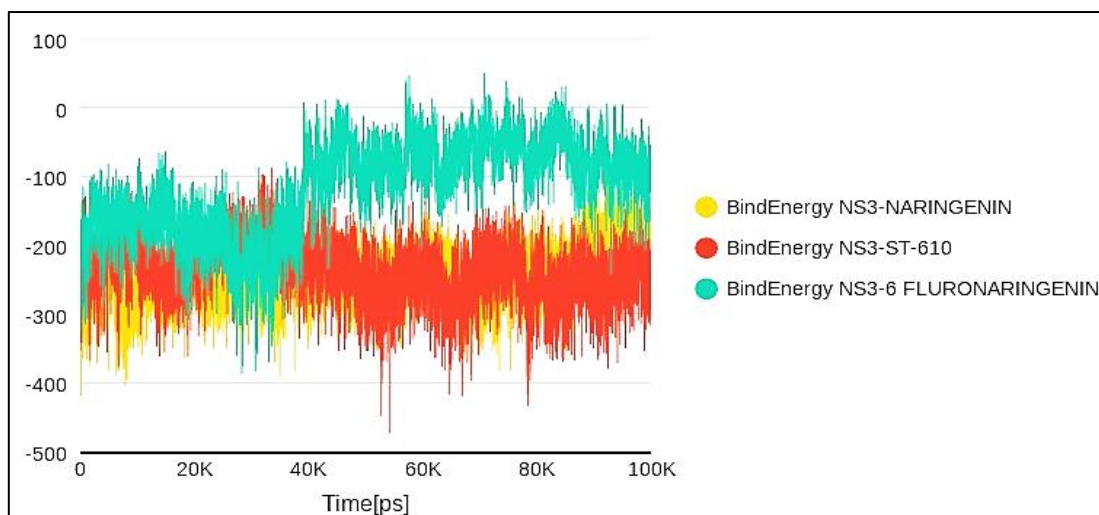


Fig. 4. The binding energy variation during simulation calculated by MM-PBSA method

Ligand movement RMSD analysis

Figure 5 illustrates the RMSD (Root Mean Square Deviation) of ligand movement for three different complexes after being superimposed on the receptor during molecular dynamics (MD) simulations over a 100 ns period. In the case of NS3-Naringenin complex during the early stage of simulation (0–20 ns), the RMSD fluctuates between 0.5 and 2.5 Å, showing significant movement of the ligand. After around 80 ns, the RMSD begins increasing and stabilizes closer to 3.5 Å, suggesting a loss of tight binding or stabilization of the ligand in a slightly shifted position. In the case of the NS3-ST-610 complex, throughout the 100-ns simulation, the RMSD stays relatively consistent, fluctuating between 3.5 and 5 Å, with maximum peaks above 5.5 Å due to some periodic deviations of the ligand. Alternatively, in the case of NS3-6-Fluoronaringenin Complex, the RMSD was observed as stable at values (below 2.5 Å), in the simulation time between 0–35 ns, indicating minimal movement. However, after 35 ns, a sharp increase occurs, stabilizing above 8 Å, with significant fluctuations observed up to 11 Å. This drastic increase suggests substantial ligand movement or disassociation from the receptor indicating unstable/weak interactions [46, 47].

Figure 5 provides the ligand RMSD profiles of the NS3 helicase complexes with naringenin, ST-610, and 6-fluoronaringenin over a 100 ns molecular dynamics simulation. The ligand RMSD values were calculated after superimposing each trajectory onto the receptor backbone to monitor the positional stability and conformational drift of the bound ligands within the active site. Differences in RMSD patterns indicate variations in binding stability and ligand adaptability during the simulation.

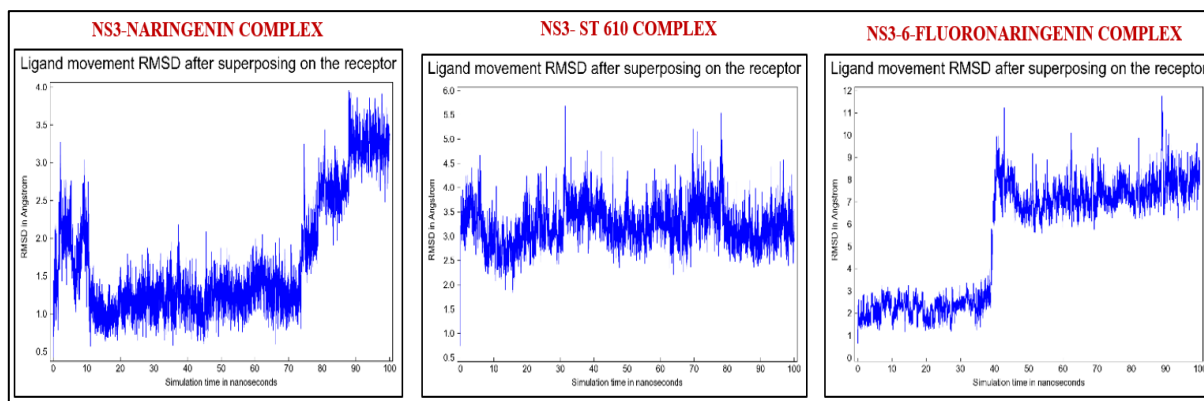


Fig. 5. Ligand movement RMSD during 100 ns MD simulation of selected ligands. [The full size image](#)

Based on these results, although 6-fluoronaringenin showed favorable interaction persistence during the early stages of the simulation, the MM-PBSA binding free energy and ligand RMSD analyses collectively indicated that wild-type naringenin is the more stable inhibitor. Recent research is mostly focused the computer-based analysis to screen, predict, and characterize novel potential antivirals before performing *in vitro* and *in vivo* experimental approaches. The availability of a vast collection of crystal structures of the viral proteins is used to compute binding affinity with several ligands including phytochemicals [48, 49]. To assess the antiviral properties of thousands of newly found phytochemicals, extensive research has been conducted during the past few decades to evaluate their anti-viral activities. Among them, a potential phytochemical (a flavanone) Naringenin, found in citrus fruits, is widely used for therapeutic applications. In addition, several derivatives of this compound have been designed and tested for several therapeutically applications [50, 51]. Yang et al., designed naringenin-O-alkylamine derivatives that are used for the effective treatment of Alzheimer's disease [52]. The effect of naringenin derivatives has shown their inhibitory effect against the G-6-P synthase enzyme of *P. mirabilis*, *P. aeruginosa*, *S. aureus*, *E. coli*, *C. albicans*, and *A. niger* with remarkable efficacy [53]. The *in-vivo*-based anti-inflammatory potential of the carboxymidamide, synthesized through the condensation reaction between naringenin and aminoguanidine was evaluated by causing reduced zymosan-induced paw edema in mice [54]. In another study, the addition of naringenin and its fluorinated derivatives proved to decrease the minimum inhibitory concentration (MIC) of ciprofloxacin for Methicillin-resistant *Staphylococcus aureus* (MRSA) by up to 50-fold. The synergistic interaction of naringenin and oxacillin against MRSA was demonstrated in another study by Souza et al., which resulted in a reduction of cell growth as measured by cell density [55]. In the viral inhibition study, naringenin was predicted as a therapeutic candidate against COVID-19 having the potential to inhibit the main protease, 3CLpro, and reducing the activity of ACE2 receptors. Apart from the COVID-19 virus, it has also shown effectiveness against other viruses such as DENV and Zika viruses also [56, 57]. Moreover, the adverse effect of the naringenin derivatives has been studied by Rajasekar et al. in the Zebrafish model and studied the correlation between dosage-dependent dysfunction of the heart and lethal toxicity of compounds after administration of the compounds [58]. Despite their anti-viral activity, the major challenges are the poor bioavailability and solubility of these compounds. So, the implementation of approaches like nanoparticle-based delivery systems might be used to improve the therapeutic efficacy of naringenin [59, 60]. Our research used computational methods to investigate the possible therapeutic use of naringenin against DENV infection. Overall, our results indicate that, compared to its derivatives, the phytochemical naringenin may serve as a more effective inhibitor of DENV-2 by targeting the viral replication machinery.

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APPENDIX. SUPPLEMENTARY TABLES

Table S1. Docking parameters used in the work

Parameter	Description / Value
Docking engine	Mz DOCK
Scoring function	Smina -based empirical scoring function
Energy unit	kcal/mol
Search algorithm	Iterated local search global optimizer
Number of poses generated	9
Exhaustiveness	8 (as implemented in Mz DOCK)
Gaussian term 1	-0.035579 (o = 0, w = 0.5, c = 8)
Gaussian term 2	-0.005156 (o = 3, w = 2, c = 8)
Repulsion	0.840245 (o = 0, c = 8)
Hydrophobic term	-0.035069 (g = 0.5, b = 1.5, c = 8)
Non-directional H-bond	-0.587439 (g = -0.7, b = 0, c = 8)
Torsional penalty	1.923 (num_tors_div)
Output ranking	Based on binding affinity (lowest energy)

Table S2. Docking pose details of Naringenin against DENV-2 NS3 helicase

Pose	Binding affinity (kcal/mol)	RMSD (lower bound, Å)	RMSD (upper bound, Å)
1	-9.2	0.000	0.000
2	-9.1	14.685	17.870
3	-8.9	1.744	6.641
4	-8.3	23.149	25.082
5	-8.3	21.056	23.571
6	-8.2	24.069	26.610
7	-8.1	13.240	16.629
8	-8.0	1.990	6.715
9	-7.9	22.444	24.089

Table S3. Docking pose details of ST-610 against DENV-2 NS3 helicase

Pose	Binding affinity (kcal/mol)	RMSD (lower bound, Å)	RMSD (upper bound, Å)
1	-8.9	0.000	0.000
2	-8.9	24.815	26.160
3	-8.8	19.174	23.932
4	-8.6	21.762	25.007
5	-8.3	23.605	25.261
6	-8.1	24.025	25.475
7	-8.1	21.719	25.287
8	-8.0	17.572	21.223
9	-7.6	22.389	25.245

Table S4 summarizes the complete simulation setup, including pH, temperature, pressure control, force field, boundary conditions, electrostatic treatment, integrator settings, constraints, and trajectory saving details. Additionally, MM-PBSA calculation parameters are also listed, including the number of frames extracted, extraction interval, solvation models (PB and non-polar), dielectric constants, computed energy components, and the binding free energy equation used for post-simulation analysis.

Table S4. Molecular dynamics Simulation Parameters used in YASARA structure tool for performing MD simulation of Protein-ligand simulation

MD simulation parameters	
Parameter	Value
pH	7.4
Ions	Na ⁺ , Cl ⁻ (0.9%)
Temperature	298 K (controlled with Berendsen thermostat, $\tau = 0.1$ ps)
Pressure control	Solvent Probe method with Berendsen barostat ($\tau = 1.0$ ps)
Density	0.99342 g/cm ³
Cell shape	Cube
Simulation duration	100,000 ps (100 ns)
Save interval	Every 10000 steps
Force field	AMBER14
Cutoff	8 Å (van der Waals interactions)
Boundary condition	Periodic
Electrostatics	Long-range Coulomb with PME
Integrator	Multiple time step leapfrog/Verlet ($\Delta t = 1.25$ fs)
Constraints	All bonds to hydrogen atoms constrained with LINCS-like algorithm (YASARA implementation)
Drift correction	Enabled
Random seed	1
MM-PBSA Calculation Parameters	
Number of frames extracted	250
Extraction interval	200 ps
Solvation model (polar)	Poisson–Boltzmann (PB)
Solvation model (non-polar)	Surface area-based term
Surface tension parameter	0.65 kJ·mol ⁻¹ ·Å ⁻²
Temperature	298 K
Dielectric constant (solute)	1.0
Dielectric constant (solvent)	80.0
Cell shape	Converted to cuboid for PB
Energy components computed	$E_{\text{pot}}(\text{rec})$, $E_{\text{sol}}(\text{rec})$, $E_{\text{pot}}(\text{lig})$, $E_{\text{sol}}(\text{lig})$, $E_{\text{pot}}(\text{complex})$, $E_{\text{sol}}(\text{complex})$
Binding energy formula	$\Delta G_{\text{bind}} = (G_{\text{rec}} + G_{\text{lig}}) - G_{\text{complex}}$

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