INFORMATICS JOURNALS

Research Article

Journal of Natural Remedies
DOI: 10.18311/jnr/2026/56108

eISSN: 2320-3358 | Vol 26(9), 2026 | pp. 2493-2515

In Silico Identification of Potential Natural Inhibitors of Dengue Virus-2 (DENV-2) NS2B–NS3 Protease

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Abstract

Background: Artificial Intelligence-driven drug discovery has recently made significant advances. Still, no Food and Drug Administration (FDA) approved antiviral drug is available for dengue treatment. The dengue virus NS2B–NS3 protease plays a critical role in viral replication and represents a promising therapeutic target. **Aim:** This study employed an integrated computational approach to identify potential phytochemical inhibitors of the NS2B–NS3 protease. **Methods:** Protein–protein interaction analysis was conducted to determine the most suitable protease conformation, and the 2FOM structure was selected based on its structural stability and active inhibitor-bound conformation. Initially, a library of over 5000 bioactive natural compounds was screened for anti-viral activity, from which 100 were shortlisted for molecular docking. **Results:** Docking analysis identified 27 compounds with high binding scores and favourable interactions with key catalytic residues. Subsequent drug-likeness and ADMET evaluation refined the candidates to nine potential compounds with acceptable pharmacokinetic and toxicity profiles. All these compounds demonstrated superior docking scores compared to the reference antiviral drugs. **Conclusion:** Curcumin, Quercetin, Gingerol, Flacourtoside A and Anacolosine emerged as the most potential lead molecules against Dengue virus infection. These findings support the potential of natural compounds as antiviral therapeutic molecules and need further molecular dynamics simulations and preclinical validation.

Major Findings: From a library of over 5000 natural antiviral compounds, nine potential inhibitors of DENV-2 NS2B-NS3 protease were identified with favourable ADMET properties and superior docking scores compared to reference antiviral drugs. Curcumin, Quercetin, Gingerol, Flacourtoside A and Anacolosine emerged as the most promising lead molecules.

Keywords: ADMET Analysis, Dengue Virus Serotype 2 (DENV-2), Molecular Docking, NS2B–NS3 Protease, Phytochemical Inhibitors

(Article Chronicle: Article Received on: 08.05.2026; Revised on: 15.06.2026; Accepted on: 20.06.2026)

1. Introduction

Dengue fever, caused by dengue viruses, is a rapidly spreading mosquito-borne disease that has become a major global public health concern, with a record of 14 million cases in 2024[1]. The virus belongs to the family *Flaviviridae*; DENV is primarily transmitted by *Aedes* mosquito bites. Infection in humans results in a wide clinical spectrum ranging from mild febrile illness to severe fever, including dengue haemorrhagic fever (DHF) and dengue shock syndrome, which are related to significant morbidity and mortality[2-4]. During the past few decades, the global incidence of dengue has increased significantly, mostly driven by rapid urbanisation, climate change, and population growth[2,5-7]. During the year 2025, more than five million dengue cases with three thousand related deaths have been reported from 106 countries/territories[8].

DENV (genome of approximately 11 kb) occurs as four antigenically distinct serotypes (DENV-1 to

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DENV-4), with a fifth serotype (DENV-5) reported lately[9]. Dengue Virus (DENV) replication is a complex process intricately linked to host cell membrane remodelling, primarily within the Endoplasmic Reticulum (ER)[10]. The genome is translated into a polyprotein, which is subsequently processed by host and viral proteases into three structural proteins, such as Capsid (C), Premembrane (prM), and Envelope (E), and seven non-structural proteins such as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. The C protein mediates nucleocapsid formation, prM contributes to virion maturation, and the E glycoprotein is essential for receptor binding, membrane fusion, and induction of neutralising antibodies. These proteins collectively govern viral entry, assembly, and infectivity[11].

Non-Structural (NS) proteins NS1-NS5 are crucial for replication, assembly, and immune evasion, while NS1, NS3, and NS5 are vital for pathogenesis and host interaction[12]. The complex formed of NS2B (membrane-associated protein cofactor) and NS3 (multifunctional enzyme), known as the NS2B-NS3 protease complex (or NS3 protease), is a hetero dimeric enzyme and is a critical enzyme in the dengue virus life cycle, responsible for cleaving the viral polyprotein into functional, structural, and non-structural proteins. The NS3 protein provides the catalytic serine protease activity, while the NS2B cofactor is essential for proper folding, activation, and stabilisation of the protease complex[13]. This coordinated interaction is indispensable for viral replication and viral maturation[2,7,11,14,15]. Disruption of NS2B–NS3 protease activity effectively halts viral replication, making it a highly conserved and validated target for antiviral drug development. Due to its essential function and high degree of conservation across dengue virus serotypes, inhibition of this protease leads to early disruption of the viral life cycle, making it a highly attractive antiviral target[11,16,17]. Dengue virus non-structural proteins interact with key host factors to suppress innate immune responses and facilitate efficient replication, thereby enhancing viral survival within infected cells[2,11]. Understanding these virus–host protein interactions provides valuable insights for the rational design of antiviral inhibitors that can disrupt critical interaction interfaces and limit dengue virus replication[11,18].

The Dengue Virus (DENV) NS2B-NS3 protease is a two-component serine protease that processes the viral polyprotein. During infection, NS2B-NS3 attacks several host cell proteins to suppress immune responses and promote viral replication. The human proteins known to be targeted or cleaved by the DENV NS2B-NS3 protease include the TRIM69 RING domain, STING, cGAS, and Mitofusins (MFN1 and MFN2). TRIM69 (PDB ID: 6YXE) plays a role in antiviral immunity by restricting viral infections, including dengue virus.

Despite the significant global health burden posed by dengue virus infection, no approved antiviral treatment is currently available. Although vaccines such as *Dengvaxia* have been developed, their use is restricted due to safety concerns and variable efficacy across different populations[19]. At present, the management of dengue fever is primarily symptomatic and supportive, focusing on complete bed rest, adequate hydration, and the use of mild analgesics and anti-pyretic agents. Paracetamol is commonly recommended for the management of fever and pain, while non-steroidal anti-inflammatory drugs are avoided due to the risk of bleeding complications. The lack of a specific antiviral therapy creates a critical gap in dengue treatment, necessitating the development of targeted antiviral compound[20]. These limitations underscore the urgent need for alternative therapeutic strategies that target essential viral proteins and virus–host interactions to reduce viral replication and disease severity[2,4]. Recent studies have demonstrated the effectiveness of natural compounds in binding to the active or allosteric sites of the NS2B–NS3 protease, suppressing viral replication. Structure-based computational approaches, including molecular docking and virtual screening, have further confirmed the suitability of this protease as a target for antiviral drug discovery, supporting its selection as the primary molecular target in the present study[17,21]. Dwivedi *et al.*[22] reported triterpenoids, such as nimbin and its derivatives, as promising anti-dengue compounds, while Stalin *et al.*[23] identified niloticin as a potential NS2B–NS3 protease inhibitor through stable active-site interactions. In addition, a comprehensive review by Altamish *et al.*[24] has highlighted medicinal plant-derived compounds such as quercetin, andrographolide, and α-mangostin, which inhibit viral entry, replication, and protease activity.

2. Materials and Methods

Compounds from natural sources, including medicinal plants, were screened for this study. The drug discovery

process includes identifying the target viral protein, screening natural compounds for antiviral activity, performing molecular docking to identify potential lead compounds, and then applying Lipinski's Rule and ADMET tests for lead optimisation. In addition to Lipinski's and ADMET tests, the lead molecules were compared with the features of known drugs with antiviral properties. Discovery Studio 2023 of BIOVIA (formerly Accelrys), a visually intuitive platform for predicting and analysing the interactions between ligands and macromolecular targets (proteins or nucleic acids), was used to define binding sites, prepare ligands and receptors, and perform precise docking with control over key parameters such as energy minimisation and pose generation[25]. The complete workflow for *in silico* prediction of NS2B–NS3 inhibitors is shown in Figure 1.

2.1 Target Protein Retrieval

Key dengue viral proteins selected for this study include the NS2B–NS3 protease complexes (PDB IDs: 2FOM, 3L6P, 4M9F, and 4M9K. Owing to the indispensable roles of NS2B–NS3 protease in the dengue virus life cycle and the availability of high-resolution structural data, these proteins are well-suited for structure-based molecular docking and virtual screening studies[11,17,22]. Dengue NS2B-NS3 Protease Complex (PDB ID: 2FOM and 4M9K of Dengue Virus 2 and 3L6P of Dengue Virus 1) were retrieved from the Protein Data Bank.

2.2 PPI Analysis, Identification, and Preparation of Target Protein

Protein-Protein Interaction (PPI) analysis identifies the actual functional interfaces (hot spots) where a drug needs to bind, revealing the complex dynamics (like "induced fit") that govern binding and helping design effective and specific inhibitors. It helps uncover disease mechanisms, provides structural context for drug action, and focuses docking efforts on biologically relevant areas for better hit identification[26]. Using the ClusPro server, detailed PPI analysis between the host protein TRIM69 (PDB ID: 6YXE) and viral proteins was performed[27,28]. These virus–host protein interactions are critical for immune evasion and viral persistence, and understanding them provides valuable insights for identifying host-associated therapeutic targets in dengue virus infection[11,19,29]. Once the target protein was identified, the protein was prepared by removing water, adding hydrogens, fixing missing loops/residues, and performing energy minimisation using CHARMM (Chemistry at HARvard Molecular Mechanics), ensuring the receptors were in the correct protonation state and geometry for binding site definition[30].

2.3 Retrieval and Refinement of Ligands

5000-plus bioactive compounds from medicinal plants such as *Azadirachta indica*, *Garcinia mangostana*, *Andrographis paniculata*, and *Ocimum tenuiflorum*, and natural sources were retrieved from PubChem and Indian Medicinal Plants, Phytochemistry and Therapeutics databases (IMPPAT). Chemical structures, identifiers, different chemical and physical properties, biological activities, and toxicity data were retrieved from PubChem, while phytochemical data were retrieved from IMPPAT 2.0. After screening these bioactive compounds, based on a critical review of literature and biological resources, 100 compounds with antiviral activity confirmed against dengue virus were selected for further molecular analysis. The structures of these compounds were cleaned by removing unwanted water molecules, by adding hydrogens, and assigning charges. The docking site or grid box was defined for calculations.

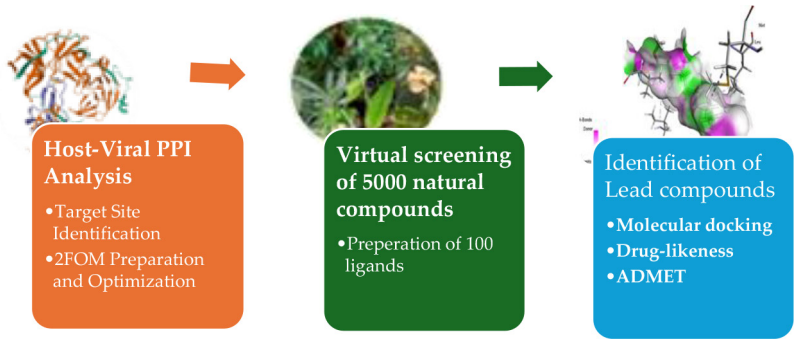


Figure 1. Workflow for the *in silico* identification of DENV-2 NS2B–NS3 inhibitors.

2.4 Molecular Docking

LibDock[31] in Discovery Studio 4.5, a high-throughput docking algorithm, was used to screen 100 selected ligands against protein targets by identifying polar and non-polar interaction sites. It uses the Conformer Algorithm based on Energy Screening and Recursive buildup (CAESAR) to generate ligand conformations. Ligand conformers are docked into the binding site based on energy and chemical complementarity to the hot spots. The generated poses are scored based on their interaction energy, allowing rapid screening.

2.4 Drug-likeness, ADME and Toxicity Prediction

Drug-likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies are critical in the early stages of drug development, ensuring that compounds possess favourable pharmacokinetic properties[32]. The studies were carried out using Discovery Studio of BIOVIA. Drug-likeness refers to the qualitative assessment of a compound's potential to become an orally active drug in humans. It evaluates various physicochemical properties such as molecular weight, lipophilicity (logP), hydrogen bond donors and acceptors, and the number of rotatable bonds. These parameters are often assessed using Lipinski's Rule of Five, wherein compounds selected should have no more than one violation of the following: molecular weight < 500 Da, logP < 5 (Lipophilicity), hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤ 10, and Polar Surface are (PSA) < 140 $Å^2$ [33]. Absorption of a drug molecule, proposed for oral administration, depends on its extent of transportation through the walls of the gastrointestinal tract. Human Intestinal Absorption (HIA%) is a crucial factor that helps predict the feasibility of drug absorption in the small intestine. Absorption assesses how well a compound passes through biological membranes and reaches systemic circulation, and is often determined by analysing intestinal absorption based on Polar Surface Area (PSA) and P-glycoprotein (P-gp) interaction. P-glycoprotein (P-gp) is an ATP-dependent transmembrane pump. Though they are protective shields for organs, they create challenges for drug delivery. It acts as a biological barrier for drugs by actively transporting them out of cells, significantly limiting oral absorption and tissue penetration. If a drug is a P-gp substrate or inhibitor, the transporter actively pumps the drug back into the gut lumen, reducing its overall HIA[34].

Distribution involves predicting the compound's ability to reach target tissues, as indicated by factors such as blood-brain barrier permeability. Metabolism evaluates the likelihood of enzymatic breakdown, particularly by liver enzymes such as cytochrome P450. Excretion focuses on how the compound and its metabolites are eliminated, and toxicity predictions assess potential risks such as hepatotoxicity, carcinogenicity, and mutagenicity.

3. Results

3.1 Target Identification – (PPI Analysis)

Based on PPI interactions, 2FOM has the highest value (-932.6), compared to 3L6P, and the literature review confirms 2FOM as a stable, inhibitor-bound, "closed" conformation of the DENV-2 protease[35,23]. Docking score and docked structure of the best docking complex (2FOM with 6YXE) based on interaction score and stability are given in Figure 2.

A better score of -932.6 was attained for the host protein 6YXE while binding with 2FOM. Literature analysis revealed key active binding sites within 2FOM notably including residues ASP75, ASN152, LYS74, LEU128, LEU76, GLY148, VAL72, and Lle65[36,37]. The active sites found in the NS2B–NS3 protease complex lead to strong binding of the ligands[22,38].

3.2 Ligand Identification and Preparation

By screening 5000 bioactive phytocompounds from medicinal plants and natural compounds, 100 phytocompounds and natural compounds with anti-viral activities were screened and selected for molecular docking studies. The imported ligands were cleaned by adding hydrogen, assigning charges, and normalising structures.

3.3 Molecular Docking (Target-ligand)

Among 100 phytocompounds screened against 2FOM, the top-scoring 27 ligands were selected for further analysis after docking. A Libdock score greater than hundred is considered a strong binding between the target and the ligand[39]. Considering the Docking Score, details of the best 27 results are given in Appendix 1 in the supplementary data.

3.4 Drug Likeness Study

For most of the ligands, favourable results were obtained for parameters such as molecular weight, logP, hydrogen bond donors, hydrogen bond acceptors, and PSA. PSA is a crucial criterion to predict oral bioavailability and membrane permeability. A PSA below 140 Å² is generally considered to have high membrane permeability, making it more likely to be absorbed through the gastrointestinal tract, and is said to have optimal absorption. Compounds with PSA below 60 Å² exhibit high intestinal absorption and are used as a stricter threshold for BBB penetration[34]. Azadirachtin and Rutin were found to have molecular weights more than the allowed limit of 500 Da, and Hyperoside reported PSA over the limit. Hyperoside, although exhibiting documented antiviral effects against equine herpesvirus type 8 and porcine reproductive and respiratory syndrome virus in both *in vitro* and *in vivo* studies[40,41], violated Lipinski's Rule of Five due to its high number of hydrogen bond acceptors, which may limit its drug-likeness. Details of compounds that have obtained favourable results in Lipinski's Test are given in Table 1.

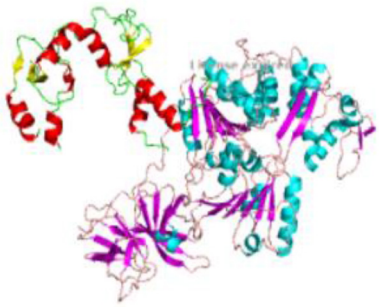


Figure 2. PPI interaction between 6YXE of host proteins and viral protein 2FOM. The docking score obtained is -932.6.

ADMET Properties of Ligands

The ADMET prediction determines whether a molecule is suitable and safe for use. The solubility Level, Blood-Brain Barrier level (BBB), CYP2D6 Prediction, Absorption Level, PPB Prediction (Plasma Protein Binding), and 2D PSA were analysed and

Table 1. Results of Lipinski's rule of five of natural compounds with high docking scores

S. No.	Ligands	Pubchem ID	Libdock Score	No. of H acceptors	No: of H donors	Molecular weight	logP	PSA
1	Garcinone C	44159808	138.41	7	5	414.4	4.608	130.308
2	Br Xanthone A	13964005	128.69	6	2	396.4	4.674	85.722
3	Curcumin	969516	118.292	6	2	368.38	3.554	94.092
4	Quercetin	5280343	112.61	7	5	302.23	1.63	130.308
5	Kushenol W	42608033	112.04	4	2	256.253	2.615	118.422
6	Flacourtoside A	21672233	111.814	8	4	376.357	1.459	127.353
7	Deoxyandrographolide	11624161	108.77	4	2	334.4	3.023	67.861
8	Isobavachalcone	5281255	105.652	5	1	368.469	3.684	79.747
9	Gingerol	442793	105.092	4	2	294.386	3.638	67.861
10	**Anacolosine**	71503226	100.833	4	2	238.28	3.401	76.232
11	Psoralidin	5281806	98.7576	5	2	336.338	4.917	80.416
12	Mycophenolic acid	446541	97.8496	6	2	320.337	3.157	94.092
13	Glabranin	124049	93.234	4	2	324.37	4.472	67.861
14	Andrographolide	5318517	91.975	5	3	350.449	2.056	88.677
15	Coumarin A	14585500	91.6535	4	1	246.259	1.919	55.976
16	Luteolin	5280445	88.6352	6	4	286.236	2.168	109.492
17	Epicatechin	72276	88.0387	6	5	290.268	2.021	113.007
18	Safficinolide	85152699	84.8039	5	1	344.402	3.719	81.648

reported. For solubility, the preferred levels are 3 or 4; 0 indicates extremely low solubility. For BBB, in the case of non-CNS drugs, 2-4 (low penetration) is preferred to avoid side effects, while 0 or 1 is preferred (high penetration) for CNS drugs. An absorption level of 0 is good; 1 indicates moderate absorption; and 2 and 3 indicate poor and very poor absorption, respectively. PPB Prediction estimates whether a compound binds strongly (>90%) or weakly (<90%) to plasma proteins, directly affecting drug efficacy and pharmacokinetics. True indicates the compound is likely to have high binding affinity, resulting in a low free-drug concentration and thus impacting therapeutic efficacy.

CYP2D6 Prediction evaluates whether a chemical compound is likely to act as a substrate or inhibitor of the Cytochrome P450 2D6 enzyme. It helps in early-stage drug discovery by predicting whether a drug candidate is metabolised by CYP2D6 (substrate) or blocks the enzyme (inhibitor), which metabolises over 20% of clinical drugs.

For CYP2D6 Prediction, all ligands except Deoxyandrographolide, Glabranin, and Luteolin show false results, indicating that the compounds are non-inhibitors, which helps avoid safety issues such as Drug-Drug Interactions (DDI). Garcinone C has low solubility and poor absorption, while Br Xanthone A has very low solubility. The blood-brain barrier permeability, favourable for non-CNS drugs, was obtained for all compounds except for Isobavachalcone and Glabranin, and these compounds were removed from the list.

3.5 Hepatotoxicity Analysis

Even though hepatotoxicity is a major safety concern, if the therapeutic benefit of the candidate molecule outweighs the associated risk, *i.e.*, if the patient is at a very critical stage, these molecules can be used as drugs while ensuring all safety measures and antidote availability. Among the predicted hepatotoxic compounds, Quercetin, Kushenol W, Psoralidin, Coumarin A, and Epicatechin, Psoralidin is proven to be highly hepatotoxic. In mouse studies, it was shown to cause hepatotoxicity by impairing fatty acid metabolism, reducing lipid oxidative catabolism, and causing mitochondrial damage[42]. Based on safety analyses conducted on phytocompounds, Kushenol W was also identified as possessing immunotoxic properties and other potential safety concerns[43]. Quercetin has been proven to be non-hepatotoxic in clinical experiments, while it is hepatotoxic in *in vivo* experiments in rats, and the toxicity is classified as Hepatic adenoma. Quercetin is a widely recognised

Table 2. The potential lead molecules with preferable absorption, solubility and BBB levels. All these compounds are non-inhibitors of CYP2D6, indicating the compound helps avoid safety issues such as Drug-Drug Interactions (DDI)

S. No	Ligand	PUBCHEM ID	Libdock score	Solubility level	BBB_Level	CYP2D6 # Prediction	Hepatotoxic # Prediction	Absorption level	PPB # Prediction
1	Curcumin	969516	118.292	3	3	FALSE	FALSE	0	TRUE
2	Quercetin	5280343	112.61	3	4	FALSE	TRUE	1	FALSE
3	Flacourtoside A	21672233	111.814	3	4	FALSE	FALSE	0	FALSE
4	Gingerol	442793	105.092	3	2	FALSE	FALSE	0	TRUE
5	Anacolosine	71503226	100.833	3	2	FALSE	FALSE	0	TRUE
6	Mycophenolic acid	446541	97.8496	3	3	FALSE	FALSE	0	TRUE
7	Andrographolide	5318517	91.975	3	3	FALSE	FALSE	0	TRUE
8	Coumarin A	14585500	91.6535	3	2	FALSE	TRUE	0	FALSE
9	Epicatechin	72276	88.0387	3	4	FALSE	TRUE	0	FALSE
10	Safficinolide	85152699	84.8039	2	2	FALSE	FALSE	0	TRUE

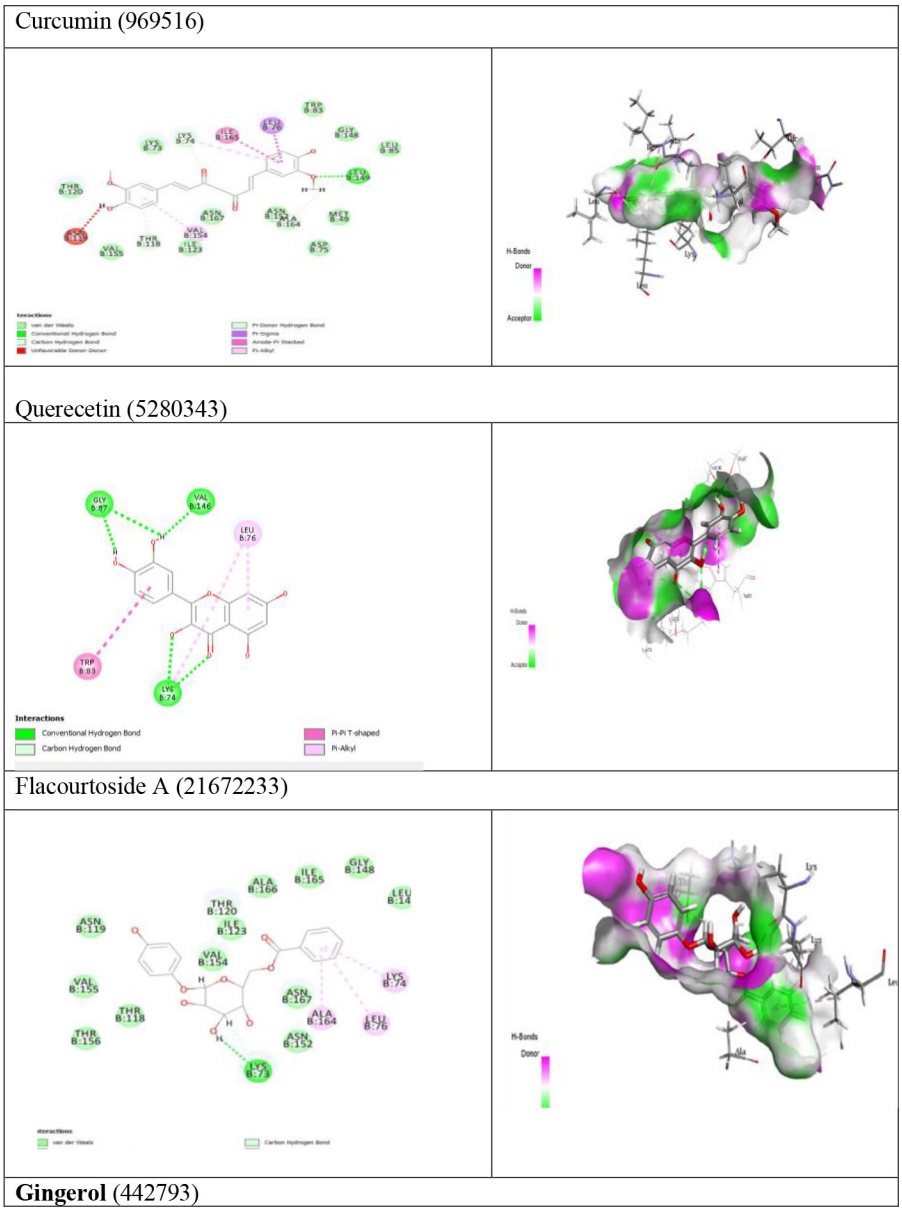
natural flavonoid with potent hepatoprotective, antioxidant, and anti-inflammatory properties, making it a promising agent against drug-induced liver injury, including those caused by acetaminophen (APAP) and ethanol[44].

Coumarin A has been experimentally shown to be edible and safe for human consumption, due to differences in metabolic pathways[45]. Epicatechin is a natural flavonoid found in green tea and cocoa and is generally considered hepatoprotective. It acts as an antioxidant, reducing oxidative stress, inflammation, and liver injury[46]. The ADMET results obtained for 10 ligand molecules after removing Kushenol W and Psoralidin, that has risky hepatotoxic levels, are given in Table 2.

3.6 Potential lead molecules against DENV2 NS2B-NS3 protease

The 2D and 3D interaction of 2FOM against the top 6 druggable molecules, namely Curcumin, Quercetin, Flacourtoside A, Gingerol, Anacolosine and Mycophenolic acid is given in Figure 3.

To compare the suitability of these top potential molecules, docking was done between 2FOM and known drugs such as Ribavirin (PID: 37542), Abacavir (PID: 441300), Mycophenolic acid (PID: 446541), and



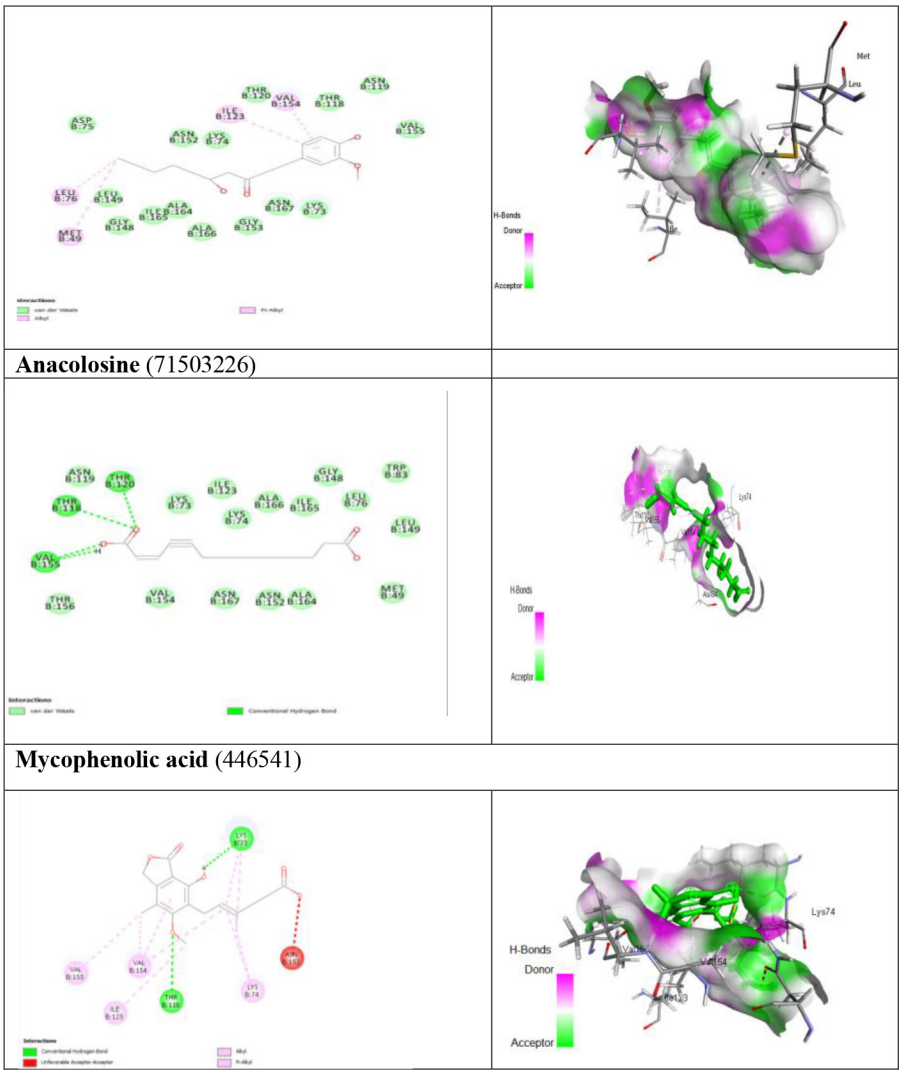


Figure 3. 2D and 3D Interaction of 2FOM with 6 lead molecules. Interaction network between 2FOM and the compounds with preferred docking score and ADMET results. In the 2D figure, H bonds are shown in green and pi-Alkyl in purple. In 3D Donor are shown in purple and Acceptors in green.

Nelfinavir (PID: 64143). These anti-viral drugs obtained docking scores of 104.069, 98.8468, 97.8496, and 82.8802, respectively. Nelfinavir is a protease inhibitor; it inhibits HIV-1, HIV-2 and inhibits maturation and export of herpes simplex virus 1[47,48]. Ribavirin (RBV) is a synthetic guanosine analogue, effective against respiratory syncytial virus, and HCV when combined with pegylated interferon-α[49]. Abacavir is a carbocyclic 2′-deoxyguanosine nucleoside reverse transcriptase inhibitor (brand name Ziagen) and is used in the treatment of HIV infection[50]. Mycophenolic acid is used as an immunosuppressant to prevent organ rejection in kidney, heart, or liver transplant patients. It acts by weakening the immune system to prevent it from attacking the new organ. It is also used to treat autoimmune conditions, such as lupus nephritis. Docking results of known drugs with 2FOM are given in Appendix 2 of Supplementary Data. Appendix 3 shows the results of Lipinski's rule of known drugs, and Appendix 4 shows the ADMET properties of known drugs.

All 10 lead molecules have better docking scores with 2FOM than the available antiviral drug, Nelfinavir. These compounds may be potential anti-dengue virus drugs, while Quercetin, Flacourtoside A, Coumarin A, and Epicatechin need to be further investigated to improve Plasma Protein Binding (PPB), which can be significantly altered by nanocarriers. When introduced

into the bloodstream, nanocarriers interact with plasma proteins, leading to their adsorption onto the carrier surface and the formation of a protein corona[51-54].

4. Discussion

The present study employed a structure-based computational strategy to identify potential natural compounds that inhibit dengue virus NS2B–NS3 protease, a key enzyme essential for viral polyprotein processing and replication. To ensure the biological relevance of the target selected, protein–protein interaction analysis was performed between two viral proteins implicated in virus replication and a host protein. Among the evaluated structures, 2FOM was selected for its stable inhibitor-bound closed conformation representing the active form of the DENV-2 protease. Following target identification, from an initial library of over 5000 natural compounds, 100 compounds were shortlisted for molecular docking against the 2FOM protease structure. Docking analysis identified 27 ligands exhibiting high LibDock scores and favourable binding orientations within the catalytic pocket. These ligands formed multiple non-covalent interactions—including hydrogen bonds, hydrophobic contacts, and van der Waals interactions—with key catalytic residues, suggesting potential inhibitory activity. Drug-likeness and pharmacokinetic profiling have further supported the suitability of the prioritised compounds, demonstrating favourable gastrointestinal absorption and acceptable toxicity predictions. The integration of molecular docking and ADMET evaluation represents an efficient early-stage strategy for antiviral drug discovery[55].

The screened compounds represented diverse chemical classes with established antiviral relevance. Flavonoids, including Quercetin and Epicatechin, are known to interfere with viral replication and enzymatic activity through hydrogen bonding and aromatic stacking interactions[56]. Curcumin, Gingerol, Coumarin A, and Anacolosine are phenolic or non-flavonoid compounds. Curcumin, a traditional medicine from *Curcuma longa*, has antiviral activity against both RNA and DNA viruses[57]. It has antifungal, antibacterial, and anti-inflammatory properties. Mycophenolic acid is another simple phenolic compound, and Flacourtoside A is a phenolic glycoside.

Gingerol, a bioactive phenolic compound derived from *Zingiber officinale*, possesses anti-inflammatory and antioxidant properties and has demonstrated indirect antiviral activity against chikungunya virus[58]. Similarly, Anacolosine ((E)-tridec-2-en-4-ynedioic acid), an acetylenic diacid isolated from *Anacolosa pervilleana*, has exhibited antiviral activity in cell-based assays against chikungunya virus[59]. Mycophenolic acid, a secondary metabolite produced by *Penicillium* species, is a clinically used immunosuppressant and antibiotic marketed as mycophenolate derivatives for transplant therapy[60,61]. In addition to its established pharmacological use, it has demonstrated antiviral activity, including reported inhibitory effects against SARS-CoV-2[62].

Flacourtoside A, derived from *Flacourtia indica*, has been reported to possess anti-inflammatory and antiviral properties, with demonstrated activity in virus-cell–based assays[63,64]. Andrographolide, a terpenoid, also exhibit favourable hydrophobic interactions within the protease binding pocket and has been widely investigated for its antiviral properties[17,65]. Andrographolide is isolated from Andrographis paniculata, and has anti-inflammatory, antiviral, and immune-modulatory effects[66-68]. Safficinolide, a diterpenoid from Salvia officinalis, has shown antiviral activity against vesicular stomatitis virus and herpes simplex virus type 1 in experimental studies[69]. Quercetin, derived from *Carica papaya* leaves, has antiviral properties and is under study as a potential antiviral compound for dengue treatment[70]. While hepatotoxicity may limit direct therapeutic application, it is noteworthy that certain clinically used antivirals, such as abacavir and nelfinavir, also exhibit hepatotoxic effects, emphasising that safety evaluation requires comprehensive experimental assessment.

5. Conclusion

The present study employed an integrated *in silico* strategy to identify potential phytochemical inhibitors targeting the dengue virus NS2B–NS3 protease, a critical enzyme involved in viral polyprotein processing and replication. 100 compounds with antiviral properties were selected from 5000 phytochemicals derived from medicinal plants and natural compounds. After molecular docking, 27 compounds with good docking scores were identified,

and Drug Likeness and ADMET Tests were performed. Among these, 10 compounds were identified that exhibited desirable drug-like properties and promising safety profiles, supporting their potential as viable antiviral candidates. **Curcumin,** Quercetin, **gingerol, flacourtoside A, and** Anacolosine emerged as the five most promising lead compounds based on docking scores and interaction stability. These compounds formed multiple non-covalent interactions, including hydrogen bonds and hydrophobic contacts with key catalytic residues of the NS2B–NS3 protease, suggesting potential competitive inhibition. Similar structure-based studies have demonstrated that phytochemical scaffolds can effectively inhibit NS2B–NS3 protease activity.

The combined use of docking and ADMET profiling demonstrates a robust and efficient strategy for early-phase drug discovery targeting dengue virus replication mechanisms. Overall, these findings highlight the therapeutic potential of structurally diverse plant-derived compounds as inhibitors of dengue virus replication. While the results from *in silico* methods are promising, further validation through molecular dynamics simulations and experimental *in vitro* and *in vivo* studies will be necessary to confirm the stability, inhibitory potential, and therapeutic applicability of the identified lead compounds.

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Author Contribution

Dr. Sheeba K. conceived and designed the study, identified the research problem, planned the methodology, conducted data collection and data processing, performed and supervised the molecular docking studies, carried out ADMET analysis, interpreted the results, revised and edited the manuscript, and served as the corresponding author. Dr. Sherin K. assisted in the literature survey, participated in ADMET analysis, analysed and interpreted the results, prepared the manuscript draft, edited the manuscript, and assisted in data collection and compilation. Dr. Shidhi P. R. contributed to methodology planning, performed molecular docking studies, and assisted in data collection and data processing. All authors have read and agreed to the published version of the manuscript.