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Research Article

In Silico Evaluation of Curcumin Binding to Zika Virus (ZS3) Protein: Insights into Antiviral Potential

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A B S T R A C T

Background: Zika virus (ZIKV) (ZS3) is a growing concern, with no approved antivirals targeting its protease. Curcumin, a natural compound with broad antiviral effects, offers potential as a therapeutic scaffold. This study evaluated curcumin's binding to the ZS3 NS3-protease (NS3-pro) via in silico molecular docking (PDB: 5ZOB, 5YOD), comparing it to Rupintrivir, Pemoline, and Ribavirin.

Methods: Molecular docking was performed using Autodock 4.5 and Discovery Studio to assess binding affinity of curcumin and the comparator ligands to NS3-pro. Key active site interactions and sub-pocket binding were analyzed.

Results: Curcumin showed favorable binding within the NS3-pro active site, interacting with catalytic residues and demonstrating higher predicted affinity than the comparator ligands, with broader sub-pocket contacts.

Conclusion: Curcumin displayed superior docking affinity and interaction stability at the ZS3 NS3-pro active site compared to known antivirals. These findings support curcumin as a promising natural lead for ZS3 antiviral development and future optimization.

Keywords: Viruses, Curcumin, Molecular Docking, antiviral, Rupintrivir, Pemoline, Ribavirin

Introduction

Zika virus (ZIKV), an arbovirus transmitted by arthropods, is classified within the Flavivirus genus, a member of the Flaviviridae family. This family encompasses a range of small, enveloped, single-stranded positive-sense RNA viruses, including significant pathogens affecting both humans and animals, such as yellow fever virus (YFV), dengue virus (DENV), West Nile virus (WNV), St. Louis encephalitis virus (SLEV), Japanese encephalitis virus (JEV), and tick-borne encephalitis virus (TBEV).[1, 2]

Data from the World Health Organization (WHO) indicates that between 2015 and 2017, a ZIKV outbreak originating in Brazil led to an estimated 0.4 to 1.5 million infections across the Americas, Africa, and Europe.[3] The ZIKV genome encodes a polyprotein which is cleaved by host or viral proteases into the structural proteins capsid (C), precursor membrane protein (prM), and envelope protein (E), as well as the non-structural proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. For the initial seven decades following its discovery, ZIKV infection was generally associated only with mild, flu-like symptoms.[4, 5]

However, more recent investigations have revealed the potential pathogenicity of ZIKV infection, particularly concerning developing fetuses and nervous tissue in humans. This can lead to congenital abnormalities such as microcephaly, as well as Guillain-Barré syndrome in adults. ZIKV transmission routes include Aedes mosquitoes, sexual contact, vertical transmission from mother to child, and blood transfusions. Several preclinical compounds exhibiting antiviral activity against ZIKV, along with vaccine candidates, have been identified.[6-10]

Currently, there are no approved antiviral treatments or vaccines available for ZIKV infection; patient care primarily relies on supportive measures. The development of a safe and effective vaccine to prevent ZIKV infection holds the potential to protect over two billion individuals residing in endemic regions. Nevertheless, a WHO project listing indicates that only a limited number of projects remain active in ZIKV vaccine development, with just a couple having progressed to phase II clinical trials. In the pursuit of anti-ZIKV drugs, several molecules have demonstrated inhibitory effects on various stages of the ZIKV life cycle. For instance, Rausch et al. reported that nanchangmycin effectively inhibits ZIKV entry and subsequent infection by disrupting clathrin-mediated endocytosis in cell-based assays.[11-13]

Zika virus (ZIKV), the four serotypes of Dengue virus (DENV1–4), and West Nile virus (WNV) are classified within the Flaviviridae family. The genomic RNA of these viruses encodes a single polyprotein precursor, which undergoes proteolytic processing mediated by both viral and host-derived proteases. Central to this process is the NS2B/NS3 serine protease, which is pivotal for cleaving the polyprotein into structural proteins—integral components of the virion—and nonstructural (NS) proteins that facilitate viral replication and maturation. Furthermore, the NS2B/NS3 protease contributes to immune evasion by targeting and cleaving the stimulator of interferon genes (STING), thereby attenuating the host's innate immune response.[14, 15] Several ZIKV protease inhibitors have been identified, which also display activity towards other flaviviruses such as DENV, WNV, and YFV.[16-20] Most of the protease inhibitors are classified as peptidic or peptidomimetic, presenting high inhibition, but displaying an unfavorable pharmacokinetic profile. Otherwise, the nonpeptidic inhibitors present drug-like properties, but lower binding affinity.[21] In light of these limitations, natural and synthetic compounds could represent new chemical scaffolds capable of inhibiting the ZIKV protease.[18]

Curcumin, a natural polyphenolic compound extracted from Curcuma longa, has garnered considerable interest due to its broad-spectrum antiviral activities. Recent studies have demonstrated that Curcumin exhibits inhibitory effects against various flaviviruses, including Zika virus (ZIKV), by targeting critical viral proteins and disrupting key stages of the viral life cycle, such as entry, replication, and protease function.[22, 23] Molecular docking and in vitro analyses suggest that Curcumin can effectively bind to the NS2B-NS3 protease, a vital enzyme for ZIKV replication, thereby impeding its catalytic activity. Additionally, Curcumin's ability to modulate host cellular pathways involved in viral propagation further enhances its antiviral potential.[22, 23] Its favorable pharmacological profile, including low toxicity and anti-inflammatory properties, supports its candidacy as a promising natural inhibitor in the development of therapeutic strategies against ZIKV infections.

Materials and methods

Protein structure preparation

The crystal structure of the non-structural protein of NS3 with (PDB IDs: 5ZOB and 5YOD) at 1.8 Å resolution was derived from the RCSB (Protein Data Bank). The surface was fully treated by using Discovery Studio and Pymol software. The protein NS3 (PDB IDs: 5ZOB and 5YOD) along with its active sites are shown in Figure 1.

Ligand Preparation

All ligands were provided from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The two and three-dimensional structures of the ligands chosen were shown in Figure 2.

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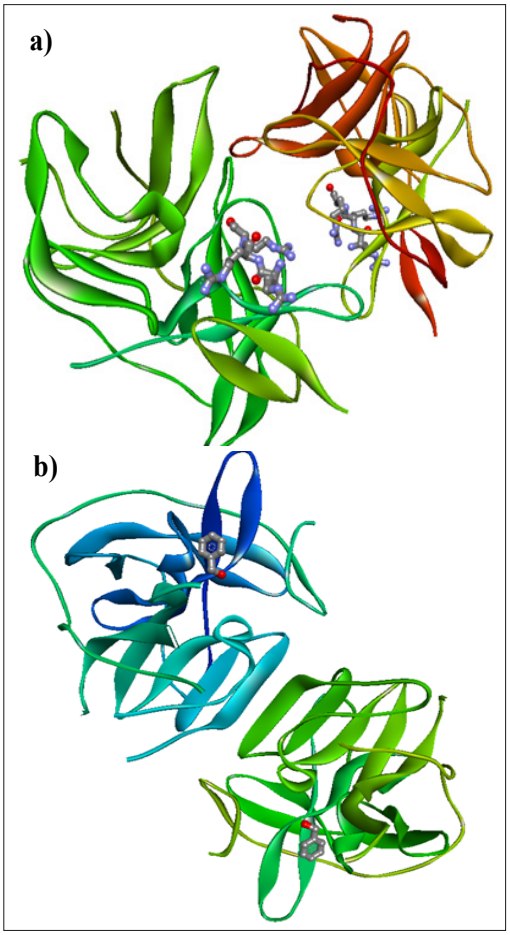

Figure 1.Active sites domains of NS3 protease (PDB IDs: a) 5ZOB and b) 5YOD)

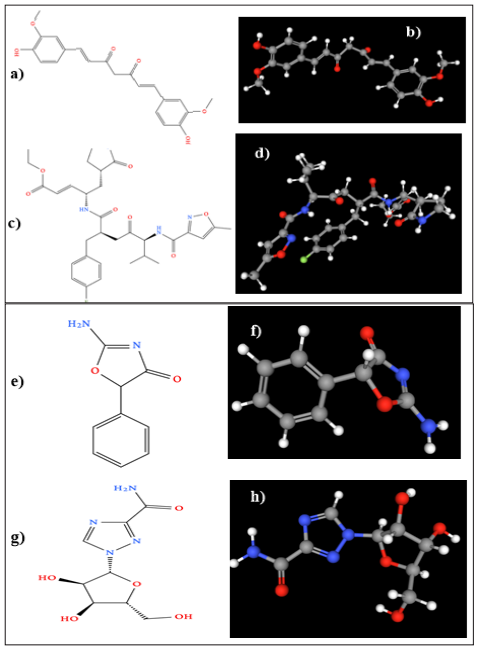

Figure 2.Two and three dimensional structure of four selected ligands: (a, and b) curcumin, (c, and d) Rupintrivir (e and f) Pemoline, and (g, and h) Ribavirin ligands respectively

In silico study and Molecular docking

The Protein Data Bank (PDB) (www.rcsb.org) serves as a resource for obtaining crystal structures of proteins, specifically PDB entries (5ZOB and 5YOD). To facilitate the docking process, the Amber force field was utilized for energy minimization. Molecular docking experiments were conducted using the MOE software. The parameters for the grid box were set at 118, 124, and 120 along the x, y, and z axes, respectively. The binding energy for the docking was assessed through a low RMSD evaluation using the Lamarckian genetic algorithm in conjunction with the Amber 10H force field. Additionally, graphical representations of the results were generated using BIOVIA Discovery Studio Visualizer 2021 (Biovia DSV, 2021). In silico molecular docking studies were performed to investigate the interactions and binding affinity of the ligands with viruses. The docking analysis was executed utilizing AutoDock 4.2 along with MGL Tools.[24] A grid point spacing of 0.375 Å was maintained during both docking procedures to encompass all potential active site residues. The results from the docking were exported to a grid. text file to rank the docked conformations based on binding affinity, as well as conducting clustering and root mean square deviation (RMSD) analyses. The most promising docked conformations of the receptor-ligand complex were preserved as pdb files for further examination of the interactions between the (curcumin, Rupintrivir, Pemoline, and Ribavirin ligands) and the binding pocket residues of the target proteins. The Kar binding affinity was represented by a negative score in units of kcal/mol.

Toxicity of Curcumin ligand

Toxicity Profiling of Ligand to confirm the safety of selected ligands for potential therapeutic application, toxicity assessments were performed using the Pro Tox-II web server (https://tox.charite.de/protox3/?site=compound_input). Toxicity profiles were evaluated for hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity, and only ligands that displayed an inactive status across these parameters were selected. Following these criteria, five natural compounds were chosen for molecular docking analysis.

Ethical Approval

This study did not involve human participants, animal subjects, or the use of biological materials. All analyses were conducted using publicly available structural data (PDB IDs: 5ZOB and 5YOD) and computational tools (AutoDock 4.5 and Discovery Studio). Therefore, ethical approval was not required.

Results and discussion

Molecular docking of Zika virus with curcumin ligand

The molecular docking analysis revealed that curcumin exhibits moderate binding affinities towards the NS2B-

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NS3 protease targets of the Zika virus (PDB IDs: 5ZOB and 5YOD), suggesting its potential as an antiviral agent. Several bonding interactions are shown as 3D and 2D representations in figures 3,4,5 and 6.

The stronger binding affinity observed with 5YOD (-6.3 kcal/mol) compared to 5ZOB (-4.9 kcal/mol) may be attributed to differences in conformational flexibility and the structural arrangement of the active sites in these two protease forms. The in silico analysis explored non-covalent interactions between flavonoids and amino acids of protein, including pi-alkyl, alkyl, carbon-hydrogen, and hydrogen bonds.

Curcumin formed two key hydrogen bonds with residues ARG D24 and GLU D17 in the 5ZOB complex, which are critical for stabilizing ligand-protein interactions. Hydrogen bonding is known to play a vital role in enhancing binding specificity and affinity within viral proteases.[25] In contrast, curcumin's interaction with 5YOD involved a single carbon-hydrogen bond with GLN D74, yet resulted in a better binding score. This indicates that hydrophobic interactions and optimal ligand orientation within the binding pocket significantly contribute to the overall binding affinity, consistent with previous studies emphasizing the importance of non-covalent interactions in protease inhibition.[26]

Curcumin, a polyphenolic compound derived from Curcuma longa, has been widely reported for its broad-spectrum antiviral properties, including activity against flaviviruses such as dengue and Zika viruses.[22, 27] Its ability to interfere with viral replication processes, particularly through inhibition of viral enzymes like proteases, has been documented in silico and in vitro.[28] The docking results in this study further support curcumin's potential role as an NS2B-NS3 protease inhibitor.

However, while curcumin demonstrates promising interaction profiles, its moderate binding energies suggest that it may serve better as a lead compound rather than a direct therapeutic agent. Structural modifications, such as enhancing hydrophobic contacts or introducing functional groups to strengthen hydrogen bonding, could improve its binding affinity and specificity, as proposed in recent medicinal chemistry studies.[29] Moreover, molecular docking offers a static perspective of ligand-protein interactions. To fully validate these findings, molecular dynamics (MD) simulations are recommended to assess the dynamic stability of the curcumin-protease complexes over time. Previous research has shown that curcumin maintains stable interactions within viral enzyme active sites during MD simulations, reinforcing its potential as a viable antiviral scaffold.[30] Both 2D and 3D interaction diagrams confirmed the proper accommodation of curcumin within the active sites of both protease targets, aligning with critical residues involved in substrate recognition and catalysis.

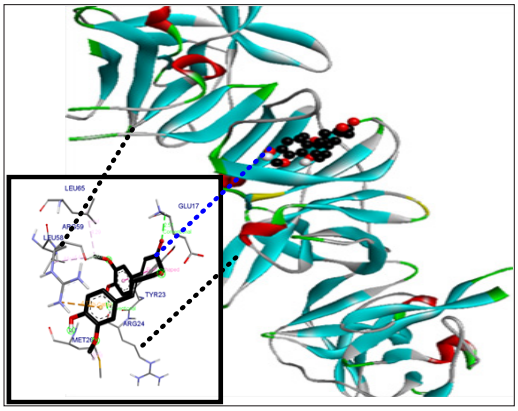

Figure 3.In silico molecular docking analysis of Zika virus (PDB IDs: 5ZOB protein: 3D representation of the interaction between curcumin and Zika virus (PDB IDs: 5ZOB

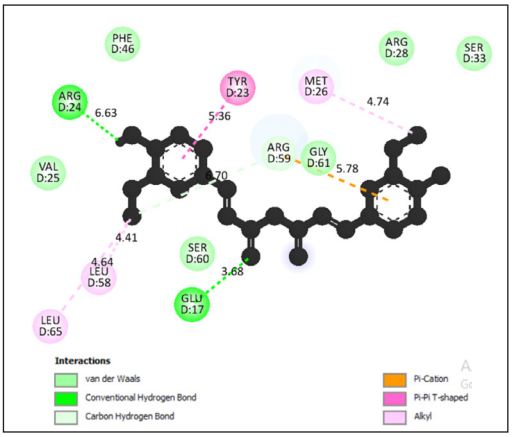

Figure. 4. In silico molecular docking analysis of Zika virus (PDB IDs: 5ZOB protein: 2D representation of the interaction between curcumin and Zika virus (PDB IDs: 5ZOB

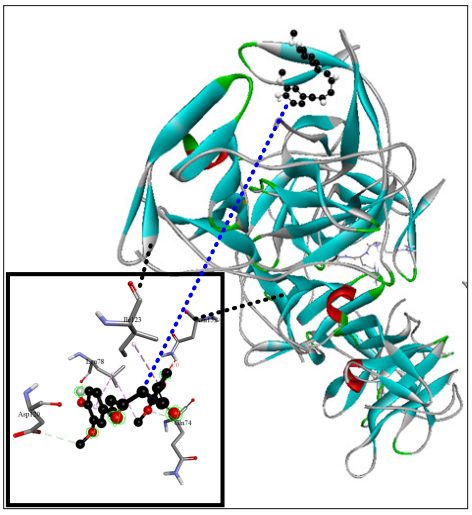

Figure 5.In silico molecular docking analysis of Zika virus (PDB IDs: 5YOD protein: 3D representation of the interaction between curcumin and Zika virus (PDB IDs: 5YOD

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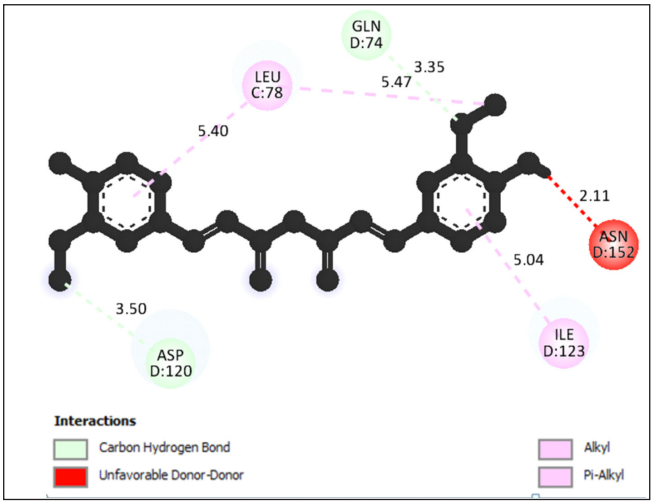

Figure 6.In silico molecular docking analysis of Zika virus (PDB IDs: 5YOD protein: 2D representation of the interaction between curcumin and Zika virus (PDB IDs: 5YOD

Curcumin Versus Conventional Inhibitors: Docking Study on Zika NS3 Protease: (5ZOB and 5YOD)

Molecular docking was conducted to evaluate the binding affinity and interaction profile of curcumin against two Zika virus NS2B-NS3 protease structures (PDB IDs: 5ZOB and 5YOD) using AutoDock and visualized via Discovery Studio.

The molecular docking analysis was conducted to evaluate the binding affinities and interaction profiles of Curcumin in comparison with known antiviral agents (Rupintrivir, Pemoline, and Ribavirin) against the NS2B-NS3 protease of Zika virus (PDB IDs: 5ZOB and 5YOD). The NS2B-NS3 protease is a well-established target due to its essential role in viral replication through the cleavage of viral polyproteins, making it a critical focus for antiviral drug discovery efforts.[31] Curcumin exhibited the most favorable binding affinity towards the 5ZOB protease, with a docking score of -6.3 kcal/mol, outperforming standard antiviral agents such as Ribavirin (-5.9 kcal/mol), Rupintrivir (-5.7 kcal/mol), and Pemoline (-5.4 kcal/mol). The interaction analysis revealed that Curcumin engages in multiple stabilizing interactions, including hydrogen bonds, pi-carbon, and alkyl interactions, which enhance its binding stability within the active site. These types of interactions are known to contribute significantly to inhibitory potency by ensuring strong and specific binding to target residues.[32]

Against the second target, 5YOD, Curcumin maintained a moderate binding affinity (-4.9 kcal/mol), supported primarily by hydrophobic interactions, suggesting its flexible binding capability across different conformations of the protease. Among the reference ligands, none demonstrated superior binding to Curcumin, highlighting the potential of this natural compound as a lead inhibitor.

Curcumin has been widely reported for its broad-spectrum antiviral activities, including inhibition against flaviviruses such as dengue and Zika viruses.[23] Its antiviral mechanism is often attributed to its ability to interfere with viral entry, replication, and protease activity. The current docking results align with these reports, further suggesting that Curcumin could serve as a promising inhibitor targeting the NS2B-NS3 protease of Zika virus. However, while molecular docking provides valuable insights into potential binding modes and affinities, it represents a static snapshot of ligand-protein interactions. Therefore, further validation through molecular dynamics (MD) simulations to assess complex stability over time, as well as binding free energy calculations (e.g., MM-PBSA or MM-GBSA), is necessary to confirm these findings under dynamic conditions.[33] Additionally, experimental studies, including enzymatic inhibition assays and antiviral activity evaluations in cell cultures, would be essential to substantiate Curcumin's inhibitory potential observed in silico. A summary of interactions is shown in figure 7. Furthermore, the binding affinities and key interactions is presented in Table 1.

Toxicity profiling of curcumin ligand

"Toxicity profiling of curcumin was conducted using the ProTox-II web server. The compound exhibited an LD_{50} of approximately 2000 mg/kg, placing it in toxicity class 5. Predictions indicated inactive profiles for hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity, suggesting a favorable safety profile. However, a potential for immunotoxicity was noted, warranting further investigation. Results are shown in Table 2.

Table 1.Type of ligands, Binding Energies, and Key Interactions of Curcumin and other ligands with NS2B-NS3 Protease Targets

Ligand	Target (PDB ID)	Binding energy: Kcal/mol	Key interactions
curcumin	5ZOB	-6.3	H-bond, Pi-carbon, Alkly
curcumin	5YOD	-4.9	Pi-carbon; Alkyl bond
Rupintrivir	5ZOB	-5.7	H-bond, Pi-carbon, Alkly
Pemoline	5ZOB	-5.4	H-bond, Pi-carbon, Alkly
Ribavirin	5ZOB	-5.9	H-bond, Alkly

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Table 2.Toxicity profiling of curcumin ligand

Toxicity Parameter	Prediction	Details
LD_{50} (oral, rat)	~2000 mg/kg	Indicates moderate acute toxicity.
Toxicity Class	Class 5	May be harmful if swallowed.
Hepatotoxicity	Inactive	No predicted liver toxicity.
Carcinogenicity	Inactive	Not predicted to be carcinogenic.
Mutagenicity	Inactive	Not prwedicted to cause genetic mutations.
Cytotoxicity	Inactive	Not predicted to be toxic to cells.

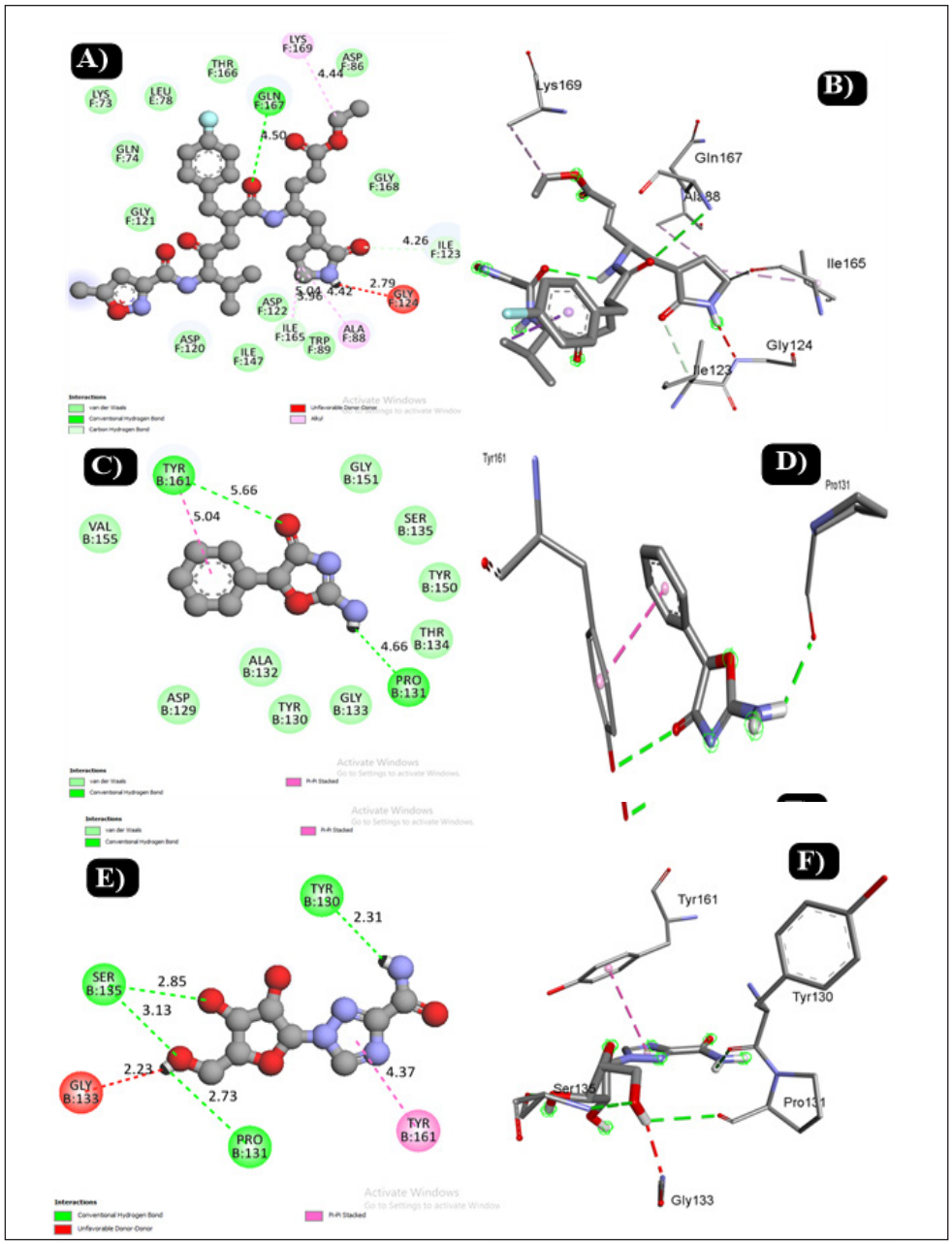

Figure 7. Molecular docking and ligand interaction of the (pdb: 5zob) (protein target) with (ligands): (A), (C), and (E). The 2D diagram of receptor-ligand interaction complexed with Rupintrivir, Pemoline, and Ribavirin ligands, respectively (B), (D), and (F). The binding model of receptor-ligand interaction complexes with Rupintrivir Pemoline and Ribavirin ligands, respectively

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Conclusion

In conclusion, this study highlights curcumin as a promising natural compound for targeting the Zika virus NS2B-NS3 protease. Further optimization and experimental validation are necessary to advance curcumin or its derivatives as potential antiviral therapeutics. The superior binding affinity and favorable interaction profile of Curcumin compared to conventional antivirals underscore its potential as a natural therapeutic candidate against Zika virus protease. Future work should focus on optimizing Curcumin derivatives to enhance bioavailability and target specificity.

Authors Contribution: UARH, TMS, AJB: Conceptualization, Methodology, Supervision, Writing – Review & Editing, Data Curation, Software (Docking Simulations), Visualization. RBQA: Software Support, Docking Validation, Graphical Representation. RA, MNS: Data Interpretation, Reference Management, Figures Preparation. AAS. Jasim: Project Administration, Final Manuscript Revision, Corresponding Author

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

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