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STRUCTURAL INSIGHTS INTO FRUTALIN BINDING TO ZIKA VIRUS NS1 AND NS5 PROTEINS REVEAL DISTINCT BINDING PROFILES

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Abstract

Frutalin (FTL), a plant lectin with recognized biotechnological potential, has demonstrated antiviral activity against Zika virus (ZIKV), although the molecular basis underlying its interaction with viral proteins remains poorly understood. This study investigated the predicted interactions between FTL and the ZIKV non-structural proteins NS1 and NS5 using molecular docking simulations to compare their binding profiles and generate structural hypotheses regarding their potential interactions. Docking analyses predicted favorable interactions with both proteins, although distinct interaction patterns were observed. The NS1–FTL complex exhibited lower predicted docking scores, a more consistent docking pose distribution, and predicted intermolecular contacts involving four amino acid residues. In contrast, FTL binding to NS5 was distributed across two alternative regions outside the catalytic site, indicating a distinct predicted interaction profile. Overall, the findings suggest that NS1 may represent a promising candidate for future experimental investigation among the viral proteins evaluated. These results provide preliminary structural insights into the potential interactions between FTL and ZIKV proteins and highlight the value of molecular docking as an exploratory

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tool for generating hypotheses to guide future biochemical, biophysical, and cell-based validation studies.

Keywords: Frutalin; Molecular docking; Zika virus; Non-structural proteins; Antiviral drug discovery.

1. Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus of major public health concern due to its association with congenital malformations and neurological disorders, including microcephaly and Guillain–Barré syndrome. Although significant advances have been achieved in understanding ZIKV biology, no specific antiviral therapy has yet been approved for clinical use. Consequently, the identification of viral molecular targets and the development of compounds capable of interfering with essential steps of viral replication remain priorities in antiviral drug discovery (Wang et al., 2018).

Among the viral proteins involved in the replication cycle, the non-structural proteins NS1 and NS5 have emerged as promising antiviral targets because of their essential roles in viral replication and pathogenesis. Understanding the molecular interactions between antiviral compounds and these proteins may contribute to the identification of novel therapeutic strategies against ZIKV.

In this context, the present study performed an exploratory molecular docking analysis to compare the predicted interactions of frutalin (FTL) with the ZIKV non-structural proteins NS1 and NS5. By evaluating predicted docking scores, interaction sites, and docking pose distributions, this work generates structural hypotheses regarding potential FTL–protein interactions. These findings provide a computational framework to guide future biochemical and functional studies investigating the antiviral potential of frutalin against ZIKV.

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2. Literature Review

Among the viral proteins involved in the replication cycle, the non-structural proteins NS1 and NS5 play essential and complementary biological roles (Figure 1). NS1 participates in viral replication, immune evasion, and host–pathogen interactions, whereas NS5 functions as the viral methyltransferase and RNA-dependent RNA polymerase responsible for genome replication. Owing to their structural conservation and indispensable biological functions, both proteins have emerged as attractive targets for the rational design of antiviral agents against ZIKV and other medically relevant flaviviruses (Weaver et al., 2016).

Among these targets, NS1 is particularly attractive because it is present in intracellular replication complexes and is also secreted as a glycosylated hexamer, contributing to immune evasion, endothelial dysfunction, and viral pathogenesis (Zeng et al., 2023). In contrast, NS5 is the largest and most conserved flaviviral protein, integrating methyltransferase and RNA-dependent RNA polymerase activities that are essential for viral RNA synthesis (Goh et al., 2024). Their distinct structural and functional characteristics make these proteins complementary targets for exploratory computational studies aimed at identifying potential antiviral interactions (Raza et al., 2020; Ahmad et al., 2020).

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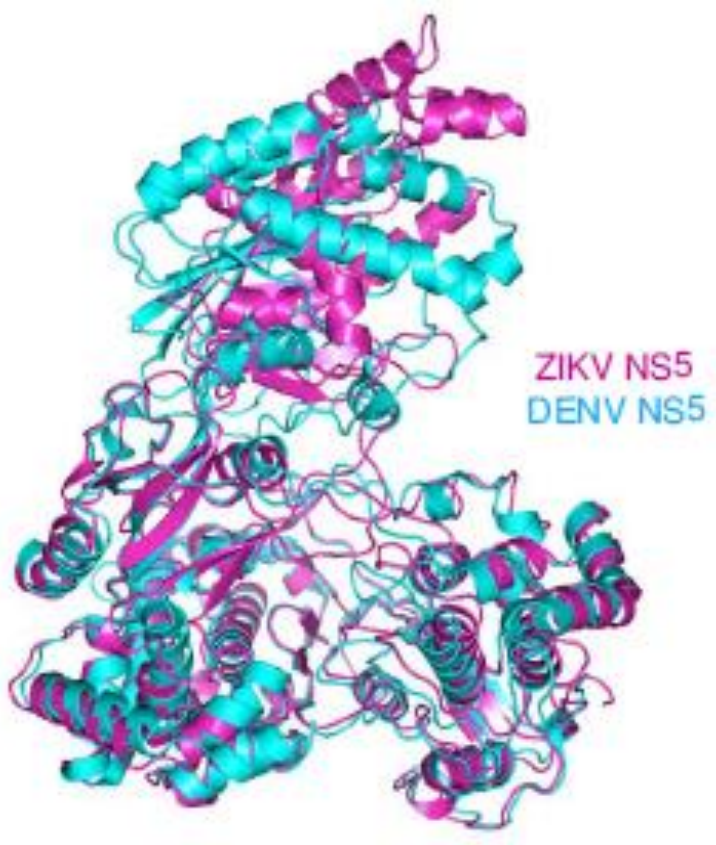
Figure 1: Overlapping of the ZIKV NS5 and DENV NS5 structures (PDB ID: 4VOQ) showing structural similarities.



Source: Zhao et al. (2016).

Plant lectins have attracted increasing attention as bioactive molecules with broad biotechnological applications, particularly because many exhibit antiviral activity through glycan recognition, interference with viral attachment and entry, and modulation of host–pathogen interactions (Gupta et al., 2024; Souza et al., 2022). These mechanisms have been described for several enveloped viruses, although evidence supporting direct interactions between lectins and intracellular viral non-structural proteins remains limited.

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Frutalin (FTL), an α-D-galactose-binding lectin isolated from *Artocarpus incisa*, has demonstrated promising biological properties, including antiviral activity against ZIKV (Vieira-Neto et al., 2019). However, despite these experimental observations, the molecular basis underlying its antiviral activity remains poorly understood, particularly regarding its potential interactions with viral non-structural proteins. This knowledge gap justifies the application of structure-based computational approaches to investigate whether NS1 and NS5 may represent potential molecular targets of frutalin and to generate hypotheses for future experimental validation.

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3. Methodology / Materials and Methods

3.1 Structural Models

The three-dimensional structures of frutalin (FTL) and the Zika virus (ZIKV) non-structural proteins NS1 and NS5 were obtained from the Protein Data Bank (PDB), which provides experimentally resolved biological macromolecular structures. The crystallographic models selected for this study corresponded to frutalin (PDB ID: 4WOG), NS1 (PDB ID: 5GS6), and NS5 (PDB ID: 5TFR). These structures were chosen because of their experimental resolution and suitability for molecular docking analyses.

The receptor and ligand structures were imported directly into the docking platform using their respective PDB accession codes. No structural modifications or mutagenesis were introduced prior to docking, and the experimentally resolved conformations available in the PDB were maintained throughout the computational analysis.

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3.2 Molecular Docking

Molecular docking simulations were performed using the SwissDock web platform, an automated molecular docking server based on the AutoDock Vina scoring function, which predicts favorable binding modes by estimating the free energy of interaction (ΔG) between molecular partners (Grosdidier et al., 2011; Trott & Olson, 2010).

Frutalin was independently docked against the ZIKV NS1 and NS5 proteins in separate docking experiments to identify potential interaction sites and compare their predicted binding profiles. SwissDock automatically generated multiple docking poses and grouped them into clusters according to their spatial similarity and predicted binding energies. For each receptor, the highest-ranked clusters, corresponding to the most energetically favorable docking solutions, were selected for subsequent structural analysis.

The docking results were expressed as predicted binding free energies (ΔG, kcal/mol), where lower energy values indicate more favorable predicted molecular interactions. Because docking calculations provide computational predictions rather than experimental binding affinities, the obtained scores were interpreted comparatively to identify potential interaction patterns between frutalin and the two viral proteins.

3.3 Structural Analysis

The predicted docking complexes were analyzed using PyMOL version 1.4.7 (DeLano, 2002). The best-ranked docking poses were visually inspected to

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characterize the spatial organization of the complexes, identify the predicted binding interfaces, and examine the amino acid residues involved in intermolecular interactions.

Comparative analyses focused on the predicted binding sites, docking pose convergence, residue-level contacts, steric compatibility, and the relative distribution of docking solutions obtained for each viral protein. The structural organization of the NS1–FTL and NS5–FTL complexes was subsequently compared to investigate differences in their predicted interaction profiles. Since molecular docking generates static structural predictions, the results were interpreted as exploratory computational hypotheses requiring further experimental validation.

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4. Results

4.1. Molecular docking predicts distinct interaction patterns between FTL and ZIKV proteins

Protein–protein docking identified favorable predicted interactions between FTL and both ZIKV non-structural proteins, although their binding profiles differed markedly. Among the 50,000 docking solutions generated for each complex, the ten highest-ranked conformations consistently indicated predicted molecular interactions for both NS1 and NS5. However, FTL exhibited a more consistent docking pose distribution toward NS1, whereas docking against NS5 resulted in two alternative interaction sites, suggesting a broader distribution of predicted docking poses (Figure 2).

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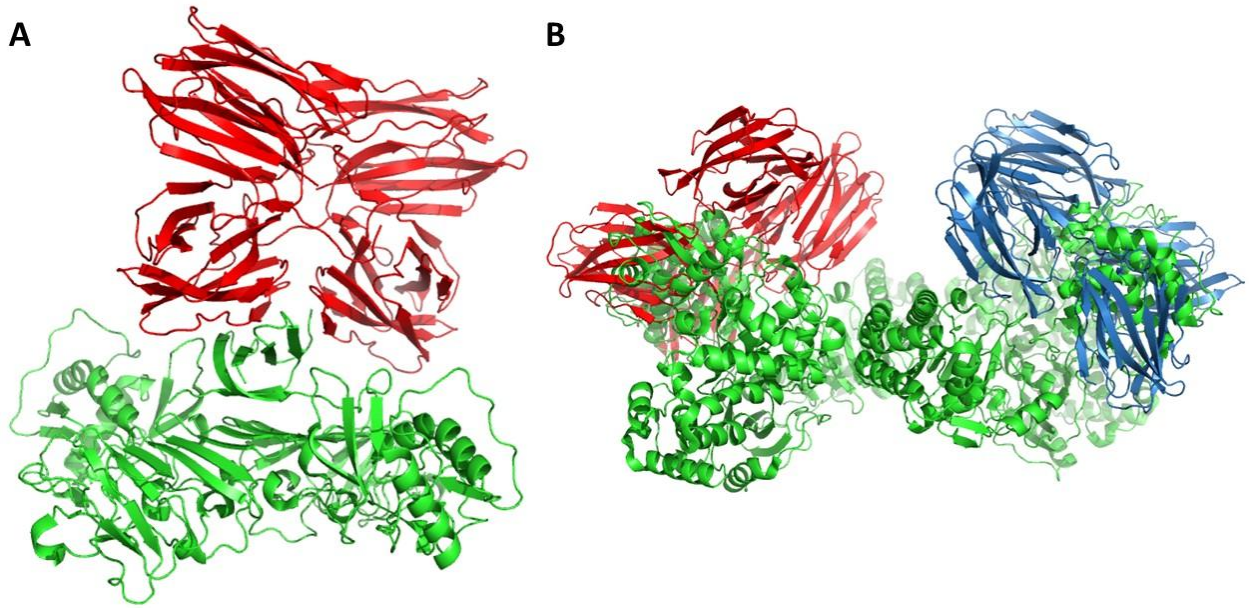
Figure 2: Predicted docking poses of FTL (red) with ZIKV NS1 (green), showing a more consistent docking pose distribution (A). Predicted docking poses of FTL (red and blue) with ZIKV NS5 (green), illustrating two alternative predicted interaction regions.



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4.2. NS1 presents lower predicted docking scores than NS5

Docking score analysis indicated that FTL interacted favorably with both viral proteins. Nevertheless, the NS1–FTL complex consistently displayed lower total interaction energies than the NS5–FTL complex, indicating more favorable predicted docking scores (Table 1). The most stable NS1 complex reached a predicted docking score of −6.51 kcal/mol, whereas the corresponding NS5 complex presented a predicted docking score of −5.24 kcal/mol.

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Table 1. Binding energies between ZIKV NS5 and ZIKV NS1 against FTL.

Cluster of FTL	E_{total} (Kcal/mol)	
	ZIKV NS5	ZIKV NS1
01	-5.24	- 6.51
02	-5.11	- 6.43
03	-5.07	- 6.26
04	-4.93	- 5.98
05	-4.90	- 5.85
06	-4.86	- 5.77
07	-4.81	- 5.62
08	-4.73	- 5.54
09	-4.60	- 5.48
10	-4.39	- 5.39

Source: author.

4.3. Residue-level interaction analysis

Detailed structural inspection of the highest-ranked docking conformations revealed distinct predicted interaction profiles for each protein. The NS1–FTL complex presented predicted intermolecular contacts involving Val6, Cys15, Thr13, and Ser9, suggesting the formation of a favorable predicted interaction interface (Figure 3). In addition, Gly25 of FTL, a residue previously associated with lectin activity, participated in the predicted interface.

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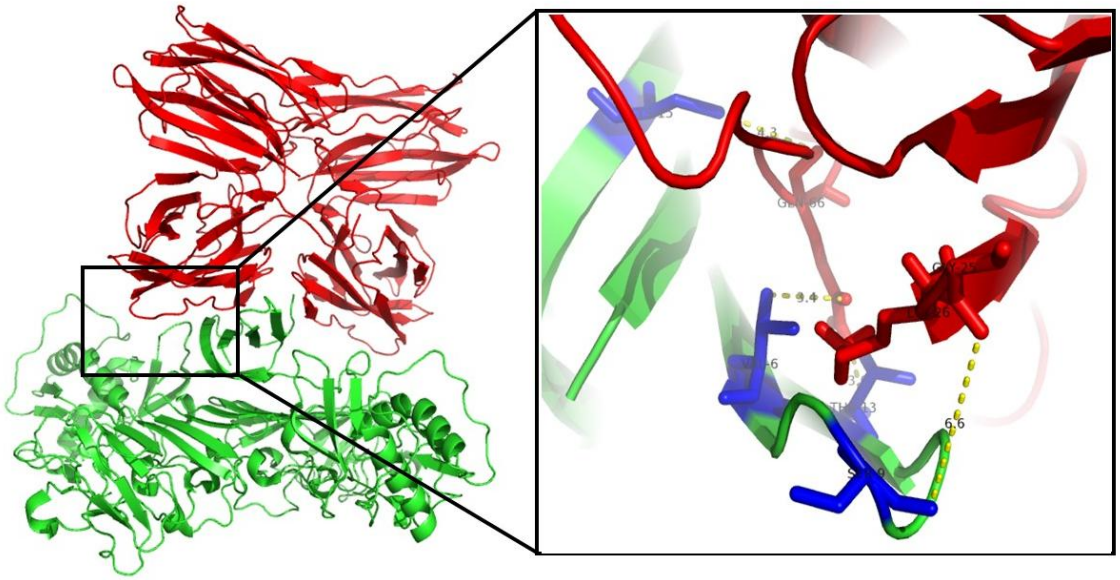
Figure 3: Predicted intermolecular contacts (3.0–6.6 Å) between FTL and ZIKV NS1 involving Val6, Cys15, Thr13, and Ser9.



Source: author.

Conversely, docking against NS5 revealed predicted contacts distributed across two alternative binding regions. Although Gly25 also participated in the predicted interaction with NS5, docking poses were more broadly distributed than those observed for NS1 (Figure 4).

Figure 4: Predicted interaction interface between FTL (red) and ZIKV NS5 (green), illustrating the distribution of predicted intermolecular contacts across alternative binding regions. Gly25 of FTL is highlighted because of its previously reported role in lectin activity.

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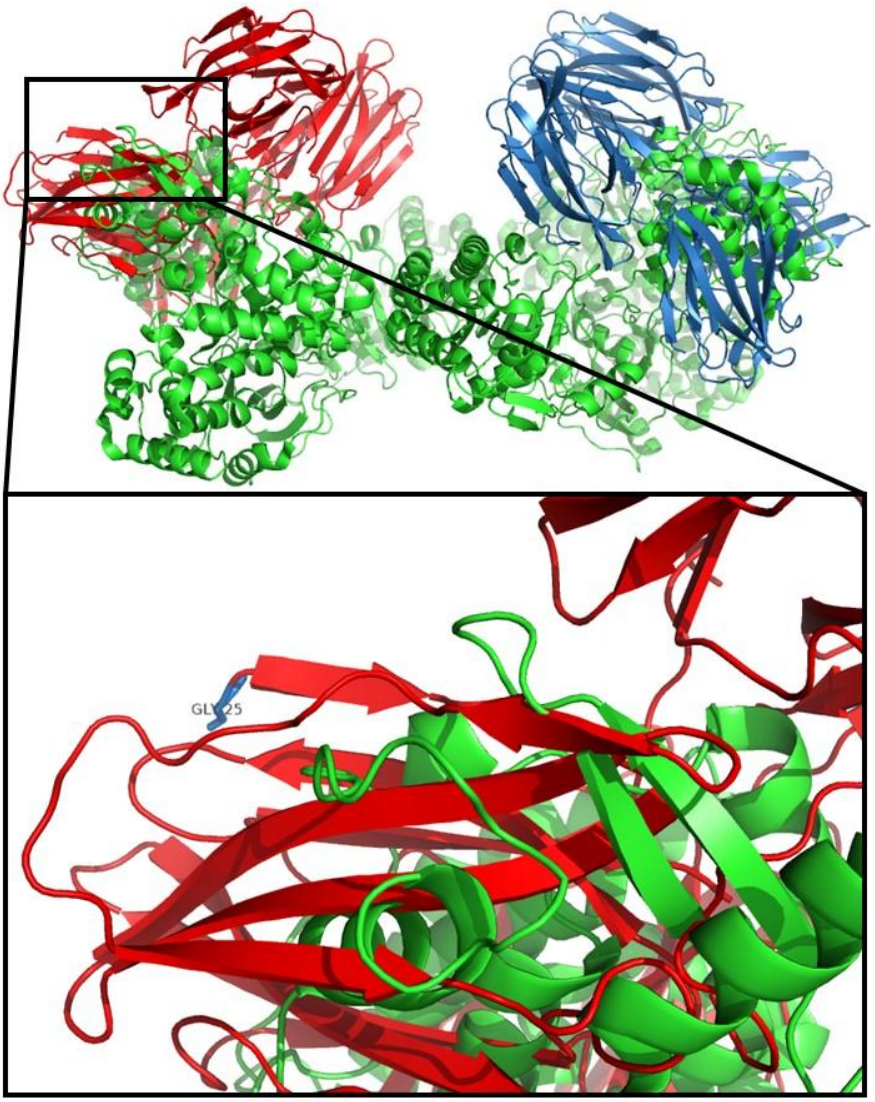

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4.4. Predicted localization of the NS5 interaction site

Mapping the predicted docking complexes onto the three-dimensional structure of NS5 indicated that the predicted FTL interaction occurred outside the catalytic RNA polymerase region (Figure 5).

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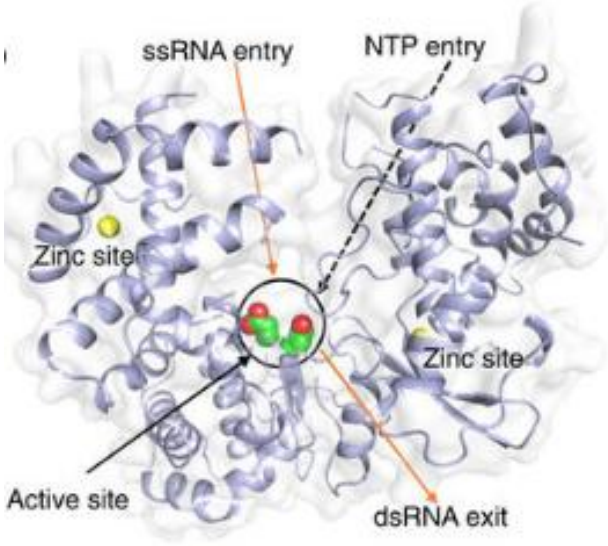
Figure 5: Surface representation of ZIKV NS5 showing the predicted interaction region of FTL relative to the catalytic site.



Source: Godoy et al. (2016).

5. Discussion

A reproducible distribution of high-ranking docking poses has been considered an important indicator of confidence in predicted interaction interfaces in protein–protein docking studies. In the present study, the convergence of docking poses toward a single region of NS1 contrasted with the broader distribution observed for NS5, suggesting distinct predicted interaction profiles. Similar observations have been reported for protein–protein docking studies involving flaviviral proteins, in which docking pose convergence has been associated with greater confidence in predicted interaction interfaces (Vakser, 2014).

Recent advances in structure-based antiviral discovery have highlighted molecular docking as an initial strategy for identifying putative interaction interfaces and prioritizing viral targets for subsequent experimental validation (Yang et al., 2022). Although docking alone cannot establish biological binding or antiviral efficacy,

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comparative analyses of docking pose convergence and predicted interaction profiles have been widely used to generate mechanistic hypotheses and guide future biochemical investigations of flaviviral proteins (Al-Nema et al., 2026; Van Den Elsen et al., 2023).

The lower predicted docking scores observed for the NS1–FTL complex suggest that NS1 may represent a promising candidate for future experimental investigation. Nevertheless, docking scores should be interpreted only within the context of the applied scoring function and do not directly measure binding affinity or biological activity. Previous protein–protein docking studies have similarly shown that favorable docking scores and pose convergence may reflect greater structural complementarity between interacting molecules (Vakser, 2014).

Because frutalin is an α-D-galactose-binding lectin, its antiviral activity has been primarily attributed to the recognition of carbohydrate-containing structures and modulation of virus–host interactions (Gupta et al., 2024; Souza et al., 2022). Whether lectins such as frutalin can directly interact with intracellular viral non-structural proteins remains largely unexplored. Therefore, the present findings should be interpreted as preliminary structural hypotheses that expand the range of potential antiviral mechanisms to be experimentally investigated rather than demonstrating a definitive antiviral mechanism.

NS1 and NS5 were selected because they represent two functionally distinct and highly conserved viral proteins that play indispensable roles in ZIKV replication and pathogenesis, making them attractive candidates for exploratory target prioritization studies. From a target prioritization perspective, NS1 participates in viral replication while also acting as a secreted glycoprotein involved in immune evasion and endothelial dysfunction (Perera et al., 2023), whereas NS5 is an intracellular multifunctional enzyme essential for viral RNA synthesis (Goh et al., 2024). Evaluating both proteins allowed the comparison of predicted interactions involving distinct biological contexts within the viral life cycle.

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The localization of the predicted NS5 interaction outside the catalytic region suggests that direct inhibition of the RNA polymerase active site may be less likely than alternative mechanisms involving modulation of molecular recognition or protein dynamics. In contrast, the lower predicted docking scores and more consistent docking pose distribution observed for NS1 suggest that this protein may represent the most promising candidate for future experimental investigation among the viral proteins evaluated.

The present study is based exclusively on molecular docking predictions obtained from static crystallographic structures. Consequently, important biological factors such as protein flexibility, glycosylation, oligomerization, solvent effects, and intracellular accessibility were not explicitly modeled. Accordingly, the proposed interactions should be interpreted as hypothesis-generating computational predictions that require validation through complementary structural, biochemical, biophysical, and cell-based studies before any conclusions regarding molecular recognition or antiviral mechanism can be established.

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6. Conclusion

This in silico study compared the predicted interactions of frutalin with the Zika virus non-structural proteins NS1 and NS5 using molecular docking. The results indicated more favorable predicted docking scores and a more consistent docking pose distribution for NS1 than for NS5, suggesting that NS1 may represent a promising candidate for future experimental investigation. Although frutalin was also predicted to interact with NS5, the docking poses were distributed across alternative binding regions outside the catalytic site, indicating a distinct predicted interaction profile. These findings provide preliminary structural insights into the potential interactions between frutalin and ZIKV proteins and should be interpreted as computational hypotheses requiring experimental validation. Overall, this study provides a

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structural basis for future biochemical, biophysical, and cell-based studies to validate these predicted interactions and further investigate the antiviral potential of frutalin against ZIKV.

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