Evaluation of Potential Inhibitors of Zika Virus Envelope Protein Through Molecular Docking and Molecular Dynamics Simulation

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Introduction

Zika virus (ZIKV) infection remains a global health threat with no approved antivirals or vaccines to date, creating an urgent need for therapeutics targeting ZIKV. The viral envelope (E) protein is critical for host cell entry and represents a validated target for antiviral intervention. We aimed to identify natural flavonoid compounds capable of inhibiting the ZIKV E protein using a dual-phase in silico screening strategy.

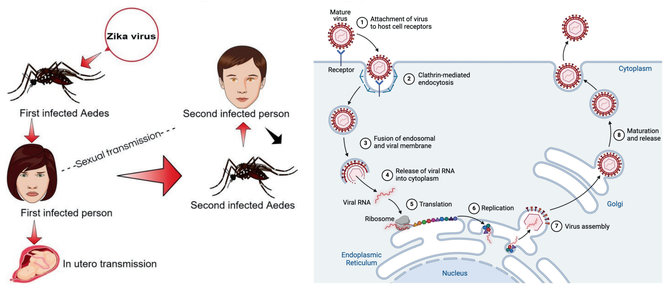


Figure 1: Zika virus transmission cycle and infection process in humans. ***Image created by BioRender.***

Methodology

First, nine natural flavonoids were selected based on their antiviral activity and structural diversity. These compounds were then optimized using DFT calculations to obtain their electronic descriptors. Drug-likeness and ADMET profiles were evaluated, followed by molecular docking with the ZIKV E protein, 100 ns molecular dynamics simulations, and pharmacophore mapping.

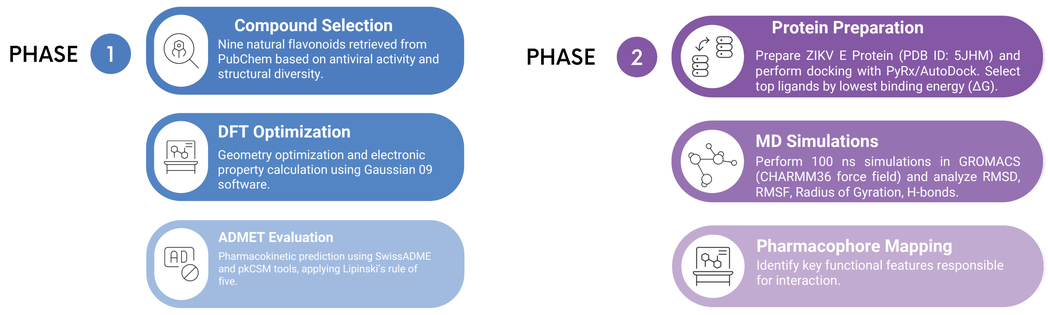
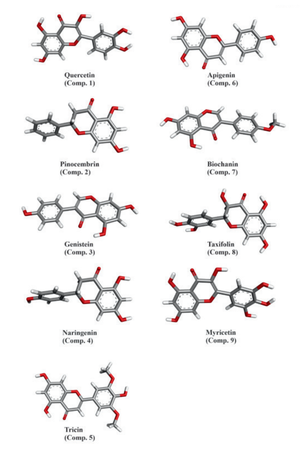


Figure 2: Overview of the Drug Discovery Methodology.

Results



PubChem CID	Ligand Name	Molecular weight	Hydrogen bond acceptor	Hydrogen bond donor	Consensus Log $P_{o/w}$	QED	Lipinski rule	
							Result	violation
5280343	Quercetin	302.34	07	05	1.23	0.43	Yes	00
68071	Pinocembrin	256.25	04	03	2.26	0.82	Yes	00
5280961	Genistein	270.24	05	03	2.04	0.63	Yes	00
439246	Naringenin	272.25	05	03	1.84	0.74	Yes	00
5281702	Tricin	330.29	07	03	2.15	0.68	Yes	00
5280443	Apigenin	270.24	05	03	2.98	0.63	Yes	00
5280373	Biochanin	284.26	05	03	2.44	0.76	Yes	00
439533	Taxifolin	304.25	07	05	0.51	0.50	Yes	00
5281672	Myricetin	318.24	08	06	0.79	0.37	Yes	01
37542	Ribavirin	244.08	09	05	−1.66	0.44	Yes	00

Figure 3. Chemical structures (left) and pharmacokinetic profiles (right) of selected flavonoid compounds based on Lipinski's Rule. Drug-likeness was evaluated through molecular weight, hydrogen bond donors/acceptors, Log P, and rule compliance.

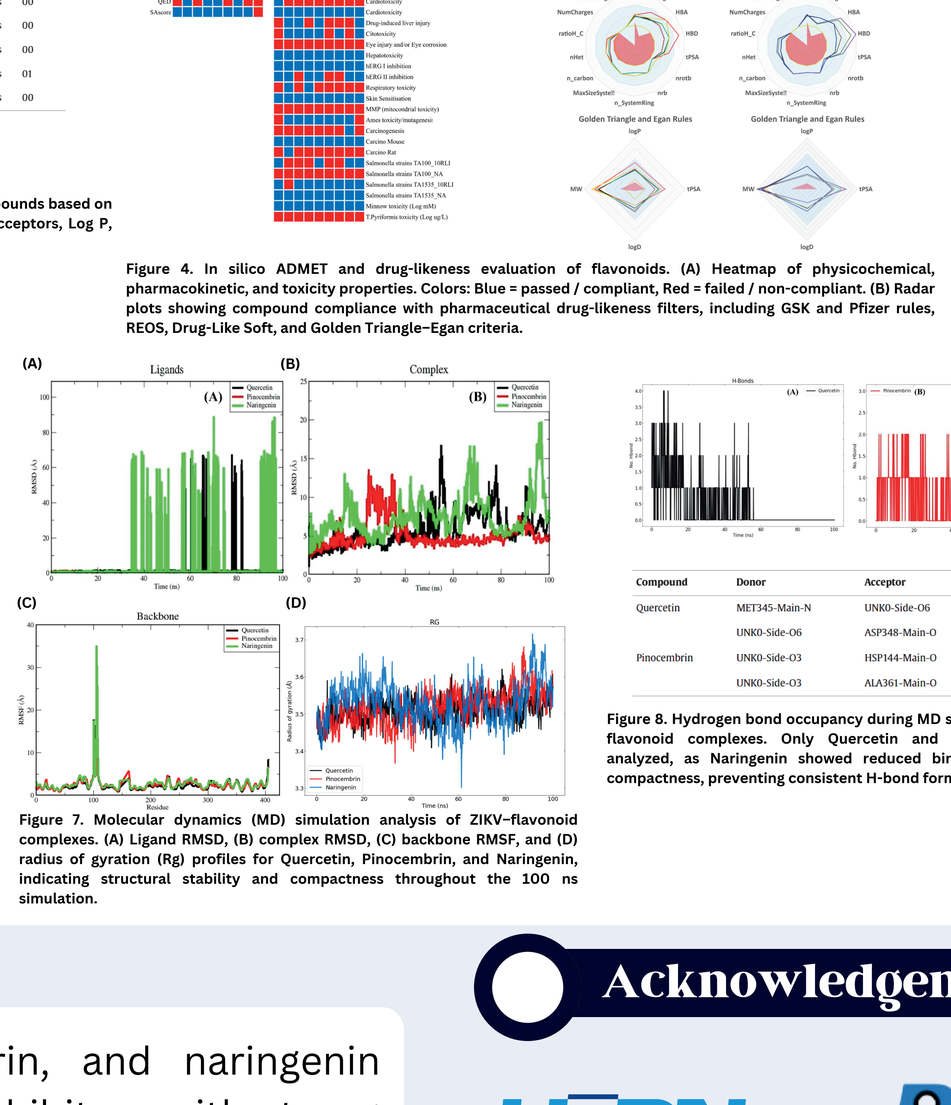


Figure 4. In silico ADMET and drug-likeness evaluation of flavonoids. (A) Heatmap of physicochemical, pharmacokinetic, and toxicity properties. Colors: Blue = passed / compliant, Red = failed / non-compliant. (B) Radar plots showing compound compliance with pharmaceutical drug-likeness filters, including GSK and Pfizer rules, REOS, Drug-Like Soft, and Golden Triangle–Egan criteria.

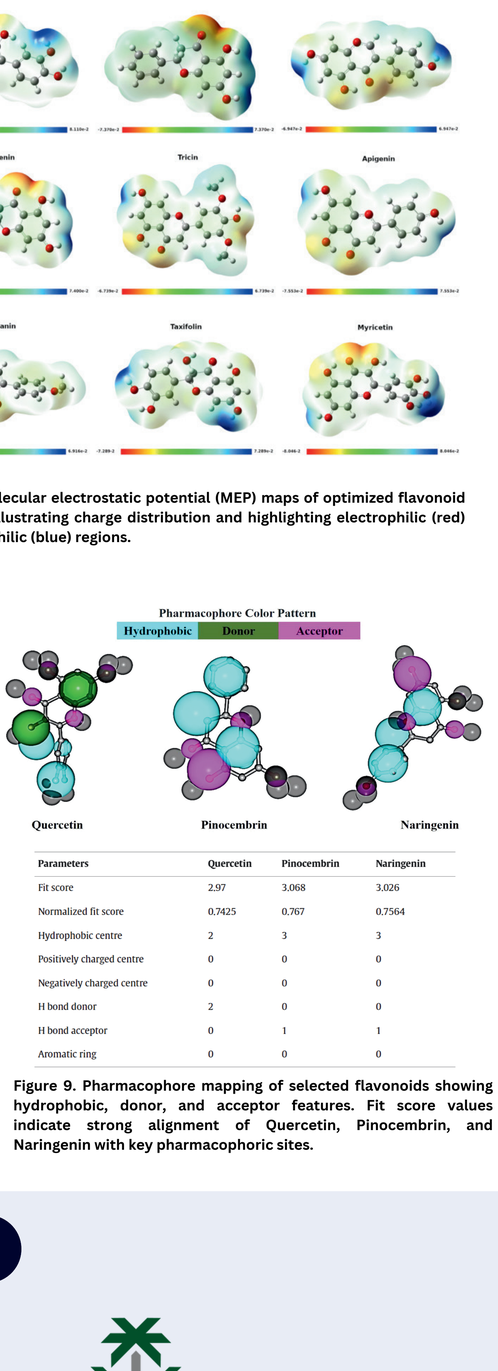
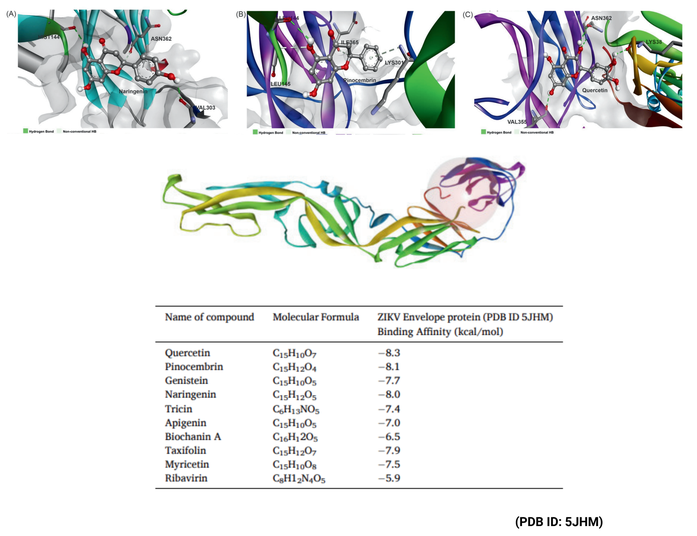


Figure 5. Molecular electrostatic potential (MEP) maps of optimized flavonoid structures, illustrating charge distribution and highlighting electrophilic (red) and nucleophilic (blue) regions.



Name of compound	Molecular Formula	ZIKV Envelope protein (PDB ID 5JHM) Binding Affinity (kcal/mol)
Quercetin	$C_{15}H_{10}O_7$	−8.3
Pinocembrin	$C_{15}H_{12}O_4$	−8.1
Genistein	$C_{15}H_{10}O_5$	−7.7
Naringenin	$C_{15}H_{12}O_5$	−8.0
Tricin	$C_6H_{13}NO_5$	−7.4
Apigenin	$C_{15}H_{10}O_5$	−7.0
Biochanin A	$C_{16}H_{12}O_5$	−6.5
Taxifolin	$C_{15}H_{12}O_7$	−7.9
Myricetin	$C_{15}H_{10}O_8$	−7.5
Ribavirin	$C_8H_{12}N_4O_5$	−5.9

(PDB ID: 5JHM)

Figure 6. Molecular docking and binding energy analysis of flavonoid ligands with the ZIKV envelope protein (PDB ID: 5JHM). (A–C) Binding interactions of top-ranked compounds within the active site. The table summarizes molecular formulas, binding affinities, and energy components. Ribavirin was used as the reference control compound.

Figure 7. Molecular dynamics (MD) simulation analysis of ZIKV–flavonoid complexes. (A) Ligand RMSD, (B) complex RMSD, (C) backbone RMSF, and (D) radius of gyration (Rg) profiles for Quercetin, Pinocembrin, and Naringenin, indicating structural stability and compactness throughout the 100 ns simulation.

Compound	Donor	Acceptor	Occupancy
Quercetin	MET345-Main-N	UNK0-Side-O6	3.29 %
	UNK0-Side-O6	ASP348-Main-O	3.19 %
Pinocembrin	UNK0-Side-O3	HSP144-Main-O	33.13 %
	UNK0-Side-O3	ALA361-Main-O	10.08 %

Figure 8. Hydrogen bond occupancy during MD simulations of ZIKV–flavonoid complexes. Only Quercetin and Pinocembrin were analyzed, as Naringenin showed reduced binding stability and compactness, preventing consistent H-bond formation.

Parameters	Quercetin	Pinocembrin	Naringenin
Fit score	2.97	3.068	3.026
Normalized fit score	0.7425	0.767	0.7564
Hydrophobic centre	2	3	3
Positively charged centre	0	0	0
Negatively charged centre	0	0	0
H bond donor	2	0	0
H bond acceptor	0	1	1
Aromatic ring	0	0	0

Figure 9. Pharmacophore mapping of selected flavonoids showing hydrophobic, donor, and acceptor features. Fit score values indicate strong alignment of Quercetin, Pinocembrin, and Naringenin with key pharmacophoric sites.

Conclusion

In conclusion, quercetin, pinocembrin, and naringenin emerge as promising ZIKV E protein inhibitors with strong target engagement and drug-like properties. Pinocembrin shows the most consistent overall performance, followed by naringenin, while quercetin displays good affinity but lower stability. Their significant translational potential as antiviral candidates warrants further in vitro and in vivo studies to confirm efficacy and safety.

Acknowledgements

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CAPES

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