International Journal of Entomology Research
www.entomologyjournals.com
ISSN: 2455-4758
Received: 08-06-2026, Accepted: 08-07-2026, Published: 23-07-2026
Volume 11, Issue 3, 2026, Page No. 125-133

Computational analysis of *Ipomoea carnea* phytocompounds as potential antiviral agents against dengue virus (*Aedes aegypti*)

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DOI: https://doi.org/10.66856/ijer.2026.11.3.11248

Abstract
The plant *Ipomoea carnea*, belonging to the family Convolvulaceae, is emerging as a potential source of bioactive compounds with insecticidal activity against *Aedes aegypti*, a vector of the Dengue virus. Molecular docking results indicated strong binding affinities of Stigmasta-5,22-dien-3-ol acetate and caryophyllene to the dengue virus envelope protein domain III (DENV1-E111) and the NS5 RNA-dependent RNA polymerase (RdRp), suggesting their potential antiviral activity. Physicochemical and drug-likeness analyses of the identified compounds showed favorable properties for drug development. These results indicate that *I. carnea* may be considered for the development of eco-friendly antivirals against the dengue virus. Additional studies are warranted to isolate active compounds and to test them in the field to determine efficacy and support the development of new plant-based vector-control strategies.

Keywords: *Ipomoea carnea*, *Aedes aegypti*, dengue, virus, docking

Introduction

The world has become a more dangerous place for mosquito-borne viruses, with *Aedes aegypti* and *Aedes albopictus* serving as the main vectors (Näslund *et al*., 2021) [24]. These species are highly adaptable and have greatly expanded their ranges, leading to recurrent epidemics of debilitating diseases such as dengue, Zika, chikungunya, and yellow fever (Näslund *et al*., 2021) [24]. The impact is unimaginable: in the Americas alone, an estimated 16.2 million people are affected by dengue each year (Côrtes *et al*., 2023). These mosquitoes' adaptability to environmental change and reliance on global transport systems have facilitated their spread into new ecological habitats, including recent incursions into parts of Europe where the mosquitoes are not indigenous and where there is no natural immunity (De Almeida *et al*., 2025) [9].

Synthetic insecticides have been the mainstay of mosquito control, but their chronic and widespread use has caused significant environmental and health issues (Li *et al*., 2021) [17]. Additionally, resistance in key vectors to chemical products has reduced the effectiveness of traditional chemical control (Li *et al*., 2021). However, because these pesticides are harmful to pollinators, plant-derived natural compounds have become crucial options in vector management, offering ecological safety and resistance management benefits (Şengül Demirak & Canpolat, 2022) [30]. Botanical bioinsecticides offer numerous advantages, including biodegradability and lower toxicity compared to synthetic counterparts (Hillary *et al*., 2024) [12]. These natural compounds consistently show strong larvicidal, adulticidal, and repellent effects (Şengül Demirak & Canpolat, 2022) [30]. Recent research also indicates that combining biological control and plant-based control practices, such as using synthetic chemical predator kairomones with *Bacillus thuringiensis* israelensis (Bti), can lead to synergistic increases in mosquito mortality (Op De Beeck *et al*., 2016) [25].

The plant *Ipomoea carnea* is a member of the Convolvulaceae family and is a well-known species with a variety of medicinal and bioactive properties (Haraguchi *et al*., 2003) [11]. The plant is renowned as a source of two important classes of glycosidase inhibitors: polyhydroxy nortropane alkaloids (calystegines) and the indolizidine alkaloid swainsonine (Cook *et al*., 2013) [6]. Interestingly, research has shown that both the plant and a fungal endosymbiont from the order Chaetothyriales produce calystegines, with swainsonine produced by the fungus (Cook *et al*., 2013) [6]. Preliminary phytochemical analysis of *I. carnea* extracts revealed a diverse array of bioactive compounds, such as alkaloids, saponins, tannins, steroids, flavonoids, and phenols, which are thought to play a role in insecticidal activity against *A. aegypti* (Haraguchi *et al*., 2003) [11].

Computational analysis is the best way to achieve the desired effect with these natural compounds and has been an essential tool in modern drug discovery (Vora *et al*., 2018) [32]. The *in-silico* approach (Vora *et al*., 2018) [32], which includes receptor-ligand docking, molecular dynamics, and prediction of ADME properties, provides a cost- and time-effective screening method for phytochemicals. These predictions can help researchers identify molecules that could inhibit viral replication by binding to specific viral targets (Murugesan *et al*., 2023) [20]. The crystal structures of essential proteins, such as the envelope protein domain III (DENV1-E111) of the dengue virus and the NS5 RNA-dependent RNA polymerase (RdRp), provide insights into potential inhibitor binding sites (Murugesan and Kaleeswaran, 2024) [18].

These digital methods enable the swift identification of compounds with drug-like properties, thereby accelerating

the development of novel antiviral drugs (Vora *et al*., 2018) [32]. Building on this, the present study involves the computational evaluation of some I. carnea phytocompounds using the docking software AutoDock Vina (Trott and Olson, 2009) [31] and physicochemical analysis to assess their potential as eco-friendly antiviral agents against the dengue virus (Trotta and Olson, 2009) [31]. The overall objective of this approach is to integrate traditional plant knowledge with contemporary pharmaceutical development to address the escalating dengue pandemic (Dass *et al*., 2024) [1].

Materials and Methods

1. Data Collection

The phytochemical components of the flower extract of *Ipomoea carnea* were determined by studying the scientific literature in its entirety. In this review, 15 unique bioactive compounds (mostly terpenoids and sterols) were chosen for computational analysis: Caryophyllene, Humulene, Germacrene D, and Stigmasta-5,22-dien-3-ol acetate. Chemical details and structural information of these ligands were obtained from the PubChem database. The three-dimensional crystal structures of key dengue virus proteins were retrieved from the RCSB Protein Data Bank (PDB) to explore potential antiviral interactions. The protein targets chosen for this study were the envelope protein domain III (DENV1-E111) (PDB ID: 4FFY) and RNA-dependent RNA polymerase (NS5) (PDB ID: 2J7U). The structures are used as template molecules to identify potential binding sites and assess the inhibitory properties of the identified phytocompounds (Table 1).

Table 1: Phytocompounds from *I. carnea* flower extract

S. No	Name of Compound	Molecular Weight	Molecular Formula
1.	Cyclopentanone, dimethylhydrazone	126.20	$C_7H_{14}N_2$
2.	Caryophyllene	204.35	$C_{15}H_{24}$
3.	Humulene	204.35	$C_{15}H_{24}$
4.	Germacrene D	204.35	$C_{15}H_{24}$
5.	Pentadecane	212.41	$C_{15}H_{32}$
6.	α-Farnesene	204.35	$C_{15}H_{24}$
7.	Stigmasta-5,22-dien-3-ol, acetate	454.71	$C_{31}H_{50}O_2$
8.	*n*-Hexadecanoic acid	256.42	$C_{16}H_{32}O_2$
9.	Heptadecane	240.47	$C_{17}H_{36}$
10.	Heptadecane, 2,6,10,15-tetramethyl-	296.57	$C_{21}H_{44}$
11.	*cis*-7-Hexadecenoic acid	254.41	$C_{16}H_{30}O_2$
12.	Octadecanoic acid	284.47	$C_{18}H_{36}O_2$
13.	Dotriacontane	450.86	$C_{32}H_{66}$
14.	Nonadecane	268.52	$C_{19}H_{40}$
15.	Docosane	310.60	$C_{22}H_{46}$

2. Lipinski rule and study of the ADMET properties of phytochemicals

The molecular compound must remain stable in its bioactive form over a long period so that the biological process within the host organism can be predictable and the compound can be effective as a ligand. Furthermore, when the compound is intended to act at a specific site, its concentration at that site should be sufficient to exert a therapeutic effect. The Swiss-ADME online tool is considered reliable and efficient for analyzing the physicochemical properties, pharmacokinetics, and drug-likeness of target compounds. This tool can be used to predict ADME using in silico methods (Murugesan *et al*., 2023) [20].

3. Ligand preparation

Phytochemicals from *I. carnea* were identified using PubChem (https://pubchem.ncbi.nlm.nih.gov/). The research involved converting "sdf" files to "pdb" format using the Discovery Studio Visualizer software. Conformational flexibility of the ligands was assessed using torsion fitting. PyRx software, specifically AutoDock Vina tools, was employed to generate the "pdbqt" file. Various chemicals have been explored for their potential interactions with sterol carrier protein-2 (IPZ4). The investigated compounds included 5-Isopropyl-2-methylphenyl heptanoate; benzene, 1-(bromomethyl)-3-nitro, Geranylacetone; Hexylamine, N, N-di(allyl), myristic acid, neophytadiene, n-hexadecanoic acid, Nonadecene; Phytol; 7-Tetradecyne; Linolenic acid; 6,10,14,18,22 Tetracosapentaen-2-ol, 3-bromo-2,6,10,15,19,23-hexamethyl, alpha-tocopherol-beta-D mannoside, Campesterin and Tetracosahexaen. These substances were selected based on their structural features and relevance to the study's objectives. For docking simulations, the lowest-energy ligands were selected and used in AutoDock Vina (Abshana Begam *et al*., 2024) [1].

4. Receptor preparation

The study investigated the protein composition of dengue strains. The crystal structures of several important proteins involved in the replication of different Dengue virus serotypes were obtained. We solved the crystal structure of DENV1-E111 (PDB ID: 4FFY), a protein that plays an important role in viral replication. In addition, we obtained the crystal structure of another key protein, NS5 RNA-dependent RNA polymerase (PDB ID: 2J7U), which is important for viral replication. These crystal structures were retrieved from the RCSB database, which contains a large number of crystal structures of biological macromolecules. Protein structures determined experimentally are available in the RCSB database. These crystal structures are valuable tools for advancing our understanding of the molecular basis of DENV1 replication. We created the "pdbqt" file using the PyRx tools. Studying the crystal structures of these proteins provides insights into their three-dimensional structures and potential inhibitor-binding sites.

5. Active site prediction

This is an important part of molecular docking that enables accurate determination of the binding pocket to which a molecule will bind. In addition, it provides essential

information regarding the number and significance of the active sites. The sitemap tool in PyRx was used for analysis in this study. The location values were used to determine the optimum site for the ligand in the grid structure. PyRx's sitemap tool performs an exhaustive analysis of the possible binding sites, including hydrophobicity, electrostatics, and surface topology. These parameters can be used to determine which binding pockets are most suitable to pursue in the future for the design of new ligands. In addition to making the drug discovery process more efficient, this approach increases the likelihood of identifying compounds with high binding affinity and specificity for the target protein.

6. Grid generation

A study was conducted to identify the optimal lattice structure for binding dengue proteins to ligands. The evaluation was performed using the Sitemap tool. In this work, a grid-based approach was used to dock ligands to the dengue protein and investigate multiple interactions between the phytochemicals and the protein. Grid generation creates a three-dimensional grid around the protein of interest, with each point representing a potential site of ligand interaction. Scientists can systematically analyze the energy characteristics and geometric constraints at each grid cell to identify areas where the ligand is likely to bind and predict its orientation within the binding cavity. This lattice-based method facilitates the screening of large compound libraries, helping researchers quickly identify potential compounds for further experimental testing and optimization.

7. Molecular docking and binding energy (PyRx)

AutoDock tools were used to prepare both the proteins and ligands. The software's appropriate modules and algorithms were used to ensure accurate and reliable preparation. The complex with the most favorable energy profile was selected after a thorough evaluation performed using the complex software program Discovery Studio Visualizer. For further analyses, the configuration with the lowest energy consumption was selected among the different docking configurations (Trott and Olson, 2009) [31].

8. Physicochemical properties of proteins

The physicochemical properties of proteins play a vital role in understanding their behavior. These properties have been studied using various approaches that provide important information about protein structure, stability, and function. The ProtParam web tool was used for this analysis. This tool provides a comprehensive analysis of various protein parameters, including molecular weight, theoretical isoelectric point, and amino acid composition. This information is crucial for understanding protein behavior under different physiological conditions and their potential interactions with other molecules. In addition, ProtParam can calculate the extinction coefficient, instability index, and grand average of hydropathicity (GRAVY) of proteins, which are significant features of protein stability and solubility.

Results

1. Molecular Docking

Denv1-E111

Molecular docking simulations were performed to assess the binding affinity of the selected bioactive compounds to the envelope protein domain III (E111) of DENV1 (PDB ID: 4FFY). Table 2 presents the docking scores and root-mean-square deviation (RMSD) values. The docking score (kcal/mol) reflects interaction strength, with lower values indicating stronger binding affinity, whereas RMSD values provide insight into the stability and accuracy of the binding poses. Stigmasta-5,22-dien-3-ol, acetate showed the strongest binding interaction among the compounds analyzed, with a docking score of -7.5 kcal/mol, indicating high affinity for the DENV1-E111 binding pocket.

Table 2: Molecular docking results of bioactive compounds with the crystal structure of DENV1-E111 (4FFY)

S. No	Compound Name	Docking score (kcal/mole)	RMSD (Å)
1.	Cyclopentanone, dimethylhydrazone	-4.5	3.059
2.	Caryophyllene	-6.5	4.188
3.	Humulene	-6.3	4.200
4.	Germacrene D	-6.4	4.359
5.	Pentadecane	-4.0	28.579
6.	α-Farnesene	-4.5	29.137
7.	Stigmasta-5,22-dien-3-ol, acetate	-7.5	7.944
8.	*n*-Hexadecanoic acid	-4.5	6.921
9.	Heptadecane	-3.8	28.459
10.	Heptadecane, 2,6,10,15-tetramethyl-	-4.3	36.429
11.	*cis*-7-Hexadecenoic acid	-4.4	15.214
12.	Octadecanoic acid	-5.0	9.410
13.	Dotriacontane	-4.3	4.332
14.	Nonadecane	-4.8	8.865
15.	Docosane	-4.8	2.986

Other compounds showing strong binding included Caryophyllene (-6.5 kcal/mol), Germacrene D (-6.4 kcal/mol), and Humulene (-6.3 kcal/mol), implying that these terpenoids might play a crucial role in inhibiting the dengue virus envelope protein. In contrast, Heptadecane (-3.8 kcal/mol) showed the weakest interaction, indicating limited binding potential. Furthermore, Heptadecane, 2,6,10,15-tetramethyl- (-4.3 kcal/mol, RMSD: 36.429 Å) and α-Farnesene (-4.5 kcal/mol, RMSD: 29.137 Å) exhibited high RMSD values, suggesting poor binding stability and unreliable docking conformations. Stigmasta-5,22-dien-3-ol and acetate interacted with PRO L:40 and PRO H:41 (Fig 1), indicating strong binding affinity. Caryophyllene bound to DENV1-E111 (Fig 2) through

interactions with residues LYS A:388 and PHE H:101. The stability of docked compounds can be assessed using RMSD values, with lower values indicating more stable docking poses and higher conformational reliability. Cyclopentanone, dimethylhydrazone (RMSD: 3.059 Å), and docosane (RMSD: 2.986 Å) were the most stable conformations, suggesting robust interactions with the viral target. Conversely, compounds with RMSD values above 25 Å, such as Pentadecane (RMSD: 28.579 Å), α-Farnesene (RMSD: 29.137 Å), and Heptadecane, 2,6,10,15-tetramethyl- (RMSD: 36.429 Å), exhibited weak or unstable docking interactions. These high RMSD values may indicate issues with binding orientation or weak intermolecular forces.

Examination of the molecular structures and docking results revealed that terpenoids and sterols, including Stigmasta-5,22-dien-3-ol, acetate, Caryophyllene, and Humulene, exhibited higher binding affinities. This was attributed to the cyclic structures and functional groups that enabled hydrogen bonding and hydrophobic interactions. In contrast, saturated hydrocarbons such as Heptadecane, Nonadecane, and Docosane exhibited weaker interactions, likely due to the absence of polar functional groups that are required for strong interactions with the viral envelope protein. These findings suggest that Stigmasta-5,22-dien-3-ol, acetate, and caryophyllene are promising candidates for further anti-dengue drug development. Their strong binding affinities indicated potential interference with DENV1-E111 function, possibly inhibiting viral entry or replication. To validate their antiviral efficacy and assess their potential as lead compounds for drug development, future research should include molecular dynamics (MD) simulations and *in vitro* assays.

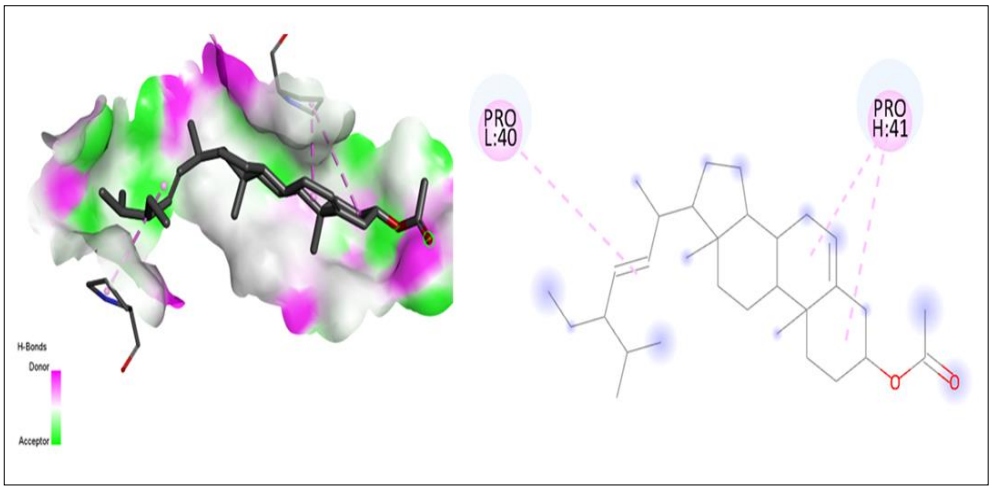

Fig 1: Crystal structure of DENV1-E111 against Stigmasta-5,22-dien-3-ol, acetate

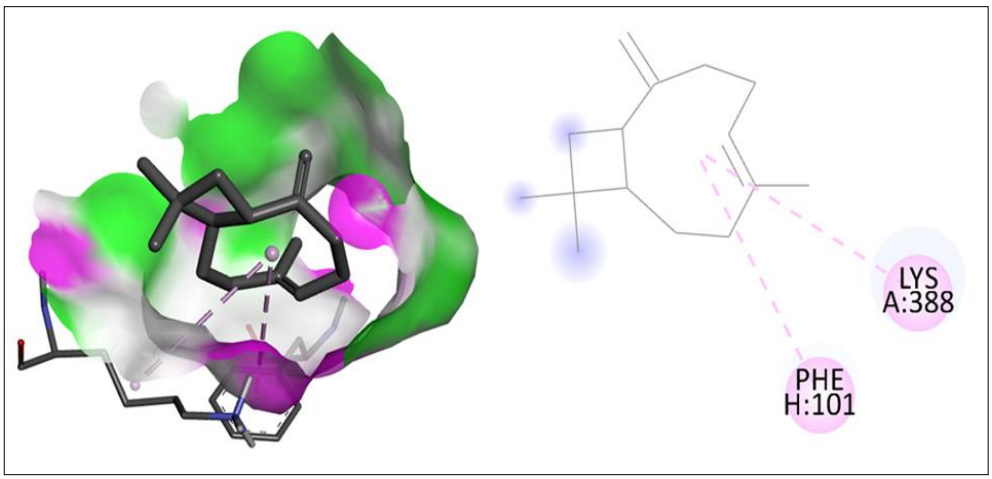

Fig 2: Crystal structure of DENV1-E111 against Caryophyllene

2. NS5 RNA-dependent RNA polymerase

Molecular docking was performed to assess the binding affinity of various bioactive compounds with the NS5 RNA-dependent RNA polymerase (RdRp) of the target pathogen (PDB ID: 2J7U). Table 3 presents the docking scores and root-mean-square deviation (RMSD) values for the selected compounds. The docking score, measured in kcal/mol, indicates the strength of the interaction between the ligand and the receptor, with more negative values suggesting stronger binding.

Among the tested compounds, Stigmasta-5,22-dien-3-ol, acetate showed the strongest binding affinity with a score of -8.2 kcal/mol. This was followed by Caryophyllene (-6.8 kcal/mol), Humulene (-6.6 kcal/mol), and Germacrene D (-6.3 kcal/mol). These results suggest that these compounds may form stable interactions with the NS5 polymerase's active site, potentially inhibiting its function. kcal/mol, with a docking score of -3.9 kcal/mol and a notably high RMSD value of 41.569 Å, indicating low binding stability.

Table 3: Molecular docking results of bioactive compounds interacting with NS5 RNA-dependent RNA polymerase (PDB ID: 2J7U)

S. No	Compound Name	Docking score (kcal/mole)	RMSD (Å)
1.	Cyclopentanone, dimethylhydrazone	-3.9	41.569
2.	Caryophyllene	-6.8	19.223
3.	Humulene	-6.6	17.825
4.	Germacrene D	-6.3	17.606
5.	Pentadecane	-4.5	17.803
6.	α-Farnesene	-5.1	5.344
7.	Stigmasta-5,22-dien-3-ol, acetate	-8.2	26.031
8.	*n*-Hexadecanoic acid	-4.8	15.309
9.	Heptadecane	-4.3	3.807
10.	Heptadecane, 2,6,10,15-tetramethyl-	-4.6	27.705
11.	*cis*-7-Hexadecenoic acid	-5.1	2.224
12.	Octadecanoic acid	-5.8	6.414
13.	Dotriacontane	-4.7	5.563
14.	Nonadecane	-5.8	6.291
15.	Docosane	-5.2	40.003

Similarly, Docosane showed poor binding, with a binding energy of -5.2 kcal/mol and a high RMSD of 40.003 Å, suggesting weak and unstable interactions. RMSD values offer insights into the stability and accuracy of docking poses, with lower values generally indicating more reliable binding conformations. In this study, cis-7-Hexadecenoic acid (RMSD: 2.224 Å) and Heptadecane (RMSD: 3.807 Å) demonstrated the most stable docking poses, supporting their potential as inhibitors.

Conversely, compounds such as cyclopentanone, dimethylhydrazone (41.569 Å), heptadecane, and 2,6,10,15-tetramethyl- (27.705 Å) showed higher RMSD values, indicating lower binding precision. Stigmasta-5,22-dien-3-ol acetate formed strong interactions with LYS A:401, VAL A:603, ILE A:797, and TYR A:606 (Fig 3), suggesting significant inhibition potential. Caryophyllene interacted with PHE A:354 and VAL A:579 (Fig 4), potentially hindering viral replication.

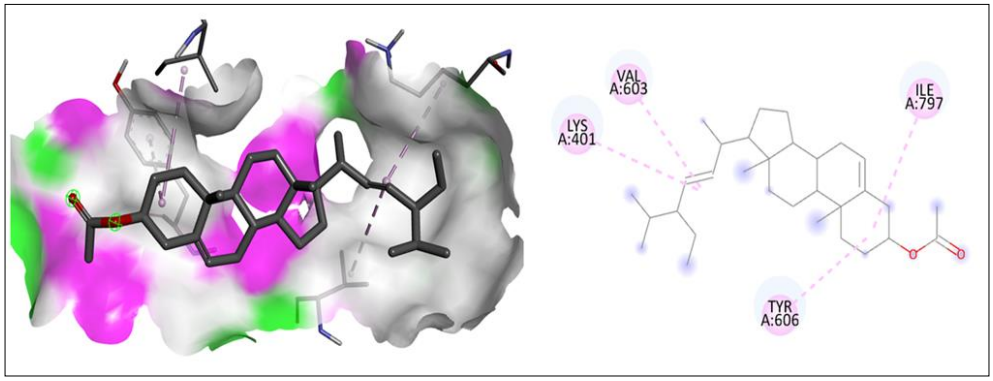

Fig 3: NS5 RNA-dependent RNA polymerase against Stigmasta-5,22-dien-3-ol, acetate

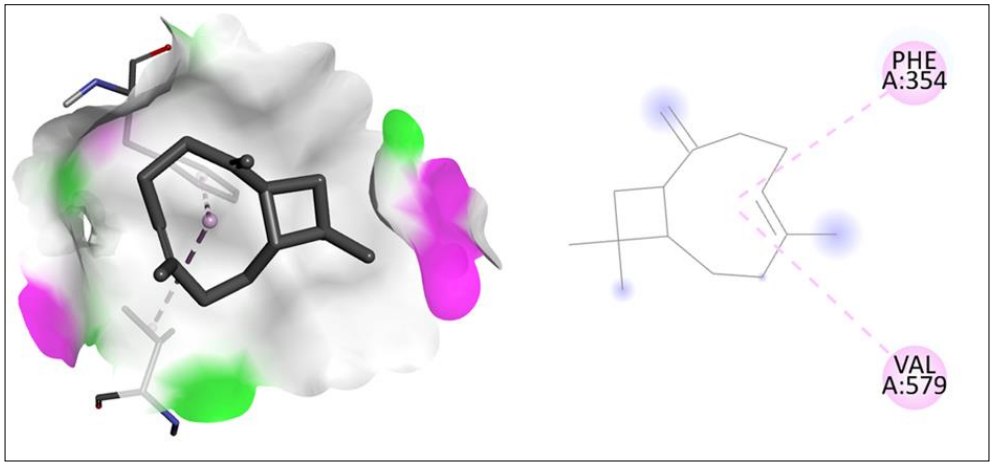

Fig 4: NS5 RNA-dependent RNA polymerase against Caryophyllene

Initial examination of the molecular structures indicated that compounds with higher levels of unsaturation and functional groups such as hydroxyl or acetate moieties (e.g., Stigmasta-5,22-dien-3-ol, acetate) exhibited superior binding affinities.

Conversely, saturated hydrocarbons (including Pentadecane, Heptadecane, and Docosane) displayed weaker interactions, presumably because of the absence of functional groups essential for hydrogen bonding or electrostatic interactions

within the NS5 polymerase active site. These results suggest that compounds such as Stigmasta-5,22-dien-3-ol acetate, Caryophyllene, and Humulene show potential as NS5 RdRp inhibitors, given their strong binding affinities and relatively stable docking conformations. Additional research, including molecular dynamics simulations and *in vitro* testing, is required to verify these interactions and to further evaluate their antiviral capabilities.

3. Physicochemical properties of dengue protein

This study investigated the structural and functional characteristics of three crucial dengue virus (DENV) proteins: RNA helicase, DENV1-E111, and NS5 RNA-dependent RNA polymerase. The physicochemical properties of the samples were examined, and a comprehensive summary is provided in Table 4. The proteins displayed differences in amino acid composition and molecular weight. RNA helicase consists of 451 amino acid residues, DENV1-E111 contains 126 residues, and NS5 RNA-dependent RNA polymerase contains 635 residues. Their respective molecular masses were determined to be 51,548.0 Da, 42,617.26 Da, and 73,489.78 Da. The isoelectric points (pIs) of the proteins were calculated as follows: 6.79 for RNA helicase, 6.37 for helicase, DENV1-E111, and 8.01 for NS5 RNA-dependent RNA polymerase.

Table 4: Physicochemical properties of dengue viruses

S. No	Physicochemical property	DENV1- E111	NS5 RNA dependent RNA polymerase
1.	Number of amino acids	126	635
2.	Molecular weight	42617.26	73489.78
3.	Theoretical pI	6.37	8.01
4.	Total number of negatively charged residues (Asp þ Glu)	46	86
5.	Total number of positively charged residues (Arg þ Lys)	41	88
6.	Total number of atoms	5905	10,229
7.	The instability index (II)	40.75	34.50
8.	Aliphatic index	71.57	70.17
9.	Grand average of hydropathicity (GRAVY)	-0.542	-0.640
10.	Allergenicity	Nil	Nil
11.	Toxicity	Nil	Nil

Among these, NS5 RNA-dependent RNA polymerase showed a higher level of basicity than the other two proteins. Examination of the charged amino acid residues revealed that RNA helicase had an almost equal distribution of negatively charged (Asp + Glu) and positively charged (Arg + Lys) residues (71 and 70, respectively). DENV1-E111 exhibited a slightly uneven distribution with 46 negatively charged and 41 positively charged residues. NS5 RNA-dependent RNA polymerase exhibited a slight predominance of positively charged residues, with 88 positively charged and 86 negatively charged residues. Structural analysis of the proteins showed that RNA helicase contained 7,241 atoms, DENV1-E111 contained 5,905 atoms, and NS5 RNA-dependent RNA polymerase consisted of 10,229 atoms. These atomic counts indicate differences in the structural complexity and size of proteins.

Instability index (II) values were calculated to assess the stability of these proteins. The findings revealed that RNA helicase and DENV1-E111 had II values of 40.96 and 40.75, respectively, suggesting moderate stability. Conversely, NS5 RNA-dependent RNA polymerase showed a slightly lower II value (34.50), indicating that it is a more stable protein. Examination of the aliphatic index yielded values of 78.78, 71.57, and 70.17 for RNA helicase, DENV1-E111, and NS5 RNA-dependent RNA polymerase, respectively. These results suggest that the RNA helicase exhibits the highest aliphatic character, which may contribute to its thermal stability. All three proteins displayed negative grand average of hydropathicity (GRAVY) scores: RNA helicase (- 0.538), DENV1-E111 (- 0.542), and NS5 RNA-dependent RNA polymerase (- 0.640). These negative GRAVY scores indicate that the proteins were hydrophilic. Further analysis of the RNA helicase DENV1-E111 and the NS5 RNA-dependent RNA polymerase revealed that neither protein was allergenic or toxic. These observations suggested that these compounds are suitable candidates for future biomedical applications.

Discussion

The phytochemical composition of the extract from the flower of *Ipomoea carnea* showed that it contained a wide range of bioactive compounds, including alkaloids, saponins, tannins, steroids, flavonoids, and phenols. The results are similar to those of earlier studies on the family Convolvulaceae, in which complex secondary metabolites such as swainsonine and calystegines were identified. 15 unique compounds were identified, with the main compounds being Caryophyllene, Humulene, Germacrene D, and Stigmasta-5,22-dien-3-ol acetate. The observed insecticidal activity is well supported by scientific evidence of the toxic properties of these compounds against a variety of insect species, including terpenoids such as Caryophyllene and Humulene (Gilardoni *et al*., 2020[10]; Li *et al*., 2008). *Solanum torvum* showed good insecticidal activity against stored, field, and mosquito insects (Murugesan *et al*., 2022; Murugesan *et al*., 2021; Rengarajan *et al*., 2024) [21, 29, 30].

The water-based extract of *I. carnea* exhibited significant larvicidal activity against fourth-instar *Aedes aegypti* larvae, with clear dose- and time-dependent toxicity. In comparison with the literature, *I. carnea* is as potent as other plant extracts. Ragavendran and Natarajan (2015) [28] reported LC_{50} values in these terms for extracts of the mycelia of *Aspergillus terreus*. Yet it is essential to have a broader perspective on the range of natural insecticides. However, some botanical sources have been found to be much more potent; for example, *Mammea siamensis* has an LC_{50} of only 4.1 µg/ml (Promsiri *et al*., 2006) [26]. Likewise, fatty acids such as oleic and linoleic acid from *Citrullus colocynthis* have LC_{50} values as low as 8.80 µg/ml. These differences do not appear to substantially detract from its potential for use as a long-term vector control agent, as a general rule in the case of *I. carnea*. This performance is better than that of some other essential oils documented, for example, *Croton*

tetradenius essential oil, which has an LC_{50} of 1.842 mg/mL (Carvalho *et al*., 2016) [5]. Although very effective, the adulticidal properties can be further improved by using nanosynthesis techniques, such as those for silver nanoparticles (AgNPs) obtained from plant extracts, as reported in recent research (Azarudeen *et al*., 2016) [3].

The insecticidal activity of *I. carnea* is due to the synergistic effect of terpenoid and phenolic compounds. Several studies have identified terpenoids, particularly caryophyllene and humulene, as the main toxins. For example, β-caryophyllene is the major compound in *Plectranthus amboinicus* essential oil and exhibits different toxicity against *A. aegypti* (Huang *et al*., 2019) [13]. These compounds appear to disrupt normal physiological functions in mosquitoes. A molecular docking study has shown that terpenoids bind to sterol carrier protein-2 (SCP-2), which plays an important role in cholesterol uptake and transport in insects (Andrade-Ochoa *et al*., 2018) [2]. In addition, SAR models indicate that molecular structural properties, such as π-bonding, LogP, and molar refractivity, play important roles in the larvicidal activity of these plant-derived molecules.

In addition to serving as vector control agents, the phytocompounds of I. carnea are suggested to exert direct antiviral activity against dengue virus based on computational analyses. Stigmasta-5,22-dien-3-ol acetate was the top hit, showing the highest binding affinities to the envelope protein domain III (DENV1-E111) (-7.5 kcal/mol) and the NS5 RNA-dependent RNA polymerase (RdRp) (-8.2 kcal/mol). This stronger binding is thought to result from the cyclic structures and functional groups of sterols and terpenoids, which enable strong hydrogen bonds and hydrophobic interactions within the viral target's active site. The NS5 RdRp target showed important interactions with LYS A:401, VAL A:603, and TYR A:606, which may contribute to inhibiting viral replication in response to Stigmasta-5,22-dien-3-ol acetate. By contrast, saturated hydrocarbons such as Heptadecane and Docosane exhibited much weaker interactions and less stable poses, presumably because they lack the polar functional groups required for protein binding. These findings align with other virtual screens of thousands of plant metabolites, which identified polyphenolic compounds, flavonoids, and sterols as the most potent ligands binding to DENV protein targets (N Powers and N Setzer, 2016) [23]. In addition, other natural inhibitors such as amentoflavone (Hossain *et al*., 2021) and catechin from Theobroma cacao (Huq *et al*., 2024) [14] showed high binding affinity for the RdRp and are promising inhibitors.

The physicochemical property evaluation of the identified compounds using the Swiss-ADME platform provided valuable information on their pharmaceutical potential. Interestingly, although Lipinski's rule of five is a general guideline, not all drugs need to follow it to be developed (Caminero Gomes Soares *et al*., 2023) [4]. Some studies have shown that about 34% of the FDA-approved oral medications since 1997 fail to strictly adhere to all of Lipinski's rules, especially the molecular weight and LogP rules. A simple example is the ent-kaurane diterpenoids, which often exhibit drug-like properties similar to those of FDA-approved drugs despite their complexity (Kibet *et al*., 2024) [15]. In addition, many of the most successful prodrugs fall outside the 500 Da range and have more than 10 hydrogen-bond acceptors (Protti *et al*., 2021) [27]. *I. carnea* contains phytochemicals that are quite large but have optimal lipophilicity and flexibility, making them promising candidates for additional experimental validation.

Moving laboratory-developed, plant-based mosquitocides into field application is challenging and involves logistical hurdles. The use of *I. carnea,* however, has many advantages, including biodegradability and ecological safety compared with synthetic chemicals such as organophosphates. Plant-derived compounds are less likely to cause widespread resistance and have a lower environmental impact. Combining these natural extracts with other biocontrol methods may be a more sustainable approach to vector management. For example, biological control methods such as Bacillus thuringiensis israelensis (Bti) have been found to be more effective in mosquito control when combined with predator kairomones, producing a synergistic effect that is more harmful to mosquito populations without harming the environment (Op De Beeck *et al*., 2016) [25].

Conclusion

Based on the above, the study results will be useful in developing novel, plant-based, potential antiviral drugs from *I. carnea*. This study uses computational docking to provide a holistic understanding of how certain plant compounds can target the dengue virus and its primary vector, *A. aegypti*. The results, in particular, indicate that the compounds Stigmasta-5,22-dien-3-ol acetate and caryophyllene have strong binding affinity for the DENV1-E111 envelope protein and the NS5 RNA-dependent RNA polymerase (RdRp), respectively, and are thus potential lead compounds. These natural insecticides exhibit larvicidal and adulticidal activity, have favorable drug-likeness properties, and are environmentally friendly, biodegradable options to synthetic insecticides. The isolation and characterization of these specific bioactive fractions is important for further understanding of individual mechanisms of action, which should be the focus of future research. Further optimization of extraction and formulation methods will also be crucial to improve the stability and field performance of *I. carnea*-based formulations. The next major task for assessing the feasibility and safety of these botanical products for large-scale dengue control and sustainable vector management will be field testing and extensive toxicological testing.

Acknowledgements

The first and corresponding author would like to thank the management of Bon Secours College for Women (A), Thanjavur, for taking the time to write this manuscript.

Data availability

Open to all

Funding

There is no funding support for doing this review.

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