

In silico screening of phytochemicals in *Simarouba glauca* towards identification of potential lead compounds to treat dengue viral infection

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Dengue is a viral disease with no specific antiviral or vaccine available for treatment. Nature has always been a source of drugs since ancient times. People have been using plants and their metabolites for various medical treatments. *Simarouba glauca*, as a potential crop, has many secondary metabolites with medicinal properties. The coumarins, quassinoids and alkaloids in various parts of *S. glauca* have been selected and predicted for their pharmacokinetics and pharmacodynamics properties. The stability during their interaction with a nonstructural protein Methyl transferase of DENV was predicted by molecular docking and Molecular Dynamic Simulation study. The study attempts to predict the phytochemicals in *S. glauca* as potential lead compounds to treat DENV infection.

Keywords: Antiviral, Dengue, Molecular docking, Molecular dynamic simulation, Quassinoids, *Simarouba glauca*

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Introduction

Dengue, a vector-borne disease, is caused by the dengue virus (DENV) transmitted by *Aedes aegypti* mosquitoes. National Center for Vector Borne Diseases Control (NCVBDC) India has reported 94,198 DENV cases and 91 deaths in the year 2023. The menacing outbreaks of DENV causes a burden on the family, society and India's healthcare system more significantly, and inflict mayhem on the Indian economy¹. WHO has also reported that DENV is an endemic infectious disease in more than 100 countries, including Africa, The Americas, the Western Pacific, Southeast Asia and The Eastern Mediterranean, of which 70% of the global disease burden is from Asia.

DENV is a RNA virus belonging to the family Flaviviridae². The three phases of DENV infection are febrile, critical and recovery. The febrile phase is characterized by a rise in body temperature, headache, nausea, vomiting, retro-orbital pain, malaise, arthralgia, and myalgia. The pathophysiological symptoms during the critical phase are thrombocytopenia, leukocytopenia, increased

permeability and extravasation of fluids, pleural effusion bleeding and shock. The critical phase lasts 24-48 hours, after which most patients enter the recovery phase.

There is no specific antiviral drug or vaccine for the treatment and prophylactics against DENV infection³. Hence, there is an imperative need for the development of drugs against DENV, as the treatment right now is based on supportive therapy using fluid replacement and analgesics⁴. DENV nonstructural 5 (NS5) is the catalytic subunit of the DENV viral replication complex. The methyltransferase (MTase) of NS5 is involved in forming type 1 cap structure (me7GpppA-me2), essential for the stability of DENV viral mRNA and effective translation during infection⁵. Traditional herbal preparations and medicines have been widely used as they elicit fewer side effects⁶.

Simarouba glauca, commonly known as Laxmitaru, the Paradise tree, dysentery-bark or bitter-wood, sorghum maram (Tamil), is grouped under the family Simaroubaceae. *S. glauca* is distributed widely in tropical regions and is native to the Bahamas, Costa Rica, Cuba, Dominican Republic, El Salvador, Florida, Guatemala, Haiti, Honduras, Jamaica, Mexico, Nicaragua⁷. *S. glauca* plant extract is known to possess

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bioactive compounds such as canthin-6-one, glaucarubin, fraxidin, melianodiol, scopoletin and ailanthone, that are known to possess significant therapeutic properties such as anticancer, antimicrobial, antiviral and antihelminthic⁸⁻¹⁰. As no specific antiviral drugs are available¹¹, the present study aims to predict the anti-DENV properties of selected bioactive compounds of *S. glauca* by *In silico* molecular docking and Molecular Dynamic Simulation studies.

Methodology

Preparation of ligand

Ligands are molecules known to modulate the protein target by binding efficiently to the target protein. Ligand molecules canthin-6-one (CID 97176), glaucarubin (CID 441794), fraxidin (CID 3083616), melianodiol (CID 15560457), scopoletin (CID 5280460) and ailanthone (CID 72965) were retrieved from PubChem database¹² (Fig. 1, Table 1). The canonical Smiles selected were converted to their structure using OpenBabel (version 2.4.1) in PDB format¹³.

Drug likeness analysis

The drug-likeness of the ligand was predicted by selecting Lipinski filter; according to this rule, an orally active drug should fulfill a minimum of four out of five criteria for drug-likeness such as molecular mass, hydrogen donor, hydrogen acceptor cLogP, and molar refractive index¹⁹. These properties were analysed by SWISS ADME (<http://www.swissadme.ch>), which is an online tool in drug discovery²⁰. Also, the properties of ligands with respect to adsorption, distribution, metabolism and excretion (ADME) were analysed by SWISS ADME. Gastrointestinal absorption and brain access are two pharmacokinetic behaviors crucial in drug discovery.

Active site prediction

Computed Atlas of Surface Topography of proteins (CASTp) is an online tool to predict all binding

pockets on a protein structure. It provides a detailed delineation of all atoms participating in their formation and measures the volume and area of each active site²¹. DENV MTase has a binding site for GTP and SAM binding, which can be a target protein for rational drug design²². The PDB id: 1R6A of the protein MTase was submitted, and the result was analysed.

Preparation of target

The docking study was done against DENV MTase using the bioactive compounds of *S. glauca* as ligands by following the earlier explained method with minor modifications²³. The target protein methyltransferase (MTase) of DENV nonstructural 5 (NS5) was

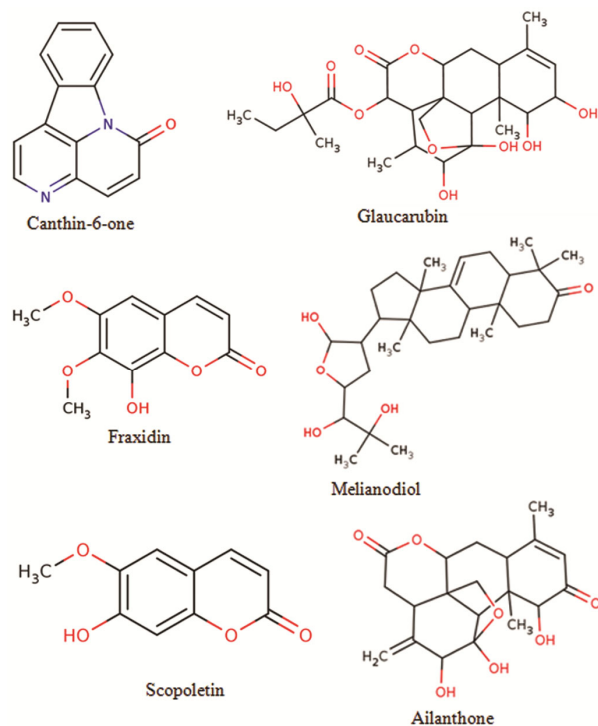


Fig. 1 — Chemical structures of the lead bioactive compounds of *Simarouba glauca*. The structures generated on ChemDB Chemoinformatics portal with canonical smiles (ChemDB Web Interface Index (uci.edu)).

Table 1 — Bioactive compounds present in *Simarouba glauca*, their chemical nature and biological properties

Bioactive compounds	Chemical nature	Biological properties
Canthin-6-one (CID 97176)	β -carboline alkaloids	Antiviral, anticancer, antimicrobial and enzyme inhibitory properties ⁵ anti-inflammatory ¹⁴ .
Glaucarubin (CID 441794)	Quassinoids	Amoebicidal, antiplasmodial and cytotoxic properties ¹⁵ .
Fraxidin (CID 3083616)	Coumarin	Nitric Oxide inhibitory activity contributes to treating septic shock, some inflammatory and autoimmune diseases ¹⁶ .
Melianodiol (CID 15560457)	Triterpenoids	Cytotoxic properties ¹⁷ .
Scopoletin (CID 5280460)	Phenolic coumarin	Antioxidant, anti-inflammatory, hypouricemic, neuroprotective effects and antidepressant ⁶ .
Ailanthone (CID 72965)	Quassinoids	Anticancer agents ¹⁸ .

retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (<http://www.rcsb.org/pdb>)²⁴

The water molecules and heteroatoms were removed from the protein. To the PDB file of the receptor, polar hydrogen atoms and the Gasteiger charge were added. The pre-calculated grid map was obtained using Autogrid, and the default optimisation parameters, a maximum number of 250,000 energy evaluations, were used. The energy of ligands was minimized to get a more stable configuration. The docking result is presented in terms of binding energy (B.E.) values given in kcal/mol and inhibition constant (Ki) in micromolar (μM). The pose or conformation with the lowest B.E. and the appropriate cluster was considered for further analysis and visualisation.

The molecular visualisation of the docked complexes was performed using the PyMol version 1.3 - PyMOL Molecular Graphics System²⁵, and ligand binding sites viewed using Discovery Studio Visualizer that generates schematic 2D diagram of protein-ligand interaction for a given PDB file²⁶.

Molecular Dynamics Simulation of protein-ligand complexes

The Molecular Dynamic (MD) simulation is used to evaluate the changes in the protein structure induced by the ligand. The molecular dynamic simulation was performed to determine the stability and conformation of the protein and its interaction with the ligand drug lead molecules. The MD simulations were performed to evaluate the stability of MTase with bioactive compounds of *S. glauca* complexes. The topology file of the ligand was generated by submitting the PDB coordinates of ligands canthin-6-one (CID 97176), glaucarubin (CID 441794), fraxidin (CID 3083616), melianodiol (CID 15560457), scopoletin (CID 5280460 and aianthone

(CID 72965) to the PRODRG 2 server (The PRODRG Server (dundee.ac.uk)²⁷.

The topology file generated by the PRODRG was submitted to the WebGro server along with the PDB format of the target protein MTase. For the Molecular dynamic simulation of the target–ligand complex Charmm 27 force field was selected and solvated with a simple point charge (SPC) water model in a cubic box. The protein-ligand complex was selected to be maintained in 0.15 M NaCl solution. The energy minimisation parameter was selected as the Steepest Descent integrator for 5000 steps. The simulation of each complex was done for 100 ns under constant temperature and pressure equilibrated. The Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation of each residue in the given structure and average number of H-bonds in each frame for 100 ns were analyzed²⁸.

Results and Discussion

Siddha and Ayurveda have been employing *Andrographis paniculata* in herbal formulations to treat DENV infection. Andrographolide from *A. paniculata* possesses anti-dengue activity against DENV-2²⁹. This study identifies *S. glauca* containing secondary metabolites such as coumarins, alkaloids, and quassinoids³⁰ as lead compounds against the DENV.

ADMET prediction analysis

Various secondary metabolites were selected from PubChem, and the canonical Smiles of the respective secondary metabolites were submitted in the SWISS ADME online tool to predict their pharmacokinetics properties. (Fig. 1) All the selected secondary metabolites were found to possess physico-chemical properties, such as water-soluble. All the molecules predicted no violation of the Lipinski rule, as shown in Table 2.

Table 2 — Physicochemical descriptors ADME parameters, pharmacokinetic properties, drug like nature predictions

Properties	Canthin-6-one	Glaucarubin	Fraxidin	Melianodiol	Scopoletin	Aianthone
Formula	C ₁₄ H ₈ N ₂ O	C ₂₅ H ₃₆ O ₁₀	C ₁₁ H ₁₀ O ₅	C ₃₀ H ₄₈ O ₅	C ₁₀ H ₈ O ₄	C ₂₀ H ₂₄ O ₇
Molecular weight in g/mol	220.23	496.55	222.19	488.70	192.17	376.40
Number of rotatable bonds	0	4	2	3	1	0
Number of H-bond acceptors	2	10	5	5	4	7
Number of H-bond donors	0	5	1	3	1	3
Solubility in water	Moderate	Soluble	Soluble	Moderate	Soluble	Soluble
Lipophilicity Log Po/w	1.99	1.44	1.99	4.13	1.86	1.92
GI absorption	High	Low	High	High	High	High
BBB permeation	yes	No	Yes	No	Yes	No
Drug likeness Lipinski rule	yes	Yes	Yes	Yes	Yes	Yes

Predicted Active site of MTase

The active site of the enzyme DENV methyltransferase (MTase) of DENV nonstructural 5 (NS5) was predicted on the CASTp server³¹. The binding pockets on MTase were predicted with a surface area of 580.830 Å² and a Volume of 519.312 Å³. The amino acid residues on the binding pocket of MTase are Lys 30, Glu 34, Glu 35, Val 36, Arg38, Lys 42, Ser 56, Arg 57, Gly 58, Lys 61, Asp 79, Gly 81, Cys 82, Gly 83, Arg 84, Gly 85, Gly 86, Trp 87, Thr 104, Lys 105, Gly 106, His 110, Glu 111, Val 130, Asp 131, Val 132, Phe 133, Asp 146, Ile 147, Gly 148, Glu 149, Arg 160, Val 164, lys 181, Leu 210, Ser 211, Arg 212, Tyr 219, Tyr 252. (Fig. 2).

Docking analysis

Molecular docking predicts the interaction between a ligand and a protein at the atomic level. The molecular docking approach is used to characterize the binding of ligands to the binding site of target proteins²⁹. In this present study, molecular docking was performed using Autodock4.2. The interaction between the target protein DENV MTase and the various bioactive compounds canthin-6-one, glaucarubin, fraxidin, melianodiol, scopoletin and ailanthone of *S. glauca* were studied, and their binding energies, Inhibition constant(Ki) and the amino acid residues that interact with the ligand molecules were predicted and shown in Table 3.

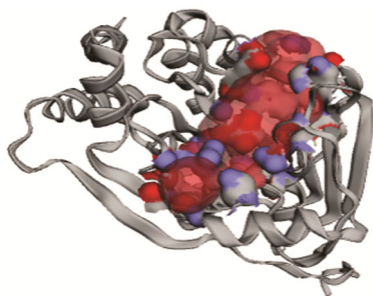


Fig. 2 — Active site predicted on CASTp online tool. The surface denotes the active site of the protein MTase.

Canthin-6-one binds to DENV MTase with a Binding energy of -6.47 kcal/mol and an Inhibition constant of 18.14 μM. The residues predicted to interact with the ligand Canthin-6-one are Gly 81, Gly 83, Arg 84, Gly 109, His 110, Glu 111, Val 132, Phe 133, Ile 147, Glu 149, Arg 160, Arg 163 (Fig. 3a).

Glaucarubin binds to DENV MTase with a Binding energy of -6.45 kcal/mol and an Inhibition constant of 18.85 μM. The residues predicted to interact with the ligand glaucarubin are Gly 107, Pro 108, Gly 109, His 110, Glu 111, Phe 133, Gly 148, Glu 149, and Arg 160 (Fig. 3b).

Fraxidin binds to DENV MTase with a Binding energy of -5.14 kcal/mol and an Inhibition constant of 170.93 μM. The residues predicted to interact with the ligand glaucarubin are Asn 175, Gln 198, Arg 199, Gly 203, Ala 206 (Fig. 3c).

Melianodiol binds to DENV MTase with a Binding energy of -6.67 kcal/mol and an Inhibition constant of 12.90 μM. The residues predicted to interact with the ligand Melianodiol are Tyr 89, Pro 113, Pro 115, Met 116, Ser 117, Trp121, Val 124, Arg 125, Leu 126, Ser 128 (Fig. 3d).

Scopoletin binds to DENV MTase with a Binding energy of -5.42kcal/mol and an Inhibition constant of 105.70 μM. The residues predicted to interact with the ligand Melianodiol are Phe 133, Phe 134, Ile 135, Pro 136, Pro 137, Leu 167 (Fig. 3e).

Ailanthone binds to DENV MTase with a Binding energy of -8.26 kcal/mol and an Inhibition constant of 1.02 μM. The residues predicted to interact with Ailanthone are Val 132, Phe 133, Ile 147, Gly 148, Glu 149, Arg 160, Arg 163, Val 164, Leu 167 (Fig. 3f).

Mostly, all the predicted binding sites are present in the active sites.

Molecular dynamic simulation

Molecular dynamics simulations are vital tools in drug discovery for understanding the physical basis of the structure and function of drug-target interaction

Table 3 — The predicted binding affinities of DENV MTase with various bioactive compounds of *Simarouba glauca*

Ligand with CID	Binding Energy (kcal/mol)	Ki (μM)	Residue interacting with the target protein
Canthin-6-one (CID 97176)	-6.47	18.14	Gly 81, Gly 83, Arg 84, Gly 109, His 110, Glu 111, Val 132, Phe 133, Ile 147, Glu 149, Arg 160, Arg 163
Glaucarubin (CID 441794)	-6.45	18.85	Gly 107, Pro 108, Gly 109, His 110, Glu 111, Phe 133, Gly 148, Glu 149, Arg 160.
Fraxidin (CID 3083616)	-5.14	170.93	Asn 175, Gln 198, Arg 199, Gly 203, Ala 206.
Melianodiol (CID 15560457)	-6.67	12.90	Tyr 89, Pro 113, Pro 115, Met 116, Ser 117, Trp121, Val 124, Arg 125, Leu 126, Ser 128.
Scopoletin (CID 5280460)	-5.42	105.70	Phe 133, Phe 134, Ile 135, Pro 136, Pro 137, Leu 167.
Ailanthone (CID 72965)	-8.26	1.02	Val 132, Phe 133, Ile 147, Gly 148, Glu 149, Arg 160, Arg 163, Val 164, Leu 167.

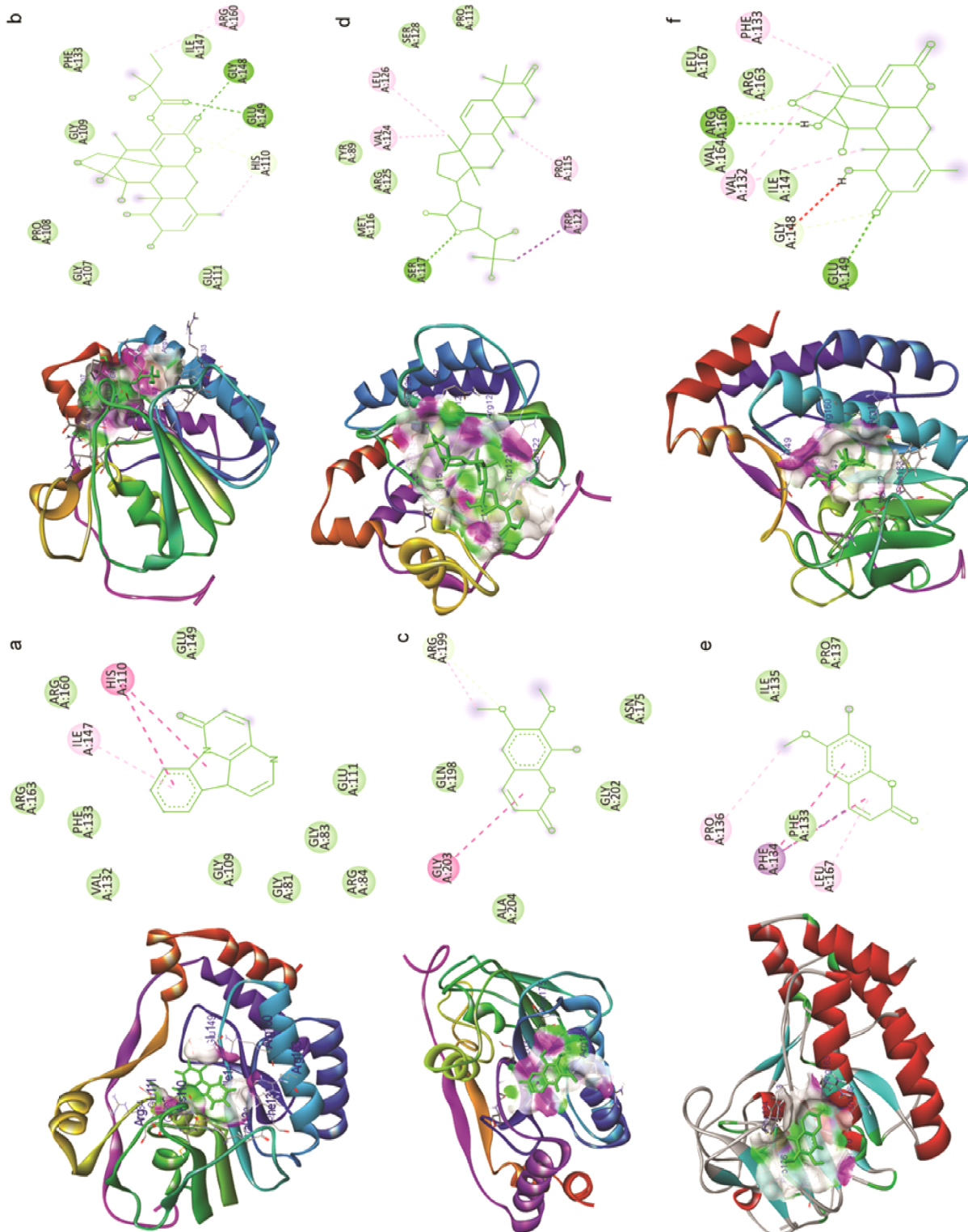


Fig. 3 — a) MTase docked with Canthin-6-one, and Residue interaction in the active site of DENV MTase; b) MTase docked with Glaucarubin, and Residue interaction in the active site of DENV MTase; c) MTase docked with Fraxidin, and Residue interaction in the active site of DENV MTase; d) MTase docked with Melianodiol, and Residue interaction in the active site of DENV MTase; e) MTase docked with Scopoletin, and Residue interaction in the active site of DENV MTase; and f) MTase docked with Ailanthone, and Residue interaction in the active site of DENV MTase.

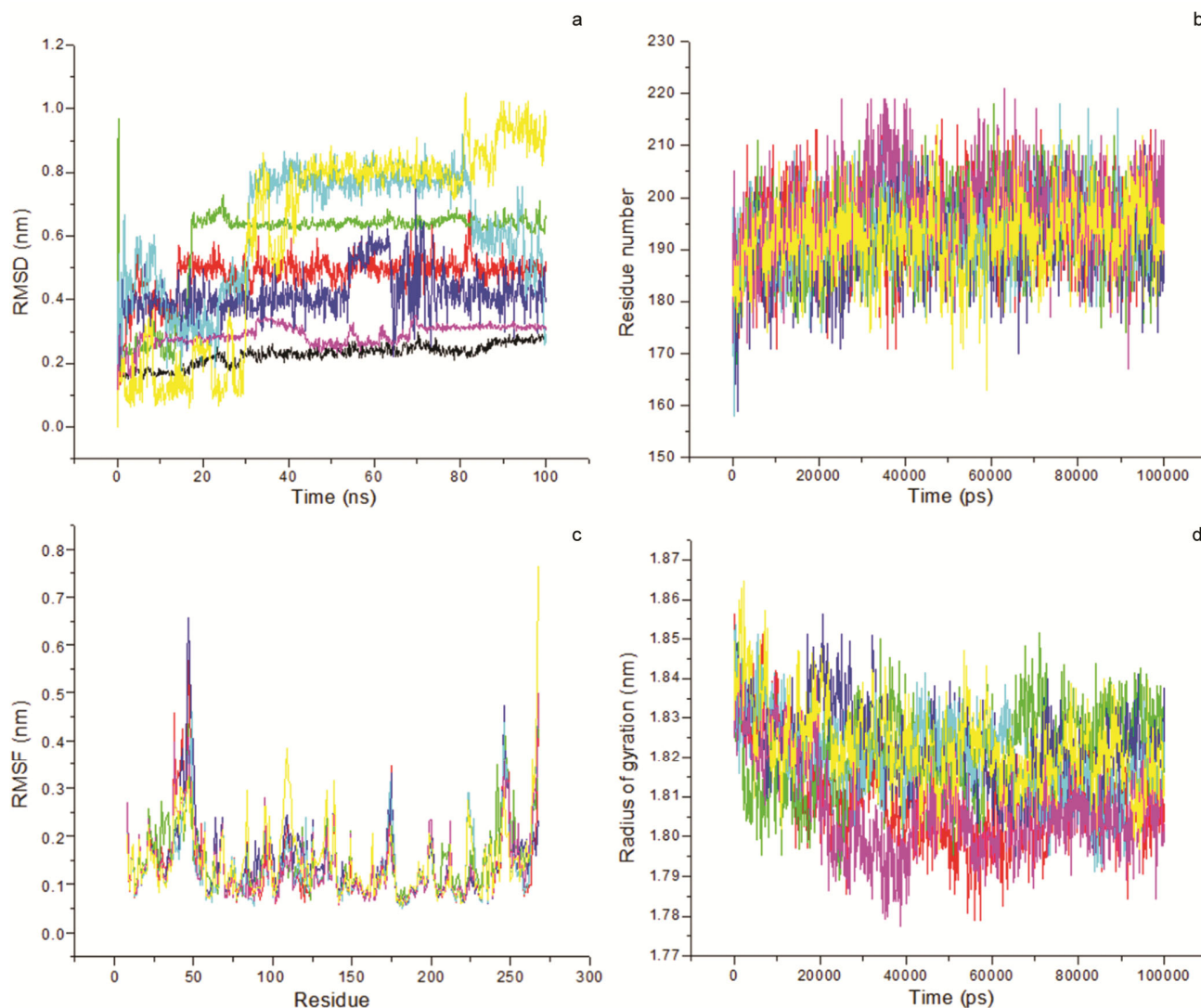


Fig. 4 — Molecular Dynamics Simulation trajectories. a) RMSD curve of DENV MTase with ligands; b) Hydrogen bonding of the residues in DENV MTase; c) RMSF curve of DENV MTase with ligands; and d) Radius of gyration curve of DENV MTase with ligands Backbone (black), glaucarubin (red), fraxidin (green), scopoletin (blue), canthin-6-one (cyan), melianodiol (magenta), ailanthone (yellow).

with the drug candidate. As proteins are not relatively rigid structures; rather, they are dynamic in nature, a model to predict the change in internal energy and the resulting conformational changes plays an essential role in drug discovery³².

The molecular dynamics simulation was performed to evaluate the stability and conformational changes of the docked complex. The degree of conformational changes in the protein (backbone) of DENV MTase and docked complexes was assessed for its Root Mean Square Deviation (RMSD) calculated for 100 ns simulation trajectories for DENV MTase with secondary metabolites canthin-6-one, glaucarubin, fraxidin, melianodiol, scopoletin and ailanthone. The

RMSD of the backbone of DEVN MTase showed stability throughout the simulation, and the peak equilibrated at an average of 0.22 nm. The RMSD of the DENV-glaucarubin complex also showed similar stability throughout the 100 ns of simulation, with the peak equilibrated on an average of 0.48 nm. Similar stability was obtained for other ligands such as fraxidin, scopoletin, canthin-6-one, melianodiol, and ailanthone with RMSD value equilibrated on an average of 0.57, 0.42, 0.62, 0.28, 0.61 nm respectively (Fig. 4a).

DENV MTase shows affinity with glaucarubin, fraxidin, scopoletin, canthin-6-one, melianodiol, ailanthone by forming Hydrogen bonds. The

hydrogen bonds are maintained throughout the 100 ns simulation. The amino acid residues between 167 and 215 were predicted to interact with glaucarubin. Similarly, the amino acid residues between 168 and 218, 159 and 210, 158 and 218, 167 and 221, 163 and 214 of DENV MTase maintain the hydrogen bond with fraxidin, scopoletin, canthin-6-one, melianodiol, and ailanthone respectively (Fig. 4b).

Root Mean Square Fluctuation (RMSF) is another essential parameter in examining the stability and flexibility of the protein-ligand complex and to analyse the steric interaction of the amino acid residues with the ligand during the simulation³³. The RMSF plot of the DENV MTase – glaucarubin complex reveals that the stable conformation is maintained with minimal fluctuations by the residues Pro43, Lys 46, Phe 47, Ala 49, Gly246, and Ile268 in the complex. Similarly, DENV MTase maintains a stable conformation with minimal fluctuations by the residues in Phe47, Gly246, Ile248 with fraxidin, Lys46, Met48, Ala49 and Gly246 with scopoletin, Lys46, Phe 47, Ala 49, Gly246 with canthin-6-one, Phe47, Ile268 with melianodiol and Lys 267 with ailanthone respectively (Fig. 4c).

Radius of gyration (Rg) of the DENV MTase complex was also analysed. Rg is the root mean square distance of the protein atoms around the rotation axis. It is an important parameter representing the changes in the protein structure compactness and its dimensions during the simulation. Higher the Rg value, the protein is less compact and flexible, whereas lower values represent higher compactness and rigidity. Rg values of backbone atoms of protein were plotted against time to examine the changes in structural compactness. The Radius of gyration of the DENV MTase with glaucarubin, fraxidin, scopoletin, canthin-6-one, melianodiol, and ailanthone were predicted to be on an average of 1.82 nm in all complexes during the entire 100 ns simulation (Fig. 4d).

From the predicted RMSD, RMSF and Radius of gyration values together with the predicted Hydrogen bonding between the drug-like molecules and the target DENV MTase. It could be concluded that all the selected bioactive compound present in *S. glauca* interacts efficiently with DENV MTase.

Conclusion

As there is no antiviral drug to treat DENV, there is a critical need for a drug. The world is moving

towards the nature of pharmacologically important products, and plants rich in bioactive secondary metabolites are the choice. The present study has predicted the bioactive compounds canthin-6-one, glaucarubin, fraxidin, melianodiol, scopoletin and ailanthone in *S. glauca* to be like candidates by ADMET prediction based on their pharmacokinetics properties. The bioactive drug-like molecules also bind efficiently with DENV MTase. The binding was confirmed by molecular docking, and the stability of the drug candidates with the DENV MTase target enzyme was confirmed by Molecular Dynamic Simulation. The identified phytochemicals may facilitate the development of effective, promising drug candidates to combat DENV. The study identified ailanthone, melianodiol, glaucarubin, canthin-6-one as the lead compounds that satisfy the physico-chemical properties like solubility in water, lipophilicity, GI absorption, do not pass through BBB, and have pharmacodynamics properties like higher binding energy and low Ki. Future research may focus on validating and optimizing these drug-like candidates, i.e. bioactive molecules of *S. glauca* by both *in vitro* and *in vivo* studies to affirm as novel compounds against DENV virus and design a suitable drug.

Conflict of interest

The author(s) declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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