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RESEARCH ARTICLES

In silico investigation and MD simulations of phytochemicals of *C. wightii* against dengue targets NS5 and E protein

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Abstract

Dengue fever continues to be a global issue which does not have a specific remedy. Many different types of studies have recently been carried out in order to find a potential treatment for the dengue virus using natural resources. *Commiphora wightti* plant is also one such medicinal plants that has been reported to have potential antiviral activity in the treatment of many viral diseases. An in silico molecular binding study is conducted on a library of 52 bioactive compounds of *Commiphora wightti* against dengue virus protein targets, E protein (PDB ID: 3UZV) and NS5 methyl transferase (PDB ID: 2J7U). The molecular docking results showed that the Commipherin (− 8.2 kcal/mol) and Myrrhanone B (− 8.0 kcal/mol) have excellent binding affinity with NS5 methyl transferase while Myrrhanone A acetate (− 11.8 kcal/mol) and Myrrhanone B (− 11.1 kcal/mol) showed it for E-protein target. From the best ten selected phytoconstituents, three have followed the Lipinski's rule and showed good drug likeness score and also satisfied all the ADME and toxicity analysis criteria, viz. Myrrhanone B (14), (13E, 17E,21E)-8-Polypoda-13,17,21-triene-3-18-diol (22) and Guggul sterol- Y (37) which were persuaded for Molecular dynamic simulations to find out new potential drug candidate against DENV. Stability of the Myrrhanone B (14)-NS5 complex was found maximum with RMSD value of 0.2nm. But on the basis of RMSF, Rg and no. of hydrogen bonds, molecule no. 37 (Guggulsterol-Y) and 22 ((13E, 17E,21E)-8-Polypoda-13,17,21-triene-3-18-diol) were found most suitable NS5 inhibitor with considerable RMSD. R_g values of NS5-22 and NS5-37 is scattered between 2.2 nm to 2.3 nm. These phytochemicals have shown significant potential of a therapeutic in *In-silico* studies and further in vitro and in vivo validation of the results is needed in view of finding potential therapeutic agent against Dengue Virus.

Keywords Docking · *Commiphora wightti* · Toxicity · Drug likeness · MD simulation

Introduction

Dengue fever is caused by Flavivirus (DENV) that is carried by mosquitoes, mainly by *Aedes aegypti* and female mosquitoes of the genus *Aedes albopictus* to a lesser extent. Dengue hemorrhagic fever (DHF) or mild dengue fever first appeared when dengue fever broke out in the Philippines and Thailand in the 1950s. Now, it has become the main cause of disease and mortality in many Latin American and Asian countries, including India (Bhatt et al).

NS5 is a non-structural protein receptor identified on the outer surface of dengue virus membranes. It is Flavivirus's biggest and most drug-targeted area, which contains methyltransferase and RNA-dependent RNA polymerase (RdRp). The RdRp catalyzes the replication of RNA via a two-step process, making it a good target for antiviral treatment (MG et al 2002)]. Antiviral molecular research is now focused on targeting important viral enzymes in the infection process by direct or indirect suppression of their biological activity or by disrupting the viral reproduction machinery (Guzman et al 2010). It has been demonstrated, for example, that peptide inhibitors of this enzyme reduce dengue virus infectiousness by 80% in cells [Halstead 2007, Rahman 2021, and Dwivedi 2016)]. The use of bioinformatics tools, molecular modelling programs, and high-speed computing has accelerated the process of creating and searching for therapeutically effective compounds in silico. [Lim 2015 and Ahmab 2020). Among various possible drug candidates, medicinal plants are well-known for their bio-active components, which are a rich source of phytochemical based medicines.

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Some drugs derived from medicinal plants are aspirin, colchicine, digoxin, morphine, quinine, quinidine, taxol, tubocurarine and ephedrine etc. (Bhardwaj 2019). Plants like *Carica papaya, Myristica fatua, Annona squamosa, Psidium guajava, Andrographis paniculate, Cymbopogon citratus, Tinospora cordifolia and Acorus calamus* have shown anti-dengue properties.

Potential inhibitors against Dengue NS5 Methyl transferase from small molecular compounds are found in Ginseng and Notoginseng. (Viwan Jarerattanachat, 2023). Various other phytochemicals like Silymarin, Flavobion, Derrisin, Isosilybin, Mundulinol, Silydianin, Isopomiferin, Narlumicine and Oxysanguinarine have potential inhibitory properties against DENV against DENV4-NS4B receptor (Qaddir et al. 2017). Natural source of Canthin-6-one 9-O-beta-glucopyranoside is Eurycoma harmandiana, which is a small plant belonging to genus Eurycoma Jack of the Simaroubaceae family and distributed in Asia, Kushenol W and Kushenol K is *Sophora favescens*. *Sophora favescens* is a Chinese medicinal herb of Sophora genus, a genus of the Fabaceae family, and widely distributed in Asian regions. These plant are found potential inhibitor of DENV (Tahir ul Qamar et al. 2019) as reported in literature.

Commiphora wightti is one such medicinal plant which has been utilized in ancient Ayurveda medicine, gum of it to treat arthritis, high cholesterol, and other skin disorders along with antiviral properties. Flavonoids, steroids, terpenoids, resin, carbohydrates, glycosides, and amino acids are all present in various portions of the *C. wightti* plant. (Rani 2013).

The aim of the present study is to evaluate the bioactivity of various phytochemicals of *C. wightii* against DENV potential protein targets through In silico studies. The drug like characters of these phytochemicals are also checked along with the molecular dynamic simulation of the docked complexes to ascertain the stability.

Material and methods

Target & lead identification

Because NS5 methyl transferase and E-protein receptor molecules are important protein targets for DENV, they were chosen for this investigation, with pdb ids 3uzv and 2j7u for E protein and NS5 methyl transferase, respectively (Trujillo-Correa 2019 and Morris 2009). The amino acid sequences of these proteins may be retrieved easily from the protein data bank [rcsb.com]. Using SPDVB, bound prosthetic groups such as NAG, Zn, Acetate ion, and Glycerol were eliminated and protein architectures were reduced.

Fifty two phytochemicals of the medicinal plant *Commiphora wightti* plant were identified for the in-silico studies against dengue virus (Table 1). The detailed structure of all the phytoconstituents is given in Table 1. The structure of all the phytochemicals was drawn in Avogadro software and converted to pdb format.

Molecular docking study

AutoDock software package version 4.0 was used to dock the *C. wightti* compounds with the target proteins, and Autogrid, which calculates these grids in advance [Jain 2022]. The active sites of both the receptor molecules were identified within a radius of 10.5 Å as per the reported literature. All ligand molecules connected to the protein were removed and SPDBV version 4.10 was used for "energy minimization." All water molecules were removed and missing hydrogen atoms were added, and after determining the atomic charge of the Kollman unit, the non-polar hydrogen was added to the corresponding carbon. A cubic grid box with a size of 60 Å in the x, y, and z directions was made and centered at the center of the compound at 0.375 Å intervals, and a grid map representing the active target site area was created. Ligand molecules were created by regulating total torsions available, resulting in a more flexible ligand (De 2020 and Jain 2018). The Lamarckian search algorithm was employed.

The binding energy of protein receptor-ligand complex was calculated for best docked pose. UCSF Chimera and Biovia Discovery studio software were used to visualize and analyze protein-ligand interactions in 3D (De 2020) and 2D representations (Laskowski 2011) in docked structure. The inhibition constant was calculated from MGL Tools of Audodock4.0 using Analyze option.

Toxicological properties prediction by admetSAR

Because toxicity is a key criterion in the development of novel pharmaceuticals, the toxicological parameters of the chosen compounds after docking analysis were acquired using the admetSAR site (http://lmmd.ecust.edu.cn/admetsar1/predict/, Jain 2022). The current study predicted AMES toxicity, carcinogenic characteristics, and rodent acute toxicity.

Molecular dynamic Simulations

Molecular dynamic simulation was performed to analyze the stability of ligand-protein interactions with respect to the physical transition of the structural aspect of macromolecules to the functional relevance of the complex. In brief, MD simulation demonstrates strength, pattern, dynamic conformational changes and intermolecular properties of the interactions (Rolta 2021).

A Linux software was used to perform molecular dynamic simulation (MD) of a protein-ligand complex.

Table 1. List of Phytoconstituents of *Commiphora Wight*ii (Rani 2013)

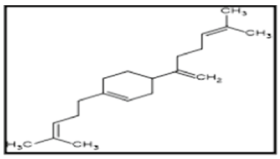
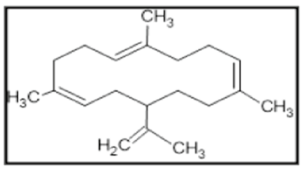
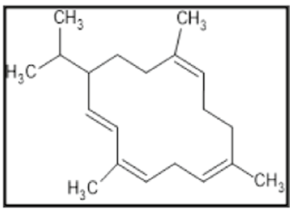
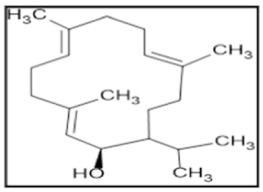
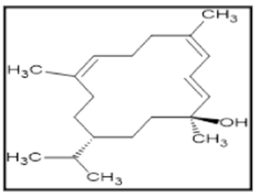
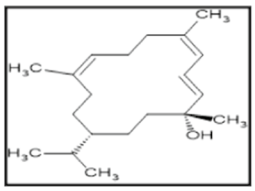
S.No	Ligand/phytochemical	Structure	Medicinal use (for treatment)
Diterpenoids			
1	α-Camphorene		Gastrointestinal disorders
2	Cembrene-A		anti-inflammatory, antibacterial
3	Cembrene		antibacterial, antiviral
4	Mukulol		Analgesic
5	Isocembrol		Cytotoxic
6	4-Epiisocembrol		antidepressant

Table 1. (continued)

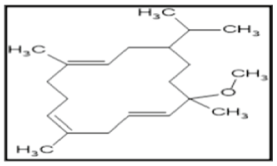
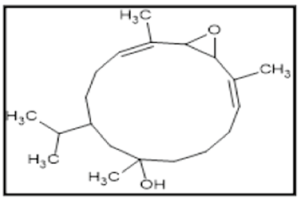
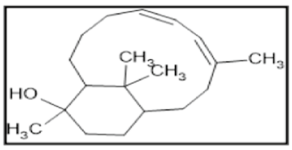
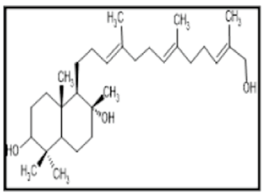
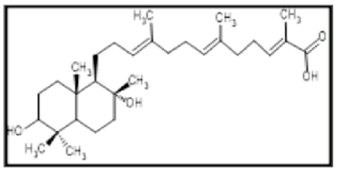
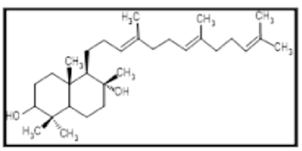
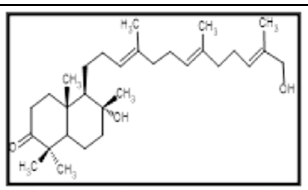
7	(1E,4E,8E)-4,8,14-Trimethyl-11-(1-methyl ethyl)-4-methoxycyclotetra deca-1,4,8-triene		anti-haemorrhoidal
8	(2E,12E)-2,7,13-Trimethyl-9-(1-methylethyl)-15-oxabicyclo [12.1.0] pentadeca 2,12-diene-7-ol		decreasing hepatic cholesterol
9	(4Z,6E)-4,7,12,15,15-Pentamethylbicyclo [9.3.1] pentadeca-4,6-diene-12-ol		anti-inflammatory
Triterpenoids			
10	Myrrhanol A		anti-inflammatory effect on exudative pouch fluid
11	Myrrhanol B		anti-inflammatory, anti-obesity, anti-coagulant
12	Myrrhanol C		promising anti-prostate cancer lead
13	Myrrhanone A		potent anti-inflammatory effect

Table 1. (continued)

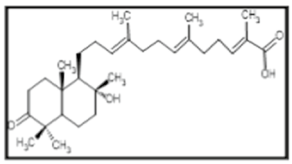
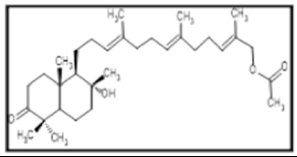
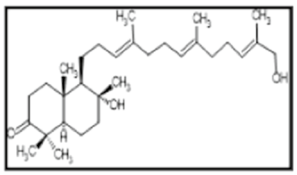
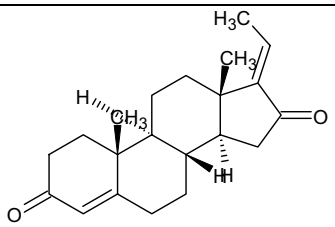
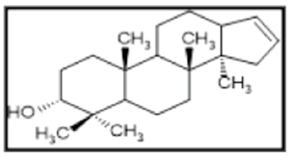
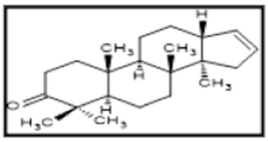
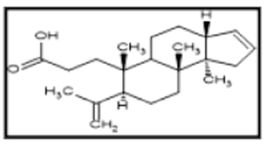
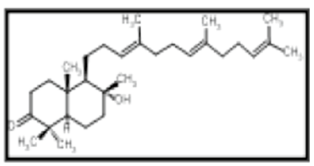
14	Myrrhanone B		Anti-inflammatory
15	Myrrhanone A acetate		treatment of arthritis, inflammation, gout
16	Commipherol		treatment of trauma, arthritis, fractures and diseases caused by blood stagnation
17	Commipherin		Treatment of arthritis, fractures
18	Epimansumbinol		astringent, anti-septic, expectorant
19	Mansumbinone		astringent and antiseptic
20	Mansumbinoic acid		treatment of arthritis, inflammation, gout
21	(13E, 17E,21E)-8-Hydroxypolypoda-13,17,21-triene-3-one		Antiinflammatory

Table 1. (continued)

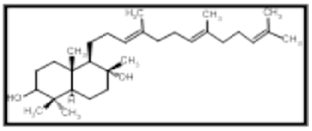
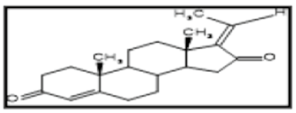
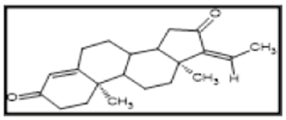
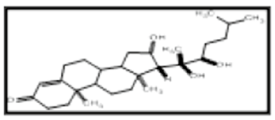
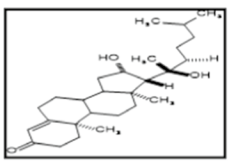
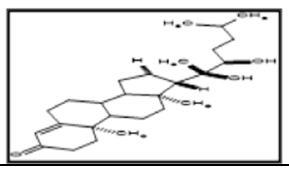
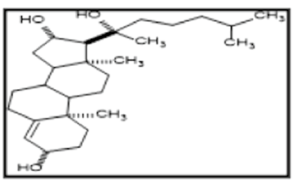
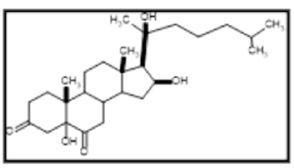
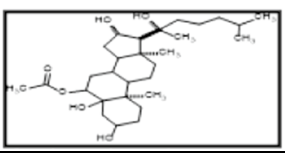
22	(13E, 17E,21E)-8-Polypoda-13,17,21-triene-3-18-diol		Antiinflammatory
Steroids			
23	E-Guggulsterone		obesity, arthritis, and hyperlipidemia.
24	Z-Guggulsterone		inhibits the growth of human prostate cancer cells by causing apoptosis
25	Guggulsterol-I		obesity, liver disorders, malignant sores and ulcers,
26	Guggulsterol-III		obesity, liver disorders, malignant sores and ulcers,
27	20R, 22R-Dihydroxycholest-4-ene-3-one		human metabolite
28	Guggulsterone-II		internal tumors, obesity
29	Guggulsterone-IV		Antiinflammatory
30	Guggulsterone-V		asthma and diabetes

Table 1. (continued)

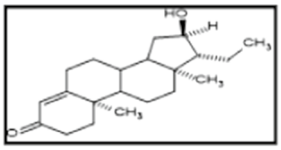
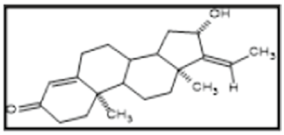
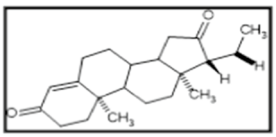
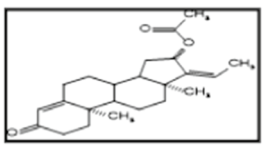
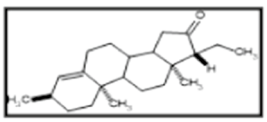
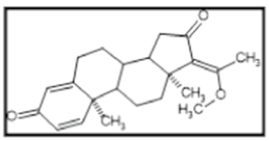
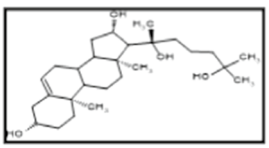
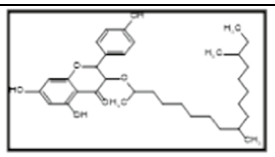
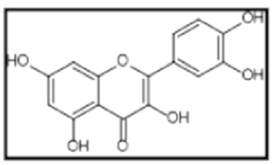
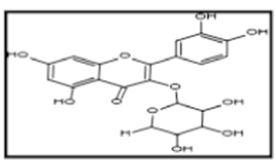
31	Guggulsterone-VI		treat obesity, arthritis, and hyperlipidemia
32	Z-Guggulsterol		human prostate cancer
33	4-Pregnene-3-16-dione		obesity, arthritis, and hyperlipidemia.
34	16β-Acetyloxy-Pregn-4,17(20)-trans-dien-3-one		wound healing
35	3α-Acetyloxy-5α-Pregnan-16-one		cytotoxic activity against cancer cells
36	Dehydroguggulsterone-M		asthma and diabetes
37	Guggulsterol-Y		treatment of arthritis, inflammation, gout, rheumatism
Flavonoids			
38	Muscanone		neurological disorders, chronic inflammation
39	Quercetin		protect against heart disease and cancer
40	Quercetin-3-O-α-L-arabinose		antioxidant properties

Table 1. (continued)

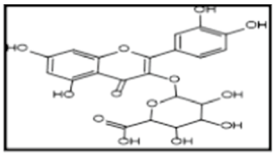
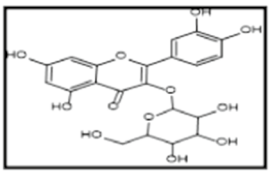
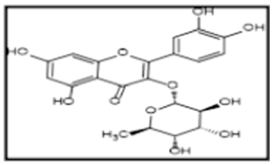
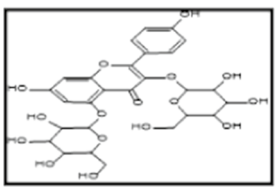
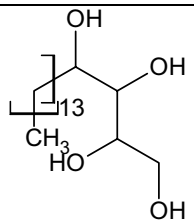
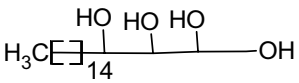
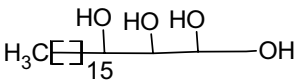
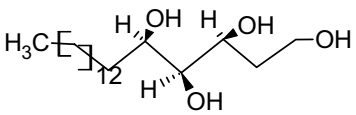
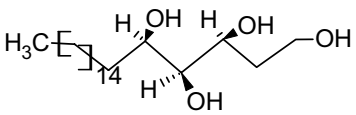
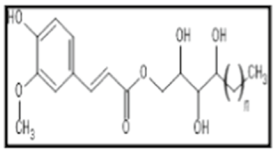
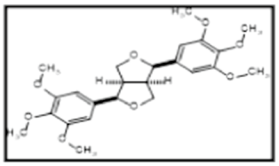
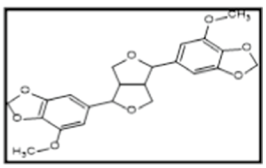
41	Quercetin-3-O-β-D-glucuronide		metabolite, an antioxidant and an antidepressant
42	Quercetin-3-O-β-D-galactoside		anticancer effects on renal cancer cells
43	Quercetin-3-O-α-L-rhammoside		antiviral activity
44	Pelargonidin-3,5-di-O-Glucoside		potent antioxidant properties
Guggultetrols			
45	Octadecan-1,2,3,4-tetrol Tetrahedral)		Anti-inflammatory properties
46	Nonadecan-1,2,3,4-tetrol (tetrahedral)		Anti-inflammatory properties
47	Eicosan-1,2,3,4-tetrol (tetrahedral)		Antipyretic
48	Guggultetrol 18		treatment of arthritis, inflammation, gout, rheumatism
49	Guggultetrol 20		diabetes, bleeding piles, dyspepsia, jaundice

Table 1. (continued)

50	Guggultetrol ferulate		anti-inflammatory, antioxidant and neuroprotective activities
Lignans			
51	Diayangambin		treatment of arthritis, inflammation, gout, rheumatism
52	5,5-Tetrahydro-1H,3H-furo [3,4,1] furan-1,4-diylbis[7-(methoxy)-1,3-benzodioxole		immune stimulant

The GROMAC 2018 was used to check the docking result and analyze the stability and binding structure of a possible compound (Shukla 2020). The simulation was run for 50 nanoseconds at a constant temperature and pressure (300K, 1 atmospheric pressure), With QtGrace /GRACE visualized potential, temperature, and pressure graphs (for linux) (Rezza 2021). The root means square deviation (RMSD), root mean square fluctuation (RMSF), intermolecular hydrogen bonds interactions, binding free energy and radius of gyration (RoG) were evaluated for the elucidation of conformational, structural and compactness of the protein-ligand complexes (Chugh et al. 2023). Molecular receptor topology was created using Gromacs software components.

Result and discussion

Molecular docking study

To validate our evaluation model, we examined if the models can reproduce the biologically active poses of the ligands by redocking (putting back the ligand). For reference data, we have selected Isoquercitrin (Viwan Jarerattanachat) molecule

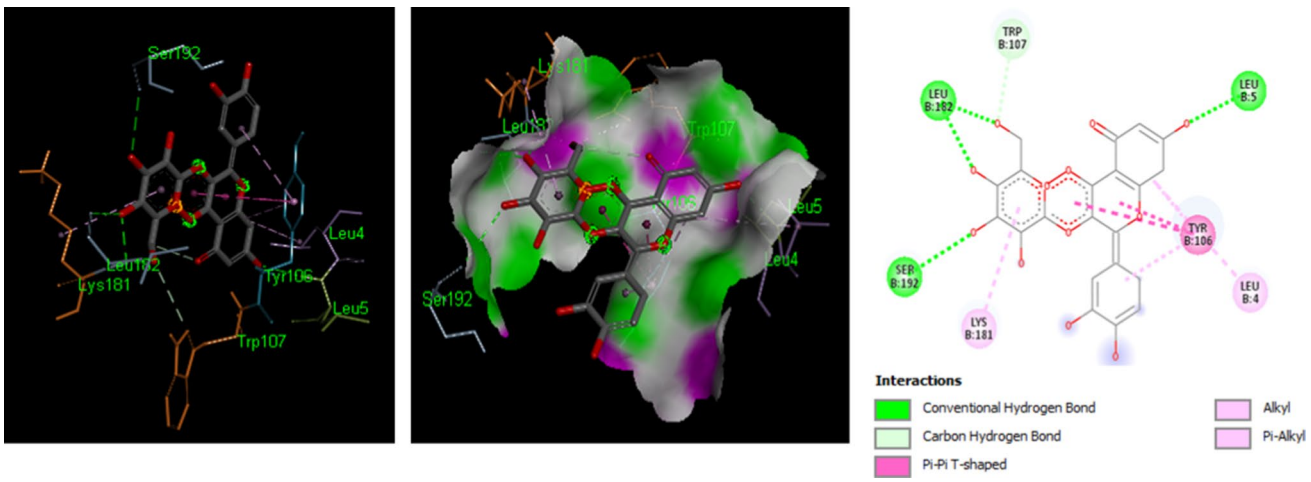


Fig. 1 Model validation, 3D and 2D structures of NS5 MTase with selected real ligand Isoquercitrin

which has shown significant binding results against the active site of biological target DENV NS5 MTase with a binding energy of − 9.0Kcal/mol also shown excellent results in in vitro analysis [Viwan Jarerattanachat, 2023], Fig. 1. Isoquercitrin has selectively binded in the active site of our selected DENV receptor target NS5 MTase(PDB ID 3UZV) and Envelop Protein(PDB Id 2j7u). The XYZ coordinates of 3uzv are − 23.8, − 4.2, − 30.7 with a grid size of 40x40x40 in XYZ directions and that of 2j7u − 23.8, − 4.2, − 30.7 with the same size of grid in XYZ direction was chosen as active site of both the receptor molecules. The molecule has shown same range of binding energy(− 9.0 Kcal/mol with RMSD 1.8 Å). Our first criterion for a suitable molecular docking model is the model predicting the top pose (pose with the lowest docking score) that resembles the reference pose with small root mean square deviations (RMSD) within an acceptable range of 2 Å.

The molecular docking results with both the target proteins show that all the phytochemicals are involved in various non-covalent interactions with receptor molecules with significant free energy of binding. Most of the interactions are hydrogen bonding and hydrophobic along with a few ionic interactions and π-π stacking between aromatic rings. Most of the hydrogen bonds have the bond length within 3 Å. The free energy of binding is negative in all the cases so all the interactions are feasible. (Powers 2016).

Among all, triterpenoids, flavonoids, and steroids phytochemicals are most potent to dock both the receptor molecules among which triterpenoids are most active in binding with the selected targets (Table 2 and 3) however other phytoconstituents have also bonded with receptors (Table S1 and S2). Ten phytoconstituents were selected based on the highest binding affinity and physiochemical properties (Table 4, 5 and 6) of those are being reported. Myrrhanone A Acetate (15) had the best binding energy of − 11.8 kcal/mol, preceded by Myrrhanone B (14) with the binding energy of − 11.1 kcal/mol for the E-protein target whereas *Commipherin* (17) and Myrrhanone B (14) predicted the best binding energy of − 8.2 kcal/mol and − 8.02 kcal/mol respectively for NS5 methyl transferase target. Figure 2 and 3 represent these molecules along with

Table 2 Interaction profile of best 11 phytoconstituents of *C. wightti* with E protein (Pdb Id:3uzv)

Ligand no.	Binding Energy (Kcal/mol)	Type of interaction				Inhibition constant (nM)
		Hydrogen bond	Bond length	Hydrophobic bond	π-π stacking	
15	−11.8	LYS181, LEU182	2.2–3.9	–GLU43B, ALA10B, VAL94B , LEU112,THR221	TYR106, PRO179	2.0
14	−11.1	LYS181, LEU182	2.9 3.3	LYS181, LEU182, TYR106, PRO179	TYR106, PRO179	7.0
12	−11.	TRP107	2.8	LYS181, LEU182, TYR106, PRO179, TRP107	PRO179	7.2
10	−11.0	GLU191, LYS 361	3.0	GLU 327, Ala105. Ile194, LYS181	TYR106	8.4
22	−10.9	–	–	GLU 327, Ala105. Ile194, LYS181, LEU182, TYR106, PRO179	LEU182	9.2
21	−10.9	–	–	LYS181, LEU182, GLU191, LEU182, TRP107	TYR106	9.6
16	−10.8	TRP 107	2.8	LYS181, LEU182, TYR106, PRO179	LYS181	11.1
37	−10.7	TYR106	1.8	GLU 327, Ala105. Ile194, LYS181, LEU182, TYR106, PRO179	LYS181, LEU182, TYR106	12.6
11	−10.7	LYS 361	2.9	TRP107, SER192, PRO180, ALA105	TYR106	13.5
17	−10.7	LYS 181	3.1	TRP107, SER192, PRO180, ALA105	TYR106	14.3
40	−8.5	GLU191, LEU182, TRP107	2.3–3.0	LYS181, LEU182, GLU191, LEU182, TRP107, SER192, PRO180, ALA105	ALA105, TRP107,	12.7

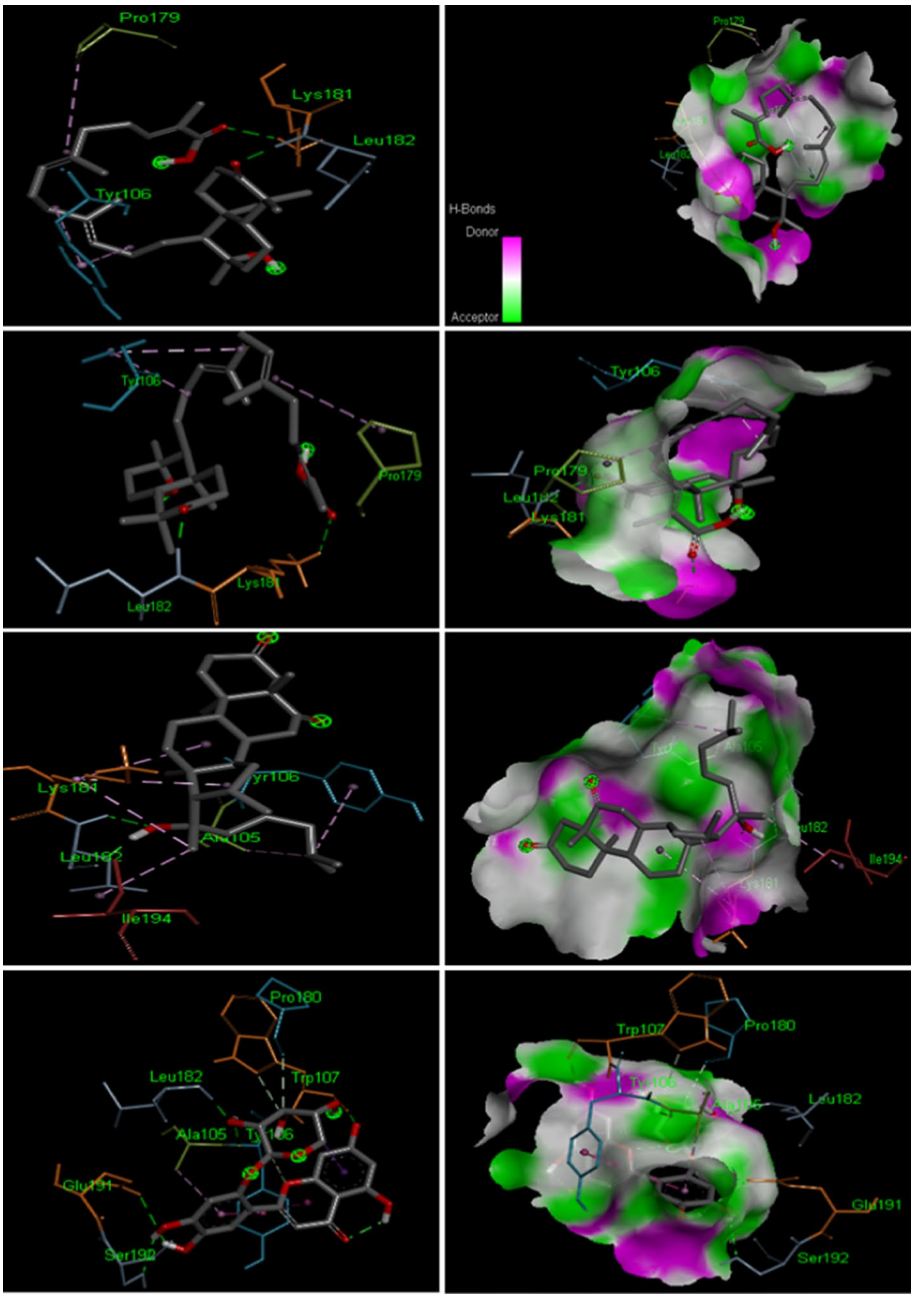


Fig. 2 Visualization of Binding Interactions in 3D Structure of Protein (3uzv) with compound no. 14,15, 37 & 40 by DS visualizer

others. All the docking results along with type of interaction are summarized in Table S1 and S2 against both the receptor molecules. The binding profile of best 10 phytochemicals against both the receptors are mentioned in Table 2 and 3. 3D structure of docked complex of most effective molecules are shown in the Figs. 2 and 3 which is visualized by Discovery studio visualizer. Figure 4 represents the interactions of COMMIPHERIN and MYRRHANONE B with NS5 methyl transferase target in two dimensions in Ligplot. It shows the insertion of ligand molecules into active site of receptor through non covalent interactions with significant inhibition constant. The 2D images of protein-ligand complex generated from Discovery studio visualizer indicates that the ligands form strong hydrogen bonds specifically with Serine residues. Similarly Fig. 5 indicates the interaction of compound no. 15 and 14 with target NS5 protein in two dimensional manners. Similarly, the similar information is represented in Figs. 6 and 7 for receptor E protein (3UZV).

ADME analysis

Table S3 summarizes the molecular properties of top 10 potential molecules which play important role in their drug likeness. In this study, only compound no. 14, 22 and 37

Table 3 Interaction profile of best ten phytoconstituents of *C.wightti* with NS5 protein (Pdb Id:2j7u)

Ligand no.	Binding Energy (kcal/mol)	Type of Interaction				Inhibition constant
		Hydrogen bond	Bond Length (Å)	Hydrophobic bond	π-π stacking	
17	−8.2	LYS 357	2.5	SER 600, LYS 357	VAL353, VAL579, PHE354	846.6 nM
11	−8.0	GLY349, VAL353	2.8–3.2	ARG 352, LYS 357, SER 600	VAL353	1.1 nM
14	−8.0	LYS 357	2.5	LYS 357, SER 600	–	1.3 nM
37	−7.6	–	–	VAL353, LYS 357, SER 600	VAL353	2.3 nM
15	−7.5	ARG 737	3.1	ARG 737, MET 342, ARG 352	–	3.1 nM
22	−7.4	–	–	ARG 352, LYS 357, SER 600	VAL353, VAL579, LYS357	3.2 nM
16	−7.4	–	–	MET 342, ARG 352	THR345, VAL353	3.6 nM
38	−7.2	ARG 352	2.6	MET 342, ARG 352	VAL353	5.0 nM
21	−7.2	LYS 357	3.0	LYS 357	VAL579	5.1 nM
10	−7.1	LYS 357	3.4	LYS 357	VAL353	5.4 nM

obeyed the Lipinski's rule and had a good drug likeness score (Table 4). MilogP results were analyzed and found below 5 for compound number 37, however it was higher in the 14 and 22 compounds indicating compound no. 37 shows good bioavailability and bioactivity score too (De Paula 2004). The TPSA of all the compounds was found to be between 40.4 and 80.9 (well below 150) and their molecular weights were less than 500. The number of hydrogen bond acceptors (< 7) and donors (< 5) were found to be within Lipinski's limit of 6 and 4, respectively, with n-violations ranging from 0 to 1 (Rosmalena 2019).

Table S4 displays the bioactivity scores of the 10 compounds chosen for computation for each protein based on nuclear receptor ligand (NRL), GPCR ligand, kinase inhibitor (KI), ion channel modulator (ICM), enzyme inhibitor (EI), and methyl transferase inhibitor (PI). For the substances, these scores might be interpreted as active (bioactivity score > 0), moderately active (bioactivity score − 5.0–0.0), or inert (bioactivity score − 5.0). The majority of the 10 compounds were found to be active or somewhat active against all of the protein enzyme targets. Furthermore, these compounds' drug-like characteristics might be improved by substituting them with their derivatives. In terms of hepatotoxic applicability, all five compounds fall within the predicted range. Detail of best 3 molecules found in ADMET analysis is mentioned in Table 5.

Toxicity effect of the compounds

The pharmacokinetics determines in the current research includes HIA, BBB penetration, plasma protein binding and CYP450 2D6 inhibitor.

The current study found that seven compounds were unable to penetrate the BBB, interpreting them negative and thus violating the ADME rule, and all the phytoconstituents were non-inhibitors that could pass via the membrane and show pharmacological effect (Table S5).

The Caco-2 permeability ranges from 0 to 1, indicating excellent absorption (Trujillo-Correa 2019). All the compounds were discovered to be non-AMES poisonous and non-carcinogenic. The BBB rating is between 0.75–0.93, which is within the acceptable range. Compound 37 exhibits greater absorption and distribution properties, as well as higher permeability of HIA, BBB, and Caco-2, indicating that its pharmacokinetics are superior to others. The chemicals are not carcinogenic or mutagenic. The rat model's determined median lethal dose (LD50) value aids in determining the compound's lethality. It was discovered that the LD 50 values of all compounds were greater than the regularly used medication streptomycin (LD50 was 1.84 mol/kg), indicating that synthesized molecules had a stronger therapeutic index.

Toxicity analyses (irritability, mutagenicity, carcinogens and AMES toxicity) of the ten selected phytoconstituents revealed that all of the phytoconstituents were non-toxic. However, seven phytochemicals were non-toxic but violating the Lipinski rule, therefore they were deemed unacceptable candidates. As a consequence, only three compounds (14, 22, 37) met all of the ADME and toxicity requirements and were chosen for future study (Table 5 and 6).

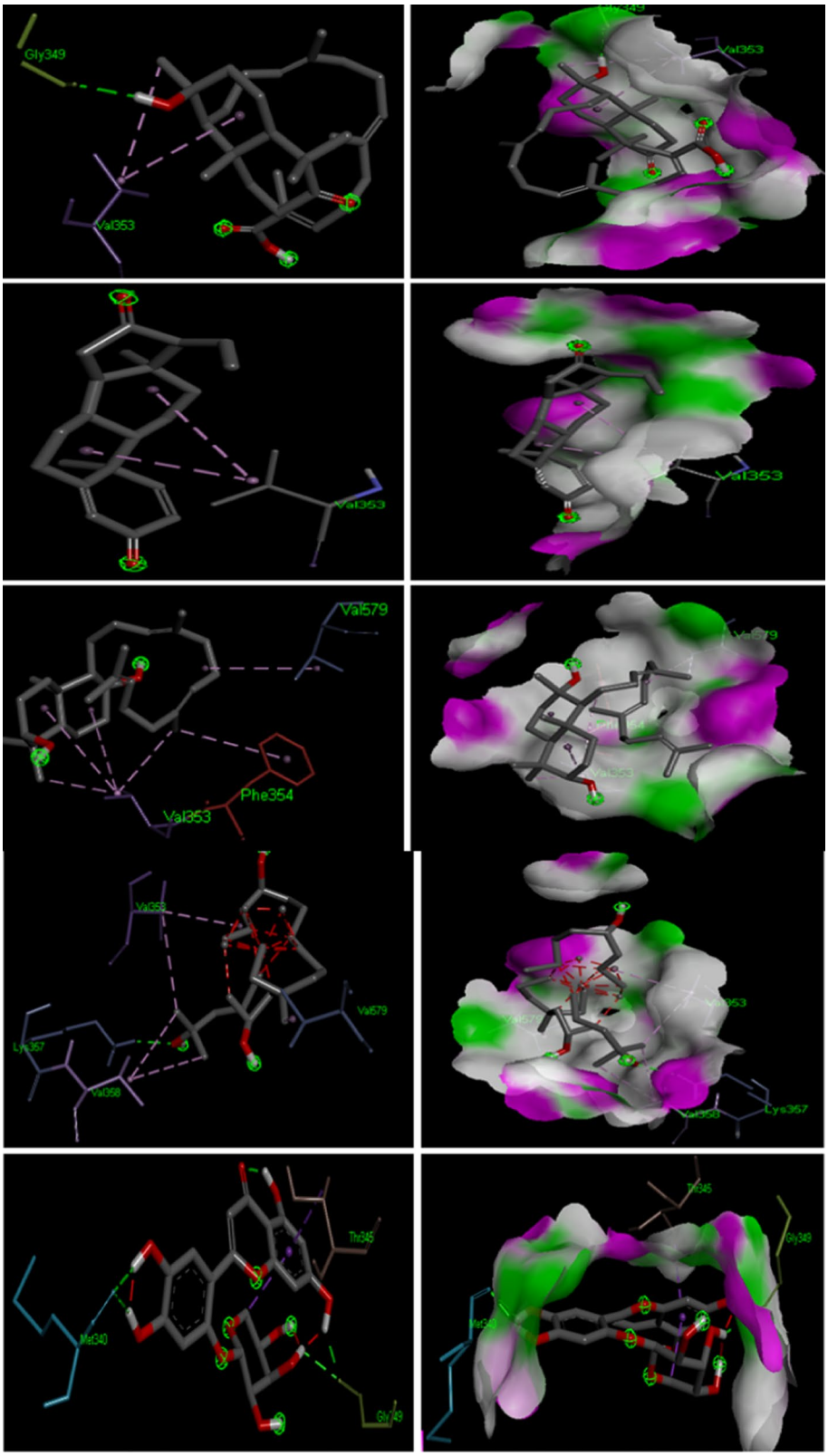


Fig. 3 Visualization of Binding Interactions in 3D/2D of Protein (2j7u/NS5 methyl transferase) with compound no. 11,37,17, 22 & 40 by DS visualizer

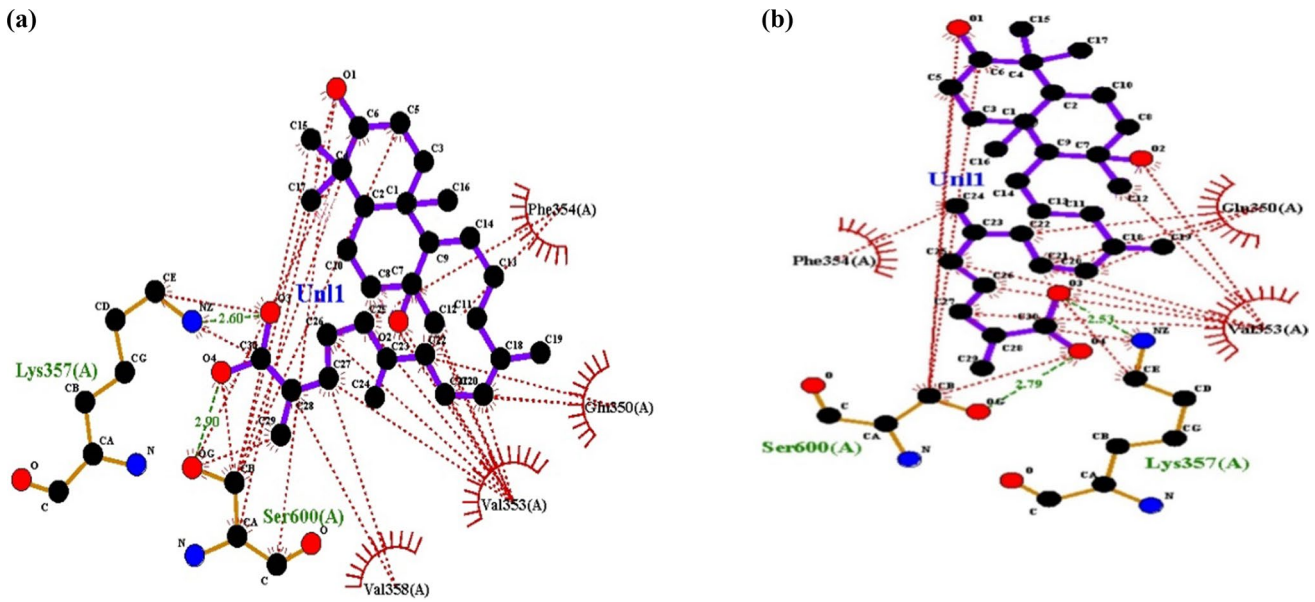


Fig. 4 2D depiction of binding interaction (Hydrophobic) of selected molecules**a** Commipherin **b** Myrrhanone B against the target NS5 methyl transferase (2j7u)

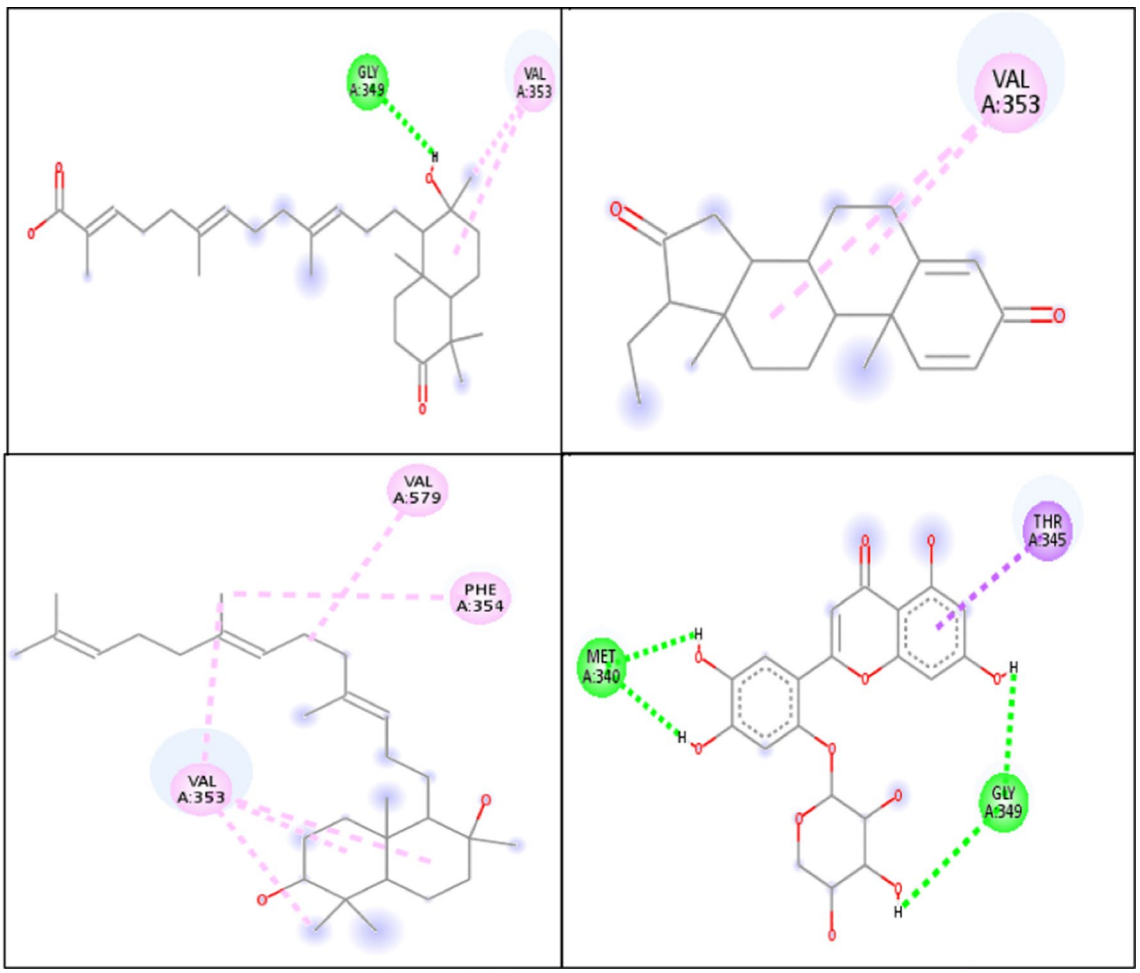


Fig. 5 2D depiction of binding interaction of selected molecules 11,17,22,40 (hydrogen bond, π-π stacking) against NS5 methyl transferase (2j7u)

Table 4 Molecular properties of the best 3 molecules

S. No	Molecular weight (≤ 500) g/mol	cLogP (≤ 5)	H-bond acceptors (≤ 10)	H-bond donors (≤ 5)
14	472.7	4.2	3	2
22	444.7	5	2	2
37	434.6	4.5	4	4

Molecular dynamic simulations

Figure 8a depicts the RMSD of the ligand-protein complexes' backbone. Individual amino acid conformational changes in protein were compared by computing the root mean square fluctuations (RMSFs) of amino acids, as shown in Fig. 8b–d. The RMSD metric suggests that proteins are reasonably stable after interacting with ligands (14, 22, 37) (Paul 2021). The radius of gyration (R_g) of the protein was used to compute the compactness of the ligand-protein complexes shown in Fig. 9. As seen in the figure, R_g values of NS5-22 and NS5-37 appear to be scattered between 2.2 nm and 2.3 nm. By having a plateau variation of R_g in the last 10–20 ns of the MD trajectories, all of the proteins demonstrated adequate stability. As a result, it is important to underline that ligand binding has no effect on the structural stability of the protein. Close examination reveals some minor differences in the fluctuations of the amino acids of proteins in ligand–protein complexes.

The number of hydrogen bonds was determined using the GROMACS program's g dist function. The distance between the centers of mass of the two groups of atoms participating in hydrogen bond formation was essentially constant throughout the simulation duration, indicating the continuity, stability, and efficacy of the hydrogen bonding. It measures the binding affinity of ligand. More no. of hydrogen bonds between the protein and Ligands showed strong binding affinity. In this study we found maximum 30 hydrogen bond at the end of 50 ns simulation.

Conclusion

Based on molecular docking study, we can postulate that these all phytochemicals of *C. wightii* has the inhibition potential against the E & NS5 methyl transferase protein targets of DENV. From all the molecules, the best binding energy of the phytochemicals against NS5 protein are Commipherin (− 8.2 kcal/mol), Myrrhanone B (− 8.0 kcal/mol) and Myrrhanone A acetate (− 11.8 kcal/mol), Myrrhanone B (− 11.1 kcal/mol) were found active against E protein receptor in molecular docking study. Only molecule no. 14, 22, and 37 from the ten selected molecules follows the Lipinski's rule and have the best drug likeness score. Three molecules

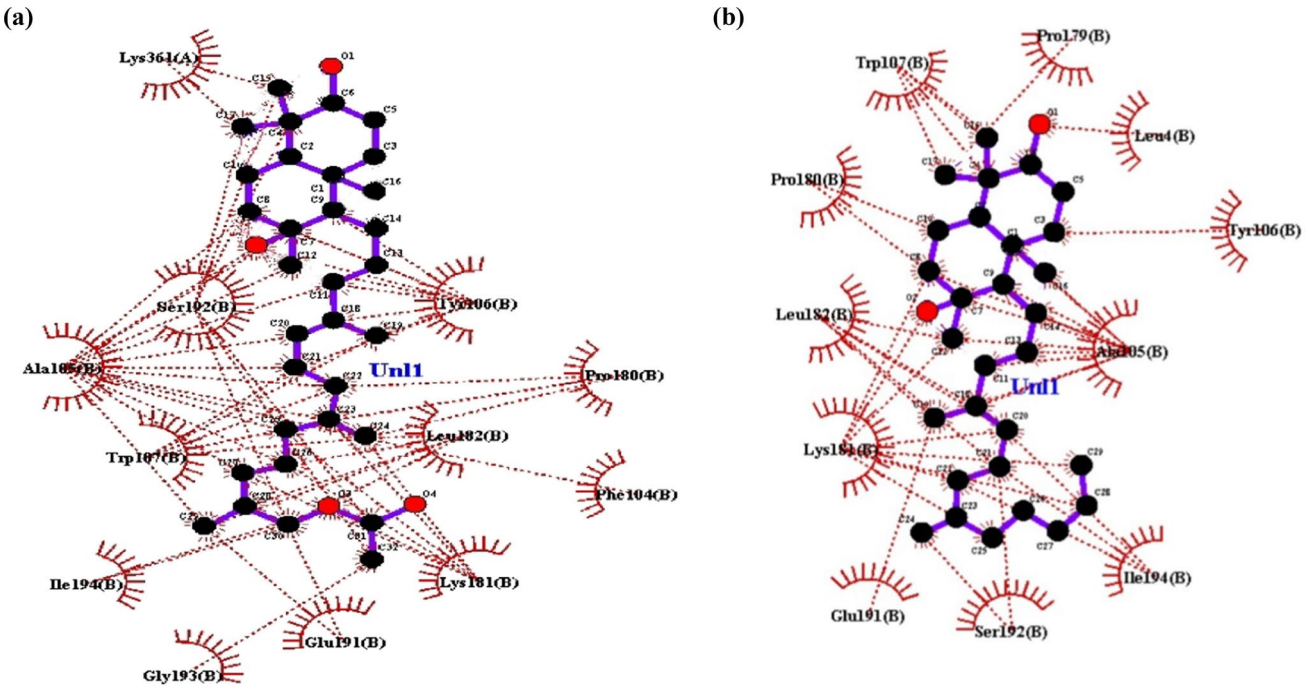


Fig. 6 Two dimensional depiction of binding interaction of selected molecules**a** Myrranone A acetate (14) **b** Myrrhanone B (15) against the target E protein/3UZV

Table 5 Drug-likeness and bioactivity score of best 3 molecules

Compound no.	Drug likeness milogP	Bioactivity scores TPSA	Nviolations	GPCRL	ICM	KI	NRL	PI	EI
14	7.3	74.6	1	0.16	0.15	−0.46	0.76	−0.07	0.52
22	8.6	40.4	1	0.24	0.25	−0.26	0.74	0.04	0.55
37	4.5	80.9	0	0.28	0.03	−0.36	0.93	−0.04	0.62

Table 6 Toxicity analysis of best 3 molecules–

S. No	HIA	BBB permeant	CYP 450 2D6 inhibitor	PPB (%)	AMES Toxicity	Carcinogens	Mutagenic	Irritant
14	+	+	Non- Inhibitor	100	Non-AMES toxic	Non- Carcinogens	–	0.9259
22	+	+	Non- Inhibitor	100	Non-AMES toxic	Non- Carcinogens	–	0.9377
37	+	-	Non- Inhibitor	100	Non-AMES toxic	Non- Carcinogens	–	0.9603

BBB blood-brain barrier, *HIA* human intestinal absorption, *PPB* plasma protein binding

(14, 22, 37) satisfied all of the ADME and toxicity analysis requirements and were chosen for some further investigation. Molecular dynamic simulation studies were performed on three potential docked complexes, among which NS5-37 complex has shown the best results in the form of stability, RMSD and RMSF value. Further in vitro and in vivo validation is needed in view of finding potential therapeutic agent against Dengue Virus.

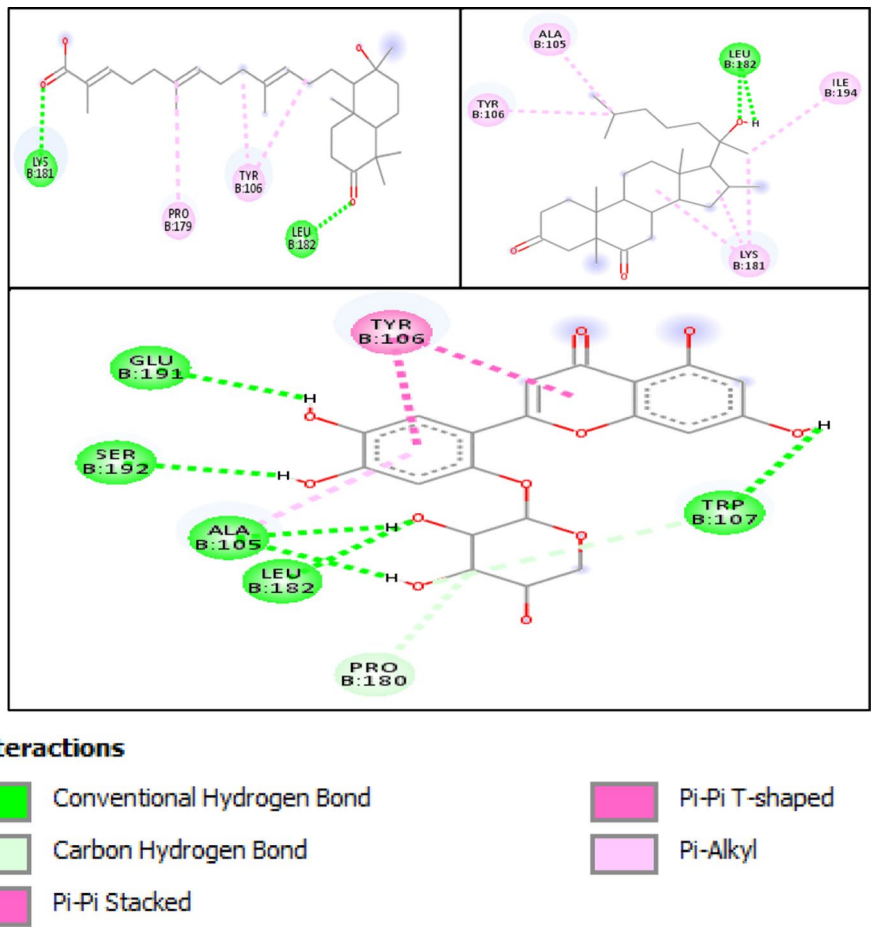


Fig. 7 Two dimensional depiction of binding interaction(hydrogen bond, π-π stacking) of selected molecules 14, 29, 40 against thetarget E protein(3UZV)

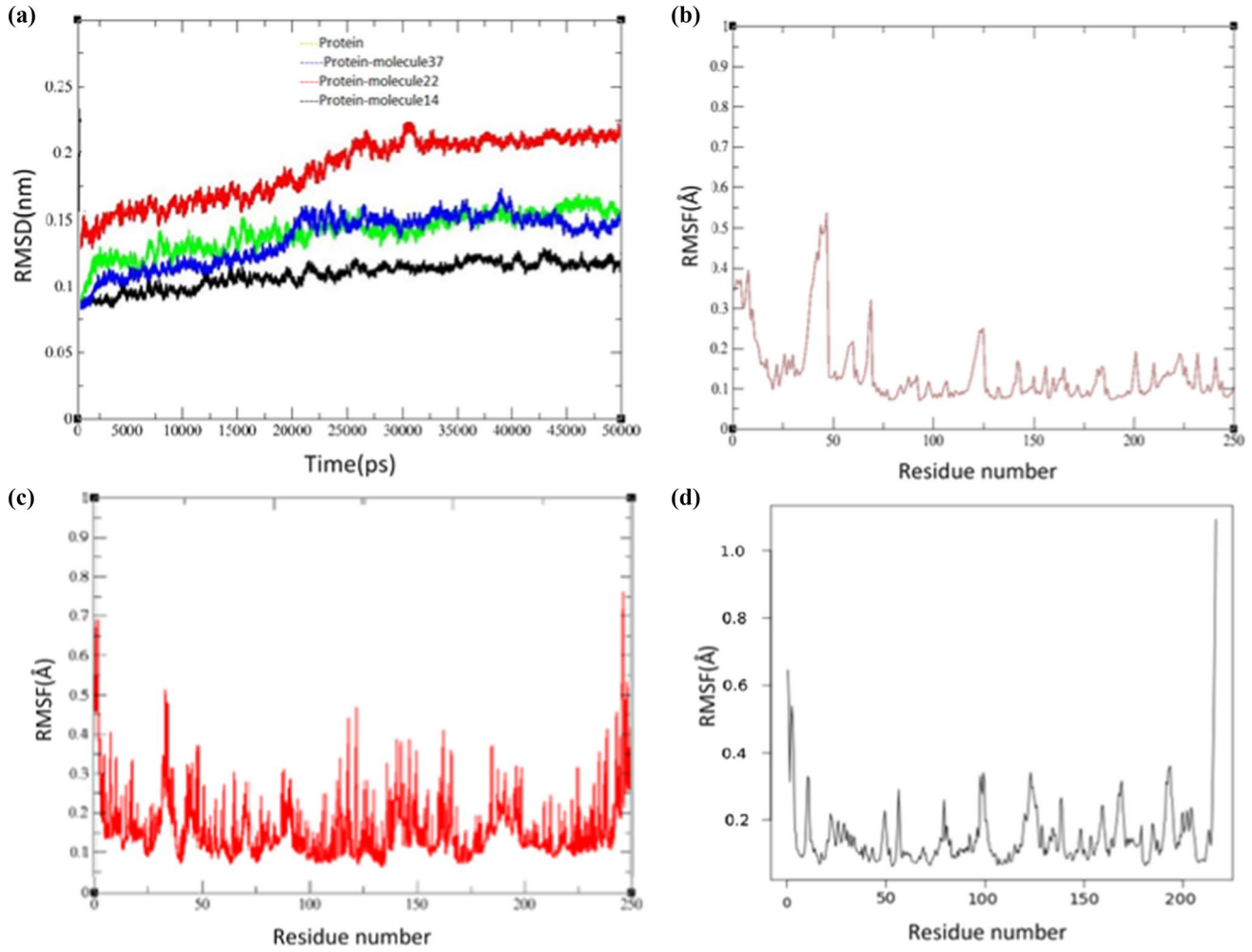


Fig. 8 **a** Relative RMSD value of docked complexes of NS5-37, NS5-14 and E-22 **b** RMSF value of NS5-37 **c** RMSF value of E-22 **d** RMSF value of NS5-14

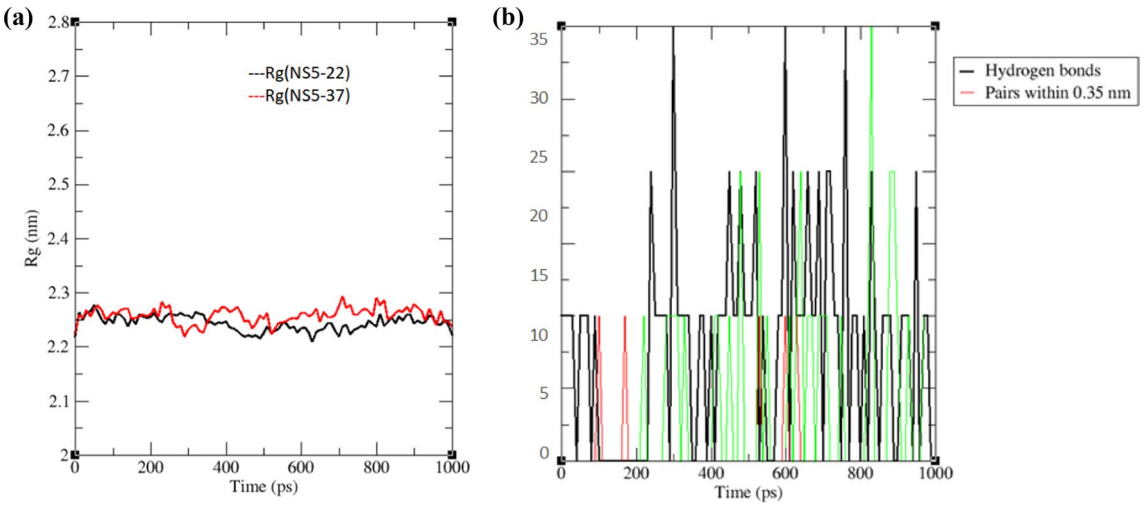


Fig. 9 Radius of gyration **a** NS5-37 & E-22 **b** No. of hydrogen bonds in NS5-37

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Author contributions PJ has contributed in Conceiving the idea, supervision, writing manuscript Conceptualization while YS and RK have contributed to Execution of work, writing manuscript.

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Data availability The data related to the reported research/findings will be provided on demand.

Declarations

Conflicts of interest There is no Conflicts of interest/Competing interests to declare for this manuscript.

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