Indian Journal of Traditional Knowledge
Vol 21(3), July 2022, pp 537-544

Molecular docking of potential Indian medicinal plant compounds against dengue viral proteins

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Received 21 March 2020; revised 16 January 2022

Dengue fever is one of the major health issue caused by Dengue virus. The present work focuses on virtual screening of compounds from the selected medicinal plants, *Azadirachta indica*, *Andrographis paniculata*, *Tinospora cordifolia* and *Carica papaya* for their anti-viral activity against dengue virus. The envelop protein and methyl transferase enzyme of dengue virus has been selected for the study. Computer aided docking of plant compounds with selected viral proteins known for its pathogenicity in humans were performed using Auto Dock software after checking their drug likeness property assessed on the basis of Lipinski's rule of five. Most of the selected compounds docked well with the viral protein in terms of their binding energy and ligand efficiency with effective drug likeness property as compared to the reference synthetic drug. Nimbocinol and Meliacinanhydride of *Azadirachta indica* were found to be the top most compounds against selected dengue viral protein displaying highest binding affinity. Andrographolide of *A. paniculata* and Tinosporide and Berberine of *T. cordifolia* also showed promising results against viral proteins. Since these naturally derived compounds have several advantages over synthetic drugs, these compounds can be used as an anti-viral drug for the treatment of dengue fever after checking their efficacy and safety by *in-vitro* and *in-vivo* experiments.

Keywords: *Andrographis paniculata*, *Azadirachta indica*, *Carica papaya*, Dengue, Docking, *Tinospora cordifolia*

IPC Code: Int Cl.[22]: A61K 36/00, A61K 36/185, A61K 39/00

Dengue virus (DENV) (family: *Flaviviridae:* genus: *Flavivirus)*, capable of infecting humans through *Aedes aegypti* mosquitoes. Infection with DENV produces a broad category of clinical symptoms in humans that includes a mild flu-like condition which is often self-limiting (dengue fever, DF) and a severe fatal form referred to as the dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). There is a serious concern worldwide since Dengue viral infection has been reported in approximately 50 million people each year and people who are at the risk of infection is more than 2.5 billion[1]. Each year approximately 50 million cases of infection are reported with 5, 00, 000 cases of haemorrhagic fever and atleast 12,000 deaths mainly among children[2]. The unavailability of vaccines or specific antiviral drugs to treat this infection increases the magnitude of symptoms and makes it difficult to manage. Several *in vitro* studies reported earlier have shown positive results upon the use of medicinal plants to treat dengue infection based on the traditional knowledge[3]. But there are very few reports available on efficacy of compounds derived from theses medicinal plants against DENV. The present work focuses on virtual screening of compounds from the selected Indian medicinal plants, *Andrographis paniculata*, *Azadirachta indica*, *Carica papaya* and *Tinospora cordifolia* for their anti-viral activity against dengue virus.

Andrographis paniculata (family: Acanthaceae), is an annual plant indigenous to Sri Lanka and India. It is one of the important traditional medicinal plant enriched with several phytoconstituents found in leaves, root, stem and whole plant. Several parts of this plant have been found to be rich in lactones (andrographolide, kalmeghin, deoxyandrographolide), flavonoids and diterpenes[4]. The plant extracts has shown immunostimulant, hepato-protective, cardio-protective, anti-diabetic, anti-inflammatory, antibacterial, anti-viral and anti-carcinogenic activity[5]. The most prominent terpenoid present in this plant is andrographolide reported to be responsible for many of its medicinal property[6].

Azadirachta indica (family: Meliaceae), is a versatile plant indigenous to India and Pakistan and propagate throughout tropical and semi-tropical regions.There are several pharmaceutically active compounds have been isolated from all most each and every parts of Neem. It has been reported to have immunostimulatory,

hepatoprotective and analgesic, hypoglycemic, anti-bacterial, anti-fungal, anti-malarial, anti-viral, anti-carcinogenic, anti-inflammatory, anti-pyretic, and anti-oxidant activity[7]. The antiviral activity against poliovirus and bovine herpes virus type 1 (BoHV-1) has been reported for polysaccharides of *A. indica*[8,9], seed kernel extracts against duck plague virus[10] and bark extract against herpes simplex virus type-1 infection[11] have also been reported. The uses of neem by mankind to treat several illness from prehistoric to contemporary has been reviewed by Kumar and Navaratnam[12].

Carica papaya (family: Caricaceae), is a tall herb growing in tropical regions worldwide, indigenous to tropical America and grown in India from 16th century onwards. The papaya leaves have been consumed conventionally to treat many diseases like jaundice, malaria, dengue, immunomodulatory conditions, allergy, digestive complaints and respiratory disorders[13]. The phenolic compounds reported to present in young leaves of *Carica* includes, caffeic acid, chlorogenic acid, and protocatechuic acid. The flavonoids kaempferol and quercetin was also present in young leaves and has shown greater anti-inflammatory, hypoglycemic, anti-fertility, wound healing potential. Many other phytochemicals with antibacterial and antiviral activity isolated from papaya are, polysaccharides, vitamins, minerals,enzymes, alkaloids, glycosides, fats, oils, lectins, saponins, flavonoids and sterols[14].

Tinospora cordifoila, (family: Menispermaceae), growing in India and China are widely used in Ayurvedic medicine for its property to stimulate immune system, and also found to have anti-inflammatory, anti-allergic, anti-diabetic, anti-stress, anti-malarial and anti-leprotic activity[15]. The different types of active compounds isolated from this plant include alkaloids, diterpenoid lactones, glycosides, steroids, lectins, peptides, sesquiterpenoid, phenolics and polysaccharides. Among these, coumarins, lectins and polypeptides are reported to have antiviral property by blocking viral fusion and adsorption[16]. The petroleum ether extract of *T. cordifolia* showed the highest inhibition of gp 120/CD4 interaction and also inhibited viral reverse transcriptase enzyme and thereby reported to have anti-HIV activity[17]. The alkaloid, tinosporide has been reported to have anti-HIV activity along with jatrorrhizine, magnoflorine, by docking well with HIV-1 protease[18]. Berberine, isolated from root and stem of this plant has been reported to have antiviral and anti-carcinogenic activity[19].

Molecular docking is the high-throughput *in silico* screening that facilitates the identification of novel plant products from plethora of compounds available which could be used for *in vitro* and *in vivo* experiments. By predicting the molecular interaction between target and ligand, docking studies saves us time, energy and resources and in turn accelerates the process of drug development.

Till date, not much information is available about the potentiality of natural plant compounds against dengue viral proteins. With this purpose, *in silico* experiment were performed to identify most suitable and successful metabolite from these medicinal plants before testing their efficacy in laboratory. Computational trials and analysis using such prediction tools helped us to short list the candidate drugs to be worked upon *in vitro.*

Materials and Methods

Ligand retrieval and preparation

The number of compounds selected for docking study based on the information available in the literature are, twelve compounds from *A. paniculata*, seven from *A. indica*, seven from *C. papaya* and nine from *T. cordifolia*. The SDF format of these compounds 3D structure were downloaded from the PubChem database[20]. Energy minimization by geometry optimization in the force field mmff94 was done for all these selected compounds using Avogadro software[21].

Prediction of drug-likeness property

Molinspiration, a free online chemiinformatics tools was used to predict the potential drug property of selected compounds[22]. The criteria based on Lipinski's rule of five includes, the compound which has less than 500 g/mol molecular weight; the compound which has less than 3 hydrogen-bond donors; less than 12 hydrogen-bond acceptors;less than 5 partition coefficient (log P) value and the compound with less than 12 number of rotatable bonds.

Retrieval of Dengue viral protein

The PDB file of dengue viral proteins, Dengue 4 envelop protein domain III ED3 (3WE1), envelop protein domain III (5B1C), Dengue 3 NS5 Methyltransferase (5EC8), Dengue virus 1 NS5 Methyl transferase (5IKM)were retrieved from the molecular

database RCSB (Research Colloboratory for Structural Bioinformatics). The associated ligand molecules and water molecules were removed using PyMOL molecular viewer[23].

Preparation of protein

The preparation of target protein was done using AutoDock tools where hydrogen atoms were added at unfulfilled valencies to correct partial charges and merging of polar bonds were carried out. After calculating Gasteiger charges of each atom of the molecule and total energy, the charged protein was saved as a PDBQT file.

Docking of the molecule to protein

A grid map was created in AutoGrid program to incorporate the active site of the compound with the point separation of 1 angstrom, and the dimensions of the grid were maximum. Molecular docking was carried out in AutoDock 4.2.6, by applying genetic algorithm[24]. The default parameters were set such as 10 runs in a population size of 150, the maximum number of configurations set to 27,000 and energetics evaluation to 2,500,000. The Lamarckian parameters were chosen to get the output and all docked conformations were visualized after saving it as dlg file. The best docking output (in terms of binding energy) were selected and this exported complex was visualised and analysed using PyMol for the better understanding of protein and ligands interaction.

Results

The number of compounds that passed Lipinski's rule of five that makes them an attractive drug candidate were found to be 10 from *A. paniculata*, 4 from *A. indica*, 6 from *C. papaya* and 7 from *T. cordifolia* (Table 1). Only these successful drug candidates were used for docking analysis against viral proteins. The result of molecular docking of above plant metabolites was further compared with the synthetic drug, acetaminophen. The criteria to select best ligand molecule is the one which has lowest binding energy with lesser inhibitory constant (KI) upon docking. A low binding energy score for a protein-ligand interaction indicates that the structure is comparatively stable. Also, the binding affinity of the ligand is always found to be higher when it has low inhibitory constant (KI) value. The binding energy score of the selected compounds ranges between -4.96 to -9.2 Kcal/mol.Out of all the *A. Paniculata* compounds selected for the docking studies, the lowest

Table 1 — Drug-likeness property of the top compounds based on Lipinski's rule

S. No	Compounds	Molecular weight (kDa)	Hydrogen bond donor (OH+NH)	Hydrogen bond acceptor (0+N)	No. of rotatable bonds	Log P
		Andrographis paniculata				
1	Andrographolide	350.45	5	3	3	1.05
2	14-deoxyandrographolide	334.46	4	2	4	1.72
3	Andrograpanin	318.46	3	1	4	2.87
4	Isoandrographolide	350.45	5	2	2	1.14
5	Neoandrographolide	480.6	8	4	7	1.17
		Azadirachta indica				
6	Isomeldenin	454.61	1	5	3	4.44
7	Meliacinanhydride	570.63	1	10	6	2.77
8	Nimbocinol	408.54	1	4	1	3.52
9	Zafaral	484.63	0	6	6	4.83
		Carica papaya				
10	Coumaric acid	164.16	3	2	2	1.43
11	Caffeic acid	180.16	4	3	2	0.94
12	Kaempferol	286.24	4	0	1	2.17
13	Protocatechuic acid	154.12	4	3	1	.88
14	Citropten	206.2	4	0	2	2.03
		Tinospora cordifolia				
15	Berberine	336.37	5	0	2	0.2
16	Tinosporide	374.39	7	1	1	2.02
17	Palmatine	352.41	5	0	4	-0.05
18	Magnoflorine	342.42	5	2	2	-1.26
19	Tinocordifolin	250.34	3	1	1	2.17
20	Acetaminophen	151.16	3	2	1	0.68

binding energy (-7.28 Kcal/mol) and a ligand efficiency of -0.32 was recorded for the compound, andrograpanin (Table 2). The KI was found to be 4.6 µM which denotes the highest binding affinity of this compound with the viral protein 5IKM. This was followed by neoandrographolide and andrographolide showing low binding energy with the same protein. Andrographolide was also found to dock well with 5B1C (binding energy of -6.51 Kcal/mol; KI: 16.94 µM) showing interaction with three aminoacids (Val333, ILE335 and ILE349) of viral protein. This denotes the efficiency of these compounds to interact with the hydrophobic amino acids which are usually present in the core of the protein.

Meliacinanhydride exhibited lowest binding of -9.2 Kcal/mol with the ligand efficiency of -0.22 and KI, 180.25 nM against 3WE1. It was able to form three hydrogen bonds with the same protein by interacting with aminoacids, ARG619, ILE616 and GLY628. Any chemical that effectively binds with viral envelope protein might inhibit its fusion with the host cell membrane rendering it as a good antiviral drug candidate.

Nimbocinol of *A. Indica* exhibited lower binding energy of -8.77, -8.06 Kcal/mol and -6.71 Kcal/mol when docked with 5IKM, 5EC8 and 5B1C respectively. It formed two hydrogen bonds by interacting with the aminoacids ARG 241 and ARG206 of 5EC8 (Fig. 1). The highest binding affinity was also shown by Nimbocinol with the lowest KI of 374.13 nM against 5IKM (Table 3).

Coumaric acid, from *C. papaya* recorded the lowest binding energy (-5.9 Kcal/mol) and a good ligand efficiency of -0.49 compared to all the other compounds (Table 4). The amino acid involved in the formation of hydrogen bond was found to be ARG57 and ARG211 of 5IKM for this particular compound. The same compound recorded lowest binding energy when docked with 3WE1 (-5.76Kcal/mol) and 5EC8 (-5.62 Kcal/mol). Kaempferol and caffeic acid also showed strong binding with most of the viral proteins. Most of the compounds of *C. papaya* were able to form appreciable number of hydrogen bonds which denotes that they can form stable compounds with the viral protein.

Table 2 — Docking properties of top three compounds of *Andrographis paniculata* against selected Dengue viral proteins

Protein name	Ligands	Binding energy (Kcal/mol)	Ligand efficiency	KI (µM)	H-bond
3WE1	14-deoxyandrographolide	-6.49	-0.28	17.63	1
	Andrograpanin	-6.49	-0.28	17.63	1
	14-acetylandrograpolide	-5.83	0.21	57.97	0
5B1C	Andrographolide	-6.51	-0.26	16.94	3
	14-deoxyandrographolide	-6.04	-0.25	37.38	2
	Andrograpanin	-5.78	-0.25	57.77	1
5EC8	14-deoxy-11-oxoandrographolide	-5.99	-0.24	40.79	1
	Isoandrographolide	-5.84	-0.23	51.95	0
	Andrograpanin	-5.67	-0.25	69.38	2
5IKM	Andrograpanin	-7.28	-0.32	4.6	0
	Neoandrographolide	-6.78	-0.20	10.77	1
	Andrographolide	-6.77	-0.27	10.92	1

Table 3 — Docking properties of top three compounds of *Azadirachta indica* against selected Dengue viral proteins

Protein name	Ligands	Binding energy (Kcal/mol)	Ligand efficiency	KI (µM)	H-bond
3WE1	Meliaacinanhydride	-9.2	-0.22	180.25 nM	3
	Nimbocinol	-6.64	-0.22	13.62	1
	Isomeldenin	-6.16	-0.18	30.58	1
5B1C	Nimbocinol	-6.71	-0.22	12.14	0
	Zafaral	-6.5	-0.19	17.15	0
	meliaacinanhydride	-5.92	-0.16	45.39	1
5EC8	Nimbocinol	-8.06	-0.27	1.23	2
	Isomeldenin	-6.39	-0.18	20.69	0
	Meliaacinanhydride	-6.36	-0.17	21.64	0
5IKM	Nimbocinol	-8.77	-0.29	374.13nM	0
	Meliaacinanhydride	-7.79	-0.21	1.96	0
	Zafaral	-7.58	-0.22	2.79	0

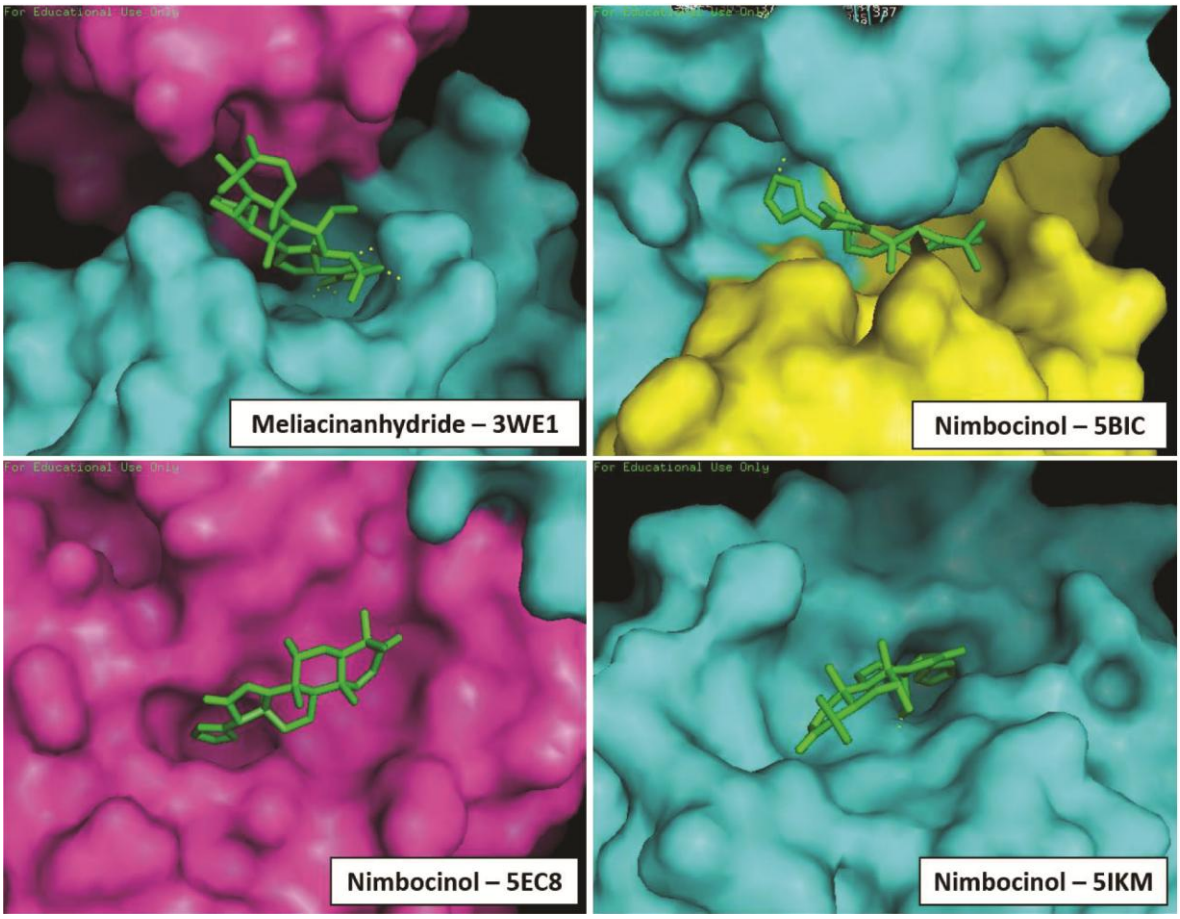

Fig. 1 — Docking conformation of top compounds with Dengue viral protein

Tinosporide and Berberine of *T. cordifolia* were found to interact well with all the selected dengue viral proteins with the lowest binding energy out of all the other compounds. Palmatine recorded lowest binding energy (-7.11 Kcal/mol) when docked with 5IKM and the KI was found to be 6.18 µM. Magnoflorine also has lowest binding energy of -6.47 Kcal/mol with the KI of 18.03 µM against 5B1C (Table 5).

Discussion

Indian medicinal plants are rich in several pharmaceutically active compounds that are traditionally practiced for treating diseases caused by bacterial, viral and fungal agents. According to the report by WHO, the number of plants used for medicinal purpose is 21,000. Of all the FDA approved drugs, more than 50% drugs are natural products or their derivatives[25]. Some of the significant drugs derived from plants are digoxin isolated from *Digitalis* spp., quinine and quinidine isolated from *Cinchona* spp., vincristrine and vinblastine isolated from *Catharanthus roseus*, atropine isolated from *Atropa belladona* and morphine and codeine isolated from *Papaver somniferum*[26]. In India, out of 2500 species have been identified for its medicinal value, 150 are used commercially by the biopharmaceutical companies as mainstream medicine.Names of few commercially accepted plant-derived drugs are Nevirapine and Indinavir isolated from *Hypericum perforatum* L. used for anti-retroviral therapy to treat HIV/AIDS[27]; Quinine isolated from *Cinchona* spp. and Artemisinin isolated from Sweet wormwood plant, *Artemisia annua*[28] which are used as antimalarial drug.

Use of plant derived compounds for drug production is in demand since they are eco-friendly, cost-effective, safe and development of drug resistance is negligible. Due to the unavailability of vaccine and antiviral drugs for the prevention as well as for the treatment of Dengue fever, several plants have been traditionally used to treat dengue infection and have shown positive results.

Table 4 — Docking properties of top three compounds of *Carica papaya* against selected Dengue viral proteins

Protein name	Ligands	Binding energy (Kcal/mol)	Ligand efficiency	KI (μM)	H-bond
3WE1	Coumaric acid	-5.76	-0.48	59.79	2
	Caffeic acid	-5.62	-0.43	76.13	3
	Kaempferol	-5	-0.24	217.99	2
5B1C	Kaempferol	-4.86	-0.23	273.73	2
	Coumaric acid	-4.67	-0.39	75.84	2
	Protocatechuic acid	-4.58	-0.42	442.56	3
5EC8	Coumaric acid	-5.62	-0.47	75.84	2
	Caffeic acid	-5.22	-0.4	149.67	2
	Protocatechuic acid	-4.97	-0.45	225.9	1
5IKM	Coumaric acid	-5.9	-0.49	47.46	2
	Citropten	-5.28	-0.35	134.37	0
	Kaempferol	-5.28	-0.25	134.86	1

Table 5 — Docking properties of top three compounds of *Tinospora cordifolia* against selected Dengue viral proteins

Protein name	Ligands	Binding energy(Kcal/mol)	Ligand efficiency	KI (μM)	H-bond
3WE1	Tinosporide	-6.6	-0.24	14.61	1
	Berberine	-5.67	-0.23	69.3	2
	Palmatine	-5.48	-0.21	95.62	1
5B1C	Magnoflorine	-6.47	-0.26	18.03	1
	Berberine	-6.01	-0.24	39.09	1
	Tinosporide	-5.83	-0.22	53.25	2
5EC8	Berberine	-6.52	-0.26	16.63	0
	Tinosporide	-5.97	-0.22	42.19	0
	Tinocordifolin	-5.69	-0.32	67.34	2
5IKM	Tinosporide	-7.54	-0.28	2.97	0
	Berberine	-7.32	-0.29	4.34	0
	Palmatine	-7.11	-0.27	6.18	0

The molecular docking technique allows the virtual screening of huge number of compounds, ranking them based on the results and proposes structural hypotheses for ligand binding with their targets. In the present study, 27 chemical compounds from selected Indian medicinal plants that passed the Lipinski's rule were selected further for docking exercise. The phytochemicals meliacinanhydride and nimbocinol of *A. indica* when docked with Dengue virus envelop protein, gave best results in terms of their lowest binding energy. Envelope proteins are known to aid the entry of dengue virus into the host cell[29,30] by enhancing the fusion of viral cell membrane with the host cell plasma membrane[31]. Blocking of virus entry and its replication inside the host cell is a widely accepted strategy to design antiviral drug[32]. These two molecules can be used to design an antiviral drug which can effectively block the viral entry either pre or post infection, since it has also been reported that the aqueous neem leaves extract inhibit *in-vitro* replication of Dengue virus type -2[33].

When compared with all the selected ten compounds of *A. paniculata*, andrographolide pose as an attractive drug candidate with the lowest binding energy against 5B1C. This is in accordance with the recent *in-vitro* study conducted by Panraksha (2017)[34] where they showed that the andrographolide has activity against dengue virus 2 with an EC50 of around 22 μM. The antiviral effects of *A. paniculata* methanol extract against DENV-1 have been reported recently[35,36]. Andrographolide and 14-deoxy 11-oxoandrographolide have also been reported to bind effectively with one of the non-structural protein NS5 of dengue[37]. The safety of Nila Vembu Kudineer in which *A. paniculata* is one of the constituents has been evaluated and found to be safer at lower doses when tested on Wistar rats[38].

Tinosporide and berberine of *T. cordifolia* exhibited strong binding affinity with both envelop proteins and Methyltransferase enzyme. The role of methyl transferase enzyme is to facilitate dengue viral RNA capping process. Sajin *et al.*[39] also performed docking with chemicals available in methanol extract of *C. papaya* leaves against envelope protein of dengue virus (type-2). Six compounds isolated from the extract recorded a binding energy score that

ranged between -9.99 to -7.22 Kcal/mol that suggest a high inhibitory activity of these compounds against the β-OG pocket of envelope protein. The aqueous extracts of papaya leaves were found to exhibit potential activity against dengue fever measured in terms of its ability to increase platelets count, WBC and neutrophils[13]. In a similar docking study carried out by us, we found that phytochemicals derived from *T. cordifolia* showed promising antiviral activity against Chikungunya virus[40].

Conclusion

Based on the present study, most of the selected compounds of these Indian medicinal plants docked well with dengue envelop protein as well as with methyl transferase enzyme. But nimbocinol and meliacinanhydride of *A. indica* have been emerged as the most promising anti-viral candidates and could be selected for further detailed *in vitro/in vivo* and pharmaceutical analysis. The drug likeliness property of the selected compounds also indicates its potency compared with the standard drug. The results also suggest that both envelop protein and methyl transferase enzyme can be used as a potential drug target.

Acknowledgement

Authors thank DBT star college scheme for their support.

Conflict of Interest

Authors declare that there is no conflict of interest.

Authors' Contributions

LM, Divya, AV and Shraddha, undergraduate students of Gargi College conducted the docking work and drafted this manuscript. SS and DG supervised and edited the manuscript.

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