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Original Research Article

ANTIVIRAL SCREENING OF *AZADIRACHTA INDICA* PHYTOCHEMICALS AS DENGUE NS5 INHIBITOR: A MOLECULAR DOCKING APPROACH

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Abstract *Dengue has been an alarming viral infection in tropical and subtropical regions of the world for the past few decades, resulting in millions of deaths. There is no effective drug to treat this arbovirus-based infection. Dengue virus non-structural protein NS5 contains N terminus methyl transferase domain and C terminus RNA-dependent RNA polymerase domain, which is involved in viral RNA replication and serves as a potential target. The current in-silico study aims to find new potential dengue virus NS5 protein inhibitors. The designed library containing eight compounds from Azadirachta Indica was used to perform molecular docking against active residues of dengue virus NS5 protein. Four compounds (Desacetyl Salanin, Azadirchtin-A, Castalagin, Vilasinin) with high negative binding energy values and zero RMSD values were selected, and their drug-likeness and ADMET analysis was performed. Among the best-docked compounds, Vilasinin (-11kcal/mol) exhibited drug-like properties as it has a molecular weight less than 500 D and has zero violation value. Moreover, it has 5 hydrogen bond donors and 10 hydrogen bond acceptors. It is well soluble in water so that it can be used as a potential inhibitor and drug candidate for the treatment of dengue infection.*

Keywords: Dengue, NS5, *Azadirachta Indica*, Phytochemicals, Molecular docking, Drug likeness

Introduction

Dengue is an acute arbovirus-based infection caused by Dengue virus (DENV) belonging to the flaviviradea family. It is RNA enveloped single-stranded virus generally found in mosquitoes and ticks. It is characterized by joint pain, severe headache, vomiting, and diarrhea, causing over 390 million infections yearly in tropical and subtropical regions (Vora et al., 2020). Despite extensive efforts, no approved vaccine (except dengvaxia) with a success rate is available, increasing the need for effective therapeutics against this virus. The increasing resistance against various antiviral medicines diverts the focus towards developing antiviral medicines based on traditional or natural sources considered less toxic than synthetic medicines (Low et al., 2017; Ullah et al., 2023a; Ullah et al., 2023b). Drug discovery against dengue virus involving natural flavonoids and other epitopes-based vaccines based on common targets in different viruses could be instrumental (Abdullah et al., 2023; Yadav et al., 2013). One potential pharmacological strategy to inhibit dengue infection is inhibiting structural and non-structural proteins of the dengue virus. Structural proteins include capsid protein and envelop protein which help the virus to find and fuse with the host cell membrane. While non-structural proteins include NS1, NS2, NS3, NS4, NS5, NS6, NS7, which are necessary for viral RNA replication in host cells (Ali et al., 2021). Natural bioactive compounds of medicinal plants are potential drug candidates, providing unique structural diversity and chemistry (Vora et al., 2020). The current study aims to identify plant compounds effective against dengue virus. For this purpose, dengue NS5 protein was targeted with different Azadirachta Indica (Neem) compounds including flavonoids, terpenoids, saponins, etc. NS5 is a potential target because DENV genome is replicated by RNA dependent RNA polymerase and NS5 methyl transferase, two domains of NS5 protein comprising 900 amino acids (Tay et al., 2016; Zhao et al., 2015).

The drug discovery processes are lengthy, costly, and time-consuming, with high failure rates in clinical trials. In such scenario. In-silico approaches that use artificial intelligence are used to improve the efficiency of the drug discovery process. The computational methods are more economical, rational, and time-saving (Dias et al., 2012; Din et al., 2023; Hassan et al., 2023). We used molecular docking and ADMET analysis to discover the most potential therapeutic candidates against dengue NS5

from phytochemicals-based ligand library. These potential ligands could be used in future clinical trials to accelerate the drug discovery against the dengue virus as their pharmacological potential and drug-likeness are also evaluated.

Materials and Methods

Target protein preparation

The 3D crystal structure of dengue virus non-structural protein (PDB ID: 5Zqk) NS5 was obtained from RCSB protein databank ((https://www.rcsb.org/). It was further optimized by removing water molecules and adding partial charges using Auto dock Vina software. As Auto dock Vina has been previously used for determining the best confirmation of proteins and ligands (Tariq et al., 2023).

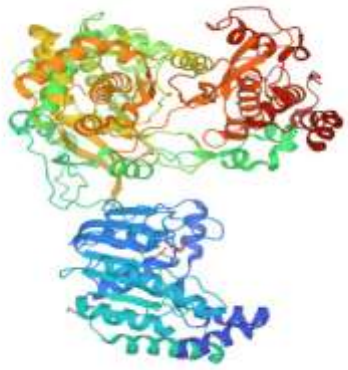

Fig 1: Dengue virus non-structural protein NS5 (PDB ID: 5Zqk)

Ligand Library preparation

Total 8 compounds of *Azadirachta Indica* (Neem) were selected for their antiviral screening against NS5 protein of dengue virus using in-silico tools. These compounds were selected based on the reported pharmacological activities. Their 3D structures were retrieved from PubChem (https://www.ncbi.nlm.nih.gov/pccompound), and the compound library was prepared in Auto Dock Vina. The ligands' energy was minimized before docking via Pymol software (https://pymol.org/2/).

Docking Analysis

Auto dock Vina (https://vina.scripps.edu/) was used to identify active sites on receptor protein dengue NS5. The prepared compound library was docked with active residues of NS5 by using Auto dock Vina. After docking, phytochemicals with the best confirmation were determined based on their S-score binding affinity values and root mean square deviation (RMSD). The best compounds were visualized using Pymol software, and their 2 D plots of ligand-receptor interaction were analyzed. The 3D plots of protein-compound complexes were obtained through Discovery Studio.

Drug likeness evaluation

Drug likeness evaluation of a drug is an important step towards drug discovery. To analyze the drug ability of best-docked compounds, different physiochemical properties were determined, including molecular weight, the number of hydrogen bond acceptors and hydrogen bond donors, and octanol-water partition coefficient log P (miLogP), using the online tool, mol-inspiration (https://www.molinspiration.com/).

ADMET Analysis

The phytochemicals' pharmacokinetic properties were evaluated to analyze their absorption, distribution, metabolism, elimination, and toxicity (ADMET) in the human body (Kar and Leszczynski, 2020). The ADMET profile of molecules was analyzed using 'SwissADME' (http://www.swissadme.ch/).

Results

Molecular Docking

Eight compounds of *Azadirchta Indica* were retrieved from literature, and their theoretical probability to bind with active residues of non-structural protein of dengue virus i.e., NS5 protein, was determined. The selected compounds were docked specifically with the active pocket of NS5 protein using Auto dock tools and Auto dock Vina. The best compounds were picked based on their binding energies and zero RMSD value, as illustrated in Table 1.

Potential Inhibitors of NS5

NS5 (PDB ID: 5ZQK) interacts best with five natural compounds that can be used as potential inhibitors of dengue virus NS5. A strong interaction between Desacetyl salanin and NS5 exhibited binding energy of -17.8 kcal/mol. This compound effectively binds with Gly85, Gly86, and other active amino acids like VAL130, Asp131, ASP79 and ASP146. Castalagin (-17.3 Kcal/mol binding affinity) is the second potential inhibitor of NS5 protein binding to the active residues, including GLU111, THR104, and VAL132. Similarly, Azadirachtin A (-13.8 Kcal/mol) and Vilasinin (-11 Kcal/mol) also showed to be good inhibitors of NS5 binding with active residues (ASP146, THR104, VAL130, GLU111 and LYS105, THR104, ASP146, ILE147) while Vanillic acid (-6 Kcal/mol), Vanillin (-5.6 Kcal/mol), Hydroxytyrosol (-5.5 Kcal/mol) and Tyrosol (-4.9 Kcal/mol) showed comparatively high binding energy with NS5 indicating they are not best inhibitors and hence cannot be used as potential drug candidates for NS5 inhibition. Hence the molecular docking process determines four multitarget Neem plant compounds that can be used as potential inhibitors against dengue NS5.

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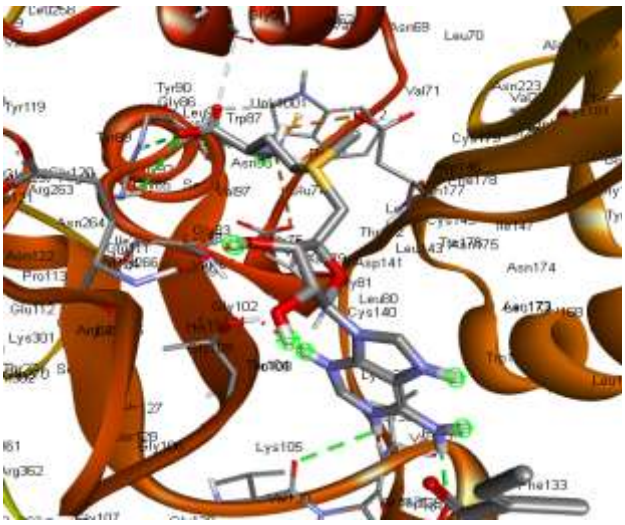
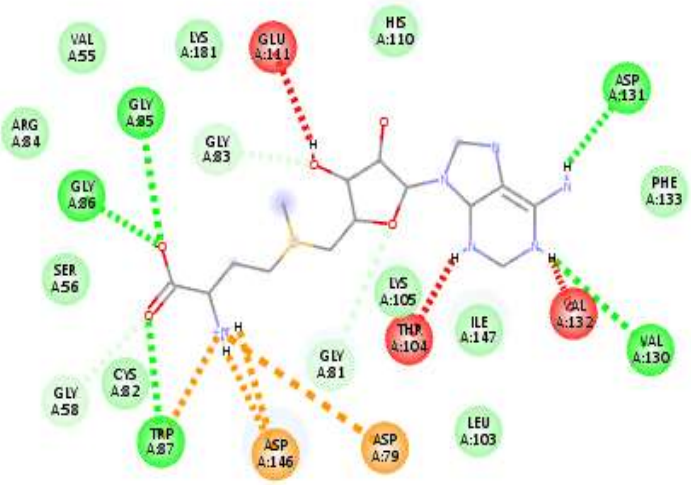
Table 1. Binding energies of different compounds along with active residues

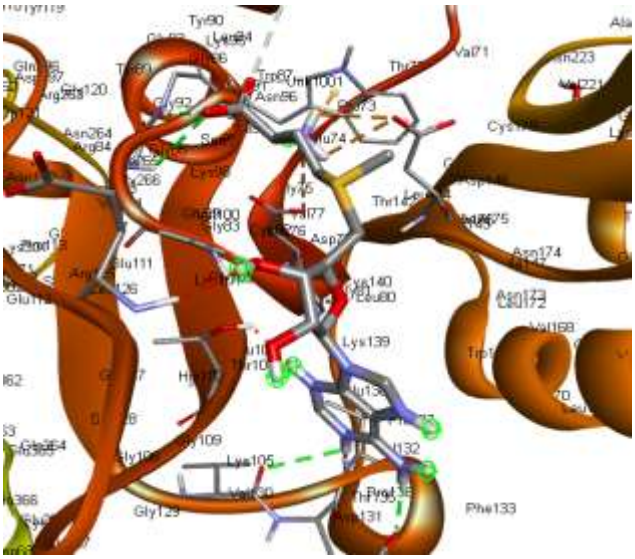
Plant Name	Compounds	PubChem ID	Binding energies(kcal/mol)	Active residues
Neem	Desacetyl salanin	14458886	-17.8	Lys131, GLU111, ASP131
Neem	Castalagin	168165	-17.3	ASP131, THR104, LYS105, AUG84
Neem	Azadirachtin-A	5281303	-13.8	GLY83, VAL132, ASP78, THR104
Neem	Vilasinin	185729	-11	GLU111, ASP131, THR104
Neem	Vanillic Acid	8468	-6	VAL132, THR104, TRP87, ASP79, GLY83
Neem	Vanillin	1183	-5.6	GLU111, GLY58, ASP146, THR104
Neem	Hydroxytyrosol	82755	-5.5	GLY57, TRP87, THR104, ASP79
Neem	Tyrosol	10393	-4.9	ASP146,GLU111, THR104,VAL132

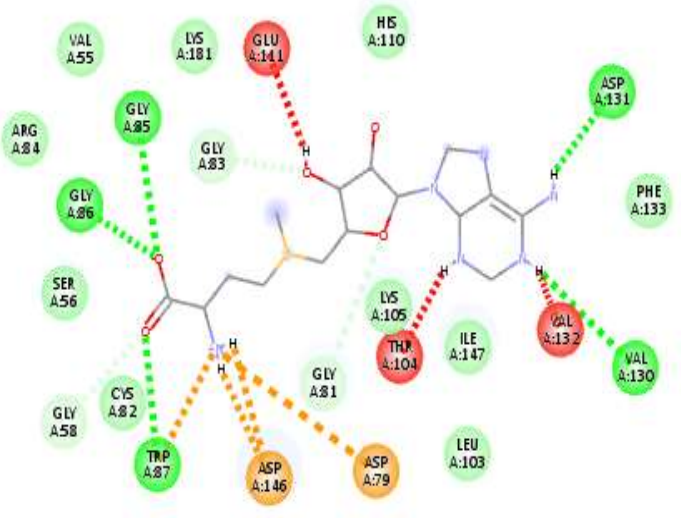
DesacetylSalanin



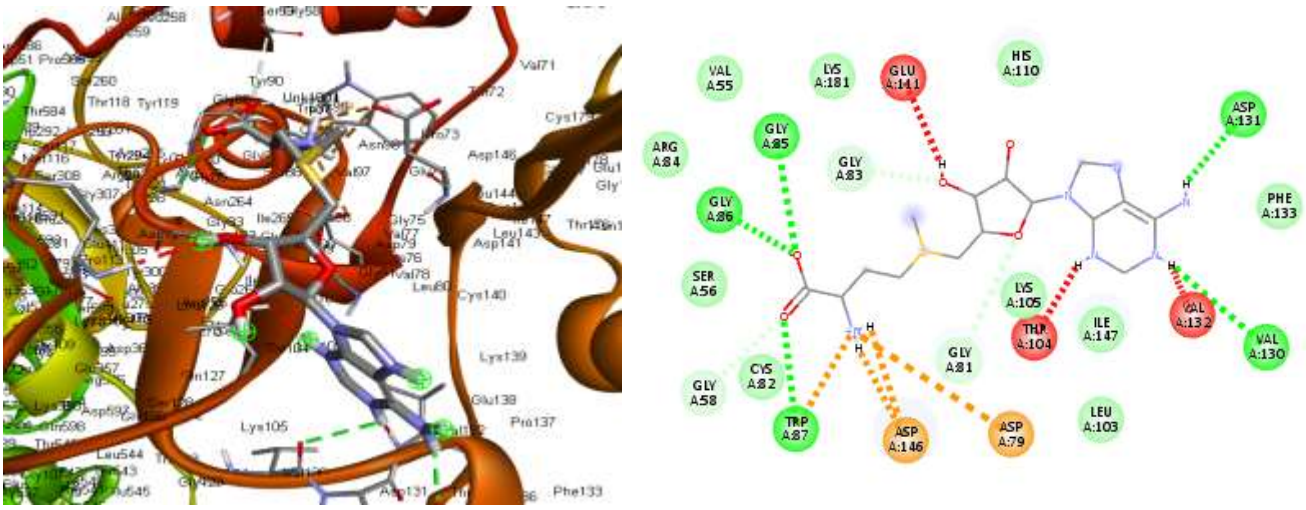


Azadirachtin-A





Castalagin



Vilasinin

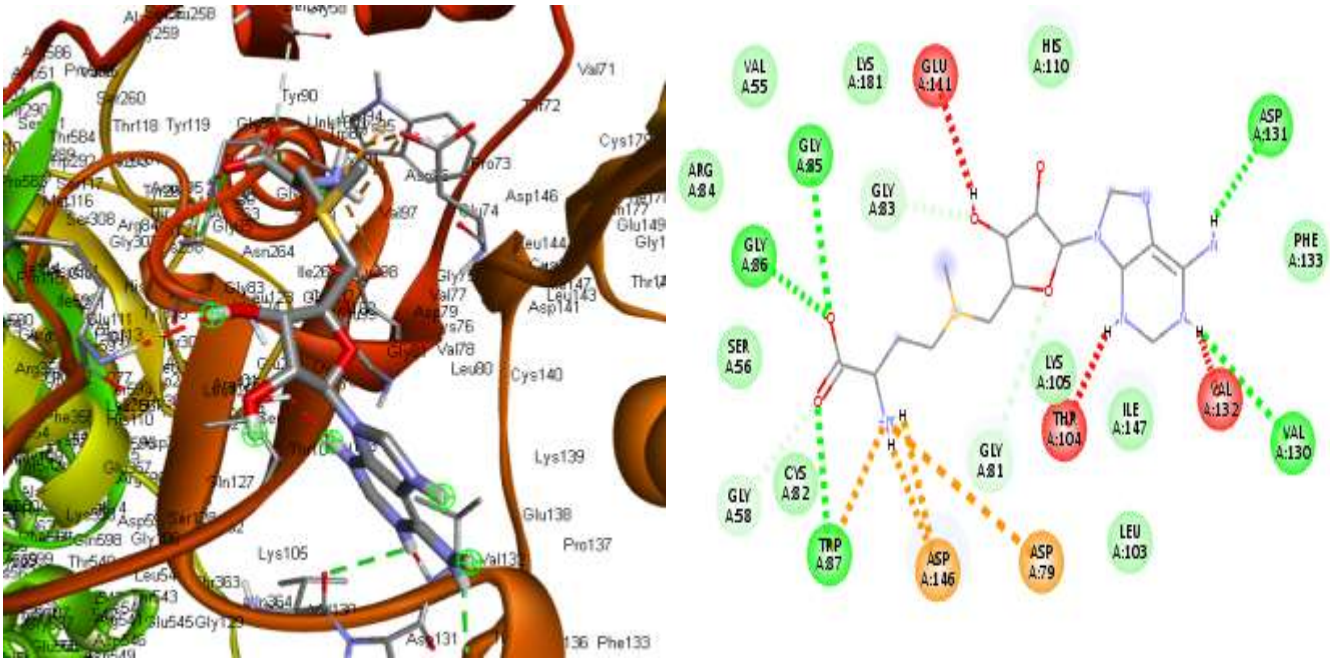


Fig 2. 2D and 3D structures showing NS5 interaction with compounds (Disacetyl salanin, Castalagin, Azadirchtin A and Vilasinin).

Drug likeness and ADMET Analysis

Drug likeness of all the compounds was determined by Lipinski's rule of 5. It shows a compound as drug-like when it achieves the following criteria: Molecular weight (<500 D), number of hydrogen bond donor (<5), and number of hydrogen bond acceptors (<10) (Chagas et al., 2018). ADME analysis of these compounds was carried out by Swiss ADME server to check their potential as a human drug for future clinical trials. The SwissADME program predicts ADME-related properties such as molecular weight, pharmacokinetics, physiochemical properties, water solubility, and lipophilicity of the active compounds to evaluate the drug potentials (Al Azzam, 2022). The different properties of compounds are shown in

Table 2, 3, 4, and 5. The molecular pharmacokinetic attributes such as blood-brain barrier penetration (BBB), gastrointestinal absorption, protein absorption, metabolism of the drug, and its distribution and elimination are presented in **Table 2**. Among the best-docked compounds, Vilasinin exhibited good gastrointestinal absorption and inhibits some gut enzymes, which can cross the brain barrier. The first three compounds (Desacetyl salanin, castalagin, and Azadirachtin) have molecular weights larger than 500D, so they are ruled out from Lipinski rule of 5. As illustrated in **Table 5**, Among all the four compounds, Vilasinin exhibited drug-like properties as it has a molecular weight of less than 500 D having zero violation value moreover, it has less than 5 hydrogen bond donors and less than 10 hydrogen bond acceptors and is well soluble in water (**Table 4**) hence showing drug-like properties and can be a potential drug candidate.

Table 2. Pharmacokinetics

Compounds	Gastrointestinal absorption	BBB	p-glycoprotein absorption	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log kp (skin permiation)
Desacetyl salanin	High	No	Yes	No	No	No	No	No	-7.3
Castalagin	Low	No	Yes	No	No	No	No	No	-11.33
Azadirachtin-A	Low	No	Yes	No	No	No	No	No	-9.92
Vilasinin	High	Yes	Yes	No	Yes	Yes	No	No	-6.71

Table 3. Lipophilicity

Compounds	Log Po/w (i-LOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log o/w (MLOGP)	Log Po/w (SILICOS IT)	Consensus LogPo/w
Desacetyl salanin	4.12	3.36	4.72	2.54	4.47	3.84
Castalagin	1.15	0.94	0.99	-3.23	-1.86	-0.4
Azadirachtin-A	3.9	1.09	-0.2	-0.47	1.07	1.08
Vilasinin	3.37	3.1	3.64	2.4	3.05	3.11

Table 4. Water Solubility

Compounds	Log S (ESOL)	Solubility	Class
Desacetyl salanin	-5.03	5.22 e-0.3 mg/ml; 9.41 e-06 mg/ml	Moderately soluble
Castalagin	-6.56	2.58e-04 mg/ml; 2.77e-07 mol/l	Poorly soluble
Azadirachtin-A	-4.34	3.33e-02 mg/ml; 4.62e-05 mol/l	Moderately Soluble
Vilasinin	-4.5	1.34e-02 mg/ml; 3.14e-05 mol/l	Soluble

Table 5. Druglikeness Effect

Compounds	MiLogP	MW (g/mol)	nON	nONHN	nviolations
Desacetyl salanin	4.69	554.68	8	1	1
Castalagin	1.49	934.63	26	16	3
Azadirachtin-A	1.42	720.72	16	3	2
Vilasinin	2.94	428.57	5	3	0

Discussion

Dengue is a complicated arthropod born virus infection causing hemorrhagic fever, in tropical and subtropical regions. It cause approximately 50000 million infections yearly (Daffis et al., 2010). Dengue virus non-structural protein NS5 is responsible for RNA replication of the virus. It is the largest and most conserved protein with 104KDA size (El Sahili and Lescar, 2017). NS5 contains an N-terminal methyl transferase (MTase) domain, which is responsible for synthesis and methylation of 5′ RNA cap, and a C-terminal RNA-dependent RNA polymerase (RdRp) domain, responsible for viral RNA synthesis (Sampath and Padmanabhan, 2009). Hence, it is a potential target for discovering new plant compounds as alternative therapeutic antiviral agents (Yap et al., 2007). *Azadirchta Indica* (neem) has been known for its antifungal, antipyretic, antibacterial and antitumor activities (Parida et al., 2002a). According to a previous study, neem leaf extract inhibited virus replication in mice models (Alzohairy, 2016). On this basis, neem plants can be used to find the active ingredient having potential anti-dengue phytochemicals. Its main compounds azadirchtin and salanin, also showed interaction with dengue NS2/NS3 and NS5 gene in a previous study (Altamish et al., 2022; Rao and Yeturu, 2020); (Parida et al., 2002b). In this study, four out of eight compounds from *A. Indica* exhibited low binding energy values, with dengue NS5 having strong interaction with active residues involving ASP,

GLY, GLU, THR, and LYS. Desacetyl salanin exhibited strong hydrophobic interaction in line with the previous study (Altamish et al., 2022); (Chavda et al., 2022). Similarly, Castalagin and Azadirachtin showed good antiviral properties against NS5 and inhibited viral replication *in vitro* (Qamar et al., 2017). In a similar previous study (Juan-Pablo et al., 2023), the neem plant exhibited antiviral properties against dengue virus NS5 protein.

Drug likeness of compounds was also determined through molinspiration, and SWISSADME performed ADMET analysis. Molecules with ADME properties are not processed further for clinical trials (Tariq et al., 2023). Among the four best docked compounds, Vilasinin has good drug-like properties with molecular weight of less than 500 and zero violation value. Moreover, it has less than 10 hydrogen bond donors and less than 5 hydrogen bond acceptors. According to previous studies, Vilasinin also exhibited antiviral properties against dengue and hepatitis virus (Velmurugan et al., 2012). So, we can say that Vilasinin originated from *A. Indica* and can be a potential candidate for discovering lead compounds against the dengue virus. Moreover, using the multi-target strategy against dengue virus might be inexpensive. Further manipulation and investigation of the phytochemicals are required to determine their potential as anti-dengue drugs.

Conclusion

The important medicinal compounds of Azadirachtin Indica (Neem plant) previously used for several antiviral applications possess inhibition potential against NS5 protein. Among the selected eight compounds, four compounds Desacetyl salanin, Castalagin, Azadirachtin-A, and Vilasinin showed high binding affinity with NS5 protein, having lowest binding energy scores. The pharmacokinetic analysis showed that among the best docked compounds, Vilasinin proved to have drug like properties. Further studies are required to screen the identified compounds through *in vitro* and *in vivo* experiments.

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Declarations

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Authors Contribution

'Aleeza Nawaz' designed the study, performed the docking and ADMET analysis, and wrote the first draft of the manuscript.

'Dr Bushra Ijaz' supervised, reviewed the study and finalized the manuscript

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Funding
Not applicable

Conflict of Interest
Regarding conflicts of interest, the authors state that their research was carried out independently without any affiliations or financial ties that could raise concerns about biases.