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Research Article

Machine Learning-Assisted in Silico Identification of Phytoconstituents as Potential NS5 RdRp Inhibitors for Dengue Therapeutics

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Abstract

The escalating global burden of dengue virus (DENV) infection and the lack of specific antiviral therapies necessitate the development of effective therapeutics targeting the highly conserved non-structural protein 5 RNA-dependent RNA polymerase (NS5 RdRp). This study employed an integrated computer-aided drug discovery (CADD) and machine learning (ML) framework to screen a library of 14 phytoconstituents against DENV-2 NS5 RdRp. Following molecular docking, the top-ranked compounds were evaluated for pharmacokinetic safety through cross-docking with CYP3A4, OATP1B1, and OATP1B3, complemented by ADMET prediction using SwissADME and ProTox-II. In parallel, ML-based quantitative structure-activity relationship (QSAR) models using Random Forest (RF) and Extreme Gradient Boosting (XGBoost) were developed using hybrid descriptors comprising Morgan fingerprints, physicochemical properties, experimental IC50 values, and docking scores derived from validated DENV RdRp inhibitors. Docking analysis identified Glycyrrhizin, Curcumin, Boswellic acid, Mangiferin, Azadirachtin, and Forskolin as promising inhibitors, exhibiting binding affinities comparable to or greater than those of remdesivir. Although several lead compounds demonstrated potential interactions with CYP3A4, their weak binding to OATP1B1 and OATP1B3 suggested a reduced risk of transporter-mediated toxicity and favorable hepatic safety, supported by ADMET predictions indicating favorable drug-like properties. Among the developed ML- based QSAR models, XGBoost outperformed RF in predicting nonlinear structure-activity relationships. Overall, the integrated molecular docking, pharmacokinetic profiling, and ML-based QSAR analyses identified Glycyrrhizin, Curcumin, Boswellic acid, and Azadirachtin as the most promising antiviral lead scaffolds and demonstrate the value of AI-driven drug discovery for accelerating antiviral lead identification. Further in vitro and in vivo studies are warranted to validate their therapeutic efficacy and safety.

Keywords

Phytoconstituents, Dengue Fever, AI & ML Models, Insilico, Computer-aided Drug Discovery (CADD), Molecular Docking, Random Forest, Extreme Gradient Boosting

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1. Introduction

Dengue virus (DENV), comprising four antigenically distinct serotypes (DENV-1 to DENV-4), is transmitted to humans through the bite of infected female Aedes mosquitoes. Approximately 390 million DENV infections occur annually, resulting in nearly 100 million symptomatic cases and approximately 40,000 deaths worldwide [1, 2]. Clinical manifestations range from mild dengue fever to severe dengue hemorrhagic fever and dengue shock syndrome. Despite its substantial global health burden, no specific antiviral therapy has been approved for the treatment of dengue infection.

Conventional drug discovery is expensive, time-consuming, and associated with a high failure rate during clinical development. Consequently, computational approaches have emerged as efficient alternatives for identifying and prioritizing promising therapeutic candidates. Computer-aided drug discovery (CADD), particularly molecular docking, enables rapid virtual screening of large compound libraries while reducing the cost and time required for experimental evaluation [3, 4]. Among the diverse chemical resources available for drug discovery, phytochemicals represent an important source of structurally diverse and biologically active molecules with a long history of therapeutic use. Advances in phytochemical characterization and the availability of curated natural-product databases have further facilitated large-scale virtual screening of plant-derived compounds against disease-associated molecular targets [5-8].

Among the viral proteins, the non-structural protein 5 RNA-dependent RNA polymerase (NS5 RdRp) is considered one of the most promising therapeutic targets for dengue antiviral development. As the largest and most highly conserved viral protein, NS5 RdRp is indispensable for viral RNA synthesis, and inhibition of its polymerase activity effectively suppresses viral replication [9]. Since RdRp is absent in mammalian host cells, it offers excellent target selectivity with a reduced risk of host toxicity [10]. Furthermore, the high sequence conservation of the RdRp catalytic domain among all four DENV serotypes suggests that inhibitors targeting this enzyme may exhibit broad-spectrum anti-dengue activity [11]. The availability of high-resolution crystal structures of NS5 RdRp, including inhibitor-bound complexes such as PDB ID: 6KR2, has greatly facilitated structure-based drug discovery and molecular docking studies [11, 12]. Moreover, both nucleoside and non-nucleoside inhibitors, including AT-9010 (derived from the prodrug AT-752) and RK-0404678, have experimentally validated the druggability of NS5 RdRp, further supporting its potential as a therapeutic target [13, 14].

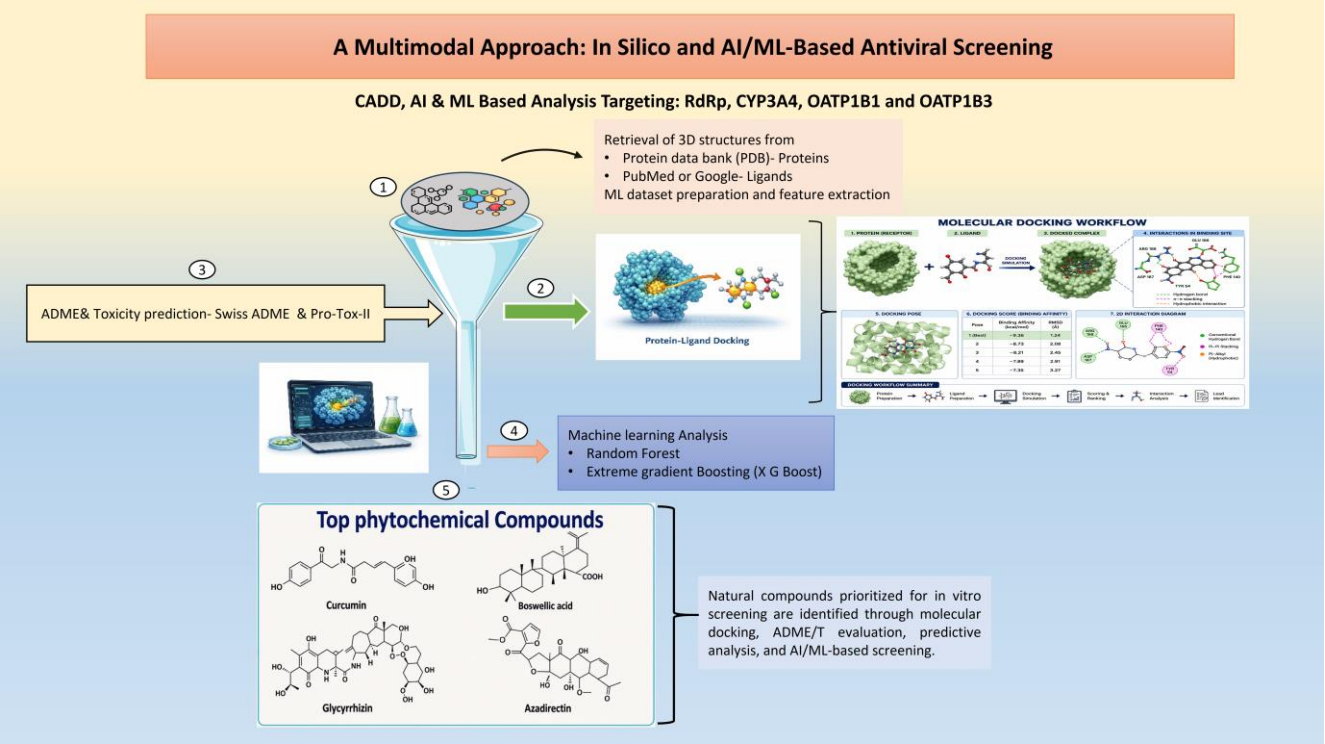

Figure 1. *The workflow integrates molecular docking, ADME/T profiling, and machine learning approaches to screen phytochemicals against Dengue virus NS5 RdRp and key pharmacokinetic proteins. Based on binding interactions, pharmacokinetic properties, and predicted IC_{50} values, Curcumin, Boswellic acid, Glycyrrhizin, and Azadirachtin emerged as promising antiviral candidates for further validation. (Courtesy: Bioicons, Diagram generator AI).*

Artificial intelligence (AI) and machine learning (ML) have transformed modern drug discovery by enabling rapid analysis of large chemical and biological datasets, improving lead identification, optimization, and prediction of pharmacological properties [15, 16]. In particular, ML-based quantitative structure-activity relationship (QSAR) models trained on experimentally validated datasets can accurately predict biological activity while reducing the need for extensive experimental screening [17]. Recent studies have demonstrated that integrating molecular descriptors, physicochemical properties, and protein-ligand interaction features significantly improves prediction accuracy and compound prioritization [17, 18]. Random Forest (RF) and Extreme Gradient Boosting (XGBoost) are widely used ML algorithms because of their ability to capture complex nonlinear relationships between molecular descriptors and biological activity while minimizing overfitting in QSAR modeling. When integrated with CADD techniques such as molecular docking and ADMET prediction, ML-based QSAR models provide a robust framework for identifying promising antiviral candidates with improved efficacy and safety profiles. The overall workflow of the present study is illustrated in Figure 1.

Based on the available literature, several phytochemicals have demonstrated antiviral activity against dengue virus through different mechanisms. Curcumin, a polyphenolic compound isolated from Curcuma longa, inhibits dengue viral proteins, including the viral protease [19, 20]. Forskolin, a diterpenoid from Coleus forskohlii, has demonstrated antiviral activity in both experimental and computational studies [21]. Glycyrrhizin, a triterpenoid saponin from Glycyrrhiza glabra, exhibits broad-spectrum antiviral properties [22, 23], while Azadirachtin from Azadirachta indica has shown inhibition of dengue virus replication and favorable interactions with NS5 RdRp in previous studies [24]. These findings support the exploration of phytochemicals as potential antiviral scaffolds for dengue drug discovery.

Therefore, the present study employed an integrated CADD and ML-based framework to identify phytochemical inhibitors targeting DENV-2 NS5 RdRp. Fourteen phytoconstituents were screened using molecular docking, followed by pharmacokinetic safety assessment through CYP3A4, OATP1B1, and OATP1B3 interaction analyses and ADMET prediction. In parallel, ML-based QSAR models using Random Forest and Extreme Gradient Boosting (XGBoost) algorithms were developed to predict inhibitory activity using hybrid molecular descriptors. Remdesivir was included as a reference antiviral to benchmark the binding interactions of the screened phytochemicals. This integrated computational strategy aims to identify promising antiviral lead scaffolds for further experimental validation against dengue virus infection.

2. Materials and Methods

In this study, phytochemical ligand structures were retrieved from the NCBI PubChem database and the ZINC database in Structure Data File (SDF) format. The crystal structures of DENV-2 NS5 RNA-dependent RNA polymerase (PDB ID: 6KR2), CYP3A4 (PDB ID: 2V0M), OATP1B1 (PDB ID: 8HNH), and OATP1B3 (PDB ID: 8PG0) were obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). Ligands were converted from SDF to Protein Data Bank (PDB) format using Open Babel v3.1, and protein and ligand preparation, including hydrogen addition, charge assignment, and conversion to Protein Data Bank, Partial Charge, and Atom Type (PDBQT) format, was performed using AutoDock 4.2.6. Molecular docking was conducted using AutoDock Vina, while protein-ligand interactions were analyzed using PyMOL and BIOVIA Discovery Studio Visualizer. In parallel, ML-based QSAR models were developed using RF and XGBoost algorithms implemented in Python within a Jupyter Notebook environment. A total of 14 phytoconstituents were evaluated against four target proteins, and their docking scores and binding affinities were compared with those of reference compounds remdesivir, rifampicin, ketoconazole, and simeprevir. Details of all compounds and target proteins are provided in Table 1.

Table 1. *List of Compounds and their target.*

S. No	Name of compounds	PubChem UID	Targeted proteins
1.	Resveratrol	445154	6KR2, 2V0M, 8HNH, 8PG0
2.	Curcumin	969516	6KR2, 2V0M, 8HNH, 8PG0.
3.	Mangiferin	5281647	6KR2, 2V0M.
4.	Glycyrrhizin	14982	6KR2, 2V0M, 8HNH, 8PG0
5.	Forskolin	47936	6KR2, 2V0M, 8HNH, 8PG0
6.	Boswillic acid	168928	6KR2, 2V0M, 8HNH, 8PG0
7.	Berberin	2353	6KR2, 2V0M, 8HNH, 8PG0

S. No	Name of compounds	PubChem UID	Targeted proteins
8.	Azadirechtin	5281303	6KR2.
9.	Andrographolide	5318517	6KR2.
10.	Phyllanthin	358901	6KR2.
11.	Nirtetralin	182644	6KR2.
12.	Niranthin	11575632	6KR2.
13.	Limonene	440917	6KR2.
14.	Beta Myrcene	31253	6KR2.
15.	Remidesivir	121304016	6KR2.

2.1. Ligand Preparation

Three-dimensional (3D) structures of all phytochemical ligands were retrieved from the PubChem and ZINC databases in SDF format, whereas reference structures for remdesivir and simeprevir were obtained from their respective co-crystallized protein structures. Ligands were converted to PDB format using Open Babel v3.1 and subsequently prepared in AutoDock 4.2.6 through hydrogen addition, charge assignment, energy minimization, and conversion to PDBQT format for molecular docking studies [25-27].

2.2. Protein Preparation

The crystal structures of DENV-2 NS5 RdRp (6KR2), CYP3A4 (2V0M), OATP1B1 (8HNH), and OATP1B3 (8PG0) were retrieved from the RCSB Protein Data Bank. Protein preparation was performed using AutoDock 4.2.6 by removing crystallographic water molecules, non-essential chains, and co-crystallized ligands or heteroatoms, followed by hydrogen addition, charge assignment, and conversion to PDBQT format for molecular docking [26, 28].

2.3. Grid Generation & Binding Pocket Identification

The docking grid was centered on the co-crystallized ligand within the active site of each target protein. Grid box dimensions and center coordinates were optimized to fully encompass the binding pocket, ensuring accurate docking of the phytochemical ligands during molecular docking [29].

2.4. Molecular Docking

Molecular docking was performed using AutoDock Vina with optimized docking parameters. Docking poses were ranked according to binding affinity, and the resulting protein-ligand complexes were visualized and analyzed using BIOVIA Discovery Studio Visualizer and PyMOL [30].

2.5. Dataset Preparation for ML Models

A dataset comprising 220 experimentally validated dengue virus NS5 RNA-dependent RNA polymerase (RdRp) inhibitors was compiled from the literature and public database for ML-based QSAR model development. The molecular descriptors used in the study are summarized in Table 2.

Table 2. *Pattern of the training data & descriptors.*

Training data descriptors				
Compound ID	Smiles	IC_{50}	Physicochemical descriptors (MW, TPSA, HBD, HBA, Log P, &RotB)	Docking Score of RDRP

Note: Molecular Weight (MW), Topological Polar Surface Area (TPSA), Hydrogen Bond Donors (HBD), Hydrogen Bond Acceptors (HBA), Rotatable Bonds (RotB), and logP.

To normalize biological activity and reduce data skewness, the experimental IC_{50} values were converted to pIC_{50} using Equation (1):

$$pIC_{50} = -\log 10(IC50) \quad (1)$$

This logarithmic transformation improves model stability and is widely used in QSAR modelling [31, 32].

2.6. Molecular Representation and Descriptor Calculation

Molecular structures were represented using canonical SMILES notation. Extended-Connectivity Fingerprints (ECFP4; Morgan fingerprints radius = 2, 1024 bits) were generated using RDKit. Hybrid descriptors comprising Morgan fingerprints, physicochemical properties (MW, TPSA, HBD, HBA, RotB, and LogP), experimental IC_{50} values, and docking scores were used as input variables for ML-based QSAR model development [18, 33]. The dataset was randomly partitioned into training (80%) and validation (20%) sets using a fixed random seed (random_state = 42) to ensure reproducibility [18, 34].

2.7. Model Development

Two machine learning algorithms were utilized: Random Forest (RF) and Extreme Gradient Boosting (XGBoost). These algorithms were chosen for their robustness, capability to manage mixed feature types, and effectiveness in modeling non-linear relationships.

2.7.1. Random Forest (RF)

Random Forest (RF) is an ensemble learning algorithm based on bootstrap aggregation (bagging). In this study, RF was employed to predict the inhibitory activity (pIC_{50}) of DENV-2 NS5 RdRp inhibitors using hybrid molecular descriptors comprising Morgan fingerprints, physicochemical properties, and molecular docking scores. The model was trained using experimentally determined pIC_{50} values obtained from the literature as the response variable. RF was selected because of its robustness in handling high-dimensional datasets and its ability to model nonlinear relationships while minimizing overfitting [18]. The prediction model is represented by Equation (2), and the workflow is illustrated in Figure 2.

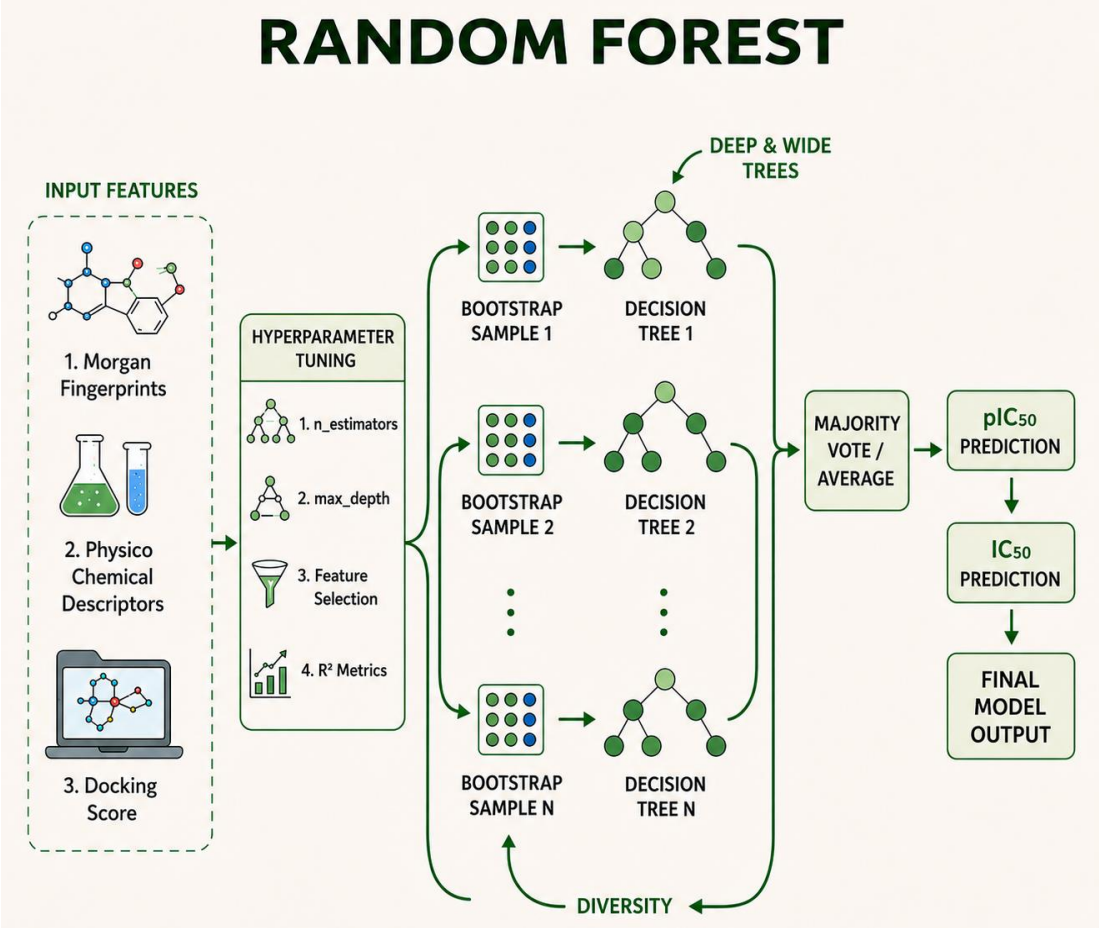

Figure 2. *The workflow illustrates the development of a Random Forest regression model using multiple input features, including Morgan fingerprints, physicochemical descriptors, and docking scores of RDRP. Hyperparameter tuning was performed by optimizing parameters such as the number of estimators, maximum tree depth, feature selection, and R^2 metrics. Multiple bootstrap samples were generated to train diverse decision trees, and the final prediction was obtained by averaging the outputs of all trees. The model predicts pIC_{50} values, which were subsequently converted into IC_{50} predictions for the final model output. (Courtesy: Bio icons, Float icons, Diagram generator AI).*

$$\hat{y} = \frac{1}{N}\sum_{i=1}^{N} T_i(x) \quad (2)$$

Where $T_i(x)$ is the prediction of the i^{th} tree and N is the total number of trees.

2.7.2. Extreme Gradient Boosting (XGBoost)

Extreme Gradient Boosting (XGBoost) is an ensemble learning algorithm based on the gradient boosting framework, in which decision trees are constructed sequentially to minimize prediction errors. In this study, XGBoost was employed to predict the inhibitory activity (pIC_{50}) of DENV-2 NS5 RdRp inhibitors using hybrid molecular descriptors comprising Morgan fingerprints, physicochemical properties, and molecular docking scores. The model was trained using experimentally determined pIC_{50} values compiled from the literature as the response variable. XGBoost was selected because of its regularization capability (L1 and L2), computational efficiency, scalability, and ability to model complex nonlinear structure-activity relationships while minimizing overfitting [34]. The objective function is represented by Equation (3), and the overall workflow is illustrated in Figure 3.

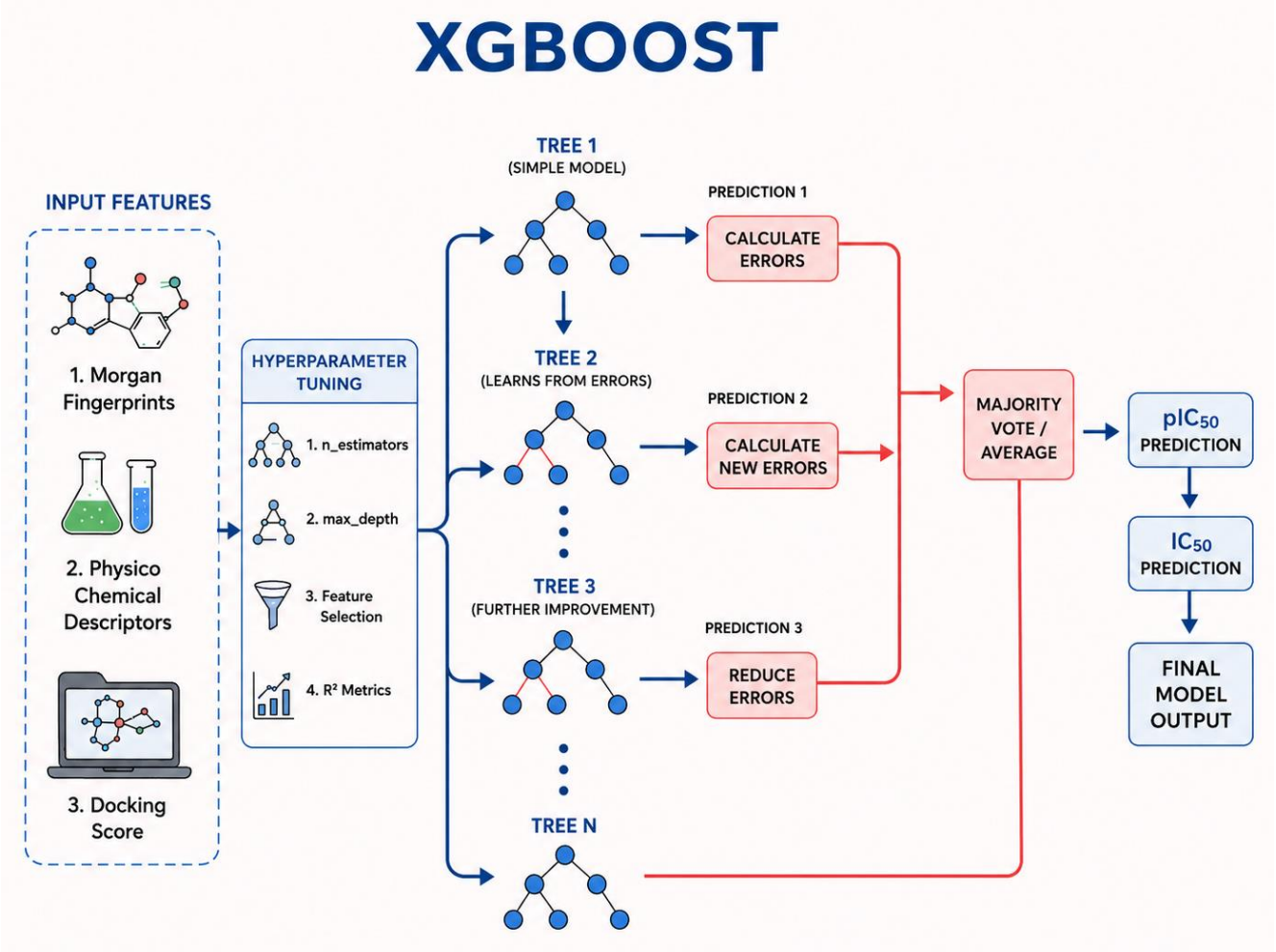

Figure 3. *The workflow illustrates the implementation of an XGBoost regression model using multiple molecular input features, including Morgan fingerprints, physicochemical descriptors, and docking scores of RDRP. Hyperparameter tuning was performed by optimizing parameters such as the number of estimators, maximum tree depth, feature selection, and R^2 metrics. In the boosting process, the first decision tree generates an initial prediction, while subsequent trees iteratively learn from the prediction errors of previous trees to improve model performance. Each new tree reduces residual errors and enhances predictive accuracy. The outputs of all trees are combined to generate the final pIC_{50} prediction, which is subsequently converted into IC_{50} values for the final model output. (Courtesy: Bio icons, Float icons, Diagram generator AI).*

$$\mathcal{L} = \sum_i l(y_i, \hat{y}_i) + \sum_k \Omega(f_k) \quad (3)$$

where l represents the loss function (e.g., squared error), and $\Omega(f_k)$ is a regularization term that penalizes the model complexity.

2.8. Model Training and Validation

The dataset was randomly divided into training (80%) and testing (20%) sets using a fixed random seed (random_state = 42). Model performance during training was evaluated using five-fold cross-validation. The predictive performance of the final Random Forest and XGBoost models was assessed on both the training and independent testing sets using the coefficient of determination (R^2) and Root Mean Square Error (RMSE). In addition, Y-randomization (Y-scrambling) was performed to evaluate model robustness and exclude the possibility of chance correlations [31, 35].

2.9. Pharmacokinetic Prediction

The pharmacokinetic properties of the top-ranked phytochemicals were predicted using SwissADME (http://www.swissadme.ch) and PreADMET (https://preadmet.bmdrc.kr/). Drug-likeness was evaluated according to Lipinski's Rule of Five. Additional ADMET parameters, were assessed to determine the pharmacokinetic suitability of the compounds. Furthermore, molecular docking against CYP3A4, OATP1B1, and OATP1B3 was performed to evaluate potential metabolic interactions and transporter-mediated safety profiles [36].

3. Results

3.1. Interaction of Ligands with RDRP (6KR2)

The molecular docking study was done to assess the ability of 14 phytochemicals to bind to dengue virus NS5 RNA dependent RNA polymerase (RdRp; PDB ID: 6KR2). All the selected compounds had greater binding affinities when compared to the reference inhibitors remdesivir, hence showing promising inhibitory properties. The ligand-protein complex formation occurred by virtue of hydrogen bond, carbon-hydrogen bond, π-alkyl, π-sigma, π-cation, π-anion, π-π stacking, and van der Waals interactions. Hydrogen bonds contributed significantly towards maintaining the orientation of ligands in the catalytic site, while hydrophobic and electrostatic interactions added up to binding affinity. The following phytochemicals, Glycyrrhizin, Mangiferin, Boswellic acid, Curcumin, Azadirachtin, and Forskolin showed the best docking scores and interactions, thus making them promising inhibitors of dengue RdRp. The binding energy and interactions of the docked molecules with NS5 RdRp (6KR2 PDB ID) are shown in Table 3.

Table 3. *Interaction with the RDRP protein (6KR2).*

S. No	Name of the compound	Binding energy (Ki) Kcal/mol	Type of bond interactions
1.	Resveratrol	-6.5 Kcal/mol	H:B - ASP 146. Pi-Sigma - LYS 105, ILE 147. Pi-Alkyl - VAL 132, ILE 147. VI - GLY 81, THR 104, GLU 111, VAL 130, ASP 131, PHE 133, LYS 181.
2.	Curcumin	-8.0 Kcal/mol	H:B - GLY 85, GLY 148, LYS 181. Pi Sigma - LYS 105, ILE 147. Alkyl - ARG 84, VAL 132. Pi Alkyl - LYS 105, LYS 87. VI - VAL 55, GLY 58, GLY 81, CYS 82, GLY 83, GLY 86, THR 104, HIS 110, GLU 111, ASP 131, PHE 133, ASP 146.
3.	Mangiferin	-8.5 Kcal/mol	H:B - MET 116, TRP 121, ARG 353, GLY 463. C:H - VAL 124, LYS 356. Pi-Alkyl - PRO 115, ALA 468. VI - TYR 89, PRO 113, ILE 114, ASN 122, ARG 125, PHE 349, GLU 464, PHE 465, LYS 469.
4.	Glycyrrhizin	-9.5 Kcal/mol	H:B - GLY 106, ASP 146, SER 150. C:H - GLY 81, GLY 83. Alkyl - ILE 147. VI - PHE 25, LYS 29, LYS 61, CYS 82, ARG 84, LEU 103, THE 104, LYS 105, HIS 110, GLU 111, VAL 132, GLY 148, GLU 149, SER 151, PRO 152, ARG 212, SER 214, THR 215, GLU 217.
5.	Forskolin	-7.6 Kcal/mol	H:B - SER 56, TRP 87, GLY 86, ASP 146. Alkyl - ILE147. Pi Sigma - TRP 87.

S. No	Name of the compound	Binding energy (Ki) Kcal/mol	Type of bond interactions
			VI - ARG 57, GLY 58, LYS 61, CYS 82, GLY 83, ARG 84, THR 104, GLU 111, LYS 181.
6.	Boswillic acid	-8.3 Kcal/mol	H:B - ARG 84. Pi-Sigma - HIS 110. Pi-Alkyl - LYS 105, HIS 110, ILE 147. VI - SER 56, GLY 81, CYS 82, GLY 83, THR 104, GLU 111, PHE 133, GLY 148, GLU 149.
7.	Berberin	-7.8 Kcal/mol	C:H - GLY 81, ASP 146. Pi-Alkyl - LYS 105, ILE 147. Pi-Cation - HIS 100. VI - GLY 83, THR 104, GLY 106, GLU 111, ASP 131, VAL 132, PHE 133, GLY 148, ARG 163, LYS 181.
8.	Azadirechtin	-7.9 Kcal/mol	H:B - LYS 61, GLU 217, SER 56. Pi-Sigma - TRP 87. VI - ARG 57, GLY 58, ASP 79, GLY 81, CYS 82, GLY 83, ARG 84, GLY 85, GLY 86, THR 104, HIS 110, GLU 111, ASP 146, ILE 147, GLY 148, ARG 212, THR 215.
9.	Andrographolide	-.6.3 Kcal/mol	H:B - VAL 124, LEU 126, SER 128. C:H - LYS 356. Alkyl - PRO 115, LEU 126. VI - TYR 89, PRO 113, ILE 114, MET 116, TRP 121, ARG 125, GLN 127, ARG 353.
10.	Phyllanthin	-6.2 Kcal/mol	H:B - SER 56, HIS 110, C:H - GLY 81, ASP 131. Pi-Cation - HIS 110, ASP 146. Pi-Alkyl - TRP 87, LYS 105, ILE 147. Pi-Sigma - ILE 147. VI - GLY 82, CYS 82, GLY 86, ARG 57, GLY 106, THR 104, GLU 111, VAL 132, PHE 133, GLY 148, GLU 149.
11.	Nirtetralin	-6.3 Kcal/mol	H:B - ARG 353, LEU 126. Pi-Akyl - PRO 113, PRO 115, LEU 126, ALA 468.
12.	Niranthin	-7.1 Kcal/mol	H:B - GLY 86. C:H - ASP 79, GLY 81, GLU 111. Pi-Sigma - TRP 87, ILE 147. Pi-Cation - HIS 110. Alkyl - LYS 105, VAL 132, ILE 147.
13.	Limonene	-5.4 Kcal/mol	Pi-Alkyl - LYS 105, VAL 132, PHE 133, ILE 147. VI - GLY 81, GLY 83, THR 104, VAL 130, ASP 131.
14.	Beta Myrcene	-4.6 Kcal/mol	Alkyl - LYS 105, HIS 110, ILE 147. VI - GLY 81, GLY 83, GLY 106, GLU 111, ASP 131, VAL 130.
15.	Remidsivir	-7.6 Kcal/mol	H:B - SER 56, GLY 86, LYS 105, GLU 111. C:H - ARG 57, GLY 81, GLY 83. Pi-Sigma - GLU 111. Alkyl - VAL 132, PHE 133, ILE 147. VI - GLY 58, CYS 82, GLY 85, TRP 87, ARG 84, GLY 109, THR 104, HIS 110, ASP 131, ASP 146.

3.2. Interaction of Ligands with CYP3A4 (2V0M)

Molecular docking study on CYP3A4 was carried out to determine the metabolic safety of the lead phytochemicals, since CYP3A4 is one of the most predominant human enzymes involved in the metabolism of the majority of drugs and xenobiotics. Any inhibition of the enzyme would affect the drug pharmacokinetics and result in increased chances of drug-drug interactions and drug toxicity [37]. According to the docking study, Glycyrrhizin, Mangiferin, Boswellic acid, Curcumin, Azadirachtin, and Forskolin showed significant affinity for

CYP3A4, showing interaction patterns either equivalent to or better than that of the known inhibitor, ketoconazole. The complexes formed were stabilized through hydrogen bonding, π-π interactions, and van der Waals forces, which show that the lead phytochemicals have good binding affinity for CYP3A4. Though the above results suggest the antiviral activity of the phytochemicals under investigation, more studies in ADME/Tox are needed in order to establish their metabolic safety. Detailed docking scores and molecular interactions of the phytochemicals with CYP3A4 are illustrated in Table 4.

Table 4. *Interactions with the CYP3A4 (2V0M).*

S. No	Name of the compounds	Binding energy Kcal/mol	Type of bond interactions
1.	Glycyrrhizin	-11.75 kcal/mol	H:B - ASP 76, PHE 220. Pi-Alkyl - PHE 108, PHE 213, PHE 220. VI - ILE 50, TYR 53, PHE 57, ARG 106, MET 114, SER 119, LEU 210, LEU 211, PHE 215, ASP 217, LEU216, ILE 223, PHE 241, ILE 301, PHE 304, GLY 481, LEU 482.
2.	Mangiferin	-8.70 kcal/mol	H:B - ARG 106, LEU 216, GLU 374. Pi-Alkyl - ILE 50. Pi-Pi T Shaped - TYR 53, PHE 57. VI - LEU 51, ASP 76, PRO 107, PHE 108, GLY 109, PHE 215, PHE 220, LEU 221, ILE 223, THR 224,
3.	Boswillic acid	-10.55 kcal/mol	H:B - LEU 216, THR 224. C:H - PHE 215. Pi-Alkyl - TYR 53. VI - ILE 50, PHE 57, ARG 106, PHE 108, PHE 213, ASP 214, ASP 217, PHE 220, LEU 221, GLU 374, GLY 481, LEU 482.
4.	Curcumin	-8.09 kcal/mol	H:B - 216. C:H - PHE 213, LEU 221. Alkyl - ILE 50, LEU221. Pi-Pi Stacked - PHE 220. VI - TYR 53, ASP 76, GLN 79, ARG 106, PRO 107, PHE 108, GLY 109, PHE 215, ASP 217, ILE 223, THR 224, PRO 227, ILE 230.
5.	Forskolin	-8.76 kcal/mol	H:B - ARG 106, THR 224. Pi-Alkyl - TYR 53, PHE 57, LEU 221. VI - ASP 76, PHE 108, PHE 213, PHE 220, GLU 374, GLY 481.
6.	Ketoconazole	-9.51 kcal/mol	H:B - THR 224. C:H - PHE 220. Pi-Akyl - ILE 50, PHE 57, PHE 108, LEU 221, LEU 216. Pi-Pi - PHE 213. VI - TYR 53, ASP 76, ILE 120, LEU 211, PHE 215, PHE 241, GLY 481.

3.3. Interactions of Ligands with OATP 1B1 & 1B3 (8HNH & 8PG0)

After analyzing the binding capacity of CYP3A4, docking studies were carried out using hepatic transporters OATP1B1 and OATP1B3 (PDB IDs: 8HNH and 8PG0), which are important for hepatic drug transport. Inhibition of these transporters may affect the pharmacokinetics of drugs and give rise to adverse drug interactions [38]. Glycyrrhizin, Mangiferin, Boswellic acid, Curcumin, Azadirachtin, and Forskolin had weak interactions with OATP1B1 and OATP1B3 with low binding affinity. Glycyrrhizin and Curcumin had unfavorable interactions like donor-donor and acceptor-acceptor interactions with OATP1B1 and OATP1B3, which would inhibit the transporter and thus have less OATP-mediated toxicity. Despite having similar interaction pattern with rifampicin and simeprevir, Glycyrrhizin and Boswellic acid were found to have strong binding to dengue NS5 RdRp with no significant interactions with the hepatic transporters. Thus, these phytochemicals had high antiviral potential along with being safe. The details about their molecular interactions are given in Tables 5 & 6.

Table 5. Interactions with the OATP 1b1 (8HNH).

S. No	Name of the compounds	Binding energy Kcal/mol	Type of bond interactions
1.	Glycyrrhizin	-9.1 kcal/mol	H:B - ASP 70, ARG 580, GLY 584. C:H - ASP 70. Pi-Alkyl - PHE 356, PHE 360. VI - ALA 45, ILE 46, LYS 49, PHE 73, GLU 74, PHE 224, ILE 353, THR 357, SER 371, ASN 375, ILE 585, PRO 588, ILE 589.
2.	Boswillic acid	-9.0 kcal/mol	Pi-Alkyl - PHE 356. VI - LYS 41, THR 42, ASN 213, ALA 216, MET 217, PRO 220, PHE 224, TYR 352, GLY 379, THR 382, ILE 383, PHE 386, LEU 545,
3.	Curcumin	-7.8 kcal/mol	Alkyl - MET 217, PRO 220, VAL 359, LEU 378, ALA 216, PHE 386, MET 390, VAL 538, VAL 542. VI - THR 42, ASN 213, TYR 352, PHE 356, PHE 360, GLY 379, THR 382, ILE 383, PHE 537, GLN 541, LEU 545.
4.	Forskolin	-6.9 kcal/mol	H:B - ASN 213. Alkyl - PHE 38, VAL 189, LEU 193, VAL 556. VI - LYS 41, VAL 349, TYR 352, ILE 353, PHE 386, MET 390, GLY 552, HIS 555, HIS 575, SER 576, ILE 579, ARG 580.
5.	Simeprevir	-11.2 kcal/mol	C:H - GLY 379. Pi-Sigma - PHE 224, THR 382. Pi-Pi - PHE 356. Alkyl - PRO 220, TYR 352, ILE 383. Pi-Sulphur - PHE 224. VI - THR 42, ILE 353, PHE 360, ASN 375, ILE 376, VAL 380, PHE 386, MET 390, GLN 541, LEU 545, ARG 580.
6.	Rifampacin	-10.9 kcal/mol	H:B - ASN 213, ARG 580. C:H - THR 42. Pi-Sigma - TYR 352, PHE 356. Pi-Cation - LYS 41. VI - PHE 38, ALA 45, ILE 46, VAL 189, LEU 193, MET 217, PRO 220, VAL 349, ILE 353, ILE 383, PHE 386, GLY 552, HIS 555, VAL 556, HIS 575, SER 576.

Table 6. Interactions with the OATP 1b3 (8PG0).

S. No	Name of the compounds	Binding energy Kcal/mol	Type of bond interactions
1.	Glycyrrhizin	-10.5 kcal/mol	H:B - LYS 49, GLU 74, ARG 181, ARG 633. C:H - PHE 73, PHE 362, SER 365. Pi-Sigma - PHE 366. Pi-Alkyl - LYS 49, PHE 73. VI - LYS 41, GLY 45, ILE 46, ILE 363, THR 382, VAL 386, GLN 422, TYR 425, GLN 541, ASN 544, SER 545, SER 548, GLY 584.
2.	Boswillic acid	-10.4 kcal/mol	H:B - ASN 544, SER 548. Pi-Alkyl PHE 356. VI - PHE 352, ILE 353, SER 355, VAL 359, THR 382, VAL 386, TYR 425, GLN 541, SER 545.
3.	Curcumin	-8.2 kcal/mol	H:B - ASP 70. Pi-Pi - PHE 356. Pi-Alkyl - PHE 352. VI - GLY 45, ILE 46, MET 48, GLY 71, PHE 73, GLU 74, ASN 178, ARG 181, THR 382, VAL 386, GLN 541, SER 545, SER 548, GLY 584,

S. No	Name of the compounds	Binding energy Kcal/mol	Type of bond interactions
4.	Forskolin	-7.3 kcal/mol	H:B - PHE 352, THR 382, GLN 541. Pi-Sigma - PHE 356. Pi-Alkyl - VAL 359, PHE 356. VI - ILE 353, SER 355, LEU 378, ILE 381, VAL 386, GLN 422, TYR 425, TYR 537, ASN 544, SER 545, SER 548, TYR 625, ARG 633.
5.	Simeprevir	-11.5 kcal/mol	H:B - GLN 541, SER 548. Pi-Cation - LYS 49, GLU 74. Pi-Sulphur - PHE 73. Pi-Pi - PHE 73. Alkyl - VAL 386, ALA 549. VI - LYS 41, ALA 42, GLY 45, ASP 70, GLY 71, ARG 181, GLU 185, ILE 353, PHE 352, PHE 356, SER 355, THR 382, ASN 544, SER 545, GLY 584, PRO 588, ARG 633.
6.	Rifampacin	-10.1 kcal/mol	H:B - GLU 185, ARG 580. C:H - GLY 584. Pi-Sigma - PHE 73. VI - TYR 38, LYS 41, ALA 42, GLY 45, ILE 46, LYS 49, GLU 74, ARG 181, ASN 213, GLY 216, PRO 220, PHE 224, VAL 349, ILE 353, PHE 356, THR 382, VAL 386, ILE 579.

3.4. Pharmacokinetic Prediction

The compounds possessing the highest binding affinities towards NS5 RNA-dependent RNA polymerase (NS5 RdRp) were analyzed by means of SwissADME regarding their pharmacokinetic characteristics. Important pharmacokinetics indicators, namely, GI absorption, BBB penetration, cytochrome P450 inhibition, lipophilicity, and water solubility, were estimated using SwissADME online server [36]. The toxicity evaluation was conducted via ProTox-II that provides information on hepatotoxicity, mutagenicity, carcinogenicity, and other endpoints, utilizing chemical similarity and machine learning approaches, with mechanistic explanation of potential molecular targets and pathways. It is noteworthy that ProTox-II provides probability-based radar charts for toxicity comparison of various compounds [39]. Results are shown in Tables 7, 8 & 9.

Table 7. *In silico Pharmacokinetic prediction.*

S. No	Compound	Water solubility	lipophilicity	Absorption GI	Permeability BBB	P-Gp Substrate	CYP3A4 inhibition	Lipinski rule
1.	Glycyrrhizin	Poorly Soluble (-6.24)	1.49	Low	No	Yes	No	No
2.	Mangiferin	Soluble (-2.44)	-0.77	Low	No	No	No	No
3.	Boswillic acid	Poorly Soluble (-7.81)	6.12	Low	No	No	No	Yes (1 violation)
4.	Curcumin	Soluble (3.94)	3.03	High	No	No	Yes	Yes
5.	Forskolin	Soluble (-2.82)	1.72	High	No	No	Yes	Yes

P-Gp: P- Glycoprotein; CYP3A4: Cytochrome 3A4; BBB: Blood brain Permeability; GI Absorption; Gastrointestinal absorption.

Table 8. Physico chemical properties.

S. No	Compound	Molecular formula	Molecular weight g/mol	No. of rotatable bonds	No. of H bond acceptors	No. of H bond donors	Molar Refractivity	TPSA
1.	Glycyrrhizin	C42H62O16	822.93	7	16	8	202.84	267.04
2.	Mangiferin	C19H18O11	422.34	2	11	8	100.70	201.28
3.	Boswillic acid	C30H48O3	456.70	1	3	2	136.91	57.53
4.	Curcumin	C21H20O6	368.38	8	6	2	102.80	93.06
5.	Forskolin	C22H34O7	410.50	3	7	3	106.70	113.29

TPSA: Total Polar Surface area.

Table 9. In silico Toxicity prediction.

S. No	Compound	Toxicity class	carcinogenic	Hepatotoxic	Nuclear signaling toxicity	Stress toxicity
1.	Glycyrrhizin	4	No	No	No	No
2.	Mangiferin	1	No	Yes	No	No
3.	Boswillic acid	2	Yes	No	No	No
4.	Curcumin	4	No	No	No	Yes
5.	Forskolin	5	No	No	Yes	Yes

3.5. Model Performance

The Random Forest model recorded has less predictive performance, in contrast to the XGBoost model on the test dataset. The superior performance of the XGBoost model is due to its enhanced capability to capture intricate relationships among structural, physicochemical, and docking-derived features, as noted in recent machine learning-based QSAR studies [18, 34]. The predicted results presented in Table 10.

Table 10. List of top compounds IC50 prediction by XG Boost and Random Forest Models.

S. No	Compound	Predicted IC 50 (µM)	
		XG Boost Regression	Random Forest Regression
1.	Glycyrrhizin	5.22	5.70
2.	Curcumin	5.25	5.85
3.	Boswellic Acid	5.81	5.88
4.	Azadirachtin	5.58	5.53
5.	Forskolin	5.6	5.83
6.	Mangiferin	6.18	6.09
7.	Berberin	5.87	6.13
8.	Andrographillide	6.1	5.8
9.	Phyllanthin	5.58	5.7
10.	Niranthin	5.9	6.05

S. No	Compound	Predicted IC 50 (µM)	
		XG Boost Regression	Random Forest Regression
11.	Beta myrcene	4.62	5.18
12.	Limonene	4.8	5.06
13.	Remdesivir	2.73	2.66

3.6. Role of Hybrid Descriptors

Combining molecular fingerprints with physicochemical descriptors and docking scores greatly enhanced the model's interpretability and predictive power. Fingerprints identify structural patterns, physicochemical descriptors reflect drug-like characteristics, IC_{50}, and docking scores provide insights into target-specific interactions. This integrated method allows for a more thorough depiction of ligand behavior and has become standard practice in contemporary AI-driven drug discovery processes [18, 33, 40].

3.7. Correlation Between CADD/AI Predicted Results and Reported Experimental Data

The QSAR predictions were consistent with the results of molecular docking and in vitro experiments. Compounds that showed promising docking scores and strong experimental activity were typically forecasted to have lower IC_{50} values. This consistency between the computational and experimental methods boosts confidence in the identified lead compounds and is consistent with recent studies that combine AI, docking, and experimental validation [33, 40, 41].

3.8. Limitations

Although various descriptors were included, the predictive accuracy was still moderate, primarily because of the limited dataset size. Expanding the dataset and adding more descriptors could enhance the model robustness, as noted in recent studies on AI-driven drug discovery [40, 42].

4. Discussion

The development of effective antiviral therapies against the dengue virus (DENV) remains challenging because of the genetic diversity of its four serotypes. The highly conserved non-structural protein 5 (NS5) RNA-dependent RNA polymerase (RdRp) is therefore an attractive target for broad-spectrum antiviral drug discovery. In the present study, an integrated computational approach combining molecular docking, ADMET profiling, and ML-based QSAR modeling identified several phytochemicals with more favorable binding affinities toward the NS5 RdRp catalytic site than the reference antiviral drug, remdesivir. Among the evaluated compounds, Glycyrrhizin, Mangiferin, Boswellic acid, Curcumin, Azadirachtin, and Forskolin exhibited the most favorable docking scores. Their ligand-protein complexes were stabilized by multiple non-covalent interactions, including hydrogen bonds, π-π stacking, π-alkyl interactions, and van der Waals forces. Hydrogen bonding played a key role in maintaining ligand orientation within the catalytic pocket. Glycyrrhizin and Curcumin demonstrated the strongest docking profiles, supporting their potential as lead candidates. These findings are consistent with previous reports describing the antiviral activities of Curcumin [19, 43] and Glycyrrhizin [44, 45] against RNA viruses, including DENV. However, molecular docking provides only a prediction of binding affinity, and experimental validation is required to confirm antiviral activity.

To evaluate the pharmacokinetic safety of the identified leads, interactions with CYP3A4, OATP1B1, and OATP1B3 were also investigated. Several phytochemicals exhibited binding affinities toward CYP3A4 comparable to or greater than ketoconazole, suggesting the possibility of CYP3A4 inhibition. Although such interactions may influence drug metabolism, they may also increase the risk of altered pharmacokinetics, drug-drug interactions, and adverse effects. Consequently, detailed CYP inhibition and pharmacokinetic studies are necessary to determine their clinical relevance. Evaluation of the hepatic uptake transporters OATP1B1 and OATP1B3 indicated that Glycyrrhizin, Boswellic acid, Curcumin, Azadirachtin, and Forskolin exhibited relatively weak binding affinities, suggesting a lower likelihood of transporter inhibition and reduced risk of transporter-mediated drug-drug interactions or drug-induced liver injury. In contrast, Mangiferin showed comparatively stronger transporter interactions together with less favorable toxicity predictions and was therefore excluded from the final lead selection despite its promising antiviral docking performance.

Hybrid QSAR models integrating molecular fingerprints, physicochemical descriptors, and docking-derived features further improved lead prioritization. Among the evaluated algorithms, XG Boost outperformed Random Forest, demonstrating its ability to capture complex relationships among molecular descriptors. The agreement between docking results, QSAR predictions, and published biological evidence supports the reliability of the integrated computational workflow for early-stage antiviral screening.

Despite these promising findings, the study has several limitations. The relatively small dataset (n = 220) may limit the generalizability of the machine learning models, while molecular docking and computational ADMET analyses cannot fully predict biological behaviour. Therefore, future studies should include larger datasets, external validation, and comprehensive experimental investigations, including enzymatic inhibition, cell-based antiviral assays, pharmacokinetic evaluation, and in vivo toxicity studies.

Overall, Glycyrrhizin, Curcumin, Boswellic acid, Azadirachtin, and Forskolin emerged as the most promising phytochemical candidates against DENV NS5 RdRp. The integrated use of molecular docking, ADMET analysis, and ML-based QSAR modeling provides an efficient computational framework for prioritizing antiviral lead compounds and supports their further experimental development as potential anti-dengue therapeutics.

5. Conclusion

To find possible phytochemical inhibitors of the dengue virus NS5 RNA-dependent RNA polymerase (RdRp), this study used an integrated computational pipeline that combined molecular docking, ADMET prediction, and machine learning-based QSAR modeling. The reference antiviral drug remdesivir was outperformed in a number of docking parameters by Glycyrrhizin, Boswellic acid, Curcumin, Mangiferin, Azadirachtin, and Forskolin, which demonstrated substantial binding affinities and stable interactions with the NS5 RdRp active site. While Glycyrrhizin, Curcumin, Boswellic acid, and Azadirachtin revealed minimal interactions with OATP1B1 and OATP1B3 transporters, indicating a lesser risk of transporter-mediated hepatotoxicity and hepatic clearance interference, ADMET analysis suggested possible CYP3A4-mediated metabolism. These results were further confirmed by QSAR analysis, where the XG Boost model outperformed Random Forest in biological activity prediction, showing how useful it is to incorporate chemical descriptors, fingerprints, IC_{50} values, and docking scores into AI-driven drug discovery workflows. Future research will create in vitro dengue infection models to assess antiviral efficacy, viral replication, cytotoxicity, and IC_{50} values of the lead compounds in order to validate these computational results. The pharmacokinetics, tissue distribution, safety, and therapeutic efficacy of promising candidates will then be evaluated in vivo. Overall, this integrated AI-assisted method emphasizes the necessity for additional experimental and clinical validation prior to therapeutic application while highlighting the potential of phytochemical scaffolds as dengue NS5 RdRp inhibitors.

Abbreviations

NS5 RDRP	Non-Structural 5 RNA Dependent RNA Polymerase
CADD	Computer-Aided Drug Design
AI&ML	Artificial Intelligence & Machine Learning
CYP3A4	Cytochrome P450 3A4
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OATP1B3	Organic Anion Transporting Polypeptide 1B3
ADME	Absorption, Distribution, Metabolism, and Excretion

Author Contributions

Lokesh Jiraka: Formal Analysis, Investigation, Methodology, Software, Writing – original draft

Jeevan Karthik Madavareddi: Data Curation, Formal Analysis, Writing – review & editing, validation

Manaswini Cheruku: Visualization, Writing – review & editing

Srinivas Rao Maddi: Conceptualization, Project Administration, Supervision

Data Availability Statement

The data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

Lokesh Jiraka is a junior Research Associate at Acubiosys Pvt. Ltd., Hyderabad, India. He received his Master of Pharmacy (M. Pharm) in Pharmacology from Acharya Nagarjuna University, Guntur, India, in 2024, and his Bachelor of Pharmacy (B. Pharm.) from Jawaharlal Nehru Technological University, Anantapur in 2022. He is involved in the end-to-end execution of in vitro, DMPK, in vivo pharmacology, and toxicology studies, including mammalian cell culture, cytotoxicity assays, efficacy, maximum tolerated dose (MTD), acute toxicity, and biological sample collection. He has experience in experimental execution, data analysis, result interpretation, and scientific documentation. His research interests include computational drug discovery, molecular docking, molecular dynamics simulations, and AI-assisted drug development. He is currently involved in computational drug discovery research, integrating molecular docking, molecular dynamics simulations, and machine learning techniques for virtual screening, lead prioritization, predictive potency modeling, and lead optimization against diverse therapeutic targets.

Jeevan Karthik Madavareddi is a senior Research Associate in the In Vitro and In Vivo Pharmacology Department at Acubiosys Private Limited, Hyderabad, India. He obtained his Master of Pharmacy (M. Pharm) in Pharmacology from Jamia Hamdard in 2023 and his Bachelor of Pharmacy (B. Pharm.) from Vishnu College of Pharmacy in 2021. His expertise includes the end-to-end execution of in vitro and in vivo pharmacology studies, encompassing 2D mammalian cell culture, pharmacological assays, DMPK studies, pharmacokinetic (PK), efficacy studies, maximum tolerated dose (MTD), acute toxicity, and genotoxicity (Mini Ames). He is experienced in study design, biological sample collection, experimental execution, data analysis, result interpretation, and scientific documentation. His research interests focus on AI-assisted drug discovery, preclinical pharmacology, ADMET prediction, and the translational evaluation of novel therapeutics for autoimmune disorders, wound healing, and infectious diseases.

Manaswini Cheruku is a junior Research Associate at Acubiosys Pvt. Ltd., Hyderabad, India. She obtained her Master of Science (M. Sc.) in Microbiology from Osmania University, Hyderabad, India, in 2024, and her Bachelor of Science (B. Sc.) in Microbiology, Zoology, and Chemistry (MZC) from Osmania University, Hyderabad, India, in 2022. She is involved in the end-to-end execution of in vitro pharmacology, DMPK studies, Mammalian cell culture, cytotoxicity assays, and biological sample processing. She has experience in experimental execution, data analysis, result interpretation, and scientific documentation. Her research interests include preclinical drug discovery, advanced in vitro models-3D cell culture systems (Spheroids, Organoids, etc.) DMPK, and the application of innovative cellular platforms for translational evaluation of novel therapeutics.

Srinivas Rao Maddi is the Founder and Chief Executive Officer (CEO) of Acubiosys Private Limited, Hyderabad, India. He has over 20 years of experience in the Contract Research Organization (CRO), pharmaceutical, and biotechnology sectors. His expertise spans preclinical drug discovery and development, pharmacology, toxicology, DMPK/ADME, translational research, drug delivery systems and regulatory science. He has successfully led multidisciplinary research programs from target identification to preclinical proof-of-concept, contributing to the development of innovative therapeutics for autoimmune, inflammatory, infectious, and metabolic disorders. His research interests include AI-assisted drug discovery, advanced in vitro models, preclinical pharmacology, and translational medicine and Nano technology drug delivery systems. Under his leadership, Acubiosys has built an integrated drug discovery platform that combines AI-driven target and lead identification, advanced in vitro models, DMPK/ADME profiling, preclinical pharmacology, and translational research to accelerate the development of safe and effective therapeutic candidates from early discovery through preclinical validation.

Research Field

Lokesh Jiraka: In vitro-In vivoPharmacology, DMPK/ADME, Preclinical toxicology, Computational Drug discovery, Machine learning in drug discovery

Jeevan Karthik Madavareddi: In vitro-In vivo Pharmacology, DMPK/ADME, Preclinical toxicology, Computational Drug discovery, Machine learning in drug discovery

Manaswini Cheruku: In vitro Cell-Based Assays, Cell Culture, DMPK/ADME, 3D Cell Culture Models, Cell-Based Screening

Srinivas Rao Maddi: Drug Discovery & Development, In Vitro Models, Preclinical Pharmacology, DMPK/ADME, AI-Assisted Drug Discovery, Nano formulation development, Novel-phyto medicine development