STM JOURNALS

Research & Reviews: A Journal of
Drug Formulation, Development and Production

ISSN: 2394-1944
Volume 13, Issue 1 2026
January–April
DOI (Journal): 10.37591/RRJoDFDP

https://journals.stmjournals.com/rrjodfdp

Research RRJODFDP

In Silico Screening of Terminalia Chebula Phytocompounds as Potential Inhibitors of NTCP and DDB1 in Hepatitis B Virus Infection

Pratyush Vasudha Naresh*

Abstract

Hepatitis B virus (HBV) infection is a major global health concern, and chronic carriers are at risk of developing cirrhosis, hepatocellular carcinoma (HCC), and even death. Existing treatments can effectively inhibit viral replication, but they achieve little eradication of the virus because of covalently closed circular DNA (cccDNA) retention. In this investigation, bioactive compounds of Terminalia chebula, a plant known for its hepatoprotective and antiviral properties in traditional medicine, were screened against NTCP (7PQQ) and DDB1 (9J6K chain A), a key host protein during HBx-mediated transcription through molecular docking. In silico drug-likeness, pharmacokinetic, toxicity profiling along with binding interaction of five ligands (syringic acid, L-ascorbic acid, shikimic acid, vanillic acid and myristic acid) were examined. The Swiss ADME platform was used to predict ADME properties (Lipinski's Rule of Five), and ProTox-II, ADMETlab 3.0 were used for toxicity predictions. Virtual screening on PyRx showed that all the ligands met Lipinski's rules and showed high-gastrointestinal absorption. Toxicity evaluations demonstrated good safety profiles among which vanillic acid and shikimic acid were less toxic. Vanillic acid exerted the highest binding affinity to NTCP (−5.3 kcal/mol) by strong H-bonds and pi-alkyl interactions and shikimic acid revealed the best interactions with DDB1 (−6.1 kcal/mol), involving H-bonds with important residues. These findings suggest that vanillic acid and shikimic acid could be potential lead compounds for novel anti-HBV agents from Terminalia chebula.

Keywords: Hepatitis B virus, *Terminalia chebula*, Molecular docking, NTCP, DDB1, SwissADME, Drug-likeness, ProTox-II, ADMETlab 3.0

INTRODUCTION

Hepatitis B virus (HBV) is a small enveloped virus of the *Hepadnaviridae* family and is a significant health issue in the world, with an estimated 296 million chronic carriers and up to 820,000 deaths each year due to cirrhosis and hepatocellular carcinoma (HCC) [1]. HBV infection may be either acute self-limiting disease or chronic disease, which is usually asymptomatic but may cause chronic inflammation, fibrosis, and HCC of the liver, particularly in individuals infected in the perinatal period or those infected early in life [2].

***Author for Correspondence**
Pratyush Vasudha Naresh
E-mail: pratyushvn0616@gmail.com

[1]Students, Department of Biotechnology, Ramaiah Institute of Technology, Bengaluru, Karnataka, India

Received Date: October 26, 2025
Accepted Date: November 15, 2025
Published Date: November 22, 2025

Citation: Pratyush Vasudha Naresh. In Silico Screening of Terminalia Chebula Phytocompounds as Potential Inhibitors of NTCP and DDB1 in Hepatitis B Virus Infection. Research & Reviews: A Journal of Drug Formulation, Development and Production. 2026; 13(1): 33–44p.

The atypical replication of HBV makes it chronic. Once taken into hepatocytes, relaxed circular DNA (rcDNA) is brought to the nucleus where it is converted into a covalently closed circular DNA (cccDNA) which is a stable episomal template of viral transcription [3]. This is promoted by viral proteins: polymerase reverse-transcribes

pregenomic RNA into cDNA, whereas viral replication is facilitated by the recruitment of a host protein (DDB1) by HBx [4]. The second important therapeutic target is sodium taurocholate co-transporting polypeptide (NTCP), which helps viruses enter cells [5]. Immune-mediated hepatocyte lysis is also caused by chronic infection and results in recurrent inflammation and liver damage [6].

Existing treatments, such as nucleoside/nucleotide analogues (NAs) and interferon-alpha (INF-alpha), can decrease the viral load and slow down the disease development, but they are unable to completely destroy the cccDNA. Long-term treatment is often complicated by relapses, drug resistance, and adverse effects [7]. These restrictions give prominence to the necessity of multitarget approaches that would be able to disrupt a variety of viral life cycle steps [8].

Medicinal plants have a promising future as a source of bioactive compounds with natural chemical diversity and multiple target properties [9]. The traditional medicine, *Terminalia chebula* (haritaki), the so-called king of medicine in Ayurveda and Siddha systems, can be used to treat respiratory, gastrointestinal, cardiovascular, and hepatic diseases [10]. It is rich in tannins, catechins, ellagic acid, flavonoids and has antimicrobial, antiviral, antioxidant and hepatoprotective effects as well [11, 12]. *T. chebula* extracts have shown antiviral activity against herpes simplex virus, HIV, and influenza, as well as antioxidant and anti-inflammatory properties that may help mitigate HBV-induced liver damage [13]. However, evidence of their direct interaction with HBV-specific host proteins remains limited.

In order to fill this gap, multitarget in-silico docking was used in the current study to identify interactions between *T. chebula* phytocompounds and the host proteins DDB1 and NTCP of HBV. Docking offers a fast and inexpensive method of finding out protein-ligand interactions, prioritizing leads, and decreasing experimental burden [8]. Simultaneously focusing on several host-virus interactions will uncover natural compounds with possible antiviral potential and will provide a molecular explanation to the historical use of *T. chebula* in liver diseases.

METHODS

Retrieval of Ligands

For docking and screening studies, an initial ligand library comprising 50 phytocompounds reported from *Terminalia chebula* was obtained from the IMPPAT database (https://cb.imsc.res.in/imppat/) [14]. Their canonical SMILES and PubChem IDs were noted and the ligands were obtained as SDF files from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [15].

Retrieval of Proteins

The following target proteins were chosen for the study: the Hepatitis B Virus X protein/the HBx–DDB1 complex (PDB ID: 9J6K) and the Human Sodium Taurocholate Co-Transporting Polypeptide (NTCP, PDB ID: 7PQQ), a transfected cell receptor that is required for HBV entry. The 9J6K entry represents the HBx–DDB1 complex. For this study, chain A (DDB1) was retained for analysis and docking, since DDB1 is the direct host partner of HBx and essential for viral transcription. The protein structures were downloaded from RCSB Protein Data Bank (https://www.rcsb.org/) in PDB format [16].

Pharmacological Studies

Pharmacological properties of the ligands were examined by SwissADME analysis (http://www.swissadme.ch/) using their physicochemical parameters: lipophilicity, solubility, polarity, and molecular flexibility [17]. The ligands were subsequently filtered by Lipinski's Rule of Five. Toxicity prediction was then conducted by the ProTox-II (https://tox.charite.de/protox3/index.php?site=home) and ADMETlab 3.0 (https://admetlab3.scbdd.com/) tools [18, 19].

Protein Purification

The crystallized water molecules in the HBx–DDB1 complex (9J6K) and NTCP (7PQQ) proteins were removed, as they do not correspond to a physiological state. In the case of 9J6K, chain B (HBx)

was removed and only chain A (DDB1, the biologically relevant host partner of HBx) was retained for docking. For 7PQQ only a single biologically relevant chain was retained, with redundant chains eliminated for steric clash avoidance. Previously existing and co-crystallized heteroatoms or ligands were removed as well to provide that any binding mode identified during docking was due only to the test ligands. Polar hydrogens were added to enhance hydrogen bonding and docking precision, and preparation was carried out using BIOVIA Discovery Studio Visualizer [20]. Structural quality was confirmed by Ramachandran plots constructed with the PDBsum Generate tool (https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/Generate.html), ensuring that both proteins were suitable for docking [21] (Figures 1 and 2).

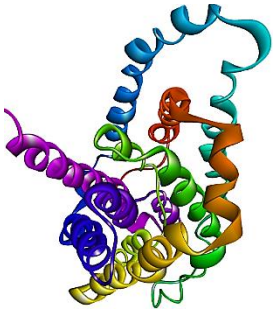


Figure 1. Purified structure of Human NTCP Protein (PDB ID: 7PQQ).

Figure 2. Purified structure of Hepatitis B Virus X Protein (PDB ID: 9J6K).

Molecular Docking

The purified proteins DDB1 (PDB ID: 9J6K) and NTCP (PDB ID: 7PQQ) were uploaded into PyRx as macromolecules, and the phytocompounds of *Terminalia chebula* were prepared as ligands. The ligands, obtained in SDF format from PubChem, were converted to PDB format using OpenBabel [22]. Docking was performed using the AutoDock Vina module integrated in PyRx [23]. The grid box dimensions were set with centre coordinates X = 145.766, Y = 142.969, Z = 137.3746 for NTCP (7PQQ) and X = 107.693, Y = 109.632, Z = 106.0372 for DDB1 (9J6K). Each ligand was docked independently, and binding affinities were calculated from docking scores. The most effective compounds identified were syringic acid, myristic acid, vanillic acid, shikimic acid, and L-ascorbic acid which showed the most favourable interactions with the target proteins.

Visualization

The docked complexes with the strongest binding affinities were visualised using BIOVIA Discovery Studio Visualizer [20]. Interactions such as hydrogen bonding and hydrophobic contacts were examined to verify the stability of the ligand–protein complexes. The conformations showing the lowest binding energies were selected, and corresponding 2D interaction diagrams along with 3D structural models were generated for detailed analysis.

RESULTS

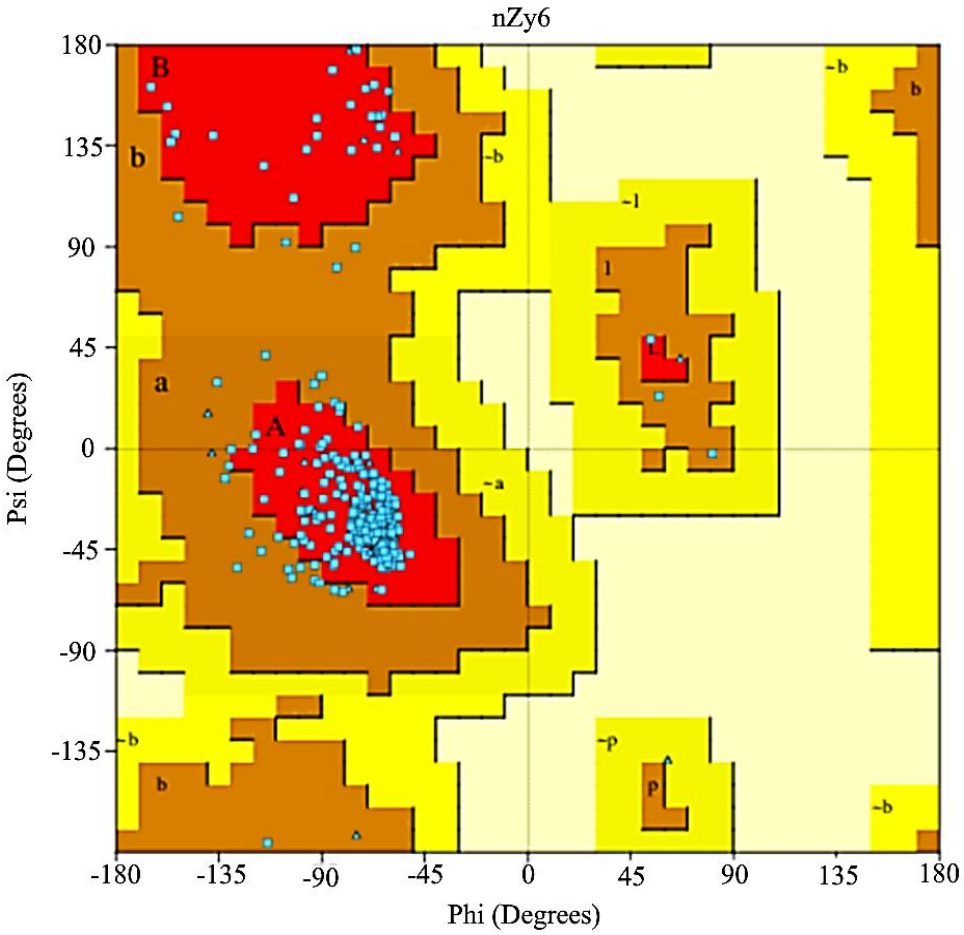
Protein Structure Analysis

The stereochemical quality of the target proteins was assessed using Ramachandran plot analysis, which evaluates the distribution of amino acid torsional angles within energetically favourable regions.

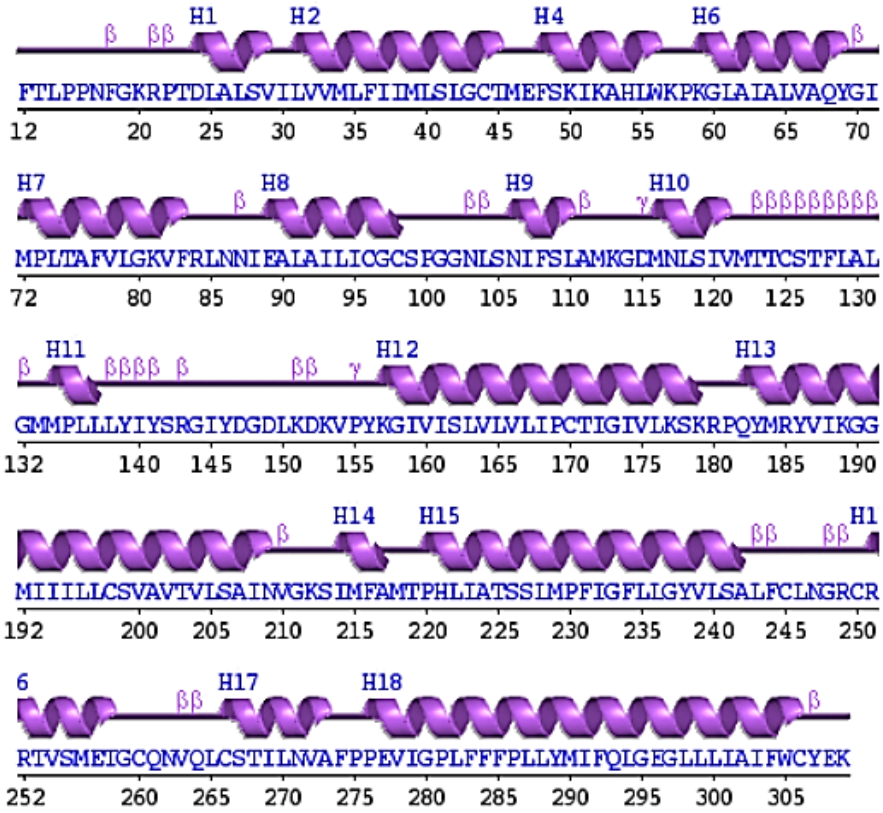
As illustrated in Figures 3 and Figure 4, the Ramachandran plots of NTCP (7PQQ) and DDB1 (9J6K) respectively are shown along with their predicted secondary structures generated using the PDBsum server. This combined representation highlights both the stereochemical constraints and the structural motifs enabling validation of the proteins prior to docking studies. Residues located in the most favoured regions correspond to stable peptide conformations, whereas residues in disallowed regions indicate potential strain. Typically, structures with over 75% residues in the favoured regions are considered reliable for molecular docking.

For NTCP (7PQQ) (Figure 3a), 90.2% of residues were found in the most favoured regions, 9.8% in additional allowed regions, and none in disallowed regions. The protein consists of 298 residues, including 24 glycine, 16 proline, and 256 non-glycine/non-proline residues. Its secondary structure profile (Figure 3b) demonstrates a predominance of α-helices with limited β-elements, consistent with its role as a transmembrane receptor. The high percentage of residues in the favoured regions, combined with the absence of disallowed residues, confirms NTCP as a structurally reliable model for docking studies.

In the case of HBx-DDB1 (9J6K) (Figure 4a), 76.7% of residues were in the most favoured regions, 23.1% in additional allowed regions, and 0.2% in generously allowed regions, with none in disallowed regions. HBx-DDB1 comprises 1,115 residues, including 79 glycine, 40 proline, and 989 non-glycine/non-proline residues. Its predicted secondary structure (Figure 4b) is mostly α-helical with loop regions interspersed with β-strands, consistent with its role as a transcriptional regulator. Though the percentage of residues in favourable region is less than 90%, absence of disallowed residues advocates its docking potential.

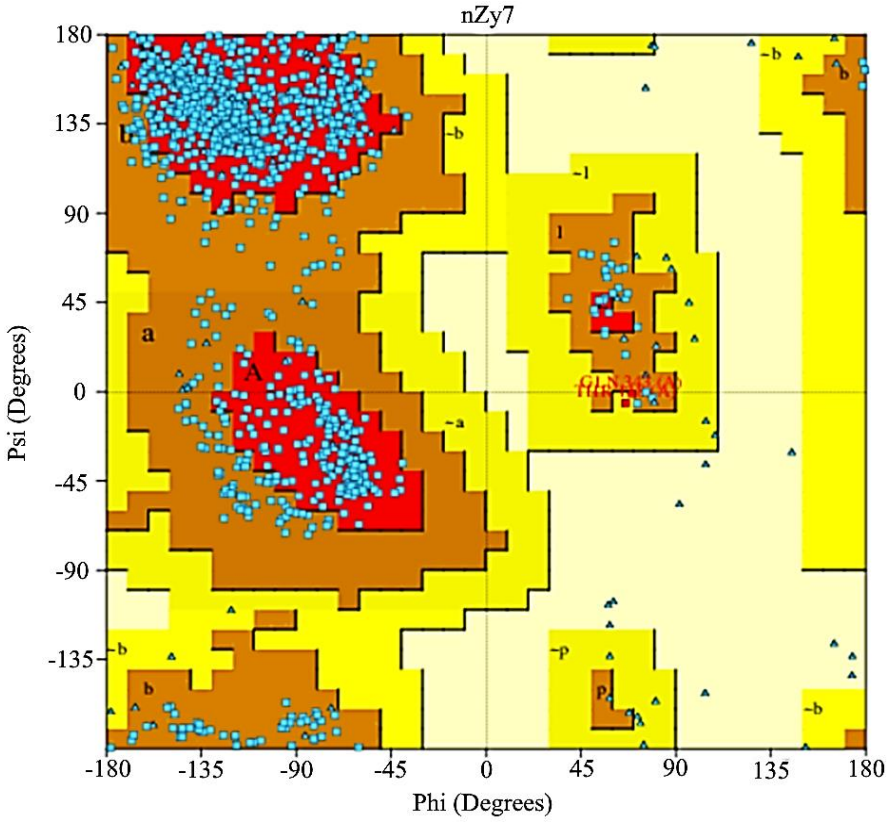


(a)

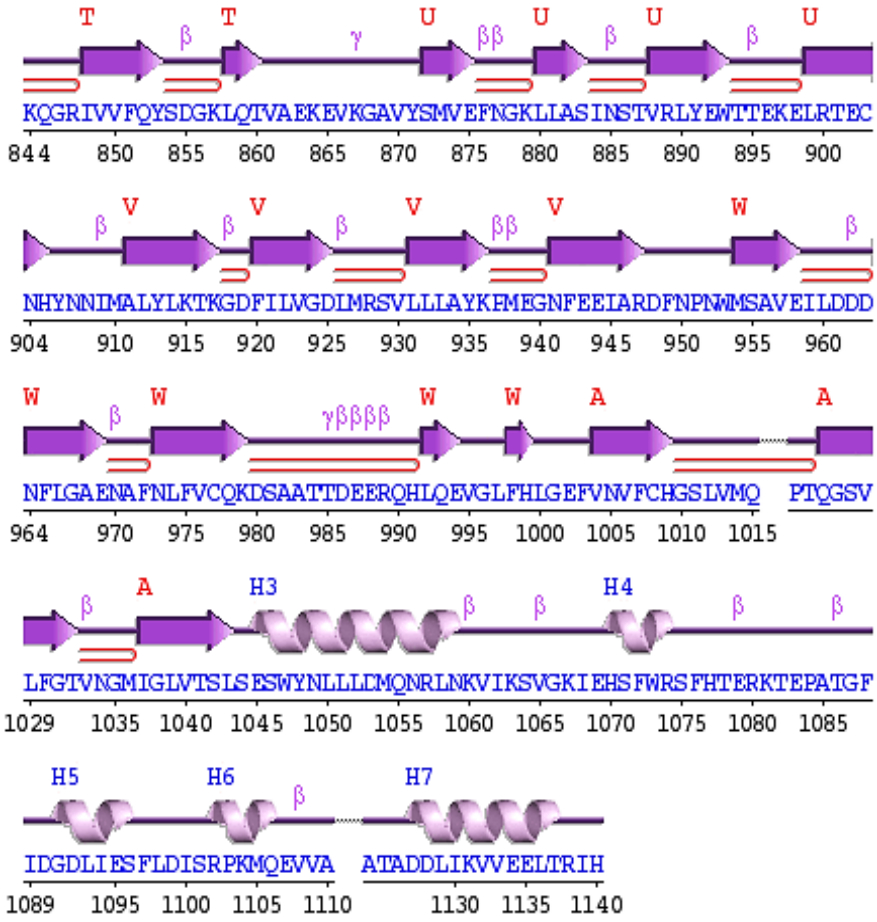


(b)

Figure 3. (a) Ramachandran plot and (b) secondary structure of NTCP protein (7PQQ) using PDBsum.



(a)



(b)

Figure 4. (a) Ramachandran plot and (b) secondary structure of HBx-DDB1 protein (9J6K) using PDBsum.

The ligands in Table 1 were found to possess favourable drug-like properties with no significant violation of Lipinski's rule, confirming their potential to be used in pharmacological study.

Therefore, Ramachandran plots in combination with secondary structure predictions support the stereochemical stability and biological significance of both proteins. NTCP presents a strong α-helical fold for studying HBV pathway and HBx-DDB1 conforms structural flexibility in line with its functional roles of regulator and immune-modulator.

Drug-Likeness Analysis

The similarity search for drugs was conducted employing the bioavailability score, which estimates oral accessibility of the ligands according to properties of small biochemicals. The Lipinski's rule of five was used to eliminate unsuitable compound and access the drug-likeness, meanwhile the PAINS filter was used for searching nonspecific substructures.

Based on the information listed in Table 1, the five ligands (Syringic acid, L-ascorbic acid, Shikimic acid, Vanillic acid, and Myristic acid) satisfied the Lipinski's rules. Their molecular weights (168.15–228.37 g/mol) ranged between 150 and 500 g/mol, MLogP values (−2.6 to 3.69) were below the cut-off of 4.15 and hydrogen bond donors (1–4) and acceptors (2–6) were within the desired ranges. The molar refractivity data were well in between (35.12-71.18 Å²) except for L-ascorbic acid which was marginally below one end of the scale.

Table 1. Data for the properties of Lipinski rule obtained using SwissADME analysis.

Ligand	Molecular Weight	MLogP	Hydrogen donors	Hydrogen acceptors	Molar refractivity
Syringic acid	198.17	0.49	2	5	48.41
L-ascorbic acid	176.12	-2.6	4	6	35.12
Shikimic acid	174.15	-1.43	4	5	38.43
Vanillic acid	168.15	0.74	2	4	41.92
Myristic acid	228.37	3.69	1	2	71.18

ADME analysis

The ADME analysis (Table 2) examined GI absorption, ligand interaction as a P-glycoprotein (P-gp) substrate and solubility. All five compounds demonstrated high GI absorption, which was consistent with oral availability for this class of agents and none were found to be substrates for P-gp, indicating that efflux is not likely to limit bioavailability. Solubility varied among the ligands; shikimic acid (1.75) and L-ascorbic acid (1.49) had high solubility, while syringic acid (−1.46), vanillic acid (−1.32), and myristic acid (−4.51) were found to have lower solubilities suggesting that although these ligands generally possess favourable absorption profiles, formulation strategies may be necessary for poorly soluble ones.

Table 2. Absorption distribution metabolism excretion data obtained using SwissADME analysis.

Ligand	BBB permeant	GI absorption	P-gp substrate	Solubility (LOGSw-SILICOS IT)
Syringic acid	No	High	No	-1.46
L-ascorbic acid	No	High	No	1.49
Shikimic acid	No	High	No	1.75
Vanillic acid	No	High	No	-1.32
Myristic acid	Yes	High	No	-4.51

Toxicity Prediction

The key components of toxicity profiling modelled in this study as a criterion for designing an effective drug were hERG block, DILI, AMES, ROA (acute oral toxicity in rats), carcinogenicity, and respiratory toxicology as well as overall toxicity class (Table 3). These are also important parameters to consider for safety and tolerability of drug candidates prior to the next round of development. The values and associated risks of the ligands exhibited diversity among toxicity endpoints, implying that the toxicity profiles of these molecules require scrutiny with respect to potential therapeutic application (Table 3) [18, 19].

Table 3. Toxicity analysis.

Ligand	hERG	DILI	AMES	ROA	Carcinogenicity	Respiratory	Toxicity class
Syringic acid	0.106	0.65	0.322	0.322	0.416	0.702	4
L-ascorbic acid	0.019	0.65	0.45	0.084	0.314	0.066	5
Shikimic acid	0.136	0.55	0.377	0.214	0.101	0.326	6
Vanillic acid	0.125	0.519	0.384	0.249	0.413	0.672	4
Myristic acid	0.377	0.198	0.063	0.134	0.293	0.906	4

Molecular Docking

The binding free energies of NTCP (7PQQ) and DDB1 (9J6K), which are associated with the selected ligands, according to PyRx were listed in Tables 4 and 5. The docking poses with the lowest binding energy were chosen for additional analysis (highest stability of interaction). Vanillic acid was found as the most interacting compound with NTCP (−5.3 kcal/mol) and shikimic acid displayed potential binding towards DDB1 (−6.1 kcal/mol). These results focused on vanillic and shikimic acids, as the most promising compounds to be further studied.

Table 4. Binding affinity of the ligands with protein NTCP (7PQQ).

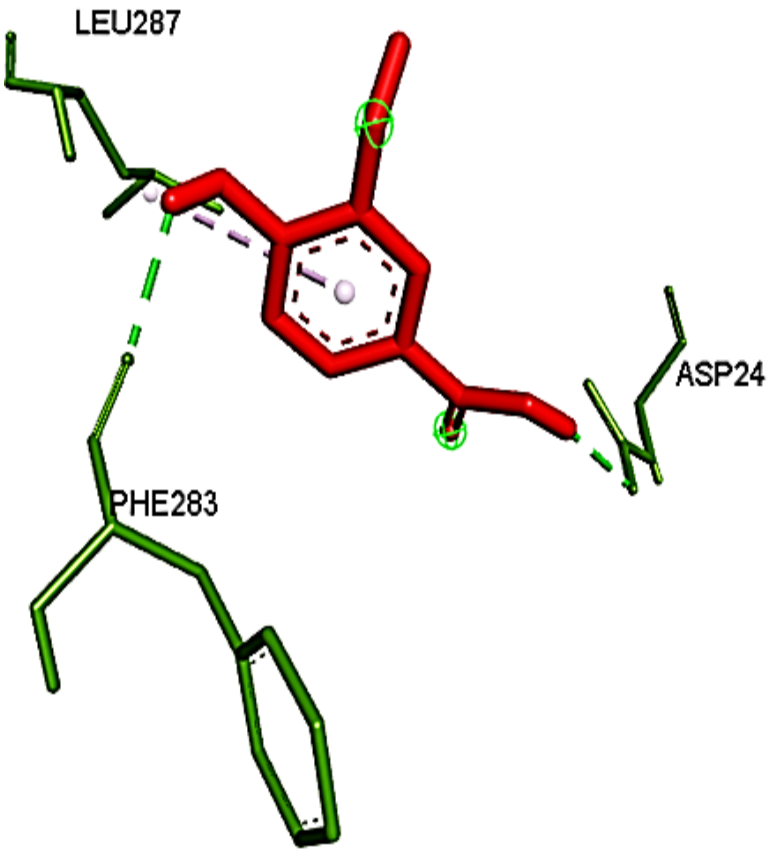
Ligand	Binding affinity (kcal/mol)
Syringic acid	-5.1
L-ascorbic acid	-4.8
Shikimic acid	-5.1
Vanillic acid	-5.3
Myristic acid	-5.2

Table 5. Binding affinity of the ligands with protein DDB1 (9J6K).

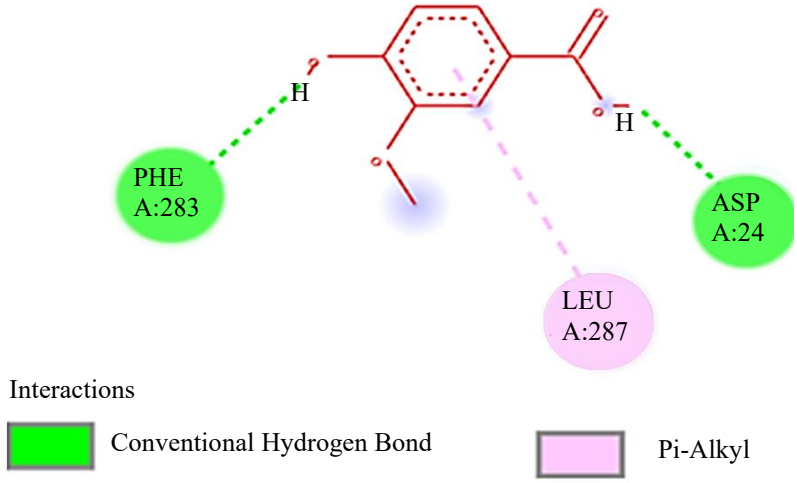
Ligand	Binding affinity (kcal/mol)
Syringic acid	-5.9
L-ascorbic acid	-5.7
Shikimic acid	-6.1
Vanillic acid	-6
Myristic acid	-4.7

Visualization

Owing to their high binding scores, the docking studies interactions of vanillic acid and NTCP (Figure 5) as well as for shikimic acid and DDB1 (Figure 6) were further analysed. Visual analysis of 2D and 3D interaction diagrams show that vanillic acid can form conventional hydrogen bonds, pi-alkyl interactions with amino acid residues such as ASP24, LEU287 and PHE283. Such hydrogen bonding interactions were also formed between shikimic acid and some important residues such as ARG639, MET679, LEU410 and TRP411. These strong and stable associations indicate that both ligands may have a potential role for therapeutic application.

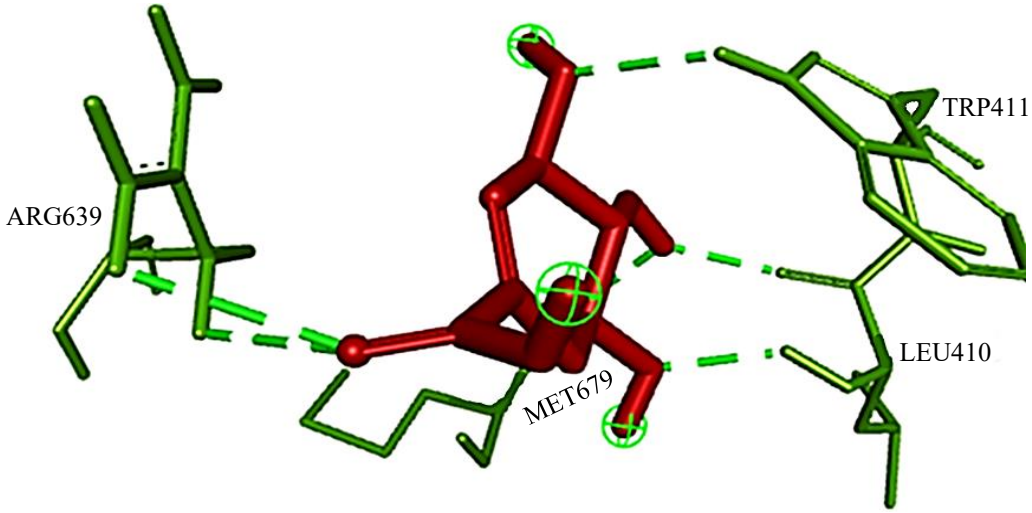


(a)

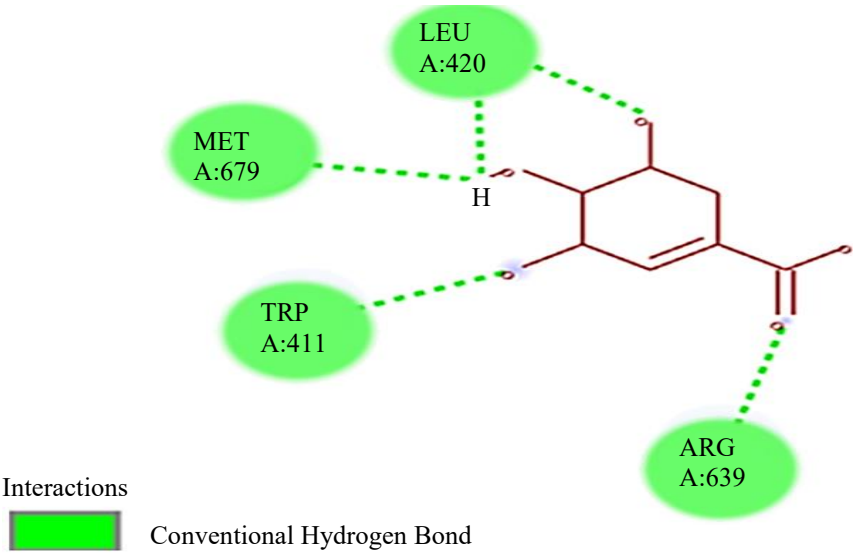


(b)

Figure 5. (a) 3D and (b) 2D interaction diagrams of vanillic acid with NTCP (7PQQ).



(a)



(b)

Figure 6. (a) 3D and (b) 2D interaction diagrams of shikimic acid with DDB1 (9J6K).

DISCUSSION

This paper analysed the drug-like, pharmacokinetics, toxicity, and binding properties of phytocompounds of *Terminalia chebula* against two host proteins relating to HBV which include NTCP (7PQQ) and HBx -DDB1 (9J6K). These proteins play a fundamental role in the regulation of the viral cycle: NTCP is required to allow HBV to enter hepatocytes and DDB1 is a host partner recruited by HBx to maintain the viral transcription and replication [5]. Identification of these points may give alternative options to curb the weakness of the existing therapies whose failure to cure the virus is usually because of cccDNA retention and is usually linked with resistance and relapse [8, 24].

The drug-likeness assessment according to Lipinski's Rule of Five revealed that all the five ligands chosen are probable to be orally active drugs, and there are no significant violations. L-ascorbic acid had slightly lower molar refractivity but this slight deviation would not have many implications on the pharmacological potential. The remaining compounds that contain syringic acid, shikimic acid, vanillic acid, and myristic acid were well within the acceptable range regarding molecular weight, lipophilicity, and hydrogen bonding parameters as previous studies had associated molecular size, polarity, and ability to form hydrogen bonds with oral absorption [25, 26].

ADME assessment also justified their potential oral usage. The gastrointestinal absorption of all ligands was high and these were not expected to be substrates of P-glycoprotein indicating the lack of risk of bioavailability loss through efflux. Shikimic acid and L-ascorbic acid were highly soluble whereas syringic acid, myristic acid and vanillic acid were less soluble. Going along with reduced solubility might lead to formulation difficulties but approaches like nano-encapsulation as well as prodrug derivatization that have been employed in analogous natural compounds may aid their delivery [27].

Predictions of toxicity revealed a variation of the ligands. Myristic acid demonstrated an increased potential of hERG inhibition indicating the potential cardiotoxicity unless optimized by structure-activity relationships (SAR) investigations. In comparison, the safety of vanillic acid and shikimic acid were more advantageous and their predicted risks of drug-induced liver injury and carcinogenicity were lower, which can justify their further development [18, 19, 28].

Mechanistic understanding was given through binding interaction analysis. Vanillic acid was the best binder of NTCP (-5.3 kcal/mol) with hydrogen bond and pi-alkyl interactions with ASP24, LEU287, and PHE283. This effect implies that the viral entry of hepatocytes in the presence of vanillic acid can be inhibited. DDB1 had the greatest affinity to shikimic acid (−6.1 kcal/mol), forming hydrogen bonds with ARG639, MET679, LEU410 and TRP411. As DDB1 is involved in transcription of cccDNA via HBx, shikimic acid can disrupt this process and inhibit viral replication. Overall, these findings indicate that vanillic acid and shikimic acid might have a complementary effect: the former might prevent viral entry, whereas the latter might prevent replication, targeting two different stages of the HBV infection. Other studies have also found natural small molecules that have the potential to disrupt interactions between NTCP and DDB1 associated with similar in-silico studies embodying further support on these observations.

These findings have a notable therapeutic importance. *T. chebula* compounds, long known in the Ayurveda and Siddha systems with antimicrobial, antioxidant, and hepatoprotective activity, presently have a molecular case to play in targeting HBV-related interactions between hosts. Its phytochemicals can serve as multitarget anti-HBV because they can simultaneously inhibit entry and replication. This mechanistic explanation reinforces not only its historical status as the king of medicine, but also its potential as a future source of new sources of antiviral drugs.

CONCLUSION

These results demonstrated that the phytocompounds of *T. chebula* appear to be promising candidates for development of anti-HBV drugs. Lipinski's Rule of Five and high GI absorption were confirmed

through complete in silico studies for all promising ligands, which also showed manageable toxicity profiles. Among them, vanillic acid and shikimic acid were the most effective compounds, based on their high binding affinities to NTCP and DDB1, respectively. Vanillic acid exerted stable interactions with NTCP residues and may potentially function as a viral entry inhibitor, whereas shikimic acid showed strong binding affinity with DDB1 (the host partner of HBx**)** and could act as a potential disruptor of the HBx–DDB1 interaction, thereby impairing viral transcription and replication. All these results are strongly in favour of an additive mode of action which may lead to the simultaneous disruption of HBV entry and replication, tackling two hotspots in the viral life cycle. Although the results are limited to in silico predictions, they present a sound rationale for further investigation through molecular dynamics (MD) simulations, followed by in vitro studies and extrapolation to animal models. Taken together, this study strengthens the potential application of *T. chebula* as a remedy and highlights the broader importance of natural products in antiviral drug development.

Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
cccDNA	covalently closed circular DNA
DDB1	DNA Damage-Binding Protein 1
HBV	Hepatitis B virus
NTCP	Sodium Taurocholate Co-Transporting Polypeptide

REFERENCES

1. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2022: a modelling study. Lancet Gastroenterol Hepatol. 2022;7(9):796–808.
2. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–9.
3. Lucifora J, Arzberger S, Durantel D, et al. Hepatitis B virus X protein is essential to initiate and maintain virus replication after infection. J Hepatol. 2011;55(5):996–1003.
4. Slagle BL, Bouchard MJ. Role of HBx in hepatitis B virus persistence and its therapeutic implications. Curr Opin Virol. 2018;30:32–8.
5. Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. eLife. 2012;1:e00049.
6. Guidotti LG, Chisari FV. Immunobiology and pathogenesis of viral hepatitis. Annu Rev Pathol. 2006;1:23–61.
7. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol. 2017;67(4):847–61.
8. Revill PA, Chisari FV, Block JM, et al. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol. 2019;4(7):545–58.
9. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, et al. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. 2015;33(8):1582–614.
10. Singh R, Ahmed S, Malemnganbi P, et al. Terminalia chebula: A multipurpose tree with immense medicinal value. Pharmacogn Rev. 2021;15(29):70–6.
11. Lee HS, Won NH, Kim KH, Lee H, Jun W, Lee KW. Antioxidant effects of aqueous extract of Terminalia chebula in vivo and in vitro. Biol Pharm Bull. 2005;28(9):1639–44.
12. Sharma A, Kumar S, Chashoo G, et al. Bioactive compounds and pharmacological activities of Terminalia chebula: a review. Asian J Pharm Clin Res. 2016;9(6):21–8.
13. Kannan R, Saraswathy A, Balasubramanian R, et al. Antiviral and anti-inflammatory potential of Terminalia chebula: experimental evidence. BMC Complement Med Ther. 2020;20:145.
14. Mohanraj K, Karthikeyan BS, Vivek-Ananth RP, et al. IMPPAT: A curated database of Indian Medicinal Plants, Phytochemistry and Therapeutics. Sci Rep. 2018;8:4329.
15. Kim S, Chen J, Cheng T, et al. PubChem 2023 update. Nucleic Acids Res. 2023;51(D1):D1373–80.

16. Berman HM, Westbrook J, Feng Z, et al. The Protein Data Bank. Nucleic Acids Res. 2000;28(1):235–42.
17. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717.
18. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018;46(W1):W257–63.
19. Xiong G, Wu Z, Yi J, et al. ADMETlab 3.0: integrating ADMET optimization for drug design. Nucleic Acids Res. 2021;49(W1):W5–14.
20. Dassault Systèmes BIOVIA. Discovery Studio Visualizer v21.1.0. San Diego: Dassault Systèmes; 2021.
21. Laskowski RA, Jabłońska J, Pravda L, Vařeková RS, Thornton JM. PDBsum: Structural summaries of PDB entries. Nucleic Acids Res. 2018;46(D1):D486–8.
22. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. J Cheminform. 2011;3:33.
23. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010;31(2):455–61.
24. Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut. 2015;64(12):1972–84.
25. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1–3):3–26.
26. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45(12):2615–23.
27. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. J Pharm Pharmacol. 2010;62(11):1607–21.
28. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. Nature. 2006;440(7083):463–9.

