

Research Article

In Silico Study of Alkaloids: Neferine and Berbamine Potentially Inhibit the SARS-CoV-2 RNA-Dependent RNA Polymerase

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has been a global concern. While there have been some vaccines and drugs, the rapid emergence of variants due to mutations has threatened public health. As the de novo drug development process is expensive and time-consuming, repurposing existing antiviral drugs against SARS-CoV-2 is an alternative and promising approach to mitigate the current situation. Several studies have indicated that some natural products exhibit inhibitory activities against SARS-CoV-2. This study is aimed at analyzing the potential of natural alkaloids, using various computational tools, as drug candidates against SARS-CoV-2. The molecular docking analysis predicted that naturally occurring alkaloids can bind with RNA-dependent RNA-polymerase (RdRP). The QSAR analysis was conducted by using the way2drug/PASS online web resource, and the pharmacokinetics and toxicity properties of these alkaloids were predicted using pkCSM, SwissADME, and ProTox-II webserver. Among the different alkaloids studied, neferine and berbamine were repurposed as potential drug candidates based on their binding affinity and interactions with RdRP. Further, molecular dynamics simulation of 90 ns revealed the conformational stability of the neferine-RdRP complex.

1. Introduction

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is believed to have emerged in humans from a zoonotic source in Wuhan, China [1]. As of June 3, 2022, there have been approximately 531 million confirmed cases of COVID-19 with approximately 6.3 million deaths globally. Despite the availability of several vaccines and drugs, there is an urgent need to develop safe and effective drugs against SARS-CoV-2 [2]. The *de novo* drug development process is expensive and time-consuming. One of the promising and alternative approaches to identifying antiviral

drugs is by drug repurposing, which is a strategy for identifying new uses of approved or investigational drugs [3, 4]. The surface of SARS-CoV-2 is covered with multiple copies of a large glycosylated spike (S) protein, which binds to the host cell receptor angiotensin-converting enzyme 2 (ACE2) as a first step in the infection process [5]. The virus enters the human cells by endocytosis, and this is followed by the release of viral RNA, replication of the RNA, synthesis of proteins, the formation of mature virions, and the release of the virus particles from the host cells [5].

There have been some efficient vaccines and drugs approved for COVID-19 [6]. However, with the emergence of new variants of SARS-CoV-2 due to mutations, there is an

urgent need to develop alternative drugs for this disease. Identification of potential drug targets is the foremost strategy in the drug discovery and development process [7]. Several studies are focused on the development of drugs that target structural and nonstructural proteins of the virus [8]. In this study, we focus on RNA-dependent RNA-polymerase (RdRP), a nonstructural protein also known as Nsp12, which is the central enzyme for viral replication [9, 10]. The RdRP is an excellent broad-spectrum antiviral target for coronaviruses as it is the most conserved protein from RNA viruses [11, 12]. The RdRP of SARS-CoV-2 is comprised of a catalytic subunit and two accessory subunits; its overall architecture resembles a righthand consisting of fingers, thumb, and palm subdomains [13]. RdRP plays a crucial role in viral replication and survival; their active sites are the most conserved, and hence designing inhibitors that bind to the active sites could be an effective approach for identifying the best inhibitors [14]. Based on molecular docking studies of the drugs either currently available in the market or in clinical trials against other viruses, several drugs, including ribavirin, remdesivir, sofosbuvir, tenofovir, and galidesivir have been proposed as potent drugs against SARS-CoV-2 as these compounds bind tightly with RdRP [15].

Natural products from plants, especially those with ethnopharmacological uses find wide applications in treating antiviral, antimicrobial, antibacterial, and antifungal diseases [16, 17]. Natural product-based secondary metabolites, such as tannins, alkaloids, polyphenols, quinoline, coumarins, and flavonoids, are believed to have medicinal and therapeutic values [17]. Among these metabolites, alkaloids have been widely studied as antiviral agents [18–21]. Multiple studies have demonstrated that alkaloids significantly impact numerous viruses, including human immunodeficiency virus (HIV), hepatitis C virus, influenza virus, and herpes simplex virus [22, 23]. There are several ongoing clinical trials on alkaloids against COVID-19 [19].

This research is aimed at identifying, utilizing computational tools, the natural alkaloids that inhibit the activity of the RdRP of SARS-CoV-2. We have selected 84 alkaloids, and the binding mechanisms of these compounds with the RdRP were explored using molecular docking. We have also evaluated the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of these alkaloids as these properties play crucial roles in every stage of drug discovery and development. The stability of the best-docked complex was further evaluated using molecular dynamics (MD) simulation up to 90 ns.

2. Materials and Methods

2.1. Computational Working Station. The computational docking studies were performed on a GNU/Linux workstation (Intel Core-i7 processor, system memory 8 GB RAM, and GPU NVidia GeForce RTX 2060 6 GB). Molecular Operating Environment (MOE) version 3.12 [24] was used for the preparation of the protein, preparation of ligands, analysis of binding sites, and the analysis of the docked complexes. This was conducted for atoms within 10 Å of the submitted binding residues in the binding pocket. The molecular docking of the ligand and protein molecules was



FIGURE 1: Chemical structures of the potent alkaloids obtained after the primary screening.

performed using Auto Dock Vina 1.5.7 [25]. The MD simulations for the neferine-6M71 complex were carried out on the GROMACS 5.1.2.

2.2. Target Selection and Protein Preparation. The SARS-CoV-2 RdRP protein sequence (PDB ID: 6M71, and PDB ID: 7B3C) was retrieved from the Protein Data Bank (PDB). The MOE protein preparation module was used to optimize the structures where water molecules were removed, energy was minimized, hydrogen atoms were added, and atomic charges were assigned to all protein atoms.

2.3. Ligand Preparation. After a literature review, the structures of 84 natural alkaloids which show antiviral activity against SARS-CoV-2 were downloaded from Pub-Chem [26]. The Open Babel software was used to convert the compounds into their mol2 format [27] and subjected to energy minimization using the MOE. Then, the alkaloids were screened based on pharmacokinetic parameters, and the structures of six selected ligands are depicted in Figure 1.

2.4. Quantitative Structure-Activity Relationship (QSAR) Analysis. Using the PASS-Way2Drug server (http://www. way2drug.com/PASSOnline/), a QSAR analysis was performed to evaluate the bioactivity of the ligands [28, 29]. The ligands are expected to exhibit antiviral activity in general or antiviral activity against specific positive single-stranded RNA virus families or viral entrance inhibitors.

2.5. In Silico ADMET and Toxicity Analysis. SwissADME web tool [30] and pkCSM webserver [31] were used to predict the pharmacokinetic parameters of the alkaloids. Further, ProTox-II was used to predict various toxicity endpoints, such as immunotoxicity, hepatotoxicity, organ toxicity, and cytotoxicity [32].

2.6. Molecular Docking and Validation. The RdRP protein (PDB ID:6M71) was refined using the MOE, where protonation, energy minimization, and addition of Gasteiger charges

were done [33]. Finally, the ligands (alkaloids) were docked into the binding sites of the refined protein. The scoring functions were set as default, and the poses were obtained as suggested in the literature [34]. The validation of molecular docking was carried out by extracting RdRP-inhibitor, remdesivir, and the respective potent alkaloids from their original binding site and redocked them into the same position [33]. The low energy poses of the first and second docked protein-ligand complexes were superimposed, and their root mean square deviation (RMSD) values were calculated. The validation is considered successful if the RMSD values are less than 2 Å [33, 35]. The BIOVIA Discovery studio visualizer was used to analyze the protein-ligand interactions.

2.7. Binding Affinity Calculation. The binding affinity of the protein-ligand complex was calculated using Auto Dock Vina 1.5.7 [25], where heteroatoms were removed and subsequently hydrogen bonds and Gasteiger charges were added. The grid box dimension was fixed at a $60 \times 60 \times 60$ Å with a spacing of 0.375 Å using AutoGrid v.4.2.

2.8. Molecular Dynamics Simulation. The protein-ligand complex (RdRP-neferine) was obtained by molecular docking as described earlier. CHARMM was used as a force field, and the parameters were generated using the Swiss Param web server. Furthermore, this force field was used to create protein topology files. The TIP3P water model was used to dissolve complexes [36], and the systems were neutralized using sodium (Na⁺) ions. Periodic boundary conditions (PBC) were set to enable Van der Waals interactions. The particle-mesh Ewald (PME) algorithm was used to model long-range electrostatic interactions. A 90 ns molecular dynamics (MD) simulation was performed to collect and analyze the data. A 2-fs integration time step was set, where the neighbor list was updated every fifth step using the Grid option. The MD simulation was performed on GROMACS V 5.1.2. The MD trajectories were analyzed using the Xmgrace visualization tool.

3. Results and Discussion

3.1. QSAR Analysis of Alkaloids. The QSAR analysis predicts the biological activities based on molecular descriptors. The results of the QSAR analysis of different alkaloids are shown in Figure 2, which showed that oxysophoridine and remdesivir exhibited general antiviral properties. Similarly, berbamine, neferine, and strychnopentamine exhibited hepatitis, hepatitis B, hepatitis C, HIV-1 integrase, and viral entry inhibitor properties. These compounds showed a threshold *Pa* less than 0.3, indicating weak antiviral activities [37, 38]. Although neferine and berbamine showed low threshold *Pa*, the *in vitro* studies on these metabolites against SARS-CoV-2 were promising [21], and thus, we performed molecular docking and MD simulation analysis.

3.2. Pharmacokinetic Analysis of Naturally Occurring Alkaloids. Important parameters useful in drug discovery and development are determined by pharmacokinetic



FIGURE 2: The predicted antiviral activities of the selected alkaloids using the PASS server.

analysis, and these properties of natural alkaloids were computed using the pkCSM web server. The absorption of a drug in humans is determined by its water solubility, Caco-2 permeability, and volume of distribution (VDss) values. berbamine, oxysophorodine, neferine, 10'-hydroxyusambarensine, strychnopentamine, and remdesivir were found to be moderately soluble in water, as shown in Table 1. Likewise, the bioavailability of a drug is determined by its Caco-2 permeability and human intestinal absorption (HIA) values. Here, seven alkaloids have a permeability value greater than 0.9, indicating they are permeable [39]. All drugs are absorbed from the gastrointestinal tract, and any compounds with more than 30% HIA values are considered to be readily absorbed in the human intestine [40]. All the top hit alkaloids have high HIA values and neferine shows 90%. On the other hand, the extent of drug distribution in the body is determined several parameters, such as VDss and fraction unbound (human). The overall dose of a drug required to provide identical blood plasma concentration is best studied by VDss values. A higher logVDss value indicates the distribution of drugs in tissue rather than plasma. This value is considered higher if it is>0.45 and lower if it is <-0.15 [41]. All the selected alkaloids have fraction unbound values between 0.095 and 0.455 as shown in Table 1.

Except for neferine and strychnopentamine, all the alkaloids listed in Table 2 are noninhibitors of cytochrome P450, an enzyme responsible for metabolism. Similarly, total clearance values and renal organic cation transporter (OCT) substrate explain the excretion of a drug from the body. Only neferine and 10'-hydroxyusambarensine were found as a substrate for renal OCT, while other alkaloids were found to be removed through different routes from the body. Toxicity analysis is crucial in predicting the usefulness of any drug candidate. Here, berbamine and 10'-hydroxyusambarensine are found to show AMES toxicity, suggesting that they may be mutagenic and carcinogenic. Our analysis showed that 10'-hydroxyusambarensine, strychnopentamine, and remdesivir are found to be hepatotoxic. Furthermore, the lethal dose (LD_{50}) value indicates the amount of a substance that causes the death of 50% of tested animals [39]. The lower the LD₅₀ value, the more toxic is the substance. All the alkaloids studied have a higher LD₅₀ value indicating less

Oxysophorodine	Berbamine	Neferine	10'- Hydroxyusambarensine	Strychnopentamine	Remdesivir
-3.921	-2.983	-3.056	-2.995	-2.945	-3.07
1.304	1.165	0.986	0.519	0.821	0.635
96.293	92.311	90.324	89.792	89.516	71.109
0.409	-0.63	-0.286	0.114	2.03	0.307
0.455	0.373	0.309	0.095	0.232	0.005
NO	NO	YES	NO	NO	NO
NO	NO	NO	NO	YES	NO
	Oxysophorodine -3.921 1.304 96.293 0.409 0.455 NO NO	Oxysophorodine Berbamine -3.921 -2.983 1.304 1.165 96.293 92.311 0.409 -0.63 0.455 0.373 NO NO NO NO	Oxysophorodine Berbamine Neferine -3.921 -2.983 -3.056 1.304 1.165 0.986 96.293 92.311 90.324 0.409 -0.63 -0.286 0.455 0.373 0.309 NO NO YES NO NO NO	Oxysophorodine Berbamine Neferine 10'- Hydroxyusambarensine -3.921 -2.983 -3.056 -2.995 1.304 1.165 0.986 0.519 96.293 92.311 90.324 89.792 0.409 -0.63 -0.286 0.114 0.455 0.373 0.309 0.095 NO NO YES NO NO NO NO NO	Oxysophorodine Berbamine Neferine 10'- Hydroxyusambarensine Strychnopentamine -3.921 -2.983 -3.056 -2.995 -2.945 1.304 1.165 0.986 0.519 0.821 96.293 92.311 90.324 89.792 89.516 0.409 -0.63 -0.286 0.114 2.03 0.455 0.373 0.309 0.095 0.232 NO NO YES NO NO

TABLE 1: The pkCSM analysis of oxysophorodine, berbamine, neferine, 10'-hydroxyusambarensine, strychnopentamine, and remdesivir (standard ligand) showing the absorption, and distribution, and metabolism profiles.

TABLE 2: The pkCSM analysis of oxysophorodine, berbamine, neferine, 10'-hydroxyusambarensine, strychnopentamine, and remdesivir (standard ligand) showing excretion and toxicity profiles.

Alkaloids	Oxysophoridine	Berbamine	Neferine	10'- Hydroxyusambarensine	Strychnopentamine	Remdesivir
Total clearance (log mL/min/kg)	1.066	0.724	1.007	1.109	0.947	0.198
Renal OCT substrate	NO	NO	YES	YES	NO	NO
AMES toxicity	NO	YES	NO	YES	NO	NO
Oral rat toxicity (LD50(mg/kg))	2.653	2.494	2.304	2.363	2.148	2.043
Hepatotoxicity	NO	NO	NO	YES	YES	YES
Toxicity class	4	4	4	4	4	4

TABLE 3: The SwissADME analysis of oxysophorodine, berbamine, neferine, 10'-hydroxyusambarensine, strychnopentamine, and remdesivir (standard ligand).

S. N	Alkaloids	PubChem ID	Molecular Mass (Da)	Hydrogen bond donor (HBD <5)	Hydrogen bond acceptor (HBA <10)	Log <i>P</i> < 5	Molar refractivity (40–130)	Drug likeness >0
1.	Oxysophoridine	114850	278.39	0	2	1.22	87.80	0.55
2.	Berbamine	275182	608.72	1	8	5.15	181.60	0.55
3.	Neferine	159654	624.77	1	8	5.47	188.02	0.55
4.	10′- Hydroxyusambarensine	10433813	448.56	3	3	4.40	142.46	0.55
5.	Strychnopentamine	6712640	549.75	3	4	4.68	180.14	0.55
6.	Remdesivir	121304016	602.58	4	12	1.50	150.43	0.17
4. 5. 6.	Hydroxyusambarensine Strychnopentamine Remdesivir	10433813 6712640 121304016	448.56 549.75 602.58	3 3 4	3 4 12	4.40 4.68 1.50	142.46 180.14 150.43	0. 0. 0.

lethal effects. Further, ProTox-II analysis revealed that all the selected alkaloids have a toxicity class of IV, as shown in Table 2. Similarly, Table 3 illustrates the results of the SwissADME analysis of those alkaloids.

3.3. Molecular Docking and Confirmational Studies. The summary of molecular docking results including S-score, RMSD refine values, interacting residues, and bond lengths of selected alkaloids with RdRP is shown in Table 4. Here, berbamine has a good S-score value of -2.6064. The lower S-score value indicates good protein-ligand interaction. Berbamine has been found to interact with ASP618 and ASP761, which are some of the catalytic residues of RdRP [42]. The bond length of interaction is found to be 4.37 nm. Moreover, the binding affinity computed using AutoDock Vina revealed that berbamine has the lowest interaction energy, i.e., -9.8 kcal/mol among other alkaloids, while standard ligand remdesivir showed an interaction energy of

-8.1 kcal/mol. In recent studies, berbamine was found to show anti-SARS-CoV-2 activity in Vero-E6 cells with an EC₅₀ of approximately 2.4 μ M [43]. Additionally, this molecule has been reported to show antiviral activity against SARS-CoV-2 [44], suggesting its potential to become a likely drug candidate against SARS-CoV-2. The molecular docking studies from the MOE and AutoDock Vina also indicated berbamine as a potential drug candidate.

Similarly, neferine also has a good S-score (-5.083), which indicates that it strongly interacts with the RdRP of SARS-CoV-2. The interaction of neferine with ASP760 residue at a bond length of 3.3 nm indicates that it inhibits the activity of RdRP. Moreover, neferine has shown a good EC₅₀ of less than 10 μ M [21]. Further, it has a lower binding free energy (-9.1 kcal/mol) as compared to that of remdesivir (-8.1 kcal/mol). The binding free energies of the top alkaloids with RdRP and the interacting residues of RdRP are summarized in Table 5. It has been reported that neferine suppresses the entry of SARS-CoV-2 and other

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	-	-		-	-	
Compounds	In vitro data	S-score	RMSD refine	Interaction	Bond length (Á)	Target site/Virus
Oxysophoridine	EC ₅₀ 0.018 μM Ref ([41])	-3.304	1.312	CY\$622	3.17	SARS-CoV-2
Berbamine	14.50 μM Ref ([35])	-2.6064	1.34	ASP618 ASP761	2.76 4.37	SARS-CoV-2
Neferine	10 µM EC ₅₀ Ref ([36])	-5.083	1.32	ASP760 TYR619	2.88 4.34	SARS-CoV-2
10'-hydroxyusambarensine	Not reported	-4.66	1.47	ASP761 GLU811	3.2 4.25	SARS-CoV-2
Strychnopentamine	Not reported	-3.64	1.067	ASP761 ARG555	SARS-CoV-2	SARS-CoV-2
Remdesivir	Not reported	-5.581	1.57	ASP618 ASP760 TYR619	3.14 2.92/3.13 3.26	

TABLE 4: Summary of Molecular docking studies of the selected naturally occurring alkaloids with RdRP.

TABLE 5: Summary of the binding free energies of A1, A2, A3, A4, A5, and A8 with RdRP and the interacting residues of RdRP.

Alkaloids	Binding free energy (kcal/mol)	Interacting residues	
Oxysophoridine	-6.8	LYS A:780 SER A:784	
Berbamine	-9.8	CYS A: 622 ASP A: 623 SER A: 682 ASP A: 760 ASP A: 761	
Neferine	-9.1	ASP A:618 TYR A:619 LYS A:621 ASP A:618 ASP A:760 LYS A:798	
10'- hydroxyusambarensine	-8.9	VAL A:315 PRO A:323 ARG A:349 GLU A:350 PRO A:461	
Strychnopentamine	-9.2	TYR A:619 ASP A:623 SER A:682 ASP A: 760 ASP A:761	
Remdesivir	-8.1	TRP A:617 ASP A:618 CYS A:622 ASP A:760 ASP A:761 CYS A:813 SER A:814	

coronaviruses by blocking host calcium channels, thereby inhibiting the Ca²⁺-dependent membrane fusion process. Neferine is also reported as a calcium channel blocker. The entry of SARS-CoV, MERS-CoV, and SARS-CoV-2 are notified to be Ca²⁺ dependent. Hence, blocking Ca²⁺-dependent membrane fusion, neferine shows its efficacious antiviral effect against different coronaviruses [45]. Based on *in silico* docking and wet-lab experiments, neferine could be



FIGURE 3: 2D interaction diagram between neferine and RdRP obtained using the MOE.



FIGURE 4: 2D interaction diagram between berbamine and RdRP obtained using the MOE.

a potent drug candidate against SARS-CoV-2. Besides, neferine shows anticancer activity by activating several pathways like cell cycle arrest, autophagy, and apoptosis induction. It has numerous therapeutic applications such as anticancerous, anti-inflammatory, and antianxiety as compared to anticancer drugs available like taxol, cisplatin, and doxorubicin [46]. Previous molecular docking analysis on neferine showed that it effectively binds to the drug-binding pockets (Mpro, PLpro, RdRP), which further justified its potential for cancer therapy [47].

Several alkaloids were previously docked against the binding site of several proteins (Mpro, PLpro, RdRP, Spike protein) of SARS-CoV-2 and have shown promising data [48]. Our studies showed that berbamine and neferine are capable of binding to the catalytic site of the palm region of RdRP, and this binding could inhibit the activity of RdRP resulting in a blockage of viral replication and transcription.

The interaction of neferine and berbamine with human serum albumin (HSA) protein (PDB ID:1A06) was also



FIGURE 5: 2D interaction diagram between remdesivir and RdRP obtained using the MOE.



FIGURE 6: 3D and 2D interaction diagrams between neferine and RdRP obtained using the Auto Dock Vina.

carried out to unveil whether the ligand binds with RdRP protein or HSA protein. But very weak interactions were observed between neferine-HSA and berbamine-HSA complexes, indicating stronger binding of neferine and berbamine with SARS-CoV-2 RdRP protein rather than HSA protein. Figures 3, 4, and 5 show the 2D interaction diagrams of neferine, berbamine, and remdesivir with RdRP, respectively, obtained using the MOE. Based on the strong SARS-CoV-2 protein-ligand interactions and their good experimental *in vitro* data and therapeutic uses, neferine was



FIGURE 7: 3D and 2D interaction diagrams between berbamine and RdRP obtained using the Auto Dock Vina.



FIGURE 8: 3D and 2D interaction diagrams between remdesivir and RdRP obtained using the Auto Dock Vina.



FIGURE 9: (a) RMSD and (b) RMSF plots for the neferine-RdRP complex.

subjected to a 90 ns long MD simulation to further explore protein-ligand stability.

3.4. Binding Affinity Analysis. The semiempirical binding affinity of the top alkaloids was calculated using AutoDock Vina, and the summary of the binding free energy of these alkaloids with RdRP and the interacting amino acid residues of RdRP is shown in Table 5. Berbamine, neferine, 10'hydroxyusambarensine, and strychnopentamine have higher binding affinity than remdesivir (standard ligand). Berbamine has the lowest BFE of -9.8 kcal/mol, and it shows interactions with CYS A:622, ASP A:623, SER A:682, ASP A: 760, and ASP A:761. Similarly, neferine has a BFE of -9.1 kcal/mol, and the interacting amino acid residues are ASP A:618, TYR A:619, LYS A:621, ASP A:618, ASP A:760, and LYS A:798. However, remdesivir has a BFE of -8.1 kcal/ mol, and the interacting amino acid residues are TRP A:617, ASP A:618, CYS A:622, ASP A:760, ASP A:761, CYS A:813, and SER A:814. Figures 6, 7, and 8 show the 3D and 2D ligand-protein interaction diagrams generated using the AutoDock Vina.

3.5. Molecular Dynamics Simulations. Among the selected alkaloids, neferine was found to show good interactions with RdRP. To learn more about ligand-receptor interactions, 90 ns MD simulations were carried out on the neferine-RdRP complex. The RMSD values of the neferine-RdRP complexes are shown in Figure 9(a). The average RMSD fluctuations for the protein and ligand are 0.26 nm. A plot of RMSF values, compared with the starting structures, against the amino acid residue number is shown in Figure 9(b). The RMSF is less than 0.19 nm for each residue surrounding the neferine-RdRP complex. Based on the MD results, the neferine-RdRP complex was found stable, and it could inhibit viral replication.

4. Conclusions

Though several vaccines and drugs are available against COVID-19, the development of effective drugs against SARS-CoV-2 is desperately required. One of the most tangible options for developing drugs against this virus is drug repurposing. In this study, we screened 84 natural alkaloids using computational tools, and among them, neferine showed excellent binding interactions with RdRP

protein. Neferine is found to interact with ASP760 and TYR619 residues of RdRP with a binding affinity of -9.1 kcal/mol. Interestingly, both the docking software, i.e., MOE, and AutoDock Vina, showed a similar type of interaction. Furthermore, It was found to possess favorable pharmacokinetic profiles and showed no AMES, hepatotoxicity, or drug-liver issues. Similarly, 90 ns MD simulations showed further stability of the protein-ligand complex thus formed. Another alkaloid that showed potential druglikeness properties is berbamine, which is found to interact with RdRP through ASP618 and ASP761 residues with a binding affinity of -9.8 kcal/mol. Both the alkaloids are found to show weak interactions with HSA. The compound neferine has previously shown antiviral properties against various coronaviruses, and this in silico study further indicates that this compound can be a potent drug candidate against SARS-CoV-2. Further, in vivo animal studies would be helpful to verify these computational predictions.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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