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Original article

Molecular docking of monkeypox (mpox) virus proteinase with FDA approved lead molecules

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ABSTRACT

Background: Monkeypox virus (mpox) disease is caused by a double-stranded DNA virus from the Poxviridae family. The mpox virus showed structural similarity with smallpox virus disease. The recent outbreak of mpox infection in the rest of African countries causes public health issues of increased pandemic potential. Mpox virus is involved in the viral replication cycle through the biocatalytic reaction of precursor polyproteins cleavage.
Objectives: The main objective of the study was to analyze the molecular interactions between mpox and FDA-approved drugs.
Methods: The primary and secondary structure of the protein was retrieved and FDA approved drug was screened using AutoDock. The best hit was analyzed and the molecular interactions were studied. Model validation analyzes the peptide, energy of hydrogen bonds, steric conflicts and bond planarity. Z-score was calculated using ProSA-web tool and the score tested the native fold from other alternative folds.
Results: The confidence level of the submitted amino acids was > 80 % and the maximum confidence score for a single template was 98.2 %. The generated proteinase model was subjected to analyze the distribution of atoms and the using ERRAT server. The overall quality score was 88.535 and this value represents the amino acid percentage with anticipated error value and the value falling below the rejection limit. The Z-score of this study result was within the Z-score range (−4.17) validated for native enzymes. The binding pockets of the enzyme were determined in this study and two binding pockets were predicted using the automatic online tool using the web server. The selected FDA-approved drugs were ordered based on their minimum binding energy to the proteinase.
Conclusions: Molecular docking studies revealed the involvement of various hydrophobic interactions between FDA-approved drugs and amino acid residues of monkeypox virus proteinase.

Introduction

In human beings, the re-emergence of various zoonotic diseases through various species is a well-described phenomenon. In 21st century, several zoonotic outbreaks were reported. The factors such as induced climate change, animal husbandry, wildlife and human contact were involved in a disease outbreak. The zoonotic infections caused several diseases and the increased mortality rate was reported in infections such as the Marburg virus diseases and Ebola [1] The global health effects of these diseases, as well as their social, economical and psychological negative effects, are reported [2]. The outbreak of infectious diseases is associated with fear, a state of anxiety and uncertainty with a circulation of unconfirmed information [3]. The widespread monkeypox disease outbreak in 2022 is a typical example of the emergence and re-emergence of zoonotic monkeypox disease. Circulation of local beliefs, rumors, fear, and unscientific beliefs ensued after the early reports of monkeypox disease in the first quarter of 2022 [4]. Therefore, continuous

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analysis of the prevalence of monkeypox disease and the scope of conspirational beliefs towards emerging virus infections-including monkeypox disease is highly useful from a pathological point of view [5]. These measures can help in designing standard communication protocols which should be guided by a proper understanding of people believes [6].

Monkeypox virus disease is a zoonotic disease and was considered endemic in Central and West Africa for about 50 years, with rare occasional outbreaks in the U.S and in Europe [7]. Monkeypox virus is a DNA virus and is classified as Orthopoxvirus and was placed together with the variola virus type. Variola virus is a causative agent of the smallpox virus and the structure of variola virus and monkeypox virus share common structural features. These two viruses cause similar clinical symptoms (cutaneous) [8]. Both monkeypox and variola viruses cause almost similar cutaneous clinical features [7]. Smallpox vaccination gives cross-protection against monkeypox virus disease and 85% protection was reported [9]. Monkeypox virus disease treatment relies on day to day care with certain drugs used to treat variola virus disease can be administered to treat monkeypox virus disease. Antibiotics are not commonly applied to treat monkeypox virus disease, nevertheless, they may be applied to manage and prevent bacterial superinfection [10]. Vaccinia immune globulin has been recommended to treat monkeypox disease in certain Middle Eastern countries, including, Saudi Arabia [11]. Antiviral agents such as Cidofovir and Tecovirimat are recommended to treat the monkeypox virus in high-risk patients [12]. Computational approaches are widely used in drug discovery research and have become an integral part of a drug screening programmes, enabling screening of various small molecule libraries to determine lead molecules which can be optimized to develop a novel lead molecule. In this study, potential FDA-approved drugs were used to screen against monkeypox virus cysteine proteinase.

Materials and methods

Screening of FDA-approved drugs

The structure of the approved drug was retrieved from the database and a structure search was performed. In this study, we screened FDA approved drug library as a potential source for ligand screening. The drug was downloaded and analyzed for 3D conformations into the drug discovery platform. The selected FDA-approved drugs were screened. The ligands were validated and prepared for docking using the LigPrep tool within the Schrodinger software suite. The screened ligands were further optimized to OPLS3e forcefield within all possible states generated at pH pH 7.0 ± 2.0 using Epik. The selected combinations with stereoisomers and tautomers were generated. The specified chirality was further retained and ligands were generated using OPLS3 force field in water using the Powell - Reeves conjugate gradient method with 2500 steps and the convergence threshold was 0.05.

Glide grid generation, docking and docking score analysis

Glide was used for the generation of the receptor grid and the active site was predicted using the software, CASTp. All the generated ligands were docked in the generated grid. Standard precision (SP) docking was applied with the flexible ligands. The grid was selected based on the generated docking score. The binding free energy was calculated and Molecular Mechanics – Generalized-Born Surface Area (MM-GBSA) was applied and protein-ligand binding free energy was analyzed. Protein-ligand binding free energy was considered as the accurate measurement of relative binding free energies for a congeneric series of ligands. The protein-ligand complexes from standard precision docking were used for the calculation of MM/GBSA. The top 10 hits obtained from virtual screening were selected. The interface to process both targets and ligands was analyzed the software was used to add Gasteiger charges and hydrogen atoms and subsequently ignore the least important amino acid residues. The top-ranked FDA-approved drug was used for docking studies and the 2D and 3D conformation of the drugs were prepared [13].

Analysis of binding pockets prediction

The binding pockets were predicted as described previously. DoGSiteScorer tool was used to predict the ligands binding sites on the enzyme. The DoGSiteScorer tool ranks the binding pockets based on the surface area, size and druggability (https://proteins.plus/) [14,15].

Validation of the model

The predicted structure quality of the model was validated. The cysteine proteinase structure was assembled using Ramachandran Plot Server (https://zlab.umassmed.edu/bu/rama/), and ProSA-web tool (https://prosa.services.came.sbg.ac.at/prosa.php), ERRAT tool (https://saves.mbi.ucla.edu/).

Results

Alignment of primary aminoacid sequence for monkeypox cysteine proteinase

The primary amino acid sequence of monkeypox cysteine proteinase was analyzed. In this study, cysteine proteinase was selected as a specific target to develop a suitable inhibitor against monkeypox virus disease. The secondary and tertiary structure of protease was analyzed. The secondary structure of monkeypox cysteine proteinase was illustrated in Fig. 1. The confidence level of the submitted amino acids was > 80 % and the maximum confidence score for a single template was 98.2 %. The tertiary structure of cysteine proteinase was described in Fig. 2.

Model validation for monkeypox cysteine proteinase

The modeled structure for monkeypox cysteine proteinase and the refined three-dimensional structure were assessed and validated using online bioinformatics tools and the result was described in Fig. 3. Ramachandran plot was used to predict the protein structure. This model analyzes the overall geometry and individual residue to determine the stereochemical property of the proposed model. Ramachandran plot analysis is preferable after the prediction of protein 3D structure. Prominent servers are used to predict the structure and quantum mechanics are used to calculate the banned regions. Model validation analyzes the peptide, energy of hydrogen bonds, steric conflicts and bond planarity. The illustrated Ramachandran plot in Fig. 3a shows the maximum preference for residues (98.05 %). The generated proteinase model was subjected to analyze the distribution of atoms and the using ERRAT server and the result was depicted in Fig. 3b. On the error axis, two lines are drawn to indicate the confidence with which it is possible to reject regions that exceed that error value. The result was expressed as the percentage of the protein for which the calculated error value falls below the 95 % rejection limit. The overall quality factor determine in this study was 88.535. Based on the Fig. 3b, the overall quality score was 88.535 and this value represents the amino acid percentage with anticipated error value and the value falling below the rejection limit. Z-score

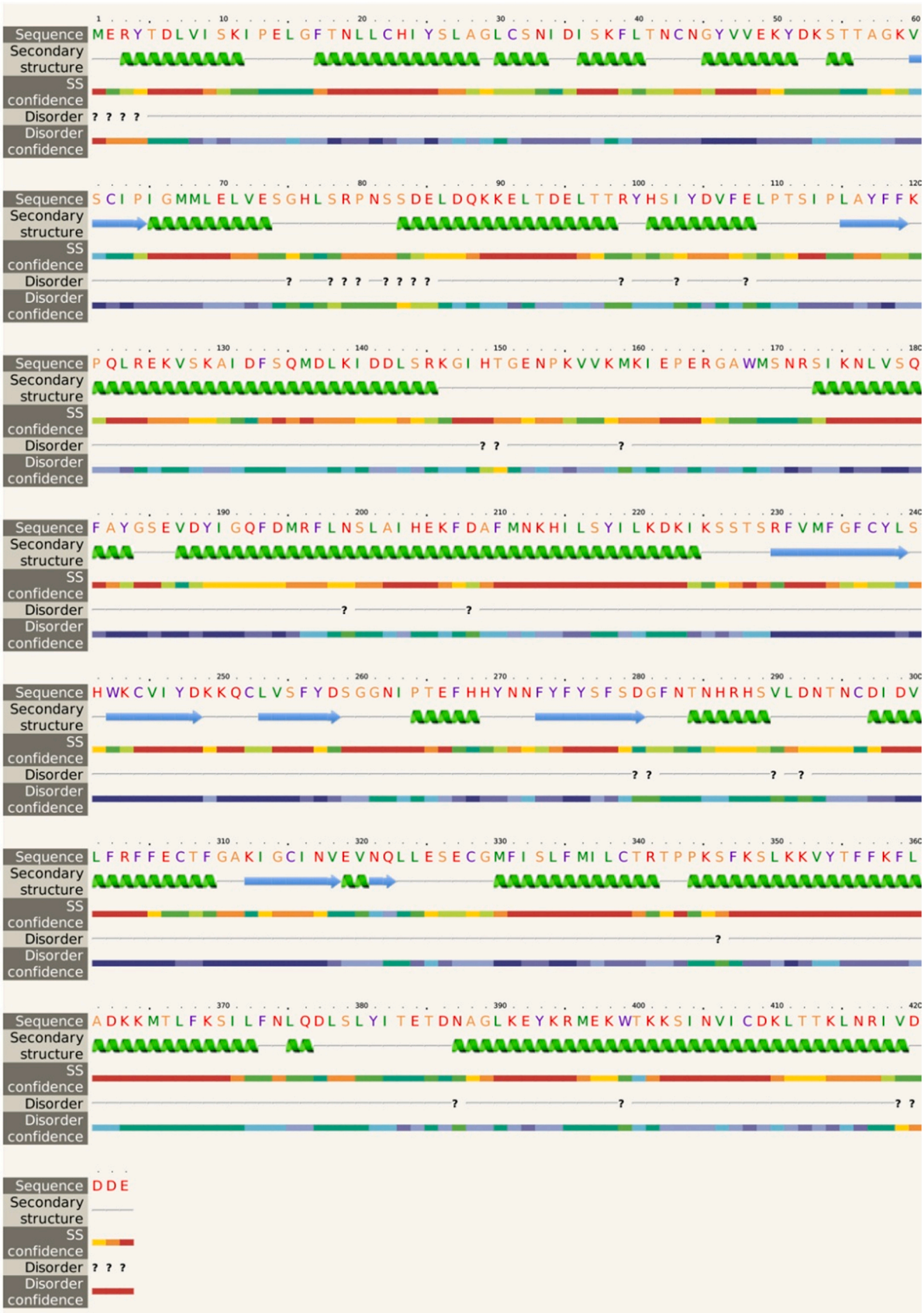

Fig. 1. Secondary structure for monkeypox cysteine proteinase.

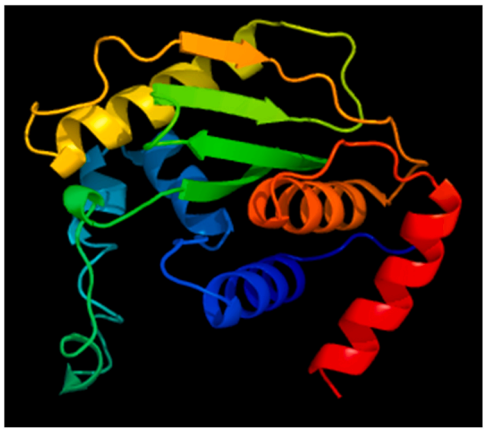

Fig. 2. Tertiary structure of monkeypox cysteinine proteinase.

was calculated using the ProSA-web tool and the score tested the native fold from other alternative folds. The Z-score of this study result was within the Z-score range (−4.17) validated for the native enzyme (Fig. 3c). The binding pockets of enzyme were determined in this study and the result was depicted in Fig. 3d. As described in Fig. 3d two binding pockets were predicted using the automatic online tool using web server. Validation was performed using ProSA-web tool and the result was depicted in Fig. 4. The binding pocket 1 showed increased volume, druggability score and surface area than binding pocket 2 (Table 1). Table 2 shows the top hit of FDA approved drugs against the cysteine proteinase of monkeypox virus. The selected FDA-approved drugs were ordered based on their minimum binding energy to the proteinase. Molecular docking studies revealed the involvement of various hydrophobic interactions between ligand and amino acid residues of the monkeypox virus proteinase. The two-dimensional image for docking analysis of Tolvaptan, Conivaptan, Nafarelin and Idarubicin has depicted in Fig. 5. Two-dimensional representation for docking of (A) Conivaptan and (B) Azelastine against 2019-nCoV main protease crystal. The colored disks represent active site residues, while dashed lines refer to interaction bonds.

Discussion

The re-emergence of monkeypox virus disease was reported in 2022 in various countries, including 94 nations with 50,000 monkeypox cases. Until today, no approved treatment is recommended

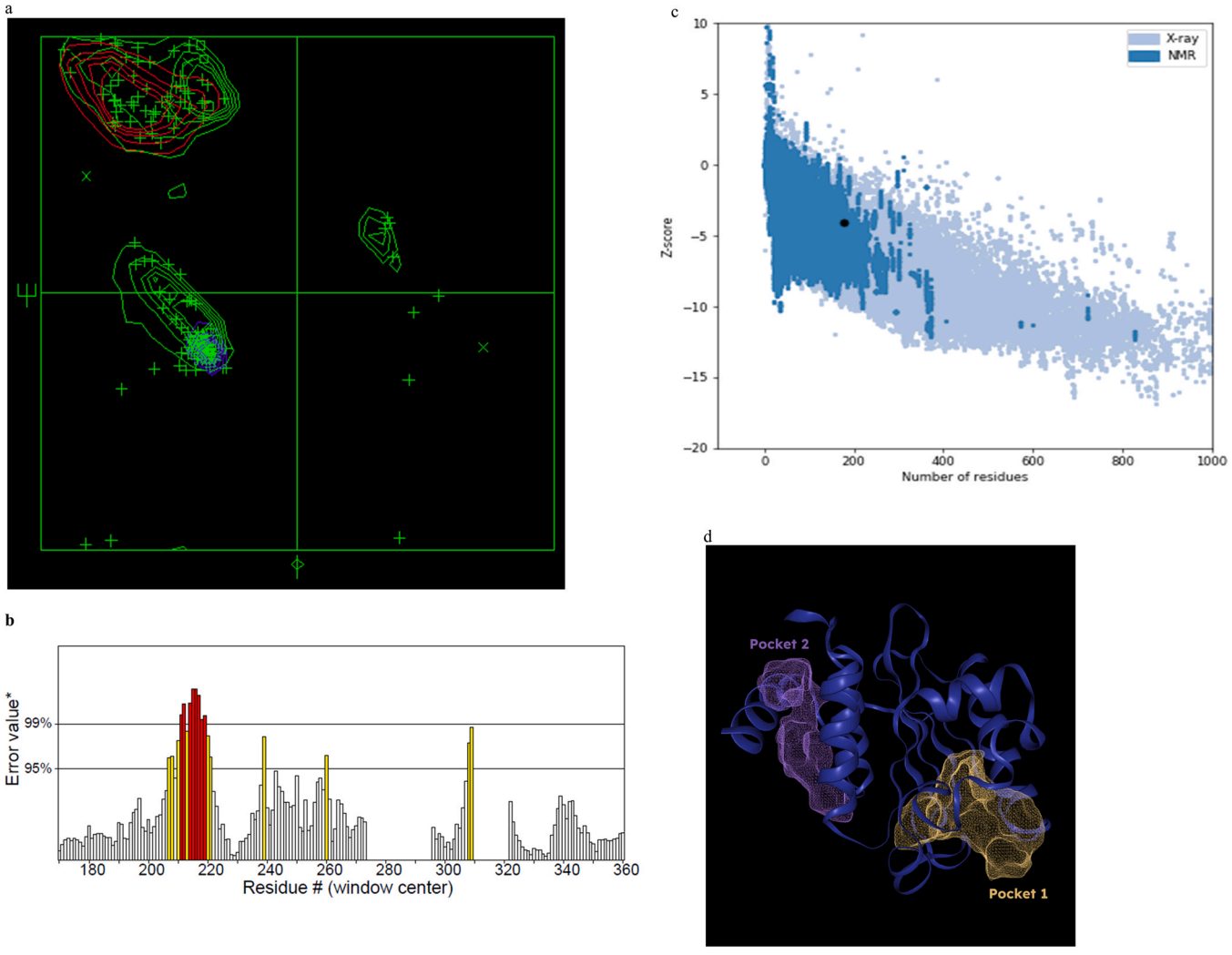

Fig. 3. Validation of the cysteine proteinase for monkeypox. Validation of the cysteine proteinase by Ramachandran plot server (a), Error value analysis (b), Z-score analysis (c) and Binding pockets analysis (d).

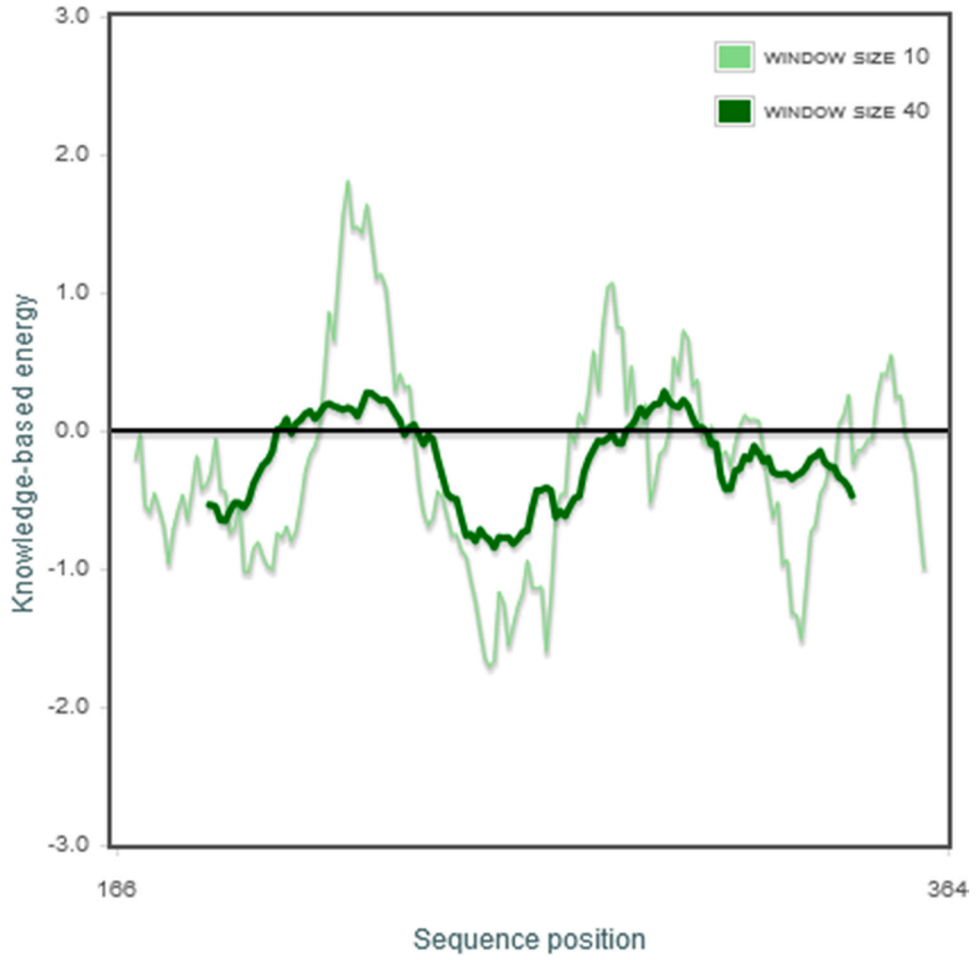

Fig. 4. Validation of the cysteine proteinase for monkeypox using ProSA-web tool.

Table 1
Analysis of binding pockets for the modeled monkeypox virus cysteine proteinase.

Pocket Number	Volume (A^3)	Surface area (A^2)	Druggability score
P_0	615.62	1163.81	0.81833
P_1	434.82	932.15	0.712166
P_2	428.67	695.43	0.641034
P_3	349.82	482.58	0.656263
P_4	312.58	683.38	0.796914
P_5	161.34	317.79	0.383722
P_6	151.42	304	0.312994
P_7	139.97	216.54	0.287946
P_8	121.28	206.92	0.511829
P_9	113.15	206.96	0.211382
P_10	110.66	270.08	0.219905

Note: A - Angstrom

to treat monkeypox virus disease. Recently, the government of the USA has suggested using tecovirimat and brincidofovir to use against monkeypox virus. Moreover, these two prescribed drugs were showed various side effects to the patients and these were prescribed to use only in critical cases [16]. The similarity of the monkeypox virus is matching with smallpox virus. Hence, the use of smallpox vaccine was also prescribed an emergency basis and the use of repurposed medicine to treat human diseases was illustrated previously [17]. Considering the importance of repurposing drugs, this study aimed to analyze various FDA-approved drugs against monkeypox virus disease using a computational approach [18]. Several molecular targets have exhibited mutation rates, the monkeypox virus may become resistant to various antiviral drugs. Multitargeting drugs may be used to treat monkeypox virus disease [19]. In the present study, we analyze the use of FDA approved drugs against monkeypox virus disease. The HTVS method is considered one of the valuable methods to develop novel pharmacological therapies because this method is simple to perform [20].

The ability of viral surface proteins to attach to the surface receptor of the target cell makes them promising candidates for vaccine development [21]. Different natural biomolecules have the ability to prevent an infection by a certain virus type *in vitro*, mainly by inhibiting the viral genome's replication machinery. Based on the maximum binding energy value (kcal/mol), which takes into account all possible favorable interactions with residues in the protein's active region, the optimum pose for each ligand was chosen. A number of FDA-approved drugs were selected by Musarra-Pizzo et al. [22] because they have demonstrated antiviral activity against diverse infections. They were applied to the test *in silico* to analyze how better they interacted with the proteins that the mpox viruses utilize to recognize their cell surface receptors. To find compounds with a broad spectrum of antiviral activity, the study focused on the viral envelope proteins of mpox and associated cell surface receptors.

Table 2
Molecular docking of selected FDA approved drugs against the cysteine proteinase of monkeypox virus. The relative binding-free energies were expressed as kcal/mol. MMGBSA dG Bind was predicted and tabulated.

Entry Name	PUBCHEM COMPOUND CID	MMGBSA dG Bind	MMGBSA dG Bind(NS)
Triptorelin2D_CID_25074470.1	25,074,470	-39.65	-72.45
Fluocinolone_CID_91488.1	91,488	-23.06	-28.89
Carfilzomib2D_CID_11556711.1	11,556,711	-37.73	-63.52
Tolvaptan_CID_216237.1	216,237	-51.96	-55.19
Fluoxymesterone_CID_6446.1	6446	-24.86	-30.46
Olaparib_CID_23725625.1	23,725,625	-39.48	-49.64
Cobicistat2D_CID_25151504.1	25,151,504	-25.96	-62.91
Idarubicin_CID_42890.1	42,890	-47.97	-53.4
Conivaptan_CID_151171.1	151,171	-57.52	-60.42
Chlortalidone_CID_2732.1	2732	-29.96	-32.57
Demeclocycline_CID_54680690.1	54,680,690	-31.09	-54.62
Tetracycline_CID_54675776.1	54,675,776	-31.32	-38.12
Candesartan_CID_2541.1	2541	-41.32	-47.43
Nafarelin_CID_5311027.1	5,311,027	-49.1	-56.02
Bimatoprost_CID_5311027.1	5,311,027	-49.1	-56.02
Atovaquone_CID_74989.1	74989	-39.32	-42.32
Tenapanor2D_CID_71587953.1	71,587,953	-59.5	-75.28
Rolapitant_CID_10311306.1	10,311,306	-40.26	-47.41
Glycerol_phenylbutyrate2D_CID_10482134.1	10,482,134	-30.69	-47.93
Lurasidone_CID_213046.1	213,046	-42.98	-51.04
Abarelix2D_CID_16131215.1	16,131,215	-6.68	-42.79
Halobetasol_CID_5311167.1	5,311,167	-33.14	-42.29
Difenoxin_CID_34328.1	34,328	-40.7	-45.77
Dutasteride_CID_6918296.1	6,918,296	-31.55	-34.18
Fluphenazine_decanoate2D_CID_3388.1	3388	-36.91	-45.92
Pimozide_CID_16362.1	16,362	-40.02	-47.18
Dihydroergotamine_CID_10531.1	10,531	-42.56	-52.02
Nilotinib_CID_644241.1	644,241	-45.33	-49.36
Naldemedine_CID_54732242.1	54,732,242	-43	-51.21
Paliperidone_CID_115237.1	115,237	-30.35	-33.07
Nandrolone_decanoate_CID_9677.1	9677	-24.56	-30.65
Chloramphenicol_palmitate2D_CID_443382.1	443,382	-23.61	-36.35
Cinacalcet_CID_156419.1	156,419	-30.64	-35.66
Irinotecan_CID_60838.1	60,838	-35.84	-47.11
Loperamide_CID_3955.1	3955	-18.2	-30.38

According to a study performed *in silico* by Balmeh et al. [23] the spike (S) envelope protein, SARS-CoV-23CL protease, RNA-dependent RNA polymerase RdRp, and bacteriocin glycocin F, both of which are derived from *Lactobacillus lactis* and *L. plantarum*, have high docking energies with these molecules. Sahoo et al. [24] conducted a computational drug repurposing analysis to find already available, approved medications that may be potential inhibitors of the important mpox viral proteins, thymidylate kinase and D9 decapping enzyme. Utilizing the comparable protein structures in the vaccinia virus, the target protein structures of the monkeypox virus were simulated. In addition, using molecular docking and molecular dynamics simulations, four potential inhibitors—Tipranavir, Cefiderocol, Doxorubicin, and Dolutegravir—were identified as candidates for repurposing against the mpox virus. In a study, Bansal et al. [25] tested phytochemicals from *Allophylus serratus* against core viral cysteine proteases from mpox virus. These compounds included N-(2-Allylcarbamoyl-4-chloro-phenyl)− 3,4-dimethoxy-benzamide, 6-Dimethylaminona phthene − 1-sulfonicacid amide, and Oleic Acid. According to the docking investigation, several ligands have a binding affinity for the target viral protein that ranges from − 5.0 to − 6.7 kcal/mol. The compound N-(2-Allylcarbamoyl-4-chloro-phenyl)− 3,4-dimethoxy-benzamide demonstrated the highest binding affinity, with a value of − 6.7 kcal/mol, and can be further studied to develop possible medications against the mpox virus. In addition, nanomaterials and lead molecules derived from the natural products such as microbes and marine samples provide an opportunity to invent the drug molecules to treat the viral diseases [26,27].

The HTVS method was useful for the screening of effective drugs from the FDA-approved drug pools. The selection was based on the binding affinity of the available drugs against the monkeypox virus. The MM/PBSA and MM/GBSA methods are useful for analyse the free energy of the binding of ligands to proteins. The binding affinity is generally based on molecular dynamics simulations of the ligand–receptor complex. These approaches are useful for the analysis of ligand-receptor interactions and have good success with varying results. A total of 35 drugs were screened and the interactions were studied with proteinase enzyme. These enzymes are applied for viral genome replication and transcription and certain enzymes are involved in the synthesis of nucleotide synthesis. The ligand-receptor interactions of top hits were analyzed and show the stable conformation modifications of the ligand-protein complexes within the molecular environment.

We acknowledge a number of limitations. Some FDA-approved drugs bioavailability is not well understood. Some drugs may be metabolized differently in the body, making FDA-approved medications ineffective. Simulators and docking are only theoretical basis. False-positive cases could not be prevented due to the shortcomings of the employed energy functions. In silico testing was unable to show the drug's true efficacy. Before the FDA approved widely used to treat monkeypox, more data, particularly from *in vivo* studies, are needed to support its efficacy.

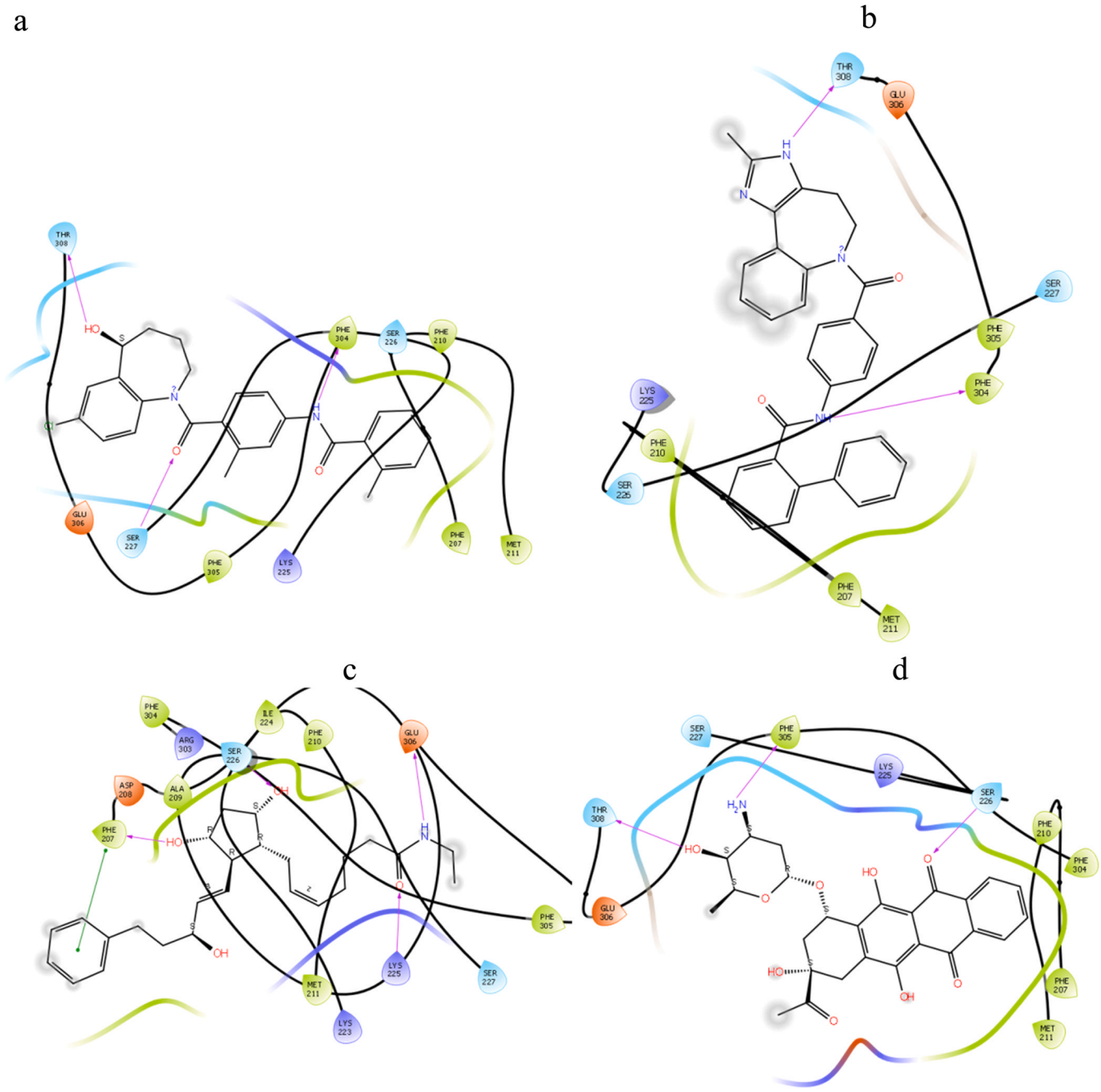

Fig. 5. Docking of tolvaptan (a), conivaptan (b), nafarelin (c) and Idarubicin (d) against monkeypox virus enzyme. The dashed lines indicate interaction bonds and the colored disks represent active site residues.

Conclusions

To prevent the pandemic monkeypox virus infection across various countries, several attempts were made to use pre-existing FDA-approved drugs. Monkeypox virus protease is involved in the proliferation of the virus, hence, protease is a target to control this disease. In this study, we analyze the molecular interactions between mpox and FDA-approved drugs. The docking score and the model were evaluated using various molecular tools. To conclude, the existing FDA-approved drugs are useful against the mpox virus disease.

Ethics statement

No human or animal has been participated.

Conflict Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

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