ERURJ **202**2, 1, 1,93-101

Mini Review

Mini review on the monkeypox: a new human threat (2007–2022)

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Received 9th October2022, Revised 31st October 2022, Accepted 31st October 2022

DOI:10.21608/ERURJ.2022.267928

ABSTRACT

While the globe is currently grappling with the coronavirus disease 2019 (COVID-19) pandemic, the appearance of a new epidemic caused by the monkeypox virus raised public health experts anxious about whether it may represent a new threat. Human monkeypox is a zoonotic orthopoxvirus that looks like smallpox. Monkeypox virus is a double stranded DNA virus of the genus orthopox viruses, which also includes variola, cowpox, and vaccinia viruses. So far, two clades of monkeypox virus have been identified in Central and West Africa, with the former causing more severe illness. When human come into contact with the infected animals, they become infected with monkeypox. According to reports, the virus can also be transmitted via direct contact (sexual or skin-to-skin), respiratory droplets, and fomites. Although, most cases of monkeypox were mild and self-limiting, there is currently no specific treatment for patients infected with the monkeypox virus. The goal of this brief review is to describe various trials conducted since 2007.

Keywords: Monkeypox, Virtual screening, Viral, Infection, treatment.

1-Introduction

While the world is still dealing with the coronavirus disease 2019 (COVID-19) pandemic, the emergence of a new outbreak caused by the monkeypox virus has public health officials

concerns about whether it will pose a new threat [1]. Monkeypox virus is a double stranded DNA virus of the genus orthopox viruses, which also includes variola, cowpox, and vaccinia viruses [2]. Monkeypox virus was first isolated from monkeys; however, rope squirrels, tree squirrels, and Gambian rats are also natural hosts of monkeypox virus [3]. So far, two clades of monkeypox virus have been identified in Central and West Africa, with the former causing more severe illness [4]. Many cases in the current outbreak have been traced to sexual transmission [4]. The virus can also spread through direct contact with infectious sores, scabs, or bodily fluids, as well as through shared clothing [4]. The signs and symptoms are similar to but less severe than smallpox, with a distinctive rash preceded by mild symptoms (e.g., fever, lymphadenopathy, and flu-like symptoms) [5]. Cases in the current outbreak are atypical, with the characteristic rash beginning in the genital and perianal areas and spreading to other parts of the body or not [6]. Patients are considered infectious once the rash appears and continues until the lesions scab and fall off. The identification of viral DNA in swabs, taken from vesicle or ulcer crusts, is the preferred method for diagnosing active monkeypox cases [4]. At the time of writing, there are no specific treatments for patients infected with the monkeypox virus [7]. Minor outbreaks, on the other hand, have been controlled with smallpox vaccines, antivirals, and vaccinia immune globulin (VIG). Monkeypox prevention and management are similar to other orthopoxvirus infections, and all confirmed orthopoxvirus cases should be treated as monkeypox until proven otherwise.

2. Research literature 2007–2022

In September 2007, Katritch, Vsevolod, et al, [8] published their study for one of the most important attractive targets for the development of smallpox antiviral drugs, ubiquitin-like poxvirus proteinase I7L. This target plays a critical role in the replication of vaccinia and other orthopox viruses, such as variola smallpox and monkeypox. Targeting the I7L proteinase represents a challenge for rational drug design because of absence of the X-ray structure of the I7L proteinase, and the low level of sequence identity with the structural template C-terminal protease domain ULP1 (PDB: 1euv). The researchers performed homology modeling of the I7L proteinase domain, active site refinement, docking, virtual screening and biochemical assay. The results of the homology modeling and active site refinement revealed that the active site of I7L represents a tube-like binding pocket with a volume of about 400 A°, suitable for rational drug design. While this core binding pocket is fully conserved between I7L and some ULP

proteinases, the non-conserved residues on both sides of the S2–S1 core can provide a basis for the design of I7L selective inhibitors (Fig1). The research group focused on the importance of S2 sub-site for I7L selectivity in the previous built model, as it seemed exposed to solvents and controlled by three different residues conserved H241, Q322 and a variable residue in position 260. They mentioned that the absence of an amino acid side chain in this position creates an additional small cleft in their model, which can be exploited to design I7L selectivity.

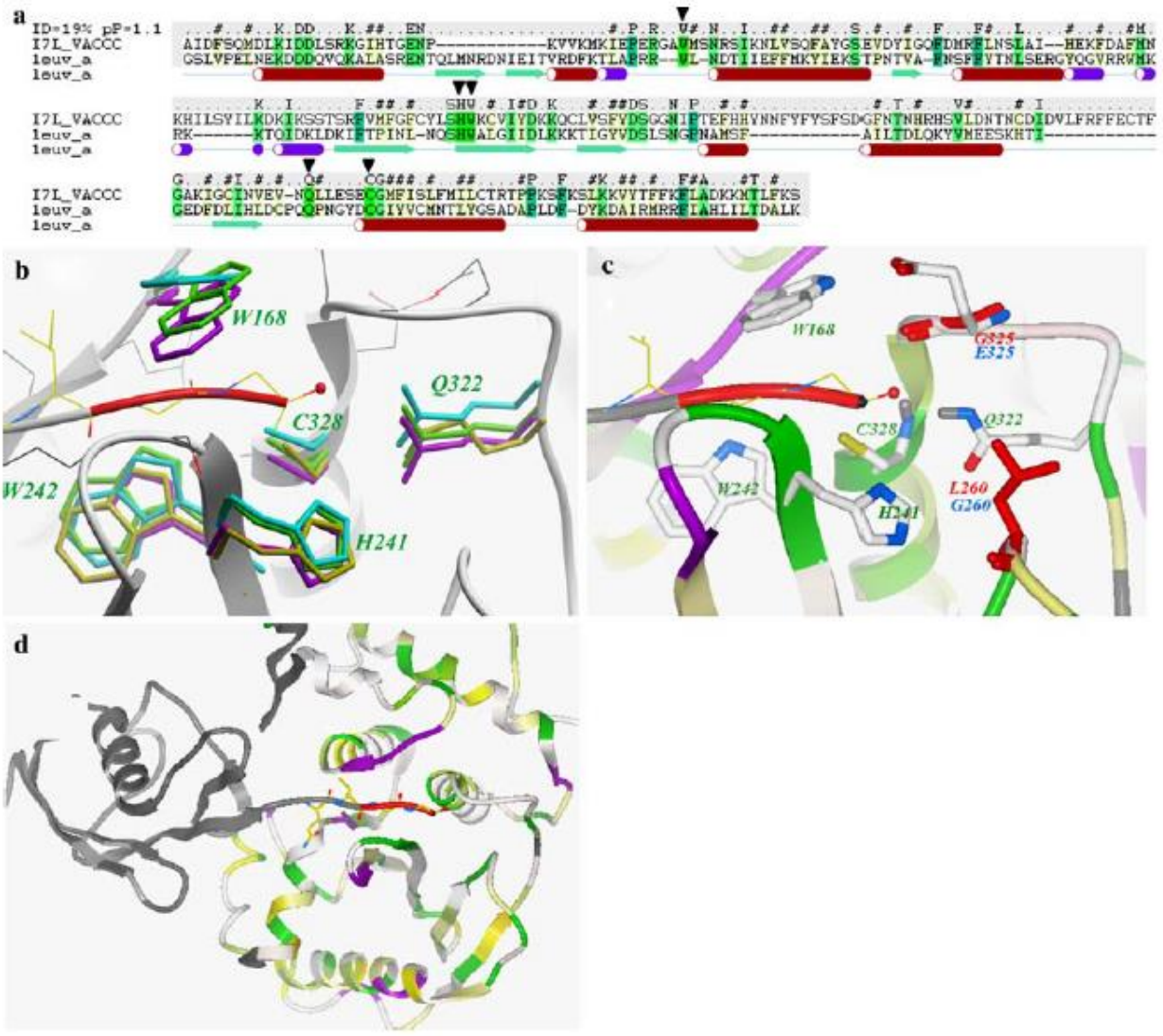

Figure 1. Structural model of I7L and its active site, based on the Ulp1 cysteine protease X-ray structure (PDB code 1euv). (a) Sequence structure alignment with I7L and Ulp1, with highly conserved ULP residues ‘‘W-HW-Q-C’’ marked by .. (b) Superimposition of ‘‘W-HW-Q-C’’ motif side chains in four different ULPs structures (green: 1euv, magenta: 1xt9, cyan: 1th0, yellow: 1avp). Backbone contact residues of Ulp1 shown in thin wire representation with grey carbons. (c) Close up of I7L model active site. Five conserved residues are shown as sticks colored by atom type with green labels. Two residues of I7L active site (G260 and E325), not conserved in Ulp1 are

shown as sticks with blue labels, the corresponding Ulp1 residues shown as red sticks. (d) Predicted overall structure of the I7L proteinase; ribbon is colored according residue identity with Ulp1 (green is fully conserved, yellow—similar residue). The Ulp1 substrate is shown as grey ribbon with C-terminal Gly-Gly residues highlighted in red [8].

Moreover, the performed virtual screening study for 230,000 compounds showed after results' filtration that only a set of 456 compounds could be suitable for biochemical testing (Fig2). Finally, the authors analyzed the biochemical testing results as most of compounds have IC50 values below 200 µM, six of them with IC50 values less than 50 µM (Fig2).

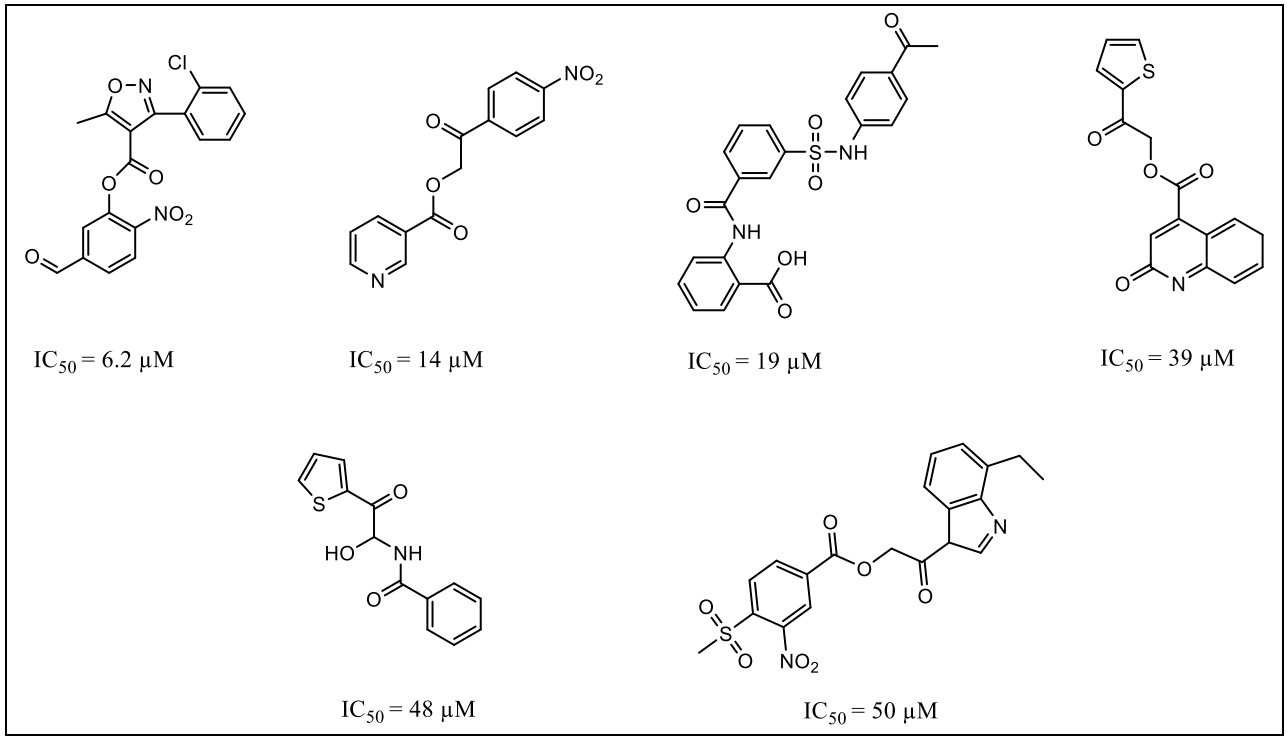

Figure 2. (a) Experimental IC50 values for most active structures of the new I7L inhibitors [8].

Sara C. Johnston et al. report in 2012 [9] a zoonotic disease known as monkeypox that was endemic in the Democratic Republic of the Congo. It was distinguished by the development of systemic lesions and prominent lymphadenopathy. The research team was looking into the prophylactic and the therapeutic potential of interferon-b (IFN-b) against the monkeypox virus. The researchers discovered that treating monkeypox viruses with human IFN-b reduces virus production and spread significantly in vitro. Furthermore, they stated that IFN-b significantly inhibited monkeypox virus when administered 6-8 hours after infection, indicating its potential

for use as a therapeutic agent. Finally, they proposed that IFN-b induced the antiviral protein (human myxovirus resistance protein 1) MxA expression in the infected cells, and that constitutive MxA expression inhibited monkeypox virus.

In 2013, Nuth, Manunya, et al. [10] developed a new class of antiviral inhibitors of the heterodimeric processivity factor required for viral replication. They built an *in silico* model of the vacinnia virus processivity factor, which is made up of two proteins A20 and D4 that are responsible for heterocomplexes formation to optimize the lead of an indole-based scaffold discovered earlier through high-throughput screening. The most effective inhibitors were 24a and 24b, which outperformed the lead scaffold (IC50 = 42 and 46 nM vs 82000 nM, respectively). (Fig3) Analyzing the lead optimization of parent scaffold, showed major increase in the antiviral activity through two drug design strategies, chain elongation and isosteric replacement of carboxylic moiety of parent compound by different alkyl amide side chains at R2 position of indole ring. Further studying for the docking results of hit compound and A20-D4 receptor revealed that the docked pose of 24a not only suggest a similar binding pattern to that of parent scaffold but also showed a higher docking score (−62.8 vs −50.0 kcal/mol, respectively). (Fig4)

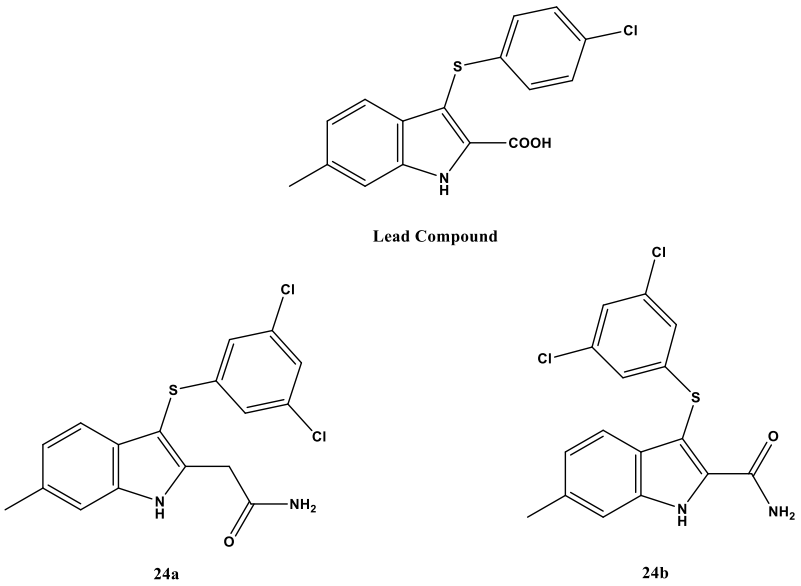

Figure 3. The most potent inhibitors were 1a and 2b [10].

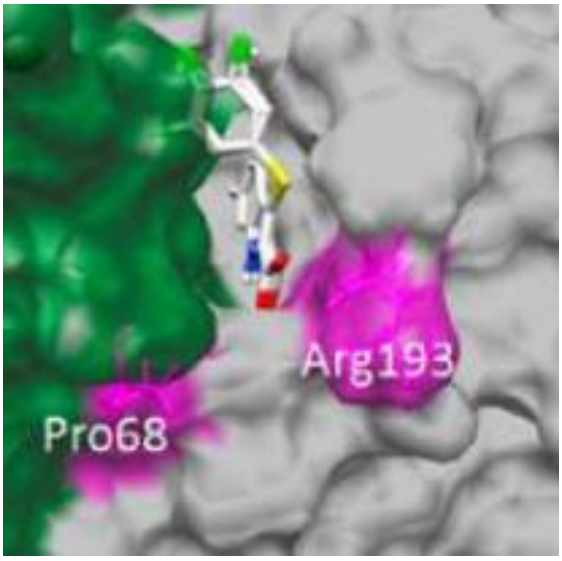

Figure 4. The docked poses of lead compound and 24a with respect to Pro68 of A20NT100 and Arg193 of D4.

[10].

Hoque, Syeda Farjana, and colleagues conducted an *in silico* bioinformatics study in 2020 to develop a novel peptide vaccine against monkeypox [11]. The researchers used reverse vaccinology (a novel technique that combine both immunogenetics and immunogenomics with in silico methods so as to present modern vaccines) to develop a peptide vaccine against monkeypox virus by studying cell surface binding protein (Poxin-Schlafen) and envelope protein. They assessed their vaccine model by employing a molecular docking approach to investigate the binding affinity of the developed vaccine and distinct human immune receptors (TLR 2, MyD88, TLR 8). Their model yielded promising results based on free binding energy.

Priyamvada, Lalita, and colleagues published their paper in April 2020 [12]. They discovered that the host Golgi-associated retrograde proteins played an important role in the formation of monkeypox (VACV) extracellular virus through retrograde endosomal transport, comprising four vacuolar protein sorting (VPS) genes – VPS51, VPS52, VPS53, and VPS54, all of which were found to be enriched in both Central African and West African clades. Small molecules like Retro-2 (Fig5) have been shown to reduce infection in vitro and to a lesser extent in vivo by inhibiting the retrograde pathway. In their study, they tested a large panel of compounds against VACV infection that contained a benzodiazepine scaffold similar to Retro-1(Fig5). They discovered that a subset of these compounds had better anti-VACV activity, resulting in less extracellular virus (EV) particle formation and viral spread when compared to Retro-1. The most

potent analogue (PA104), with a high selectivity index, inhibited 90% viral spread at 1.3 µM. (Fig5) Furthermore, PA104 strongly inhibited two distinct ST-246-resistant viruses, indicating its potential utility in combination therapy with ST-246 (The only US Food and Drug Administration-approved drug to treat smallpox, Tecovirimat®).

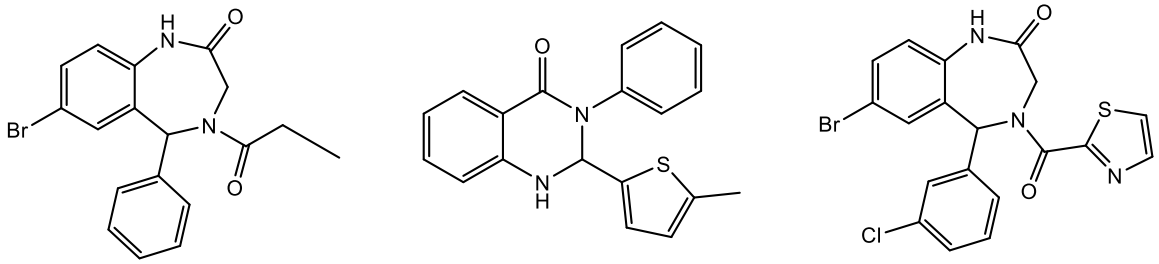

Figure 5. Structures of Retro-1 and the most potent compound of the study PA104.

In 2022, Zheng, Liangzhen, and colleagues attempted to accelerate the development of monkeypox vaccines, neutralising antibodies, and therapeutic drugs in response to the global increase in monkeypox cases [7]. More than 600 protein structures were predicted, and functional annotations of proteins from monkeypox virus proteomes were added for public use. Using the PointSite algorithm (an accurate identification of protein ligand binding atoms, which performs protein ligand binding sites identification at the atomic level), they provided extensive annotations and labelled the small-molecule-binding regions with high confidence for all 600+ predicted structures. Meanwhile, experimentally determined structures that shared a high degree of similarity with monkeypox proteins were vetted using the structure-alignment algorithm.

3. Conclusion

Even in the absence of a specific therapy, many individuals infected with the monkeypox virus have a mild, self-limiting disease course; however, the prognosis for monkeypox may depend on multiple factors such as previous vaccination status, initial health status, and concurrent illnesses or comorbidities.

The use of computers in drug discovery has resulted in a fundamental shift in the drug design process. Initially, the drug design process was time-consuming, arduous, and expensive, with a high risk of failure. However, due to the availability of a large amount of genomic and proteomic information, as well as the use of tools for modelling, ligand design, pharmacophore mapping, protein-ligand simulation, molecular descriptions, and toxicity prediction, the drug discovery process has become more reliable, accurate, and cost effective. With the adoption of advanced

computing systems and the application of high-performance techniques and algorithms, it is now possible to tackle biological problems quickly and accurately.

Thus, in silico studies and bioinformatics can be regarded as a promising technique for identifying a novel effective drug candidate for treatment or vaccine development against extremely pathogenic living beings.

- **Conflict of Interest**

The author has declared no conflict of interest.

5. References

[1] Bhattacharya M, Dhama K, Chakraborty C. Recently spreading human monkeypox virus infection and its transmission during COVID-19 pandemic period: A travelers' prospective. Travel Medicine and Infectious Disease. 2022 Sep 1;49:102398.

[2] Park C, Walsh D. RACK1 Regulates Poxvirus Protein Synthesis Independently of Its Role in Ribosome-Based Stress Signaling. Journal of Virology. 2022 Sep 28;96(18):e01093-22.

[3] Guarner J, Del Rio C, Malani PN. Monkeypox in 2022—what clinicians need to know. Jama. 2022 Jul 12;328(2):139-40.

[4] Alah MA, Abdeen S, Tayar E, Bougmiza I. The story behind the first few cases of monkeypox infection in non-endemic countries, 2022. Journal of Infection and Public Health. 2022 Aug 5.

[5] Kumar N, Acharya A, Gendelman HE, Byrareddy SN. The 2022 outbreak and the pathobiology of the monkeypox virus. Journal of Autoimmunity. 2022 Jun 25:102855.

[6] Rao A, Bachmann LH, Petersen B. What clinicians need to know about monkeypox in the United States and other countries.

[7] Rizk JG, Lippi G, Henry BM, Forthal DN, Rizk Y. Prevention and treatment of monkeypox. Drugs. 2022 Jun 28:1-7.

[8] Katritch V, Byrd CM, Tseitin V, Dai D, Raush E, Totrov M, Abagyan R, Jordan R, Hruby DE. Discovery of small molecule inhibitors of ubiquitin-like poxvirus proteinase I7L using homology modeling and covalent docking approaches. Journal of Computer-Aided Molecular Design. 2007 Oct;21(10):549-58.

[9] Johnston SC, Lin KL, Connor JH, Ruthel G, Goff A, Hensley LE. In vitro inhibition of monkeypox virus production and spread by Interferon-β. Virology journal. 2012 Dec;9(1):1-5.

[10] Nuth M, Guan H, Zhukovskaya N, Saw YL, Ricciardi RP. Design of potent poxvirus inhibitors of the heterodimeric processivity factor required for viral replication. Journal of Medicinal Chemistry. 2013 Apr 25;56(8):3235-46.

[11] Akhand MR, Azim KF, Hoque SF, Moli MA, Joy BD, Akter H, Afif IK, Ahmed N, Hasan M. Genome based evolutionary lineage of SARS-CoV-2 towards the development of novel chimeric vaccine. Infection, Genetics and Evolution. 2020 Nov 1;85:104517.

[12] Priyamvada L, Alabi P, Leon A, Kumar A, Sambhara S, Olson VA, Sello JK, Satheshkumar PS. Discovery of Retro-1 Analogs Exhibiting Enhanced Anti-vaccinia Virus Activity. Frontiers in Microbiology. 2020 Apr 23;11:603.