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A Comparative Review of Molecular Docking Studies on Monkey Pox Virus Using Various Ligands

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ABSTRACT

The monkeypox virus (MPXV) has resurfaced as a serious public health threat, requiring the rapid development of efficient treatments. Molecular docking has been an essential method for finding possible MPXV inhibitors. The objective of this review is to conduct a thorough analysis and comparison of molecular docking experiments against MPXV proteins using different ligands. We examined the binding affinities, interactions, and structural requirements of 15 ligands in 15 docking studies. Based on our investigation, it was shown that the ligand had encouraging inhibitory potential against the MPXV protein. In addition, we found that critical residues and chemical connections that are essential for efficient ligand binding. We do a detailed examination of the results obtained from these studies, including the molecular interactions, binding affinities, and structural insights obtained from docking simulations.

KEYWORDS: Monkeypox virus, Molecular docking, Monkey pox virus protein, ligand-based design, structure-based design, antiviral therapeutics.

INTRODUCTION

A highly severe zoonotic infection that affects people worldwide is the monkey pox virus (MPXV). With so few effective medications available, molecular docking has emerged as a crucial method for identifying potential treatments. This article provides a comprehensive overview of the molecular docking studies conducted on MPXV, focusing on the various ligands that have been investigated as potential inhibitors. Humans can contract monkey pox by coming into close contact with sick individuals or animals, as well as by coming into touch with objects contaminated with the virus. Fever, rash, and enlarged lymph nodes are just a few of the problems that can arise from a human monkey pox infection. Monkey pox can result in pneumonia, encephalitis, vision-threatening keratitis, and subsequent bacterial infections [1].

OBJECTIVES

1. To examine which ligand have the highest binding affinity for the proteins of the monkey pox virus in order to find possible barriers to the entry or reproduction of the virus.
2. To create ligands with better binding affinity and specificity for the proteins of the monkey pox virus by using molecular docking.

BACKGROUND STUDIES

Since, 1970 the disease was first appeared, but still there is no specific drug or vaccine against monkey pox virus. MPOX infections have emerged in other African countries, posing a public health problem with increasing pandemic potential [2]. The widespread monkey pox disease outbreak in 2022 is a typical example of the emergence and re-emergence of zoonotic monkey pox disease [3].

LIGAND WITH TARGET INTERACTIONS

S.NO	TARGET PROTEIN	LIGAND	KEY RESIDUE	INTERACTION TYPE	BINDING AFFINITY
1	Profilin like Protein [4]	Amentoflavone	ILE A:32, ILE A:59	Pi-sigma bond Pi-alkyl bond Hydrogen bond	-9.5
2	Babesia microtilactate Dehydrogenase [4]	Dieckol	GLY A:32, GLY A:97, ASP A:195, GLY A:246, VAL A:31, ALA A:99, ALA A:238	Hydrogen bond Pi-alkyl bond Vanderwaals and pi-sigma bond	-10.5
3	Methyl transferase vp39 [5]	Fucoxanthin	Ser15(B), Arg93(B), Asp13(B), Glu142(B), Asn37(B), Thr18(B)	Hydrogen bond	-5 to -6.7
4	DdRp [6]	Tigecycline	Asp415 (2), Asp417 (2), Asp419, Arg287,	Hydrogen bond	-8.88
5	DdRp [6]	Eravacycline	Asp415, Gly418, Glu420, Gln318	Hydrogen bond	-7.87
6	Topoisomerase 1[7]	Rosmarinic acid, Myri Citric acid, quercitrin	TYR274	Hydrogen bond, hydrophobic bond	-
7	Cysteine Protease Protein [8]	Gallicynoic acid	Arg3, Tyr4 Lys358 Leu360, Asp362	Hydrogen bond, hydrophobic bond	-10.56

			Met1, Tyr4, Leu7, Phe17 Leu21, Met136, Phe278, Val320, Leu323, Phe357, Phe359, Leu360,		
8	Cysteine Protease Protein [8]	H2-erythroneopterin	Arg3, Tyr4, Gln322, Lys358, Leu360	Hydrogen bond, hydrophobic bond	-9.64
9	DNA polymerase [10]	ZINC000239038527	ARG634, LYS638, SER552, LEU553, ASN551, ASP753	Hydrogen bond, salt bridge	-9.0
10	Monkey pox virus protein [9]	3-((5-(4-carboxy phenoxy)-4-oxo-2-phenyl chroman-7-yl)oxy)benzoic acid	HIS-5, SER-12, LYS-13, PHE-17, ILE-35, ILE-35, PRO-36	Hydrogen bond	−10.3
11	Monkey pox virus protein [10]	7-(3-amino phenoxy)-5-(4-aminophenoxy)-2-phenyl chroman-4-one	SER-12 LYS-13, GLU-18 ILE-35, ILE-35 ILE-35, PRO-36	Hydrogen bond	−9.6
12	DNA Polymeraase	ZINC000025628231	LYS638, ARG634, ASN551, SER552, ASP753	H-bond and Salt-bridge interacting	−10.4
13	methyltransferase VP39[10]	CMNPD15724 CMNPD28811 CMNPD30883 CMNPD18569	Asp138, Ser141, Val116, Arg97, Leu42, Val139, Ile94	hydrogen bonds and hydrophobic interaction	− 9.4 − 8.9 − 9.2 − 9.4
14	monkeypox virus envelope protein E8[11]	Maraviroc	Val62, Trp96, Lys98, Tyr104, Trp96	hydrogen bonds and hydrophobic interaction	− 9.1
15	monkeypox virus envelope protein E8[12]	Punicalagin	Phe56, Tyr232, Leu170, Glu230, Glu230, Asp228	hydrogen bonds and hydrophobic interaction	− 7.8

FUTURE ASPECTS:

The National Institutes of Health are conducting clinical trials to evaluate the safety and efficacy of antiviral medications for treating monkeypox. Researchers are exploring combination therapies to prevent drug resistance and improve treatment outcome

UNDER INVESTIGATION:

- **Antiviral drugs**:
  - Ribavirin
  - Favipiravir
- **Immunomodulatory therapies:**
  - Interferon-alpha
  - Interferon-beta
  - Immunoglobulin
- **Vaccine candidates:**
  - MVA-BN (Imvamune)
  - ACAM-3000
  - Jynneos (approved for smallpox)
  - Bavarian Nordic's MVA-BN-based vaccine

In Clinical Trials:

1. Tecovirimat (TPOXX) - Phase 3 trial for monkeypox treatment
2. Brincidofovir - Phase 2 trial for monkeypox treatment
3. Cidofovir - Phase 2 trial for monkeypox treatment
4. Vero Cell-based vaccine - Phase 3 trial for monkeypox prevention

Preclinical Development:

- Small molecule inhibitors:
  - ST-246 (tecovirimat analog)
- Monoclonal antibodies:
  - Anti-monkeypox virus monoclonal antibodies
- RNA-based therapies:
  - mRNA-based vaccines

Future Directions:

1. Nanoparticle-based vaccines
2. Virus-like particle (VLP) vaccines
3. Recombinant protein-based vaccines
4. Gene editing technologies (CRISPR/Cas9)
5. Host-directed therapies (targeting host cellular processes)

Research Collaborations:

1. National Institutes of Health (NIH)
2. World Health Organization (WHO)

3. Centers for Disease Control and Prevention (CDC)
4. European Medicines Agency (EMA)
5. Pharmaceutical companies (e.g., Bavarian Nordic, SIGA Technologies)

SUMMARY

An extensive summary of molecular docking research on the monkeypox virus (MPXV) using different ligands is given in this article. We examined a number of docking studies that looked into the affinity of various ligands, including as host cell factors for binding to MPXV proteins. The discovery of possible inhibitors and therapeutic targets was made possible by the investigations' revelation of important residues and binding modes involved in virus-ligand interactions. We talked about the recent and future aspects of docking studies in monkey pox virus. Our knowledge of MPXV-ligand interactions has been increased because to molecular docking studies, which have also provided important new information for the creation of antiviral treatments. The logical design of inhibitors that target viral entry, replication, and transmission has been made possible by the identification of important residues and binding mechanisms.

CONCLUSION

This thorough analysis emphasizes the noteworthy advancements achieved in our knowledge of the molecular relationships that the monkeypox virus with different ligands as a result of docking studies. the combined results of these investigations. Molecular docking has the potential to remain a vital tool in the fight against orthopoxviral infections, such as monkeypox, helping to develop preventative and therapeutic measures.

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