Extended Abstract

Molecular Docking Analysis of Repurposed HIV And Antiviral Drugs Against Monkeypox Target Protein: Evaluating Docking Scores and Hydrogen Bond Interactions

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ABSTRACT

The rising threat of monkeypox has driven efforts to repurpose existing HIV and antiviral drugs using in silico molecular docking for cost-effective and rapid drug discovery. This study evaluated the binding affinities and hydrogen bond interactions of HIV drugs (Atazanavir, Darunavir, Fosamprenavir, Lopinavir, Ritonavir) and antiviral agents (Brincidovir, Favipiravir, Galidesivir, Remdesivir, Ribavirin) against a monkeypox protein target (PDB ID: 8B07). The four-step molecular docking workflow included target protein preparation, ligand preparation, docking simulation, and interaction visualisation. Results showed that HIV drugs had higher docking scores, with Lopinavir (-10.6) and Atazanavir (-10.1) emerging as top candidates, while antiviral agents displayed lower affinities (Remdesivir: -6.6). The study highlights the advantages of computational drug screening for rapid drug identification. The strong hydrogen bond interactions of Lopinavir and Atazanavir with the monkeypox protein suggest their potential for therapeutic repurposing. This research underscores the applicability of computer-aided drug design (CADD) in accelerating drug discovery. Further experimental and clinical validation is necessary to confirm efficacy. These findings provide a framework for repurposing drugs against emerging viral infections, offering a strategic approach to public health preparedness.

Keywords: Docking score, Drug repurposing, Emerging viral threats, Molecular docking, Monkeypox

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1.0 Introduction

The emergence and recurrence of viral diseases, such as COVID-19, Ebola, and Zika, present significant global health challenges due to their high infectivity, constant mutation, and resistance to conventional treatments. Monkeypox, a viral disease caused by the Orthopoxvirus related to the variola virus (responsible for smallpox), has recently garnered global attention due to its outbreaks in non-endemic regions (1). Although vaccines and supportive care are available for monkeypox, no direct antiviral treatments currently exist. The development of new antiviral agents typically demands significant time and financial resources, making it difficult to respond promptly during emerging outbreaks.

This scenario underscores the importance of drug repurposing a strategy that seeks new therapeutic uses for drugs already approved for human use (2). Notably, certain HIV drugs, such as protease inhibitors and reverse transcriptase inhibitors, have been shown to exhibit broad-spectrum antiviral activities by targeting conserved replication pathways in different viruses. Given the similarities in viral replication mechanisms between HIV and monkeypox, these drugs present a promising option for repurposing to treat monkeypox (3).

Due to the rising incidence of monkeypox worldwide, computational approaches like molecular docking have gained significance in evaluating the binding affinity between potential drug candidates and viral proteins. Molecular docking enables researchers to predict the binding affinities of chemical compounds, providing insight into their potential effectiveness as therapeutic agents (4). This study leverages molecular docking to assess the binding interactions of selected HIV (Atazanavir, Darunavir, Fosamprenavir, Lopinavir, and Ritonavir) and antiviral agents (Brincidovir, Favipiravir, Galidesivir, Remdesivir, and Ribavirin) against a specific monkeypox protein target (PDB ID: 8B07) thereby exploring the feasibility of repurposing these drugs.

The study's findings revealed that certain HIV drugs, particularly Lopinavir and Atazanavir, exhibit higher binding affinities and stronger hydrogen bond interactions with the monkeypox protein target, indicating their potential as repurposed therapies. This research not only addresses the urgent need for effective monkeypox treatment options but also highlights the broader applicability of computational drug design for other emerging viral diseases.

The outcomes of this study could inform future experimental research and optimise methodological approaches in clinical trials, thereby contributing to an enhanced international response to monkeypox and other orthopoxvirus infections (5). By establishing a foundation for computational drug repurposing strategies, this work supports public health efforts to develop rapid therapeutic interventions during viral outbreaks and sets a precedent for addressing similar challenges in the future.

2.0 Innovation

Drug repurposing offers a streamlined approach to drug development by leveraging the established safety and efficacy profiles of existing drugs, thereby reducing costs, development timelines, and the risk of failure (2). This strategy bypasses early discovery phases and simplifies regulatory procedures, increasing the probability of successful market introduction (6). Repurposed drugs require fewer resources and less time to reach the market, making them a cost-effective option compared to traditional development pathways (7). The known pharmacokinetic and pharmacodynamic profiles of these drugs facilitate a smoother transition through later

development stages, providing more affordable and faster treatment options (2).

Beyond economic and time efficiencies, drug repurposing also addresses public health needs by offering new therapies for diseases with limited treatment options, such as rare or neglected conditions (3). Moreover, it supports sustainable development by reducing the need for new drug synthesis, thus minimising chemical waste and environmental impact (1). This approach also enables pharmaceutical companies to explore new therapeutic applications for existing drugs, creating opportunities for expanding their market presence (5).

In response to the growing threat of monkeypox, researchers turned to drug repurposing using in silico molecular docking to explore existing HIV and antiviral drugs. Targeting the monkeypox protein (PDB ID: 8B07) (8), the study revealed that HIV drugs (Table 1) (9), particularly Lopinavir and Atazanavir, showed stronger binding affinities (-10.6 and -10.1, respectively) compared to antivirals (10,11). Lopinavir, forming four hydrogen bonds with key residues, demonstrated the most stable interaction, while Remdesivir, the top antiviral candidate, showed a docking score of -6.6 with three hydrogen bonds (12, 13). The number and strength of hydrogen bond interactions were key indicators of potential efficacy. These findings highlight the promise of Lopinavir and Remdesivir as repurposed treatments for monkeypox, showcasing the power of computer-aided drug design (CADD) to fast-track therapeutic discovery during outbreaks (14). Though further validation is needed, this research offers a practical framework for applying AI-driven repurposing strategies to emerging viral diseases, bridging science and speed in global health response.

Table 1: Molecular Docking Results and Hydrogen Bond Interactions of HIV and Antiviral Drugs Against Monkeypox Target Protein (PDB ID: 8B07) using computational approaches.

Drug	Score	Hydrogen Bond Interactions
Atazanavir	-10.1	3 hydrogen bonds with GLU299, THR232, and SER207
Darunavir	-9.3	4 hydrogen bonds with ASP245, GLY300, and ASN301
Fosamprenavir	-8.8	2 hydrogen bonds with HIS227 and THR232
Lopinavir	-10.6	4 hydrogen bonds with THR232, GLU299, and GLY300
Ritonavir	-9.3	3 hydrogen bonds with ASN301, GLY300, and ASP245
Brincidovir	-6.5	2 hydrogen bonds with GLU299 and ASN301
Favipiravir	-5.8	1 hydrogen bond with GLY300
Galidesivir	-5.8	2 hydrogen bonds with ASP245 and GLU299
Remdesivir	-6.6	3 hydrogen bonds with GLU299, ASN301, and GLY300
Ribavirin	-6.9	2 hydrogen bonds with GLU299 and ASP245

3.0 Uniqueness

This study presents a novel approach by utilising *in silico* molecular docking to evaluate the potential repurposing of HIV and antiviral drugs against a specific monkeypox protein target. The originality of this research lies in its innovative use of computational methods to identify promising drug candidates for monkeypox treatment. By focusing on HIV drugs with broad-spectrum antiviral properties, the study addresses an urgent need for effective monkeypox therapies, offering a potential solution without the time and cost constraints associated with traditional drug discovery (Figure 1). The comprehensive analysis of

docking scores and hydrogen bond interactions further contributes to the uniqueness of this research, as it establishes a foundation for identifying repurposed drugs that can be rapidly implemented for clinical use in future monkeypox outbreaks. This strategy not only provides a practical approach for addressing emerging viral diseases but also demonstrates the potential of computational drug design in accelerating the discovery of therapeutic options for underexplored viral targets.

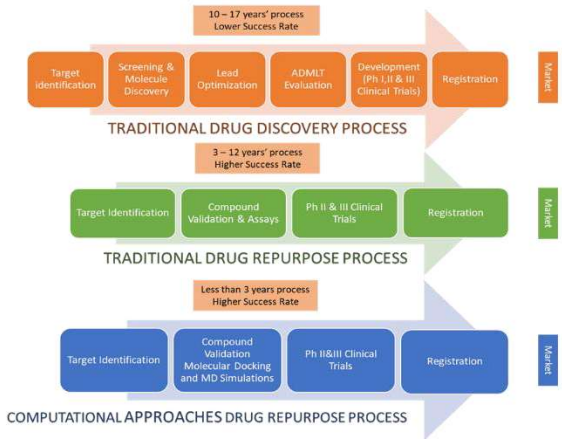

Figure 1: Comparison of methodologies, timelines, processes, and success rates of three different approaches.

4.0 Commercialisation Potential

The findings from this study suggest a strong commercialisation potential for repurposed HIV drugs, particularly Lopinavir and Atazanavir, as treatments for monkeypox. The high docking scores and favorable hydrogen bond interactions demonstrated by these drugs indicate their potential efficacy against the monkeypox virus. This creates an opportunity to reposition these existing pharmaceuticals for an emerging health threat, providing a quicker path to market compared to traditional drug development.

Given that Lopinavir and Atazanavir are already approved and widely used for treating HIV, their known safety and pharmacokinetic profiles could significantly streamline the regulatory approval process for their new indication against monkeypox. This would allow for a rapid market entry, reducing development costs and timelines while meeting an urgent therapeutic need. Additionally, the established manufacturing and distribution infrastructure for these drugs can further support their quick deployment and commercialisation for monkeypox treatment.

Furthermore, drug repurposing reduces the financial risk associated with early-stage drug discovery and presents an economically viable solution for pharmaceutical companies looking to expand their market portfolios. The demonstrated effectiveness of computational methods, such as the *in-silico* docking approach used in this study, can facilitate cost-effective screening of additional compounds for other viral infections, broadening the commercial scope of this research.

In summary, the commercialisation potential of repurposing HIV drugs for monkeypox treatment is considerable, given the existing regulatory approvals, safety profiles, and manufacturing capabilities. This approach could accelerate market availability, meet a pressing public health need, and create new business opportunities for the pharmaceutical industry. Further experimental validation and clinical trials would be the next step to fully realise this potential and establish a novel therapeutic option for managing monkeypox outbreaks

5.0 Impact on Quintuple Helix

5.1 Society

Repurposing HIV drugs for monkeypox offers timely, accessible treatment during outbreaks, reducing disease burden and improving public health. Using well-known drugs fosters patient trust and societal resilience against emerging threats.

5.2 Academia

This study advances the use of in silico molecular docking in drug repurposing, promoting interdisciplinary research in computational drug design and encouraging further exploration across virology, pharmacology, and bioinformatics.

5.3 Government

Repurposing supports faster regulatory approval and public health response, aligning with national preparedness goals. It enables governments to act swiftly using safe, pre-approved treatments during health emergencies.

5.4 Industry

Pharmaceutical companies benefit from lower R&D costs and faster commercialisation by repurposing existing drugs. This creates new revenue streams and encourages innovation by expanding drug applications.

5.5 Environment

By reducing the need for new chemical synthesis, drug repurposing lowers carbon emissions and chemical waste. It promotes sustainable practices by maximising the utility of existing pharmaceutical resources.

6.0 Conclusion

This study reveals the promising potential of repurposing HIV drugs, particularly Lopinavir and Atazanavir, as immediate therapeutic solutions for monkeypox. Using a novel *in silico* molecular docking approach, these drugs demonstrated strong interactions with the monkeypox protein target, highlighting their viability for rapid deployment. This innovative strategy significantly reduces development time, costs, and risks, while addressing a critical public health need. The results lay a strong foundation for advancing clinical research and revolutionising how we respond to emerging viral threats, offering a transformative approach to accelerate drug discovery and enhance global health preparedness.

Authorship contribution statement

NBR, **SNAH**, **EASA:** Data analysis, visualisation, Resources, **NSN**: Writing-review, Resources. **NAS**: Supervision, Funding acquisition, Methodology, Writing, review & editing, correction draft.

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Conflict of Interest

The authors declared that they have no conflicts of interest to disclose.

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