

Review

Deciphering Drug Repurposing Strategies: Antiviral Properties of Candidate Agents Against the Mpox Virus

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Abstract

Monkeypox (Mpox) has re-emerged as a global public health threat, with recent outbreaks linked to novel mutations that enhance viral transmissibility and immune evasion. The Mpox virus (MPXV), a double-stranded deoxyribonucleic acid (DNA) orthopoxvirus, shares high structural and enzymatic similarity with the variola virus, underscoring the need for urgent therapeutic interventions. While conventional antiviral development is time-intensive and costly, drug repurposing offers a rapid and cost-effective strategy by leveraging the established safety and pharmacological profiles of existing medications. This is a narrative integrative review synthesizing published evidence on drug repurposing strategies against MPXV. To address these issues, this review explores MPXV molecular targets critical for genome replication, transcription, and viral assembly, highlighting how the Food and Drug Administration (FDA)-approved antivirals (cidofovir, tecovirimat), antibiotics (minocycline, nitroxoline), antimalarials (atovaquone, mefloquine), immunomodulators (infliximab, adalimumab), and chemotherapeutics (doxorubicin) have demonstrated inhibitory activity against the virus using computational or experimental approaches. This review further evaluates advances in computational methodologies that have accelerated the identification of host-directed and viral-directed therapeutic candidates. Nonetheless, translational challenges persist, including pharmacokinetic limitations, toxicity concerns, and the limited efficacy of current antivirals such as tecovirimat in severe Mpox cases. Future research should integrate computational predictions with high-throughput screening, organ-on-chip technologies, and clinical pipelines, while using real-time genomic surveillance to track viral evolution. These strategies establish a scalable and sustainable framework for the MPXV drug discovery.

Keywords: Mpox; MPXV; drug repurposing; tecovirimat; molecular docking and dynamics; AI-driven therapeutics; emerging viral threats

Academic Editors: Lenuta Profire and Ioana Mirela Vasincu

Received: 26 August 2025

Revised: 13 October 2025

Accepted: 14 October 2025

Published: 17 October 2025

Citation: Mushebenge, A.G.-A.; Mphuthi, D.D. Deciphering Drug Repurposing Strategies: Antiviral Properties of Candidate Agents Against the Mpox Virus. *Sci. Pharm.* **2025**, *93*, 51. <https://doi.org/10.3390/scipharm93040051>

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1. Introduction

The re-emergence of Mpox, caused by the Mpox virus (MPXV), has escalated from an endemic disease in Central and West Africa to a global health concern [1–3]. With a wide geographic dispersion in more than 116 nations and new forms of transmission, such as sexual contact, the outbreak in 2022 brought it to the public's attention [4]. The cessation of smallpox vaccination programs increased susceptibility by creating an immunity gap in the community. Mpox has historically been associated with zoonotic spillover from animal reservoirs, such as rats [5,6]. Environmental change, human behaviour, and

globalization drive the re-emergence of Mpox [7]. This underscores the need for rapid and effective countermeasures.

Because of the advent of virulent and genetically varied clades such as clade I, Mpox poses distinct hurdles in diagnosis, treatment, and containment, despite its clinical similarity to smallpox. The global health threat posed by Mpox led the World Health Organization (WHO) to declare it a Public Health Emergency of International Concern (PHEIC), while inequitable healthcare access, disinformation, and stigma continue to delay treatment and create major public health barriers (<https://www.who.int/news-room/fact-sheets/detail/Mpox>, accessed on 4 October 2025) [8]. In addition, most outbreaks arise from viruses without approved medication. Previously, virus-specific drugs followed the traditional discovery approach, but the re-emergence of Mpox underscores the need for broad-spectrum antivirals.

These challenges require specialized therapies to address the evolving epidemiological landscape. Although vaccination remains crucial, current smallpox vaccines such as JYNNEOS offer limited protection against Mpox and face challenges in coverage, distribution, and public acceptance in endemic regions [9,10]. Furthermore, the rapid evolution of MPXV calls for creating polyvalent vaccinations that target several circulating clades [9]. Novel approaches to improve vaccination tactics have been made possible by developments in nanotechnology-based delivery systems, which have demonstrated promise in enhancing vaccine durability and bioavailability [11]. However, the emphasis needs to change to therapeutic options because immunization might not be enough to stop the pandemic.

One crucial tactic for meeting the pressing need for efficient Mpox therapies is drug repurposing (DR). De novo drug discovery is more expensive and time-consuming than using current pharmacological resources [12]. Finding possible antiviral drugs that target the MPXV replication and immune evasion pathways has been made possible in large part by computational methods, including molecular docking and dynamics simulations [13]. The efficacy of repurposed drugs such as tecovirimat (TPOXX®), cidofovir, and brincidofovir varies, while host-targeted therapies such as mycophenolate mofetil (MMF) and IMP-1088 are under investigation for their synergistic effects with direct-acting antivirals [14–16].

Relevant comprehensive literature was identified through structured searches in PubMed, Scopus, ScienceDirect, Web of Science, Google Scholar and preprints, among others, and publisher archives covering publications from 2006 to October 2025. Keyword searches combined ‘Mpox virus’, ‘monkeypox’, ‘drug repurposing’, ‘antiviral’, and ‘in silico docking.’ Studies were screened for relevance to MPXV antiviral activity, computational predictions, or mechanistic insights into viral inhibition. Review articles, molecular docking analyses, and experimental studies were all considered for inclusion, while commentaries and methodological papers were omitted. This is a narrative integrative review that highlights the milestones, developments, and prospects of repurposed medications in the fight against Mpox, with particular emphasis on integrating preclinical and clinical findings into feasible treatment strategies. This underscores the importance of cutting-edge technologies, especially computational approaches, in improving therapeutic outcomes. Viral and host protein targets have been evaluated with diverse drugs in silico, in vitro, and in vivo, with several showing promising activity for potential MPXV repurposing. However, Mpox eradication cannot rely solely on the conventional drug discovery pipeline, despite the remarkable advances in computational and experimental methods in recent decades. DR has emerged as a successful strategy for identifying candidate antivirals against MPXV, a member of the Orthopoxvirus genus. This review further advocates a coordinated global response via a One Health framework integrating human, animal, and environmental health. Evidence underscores the need for interdisciplinary

collaboration to accelerate antiviral development, mitigate future outbreaks, and strengthen global health resilience.

2. Mpox Virus Biology and Pathogenesis

2.1. Genomic Characteristics and the Viral Lifecycle

MPXV, a zoonotic orthopoxvirus, has drawn significant attention due to its rapid global spread and designation as a PHEIC [7,17]. The conserved and specialized genes that make up the viral genome allow MPXV to infect a variety of species, withstand host immune responses, and continue to spread from person to person [18]. The deletion of functional *OPG041* (*K3L*) and *OPG065* (*E3L*) genes distinguishes MPXV from other orthopoxviruses and reflects its strategies to evade host antiviral defenses. These modifications, which include decreased the double-stranded ribonucleic acid (dsRNA) production and altered interferon (IFN) responses, highlight the virus's capacity to infect humans and small rodents [19]. The evolution of MPXV toward improved human adaptation is highlighted by the formation of Clade I and Clade II MPXV lineages, each of which is distinguished by unique virulence factors and transmission dynamics [13]. Continuous mutation and selection further shape the virus's pathogenic capacity, driven by genomic reduction and codon optimization via the human apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) editing [13,20].

Ankyrin-containing and Bcl-2-like proteins, which are essential for immune evasion and host range, form part of MPXV's genomic toolkit and are closely linked to its lifecycle and pathogenesis [13]. Comparative studies have shown that MPXV contains distinct virulence genes, including *OPG174* (*A44L*), which facilitates persistent infections by enabling immunosuppression through the synthesis of glucocorticoids [19]. There are still significant gaps in the knowledge of MPXV biology that need to be filled to fully comprehend the molecular mechanisms behind viral replication and host interactions. For the development of antiviral medications, computational methods have found conserved viral targets such as DNA polymerase and thymidine kinase [13,21]. However, mutations in therapeutic targets highlight the need for new treatment approaches that focus on low-mutation viral areas and raise concerns about drug resistance [22]. In-depth functional research and ongoing genetic surveillance are crucial for creating potent antiviral medications, anticipating future outbreaks, and reducing the harm MPXV poses to the world health.

2.2. Key Molecular Targets for Therapeutic Intervention

Finding and confirming molecular targets within the MPXV that may be viable candidates for antiviral development is an essential objective in this effort. Using genomic and subtractive proteomics, researchers identified the highly druggable core proteins A20R, I7L, Top1B, and VETF5 conserved across MPXV strains and non-homologous to human proteins [23]. Potential inhibitors have been identified using high-throughput virtual screening of already available medications [13,23]. Molecular dynamics (MD) simulations have confirmed these inhibitors' interactions. These discoveries accelerate treatment development by enabling the repurposing of existing compounds against MPXV, as shown in Figure 1 [24].

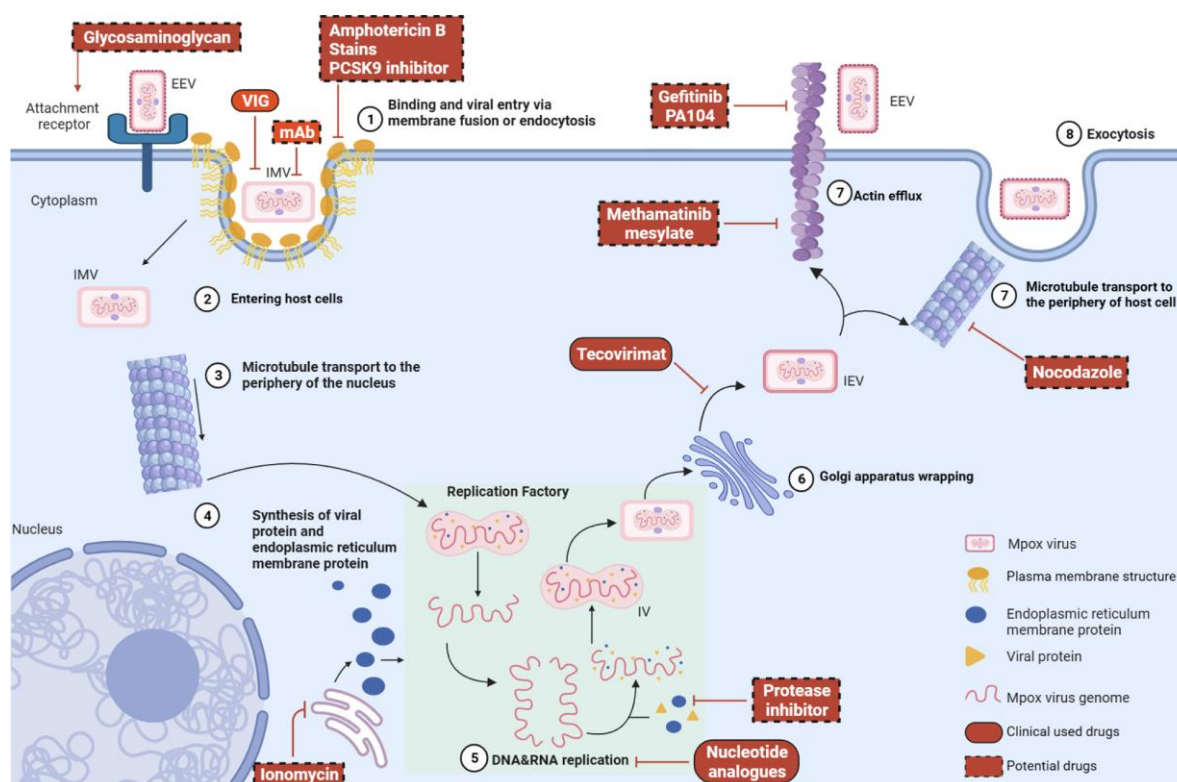


Figure 1. Schematic representation of the life cycle of MPXV replication in hosts and potential targets for anti-MPXV drugs as adapted from [24] under Creative Commons Attribution 4.0 International License (CC BY 4.0). The MPXV undergoes a complete life cycle, beginning with host cell entry and concluding with excretion. Both extracellular enveloped virions (EEV) and intracellular mature virions (IMV) enter host cells through membrane fusion and endocytosis, using glycosaminoglycans (GAGs) as receptors. IMV particles travel along microtubules to the perinuclear replication factory, where the viral genome templates DNA replication. They then envelop the virions via the Golgi apparatus to form intracellular enveloped virions (IEVs), which they transport to the cell surface along actin filaments or microtubules. Structurally and functionally, IMVs and EEVs differ: IMVs possess a single membrane, making them more robust and resistant to external damage, yet more detectable by the immune system. In contrast, EEVs, with their double membrane, are more effective at spreading within the host. Cholesterol plays a critical role in viral entry by stabilizing lipid rafts on the host cell membrane. Disrupting these rafts using amphotericin B or cholesterol-lowering drugs such as statins and PCSK9 inhibitors can inhibit viral entry. In addition, marine sulfated polysaccharides, which mimic GAGs, can block viral attachment and entry.

Other important viral proteins, including DNA polymerase, Topoisomerase 1, D9 decapping enzyme, and thymidylate kinase, have also been investigated as potential therapeutic targets [25]. Functional and structural studies have enhanced our understanding of the roles these proteins play in immune evasion and viral replication. Efforts have mapped MPXV–host protein interactions to identify key viral proteins, such as OPG054, OPG084, and OPG190, as therapeutic targets [26]. Moreover, broad-spectrum antiviral drugs targeted host proteins implicated in immunological pathways, including the most interacting MPXV-interacting proteins [26]. The combination of experimental data and computational tools emphasizes how crucial a systems biology approach is to solve the problems caused by the MPXV.

The rapid genomic evolution of MPXV and the emergence of mutant strains resistant to existing treatments underscore the urgent need for alternative antiviral strategies. Advances in artificial intelligence and bioinformatics have facilitated the identification of immunogenic antigens and druggable targets, enabling the development of novel small-

molecule inhibitors and multi-epitope vaccines [27]. Focusing on key viral and host biological targets, coupled with an enhanced understanding of virus–host interactions, will enable the development of more effective therapies. Supported by genomic surveillance, these initiatives are essential to mitigate the impact of MPXV outbreaks and strengthen preparedness for future public health threats.

2.3. Host–Pathogen Interactions

MPXV exhibits complex host–pathogen interactions that influence disease severity and progression (<https://www.who.int/news-room/fact-sheets/detail/Mpox>, accessed on 4 October 2025). The virus rapidly replicates in keratinocytes, fibroblasts, and antigen-presenting cells following infection via mucosal surfaces or skin breaks [22,28]. Lesions are dispersed based on lymphatic propagation, resulting in systemic viremia that affects vital organs such as the liver, spleen, and lungs. This permits systemic dispersion through both hematogenous and lymphatic routes [29,30]. With CD4+ and CD8+ T cells driving the removal of infected macrophages and the generation of cytokines such as IFN- γ and TNF, cellular immune responses are essential for viral control [31]. Nevertheless, MPXV has evolved defenses against immunological reactions, such as inhibiting T-cell activation [13]. Studies on human skin organoids revealed productive keratinocyte replication and multiple phases of intracellular virus assembly, highlighting the virus's affinity for skin epithelial cells and the potential for severe localized or systemic symptoms influenced by host and viral factors [32].

The pathophysiology of MPXV has been further clarified by non-human primate models, which show that inoculation routes such as aerosol or intravenous exposure affect the course of the disease [33]. Aerosolized MPXV closely resembles human Mpox pathophysiology in that it produces severe bronchopneumonia and systemic dissemination [13]. Important genes that improve viral transmissibility and immune evasion have been identified through molecular research, including *OPG027* and *D1L* [13]. Computational studies of host–pathogen interactions have identified key host proteins and signalling pathways, including AKT, STAT3, and NF- κ B, as potential therapeutic targets in MPXV infection [34]. There is promise for repurposed treatments because promising FDA-approved drugs have demonstrated potential in targeting these pathways [34]. While antiviral therapies target viral envelope proteins and DNA polymerases, their clinical efficacy in real-world settings has been inconsistent, especially against Clade I strains with severe disease manifestations [35]. Furthermore, the MPXV genome shows potential for rapid adaptive mutations, particularly under antiviral pressure, which could compromise long-term efficacy [13]. In addition, MPXV encodes immunomodulatory proteins that allow it to evade host immune responses, limiting the therapeutic window of antivirals [13].

3. The Rationale for Drug Repurposing in Mpox Management

3.1. Advantages of Repurposed Drugs in Addressing MPXV

High MPXV mutability and the emergence of drug-resistant strains hinder the development of traditional antiviral drugs [24]. Repurposing drugs has become a crucial strategy in the fight against new viral illnesses. This approach, which is faster and inexpensive than traditional drug development, involves identifying new therapeutic uses for already approved medications. Advances in computational techniques have greatly facilitated this process by enabling the analysis of gene expression patterns, host–pathogen interactions, and protein–protein interaction (PPI) networks [36]. PPIs during MPXV infections may be predicted with excellent accuracy using ensemble feature-based deep learning models [37]. From FDA-approved databases, this method, which is supplemented by molecular docking and dynamics simulations, has found possible therapeutic targets and

repurposed medications such as cannabidiol and fostamatinib [37]. These results highlight how DR works to combat the pressing demand for antiviral treatments against Mpox and related infectious illnesses.

Drug repurposing leverages approved drugs with established safety profiles, reducing the time needed for clinical application. A literature review identified 160 human-host proteins associated with MPXV and related viruses, highlighting 15 key targets via network-based drug discovery. Approved drugs such as baricitinib and adalimumab have emerged as promising repurposing candidates [38]. These outcomes shed light on the molecular processes of MPXV and demonstrate how repurposed medications may be used to address the dual problems of treatment resistance and the virus's evolving nature.

In addition to improving Mpox treatment, combining computational and experimental methods in drug repurposing establishes a standard approach for tackling emerging viruses. Novel treatments have been made possible by insights from molecular diagnostics and therapeutic target identification, such as VP39 and thymidine kinase proteins [13]. They have also strengthened the arsenal against Mpox by developing nanomedicine, using herbal therapies, and creating contemporary diagnostic platforms such as the clustered regularly interspaced short palindromic repeats (CRISPR)-based techniques [39]. These initiatives underscore the critical role of DR in public health, enabling rapid and effective responses to emerging viral threats. By integrating advanced technologies and leveraging existing resources, drug repurposing provides a robust framework to mitigate the global impact of viral epidemics.

3.2. Historical Success of Drug Repurposing in Viral Outbreaks

The historical effectiveness of therapeutic repurposing in controlling viral outbreaks provides a promising way to combat the growing threat of Mpox. Because poxviruses share evolutionarily conserved proteins and functional traits, they allow effective cross-species treatments. [33]. The smallpox vaccine, which was created for a similar orthopoxvirus, showed 85% effectiveness in preventing Mpox infection [40]. Baricitinib, initially an anti-rheumatoid arthritis agent, was successfully repurposed for the coronavirus disease of 2019 (COVID-19) treatment, reducing mortality by 38% in hospitalized patients. Remdesivir, initially developed for Ebola, showed moderate success against the Severe acute respiratory syndrome coronavirus 2 but with variable clinical outcomes [41]. Favipiravir, another repurposed antiviral for influenza, displayed inconsistent efficacy in the COVID-19 trials. Similarly, tecovirimat, originally developed to combat smallpox, has been used to treat Mpox cases in Europe, demonstrating the value of repurposing already approved antiviral medications [42,43]. Thus, the DR strategy minimizes the time and expense involved in developing new therapies while highlighting the benefits of repurposing medications that have demonstrated efficacy against the genus Orthopoxvirus. However, repurposing success rates remain low, with only ~5% of antiviral candidates advancing to clinical approval [44]. Factors such as differences in viral replication mechanisms, host–pathogen interactions, and pharmacokinetics often hinder successful translation.

Computational and experimental approaches targeting viral and host proteins have identified promising candidates, including brincidofovir and cidofovir, with the potential to reduce Mpox infections [24,45]. The use of medication repurposing for Mpox demonstrates both its promise and the necessity of investigating other therapeutic approaches, considering the shortcomings of the available treatments. Repurposed medications, including tecovirimat and nucleoside analogues, serve as first-line defenses, despite the WHO not recommending mass vaccination and the lack of antivirals specifically approved for Mpox [24]. Developments in structural biology have helped us to rationally select and optimize nucleoside analogs by shedding light on the distinctive characteristics of viral DNA polymerases. These focused strategies highlight the wider significance of

understanding viral protein structures and functions, enabling the development of effective and selective antiviral treatments [46]. DR is a crucial and flexible tactic to counteract Mpox and other new viral threats, given its ongoing development and potential for cross-species transmission.

3.3. Criteria for Selecting Candidate Drugs

Given the absence of specific antivirals or vaccines and the rapid global spread to 82 non-endemic countries, selecting suitable therapeutic options has become a crucial task. This challenge stems from several factors: declining population immunity after smallpox eradication, facilitating global susceptibility; international travel and social gatherings, enabling undetected transmission; and underestimation of asymptomatic or subclinical cases, hindering early detection and intervention [47–49]. Computational techniques such as subtractive proteomics and genomics have been used to identify possible therapeutic targets within the MPXV proteome [23]. Four highly druggable targets were identified from 69 conserved proteins found in 125 publicly accessible MPXV genomes [23]. Three frequent inhibitors, batefenterol, burixafor, and eluxadoline, that showed considerable binding affinities were found by high-throughput virtual screening of 5,893 licensed and experimental medications [23]. MD simulations confirmed stable and favourable binding patterns for these inhibitors, identifying them as strong candidates for repurposing. This approach highlights the value of computational methods in prioritizing compounds for experimental validation. Advanced computational tools further facilitate the prediction of new inhibitors targeting key MPXV proteins, such as the cysteine proteinase, leading to the discovery of molecules such as ChEMBL32926 and ChEMBL4861364 with high binding affinity and drug-like properties [46]. Strong protein-ligand interactions were observed by researchers using ensemble docking and MD simulations, which were corroborated by advantageous binding free energy predictions [50]. The therapeutic landscape was further expanded by the discovery of analogues of these drugs with comparable characteristics that were anticipated to have potent inhibitory efficacy [46,50].

4. Computational Approaches in Drug Repurposing

4.1. Molecular Docking and Dynamics Simulations

Molecular docking predicts the preferred orientation of a ligand bound to a target macromolecule, such as a viral protein, and estimates the binding affinity. It provides a cost-effective primary screening method [51,52]. However, docking relies on rigid receptor structures and may not fully account for protein flexibility or solvation effects, which are critical in biological systems. MD simulations complement docking by modeling atomic-level movements over time, allowing exploration of binding stability and conformational changes under near-physiological conditions [52,53]. Despite their strengths, MD simulations are computationally intensive and depend on the accuracy of the applied force fields. The process depicted in Figure 2 below emerged as a revolutionary strategy in tackling the worldwide issue. *In silico*, drug design follows two main routes. Route B encompasses pharmacophore development and validation (B1), database exploration for structurally similar compounds (B2), the absorption; distribution; metabolism; excretion; and toxicity (ADMET) and the blood-brain barrier (BBB) filtering to select candidates with favourable pharmacokinetic properties (B3), high-throughput virtual screening (B4), protein structure preparation (B5), and molecular docking (B6) to predict binding modes and affinities. Route A employs the quantitative structure-activity relationship (QSAR) modeling (A1–A2) to establish quantitative relationships between chemical structures and biological activity, followed by molecular docking (A3) and MD simulations with molecular mechanics generalized born surface area (MM-GBSA) to assess the binding stability and

energetics. Together, these integrated workflows provide an efficient and comprehensive strategy to prioritize drug candidates for experimental validation [54].

In Silico Drug Design Methods

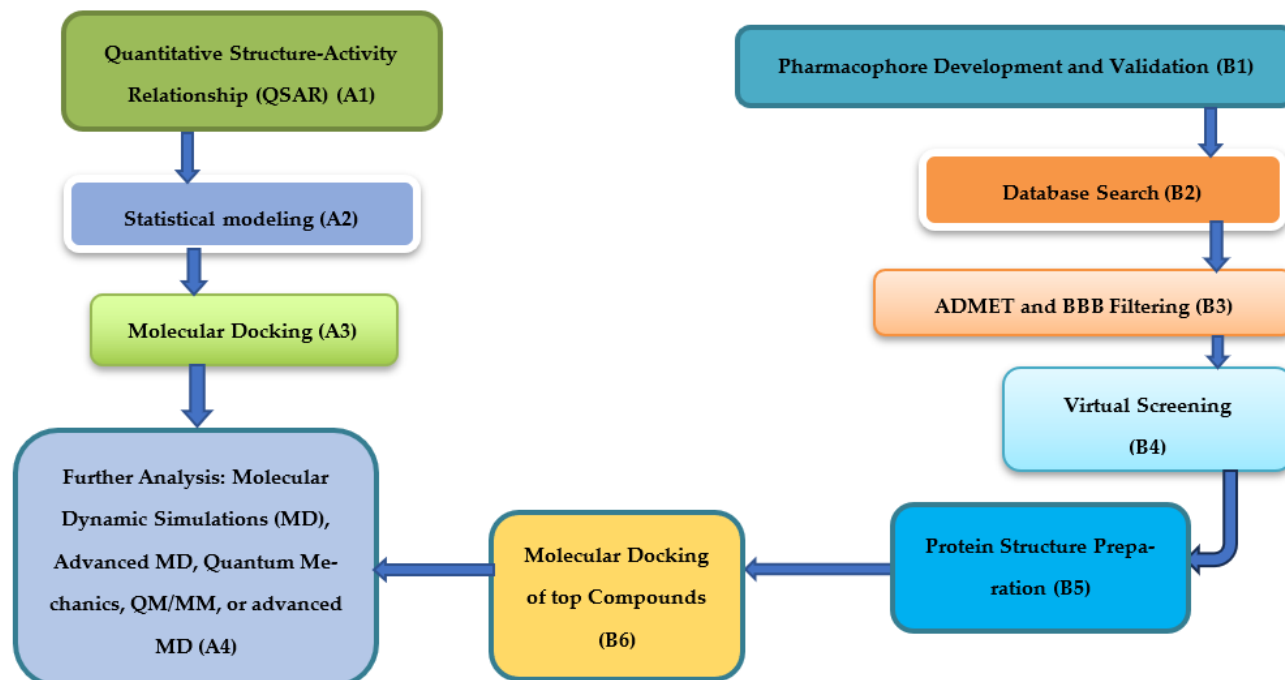


Figure 2. Proposed translational pipeline of in silico drug design methods. Figure created by the authors as adapted from the cited sources [54,55].

In silico docking, MD simulations, AI-driven structure prediction, high-throughput screening, Cryo-electron microscopy (Cryo-EM), phenotypic assays, and multi-omics integration contribute uniquely to the MPXV therapeutic pipeline (Table 1). High-throughput virtual screening has identified potential inhibitors targeting viral proteins essential for replication and survival. Antibiotics derived from tetracyclines, such as tigecycline and eravacycline, showed substantial binding affinities to DNA-dependent RNA polymerase (DdRp) [56]. MD simulations confirmed this, showing persistent protein-ligand interactions. Similarly, substances such as minocycline and omadacycline efficiently targeted viral proteinases, highlighting the possibility of repurposing antibiotics [56]. Principal component analysis and binding free energy computations supported the stability and specificity of these inhibitors, underscoring their potential as therapeutics [56]. Screening of FDA-approved drugs and plant-derived metabolites identified promising candidates, including DB16335, punicalagin, and nilotinib, after prior studies used structural insights to target MPXV proteins such as thymidylate kinase and the E8 envelope protein [57–59]. The studies further confirmed the compounds' favorable docking scores, dynamic stability, and binding affinities using molecular mechanics Poisson–Boltzmann surface area (MM/PBSA) calculations and MD simulations.

Table 1. Comparative landscape of technological approaches used in Mpox (MPXV) therapeutic discovery.

Technological Approach	What It Does (Scope)/Typical Inputs	Primary Readouts/Outputs	Key Strengths/Principal Limitations	Validation/Next Steps	Example MPXV Applications	Best Used for/Pipeline Stage	Refs
Structure-based in silico docking	Predicts ligand binding poses/affinities to viral or host targets/3D target structures (experimental or predicted), prepared ligand libraries	Docking scores, predicted poses, interaction maps	Fast, low cost; screens 10 ⁴ –10 ⁶ compounds; hypothesis generation for SAR/Dependent for structure quality and protonation; ignores full dynamics/solvent; risk of false positives	Re-dock known ligands; MM/GBSA rescoring; move hits to MD, biophysics (isothermal titration calorimetry and surface plasmon resonance), and cell assays	Docking to MPXV enzymes (e.g., VP39 cap MTase, D1/D12 polymerase complex) and host JAK1; prioritization of nitroxoline, atovaquone, tilorone, ZINC leads	Early hit identification and triage	[60]
Molecular dynamics (MD) simulations	Tests the stability and dynamics of protein–ligand complexes; refines docking/protein–ligand complexes, force fields, explicit solvent/ions	Root Mean Square Deviation/Root Mean Square Fluctuation, H-bond occupancy, binding free energy (e.g., MM/PBSA), conformational ensembles	Captures flexibility, water networks; filters docking artifacts; supports binding hypotheses/Compute-intensive; sensitive to parameters/time-scale; not a direct measure of potency	Orthogonal biophysics; mutagenesis; enzymatic half-maximal inhibitory concentration (IC ₅₀ /EC ₅₀)/Ki; cell-based EC ₅₀	Stability of candidate inhibitors in MPXV VP39 pocket; MD of host-targeted the Janus kinase-signal transducer and activator of transcription (JAK/STAT) modulators	Post-docking refinement; pre-experimental risk reduction	[58]
AI-driven structure prediction (e.g., AlphaFold/ColabFold)	Predicts protein 3D structures and complexes; maps pockets/amino-acid sequences, multiple sequence alignments, co-evolution data	3D models with confidence metrics (predicted local distance difference test, predicted aligned error), interface predictions	Enables targets lacking structures; rapid; broad proteome coverage/Accuracy varies for flexible regions/complexes; requires experimental validation	Cryo-EM/X-ray/Nuclear Magnetic Resonance confirmation; benchmarking via known domains	Models for MPXV proteins without PDB structures to enable docking/MD	Target Enablement and Pocket Discovery	[61]
High-throughput screening (HTS)	Empirical activity screening across large libraries/cell-based infection assays or enzymatic assays; 10 ³ –10 ⁶ compounds	Hit rates, EC ₅₀ /IC ₅₀ , 50% cytotoxic concentration (CC50), selectivity index (SI)	Direct activity readout; unbiased mechanism of action (MoA) discovery; scalable robotics/costly infrastructure; false positives; assay interference; needs robust BSL-2/3 models	Hit confirmation, counter-screens, MoA deconvolution, medicinal chemistry	Cell-based screens of FDA libraries against orthopox/MPXV surrogates; identification of DNA synthesis and egress blockers	Primary empirical discovery; lead finding	[62]
Cryo-electron microscopy (Cryo-EM)	Determines the near-native structures of large assemblies/Purified proteins/complexes/virions, vitrification	3–5 Å (or better) maps; atomic models; ligand density	Captures native states and complexes; ideal for large pox proteins/assemblies/high cost; expertise; not high throughput	Functional assays; docking/MD guided by EM maps; fragment campaigns	Structural analysis of pox-virus polymerase and capping machinery; guide structure-based design	Structure determination; hit-to-lead optimization	[63]

Phenotypic assays (infection-based)	Measure the antiviral effect in relevant biology without prior target/Live virus or pseudo-typed systems; human cell lines/organoids	Viral load reduction (quantitative polymerase chain reaction (qPCR)/plaques), CPE rescue, imaging, SI	Physiological relevance; reveals host-directed MoAs; detects polypharmacology/Target unknown; off-target/cytotoxicity risk; model dependence	Target deconvolution (proteomics/CRISPR), pharmacokinetic pharmacodynamic (PK/PD), in vivo	MPXV infection assays in primary keratinocytes and organoids; validation of tecovirimat alternatives	Hit validation, MoA discovery, prioritization [13,34]
Multi-omics integration (genomics/proteomics/transcriptomics/metabolomics)	Maps virus–host networks; identifies targets/pathways and biomarkers/bulk/single-cell RNA-seq, proteomics, phospho-proteomics, metabolomics	Differential pathways, network hubs, drug–gen signatures	Systems-level insight; reveals host targets and combinations/Complex analysis; batch effects; causal inference is hard	Network pharmacology, CRISPR perturbations, small-molecule probing	Host interactome proximity analyses suggesting JAK/STAT and NF-κB modulators; signatures guiding baricitinib/infliximab hypotheses	Target nomination; combination strategy design [64]
AI/ML-guided repurposing (knowledge graphs, graphs/Curated corpora, drug–signature matching)	Prioritizes candidates using literature, omics, and chemistry graphs/Curated corpora, drug–target networks, and disease signatures	Ranked candidates, mechanism hypotheses, polypharmacy suggestions	Leverages existing data; scalable; uncovers non-obvious links/Data bias; spurious correlations; requires wet-lab confirmation	Prospective validation in phenotypic assays and animal models	Prioritized immunomodulators (such as JAK inhibitors and anti-TNF agents) and DNA metabolism inhibitors for MPXV	Hypothesis generation; portfolio triage [65,66]
Organoid/3D tissue models	Human-relevant platforms for efficacy/toxicity/skin/mucosal organoids, immune co-cultures	Viral replication kinetics, barrier integrity, cytokine profiling	Closer to human physiology; detects tissue-specific effects/Throughput lower than 2D; cost; standardization	Bridge to in vivo; PK/PD translation; safety pharmacology	MPXV replication and drug testing in skin organoids relevant to lesion tropism	Preclinical validation; safety/efficacy translation [67]
Animal models (marmoset, prairie dog, and mouse with VACV/ectromelia models)	In vivo efficacy and safety assessment/infected animals; candidate dosing	Survival, lesion burden, viral load, PK/PD	Integrates immunity/ADME; regulatory credibility/species differences; ethics; BSL-3; cost	Dose optimization, toxic studies; clinical trial design	Benchmarking tecovirimat; testing host-directed combinations	Late preclinical go/no-go [68]

The range of computational DR broaden the computational drug-repurposing efforts for MPXV by integrating genomic data, applying subtractive proteomics, and leveraging artificial intelligence [23]. Database mining identified conserved viral proteins, including A20R, I7L, and Top1B, as druggable targets. High-throughput virtual screening of approved drugs yielded potential multi-target inhibitors, such as burixafor, batefenterol, and eluxadoline, with binding affinities confirmed by MD simulations [23]. FDA-approved drugs, such as elvitegravir, have been prioritized by advanced AI-based platforms such as DeepRepurpose, which employ rigorous computational workflows incorporating homology modelling and metadynamics [61]. Beyond small molecules, plant-derived compounds such as pseudohypericin and amentoflavone exhibit dynamic stability and strong binding, highlighting the utility of bioinformatics for exploring antiviral plant metabolites [13,69].

4.2. Virtual Screening for Antiviral Candidates

Virtual screening, an advanced computational approach that leverages publicly available MPXV genomes and molecular docking techniques, has proven essential for identifying potential antiviral candidates [13,58,70]. Ligand-based and structure-based virtual screening emphasize their potential to address the pressing demand for MPXV treatment. Targeting viral proteins such as A6R (DNA-dependent RNA polymerase), E8 (envelope attachment factor), and thymidylate kinase has identified promising repurposed drugs. Nilotinib, conivaptan, and ponatinib showed favourable binding energies (~ -7.5 kcal/mol) against A6R [71], while punicalagin outperformed maraviroc in docking to E8 (-9.1 vs. -7.8 kcal/mol), supported by 100 ns MD simulations and MM-PBSA binding energy calculations [58]. Small-molecule scaffolds such as tipranavir, cefiderocol, and dolutegravir emerged as potential inhibitors of thymidylate kinase and the D9 decapping enzyme [72], while novel heterocyclic compounds such as EH4 exhibited strong binding scores in docking and MD simulations [73]. Furthermore, several computer models have assessed how tecovirimat substitutes interact with viral proteins, including the p37 receptor, showing a high potential for viral inhibition [15,24]. Novel inhibitors that target viral replication pathways and capsid proteins essential to the MPXV lifecycle have been discovered, with potential potency exceeding that of tecovirimat [24,74]. These results highlight the need to integrate MD, genomics, and structure-based design to speed up the identification of antivirals. In addition, integrative platforms such as the Mpox Virus Docking Server offer a convenient and collaborative way to conduct research on target-ligand interactions [75].

DR processes are further enhanced by AI-driven protein modeling and pharmacophore ligand-based approaches, bridging the gap between in silico predictions and experimental validation [12]. These computational pipelines, combined with free-energy calculations and normal mode analysis, prioritize candidates for phenotypic validation and in vivo testing, thus streamlining Mpox drug discovery.

4.3. Phenotypical Drug Repurposing Approaches

Phenotypic DR for MPXV therapeutics leverages assays that identify compounds capable of inhibiting any stage of the viral lifecycle, including entry, uncoating, replication, assembly, or egress or modulating host pathways critical for infection, without requiring prior structural target information [34]. Recent high-throughput cytopathic effect (CPE) and foci-reduction screens in permissive cell lines (Vero E6 and BSC-40) and primary human dermal fibroblasts have identified diverse active scaffolds from FDA-approved drug libraries, including nucleotide polymerase inhibitors (cidofovir, brincidofovir), VP37 egress inhibitors (tecovirimat; nanomolar EC_{50}), antiparasitic (nitazoxanide), antimalarials (mefloquine), and antibiotics with unexpected antiviral activity (nitroxoline, minocycline)

[68,76]. Translational workflows use cytotoxicity screens to calculate selectivity indices, orthogonal assays (plaque/foci reduction, qPCR, viral yield), time-of-addition studies to map intervention points, and in vivo testing in CAST/EiJ mice or primates to assess PK/PD and safety [77,78]. Tecovirimat's clinical use has validated this pipeline while revealing rare *F13L/VP37* mutations in immunocompromised patients, highlighting the need for genomic surveillance and resistance monitoring [79]. Phenotypic repurposing captures host-directed and multi-mechanistic antivirals, enabling first-in-class discoveries, but is prone to false positives from cytotoxicity or plasma-protein binding, and many hits fail due to poor PK/PD or toxicity at therapeutic doses [80]. Current best practices integrate phenotypic screening with rapid mechanism deconvolution (chemical genetics, resistance selection, proteomics), in silico ADME/Tox modelling, and combination-matrix assays to identify synergistic drug pairs, raising the genetic barrier to resistance as shown in the human immunodeficiency virus (HIV) and Hepatitis C Virus models [81]. Hybrid pipelines that combine high-content phenotypic assays with computational docking, MD, and AI-driven network pharmacology provide a pragmatic route from the bench to bedside in MPXV drug discovery.

4.4. Systems Biology and Network Pharmacology in Drug Discovery

Systems biology and network pharmacology offer critical insights into the complex dynamics of host–pathogen interactions and therapeutic targeting. In a recent study, 39 major hub proteins were identified as possible therapeutic targets for the human MPXV using a network-based approach that created human-host protein interactomes [38,82]. Analysis revealed that 15 of these targets were already linked to existing drugs, indicating potential for DR [38]. Additionally, the functional enrichment of these hubs revealed pathways associated with viral replication and immune response, highlighting the effect of MPXV infection at the systems level. Baricitinib, infliximab, adalimumab, and etanercept emerged as promising repurposed candidates, while ZINC22060520 was identified as a novel molecule with potential antiviral activity via pharmacophore-based screening [38].

Network pharmacology speeds up the development of targeted therapies by providing a comprehensive understanding of the molecular interactions. Traditional medicine and computational methods have demonstrated potential in discovering new treatment routes to supplement this strategy. Using network pharmacology and molecular docking, research on the traditional Chinese medicinal Shengma-Gegen decoction showed promise against MPXV [83]. Protein–protein interaction analysis identified eight hub targets and 94 active components linked to key viral replication and inflammatory pathways, including TNF, IL-17, and MAPK signaling [38,83]. Similarly, computer modelling revealed that curcumin, a naturally occurring polyphenolic molecule, is a multi-target antiviral drug that targets host pathways including TNF and NF- κ B as well as viral proteins [84]. By integrating multi-omics data, computational predictions, and experimental validation, these studies link systems biology with network pharmacology and advance drug discovery against emerging threats.

5. Repurposed Drug Candidates for Mpox Virus

5.1. Antiviral Agents with Potential Efficacy Against Mpox

Several bioactive chemicals that may be used to treat MPXV have been identified using in silico virtual screening, as depicted in the non-exhaustive Table 1 below. A virtual screen of 10,640 compounds identified tucatinib, bictegrovir, dolutegravir, and glecaprevir as potential inhibitors of *VP37*, the MPXV *F13* gene product [85]. A similar AlphaFold2-based study predicted the MPXV protein structures and identified trypan

blue and catharanthine as candidates with strong binding affinities to multiple viral proteins [62].

DR efforts have also targeted conserved orthopoxvirus proteins involved in host cell interactions and viral DNA replication, alongside computational approaches [13,38,62]. During recent outbreaks, the anti-smallpox medication tecovirimat was repurposed to treat Mpox because it has already been demonstrated to block MPXV replication. Other drugs, including nucleoside/nucleotide analogs such as cidofovir and brincidofovir, have shown antiviral activity against MPXV by chain termination or inhibition of viral DNA polymerase, thereby blocking replication [86,87]. Furthermore, atovaquone and molnupiravir may be able to target the MPXV post-entry processes, according to a recent study on their activity. When combined with tecovirimat, mathematical models indicate that the virus will be significantly cleared [88]. This further highlights how combinatorial treatment can improve antiviral effectiveness. While several repurposed medications show promise, issues such as resistance, toxicity, and the need for more precisely targeted treatments remain. Nitroxoline, an antibiotic with antiviral activity, shows effectiveness against MPXV and retains efficacy against tecovirimat-resistant strains, making it a promising combination therapy option [11,88]. There is potential for the creation of new antivirals through the investigation of novel druggable targets (Table 2), such as those found through proteomics and protein–protein interaction (PPI) networks [37,38,82]. Medications such as fostamatinib, trilostane, and raloxifene suppress host and viral proteins essential for MPXV replication [26]. Combating MPXV and preparing for future outbreaks requires a combination of *in silico* predictions, experimental validation, and strategic DR.

Table 2. Repurposed Drug Candidates for MPXV Therapy identified through in silico methods.

Drug Name	Original Indication	Target Protein in MPXV	Mechanism of Action	Computational Method Used	In Vitro/In Vivo Evidence	Potential Benefits	Limitations/Challenges	Refs
Adalimumab	Rheumatoid arthritis	TNF- α (host)	Reduces inflammation and viral pathogenesis	Network-based approach	Computational analysis suggests anti-inflammatory benefit	Well-studied immune modulator	May not directly inhibit viral replication	[38,89]
Atovaquone	Antimalarial	D13L capsid protein	Inhibits viral assembly by targeting structural proteins	Molecular docking, MD simulations	In vitro inhibition of poxvirus replication	FDA-approved, well-tolerated	Requires further clinical validation	[90]
Baricitinib	Rheumatoid arthritis	JAK1/JAK2 (host pathway)	Reduces hyperinflammatory response	Network-based pharmacology	Identified via AI; suppresses MPXV-driven inflammation	FDA-approved immunomodulator	Indirect antiviral activity; risk of immunosuppression	[38]
Batefenterol	Chronic Obstructive Pulmonary Disease (COPD) (β -agonist)	Unknown (Host target)	Modulates immune and inflammatory response	AI-based drug screening	Suggested in silico as host-modulatory agent	Potential host-targeted antiviral strategy	No experimental validation yet	[13]
Batefenterol	COPD	DNA-dependent RNA polymerase	Inhibits viral transcription machinery	Molecular docking, MD simulations	Potential activity suggested by computational studies	High specificity, existing safety profile	Lacks direct antiviral validation	[13]
Brincidofovir	Cytomegalovirus, Adenovirus	DNA Polymerase (D5R)	Inhibits viral DNA polymerization	Virtual screening, docking	In vivo studies show partial MPXV inhibition	Oral bioavailability; lipid-modified for uptake	Gastrointestinal toxicity; mixed clinical efficacy	[62]
Burixafor	Stem cell mobilizer	DNA-dependent RNA polymerase	Inhibits viral transcription	Molecular docking, MD simulations	Predicted inhibition in in silico models	Potential for rapid repurposing	No in vivo validation yet	[13]
Cidofovir	Antiviral (CMV)	Viral DNA polymerase	Inhibits viral DNA synthesis	Molecular docking, MD simulations	Effective against MPXV in vitro and in vivo	Established antiviral, broad-spectrum	High nephrotoxicity risk	[62,91]
Deoxyuridine Analogs	Herpesvirus infections	DNA Polymerase (D5R)	Inhibits viral DNA elongation	Pharmacophore modeling, MD simulations	Strong docking scores & molecular stability	Potential for combination therapy	No in vivo validation yet	[62]
Doxorubicin	Chemotherapy	Viral DNA polymerase	Inhibits viral DNA replication	Molecular docking, MD simulations	Shows inhibition in computational and preliminary in vitro studies	Existing FDA approval, known safety profile	High cytotoxicity limits therapeutic window	[92,93]
Eluxadoline	IBS treatment	DNA-dependent RNA polymerase	Blocks viral transcription	Molecular docking, MD simulations	Identified via computational screening	FDA-approved, potential oral formulation	Lacks clinical validation	[13,94]

Elvitegravir	HIV integrase inhibitor	VP39 / DNA replication complex (putative)	Binds nucleic-acid-processing pockets	Docking (AutoDock/Vina), ADMET filters	None for MPXV wet lab	Known human PK, safety	Off-target risk; needs efficacy data	[61]
Etanercept	Autoimmune disorders	TNF- α (host)	Prevents cytokine overproduction	Network-based approach	Identified as a potential adjunctive therapy	Could reduce MPXV disease severity	May impair immune response to infection	[38]
Fostamatinib	SYK inhibitor (ITP)	VP39 (mRNA cap 2'-O-MTase); host SYK pathway	Interference with RNA capping; host immune modulation	Docking to VP39 (PDB 8CEQ), MD refinement	None specific to MPXV in cited papers	Oral, known safety profile	Off-target immunomodulation; needs MPXV validation	[34,37]
Infliximab	Autoimmune diseases (TNF- α inhibitor)	TNF- α (Host pathway)	Suppresses immune hyperactivation	Protein-ligand interaction networks	Reduces cytokine storm in MPXV cases	Prevents immune overactivation	Potential immunosuppressive side effects	[38]
Infliximab	Autoimmune disorders	TNF- α (host)	Modulates immune response, reducing viral pathogenesis	Network-based approach	Potential benefit in controlling cytokine storm in MPXV cases	Immunomodulatory effects	Risk of immune suppression	[38]
Mefloquine	Antimalarial	D13L capsid protein	Disrupts viral assembly and replication	Molecular docking, MD simulations	Effective against poxviruses in preclinical studies	Long half-life, immune-modulatory properties	CNS side effects limit broad use	[92,95]
Methisazone (Marboran)	Historical anti-pox	Host translation (eIF-2-dependent early protein synthesis)	Inhibits early viral protein synthesis	(historic pharmacology)	Historical prophylaxis/limited efficacy vs. variola/vaccinia in older reports; not used currently	Mechanistic precedent for pox antivirals	Poor efficacy/tolerability; obsolete	[96]
Minocycline	Antibiotic	DNA-dependent RNA polymerase	Inhibits viral transcription	Molecular docking, MD simulations	Computational predictions suggest strong inhibition	FDA-approved, broad antiviral potential	Requires further in vivo validation	[56]
Niclosamide	Anthelmintic	VP37/F13 (envelopment/egress)	Inhibits virion egress by binding F13 pocket (putative)	Structure-based docking to F13/VP37	No MPXV wet-lab signal reported in cited work	Oral, generic, broad antiviral reports	Poor solubility; primarily computational evidence here	[34]
Nitroxoline	Urinary tract infections (UTI)	Thymidylate kinase (TMPK)	Blocks DNA synthesis and viral replication	AI-driven screening, QSAR	In vitro antiviral activity confirmed	FDA-approved; broad-spectrum activity	Requires systemic efficacy validation	[97]
Remdesivir	RdRp inhibitor (Ebola/COVID-19)	MPXV DNA polymerase complex (off-target)	Nucleoside analogue mismatch (unlikely optimal for DNA viruses)	Docking screens	Weak/variable activity vs. orthopox in vitro; no MPXV clinical signal	Known safety; IV	Limited mechanism fit for DNA poxviruses	[41,98]

Ribavirin	Broad-spectrum antiviral	IMPDH/guanosine pools; viral polymerases	Depletes GTP; error catastrophe (RNA-virus-centric)	(mechanistic repurposing)	Limited/variable anti-orthopox effects in vitro; toxicity at doses required	Oral option; cheap	Hemolysis; limited pox efficacy	[98]
Tecovirimat (ST-246)	Smallpox (Orthopoxviruses)	F13L (Envelope protein)	Inhibits viral egress and prevents virion maturation	Molecular docking, MD simulations	FDA-approved; in vitro MPXV efficacy confirmed	Specific to orthopoxviruses; FDA-approved	Resistance mutations (F13L escape variants)	[99]
Tigecycline /Omadacycline	Tetracycline antibiotic	Multi-target: thymidylate kinase, DNA topoisomerase I, F13 (p37)	Binds nucleotide/ATP pockets; blocks DNA synthesis/egress (putative)	Multi-target docking, MM-GBSA rescoring, MD	No MPXV wet lab in cited study	Multi-site binding; favorable docking energies	IV use; antibacterial AEs; translational gap	[56]
Tilorone	Antiviral (Influenza)	Viral helicase	Disrupts viral genome processing	Molecular docking, MD simulations	Computationally predicted to inhibit MPXV replication	Broad-spectrum antiviral, immune modulating	Requires further in vivo and clinical testing	[100]
ZINC22060520	Not approved (In silico lead)	JAK1	Targets host immune pathways	Pharmacophore modeling, MD simulations	Strong binding affinity in MD simulations	Novel candidate with high specificity	No clinical validation yet	[38]

5.2. Immunomodulatory Drugs for Symptom Management

Immunomodulatory drugs are at the forefront of the DR approach, especially when it comes to addressing the symptoms and immune responses associated with MPXV infection [98]. Tecovirimat and Brincidofovir have demonstrated limited efficacy in treating Mpox, highlighting the urgent need for novel therapeutic strategies [101]. Recent studies have identified potential candidates through diverse DR efforts targeting viral proteins such as envelope proteins, DNA polymerase, and thymidylate kinase [13]. These drugs have the potential to modulate the immune system effectively, providing an alternative method of managing the immune dysregulation seen in Mpox infections [13,24,34]. Immunomodulatory compounds with antiviral properties, such as polyphenols and isoquinoline alkaloids, may reduce disease severity, particularly in immunocompromised individuals [102].

The expanding research on immunomodulatory drugs for Mpox underscores the central role of the immune system in MPXV pathophysiology, as poxviruses such as the MPXV disrupt key mediators, including interleukins, interferons, and tumour necrosis factors [103]. This results in immunological suppression and an accelerated viral replication cycle. By focusing on essential viral enzymes such as thymidine kinase and DNA Topoisomerase I, polyphenolic drugs such as rosmarinic acid and resveratrol have been shown in recent research to suppress MPXV and other poxviruses [102]. By regulating immune responses and preventing viral replication, these bioactive ingredients have the potential to be used as supplemental medicines for symptom control [102,103]. Their anti-inflammatory and antioxidant properties may reduce infection-induced inflammation and improve outcomes, especially in immunocompromised patients prone to severe disease [102,103].

Recent computational and network-based approaches have identified 268 drug candidates, including bioactive compounds, with potential activity against Mpox [82,104]. These candidates were selected for their ability to interact with viral proteins involved in immune regulation [104]. Network medicine has enabled the discovery of immunomodulatory agents targeting key immune hubs, which may prevent MPXV-driven immune disruption [105]. Repurposing such agents could be critical not only for Mpox therapy but also for managing co-infections and associated immunological complications [24,98]. Researchers can accelerate Mpox treatment development by repurposing existing drugs, particularly for vulnerable populations such as individuals with HIV or other immunocompromising conditions.

5.3. Drugs Targeting Mpox-Specific Molecular Pathways

The major viral proteins and enzymes required for the virus reproduction and morphogenesis are the focus of medications that target Mpox-specific biological pathways [18]. Tecovirimat targets the p37 envelope protein, which is essential for the maturation of viruses and the creation of enveloped virions, such as intracellular enveloped virions (IEVs) [18]. By blocking virion release, this protein disrupts the viral life cycle and limits propagation. Additionally, drugs such as brincidofovir target orthopoxvirus DNA polymerase, a key enzyme required for replicating the double-stranded viral genome. However, genetic changes have generated resistance [98]. Methisazone inhibits viral RNA polymerases, which are among the other targets [96,106]. Current antiviral development focuses on targeting replication factors, including thymidine/thymidylate kinases, Abl- and Src-family tyrosine kinases, and key proteases encoded by *I7L* and *G1L* [107]. Cellular kinases and transcription factors drive the Mpox infection process, in addition to viral enzymes and proteins [18]. Multi-omics studies have identified numerous host proteins involved in immune evasion and viral replication, highlighting potential targets for

therapeutic repurposing [108]. Mpox exploits transcription factors, including STAT3 and NF- κ B, and kinases such as ERK1/2, CDK4, and GSK3B, to regulate key cellular functions [34]. FDA-approved kinase inhibitors and steroid hormone receptor agonists have been proposed as repurposing candidates [34]. By modulating host signaling pathways, including Wnt, AP-1, and IFN, these agents may simultaneously inhibit viral replication and enhance immune responses [34]. Interestingly, niclosamide activates antiviral pathways, presenting a potential therapeutic option for Mpox [34]. Researchers have also leveraged the Mpox–human interactome to identify potential therapeutic targets through a comprehensive network-based approach [37,82]. With considerable overlap in proteins linked to immune response pathways, this approach shows that Mpox preferentially targets hubs in the human protein network [70,103]. Repurposing existing drugs to target viral–host protein interactions shows promise, including agents against viral structural proteins A50R and D13L and kinase inhibitors that disrupt key replication pathways [109–111]. Understanding these interactions advances Mpox pathophysiology and guides the translation of candidates into preclinical and clinical evaluation.

6. Preclinical and Clinical Evaluation of Repurposed Drugs

6.1. *In Vitro and In Vivo Studies on Drug Efficacy*

Developing effective therapies for emerging infections such as MPXV requires preclinical and clinical evaluation of repurposed drugs. Candidates include agents effective against other Orthopoxvirus members [112]. TPOXX®, originally developed for smallpox, remains highly effective against circulating MPXV strains in vitro and in vivo, including CAST/EiJ mouse models [18]. It inhibits viral replication at nanomolar concentrations and significantly reduces tissue viral titers, supporting its use in the current outbreak [113]. DNA replication inhibitors cidofovir and its prodrug brincidofovir also show broad-spectrum activity against orthopoxviruses in multiple animal models [105]. Mefloquine, a long-acting antimalarial with known neuropsychiatric and cardiac risks, demonstrated antiviral activity against MPXV clade Ib in foci-reduction assays ($IC_{50} \approx 0.51\text{--}5.2 \mu\text{M}$) and docking studies predict engagement with polymerase and envelope-associated proteins, indicating both direct and host-mediated effects [114]. Minocycline, a tetracycline antibiotic ($t_{1/2} \sim 11\text{--}22 \text{ h}$) with anti-inflammatory properties, emerged from docking and network-pharmacology analyses as a binder to MPXV methyltransferases and host kinases, potentially modulating NF- κ B and microglial activation [60]. Whereas mefloquine has corroborating in vitro efficacy, minocycline's activity remains largely computational and requires phenotypic validation in plaque/foci reduction, cytotoxicity, and time-of-addition assays [89,115]. Mefloquine's translational use is limited by its safety profile, long persistence, and drug–drug interaction potential. Minocycline carries pregnancy contraindications and interactions with divalent cations that could restrict use [116]. These medications have a potential for DR in MPXV treatment, which is further supported by their effectiveness in animal models. Even while preclinical research has shown promise, practical applications must carefully consider constraints such as the changing nature of MPXV strains and possible antiviral resistance.

Furthermore, nucleoside/nucleotide analogues (cidofovir, brincidofovir) exhibit broad orthopoxvirus activity in vitro and in animal models but carry dose-limiting host toxicities (notably cidofovir-associated nephrotoxicity and brincidofovir-associated transaminase elevations) that constrain clinical use (FDA Tembexa prescribing information; product labels) [117]. High-throughput in vitro screening and in silico docking/MD pipelines identified repurposed candidates, including nitroxoline, niclosamide, mefloquine, atovaquone, and several kinase inhibitors. These compounds show high predicted binding affinities to MPXV targets (VP39 methyltransferase, DNA polymerase, and host kinases) and exhibit antiviral activity in plaque and foci-reduction assays [114,118].

Tecovirimat represents a promising treatment, reducing viral load and improving patient outcomes, as shown in early clinical studies and compassionate use data [119–121]. Remdesivir, molnupiravir, and ribavirin also exhibit antiviral activity against MPXV, though their efficacy varies, and further studies are needed to assess their full therapeutic potential [98]. Importantly, MD simulations combined with consensus docking have strengthened confidence in ligand–target interactions by reducing false positives, while phenotypic assays (live-virus inhibition, EC_{50} determinations) remain essential, as several candidates with favorable docking scores fail to reach therapeutic levels in cell culture or animal models due to pharmacokinetic limitations (poor bioavailability, high protein binding) or safety concerns [122]. Thus, integrating drug repurposing with in vitro, in vivo, and clinical evaluations is crucial to mitigate MPXV impact.

6.2. Insights from Case Studies and Small-Scale Clinical Trials

Antivirals initially developed for smallpox, including tecovirimat, cidofovir, and brincidofovir, demonstrate activity against MPXV and are under evaluation for treating Mpox, particularly in immunocompromised individuals such as people with HIV (<https://www.cdc.gov/monkeypox/hcp/clinical-care/immunocompromised-people.html>, accessed on 4 October 2025) [15,123]. Tecovirimat is the best-characterized agent, showing robust nanomolar in vitro inhibition and protection in animal models, though clinical outcomes remain heterogeneous [18,124]. Clinical trials and case reports suggest it can reduce viral replication and lesion formation, supported by multicenter registries indicating higher systemic symptoms and lesion incidence in solid organ transplant recipients [31,119,125]. However, many small-scale trials suffer from design limitations and inadequate sample sizes, introducing potential type II errors and underestimating drug efficacy (<https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON522>, accessed on 4 October 2025) [126]. Consequently, there is growing consensus that larger, well-designed studies are required to accurately assess the therapeutic potential of antivirals such as tecovirimat and smallpox vaccines such as JYNNEOS [127].

6.3. Challenges in Scaling Drug Trials for Emerging Viruses

Scaling medication trials for new viruses raises several pressing issues, especially in preclinical and clinical assessments. Emerging infectious diseases, often vector-borne or zoonotic, remain a major public health threat, exacerbated by environmental changes and global trade [128]. The COVID-19 pandemic demonstrated how rapidly novel viral threats can arise, necessitating swift and coordinated efforts in drug research. The rapid development and deployment of treatments within two years revealed key barriers, including the scarcity of high-quality chemical probes targeting poorly characterized viral proteins. Future medication discovery depends on addressing these issues, particularly for newly emerging viruses such as MPXV, whose genetic drift and changing viral dynamics make diagnostics and treatment approaches more difficult [129]. Enhancing the screening of potential antiviral candidates is a critical priority. This requires leveraging omics technologies and computational power to identify and characterize prospective therapies, while emphasizing rational drug design strategies [13,108].

Large-scale clinical trials for emerging viruses face challenges from diagnostic limitations, variable disease presentations, and complexities in drug evaluation [130,131]. Because of its clinical overlap with other illnesses such as varicella, the diagnosis of MPXV is challenging [18,112]. Low inter-rater reliability plagues accurate lesion evaluation, which is crucial for assessing patient outcomes in clinical trials, particularly in areas with limited resources and diagnostic competence [132]. Furthermore, considering the quickly evolving epidemiology, determining important research goals is crucial, as demonstrated by the global comeback of Mpox in 2022. Successful clinical trials and interventions must

ensure equity and inclusivity in developing therapies and vaccines, overcoming logistical and diagnostic obstacles while emphasizing innovative research and public health preparedness against emerging viral threats [125].

7. Limitations and Challenges in Repurposing Drugs for Mpox

In silico models accelerate target identification but face challenges related to data bias, oversimplification of biological complexity, and limited predictive power for dynamic protein-ligand interactions [133]. Furthermore, computational models cannot fully predict pharmacokinetics, off-target effects, or immune responses, necessitating empirical validation.

7.1. Drug–Drug Interactions and Safety Concerns

The network proximity technique, which measures the separation between drug targets on the human interactome and host proteins that Mpox targets, is a significant barrier to finding possible medications [134]. This approach requires further experimental validation, as it cannot distinguish between activation and inhibition or account for dynamic network changes during infection [134,135]. Furthermore, medications found with this static technique may not be effective at every stage of Mpox infection. Applying diverse computational techniques, such as graph convolutional networks and network diffusion algorithms, can provide complementary insights for drug repurposing strategies [37,136]. Access to shelved medications and their trial data is hampered by intellectual property laws and a lack of data openness, which further exacerbates the shortcomings of existing strategies [137,138]. DR still necessitates a substantial financial commitment, estimated to be between hundreds of millions and billions of dollars, while avoiding the expenses of preclinical research [139].

Another significant issue is drug–drug interactions, especially for patients who also have co-infections such as HIV [140,141]. Significant pharmacokinetic variations in tecovirimat exposure between those with and without HIV were found in recent research, including 14 male Mpox patients who were hospitalized. Compared with HIV-negative individuals, people with HIV receiving antiretroviral therapy (ART) showed reduced plasma tecovirimat levels, with minimum and maximum concentrations decreased by 42% and 39%, respectively [141,142]. These variations did not substantially affect clinical results, and all measured drug levels remained above the 90% inhibitory concentration [142]. The study's limitations, including small sample size, single-centre design, and variability in ART regimen, restrict the generalizability of its findings. Variations in food intake and the absence of free plasma tecovirimat concentration measurements further complicate the understanding of pharmacokinetic interactions [40,142]. These findings underscore the need for extensive clinical trials and real-world data to optimize dosing, prevent resistance, and ensure the safe, effective use of repurposed Mpox therapies.

7.2. Addressing Obstacles and Viral Resistance to Repurposed Agents

Although MPXV, a DNA virus, mutates more slowly than RNA viruses, recent outbreaks show accelerated microevolution, likely from APOBEC3-induced mutations. TPOXX® clinical data reveal heterogeneous outcomes and *F13L* resistance mutations during prolonged therapy in immunocompromised patients [143,144]. According to reports, the EC₅₀ values of resistant variants are 85–230 times higher than those of wild-type isolates [99,145]. Furthermore, tecovirimat's limited efficacy against clade I Mpox and its inability to fully suppress viral shedding underscore the urgent need for alternative therapeutic strategies [134]. Other repurposed drugs, such as cidofovir and brincidofovir, have serious adverse effects that prevent them from being used as supplementary therapies [15,146–148]. These include renal problems and liver toxicity, respectively [15,24].

Additionally, the logistical and legal obstacles related to the use of these medications make it more difficult to guarantee fair access, particularly in areas with limited resources [149,150].

Combination therapy that targets multiple viral and host pathways offers a promising strategy to address these challenges [14,24]. This necessitates a paradigm shift toward combination therapies pairing tecovirimat with brincidofovir or immunomodulatory agents targeting host pathways (JAK-STAT inhibitors). In preclinical investigations, tecovirimat has shown synergistic efficacy against Mpox when combined with MMF or N-myrystoyltransferase (NMT) inhibitors such as IMP-1088 [14]. By raising the genetic barrier to mutations, these combinations increase antiviral effectiveness and reduce the chance of resistance [18,134,146,150]. Clinical studies of NMT inhibitors such as PCLX-001, now in phase II, demonstrate the promise of host-targeted therapies [14]. Combination treatments also reduce the required dosages of individual drugs, lowering associated adverse effects [18,112,134,146]. Implementing such techniques requires robust clinical validation and a determined commitment to expanding access to cutting-edge medicines in both endemic and non-endemic areas.

7.3. Regulatory and Ethical Considerations

Repurposing medications for Mpox faces notable ethical and regulatory challenges. Despite the urgency highlighted by the ongoing multi-country outbreak, gaps remain in understanding transmission dynamics, community-specific effects, and optimal treatment strategies [98,151]. Ensuring the safety and efficacy of vaccines and therapeutics requires robust regulatory oversight and health policy reform. Currently, tecovirimat is accessible for Mpox only under expanded access or compassionate use protocols, necessitating physician registration, informed consent, and continuous data reporting [152]. The WHO recommends using antivirals such as tecovirimat, despite unproven human efficacy, only within clinical trials or under the Monitored Emergency Use of Unregistered Interventions (MEURI) framework, which requires social value, scientific validity, regulatory oversight, informed consent, and contribution to knowledge (<https://www.who.int/teams/health-care-readiness/clinical-management-of-monkeypox>, accessed on 4 October 2025). Moreover, international regulatory bodies, including the International Coalition of Medicines Regulatory Authorities and the European Medicines Agency, emphasize that coordinated global collaboration, harmonized data collection, and large-scale trials are vital for accelerated but evidence-generating approval pathways for Mpox therapies (<https://www.ema.europa.eu/en/news/fostering-regulatory-collaboration-improve-access-mpox-medicines>, accessed on 4 October 2025).

ACAM2000, MVA-BN, and LC16 are the three licensed Mpox vaccines; however, further research must clarify their safety and cross-protection profiles [153]. Vulnerable groups, including children, expectant mothers, and those with impaired immune systems, are disproportionately affected by vaccine shortages and uneven supply chains, which further impede fair distribution (<https://press.un.org/en/2021/sc14438.doc.htm>, accessed on 4 October 2025). Regulatory obstacles such as safety investigations, clinical trials, and authorization procedures delay access and worsen preexisting health inequities [154]. Addressing these ethical and regulatory challenges requires international collaboration to advance vaccine development, strengthen research, and ensure equitable distribution.

8. Future Directions in Mpox Therapeutics

8.1. Integrating Artificial Intelligence and Machine Learning in Drug Repurposing

Mpox therapeutics' future is situated at the nexus of computational DR, machine learning, and artificial intelligence. There is a gap in targeted therapeutics for Mpox, and integrating artificial intelligence and machine learning (AI/ML) in drug development has shown great promise in discovering possible therapeutic molecules [24,94]. Recent advances, such as identifying PPIs during MPXV infection with ensemble-based deep learning algorithms, have enabled the discovery of promising therapeutic targets [37,155]. Research has used molecular docking and dynamic simulation analysis to identify FDA-approved medications such as fostamatinib, cannabidiol, and nicotinamide adenine dinucleotide + hydrogen as viable possibilities [37]. These computational methods reduce side effects and resistance associated with existing drugs such as Tecovirimat, providing a rapid and cost-effective option to repurpose approved medications. Furthermore, ML-powered algorithms, such as support vector machines and convolutional neural networks, have demonstrated high precision in diagnostic applications, using imaging and clinical data for early detection; a crucial aspect of outbreak control [156,157].

Although there are still obstacles to overcome, further research into AI/ML technology is likely to transform the development of Mpox treatments. Persistent challenges that call for cooperative international efforts to standardize data collecting and sharing include data unpredictability and the requirement for sizable, high-quality databases [134,158]. Thorough clinical studies of repurposed therapies, supported by equitable funding and infrastructure, are essential to address drug resistance and safety concerns. AI-driven, data-informed approaches enable the development of effective antivirals and establish a robust framework for tackling emerging infectious diseases.

8.2. Advancing Combination Therapies and Technologies for Enhanced Efficacy

Future directions in Mpox therapeutics emphasize the urgent need to develop combination therapies, integrating insights from virus–host interactions, viral evolution, and innovative treatment strategies. Identifying effective treatment targets requires understanding the MPXV lifecycle and immune evasion strategies, such as its use of the endoplasmic reticulum as replication factories [112]. The discovery of host components exploited by MPXV through high-throughput screening now enables deeper investigation into viral replication and immune evasion pathways [13]. The emergence of novel lineages, such as IIb C.1, underscores the need for genomic monitoring to track recombination events that drive genetic diversity and immune evasion [13,159,160]. The development of specific antiviral treatments while reducing resistance can be guided by cooperative research into immunomodulatory genes, which influence virus fitness and host immune responses.

The future of Mpox therapy is being shaped by cutting-edge biotechnological techniques, including treatments based on nanotechnology. Through dose-dependent inhibitory effects, nanoparticles such as silver nanoparticles have demonstrated potential in lowering MPXV infectivity [161]. By improving the physicochemical characteristics of antivirals at the nanoscale, these treatments can provide more precise administration and better pharmacokinetic profiles [161,162]. Furthermore, accurate medication design with fewer side effects and resistance is made possible by bioinformatics-driven biomarker-based therapeutics [163]. Incorporating computational models into drug development pipelines can optimize treatment strategies by predicting resistance mutations and enhancing antiviral efficacy. Early diagnosis and outbreak control require advanced diagnostics and expanded genomic surveillance [164,165].

8.3. Establishing Global Networks for Collaborative Research

Prospects for Mpox treatments necessitate the creation of international networks to support cooperative research, especially considering the 2024 outbreak that has affected 15 African countries, leading to more than 6,201 confirmed cases and 32 fatalities in just eight months (https://cdn.who.int/media/docs/default-source/documents/emergencies/20240922_mpox_external-sitrep_-37.pdf?download=true&sfvrsn=1c5db9d1_1, accessed on 4 October 2025). The need for fair cooperation between high- and low-income nations is highlighted by notable research gaps in epidemiology, genetic monitoring, and localized health systems. In the past, the United States has spearheaded global research initiatives, collaborating with endemic areas such as the Democratic Republic of Congo (<https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON522>, accessed on 4 October 2025) [166]. The prominence of African researchers in leadership roles underscores the need to support indigenous scientists. Strengthening such networks, as shown during COVID-19, can accelerate vaccine delivery, enhance real-time data sharing, and improve genomic surveillance of viral evolution.

The Africa Centers for Disease Control and Prevention (CDC) and the WHO are leading the continent's response, which includes a \$0.6 billion Mpox Continental Preparedness and Response Plan that prioritizes strong health infrastructure, equitable resource distribution, and regional leadership (<https://africacdc.org/download/mpox-continental-preparedness-and-response-plan-for-africa/>, accessed on 4 October 2025). Reducing reliance on outside sources requires investments in domestic production capacities for medications, vaccines, and diagnostics. Although recent advances, such as the WHO prequalification of a new Mpox vaccine in 2024, show promise, they require improved accessibility and scalable production. Equipping African scientists with the tools to implement context-specific, sustainable solutions will build long-term resilience and enable the continent to manage public health crises more effectively.

9. Conclusions

Recent advances in repurposing existing drugs against the Mpox virus (MPXV) underscore the urgent need for innovative yet pragmatic therapeutic strategies against this re-emerging zoonotic threat. The high genetic similarity between MPXV and variola virus, along with MPXV's rapid adaptation via mutations in immune evasion and transmissibility genes, underscores the need to leverage safe, well-characterized therapeutics. Promising candidates such as tecovirimat, brincidofovir, nitroxoline, and deoxyuridine analogues, alongside host-directed immunomodulators such as baricitinib and infliximab, illustrate the therapeutic potential of repurposing pipelines. Integration of computational approaches, including molecular docking, pharmacophore modelling, and AI-enhanced structural predictions, has accelerated target identification and candidate prioritization, complementing experimental validation and offering affordable alternatives to conventional antiviral discovery. These developments establish a tiered drug discovery framework, where computational screening, in vitro and in vivo validation, and controlled clinical trials work in synergy to rapidly expand therapeutic options for Mpox.

Despite these advances, significant translational and implementation challenges remain. Repurposed drugs must overcome pharmacokinetic limitations, tissue penetration barriers in systemic and cutaneous disease, and variable efficacy across MPXV clades, as seen in clinical trials such as PALM007. Bridging these gaps demands integrating preclinical-to-clinical pipelines that monitor resistance, test host-directed and combination regimens, and incorporate ADME/Tox profiling early. Future Mpox preparedness should therefore focus on expanding computational-experimental integration, employing organ-on-chip systems, CRISPR-based functional genomics, and Cryo-EM structural validation to enhance translational accuracy. Parallel innovations in vaccines, diagnostics, and

equitable access strategies, particularly in under-resourced endemic regions, will be essential to global resilience. Ultimately, successful Mpox DR depends on coordinated international collaboration, harmonized regulatory frameworks, and robust One Health strategies that simultaneously target human, animal, and environmental reservoirs of infection.

Author Contributions: Conceptualization—A.G.-A.M.; writing—original draft preparation, A.G.-A.M.; writing—review and editing, A.G.-A.M. and D.D.M.; supervision, D.D.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Authors acknowledge Samuel Chima Ugbaja, Tambwe Willy Muzumbukilwa, Mukanda Gedeon Kadima and Nonjabulo Ntombikhona Magwaza for reading and correcting the final version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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