

## Review

# Natural Product-Based Drug Discovery for Monkeypox Virus: Integrating In Silico Approaches and Therapeutic Development Strategies

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## Abstract

The global spread of Monkeypox virus (MPXV) has emerged as a major public health concern, with the 2022 outbreak underscoring the urgent need for effective antiviral therapies. Current treatment options are limited because no drugs specifically target Mpox, and existing recommendations rely on repurposed smallpox antivirals that may cause resistance. This highlights the critical need for novel therapeutic agents targeting key viral and host factors involved in MPXV pathogenesis. Medicinal plants provide a rich reservoir of bioactive compounds with potential antiviral activity, particularly in low- and middle-income countries where they play an essential role in healthcare. To address this issue, we conducted a review exploring innovative in silico approaches for natural product-based drug discovery against MPXV. Computational studies identified phytochemicals such as curcumin, punicalagin, rosmarinic acid, and quercitrin with strong affinities for key viral proteins including DNA polymerase, TMPK, DdRp, A42R, MTase, p37, and envelope proteins and favorable pharmacokinetic profiles. Despite these promising findings, fragmented biological datasets, viral mutability, and limited in vitro and in vivo validation hinder clinical translation. Our analysis highlights integrating AI-driven virtual screening with experimental validation to accelerate MPXV drug discovery, providing a scalable framework for managing emerging viral threats.

**Keywords:** monkeypox virus; plant-based therapeutics; antiviral drug repurposing; in silico drug discovery; molecular docking; ADMET



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## 1. Introduction

The zoonotic double-stranded DNA monkeypox virus (MPXV), belonging to the *Orthopoxvirus* genus of the *Poxviridae* family [1], re-emerged as a significant global health threat during the 2022 outbreak, spreading across more than 110 countries and causing over 84,000 confirmed cases by early 2023. Previously endemic to Central and West Africa, MPXV is now recognized as a global hazard, prompting the World Health Organization (WHO) to declare it a public health emergency [1,2]. The virus comprises two major clades, Clade I (Central African) and Clade II (West African), which differ in their virulence and case fatality rates. Transmission occurs through direct contact with lesions, respiratory droplets, body fluids, or contaminated surfaces. Recent outbreaks have further underscored the risk of sustained human-to-human spread, particularly within high-risk groups [3]. Clinically, Mpox manifests with fever, rash, and lymphadenopathy, and in severe cases can

progress to life-threatening complications such as encephalitis, pneumonia, and secondary infections [4,5].

Although global awareness has increased, effective therapeutic options remain limited. Current pharmacological management relies primarily on antivirals originally developed for orthopoxviruses, including tecovirimat (TPOXX<sup>®</sup>, a VP37/F13L inhibitor) and nucleotide analogs such as cidofovir and brincidofovir, which demonstrate nanomolar to micromolar inhibition in vitro and reduce viral titers in animal models [6]. However, clinical outcomes have been variable, and their use is constrained by high costs, limited accessibility, and waning orthopoxvirus immunity in the general population [7]. Vaccines such as ACAM2000 and JYNNEOS provide partial protection but face challenges in coverage and deployment. In addition, several viral proteins, including methyltransferase (MTase) and thymidylate kinase (TMPK), which are critical for immune evasion and replication, remain underexploited as therapeutic targets [7,8]. Furthermore, the complexity of viral–host interactions and research infrastructure gaps hinder the rapid development of targeted antivirals [9]. These limitations underscore the urgent need for innovative and cost-effective therapeutic strategies.

Natural product-based drug discovery is gaining momentum as a potential complementary avenue in Mpox management. Emerging *in silico* and *in vitro* evidence identifies phytochemicals, such as polyphenols (curcumin, kaempferol, myricetin), bioflavonoids (amentoflavone), phlorotannins (dieckol), and glycosides (theasinensins, kaempferol-O-rhamnosides), with strong binding affinities toward key MPXV targets, including D13, F13/VP37, I7L protease, VP39 MTase, and the DNA polymerase complex [8]. High-throughput virtual screening of phytochemical libraries such as the IMMPAT, has identified top candidates with docking scores and binding energies comparable to, or even surpassing, reference antivirals. Molecular dynamics (MD) simulations further confirm the stability of these ligand–protein interactions, positioning natural compounds as credible scaffolds for lead optimization [8]. Several potential inhibitors have been reported, including folic acid, punicalagin, and CID40777874, which target MTase and TMPK with favorable docking and stability profiles [10]. Nonetheless, many remain at the preclinical stage due to pharmacokinetic limitations such as poor solubility and low bioavailability, as observed with niclosamide [11]. Strategies including nanocarrier systems, hybrid formulations, and advanced absorption, distribution, metabolism, excretion, toxicity (ADMET)-guided optimization are therefore crucial for translation. Broader classes of natural compounds, such as flavonoids, alkaloids, terpenoids, and marine-derived bioactives, consistently demonstrate *in silico* antiviral potential but require standardized evaluation and regulatory pathways before clinical adoption [12].

Drug repurposing of natural products offers a rapid and cost-effective route to therapeutic development. Notably, traditional Japanese Kampo-derived phytochemicals such as oleanolic, ursolic, and glycyrrhizinic acids show strong affinities and stable MD interactions with MPXV enzymes TMPK and DNA-dependent RNA polymerase (DdRp) [13,14]. Repurposing FDA-approved natural derivatives with known safety profiles enhances their translational potential, supporting the integration of natural product-based strategies into Mpox drug discovery, especially in resource-limited, outbreak-prone regions. Previous studies on SARS-CoV-2, Ebola, and other viral pathogens support this strategy, showing that combining docking, QSAR, and structural biology approaches can accelerate lead optimization [6,15–18]. However, researchers must validate *in silico* predictions through *in vitro* and *in vivo* experiments to resolve limitations like toxicity overestimation. This review therefore explores the potential of natural product-based compounds and recent advances in computational screening, pharmacokinetic prediction, and translational strategies for natural antivirals. By highlighting structural insights, *in silico* evidence, ADMET-guided

validation, and therapeutic development prospects, this study provides a foundation for harnessing natural scaffolds to combat Mpox and related viral threats.

## 2. Natural Compounds in Antiviral Drug Discovery

### 2.1. Potential of Bioactive Natural Compounds as Antiviral Agents

Recent advances in computational biology and cheminformatics have substantially expanded the landscape of natural product-based drug discovery. These techniques have enabled the systematic screening of diverse plant-derived compounds against essential Mpox viral proteins [19]. Among the leading candidates, curcumin, celastrol, and quercetin consistently demonstrated high stability and multi-target affinities, in several cases surpassing reference antivirals such as tecovirimat and cidofovir [20]. Importantly, curcumin and its derivatives enhance antiviral potential by modulating host pathways (TNF, NF- $\kappa$ B, MAPK), demonstrating polypharmacology and reinforcing their multi-target, broad-spectrum therapeutic promise (see Table 1) [20,21].

Phytochemicals across major classes including alkaloids, terpenoids, and flavonoids block viral entry and suppress Mpox replication [22]. Gallotannin, rosmarinic acid, and gingerol may block viral entry, while *Vernonia amygdalina* bioactives such as luteolin, luteolin-7-O- $\beta$ -glucoside, vernodalol, vernolepin, and vernodalin inhibit key poxvirus proteins [19,23]. Theaflavin binds strongly to the A42R profilin-like protein [19,24], while punicalagin outperformed maraviroc in binding affinity for the E8 viral envelope protein, highlighting its antiviral potential [19].

Beyond individual compounds, high-throughput virtual screening of chemical libraries revealed new bioactive scaffolds with potential antiviral profiles. Aurachin A and soraphinol A showed robust and stable interactions with TMPK, while vaccinol M and galli-cynoic acid F consistently bound to Mpox proteinases, suggesting durable inhibition [25–27]. Polyphenols like dieckol, isoquinoline alkaloids, and compounds from *Plantago lanceolata* and *Zingiber officinale* inhibit viral serine/threonine kinases and proteases [19,22,28,29].

**Table 1.** Non-exhaustive list of common natural compounds derived from plants with reported potential as antiviral agents.

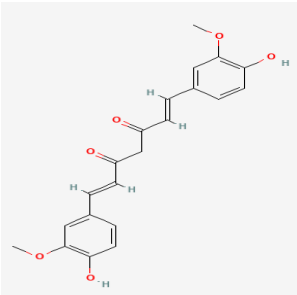
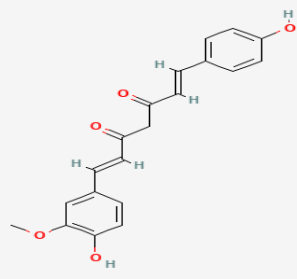
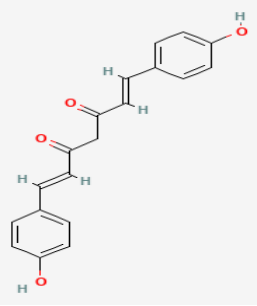
| Natural Compound and Chemical Structure                                                                                               | Plant Source                    | Molecular Target                                                                        | Antiviral Activity                        | Other reported Therapeutic Indications/Benefits                                                                                                      | Probable Mechanism of Action Against Poxviruses                                                                  | Refs    |
|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|---------|
| <div>Curcumin</div> <div></div>                      | <i>Curcuma longa</i> (Turmeric) | DNA Polymerase, Methyltransferase VP39, A42R Profilin-like Protein, Envelope Protein E8 | Inhibits viral replication                | Anti-inflammatory, Antioxidant, Anticancer, Neurological Health, Cardiovascular Support, Metabolic Disorders                                         | Inhibit viral replication by binding to viral proteins and exhibit antioxidant and anti-inflammatory properties. | [20,30] |
| <div>Demethoxycurcumin (DMC)</div> <div></div>       | <i>Curcuma longa</i> (Turmeric) | DNA Polymerase, Thymidylate Kinase, Profilin-like Protein                               | Potential inhibition of viral activity    | Anti-inflammatory, Antioxidant, Apoptosis Induction, Inhibition of Cancer Cell Invasion, Neuroprotective Effects, Inhibition of Cancer Cell Invasion | Interacts with viral proteins, potentially inhibiting their function                                             | [31]    |
| <div>Bisdemethoxycurcumin (BDMC)</div> <div></div> | <i>Curcuma longa</i> (Turmeric) | Thymidylate Kinase                                                                      | Potential disruption of viral replication | Anti-inflammatory, Antioxidant, Apoptosis Induction, Antimicrobial Activity                                                                          | Contributes to therapeutic efficacy through complementary biological effects.                                    | [30]    |

Table 1. Cont.

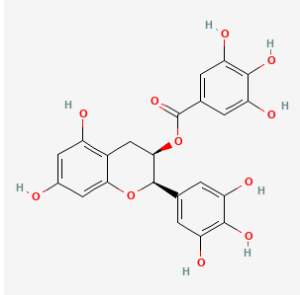
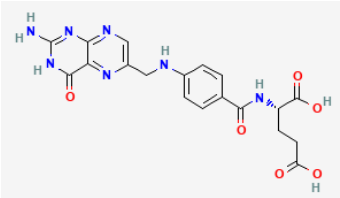
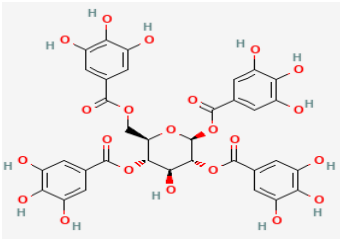
| Natural Compound and Chemical Structure                                                                              | Plant Source                         | Molecular Target                                                              | Antiviral Activity                                                                                     | Other reported Therapeutic Indications/Benefits                                                                                                                         | Probable Mechanism of Action Against Poxviruses                                               | Refs    |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------|
| Epigallocatechin Gallate (EGCG)<br> | <i>Camellia sinensis</i> (Green Tea) | Under investigation<br>(Interact with viral proteins and host cell receptors) | Inhibits viral infections by directly binding to viral particles, preventing attachment to host cells. | modulates various signaling pathways, including the MAPK, PI3K/Akt, and NF-κB pathways, Cancer Suppression, Neuroprotection, Diabetes Management, Cardiovascular Health | Exhibits virucidal effects by binding to viral particles and inhibiting host cell attachment. | [32,33] |
| Folic Acid<br>                      |                                      |                                                                               | Inhibits MTase activity, reducing viral replication                                                    | Essential vitamin for DNA synthesis and repair. Possesses therapeutic potential in neurological disorders, cancer, cardiovascular diseases, and metabolic syndromes.    | Occupies active site of MTase, hindering its interaction with mRNA substrate                  | [34]    |
| 1,2,4,6-Tetragalloylglucose<br>    | Various plant sources                | Methyltransferase (MTase)                                                     | Inhibits MTase activity, reducing viral replication                                                    | Antioxidant, Antimicrobial, Anticomplement Activity, UDP Glucuronosyl-transferase Inhibition                                                                            | Binds to MTase, inhibiting its function                                                       | [34]    |

Table 1. Cont.

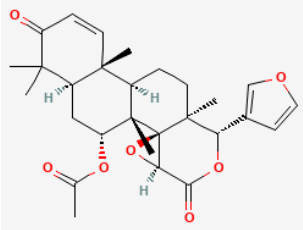
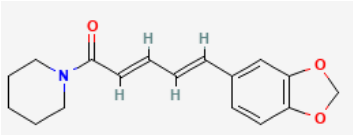
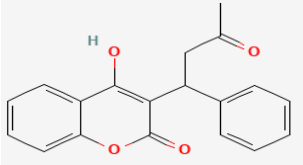
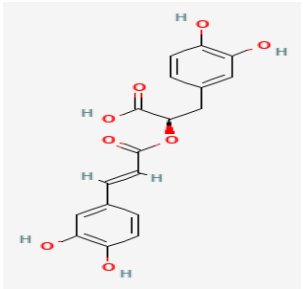
| Natural Compound and Chemical Structure                                                                                     | Plant Source                                                                  | Molecular Target       | Antiviral Activity                        | Other reported Therapeutic Indications/Benefits                                                                                         | Probable Mechanism of Action Against Poxviruses               | Refs    |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------|
| <div>Gedunin</div> <div></div>             | <i>Azadirachta indica</i> (Neem)                                              | Profilin-like Protein  | Potential inhibition of viral replication | Antimalarial, Anticancer (Inhibition of Hsp90, modulates the Shh/Gli signaling pathway), Neuroprotection                                | Binds to profilin-like protein, disrupting its function       | [28]    |
| <div>Piperine</div> <div></div>            | <i>Piper nigrum</i> (Black Pepper)                                            |                        | Potential inhibition of viral replication | Bioavailability enhancer, Anti-Inflammatory and Antioxidant Effects, Blood Sugar Regulation, Cholesterol Management, Cognitive Function | Interacts with profilin-like protein, inhibiting its activity | [28,35] |
| <div>Coumadin (Warfarin)</div> <div></div> | Synthetic derivative of natural compounds                                     |                        | Potential inhibition of viral replication | Anticoagulant                                                                                                                           | Binds to profilin-like protein, disrupting its function       | [22,28] |
| <div>Rosmarinic Acid</div> <div></div>   | <i>Rosmarinus officinalis</i> (Rosemary)/ <i>Salvia rosmarinus</i> (Rosemary) | Various viral proteins | Antiviral activity against poxviruses     | Anti-inflammatory, Antioxidant, Neuroprotective Properties, Anticancer Potential, Cardioprotective Effects, Metabolic Benefits          | Inhibits viral replication through multiple mechanisms        | [36–38] |

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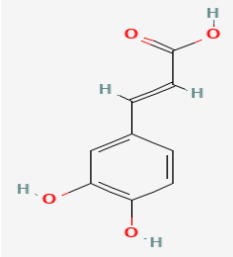
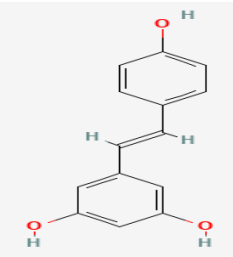
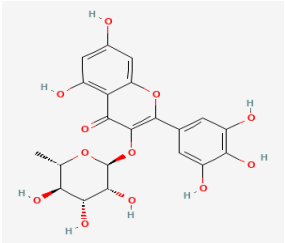
| Natural Compound and Chemical Structure                                                                              | Plant Source                   | Molecular Target       | Antiviral Activity                    | Other reported Therapeutic Indications/Benefits                                                                                        | Probable Mechanism of Action Against Poxviruses        | Refs    |
|----------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------|---------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|---------|
| <div>Caffeic Acid</div> <div></div> | Various plant sources          | Various viral proteins | Antiviral activity against poxviruses | Anti-inflammatory, Antioxidant, Cancer Treatment Adjuvant,                                                                             | Inhibits viral replication through multiple mechanisms | [37]    |
| <div>Resveratrol</div> <div></div>  | <i>Vitis vinifera</i> (Grapes) | Various viral proteins | Antiviral activity against poxviruses | Cardioprotective (Cardiovascular Health), Antioxidant, Metabolic Effects, Anti-Aging and Longevity, Cancer Prevention, Neuroprotection | Inhibits viral replication through multiple mechanisms | [37,39] |
| <div>Myricitrin</div> <div></div>  | Various plant sources          | Various viral proteins | Antiviral activity against poxviruses | Anti-inflammatory, Antioxidant, Neuropharmacological Effects, Inhibition of Nitric Oxide and Protein Kinase C                          | Inhibits viral replication through multiple mechanisms | [38,40] |

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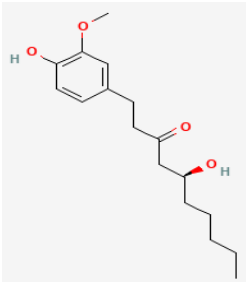
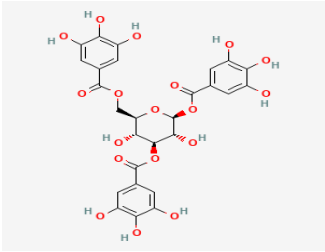
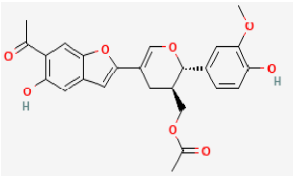
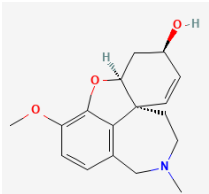
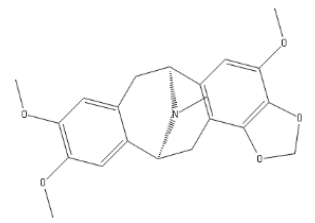
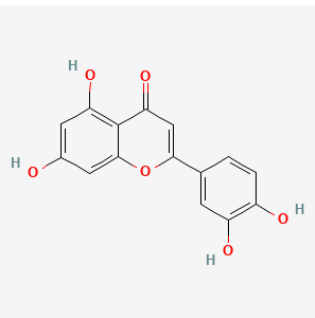
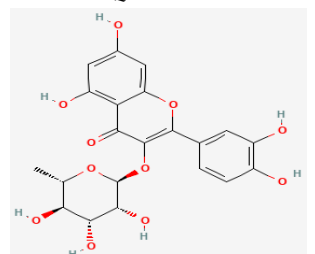
| Natural Compound and Chemical Structure                                                                                   | Plant Source                              | Molecular Target       | Antiviral Activity                    | Other reported Therapeutic Indications/Benefits                                                                                                                                       | Probable Mechanism of Action Against Poxviruses        | Refs       |
|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|------------|
| <div><p>Gingerol</p></div>               | <i>Zingiber officinale</i> (Ginger)       | Various viral proteins | Antiviral activity against poxviruses | Anti-inflammatory and Immunomodulatory Effects, Antioxidant, Anticancer Properties, Neuroprotective Effects, Antimicrobial Activity, Inhibition of Nitric Oxide and Protein Kinase C/ | Inhibits viral replication through multiple mechanisms | [19,41,42] |
| <div><p>Gallotannins</p></div>           | Various plant sources                     | Various viral proteins | Antiviral activity against poxviruses | Antioxidant, Antimicrobial, Anticancer Properties, Anti-inflammatory Action                                                                                                           | Inhibits viral replication through multiple mechanisms | [19,22]    |
| <div><p>Propolis-benzofuran A</p></div> | <i>Apis mellifera</i> (Honeybee Propolis) | Various viral proteins | Antiviral activity against poxviruses | Antimicrobial Photodynamic Therapy, Anti-inflammatory, Cytotoxic Activity,                                                                                                            | Inhibits viral replication through multiple mechanisms | [43,44]    |
| <div><p>Galanthamine</p></div>         | <i>Galanthus</i> species (Snowdrop)       | Various viral proteins | Antiviral activity against poxviruses | Treatment of Alzheimer disease, Vascular Dementia, Cognitive Impairment in Various Conditions, Autism Spectrum Disorders, Organophosphate Poisoning                                   | Inhibits viral replication through multiple mechanisms | [22,45]    |

Table 1. Cont.

| Natural Compound and Chemical Structure                                                              | Plant Source                                            | Molecular Target       | Antiviral Activity                    | Other reported Therapeutic Indications/Benefits                                                      | Probable Mechanism of Action Against Poxviruses                                                                                                                                        | Refs    |
|------------------------------------------------------------------------------------------------------|---------------------------------------------------------|------------------------|---------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| <p>Thalimonine</p>  |                                                         |                        | Antiviral activity against poxviruses | Antimicrobial.                                                                                       | Inhibits viral replication through multiple mechanisms                                                                                                                                 | [22,46] |
| <p>Luteolin</p>     | Various plant sources ( <i>Thalictrum simplex</i> ,...) | Various viral proteins | Potential inhibition of viral entry   | Anti-inflammatory, Antioxidant, Antiviral Activity, Anticancer Potential, Neuroprotective Properties | Modulates various cellular pathways, including inhibition of pro-inflammatory cytokines and enzymes, suppression of cancer cell proliferation, and enhancement of antioxidant defenses | [19,47] |
| <p>Quercitrin</p>  |                                                         |                        | Antiviral activity against poxviruses | Anti-inflammatory, Antioxidant, Cardiovascular protection, antimicrobial properties                  | Inhibits quinone reductase 2 (QR2)                                                                                                                                                     | [48–50] |

## 2.2. Historical Success of Natural Products in Drug Development

Natural products have historically provided direct therapeutics and templates for synthetic derivatives, with over 60% of approved drugs originating from natural scaffolds, continuing to guide antiviral discovery [51]. Iconic discoveries such as penicillin, the prototype antibiotic from *Penicillium notatum*, paclitaxel from *Taxus brevifolia* in cancer therapy, camptothecin derivatives in oncology, cyclosporine as an immunosuppressant and artemisinin from *Artemisia annua* in malaria, transformed the treatment of infectious diseases and cancers [1,7,52]. In the antiviral field, the nucleoside analog cidofovir and its lipid conjugate brincidofovir, whose scaffolds were originally inspired by natural metabolites and remain relevant against orthopoxviruses [53]. Similarly, plant-derived polyphenols, flavonoids, and alkaloids have exhibited inhibitory activity against poxviruses by targeting essential viral enzymes and host immune modulators [54]. Broad-spectrum compounds such as resveratrol and quercetin, originally studied against other viruses, show promise for Mpox therapy, demonstrating the translational potential of natural scaffolds [55].

Despite temporary declines due to synthetic chemistry, the historical trajectory of natural products demonstrates how bioactive scaffolds, once optimized for pharmacokinetics and toxicity, can be successfully translated into frontline therapies. Challenges in the isolation and synthesis of complex molecules temporarily reduced pharmaceutical investment, recent advances have revitalized interest in natural product-based pipelines [56]. As illustrated in Figure 1, modern approaches combine high-throughput screening, bioactivity-guided fractionation, and expansion of virtual natural compound libraries to accelerate lead discovery from complex extracts [57]. A particularly transformative concept is polypharmacology, whereby natural products simultaneously modulate multiple molecular targets, mirroring the multifactorial nature of viral infections and host–pathogen interactions [58]. This systems-level perspective, enhanced by cheminformatics, systems biology, and synthetic biology, not only improves scalability but also expands the therapeutic potential of natural molecules [59].

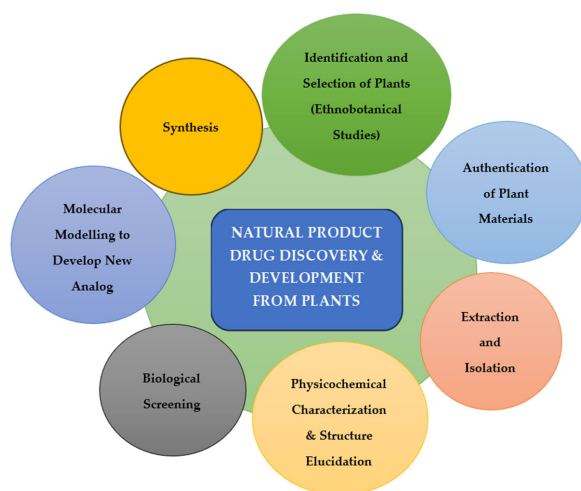


**Figure 1.** Descriptive diagram of major processes in discovering and developing natural products as antiviral agents (adapted from cited source): The bioactive natural compound discovery pipeline follows a systematic, multi-step phytopharmaceutical framework. The process begins with the selection of potential plant sources, often guided by ecological knowledge and ethnobotanical evidence. This step follows with bioactivity-guided extraction and fractionation, which separates crude extracts to isolate fractions with potential biological activity. These fractions undergo biological evaluation to assess their antiviral potential, leading to the identification of lead compounds. Structural elucidation of these leads is achieved using advanced phytochemical and spectroscopic techniques. In silico modeling, docking, and virtual screening are employed to design optimized analogs with improved pharmacokinetic properties, selectivity, and antiviral efficacy [57].

Importantly, the repurposing of smallpox antiviral compounds against MPXV underscores the utility of exploiting conserved orthopoxvirus pathways [7,30]. Beyond direct antiviral action, natural products are increasingly recognized as adjuvants in vaccines and synergistic partners in combination therapies [7]. Together, these advancements show how integrating traditional knowledge, computational innovation, and pharmacological validation positions natural products at the forefront of biomedical innovation and sustains their relevance against emerging viral threats [60].

### 2.3. Existing Evidence of Natural Compounds with Antiviral Activity Against Poxviruses

Polyphenolic compounds such as curcumin, rosmarinic acid, caffeic acid, resveratrol, quercitrin, and myricitrin show strong antiviral activity against poxviruses by targeting key proteins involved in replication and immune evasion [22,61]. These natural products inhibit critical components including DNA topoisomerase I (TOP1), thymidine kinase, serine/threonine protein kinase (Ser/Thr kinase), and protein A48R, thereby suppressing the viral activity. Virtual screening of natural compounds libraries against the DNA-dependent RNA polymerase of poxviruses identified top hits with binding energies comparable to the physiological nucleotide GTP [61,62]. Network pharmacology and docking studies show that curcumin acts as a multi-target antiviral, surpassing cidofovir in binding strength while modulating host NF- $\kappa$ B and MAPK pathways [20].

Beyond individual compounds, plant-derived bioactive extracts have also demonstrated broad-spectrum activity against MPXV, vaccinia, variola, buffalopox, fowlpox, and cowpox viruses. Prominent examples include *Guiera senegalensis*, *Larrea tridentata*, *Sarracenia purpurea*, *Kalanchoe pinnata*, *Zingiber officinale*, *Quercus infectoria*, *Rhus chinensis*, *Prunella vulgaris*, *Salvia rosmarinus*, and *Origanum vulgare* [22]. Complementary evidence comes from chemical scaffolds such as diphenyl ether-based compounds, which inhibited vaccinia virus in vitro [24], and terameprocol, a natural antioxidant with anti-inflammatory properties, which significantly reduced viral production in cowpox and vaccinia infections [63]. Further docking analyses reported that kaempferol and piperine exhibited good activity against the A42R profilin-like protein [29]. Triterpenes such as madecassic acid and maslinic acid form stable hydrogen, hydrophobic, and  $\pi$ - $\pi$  interactions, demonstrating potent inhibition of viral enzymes and modulation of host immune pathways [64].

## 3. In Silico Strategies for Drug Repurposing in Mpox

Structure-based drug design, molecular docking, MD simulations, network pharmacology and AI assisted pipelines have revolutionized Mpox drug repurposing by enabling rapid, cost-effective screening of FDA-approved drugs, phytochemicals, and natural product libraries [29,65,66]. These computational approaches have identified high-affinity inhibitors targeting key MPXV proteins, including DNA-dependent RNA polymerase (E9L), DNA polymerase, TMPK, I7L protease, cysteine proteinases, and the E8L envelope protein [7,56,66]. Beyond conventional docking, AI-driven pipelines integrating deep learning, pharmacophore modeling, and host-virus protein-protein interaction (PPI) networks have identified isoquinoline alkaloids and polyphenolics that inhibit viral replication and modulate host immune pathways [67]. Importantly, the integration of ADMET filtering and blood-brain barrier (BBB) predictions has streamlined prioritization of leads with favorable pharmacokinetic properties [68].

Recent advances have expanded the computational repertoire for MPXV drug discovery. AlphaFolds2-based structural modeling has resolved previously uncharacterized MPXV proteins such as the I7L, M1R, A29, L1R, H3L, E8L, A29, M1R, A35, B6R and L1R, unlocking new docking-ready targets [69]. Large-scale virtual screening of natural product-derived libraries has also revealed potential leads, such as TCM26463 and

SANC00984 against TMPK, which maintained exceptional stability across extended MD trajectories [42]. Similarly, network-based drug repurposing strategies shortlist 23 low-toxicity candidates out of 268 predicted compounds, highlighting the scalability of integrative computational workflows [59]. Pharmacokinetic modeling further strengthens translational relevance by identifying candidates with drug-likeness, high gastrointestinal absorption, non-carcinogenicity, and compliance with Lipinski's rule of five (RO5) [66]. Coupling these insights with QSAR modeling, PPI networks, and advanced machine learning algorithms (such as random forest, support vector machines, and deep learning) have accelerated hit-to-lead optimization [70].

Polypharmacological behavior offers therapeutic breadth and increases the resistance barrier, though it necessitates careful mechanistic validation using proteomics and resistance-selection studies. To further expand candidate space, the Bayesian-based Prediction of Activity Spectra for Substances (PASS) has emerged as a versatile tool, prioritizing antiviral compounds from simple 2D structural inputs [71]. PASS predicted the antiviral and immunomodulatory potential of flavonoids such as myricetin and kaempferol-O-rhamnosides, later confirmed by docking and MD simulations showing stable binding to MPXV proteins D13 and E8L [71]. Likewise, PASS highlighted curcumin's multi-target activity, which was experimentally supported by docking analyses against both viral enzymes and host immune mediators. PASS also prioritizes compounds with drug-like properties, Lipinski's RO5 compliance, and favorable ADMET profiles, providing a strategic filter to accelerate experimental validation [72].

## 4. Molecular Docking and Binding Affinity

### 4.1. Identifying Key Monkeypox Viral Proteins as Therapeutic Targets

Structural modeling and validation identify the DNA polymerase holoenzyme and MTase as key enzymes essential for viral DNA synthesis, mRNA capping, and propagation [7,73,74]. TOP1, a conserved enzyme with limited similarity to human homologs, has also been identified as a selective antiviral target, offering opportunities to minimize host off-target toxicity [38]. Similarly, TMPK, an essential enzyme essential in pyrimidine nucleotide metabolism, has emerged as a potential candidate to disrupt viral DNA synthesis [7]. Structural analyses of accessory viral proteins, including A42R and envelope proteins (E8, D13, A26), reveal distinct binding pockets and key residues suitable for therapeutic targeting [19,20,24].

Network pharmacology and QSAR modeling expand druggable MPXV targets, notably viral proteinases, cysteine proteases, and the F13 (p37) envelope protein critical for viral assembly and egress [27]. High-throughput screening of natural product libraries, integrated with advanced MD simulations, has highlighted several stable and the stability and high-affinity binding natural ligands [27,38]. Importantly, polypharmacology-based strategies such as co-targeting p37, TMPK, and TOP1 are being explored to reduce the likelihood of resistance that often arises with single-target inhibitors [10].

Despite this progress, a persistent challenge lies in the drug-likeness limitations of natural products, many of which possess high molecular weights, elevated polarity, or rapid metabolic degradation. Researchers investigate formulation strategies, nanocarriers, prodrugs, semi-synthetic modifications, and topical delivery to enhance bioavailability and pharmacokinetic stability [75]. As illustrated in Table 2, classes of natural compounds, including flavonoids, alkaloids, terpenoids, and nucleoside analogs, often act through multi-mechanistic pathways, directly inhibiting viral proteins while also modulating host immune responses. This dual mechanism not only broadens the antiviral spectrum but also raises the genetic barrier to resistance [76]. However, such mechanistic complexity complicates safety profiling and target deconvolution, necessitating integrative approaches

such as chemical genetics, resistance selection sequencing, and proteomics-based analyses to elucidate precise modes of action.

**Table 2.** Ligand–target interactions for natural product–based compounds in MPXV drug discovery.

| Compound Class                            | Representative Natural Compounds                 | Putative MPXV Viral/Host Targets                                                | Proposed Mechanism of Interaction                                                                                                     | Evidence Level (Typical)                                                                               | Translational Notes/Limitations                                                                                                                                   | Refs    |
|-------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Flavonoids                                | Amentoflavone, Quercetin derivatives, Rutin      | Viral proteases (I7L), VP39 methyltransferase, envelope/attachment factors (E8) | Direct binding to catalytic or substrate pockets → inhibition of proteolysis or methylation; also host-kinase modulation (MAPK/NF-κB) | Mostly in silico docking + MD; occasional orthogonal in vitro antiviral assays in related poxviruses   | Exhibit high polarity, poor oral bioavailability, and rapid metabolism. Require formulation (nanocarriers) or semi-synthetic optimization.                        | [38,77] |
| Alkaloids                                 | Catharanthine, Harmine-type analogs              | I7L protease, structural proteins (D13L), host kinases                          | Occupy protease active sites or allosteric pockets; some show predicted multi-target binding to host factors that virus co-opts       | In silico docking/MD with some cross-study consensus; limited phenotypic follow-up                     | Exhibit potential cytotoxicity at high doses, interact with P-glycoprotein, and cause drug–drug interactions; require cytotoxicity and pharmacokinetic profiling. | [22,38] |
| Polyphenols/Tannins                       | Punicalagin, EGCG (epigallocatechin gallate)     | Envelope/attachment proteins (E8), entry mediators, viral surface proteins      | High-affinity surface binding that can block attachment/entry; may also chelate metal cofactors                                       | In silico + some in vitro viral inhibition (plaque/foci assays) in related viruses                     | Very polar, large MW → poor systemic exposure; topical or localized delivery may be more practical.                                                               | [32,46] |
| Phenolic acids                            | Rosmarinic acid, Caffeic acid derivatives        | Host signaling hubs (STAT3, NF-κB), viral envelope proteins                     | Modulate host inflammatory pathways and may indirectly reduce viral replication; predicted binding to envelope proteins               | In silico + supporting literature on host modulation (limited direct MPXV phenotypic data)             | Anti-inflammatory benefit may reduce immunopathology but not a direct antiviral; ADME optimization needed.                                                        | [22,78] |
| Naphthodianthrones/Photoactive polycycles | Pseudohypericin, Hypericin-like                  | Multi-target binding (VP39, F13L/VP37, polymerase interfaces)                   | Predicted stable binding to several viral proteins; photodynamic activity reported for related viruses                                | In silico docking/MD; known antiviral activity in other viruses (photoactivated) but MPXV data limited | Phototoxicity and formulation challenges; safety concerns require careful evaluation.                                                                             | [62,79] |
| Terpenoids/Triterpenes                    | Betulonic acid derivatives, Ursolic acid analogs | Viral envelope maturation factors, host membrane processes                      | Disrupt membrane fusion/egress by interacting with viral envelope proteins or host lipid pathways                                     | In silico + some cell-based assays against enveloped viruses                                           | Low water solubility; chemical modification or nanoparticle delivery often required.                                                                              | [22,46] |
| Stilbenoids & Resveratrol-type            | Resveratrol, Pterostilbene                       | Host factors (SIRT, NF-κB) and putative weak binding to viral enzymes           | Host-directed immunomodulation and modest direct inhibition predicted against replication/minor viral enzymes                         | In silico + broad antiviral literature; limited direct MPXV phenotypic validation                      | Rapid metabolism and low plasma exposure; prodrugs or sustained-release formulations may help.                                                                    | [39,80] |
| Coumarins & other phenolics               | Esculetin, Scopoletin                            | Viral decapping enzymes (D9), replication-associated proteins                   | Predicted competitive binding to enzyme active sites, possible synergy with nucleoside analogs                                        | In silico with occasional MD refinement                                                                | Moderate drug-likeness; further target deconvolution and ADME profiling needed.                                                                                   | [22,30] |

#### 4.2. Docking Natural Compounds Against Viral Proteins

Recent studies have demonstrated that molecular docking serves as a powerful in silico tool to predict interactions between natural compounds and Mpox viral proteins. By targeting critical enzymes, phytochemicals can disrupt replication and viral entry. Phytochemical compounds bind strongly, often surpassing standard antivirals in docking performance [20]. Large-scale screening of COCONUT, SANCDB, IMMPAT, and Traditional Chinese Medicine (TCM) libraries identified antiviral compounds with strong binding to DNA-dependent RNA polymerase, a key viral transcription enzyme [25,81]. Gallicynoic acid F and H<sub>2</sub>-Erythro-Neopterin strongly inhibited MPXV proteinase, with binding free energies of −61.42 and −61.09 kcal/mol, respectively, surpassing the benchmark TTP-6171 [27,82]. Additionally, folic acid and 1,2,4,6-tetragalloylglucose derived from Middle Eastern medicinal plants exhibited robust docking scores and MM/GBSA free energies (−51.87 and −60.61 kcal/mol), with MD simulations confirming their stable interactions with MTase, surpassing the controls (TO1119 at −35.71 kcal/mol and sinefungin at −31.51 kcal/mol) [34].

Beyond polymerases and proteases, docking approaches have extended to envelope proteins and accessory proteins, further expanding the therapeutic landscape of natural products. Using state-of-the-art machine learning techniques, high-throughput virtual

screening methodology of potent natural compounds on envelope proteins A36R and F13 identified antiviral peptides and polyphenols, including myricetin and demethoxycurcumin, forming stable complexes with binding energies of  $-6.1$  to  $-9.8$  kcal/mol, supported by Glide SP, XP, RMSD and MM/GBSA analyses [40,83]. Similarly, piperine and kaempferol exhibited binding affinities of  $-5.57$  and  $-6.98$  kcal/mol, respectively, against A42R profilin-like protein. They gave best-pose ligand-binding energies in selected six phytochemicals found in the medicinal plant *Ficus religiosa* (abundant in India) [29]. In addition, advanced screening pipelines identified compounds such as comp289, comp295, comp441, and comp449, with binding affinities ranging from  $-10.79 \pm 4.49$  to  $-17.06 \pm 2.96$  kcal/mol, values comparable to physiological ligands of DNA polymerase [62]. These findings highlight the versatility of bioactive natural compounds as multi-target inhibitors, capable of modulating diverse viral proteins.

#### 4.3. Evaluating Binding Affinity and Interaction Mechanisms

Computational studies have been indispensable in elucidating the binding affinities and interaction mechanisms of natural compounds against key MPXV proteins. An integrated library of 4103 natural products was screened via Glide docking among which rosmarinic acid, myricitrin, quercitrin, and ofloxacin showed MM/PBSA binding energies down from  $-9.40$  kcal/mol to  $-16.18$  kcal/mol and dissociation constants of  $2.16$ – $5.46$   $\mu$ M against viral DNA TOP1 [38,84]. These compounds are engaged with TOP1 residues (TYR274, LYS167, GLY132, LYS133, etc.). TYR274 was predicted to be a pivotal via hydrogen bonds, hydrophobic contacts, and water-mediated bridges, enhancing complex stability [38].

Beyond TOP1, the I7L protease, an essential enzyme in viral maturation, has been highlighted as a particularly potential antiviral target [5]. Leveraging structural predictions generated and refined by AlphaFold2, researchers have achieved high-confidence models suitable for virtual screening campaigns [81,85]. Benchmark docking studies with the known inhibitor TTP-6171 (control) revealed multiple stabilizing interactions, including hydrogen bonds and hydrophobic as well as  $\pi$ - $\pi$  contacts with residues such as Met169, Ser240, Leu323, and Cys328 [81]. Virtual screening of TCM libraries identified TCM27763 and TCM33057 as stronger inhibitors than TTP-6171, interacting with key residues Trp168, Asn171, Arg196, Ser240, Glu325, Ser326, and Cys328 [81]. Notably, alnuside B, structurally related to TCM33057, achieved a docking score of  $-11.62$  kcal/mol, forming multiple hydrogen bonds and hydrophobic interactions, indicative of potent suppression of I7L protease activity (Figure 2).

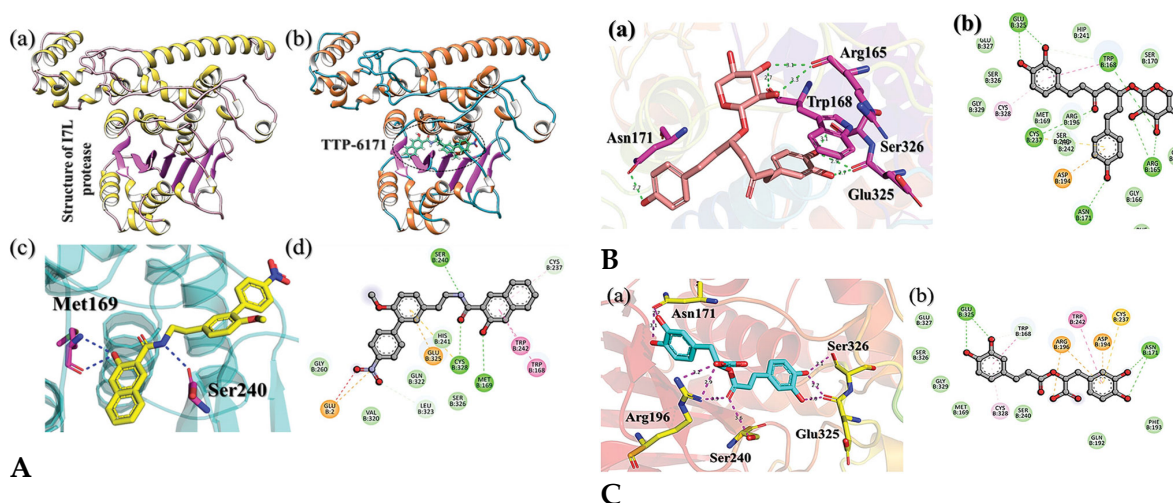


Figure 2. Cont.

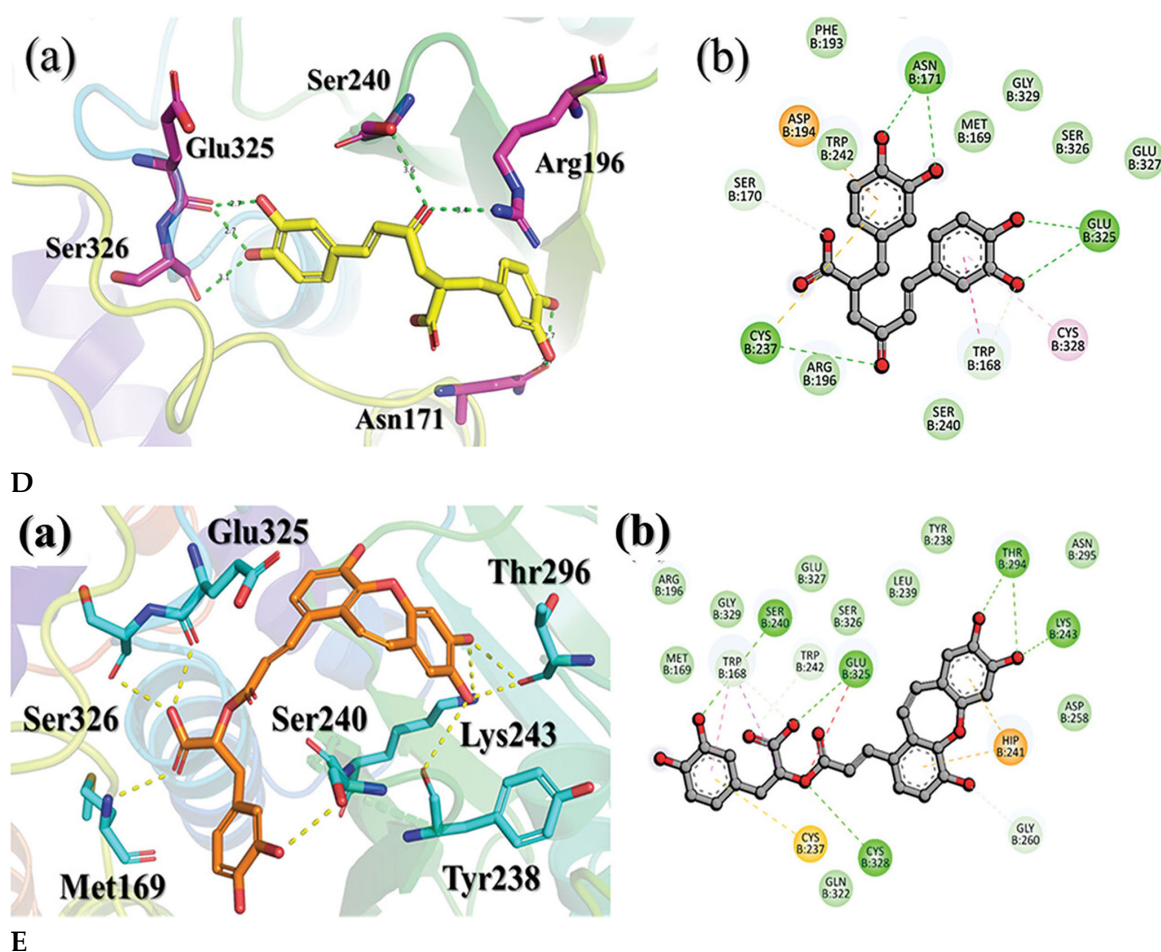


**Figure 2.** Redrawn Diagram Binding mode of TCM (34450, 33057, 31564, 27763) with the active site residues of I7L protease from mpox virus as adapted from the cited source under Creative Commons Attribution 4.0 International License (CC BY 4.0): (A). Structural and binding analysis of I7L protease. (a) modeled 3D structure of I7L, (b) control drug, TTP-6171, bound to the active site of protease (c,d) 3D and 2D interaction pattern of TTP-6171. (D). Binding mode of TCM27763 with the active site residues of I7L protease from mpox. (a) shows the 3D interaction pattern while, (b) shows the 2D interaction pattern of TCM27763. (E). Binding mode of TCM33057 with the active site residues of I7L protease from mpox. (a) shows the 3D interaction pattern while (b) shows the 2D interaction pattern of TCM33057. (C). Binding mode of TCM34450 with the active site residues of I7L protease from mpox. (a) shows the 3D interaction pattern while, (b) shows the 2D interaction pattern of TCM34450. (E). Binding mode of TCM31564 with the active site residues of I7L protease from mpox. (a) shows the 3D interaction pattern while, (b) shows the 2D interaction pattern of TCM31564 [81].

## 5. Pharmacokinetics and ADMET Predictions in MPXV Drug Discovery

### 5.1. Importance of Drug-Likeness, and ADMET Profiling

Drug-likeness and ADMET properties are critical determinants of a compound's safety, efficacy, and clinical suitability, forming the cornerstone of early-stage antiviral drug discovery. Studies have demonstrated that natural compounds frequently exhibit favorable pharmacokinetic profiles, reinforcing their potential as potential antiviral agents. Curcumin derivatives showed exceptional ADMET profiles in silico, with the top candidate exhibiting  $-8.90$  kcal/mol binding affinity and docking scores above  $6.80$  kcal/mol, better than the standard medications, indicating strong stability and bioavailability [30]. ADMET evaluation of 146 *Moringa oleifera* phytochemicals identified gossypetin, riboflavin, and ellagic acid as potent DNA polymerase inhibitors ( $-7.8$ ,  $-7.6$ ,  $-7.6$  kcal/mol), outperforming Cidofovir ( $-6.0$  kcal/mol) and Brincidofovir ( $-5.1$  kcal/mol) [6,86]. Virtual screening of

500 compounds against the MPXV-Congo\_8-156 protease (explored with bioinformatics tools like PROTPARAM, SOPMA, SWISS-MODEL and PROCHECK) identified five leads (PubChem CIDs: 4061636, 4422538, 3583576, 4856107, and 4800629) alongside the control (Cidofovir). At 100 ns each, confirmed strong structural stability and favorable safety, as confirmed by RMSD, RMSF, and MM-PBSA analyses, highlighting the value of ADMET profiling. Further, skin-penetrating natural compounds demonstrated antiviral potential with docking scores between  $-9.2$  and  $-8.8$  kcal/mol, coupled with the absence of predicted AMES toxicity or carcinogenicity in toxicological assessments, underscoring their therapeutic safety [87]. While, the evaluated log  $p$  values for brincidofovir and tecovirimat were higher than those of the other drugs in the QSAR study, complementary QSAR-based analyses also revealed that theaflavin possesses a log  $p$  value of 4.77, indicative of high biological activity and favorable drug-like characteristics [88].

The integration of ADMET profiling with molecular docking and MD simulations enhances the predictive power of computational pipelines, allowing for more robust validation of candidate suitability. The Random Forest and Ridge regression models demonstrated the strongest correlation between predicted and observed  $EC_{50}$  values. These optimized models were subsequently employed to screen phytochemicals from the Maliaceae family against the MPXV cysteine proteinase. IMPHY010637, a putative MPXV cysteine proteinase inhibitor, maintained stable binding over 100 ns MD simulations, with consistent RMSD values and multiple hydrogen bonds, while exhibiting an acceptable drug-like profile [89,90]. These results highlight ADMET profiling as essential for translating predictions into validated natural product leads combining safety, efficacy, and drug-likeness for MPXV preclinical development.

## 5.2. Computational Tools for Assessing Pharmacokinetics Properties of Repurposed Compounds

Predicting the ADMET profiles of repurposed natural compounds is a cornerstone of modern antiviral drug discovery, ensuring early prioritization of candidates with optimal pharmacokinetics and safety. Computational platforms such as SwissADME, pKCSM, and preADMET v2.0 predict key parameters, including solubility, intestinal absorption, BBB permeability, CYP450 inhibition, and toxicity risks such as hepatotoxicity, mutagenicity, and skin sensitization [86,91]. In silico models enabled high-throughput screening of 5715 phytochemicals from 266 medicinal plants, identifying candidates with strong MPXV binding and favorable pharmacokinetics, validating their translational antiviral potential [29].

Recent advances in AI-driven pharmacokinetic modeling have further expanded predictive accuracy and reliability. Platforms such as HelixADMET, which leverage self-supervised learning and multi-task frameworks, now allow extrapolation across chemically diverse scaffolds with minimal experimental training data [92,93]. Similarly, integrative initiatives like the eTOX project combine cheminformatics, toxicogenomics, and bioinformatics datasets to generate expert systems for early in silico toxicity forecasting, significantly reducing late-stage attrition [94,95].

Crucially, the integration of ADMET profiling with molecular docking and MD simulations provides a synergistic framework for evaluating compound stability and therapeutic potential under near-physiological conditions. In docking-based screening, top three candidates were selected, which ranked using the ML model. These three compounds were then examined under MD simulation and MM/GBSA-binding free energy analysis against TMPK identified Chlorhexidine HCl with an exceptional MM/GBSA binding free energy of  $-62.41$  kcal/mol, accompanied by high conformational stability ( $RMSD < 0.3$  nm) [89]. Likewise, flavonoids screened against vaccinia virus TMPK yielded docking scores ranging from  $-7.0$  to  $-9.3$  kcal/mol compared to reference drug (ganciclovir), with subsequent AD-

MET assessments confirming good oral bioavailability, low toxicity, and potential drug-like profiles [88,96].

### 5.3. Case Studies of Natural Compounds with Favorable ADMET Properties

Screening 5715 phytochemicals from 266 IMMPAT plant species identified terchebin, isocinchophyllamine, ruberythric acid, theasinensin F, theasinensin A, and sythiaside as potent inhibitors of viral enzymes E9L and A48R [27,29]. These compounds not only exhibited positive drug-likeness and predicted pharmacokinetics but also demonstrated superior target selectivity compared to the currently approved antivirals tecovirimat and brincidofovir [29,88].

Medicinal plant-derived compounds from diverse geographic regions have also yielded encouraging results. Of note, folic acid and 1,2,4,6-tetragalloylglucose, identified from Middle Eastern flora, achieved stronger docking scores and more favorable binding free energies against MPXV MTase than reference inhibitors sinefungin and TO1119 [34]. Folic acid occupies the MTase catalytic pocket, forms stable hydrogen bonds, and blocks viral mRNA capping, demonstrating natural molecules' ability to inhibit key viral enzymes [97].

Individual case studies further reinforce the therapeutic promise of natural compounds. Curcumin, widely studied for its pleiotropic activity, inhibits DNA polymerase holoenzyme and VP39 MTase while modulating host TNF, NF- $\kappa$ B, and MAPK pathways, providing combined antiviral and immunomodulatory effects [20,30]. Kaempferol and piperine from *Ficus religiosa* bind strongly to A42R, with non-mutagenic ADMET profiles and favorable IC<sub>50</sub> values of 7.63  $\mu$ M and 82  $\mu$ M, they may be suitable lead candidates for developing mpox therapeutic drugs [29]. In another study, ellagic acid and riboflavin emerged as stable and non-toxic DNA polymerase inhibitors, outperforming brincidofovir and cidofovir in molecular dynamics stability and binding free energy profiles [86]. These natural compounds with favorable ADMET properties not only rival but may surpass currently approved antivirals.

## 6. Future Perspectives and Challenges

Phytochemicals represent attractive scaffolds due to their low toxicity, availability, and antiviral potential for MPXV, particularly in low-resource settings. Tools such as molecular docking, MD simulations, and AI-driven interaction models have identified high-affinity ligands and druggable viral targets, but a major gap persists in experimental validation [98]. Natural compounds such as curcumin and folic acid show strong binding and stability with viral and host proteins, while aurachin A and soraphinol analogs maintain TMPK integrity in silico, but lack in vitro and in vivo validation [99].

Despite the rapid advances in computational approaches for antiviral discovery, significant challenges remain in translating MPXV therapies of phytochemical compounds from in silico predictions to clinically validated treatments. The clinical translation is hindered by poor solubility, low membrane permeability, rapid metabolism, and off targets affect that limit bioavailability and therapeutic efficacy. Advances such as nanocarrier-based delivery systems including liposomes, solid lipid nanoparticles, polymeric nanoparticles, prodrug approaches, and semi-synthetic scaffolds optimization have shown promise in overcoming these barriers. Notably, curcumin-loaded nanoparticles significantly improved potency and stability compared to free curcumin, while glycyrrhizin derivatives and betulinic acid analogs demonstrated enhanced absorption and reduced toxicity through rational modification [100]. Despite these advances, the lack of comprehensive clinical studies, formulation stability data, and pharmacokinetic evaluation continues to restrict clinical application.

Another challenge is the high mutability of MPXV, which may enable variants to evade inhibitors derived from unrelated systems. This underscores the need for real-time genomic surveillance, as AI and machine learning remain limited by incomplete datasets, reducing prediction accuracy and generalizability [101]. To strengthen translational potential, future efforts should integrate systems biology models, multi-omics datasets (transcriptomics, proteomics, and metabolomics), and high-resolution structural biology to refine target validation and drug design [101,102].

Computational pipelines generate hypotheses rather than guarantees, as docking, QSAR, and ADMET predictions often overlook off-target effects, metabolic instability, and immune modulation that drive therapeutic failure. This gap emphasizes the need for integrative workflows that combine computational screening with biophysical characterization, cell-based assays, animal models, and pharmacokinetic studies. Moving forward, interdisciplinary collaborations linking computational biology, medicinal chemistry, pharmacology and clinical sciences will be essential. Establishing robust translational pipelines and leveraging advanced formulation technologies will enhance the pharmacological performance of natural product-derived antivirals, supporting their clinical adoption and natural compound-based antiviral discovery applicable to future viral epidemics.

## 7. Conclusions

The WHO and the Centers for Disease Control and Prevention have recently classified Mpox as a Public Health Emergency of International Concern, underscoring its global health relevance. At present, there are no antiviral therapeutics specifically approved for Mpox, and access to vaccines remains constrained, particularly in endemic and resource-limited regions. In this context, plant-derived bioactive compounds represent a potential reservoir for novel therapeutic development. Computational approaches have enabled the rapid identification of potent inhibitors by elucidating critical interactions between candidate compounds and viral proteins. These natural compounds have good binding properties, good pharmacokinetics, little toxicity, and multifunctional therapeutic potential compared to existing antivirals. Their favorable pharmacokinetics, low toxicity, and multifunctional properties further position them as potential candidates for both therapeutic and prophylactic interventions, particularly in resource-limited settings.

Modeling facilitates the rapid identification of druggable viral targets, enabling high-throughput screening of phytochemicals with demonstrated antiviral and immunomodulatory potential. From a computational biochemistry and natural products perspective, *in silico* pipelines, ranging from docking to AI-driven pharmacophore modeling deliver true value only when paired with rigorous experimental validation. Computational predictions alone cannot resolve critical translational challenges such as poor availability, limited solubility, rapid metabolic clearance, or off-target toxicities. Potential compounds with favorable docking scores may fail *in vivo* unless supported by nanocarrier delivery systems, semi-synthetic modifications, or prodrug strategies to enhance stability and systemic exposure. The future of Mpox drug discovery relies on integrating computational screening with pharmacological, biochemical, and clinical pipelines to refine *in silico* leads into safe, effective therapies. This review underscores the essential role of *in silico* approaches in modern antiviral development and highlights the untapped potential of natural compounds in bridging the current therapeutic gaps against MPXV. Combining computational modeling with experimental validation and ethnopharmacological insights, global preparedness and response to emerging viral threats can be substantially strengthened.

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