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Evolving Epidemiology, Pathogenesis, and Therapeutic Frontiers of Mpox (Monkeypox): A Comprehensive Review of 2022–2026

Parul Kashyap [1*], Vivek Kumar [2], Ashok Kumar Rajpoot [3]

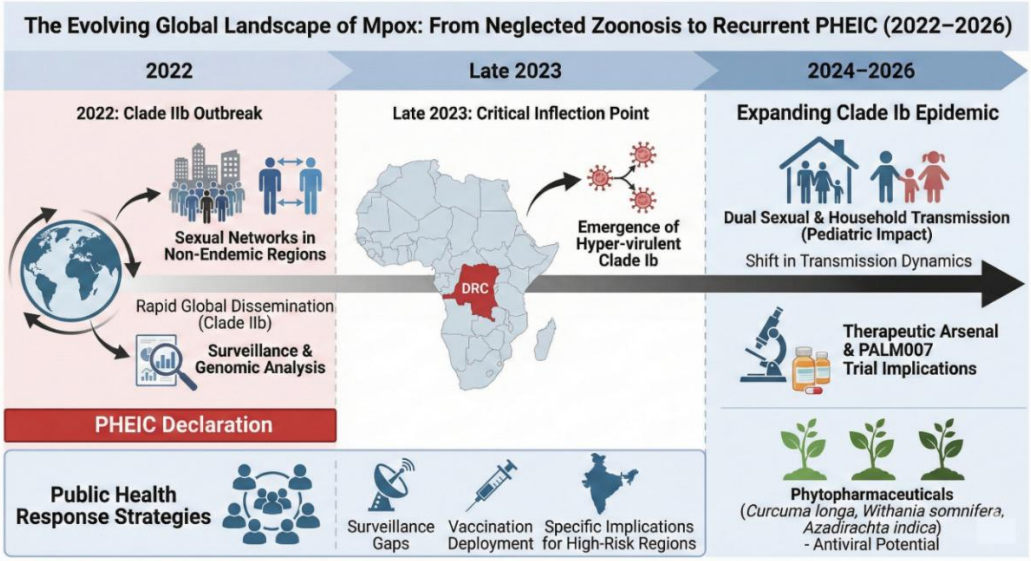
[1,2,3] Moradabad Educational Trust, Group of Institutions, Faculty of Pharmacy, Moradabad-244001, UP., India;
* Correspondence: kashyapparul90@gmail.com (P.K.);

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Abstract: Compared to 2022, the global situation regarding Mpox, formerly known as monkeypox, has significantly changed and is expected to continue evolving until 2026. It has become an international public health crisis as a disease that nobody paid attention to before but has now captured an international concern, especially in those countries in Central and West Africa (PHEIC). Subsequent to the widespread transmission of Clade IIb in 2022, mainly among sexual networks outside of Africa, a new highly virulent Clade Ib strain of the virus appeared at the end of 2023 in the Democratic Republic of the Congo (DRC). In this paper, the surveillance, genetic, and clinical information related to the multi-country outbreak of 2022, with particular focus on the rising Clade Ib epidemic up to 2026, will be discussed. We consider the changes in the transmission and juxtapose the sexual transmission of Clade IIb with the sexual and household spread, which has mainly occurred among children in East Africa and is mainly of Clade Ib. We review ongoing treatment, evaluate the outcomes of the PALM007 trial of tecovirimat, and examine the science of combination therapy. Specifically, we analyze in silico and in vitro evidence that can justify the concept of using natural products as supplementary countermeasures, which include Curcuma longa, Withania somnifera, and Azadirachta indica. Lastly, we present the strategies of public health, particularly in the areas where there is a deficiency in surveillance, and we present the plans of vaccination and certain issues in high-neck places like India.

Keywords: Mpox Clade Ib, Genomic Surveillance, Tecovirimat, PALM007, Integrative Medicine, Phytochemicals.

Graphical Abstract



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1. Introduction

Monkeypox (sometimes referred to as mpox) is a disease caused by the monkeypox virus (MPXV), an enveloped, manually bi-stranded DNA virus of the genus of *Orthopoxvirus* (family Poxviridae). It has major structural and antigenic similarities with smallpox (Variola virus) and the vaccine strain, Vaccinia virus. In the past, the virus inhabited the congo basin and West Africa tropical forests. Recently it has been initially observed in captive macaques in Copenhagen in 1958, and the first human case was documented in 1970 in a 9-month-old infant in the DRC[1].

For over half a century, Mpox was also an untreated tropical disease. It led to the occasional spill-over of wild mammals rope squirrels (*Funisciurus spp*.), tree squirrels (*Heliosciurus spp.*), Gambian pouched rats and dormice to humans and minimal secondary contagion. After routine smallpox vaccinations stopped and an ecological niche for *orthopoxviruses* was reestablished, population immunity dropped in 1980[2].

A different strain of the virus, Clade IIb, escaped in May 2022 and rapidly spread in Europe, Americas, and Asia. It was predominantly spread in sexual contact in networks of men who have sex with men (MSM). It was an outbreak that was like no other and led to the declaration of PHEIC by the World Health Organization (WHO) in July 2022. The Clade 2b epidemic, which had been mostly contained in high-income nations by means of behavioural modification and specific vaccination, did not stop but meant that the virus kept on developing in its African haven[3].

A new, even deadlier variant, Clade Ib, was identified in South Kivu, DRC, in December 2023. It transmits easily via close contact, both sexual and non-sexual, within households and populations. Clade Ib, however, did not stay in one place for long and soon spread to Burundi, Rwanda, Uganda, and Kenya. Its quick dissemination led to a second Public Health Emergency of International Concern in August 2024. By early 2026, it had become a recurring theme in East Africa and had resulted in sporadic cases in India, Sweden, Thailand, and the US. This is a critical, evidence-based examination of the current condition of Mpox research relationships bridging traditional virology and new integrated therapies[4,5].

2. Virology and Genomic Evolution

Knowledge of MPXV biology is vital in elucidating the reason behind the difference in the severity of clinical manifestations and dissemination by different clades[6].

2.1 Viral Structure and Lifecycle

MPXV is a big virion which is brick-shaped approximately 200-250nm wide with a height of 200-300nm. It has a linear, double stranded, DNA genome, about 197kb long, encoding approximately 190 proteins that aid in the replication of the virus, host selection, and avoidance of immunity. In contrast to most DNA viruses, poxviruses replicate within the cytoplasm of the infected cells and as such, they contain all the enzymes they require to replicate DNA, transpose and process mRNA. Two infectious forms are the production of the replication cycle. The Intracellular Mature Virion (IMV) appears to be not sensitive to the environment and propagates primarily by close contact or fomites. The virus obtains an additional membrane of host origin through the viral protein F13L. EEVs assist the virus to travel between the cells and avoid neutralising antibodies[6–8].

2.2 Phylogenetic Classification and Nomenclature

In 2022, WHO brought together experts to name the viral clades based on where they came from, but without a formal taxonomy, to avoid stigma and follow best-practice taxonomy[9].

Table 1: Phylogeny and Characteristics of Mpox Virus Clades[10,11]

Feature	Clade I (formerly Congo Basin)	Clade II (formerly West African)
Subclades	**Clade Ia:** The "classic" endemic strain circulating in rural Central Africa (DRC, CAR). **Clade Ib:** The novel epidemic strain emerging in late 2023 in Eastern DRC.	**Clade IIa:** Historical West African strains. **Clade IIb:** The driver of the 2022 global outbreak.
Genomic Size	~197 kb	~190 kb (Impacted by deletions)
Virulence	High (CFR historically up to 10%)	Low (CFR < 0.1–1%)
Transmission	Zoonotic dominant (Ia); Human-to-Human dominant (Ib)	Human-to-Human dominant (IIb)
Reservoirs	Rodents, Non-human primates	Rodents

2.3 Accelerated Evolution: The Role of the APOBEC3

The Clade2b and Clade1b strains exhibit very high rate of evolution of the orthopoxvirus. It has been demonstrated that genome sequencing of 2022-2026 cases shows a mutational pattern TC mutation to TT in which the host enzyme APOBEC3 is implicated. Usually, APOBEC3 kills viral DNA through the insertion of poisonous mutations in viral genomes as the immune reaction. In MPXV, APOBEC3 editing, however, is observed to aid the virus in adapting to humans, which may enhance the transmissibility and alter virulence. Specifically, Clade Ib has deletions and rearrangements in genes that deal with immune evasion, and this is likely the reason responsible why Clade Ib can preserve human-to-human chains more than the older Clade Ia[12].

3. Global Epidemiology (2022–2026)

The epidemiology of Mpox has changed where it used to be limited to isolated spillovers between animals and humans to permanent global spread with two simultaneous epidemics[13].

3.1 The 2022 Clade IIb Worldwide Epidemic

The Mpox virus of Clade IIb spread swiftly starting in May 2022 because sexual networks are so closely linked. This led to a pandemic that went undetected and spread over the world. According to epidemiologic statistics, the outbreak had a disproportionately high number of men who have sex with men (MSM), as more than 95% of the outbreak were found in non-endemic regions, the median patient age was 34 years. The transmission route was mainly by sexual contact and it had direct correlation with more than one partner, close-contact interactions and large parties. By the end of 2023, the disease had been reported in more than 118 countries, with more than 97,000 confirmed cases and around 200 deaths. Despite a lot of vaccination and behavior modification, which lessened the number of cases, low-level transmission is still evident around the globe[3,14].

3.2 The 2024–2026 Clade Ib Epidemic

Clade 1b is the main cause of the present epidemic. It started in Kamituga, South Kivu, Democratic Republic of the Congo, during the COVID-19 pandemic in September 2023. Being a mining rich area, the area experiences high population mobility and commercial sex and this feature of the area increased the rate at which the viruses spread locally. The Clade Ib did not

restrict itself to national borders at an early stage as Clade Ia did; it was was creative over borders and had been spreading through rural woodlands. By the middle of 2024, the confirmed cases turned out in Burundi, Rwanda, Uganda, and Kenya, where there were no previous Mpox outbreaks, which speaks of a transition to regional distribution[15,16].

Clade Ib has two ways that things can be transmitted. Sexual transmission has been a key source of infection between adults, particularly with female sex workers and their clients, whereas non-sexual domestic transmission has risen. This has resulted in a big burden of disease in pediatrics with children having the virus through close contact with their caregivers or through tainted objects. Early DRC surveillance has forecast a case-fatality rate (CFR) of 0.5%–3.0%, which is greater than previous. This is compared to the sub 0.1% of Clade IIb in 2022. Kids under the age of 15 and immunocompromised people have significantly lower mortality and, thus, the severity of the epidemic becomes very clear[4].

3.3 Cases of Seeding and Travel around the World

The higher transmissibility and spread of Clade Ib in regions have resulted in some long-range seeding events due to international travel. As of 2024, Sweden and Germany had imported cases of Clade Ib. By the end of 2025, there had been very few reports of secondary local transmission in the UK and Spain. The fact that these things happen so often shows that the virus can spread beyond its epicenter since it can move around[17].

Thailand reported confirmed cases of Clade Ib in Asia in 2024, showing that it was still spreading around the world. California was the first state in the Americas to report a case of Clade Ib in November 2024. Later genomic surveillance revealed a cluster of cases in early 2026 with no recent history of travel, and this suggests that these cases are likely to have been transmitted within the community and that extending surveillance in the world and implementing rapid measures to contain infection is necessary[18].

3.4 Epidemiological Situation in India (2024-2026)

The huge population of India and a large trade and travel connection with the Middle East and Africa puts the nation in an ideal position of Mpox monitoring. The country recorded few cases of Clade IIb in 2022 in 2022-2023, mostly in travelers into the country, predominantly of the United Arab Emirates (UAE). The Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV) found Clade Ib toward the end of 2025. Out of ten Kerala cases, nine were closely associated with recent travel to UAE and Oman whereas one had no travel history which indicated local household transmission. By February, 2026, the National Centre for Disease Control (NCDC) remains on the alert to monitor clusters, and has increased sentinel surveillance in major international airports in the country, such as Mumbai, Delhi, Kochi, as well as in STIs clinics across the country [13,19](figure 1).

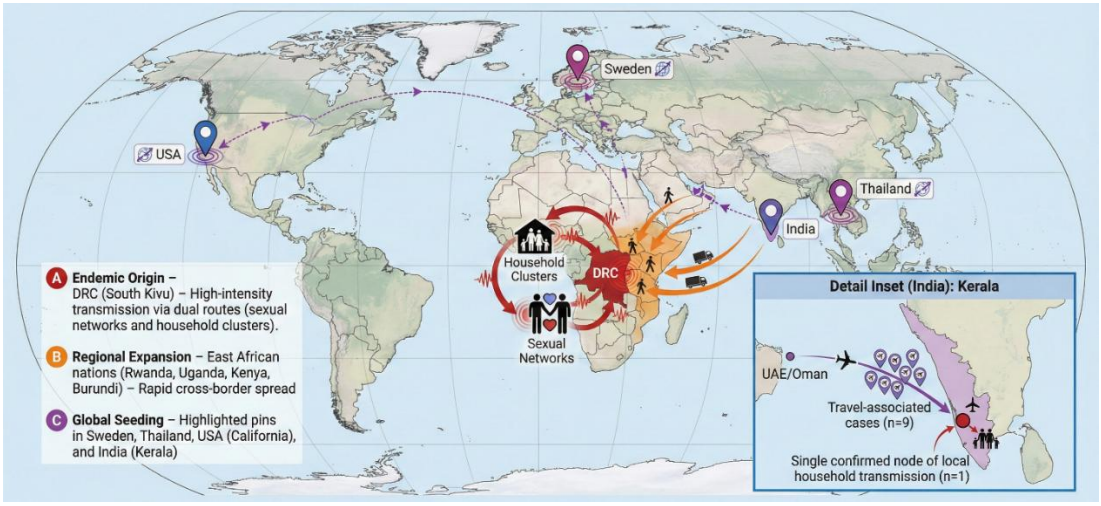


Figure 1: Global and Regional Transmission Dynamics of Mpox Clade Ib (2024–2026).

4. Clinical Manifestations

The clinical manifestation of mpox has changed, and Clade Ib and IIb infection are not always characteristic of the typical description of zoonotic Clade Ia[5].

4.1 Incubation and Prodrome

The incubation period varies between 6 -13 days plus during some cases to 21 days. The prototypical prodrome encompasses climate of fever, profound headache, high degree of lymphadenopathy (one of the defining aspects separating Mpox and smallpox), myalgia, back pains and deep-rooted asthenia. But in the 2022-2026 dominant sexual transmission outbreaks, there is an increased atypical presentation. A prodrome is mild or absent in many patients and the initial lesions seen are on the skin or the mucosa with systemic symptoms being acquired only in time as the rash develops[3,6].

4.2 Dermatological and Mucousal appearances

The Mpox rash undergoes clear stages namely macules, papules, vesicles, pustules, central umbilication, and forming crusts before healing. Distribution Clinical distribution differs by clade. Lesions in Clade Ia tend to have a centrifugal distribution, especially on the face (95 %), palms and soles (75 %) and on the mucous membranes (70 %). Altogether, Clade Ib and IIb infections due to sexual transmission (sexually transmitted outbreaks in particular) tend to manifest as localization to the point of inoculation followed by the potentially secondary proliferation (i.e., the genital, perianal, and oropharyngeal areas). Proctitis has become recognised as a specific, debilitating expression in vulnerable populations, i.e., MSM and Clade Ib women with a severe presentation of anorectal pain, tenesmus, rectal bleeding, purulent discharge, and apparent perianal ulceration with no overall rash. Pharyngeal involvement such as tonsillar edema, pustules and ulceration can lead to severe odynophagia, dehydration and sometimes may necessitate hospitalization and parenteral nutrition[20,21].

4.3 Complications

Individuals with compromised immunity, pregnant women, and children are more susceptible to mpox-related problems. If the lesions develop secondary infections like cellulitis or abscesses due to bacteria like Staphylococcus aureus or Streptococcus pyogenes, it can cause serious diseases like sepsis. In the case of the eyes, scarring can occur and can lead to permanent blindness if the mpox virus auto-inoculates into the eye and causes keratitis. Neurological symptoms like encephalitis, seizures, and sudden disorientation can also occur but are less common (<1%). Infections caused by Clade I mpox can lead to more respiratory symptoms like respiratory distress and bronchopneumonia. Severe necrotizing mpox with

widespread lung and other organ involvement with high mortality rates is associated with HIV-positive patients with a CD4 count below 200 cells/μL[22,23].

5. Diagnostic Strategies

To stop the spread of disease, quick and accurate diagnosis is necessary.

5.1 Collecting Samples and Biosafety

Take samples in line with the biosafety regulations and appropriate personal protective equipment (PPE). The most powerful specimen is obtained through the vigorous swabbing of the exudation, roof or crust- the places that contain the maximum amount of virus. Different lesions should be covered by two swabs and several swabs in order to enhance sensitivity.

Other samples, such throat swabs, urine, or EDTA-blood, can be taken, but they are not as sensitive as lesion swabs for the first diagnosis. Even in cases of viral spreading or shedding, they can be used[24,25].

5.2 Laboratory Modalities

The nucleic acid amplification test, in particular, the RT-PCR, is the gold standard test.

These are conserved *orthopoxvirus genes* (e.g., DNA polymerase E9L) or Mpox-specific genes such as the TNF-binding protein gene, thus making them highly sensitive and specific.

Due to the possibility of Clade I and Clade II simultaneous transmission, the inter-clade differentiating assays are highly recommended; Clade Ib presents an increased menace to health in the population.

Whole-genome sequencing (WGS) plays an important role in monitoring the evolution of the virus and finding patterns of mutation including APOBEC3 signatures and explaining the connection of the transmission when the epidemiology is uncertain[26,27].

5.3 Differential Diagnosis

In order to diagnose it properly, it is important to differentiate it from other vesiculopustular and rash-associated diseases. In the case of varicella or chickenpox, the lesions are superficial and appear in successive crops with a centripetal pattern that mostly affects the truncal area. In addition, lymphadenopathy is uncommon. In the event that the presentation is similar to that of Mpox, it is important to use the results of the polymerase chain reaction to properly distinguish it from other diseases like herpes simplex virus infection, which is associated with localized and recurring vesicular lesions that mostly appear in the vaginal area. A rash appearing on the palms and the soles is an early sign of secondary syphilis but can also appear with Mpox co-infection, although it is mostly maculopapular rather than vesicular. Hand, foot, and mouth disease is associated with the presence of vesicles on the hands, feet, and the oral mucosa and mostly affects children[21,28].

6. Therapeutics and Management of Pharmacology

Antiviral drugs initially designed against smallpox are the key to the treatment of mpox, yet current research indicates that they are not highly effective.

6.1 Supportive Care

Patients with mild to moderate Mpox rely on supportive care as the basis of treatment.

It is necessary to have their pain managed, particularly where discomfort is brought about by proctitis or lesions in the mouth.

The first lines include acetaminophen and NSAIDs; the serious pain might require the short-term use of opioids or neuropathic medications, such as gabapentin.

Maintain good hydration and nutrition of patients, particularly when they have a sore throat to swallow.

Proper wound care in order to avoid secondary bacterial infection that includes keeping lesions clean and dry; topical antibiotics should only be used in case of evident superinfection[29,30].

6.2 Antiviral Therapies

Specialized antivirals are normally only used in severe, immunocompromised, or otherwise high-risk situations, and they are harder to find in places where people don't have a lot of money.

Genomic data indicate that the virus developed rapidly, and that host APOBEC3 activity is associated with TC-TT alterations. The virus can be evolving to this defense, changing immune evasion proteins[31].

Key drug targets include:

- F13L phospholipase, which is required in the formation of extracellular enveloped virions[32].
- E9L DNA polymerase which is essential in replication.
- A42R profilin-like protein, which takes part in interactions with cytoskeleton[33].

All these findings inform the rational antiviral design[34] (see Table 2).

Table 2: Antiviral Agents for Mpox Treatment[35–38]

Drug	Mechanism of Action	Clinical Status and 2024–2026 Updates
Tecovirimat (TPOXX)	Inhibits the viral **VP37 (F13L)** protein, preventing the wrapping of intracellular mature virions (IMV) to form extracellular enveloped virions (EEV), thereby blocking viral egress and dissemination.[9]	Considered the primary therapeutic. However, the **PALM007 trial** (DRC, 2022–2024) demonstrated that tecovirimat did **not** significantly reduce the time to lesion resolution compared to placebo in Clade I patients, although it was safe. This finding has challenged its routine use for mild cases, though it remains recommended for severe/immunocompromised patients.
Brincidofovir	A lipid-conjugate prodrug of cidofovir. It is converted intracellularly to cidofovir diphosphate, which inhibits viral **DNA polymerase**.	An oral alternative to tecovirimat. It has lower nephrotoxicity than cidofovir but is associated with gastrointestinal side effects and liver enzyme elevations. Efficacy data against Clade Ib is limited but *in vitro* activity is retained.
Cidofovir	A nucleoside phosphonate analogue that inhibits viral DNA polymerase.	Used as a third-line agent. Its utility is limited by significant nephrotoxicity, requiring co-administration with probenecid and aggressive hydration.
Vaccinia Immune Globulin (VIG)	Passive immunization using pooled antibodies from recent smallpox vaccinees.	Reserved for treatment of severe complications (e.g., progressive vaccinia, severe Mpox) where antivirals are contraindicated or ineffective.

6.3 The Tecovirimat Paradox

PALM007 trial revealed that tecovirimat which is a safe and acts on one of the conserved mechanisms failed to accelerate the recovery of most Clade I patients.

Potential causes: Viral dynamics of humans are not similar to those of animals, or therapy was not applied in time (usually days after rash).

This indicates why there is an urgent need to have the combination therapies or new drugs that strike at different stages of the viral life cycle[39], also shown in figure 2.

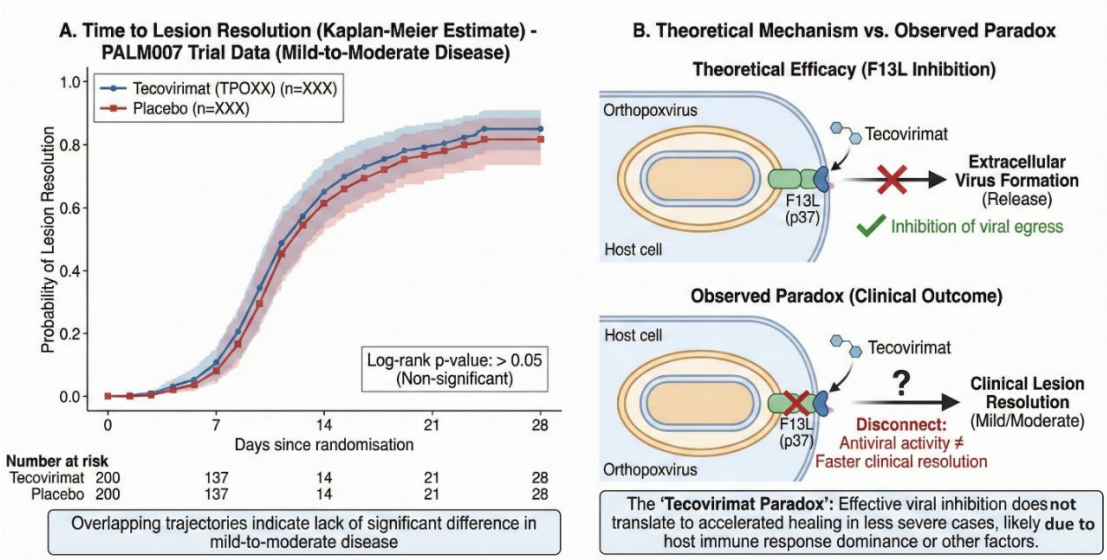


Figure 2. The "Tecovirimat Paradox" and Clinical Efficacy.

7. Prospects with Integrative and Phytopharmaceutical

Considering the lack of access to the current antivirals in the Global South and the unknown effectiveness of monotherapy, integrative technologies are becoming a point of interest.

Ayurvedic and Traditional Chinese Medicine (TCM) have numerous potential antiviral compounds found in plants. There is also an emerging trend of using modern methods to describe the mode of action of these phytochemicals against MPXV, such as molecular docking and dynamics simulations[40].

7.1 Curcuma longa (Curcumin)

Curcumin, the principal bioactive polyphenol derived from Curcuma longa, has been extensively investigated for its broad-spectrum antiviral and immunomodulatory properties. Recent computational studies (2024–2025) have identified curcumin as a potential high-affinity inhibitor of multiple Mpox virus (MPXV) proteins. Molecular docking analyses demonstrate favorable binding to the viral DNA polymerase holoenzyme (E9L), with predicted binding energies lower than those reported for cidofovir, suggesting strong inhibitory potential. Additionally, curcumin exhibits significant interaction with the A42R profilin-like protein, implicated in viral assembly and cytoskeletal modulation. Beyond direct antiviral activity, curcumin suppresses key inflammatory pathways by downregulating NF-κB signaling and reducing pro-inflammatory cytokines such as TNF-α and IL-6, potentially attenuating hyperinflammatory responses in severe Mpox cases. However, its clinical translation is limited by poor oral bioavailability, necessitating advanced delivery systems, including nano-formulations and liposomal carriers, to enhance systemic exposure and therapeutic efficacy[41], also shown in figure 3.

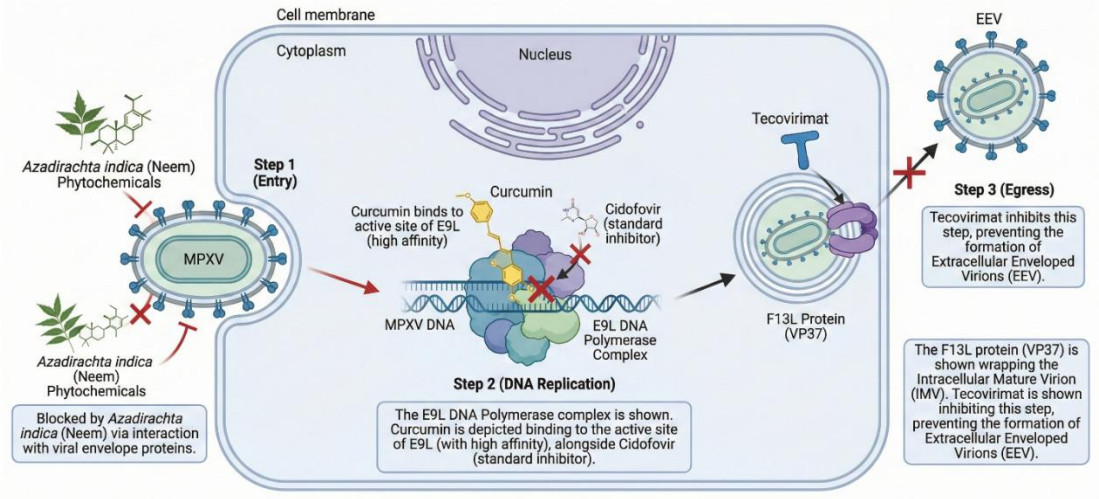


Figure 3: Molecular Targets for Integrative Mpox Therapeutics.

7.2 Azadirachta indica (Neem)

Azadirachta indica (Neem) is a multifunctional Indian herb with its traditional uses in the treatment of cutaneous viral infections such as diseases related to chickenpox and smallpox. New in vitro investigations also prove that Herpes Simplex Virus-1 (HSV-1) entry into host cells is prevented by aqueous extracts of neem bark, which confirms its antiviral efficacy. Other recent computational studies also implicate the action of neem-derived triterpenoids, including azadirachtin and nimbin, in contacting the viral F13L protein- an essential mediator of formation of the envelope virions and other envelope-associated proteins, thus possibly weakening viral egress and cell-to-cell spread. Also, putative antiviral properties, neem has important antibacterial activity that can be useful in the topical treatment of Mpox lesions by preventing secondary staphylococcal and secondary infections due to staphylococcus and improving the risk of scarring[42].

7.3 Withania somnifera (Ashwagandha)

One of the important Ayurvedic adaptogenic herbs is *Withania somnifera*, also known as Indian *Ginseng*. *Withanolides, withanferin A* and *withanone* of which are its main bioactive constituents, have varied pharmacological actions. In silico studies indicate that *Withanone* has the potential to form interactions with viral proteases and envelope-associated proteins of enveloped viruses such as Mpox virus surrogates, and is likely to exert direct antiviral actions. Besides having direct viral targeting, *W. somnifera* has an effective immunomodulatory effect through the promotion of Th1-mediated immunity, interferon-g (IFN-g) secretion, and natural killer (NK) cell activity. Since the clearance of *orthopoxvirus* infections depends heavily on the presence of strong cellular immunity, such immunostimulatory functions could be used to provide supportive effect in prophylaxis or at the initial stages of Mpox infection[43].

7.4 Other Promising Phytochemical Candidates

A number of other phytochemicals demonstrate supportive or possible antiviral implications in the management of Mpox. The bioactive compounds present in aloe vera include *anthraquinones (e.g., aloin) and acemannan*, which are the main agents of action of wound healing by stimulating collagen synthesis and speeding up the re-epithelialization of cutaneous wounds, and relieving pruritus and local discomfort. *Bacopa monnieri (Brahmi)*, which is mostly attributed the property of neuroprotectant, may have supportive effects in the management of neurological manifestation or post-viral fatigue and cognitive impairment, possibly by regulating pro-inflammatory cytokines such as TNF-a and IL-6. *Glycyrrhiza glabra (Licorice)* had *glycyrrhizin*, which showed in vitro antiviral effects against vaccinia

virus by blocking viral entry and membrane fusion, and thus could be an excellent candidate as a source of in vitro antiviral activity against Mpox virus[40,44].

Table 3: Validated and Predicted Phytochemical Targets in Mpox Management[41,42,45,46]

Phytochemical	Source Plant	Putative Viral/Host Target	Mechanism of Action	Evidence Base
Curcumin	*Curcuma longa*	DNA Polymerase (E9L); NF-κB (Host)	Replication inhibition; Anti-inflammatory	*In silico* (High affinity docking); *In vitro* (Surrogates)
Azadirachtin	*Azadirachta indica*	F13L (Phospholipase D)	Egress inhibition	*In silico*; Traditional evidence
Withaferin A	*Withania somnifera*	Viral Proteases; Th1 pathway (Host)	Entry blockade; Immunostimulation	*In silico*; *In vitro* (Host modulation)
Glycyrrhizin	*Glycyrrhiza glabra*	Viral Membrane	Membrane fusion inhibition	*In vitro* (Orthopoxviruses)
Acemannan	*Aloe barbadensis*	Fibroblasts (Host)	Wound healing; Re-epithelialization	*In vivo* (Wound models)

8. Prevention and Public Health Control

8.1 Vaccination Strategies

The best way of preventing Mpox infection and minimizing the severity of the disease is through vaccination. The third-generation non-replicating live vaccine, known as Imvamune/Imvanex (JYNNEOS), utilizes the Modified Vaccinia Ankara strain. The third-generation live vaccine is the most prevalent globally due to the strong safety profile of the vaccine, especially in those whose immune systems are compromised. The outcome of the 2022 outbreak indicates that it is 66-85 percent effective after two doses. This is either given subcutaneously or intradermally and intradermal route enables dose saving (one-fifth dose) in case there are shortages of supply[47]. There is an important role of LC16m8, a replicating attenuated vaccine that was developed in Japan and recently approved by the WHO as emergency use listing, in the outbreak context, specifically in the pediatric demographic of the DRC[48]. As an effective treatment measure, ACAVS2000 has some associated risks, such as myopericarditis and progressive vaccinia, which restrict its application in immunocompromised underprivileged patients, as well as in patients with atopic dermatitis. Besides, moderna and BioNTech are in a phase of clinical trials (2025-2026) of mRNA-based Mpox vaccines that will enhance efficacy and surgical manufacturability[49].

8.2 Public health Response and One Health

The core element of Mpox control is strong surveillance systems, especially using genomic surveillance that would distinguish between Clade Ia, Ib, and IIb strain, thus proposing risk-stratified public health actions. International ports of entry which comprise sentinel surveillance like that enforced in India offer a good system of cases of importation being detected early. There must be tailored prevention and control (IPC) against infection wherein the patient ought to stay isolated until the lesion heals entirely characterized by crusting, separation of scabs, and re-epithelialization that usually takes 2-4 weeks. The healthcare staff is advised to use contact precautions and airborne protection (such as using

N95 respirators) when performing aerosol-generating interventions or when manipulating infected substances. Notably, the strategies of public health communication should go in the right direction by being proactive to avoid the use of stigmatization of the affected groups since stigmatization can hinder the contact tracing process, delay the seeking of healthcare services, and hamper the containment of the outbreaks[4,11,50].

9. Conclusion and Future Perspectives

The history of Mpox as a forgotten zoonosis to a recurrent global health menace speaks of the vulnerability of our biosecurity in a globalized society. The development of Clade Ib in 2024-2026 is a serious increase in the potential of the pathogen, supported by genomic changes that allow the free movement of a person to a person through various pathways.

Even with significant advances since 2022, so-called "Tecovirimat paradox" of the primary antiviral proving of little clinical use in mild cases of Mpox indicates a serious failure in current medical countermeasures. This absence requires a tactical re-instrumentation of international response systems. To improve the treatment efficacy and preparedness to combat outbreaks, first, it is necessary to provide accelerated research and development of next-generation antivirals and mRNA-based vaccines. Second, based on promising in silico findings, integrated translational research must progress phytopharmaceutical candidates to stringent clinical proof-of-concept trials. Bioactive substances like curcumin and triterpenoids from neem should be carefully tested as easy-to-get, dose-sparing additions, especially in places where resources are limited. Third, fair global sharing of effective vaccines such as LC16m8 and MVA-BN to endemic countries in Africa is both ethical requirement and an epidemiological requirement to reduce the long-time transmission and avoid future occurrences of international spillover.

The Clade Ib study underscores the importance of stringent vigilance concerning India. The public health systems will be able to develop resilience against this emerging viral threat through the incorporation of advanced genomic surveillance with a comprehensive strategy of managing such viruses through the integration of both modern virology and evidence-based traditional medicine.

Author Contributions

Conceptualization, P.K.; methodology, P.K. and V.K.; literature search and data curation, P.K. and V.K.; formal analysis, P.K., V.K., and A.K.R.; writing—original draft preparation, P.K.; writing—review and editing, V.K. and A.K.R.; visualization, P.K. and A.K.R.; supervision, A.K.R.; project administration, A.K.R. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

Abbreviation	Definition
APOBEC3	Apolipoprotein B mRNA Editing Catalytic Polypeptide-like 3
CFR	Case Fatality Rate
COVID-19	Coronavirus Disease 2019
DRC	Democratic Republic of the Congo
DNA	Deoxyribonucleic Acid
EEV	Extracellular Enveloped Virion
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
ICMR	Indian Council of Medical Research
IFN-γ	Interferon Gamma
IMV	Intracellular Mature Virion
IPC	Infection Prevention and Control
MPXV	Monkeypox Virus
Mpox	Monkeypox
MSM	Men Who Have Sex with Men
MVA-BN	Modified Vaccinia Ankara–Bavarian Nordic Vaccine
NCDC	National Centre for Disease Control
NF-κB	Nuclear Factor Kappa B
NIV	National Institute of Virology
NK	Natural Killer
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PALM007	Program for Mpox Antiviral and Clinical Management Trial 007
PCR	Polymerase Chain Reaction

PHEIC	Public Health Emergency of International Concern
PPE	Personal Protective Equipment
RT-PCR	Real-Time Polymerase Chain Reaction
STI	Sexually Transmitted Infection
TCM	Traditional Chinese Medicine
UAE	United Arab Emirates
VIG	Vaccinia Immune Globulin
WHO	World Health Organization
WGS	Whole-Genome Sequencing

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