TROPICAL LIFE SCIENCES RESEARCH

INVITED REVIEW

Mpox: Transmission Insights, Pathogenesis, and Emerging Therapeutics

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Highlights

- Integration of findings from current mpox studies through the lens of clinical medicine, molecular biology (including diagnostics and pathogenesis), and public health.
- Evidence on climate change, animal reservoirs, and zoonotic spillover, encompassing the concept of One Health.
- Exploration of viral immunomodulatory mechanisms, aerosol kinetics, and pathogen-host interactions of mpox infections, as well as nanotechnology-based vaccines, nanoparticle antivirals, and ethnopharmaceuticals.

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EARLY VIEW

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Mpox: Transmission Insights, Pathogenesis, and Emerging Therapeutics

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Running title: Mpox: Integrated Global Perspectives

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Abstract: Introduction: Mpox is a re-emerging zoonotic disease that has experienced a global resurgence. Contributing factors include discontinuing smallpox vaccination and climate change-related events, such as species migration and the urbanization of forest areas. **Methods:** A comprehensive analysis of related literature was conducted. This literature review covers topics on the transmission routes of the monkeypox virus, infection control, diagnosis, treatment, and potential new technologies or ethnopharmaceuticals to inhibit infection. **Results:** This review paper is divided into four major parts: (1) transmission pathways: airborne and contact routes of respiratory pathogens, (2) mpox diagnosis: from clinical presentation to laboratory testing, (3) pathogenesis of mpox and interaction with other co-existing diseases, and (4) mpox prevention and treatment strategies. The last section is divided into subsections: vaccine, antivirals, and exploring alternative approaches against mpox. The alternative approaches cover topics on the application of nanotechnology and plant-based therapies. The paper concludes with a discussion of future directions for mpox. **Conclusion:** Research on mpox underscores the urgent need for improved diagnostics, treatment evaluation, and prevention strategies. The current outbreak highlights gaps in our understanding of the virus, particularly its transmission dynamics and the long-term efficacy of existing therapies. Advancing research into alternative treatments, such as nanotechnology and medicinal plants, alongside enhanced global surveillance and rapid response systems, will mitigate future outbreaks and improve public health outcomes.

Keywords: Monkeypox, Transmission, Prevention, Aerosols, Diagnosis, Natural Products, Nanomaterials, Phytochemicals

INTRODUCTION

Mpox, previously known as monkeypox, is a re-emerging zoonotic infectious disease that has become a global concern worldwide (Yang 2022) [1]. The monkeypox virus (Poxviridae) belongs to the Orthopoxvirus genus (Wang et al. 2023) [2]. It has a double-stranded DNA genome encapsulated in a protein nucleocapsid and shares close similarities with the smallpox virus.

The first human cases of mpox were reported in the 1970s in the Democratic Republic of Congo. Since then, two clades have been identified based on genetic differences– the West African and the Congo Basin clades (Likos et al. 2005) [3]. In 2022, an outbreak was reported that affected several regions of the globe. It was primarily associated with the West African clade, as indicated by viral genome sequencing from a patient in Portugal (Europe) (Isidro et al. 2022) [4].

This outbreak appeared to be under control, with cases stabilizing in 2023. However, in 2024, the World Health Organization (WHO) declared mpox a public health emergency of international concern, again. According to the external situation report published on December 8th, from January 1st to October 31st, 2025, there have been a total of 47, 980 laboratory-confirmed cases of mpox with 201 deaths across 94 territories (WHO 2025a) [5]. WHO temporarily designated mpox as a public health emergency of international concern (PHEIC) during successive Emergency Committee meetings through 2025, and although the PHEIC status was lifted on 5 September 2025, WHO continues, to recommend optimized clinical care, early HIV testing for people with suspected mpox, and rapid initiation of antiretroviral therapy (ART) for people living with untreated HIV, given the higher risk of severe disease and death associated with advanced HIV infection (WHO 2025b) [6]. A 2025 epidemiological update from the European Centre for Disease Prevention and Control (ECDC) highlights the geographical expansion of clade I MPXV cases beyond endemic areas since mid-2024, underscoring the role of routine indicator and event-based surveillance in tracking trends (ECDC 2025) [7].

As a zoonotic disease exhibits symptoms like smallpox, such as fever, chills, headache, and the subsequent development of rashes that start on the face and spread to other parts of the body (CDC 2024a) [8]. It is transmitted to human populations through contact with an unidentified animal reservoir (Grant et al. 2020) [9]. Climate change-induced demographic changes can increase human exposure to these reservoir species (Jamil et al. 2022) [10], highlighting the importance of the One Health concept. One Health is a transdisciplinary disease prevention strategy that considers the interconnectedness of human and animal health. It aims to improve the response and prevention of zoonotic disease outbreaks (Reynolds et al. 2019; CDC 2024b)[11-12].

Another route of mpox spread is human-to-human transmission, which often occurs through direct contact with patient blisters (Sah et al. 2022) [13]. Respiratory droplets contaminated surfaces, and clothing can also contribute to transmission. Understanding the viability of viral particles on surfaces (Petersen et al. 2019) [14] is crucial, particularly in hospital settings, where healthcare professionals may be at risk of hospital-acquired infections (Gould et

al. 2022) [15]. Therefore, it is necessary to develop updated protocols for healthcare professionals' safety based on a comprehensive characterization of contamination sources.

Diagnosing mpox relies on several methods, including genetic and immunological approaches. Among these methods, the polymerase chain reaction (PCR) has proven to be the most accurate in diagnosing the disease (Hraib et al. 2022) [16]. Additionally, a patient's immunization history is crucial when diagnosing mpox, as previous smallpox immunization provides some protection against monkeypox. It is believed that the termination of smallpox vaccination may have allowed the virus to spread in human populations (Nguyen et al. 2021) [17]. To effectively address the interaction of pox with other viruses or diseases, preventive measures such as vaccines should be combined (Rizk et al. 2022) [18].

For treatment, antivirals like tecovirimat (TPOXX), Vistide (cidofovir), and Tembexa (brincidofovir) have been approved to manage pox symptoms (CDC 2024c; 2024d) [19-20]. Furthermore, natural products commonly used in traditional medicine have shown promise in enhancing immunity and controlling symptoms (Abubakar et al. 2022) [21].

In this review, our goal is to provide an overview of mpox and the associated outbreak. We will discuss the transmission routes of the monkeypox virus, implications for healthcare professionals and infection control, interactions with other diseases, diagnosis, treatment, and potential new technologies or ethnopharmaceuticals to inhibit infection.

TRANSMISSION PATHWAYS: AIRBORNE AND CONTACT ROUTES OF RESPIRATORY PATHOGENS

The monkeypox virus has two main routes of transmission: animal-to-human and human-to-human. Mpox is a disease originating in animals and is transmitted to humans through the first route. This occurs in areas where the disease is endemic and during outbreaks, such as the one in the United States in 2003 (Reed et al. 2004) [22]. Several animal species, including *Monodelphis domestica* (gray short-tailed opossum), *Oryctolagus cuniculus* (white rabbit), and *Mus musculus* (laboratory mouse), have been found to acquire and transmit the infection (Reynolds et al. 2019) [11], potentially creating reservoirs. Humans can contract the virus through direct contact with these animals, such as hunting or processing infected animals for food. Factors like climate change, armed conflicts, and deforestation have increased contact between humans and these species, causing populations to move closer to these reservoirs (Thomassen et al. 2013) [23]. This highlights the need for an intersectoral approach to prevent mpox outbreaks from

these contacts. Such an approach must consider not only epidemiological concepts but also ecological ones.

In the 2022 outbreak, there is a link between individuals who traveled to endemic countries and attended large gatherings, indicating that human-to-human transmission is the main route of infection (Bragazzi et al. 2023) [24]. This infection is known to spread through skin lesions and body fluids, leading researchers to investigate the presence of viral DNA in semen samples and confirm the shedding of the virus in seminal fluid (Lapa et al. 2022) [25]. Initially, there were concerns that mpox was a sexually transmitted disease due to most infected individuals being men who have sex with men (MSM) (Sah et al 2022; Bragazzi et al. 2023; Rodriguez-Morales & Lopardo 2022) [13, 24, 26]. However, it is important to note that transmission can occur during sexual activity, but it is not exclusive to it. Any contact with infectious rashes, blisters, scabs, crusts, or fluids from sores can be a source of infection. This clarifies that mpox is not solely a sexually transmitted disease. However, sexual contact does pose a high risk of transmission due to the presence of genital lesions in infected patients (Low et al. 2023) [27].

Another type of human-to-human transmission is through respiratory droplets and contaminated surfaces. Although not as common as infection via contact with blisters, this pathway is highly important to create suitable risk assessment measures and protocols. In the 2022 mpox outbreak, healthcare professionals reported hospital-acquired infections without direct contact with the patient's lesions. After one of these reports in the UK, a study detected viable viral particles in air samples obtained around an area close to the bed during changing. Therefore, sustaining the appropriate protection equipment is important since it shows that viral particles can be re-aerosolized (Gould et al. 2022) [15].

Regarding aerosol transmission, few studies have previously demonstrated that viral particles can be detected up to 90 h in air samples (Verreault et al. 2013; Nalca et al. 2010) [28-29]. However, viral kinetics still needs further research, primarily due to its high unpredictability, since viral particles depend on several factors to remain viable in aerosols, such as humidity and temperature Nalca et al. 2010 [29]. As for surface contamination, it has been shown that mpox viral particles can be detected at distances greater than 1 m and heights taller than 2 m (Gould et al. 2022) [15], and they can be found on several surfaces like door handles, floors, bedding, and even the doctor's/nurse's gloves, posing a significant risk for healthcare professionals (Nörz et al. 2022) [30]. Figure 1 presents the transmission pathways of the mpox virus.

The use of proper protection equipment and suitable facilities are two critical factors for the proper prevention of transmission from contaminated surfaces and aerosols. According to the Centers for Disease Control and Prevention (CDC), healthcare professionals must use personal

protective equipment, such as gloves, gowns, and ocular and respiratory protection Nalca et al. 2010 [29]. It is also important to establish the safety of healthcare facilities regarding proper isolation spaces for patients and adequate ventilation and disinfection of these areas to assure the protection of healthcare professionals (CDC 2024e) [31]. In May 2025, the WHO issued guidelines for the clinical management and infection prevention and control of mpox, where recommendations include both patients and healthcare professionals, mild and severe diseases and even psychological support. In healthcare settings, infection prevention and control (IPC) measures should include spaces designed to reduce airborne and contact exposure risks including: airborne infection isolation rooms (AIIRs) (negative pressure rooms) for patients with suspected or confirmed mpox, especially during aerosol-generating procedures and when handling contaminated linens or clinical waste; appropriate air changes per hour (ACH) and high-efficiency particulate air (HEPA) filtration to dilute and remove potentially infectious particles from the air; controlled ventilation systems that maintain directional airflow away from healthcare workers and other patients (WHO 2025c) [32].

Further understanding of the viral kinetics of mpox and the viability of viral particles in various environments. The strategic preparedness, readiness, and response plan of WHO identifies this as a critical area requiring urgent research (WHO 2024a) [33]. This research is essential for implementing enhanced safety protocols, particularly in healthcare settings.

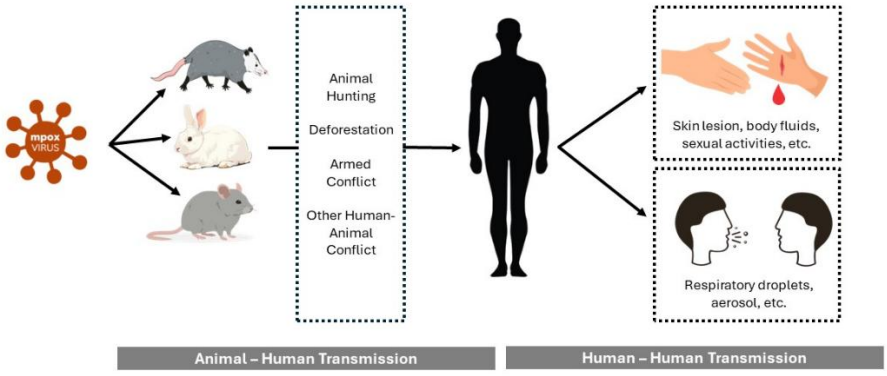

Figure 1. Conceptual overview of monkeypox (mpox) virus transmission pathways. ©RVL The diagram illustrates zoonotic spillover from animal reservoirs, such as *Monodelphis domestica* (gray short-tailed opossum), *Oryctolagus cuniculus* (white rabbit), and *Mus musculus* (laboratory mouse) to humans through human activities such as hunting and deforestation. The transmission

is established through human-animal contact, followed by sustained inter-human transmission via direct contact with skin lesions, body fluids, sexual contact, and exposure to respiratory droplets or aerosols. This figure is synthesized from published epidemiological evidence (WHO and CDC, 2022-2024) and outbreak reports and is not derived from primary quantitative data.

MPOX DIAGNOSIS: FROM CLINICAL PRESENTATION TO LABORATORY TESTING

To start the diagnosis of mpox, standard operating procedures (SOPs) must be followed to guarantee the safety of medical/laboratory personnel. These include proper collection, transportation, and handling of samples (Nakhaie et al. 2023) [34] that follow identical guidelines internationally (NICD 2023) [35]. The SOPs ensure the safety of frontline workers but also protect the entire community, relying on several practice rules when handling patients in hospitals and biological samples during laboratory testing. According to the CDC, the SOPs for handling laboratory samples include the following: performing tests in appropriate facilities (BSL-2 labs), ensuring complete viral inactivation of the sample before subjecting it to aerosol-generating procedures, adequately decontaminating all laboratory materials using methods such as autoclaving, disposing of waste in leak-proof containers, and requiring all personnel involved to wear personal protective equipment (CDC 2024f) [36].

Several diagnostic methods are available for mpox. One of these methods is polymerase chain reaction (PCR), which is standardized as the preferred technique for detecting mpox due to its high accuracy and speed. PCR allows for assessing factors such as viral load shedding and strain (León-Figueroa et al. 2023; Elbaz et al. 2023) [37-38]. Specifically, real-time PCR has been used for mpox diagnosis for over a decade. It targets the B6R protein gene in the viral envelope, providing a reliable and diagnostic tool (Li et al. 2010; 2006) [39-40]. Recent studies have further improved PCR methodology to differentiate between the two mpox clades. Two multiplex real-time PCR assays have been developed for this purpose, with specific primers designed to amplify the regions of the clade-specific mutations (Huo et al. 2022) [41].

One automated platform, GeneXpert® (Cepheid, USA), based on PCR methodology, has been proven to identify the monkeypox virus in various collected specimens accurately. This technology utilizes real-time PCR in a closed and automated system, minimizing the risk of contamination and enhancing usability in resource-limited areas. It provides rapid and accurate detection of mpox in a minimal timeframe (Li et al. 2017) [42].

Recombinase polymerase amplification (RPA) serves as an alternative to PCR-based methods. RPA is an isothermal amplification technique that uses enzymes to amplify DNA. It

specifically targets the G2R gene, which encodes a protein that binds to tumor necrosis factor and can be found in duplicate in the monkeypox virus genome (Davi et al. 2019) [43]. This method can be performed at temperatures ranging from 37 to 42 °C, eliminating the need for complex thermal cycling equipment. RPA is faster and easier to use than PCR, offering high specificity and sensitivity. These characteristics make it well-suited for settings with limited resources (Mills et al. 2023) [44]. Figure 2 presents the key molecular diagnostic methods for mpox and their distinguishing characteristics.

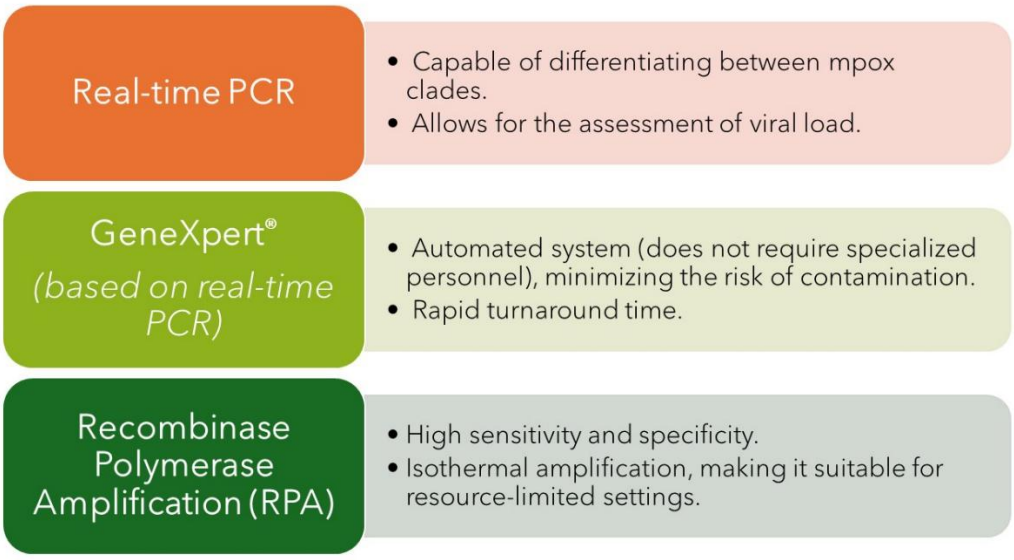

Figure 2. A comparison of three key molecular diagnostic methods for mpox and their unique advantages. PCR, polymerase chain reaction; GeneXpert®, a rapid, automated molecular diagnostic system from Cepheid®.

Methods that rely on serological or protein-based assays can be used to identify and characterize human mpox-specific antibodies (Keasey et al. 2010; Manenti et al. 2023; Gao et al. 2023) [45-47]. For instance, studies have focused on mAb 69-126-3-7, which has been proven to differentiate and can be utilized for mpox diagnosis (Hughes et al. 2014) [48]. An interesting development involves the production of glycovariants of 7D11, a monoclonal IgG antibody that targets the transmembrane protein L1 of the *Vaccinia* virus. These glycovariants were synthesized in *Nicotiana benthamiana*, a plant-based system, and could correctly fold into the tetrameric structure of IgG. They demonstrated the capability to bind to their specific antigen on mpox-infected cells (Esqueda et al. 2023) [49]. Moreover, plant-based synthesis of antibodies offers cost-effectiveness compared to traditional mammalian cell culture, reducing production costs by

approximately 50% and thus increasing availability (Nandi et al. 2016) [50].

Another point-of-care diagnosis technique is the ABICAP (Antibody Immuno-Column for Analytical Processes) immunofiltration system. It utilizes a capture antibody immobilized on a larger surface area than ELISA, leading to shorter incubation periods, ease of use, and the ability to detect monkeypox virus even with low viral loads (Stern et al. 2016) [51]. Point-of-care diagnostic tools like ABICAP or GeneXpert® help assure prevention in outbreak scenarios by facilitating access to clinical diagnostics. These and other diagnostic methods that can be performed without elaborate equipment and facilities and without highly specialized personnel constitute an important step in ensuring equal access to public health in underdeveloped areas (Wang et al. 2021) [52].

Medical imaging is also useful in detecting viral infections and predicting disease outcomes. Positron emission tomography/computed tomography (PET/CT) uses [18F]-fluorodeoxyglucose as a marker for glycolytic metabolism, allowing the observation of elevated glucose uptake as a sign of inflammation (Manta et al. 2023) [53]. This method has been proven to monitor disease progression and differentiate disease outcomes by obtaining real-time imaging of the immune response in lymphoid tissue and hypermetabolic cutaneous lesions in different body areas (Dyall et al. 2017; Dyall et al. 2011) [54-55]. CT scans, specifically abdominopelvic scans, have helped monitor mpox lesions and have allowed researchers to infer that proctitis is a common manifestation associated with mpox infections (Singh et al. 2023; Ola et al. 2023) [56-57].

Several diagnostic methods for mpox are currently available, relying on different approaches ranging from molecular to immunological techniques, microscopy, and cell culture (Nakhaie et al. 2023) [34].

MPOX PATHOGENESIS AND INTERACTIONS WITH OTHER CO-EXISTING DISEASES

The pathogenesis of the monkeypox virus involves three main steps: adsorption, membrane fusion, and core invasion (Gong et al. 2022) [58]. Poxviruses have immunomodulatory proteins that allow them to bind to the cell surface by interacting with glycosaminoglycans (GAGs), which are found in mammalian cells. One of these proteins is vIL-18BP, which aids in this binding process. Additionally, there is vIFNα/βBP, which can inhibit the antiviral cytokines IFN-I α/β responsible for activating the antiviral response. Poxviruses also possess complement inhibitors that bind to complement regulators C3b and C4b, manipulating them to keep the complement system inactive. These complement inhibitors, like the first immunomodulatory protein mentioned,

can also bind to GAGs, making it easier for them to attach to the host's cells (Hernaez & Alcami 2018) [59].

Once inside a healthy cell through endocytosis, the viral envelope of the monkeypox virus uncoats in the cytosol and releases DNA. This DNA undergoes replication, providing a template for mRNA synthesis. Subsequently, the viral genetic material is packed, forming a mature virion (MV) with a single external membrane. Some MVs can be wrapped by an endosomal membrane or the Golgi apparatus, becoming wrapped virions (WVs). These MVs can be transported along microtubules and fused with the plasma membrane, resulting in their release outside the cell as enveloped virions (EVs) (Moss 2012) [60] (Figure 3). Once released, the virus spreads to various organs, including the skin, causing characteristics of rashes and lesions associated with infection by this virus (Huang et al. 2022) [61]. The specific virulence of mpox, when compared to other orthopoxviruses, can be explained by the differences in their immunomodulatory proteins. Despite their differences, the resemblances between these viruses and the lack of immunity once sustained by smallpox vaccination may be why its cessation led to new mpox outbreaks.

Infection by the monkeypox virus can impact the epidemiology and outcomes of other infectious diseases. However, relatively few studies have been conducted on this subject. Most of the available information pertains to the interaction between monkeypox and sexually transmitted diseases, particularly HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome). Mathematical models have been employed to demonstrate this interaction and have shown that mpox infection can enhance HIV infection and vice versa (Bhunu et al. 2012; Bragazzi et al. 2022) [62,63]. These immunosuppressed individuals, constitute a population at markedly increased risk of severe mpox disease, complications, and mortality. Clinical evidence accumulated during recent outbreaks indicates that mpox infection in patients with profound immune dysfunction, especially those with $CD4^+$ T-cell counts below 200 cells/μL, frequently deviates from the self-limited clinical course typically observed in immunocompetent hosts. In this context, impaired cell-mediated immunity compromises viral clearance and facilitates extensive viral replication, resulting in atypical, progressive, and often disseminated disease manifestations (Azzam et al. 2024) [64].

In individuals with advanced immunosuppression, mpox may present with widespread, necrotic, or non-healing cutaneous lesions, often accompanied by confluent ulceration and secondary bacterial infections. Lesion evolution may be prolonged, with delayed crusting or failure to resolve, reflecting persistent viral replication (O'Shea et al. 2024) [65]. Importantly, systemic dissemination is more frequently observed in this population, with reported involvement of the respiratory tract, gastrointestinal system, liver, and, in severe cases, progression to sepsis and

multiorgan dysfunction. Pulmonary manifestations, including viral pneumonitis, and severe gastrointestinal disease, such as proctitis or enterocolitis, have been described and are associated with poor clinical outcomes. In some cases, cutaneous manifestations may be attenuated or absent, complicating clinical recognition and delaying diagnosis, particularly in healthcare settings that rely on rash-based case definitions (Taha et al. 2024; Pinnetti et al. 2024) [66,67].

Prolonged viral replication in severely immunosuppressed patients has been associated with extended viral shedding from multiple anatomical sites, including blood, respiratory secretions, and mucosal surfaces. This raises concerns regarding prolonged infectivity, increased risk of nosocomial transmission, and the potential for within-host viral evolution under selective immune pressure. These features underscore the importance of early diagnosis, rigorous infection prevention and control measures, and close clinical monitoring in immunocompromised populations (Schildhauer et al. 2025; Mitjà et al. 2023) [68, 69].

In response to these observations, the World Health Organization has recommended routine HIV testing for all patients with suspected or confirmed mpox, as well as rapid initiation or optimization of antiretroviral therapy in those diagnosed with HIV, given the critical role of immune reconstitution in controlling disease progression. The management of mpox in severely immunosuppressed individuals therefore requires a proactive and multidisciplinary approach. Prompt diagnostic confirmation is essential, even in the absence of typical skin lesions, and early initiation or re-initiation of antiretroviral therapy should be prioritized in people living with HIV. Supportive care remains central to management and includes adequate pain control, treatment of secondary bacterial infections, maintenance of fluid and electrolyte balance, and nutritional support. Close monitoring for systemic complications, such as respiratory failure, gastrointestinal bleeding, and sepsis, is warranted, and early involvement of infectious disease specialists is recommended for patients with progressive or severe disease (WHO 2024a) [33]. Taking together, the disproportionate burden of severe disease observed in immunosuppressed populations highlights the need for integrated clinical and public health approaches that link mpox diagnosis and management with HIV testing, treatment, and care. Strengthening surveillance, ensuring equitable access to diagnostics and clinical support, and tailoring management strategies for vulnerable populations are essential to reducing morbidity and mortality associated with mpox in the context of severe immunosuppression.

Given that COVID-19 cases are still prevalent, it is also important to consider the possibility of coinfection with the mpox virus. This coinfection can challenge clinicians' diagnosis, as mpox and COVID-19 infections share similar symptoms, such as fatigue, headaches, and sore throat.

Furthermore, some patients infected with mpox may not develop skin rashes, further complicating the diagnostic process (Mukherjee et al. 2022) [70]. Accurate diagnosis is crucial to provide appropriate treatment and ensure patient safety. For instance, if a patient does not exhibit skin rashes, mpox may go undiagnosed, resulting in inadequate treatment (Lai et al. 2020) [71]. Additionally, coinfection not only presents challenges for accurate diagnosis and treatment but may also give rise to new variants of both viruses. This presents further difficulties in effectively managing the pandemic, implementing public health measures, and predicting outcomes (Aghbash et al. 2021) [72].

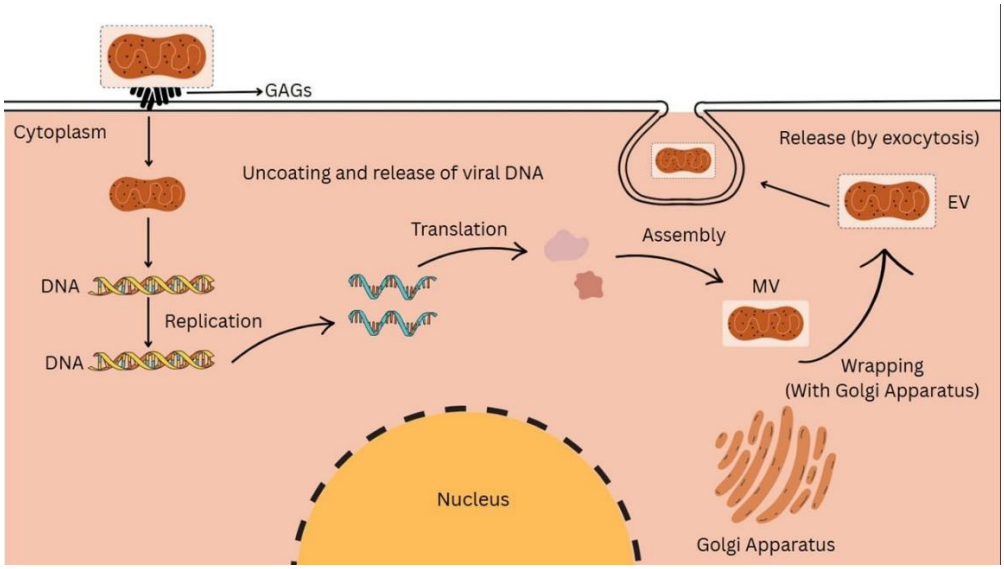

Figure 3. Schematic of the monkeypox (mpox) virus lifecycle. The mpox virus undergoes adsorption on the host cellular membrane and binds to glycosaminoglycans (GAGs) with the help of immunomodulatory proteins (vIL-18BP and vIFNα/βBP) and complement inhibitors. It then fuses with the host cell membrane and core invasion occurs with uncoating and the release of DNA that subsequently replicates and is transcribed. After translation of the mRNA, a mature virion (MV) is formed which is then wrapped by the Golgi apparatus, forming an enveloped virion (EV). The EV is the final form that is released by the cells and spread across the body. This figure is a conceptual illustration synthesized from published evidence (created using BioRender.com).

MPOX PREVENTION AND TREATMENT STRATEGIES

Mpox prevention is paramount to safeguarding public health and minimizing the risk of outbreaks. When implemented in combination, some measures prove significant in achieving this goal. The mpox prevention and treatment strategies are presented in Table 1.

Table 1. Mpox prevention and treatment strategies.

Measures for Prevention and Treatment	Brief Background	Reference
Vaccination	The smallpox vaccine, which provides cross-protection against mpox, has been used for prevention. Additionally, specific mpox vaccines are under development that can be used for prevention and symptom management.	(Aghbash et al. 2021; Rimoin et al. 2010; Poland et al. 2022) [72-74]
Early Detection	Regular monitoring of mpox cases, along with rapid diagnosis and reporting, is crucial for the early detection and containment of outbreaks.	(WHO 2024a) [33]
Personal Protective Measures	Encouraging individuals to practice good hygiene, including regular handwashing, can help reduce the risk of transmission.	(CDC 2024g) [75]
Animal Contact Precautions	Limiting contact with potentially infected animals, especially rodents and other small mammals, can prevent exposure to the virus.	(CDC 2024h) [76]
Isolation and Quarantine	Promptly isolating suspected or confirmed cases and implementing quarantine measures for close contacts can help prevent further spread.	(CDC 2024i) [77]
Infection Control in Healthcare Settings	Strict infection control protocols in healthcare facilities are essential to prevent nosocomial transmission. Additionally, proper organizational infrastructure can be pivotal.	(CDC 2024e) [31]
Public Health Awareness	Raising awareness about mpox, its symptoms, and preventive measures can help the public recognize and respond to potential cases.	(Ren et al. 2023) [78]

International Travel Guidelines	Health authorities may implement travel advisories or guidelines for regions with mpox outbreaks to limit international transmission.	(CDC 2024j) [79]
Contact Tracing	Identifying and monitoring individuals in contact with confirmed cases can help break the chain of transmission.	(WHO 2024) [80]
Research and Surveillance	Monitoring mpox virus activity, researching transmission patterns, and identifying potential reservoirs are critical for improving prevention strategies.	(WHO 2024) [80]

Vaccines

Many experts attribute the current outbreak of mpox to the cessation of smallpox vaccination, leaving naïve populations at higher risk (Nguyen et al. 2021; Rimoin et al. 2010) [17,73]. To address this, two FDA-approved vaccines are available for mpox: Bavarian Nordic JYNNEOS® and ACAM2000™ (Karim et al. 2022) [81]. JYNNEOS® is a modified vaccinia Ankara strain vaccine containing the virus in a modified form, stopping it from multiplying in the human body (Australian Government Department of Health and Aged Care 2024) [82]. JYNNEOS® reports a low incidence of severe adverse effects, and most of the registered adverse effects are related to erythema and swelling of the injection site (Duffy et al. 2022) [83]. ACAM2000™ is a live-attenuated replication-competent smallpox vaccine approved for use against mpox (Australian Government Department of Health and Aged Care 2024) [82]. ACAM2000™ registers more severe effects than the previous one, given its live form, and most of the adverse effects are related to myocarditis and pericarditis (Katamesh et al. 2023) [84]. These vaccines are recommended for prevention and can also be administered post-exposure to attenuate symptoms and reduce the risk of severe illness (Schildhauer et al. 2025) [68]. However, it is worth noting that vaccine acceptance is not universal, and the acceptance rate for mpox vaccines seems lower than surveys regarding COVID-19 vaccination (Ulloque-Badaracco et al. 2022) [85]. For now, this lower acceptance does not pose a significant problem for the population since mass vaccination is not yet required, and the outbreak appears to be stabilized. Moreover, general immunization is not recommended due to limited supply (Gruber 2022) [86]. However, suppose the monkeypox virus spread worsens, and/or we encounter viral mutations that result in higher disease severity and mortality. In that case, the fact that many people might not accept vaccination pro-grams may present challenges in controlling disease transmission. Therefore, proactive planning, prevention

strategies, and proper infection control guidelines are essential to complement vaccination efforts and ensure comprehensive public health measures.

Antivirals

No specific antiviral medications have been approved for treating monkeypox virus infections. Supportive care is the mainstay of treatment for mpox, which includes man-aging symptoms and providing relief for fever, pain, and skin lesions. The most common antivirals being used are cidofovir (CDV), brincidofovir (BCV), and tecovirimat (TPOXX) (Australian Human Monkeypox Treatment 2022) [87]. The first two are effective against mpox, smallpox, and other dsDNA viruses. At the same time, the third is known to be beneficial against orthopoxviruses only, having no proven effect against other dsDNA viruses (Siegrist & Sassine 2022) [88]. The cidofovir antiviral drug is shown to be very effective against poxvirus infections and is particularly recommended for use in immunosuppressed patients at risk of developing severe illness. Besides being beneficial against monkeypox virus infections, it is currently only approved for use against cytomegalovirus (CMV) retinitis in adult patients with HIV/AIDS and without renal dysfunction. This antiviral is only available for intravenous administration since it is poorly ab-sorbed orally (Ortiz-Saavedra et al. 2022; De Clercq 2002) [89-90].

As for brincidofovir, this antiviral has been widely used for symptom management and treatment of smallpox as it presents less potential to trigger drug resistance than other antivirals. Since it has shown its efficacy against smallpox and several other dsDNA viruses, it also constitutes a good option for use against mpox due to similarities between the two viruses (Chan-Tack et al. 2021; Florescu & Keck 2014) [91-92].

The third widely used antiviral drug is tecovirimat, which was also initially approved for use against smallpox. After being proven effective against smallpox and revealing no severe adverse effects, tecovirimat was approved to be used against mpox (Almehmadi et al. 2022; Hoy 2018) [93-94]. The antiviral was approved in the United States and the European Union, based on animal efficacy data and human safety profiles. Regulatory approvals relied on demonstrated survival benefit in non-human primate and rabbitpox models and safety in healthy volunteers. However, recently randomized clinical trial evidence challenges the assumption of clinical efficacy for monotherapy in human mpox. Data from the STOMP trial (Study of Tecovirimat for Human Mpox), conducted by the NIH-funded AIDS Clinical Trials Group (ACTG), indicated that tecovirimat did not significantly reduce time to clinical resolution of lesions nor improve pain outcomes among adults with clade II mpox relative to the study population’s expected clinical

course, leading to stopping enrollment after an interim analysis in late 2024. Similarly, initial analyses from the PALM007 trial in the Democratic Republic of Congo did not demonstrate a reduction in lesion duration compared with control populations in individuals with clade I mpox. The emerging evidence suggests that while tecovirimat is safe, its monotherapy clinical benefit in mpox patients has not been definitively established. Considering these findings, supportive care remains the cornerstone of clinical management, and further research is required to delineate patient subgroups, combination therapies, or timing of intervention that may yield therapeutic benefit (FDA 2025; NIH 2025) [95-96].

Concerns related to the rapid global spread of mpox, and the shortage of antivirals have prompted the search for alternative treatments. In response to this need, a study investigated the potential of already approved drugs (atovaquone, mefloquine, and molnupiravir) in combating the monkeypox virus. The study yielded promising results, showing these drugs are effective against monkeypox infection. Antivirals have been proven to play a crucial role in treating monkeypox, as their administration has been found to be more effective in reducing mortality compared to vaccination (Akazawa et al. 2023; Stittelaar et al. 2006) [97-98].

Exploring Alternative Approaches Against Mpox

The application of nanotechnology

Vaccination and antiviral drugs are often the primary resources when facing an out-break of an infectious disease. However, other approaches can be explored. Studies ap-plying nanotechnology and nanomaterials to medicine have been growing exponentially, including some studies exploring the inhibition of viruses like smallpox using nanomaterials (Stiepe et al. 2023) [99]. One study assessed the activity of silver nanoparticles (NPs) in inhibiting the monkeypox virus. It showed that silver-based nanoparticles of only 10 nm effectively inhibit the mpox infection in vitro (Rogers et al. 2008) [100]. This supports the utility of silver nanoparticles against mpox, as was previously shown in a study reporting that polysaccharide-coated silver nanoparticles can reduce HIV-I infectivity (Elechiguerra et al. 2005) [101].

A recent study has developed an mRNA-lipid nanoparticle vaccine against mpox. The vaccine contains lipid nanoparticles that consist of four highly conserved proteins from the monkeypox virus. The proteins M1 and A29 are involved in cellular entry and can be found in the mature virion stage during the mpox life cycle. The proteins A35 and B6 are involved in transmission and are present in the enveloped virion. Targeting these proteins allows the lipid

nanoparticle-based vaccine to neutralize the monkeypox virus (Freyn et al. 2023) [102]. In addition to this approach, other nano-based methods have been explored. Metal-based nanoparticles, such as iron oxide nanoparticles, can block the interaction be-tween the host and the virus during mpox infection. Specifically, iron oxide nanoparticles can be used to chelate the virus circulating in the blood (Mohamed et al. 2023) [103]. Since nanotechnology has significantly advanced in the past, applying different nanoparticles for mpox infections is an area of study that is prone to revealing promising results.

Plant-based therapies for mpox: Exploring nature's remedies against the virus

Monkeypox poses significant public health challenges worldwide. While vaccination and antiviral drugs remain crucial resources for outbreak management, exploring alternative approaches for monkeypox treatment has garnered increasing attention. Traditional medicine, with its historical use of medicinal plants for various ailments, offers a promising avenue for investigation.

In places like northern Nigeria, traditional medicine is widely used. An extensive review of the species used, and their purposes highlights many species available for treating various infectious diseases (Abubakar et al. 2022) [21]. One of these diseases is monkeypox. The study reveals that species like *Lagenaria breviflora*, *Balanites aegyptiaca, Eleusine coracana,* and *Lawsonia inermis* are used in different states of northern Nigeria to treat monkeypox symptoms. However, these results are yet to be demonstrated in vitro, emphasizing the need for further studies to identify and characterize specific compounds of these species for their therapeutic properties (Abubakar et al. 2022) [21].

Another species effective against mpox symptoms is *Plantago lanceolata* (ribwort plant or lamb’s tongue). This species is known for its properties in wound healing and immunity enhancement. It has been studied for the presence of antiviral compounds against monkeypox, and the positive results suggest that *P. lanceolata* can be considered a good candidate for developing novel mpox therapies (Bajrai et al. 2022) [104].

Myrianthus arboreus, commonly used as an analgesic by the Ngbaka tribe from the Democratic Republic of Congo, is one of the primary choices for monkeypox treatment in the Nord Ubangi region (Bobuya et al. 2022) [105]. *Sarracenia purpurea* (purple pitcher plant) has been used to treat smallpox since the nineteenth century. It has also been investigated and proven to inhibit the replication of poxviruses, preventing early viral transcription. These features make *S. purpurea* another candidate for the development of therapeutics against monkeypox (Arndt et al. 2012) [106] (Figure 4).

These herbal species and others suitable for this purpose can be administrated in different ways and by using different parts of the species. Leaves stems, roots, flowers, fruits, or the whole organism can be treated, depending on which part is more beneficial. The mode of preparation and the route of administration are just as variable as the part of the organism used, and they all depend on the optimal effect of the treatment. Interestingly, in silico studies suggest that several plant-based compounds like rosmarinic acid, myricitrin, and quercitrin can be effective inhibitors of monkeypox DNA topoisomerase 1, which is a highly conserved viral DNA repair enzyme and so can make an effective therapeutic target (Hu et al. 2023) [107] (Figure 5). Another compound, berberine, a natural isoquinoline alkaloid in various medicinal plants like *Berberis vulgaris, Coptis chinensis,* or *Hydrastis canadensis,* is a good target for new studies. This compound has anti-inflammatory activity by stopping inflammatory cell infiltration and antiviral activity by acting against viral cell entry and replication (Warowicka et al. 2020) [108]. Like berberine, compounds like saikosaponins have the same properties and can attenuate pro-inflammatory cytokines (Xiaojiaoyang et al. 2018) [109], highlighting the need for further comprehensive research based on plant-active compounds or ethnophytochemicals.

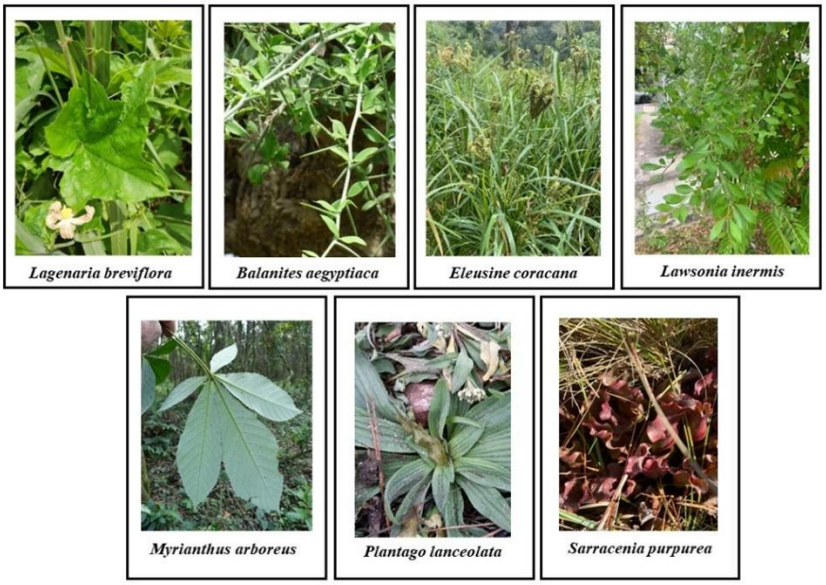

Figure 4. Photographic representation of plant species used as natural therapeutic bioactive extracts against mpox. All images were obtained from the Global Biodiversity Information Facility (GBIF) database: *Lagenaria breviflora* (observed in Sao Tome and Principe by Luis Silva); *Balanites aegyptiaca* (observed in Nigeria by Abubakar S. Ringim); *Eleusine coracana* (observed in Nepal by karisaunders); *Lawsonia inermis* (observed in Singapore by anapom); *Myrianthus*

arboreus (observed in Liberia by Carel Jongkind); *Plantago lanceolata* (observed in Russian Federation by Maria Kohanovskaya); *Sarracenia purpurea* (observed in United States of America by mattiemc) (www.gbif.org).

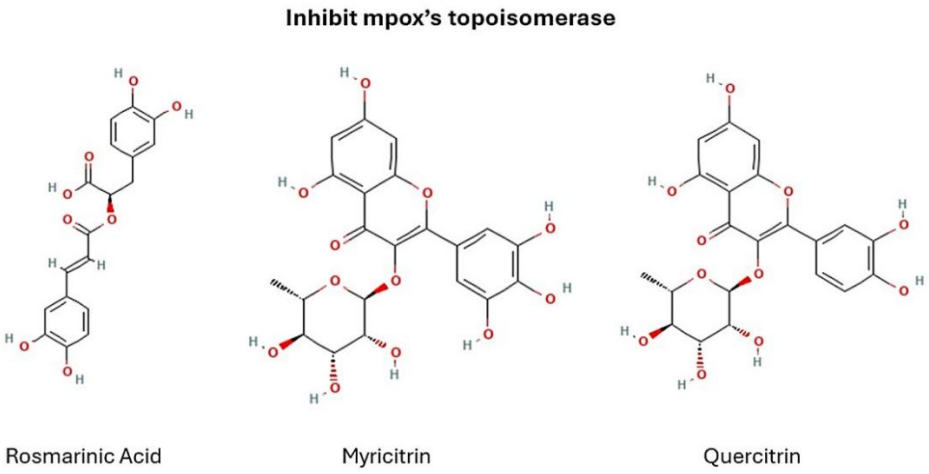

Figure 5. Chemical representation of plant compounds which have been found to be effective against mpox. All images were obtained from PubChem. These compounds have demonstrated the enhanced capability of inhibiting mpox's topoisomerase one than a clinical molecule (ofloxacin) [96]: Rosmarinic acid – IUPAC name (2R)-3-(3,4-dihydroxyphenyl) -2- [(E)-3- (3,4-dihydroxyphenyl) prop-2-enoyl]oxypropanoic acid; Myricitrin – IUPAC name 5,7-dihydroxy-3-[(2S,3R,4R,5R,6S) -3,4,5-trihydroxy-6-methyloxan-2-yl] oxy-2-(3,4,5-trihydroxyphenyl) chromen-4-one; Quercitrin – IUPAC name 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxychromen-4-one (https://pubchem.ncbi.nlm.nih.gov/).

Lastly, the species identified here are just a few of the many available for treating symptoms of infectious diseases (Ben-Shabat et al. 2020) [110]. Other species/genera with potential effects against mpox are presented in Table 2. For example, the echinacea genus is widely used to enhance immunity (Dobrange et al. 2019) [111]. It has been proven to regulate immunomodulatory pathways, making it a potential target for direct properties against mpox. *Kalanchoe pinnata, Alchemilla vulgaris,* and *Solanum paniculatum* have shown antiviral effects against viruses from the same genus as mpox (Cryer et al. 2017; Filippova 2017; Valadares et al. 2009) [112-113,119].

Quillaja saponaria can destroy viral envelopes (Roner et al. 2007; Tam & Roner 2011) [117-118], which mpox possesses, and *Nigella sativa* and the *Elsholtzia* genus have anti-inflammatory properties (Koshak et al. 2021; Chen et al. 2022) [115-116]. Therefore, the plants listed in this table can be potential targets for future studies on their therapeutic properties, which can be repurposed against mpox and serve as starting points for developing new therapies. Further characterization of these and other species is still needed as they can be alternative treatments that help clinicians attenuate severe symptoms in patients. Natural products that have already demonstrated efficacy against HIV, HSV, influenza, hepatitis, coxsackievirus, and COVID-19 (Akram et al. 2018; Boozari & Hosseinzadeh 2021) [120-121] should also be considered for the treatment and prevention of mpox, as their antiviral activity may be effective against mpox. Products derived from these species may also be easier to manufacture and distribute. However, it is necessary to consider the sustainable use of one or more species and ensure that nature's exploitation is always accounted for.

Table 2. Summary of the anti-inflammatory and/or antiviral properties of medicinal plant species/genus suitable for consideration as potential mpox treatment.

Medicinal plants	Site of extraction	Properties	References
Echinacea (genus)	Extracts from roots or aerial parts	Antiviral and anti-inflammatory properties in several species from this genus, from purified compounds like glycoproteins, soluble polysaccharides, phenolic compounds, and alkamides that can regulate immunomodulatory pathways	(Dobrange et al. 2019) [111]
Kalanchoe pinnata (species)	Extracts from roots	Compounds such as flavonoids, phenols, and bufadienolides show antiviral activity in *in vivo* and *in vitro* studies. Compound KPB-100 has already been proven effective against vaccinia virus	(Cryer et al. 2017) [112]
Alchemilla vulgaris (species)	Extracts from roots and aerial parts	Extracts contain catechins, leukoantocyans, and flavonoids and demonstrated antiviral activity suppressing reproduction of orthopoxviruses	(Filippova 2017) [113]

Nigella sativa (species)	Extracts from seeds	Immunomodulatory effects through the stimulation of cytokine production. It also shows a significant effect in alleviating COVID-19 symptoms	(Gholamnezhad et al. 2014; Koshak et al. 2021) [114-115]
Elsholtzia (genus)	Extracts from roots and aerial parts	Active components such as flavonoids and terpenoids from the species of this genus provide antiviral activity by inhibiting viral cell fusion and viral replication, blocking viral receptors, or suppressing the inflammatory response	(Chen et al. 2022) [116]
Quillaja Saponaria (species)	Extracts from the bark	Aqueous extracts from this species possess triterpenoid saponins with antiviral properties such as the ability to destroy viral envelopes and to lead to the loss of viral binding sites	(Roner et al. 2007; Tam & Roner 2011) [117-118]
Solanum paniculatum (species)	Extracts from leaves	Steroidal glycosides have demonstrated antiviral activity, and the presence of $\Delta^{25(27)}$-tigogenin-3-*O*-*β*-D-glucopyranoside has been proven to be responsible for antiviral activity against vaccinia virus	(Valadares et al. 2009) [119]

Footnote: COVID-19, Coronavirus disease 2019

CONCLUSION AND FUTURE DIRECTIONS

The re-emergence of the monkeypox virus, which is currently causing the outbreak, can be attributed to several factors. These include discontinuing smallpox vaccination, issues related to climate change, such as species migration, and demographic changes resulting from deforestation. Deforestation has brought people closer to reservoirs, as we have demonstrated. Various diagnostic methods are currently available for mpox, as dis-cussed in this paper. In terms of treatment, there are options; however, further research is needed to evaluate the safety and effectiveness of most available treatments, according to the reviewed papers. It is important to consider alternative methods for treating mpox symptoms, such as exploring nanomaterials that can inhibit viral activity. These materials can be used for the development of new therapeutics. Natural products are also a potential source of treatments, but further research and

characterization are required. These products have been used in traditional medicine for centuries. With the help of modern science, they can be further developed to create more effective and safer therapeutics.

Preventing outbreaks like the one we are currently experiencing with mpox, as well as with COVID-19, requires consideration of several factors. Ongoing surveillance of out-break development is crucial to ensure that measures are updated and suitable for the situation. One important factor to pay close attention to is aerosol transmission, as explored in this article. Safety measures must be based on a deep understanding of viral kinetics to determine how long viral particles can remain viable in aerosols and on surfaces, as these are the primary risk factors in healthcare settings. Further studies are needed to fully characterize these variables, which are key in creating global prevention protocols.

Preventing outbreaks also relies on the ability to monitor risk groups and patterns of disease spread. Some studies have explored different methods for this purpose, such as monitoring potential clusters of infection through environmental and wastewater surveil-lance, as viral DNA can be found in these sources (Tiwari et al. 2023; de Jonge et al. 2022) [122-123]. Other methods, including technology and artificial intelligence (AI), are being explored as new tools to predict spreading patterns and assist with monitoring and prevention (Bhalla & Payam 2023; Patel et al. 2022) [124-125]. Lastly, more institutions need to invest in medicinal plant research, as it has been relatively scarce in the European region compared to countries like China, India, and Brazil, which are leading in research on this topic (Salmerón-Manzano et al. 2020) [126].

The species presented in this review serve as a starting point for studies, allowing them to be directed and adapted for mpox therapies. In addition to discovering new plant species and compounds, it is also crucial to learn how to cultivate and domesticate the ones already known to be effective. The compounding interest in plant-derived compounds as potential sources of antiviral agents against mpox also raises important considerations related to sustainability, ethical bioprospecting, and equitable benefit-sharing. Many medicinal plants investigated for antiviral activity are sourced from biodiverse regions, including tropical and subtropical ecosystems, where overharvesting and habitat degradation pose significant risks to ecological balance. Unsustainable extraction of bioactive plant materials may threaten local plant populations and undermine long-term availability, highlighting the need for responsible sourcing practices, cultivation strategies, and adherence to conservation principles in the development of plant-based therapeutics. From a translational perspective, integrating sustainability and ethics into early-stage drug discovery may also facilitate regulatory acceptance and public trust. Strategies such as synthetic or semi-synthetic production of lead compounds, use of plant cell cultures, and

prioritization of renewable plant parts (for instance, leaves rather than roots or bark) can reduce ecological impact while maintaining pharmacological viability. Together, these considerations underscore that the development of plant-based antiviral therapies for mpox should be guided not only by efficacy and safety, but also by environmental stewardship, ethical responsibility, and social equity (WHO 2025) [127]. This will enable their application in therapies and their production for worldwide use.

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