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Monkeypox infection: The past, present, and future

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ABSTRACT

Monkeypox is a zoonotic illness caused by the monkeypox virus (MPXV) that has a similar etiology to smallpox. The first case of monkeypox was reported in Western and Central Africa in 1971, and in 2003, there was an outbreak of monkeypox viruses outside Africa. According to the World Health Organization (WHO) and Center for Disease Control and Prevention (CDC), monkeypox is transmitted through direct contact with infected animals or persons exposed to infectious sores, scabs, or body fluids. Also, intimate contact between people during sex, kissing, cuddling, or touching parts of the body can result in the spreading of this disease. The use of the smallpox vaccine against monkeypox has several challenges and hence anti-virals such as cidofovir, brincidofovir, and tecovirimat have been used for the symptomatic relief of patients and reversing the lesion formation on the skin. Despite the recent outbreak of monkeypox most especially in hitherto non-endemic countries, there is still a lack of definitive treatment for monkeypox. In the present review, emphasis was focused on etiopathology, transmission, currently available therapeutic agents, and future targets that could be explored to halt the progression of monkeypox. From our review we can postulate that owing to the lack of a definitive cure to this reemerging disorder, there is a need for general awareness about the transmission as well as to develop appropriate diagnostic procedures, immunizations, and antiviral medication.

1. Introduction

Monkeypox is a zoonotic infection caused by the monkeypox virus, an orthopoxvirus closely related to the variola virus that causes smallpox [1]. In 1958, first incidence of monkeypox was reported among monkeys who were housed for research purposes, therefore it was named “monkeypox” [2]. The first human case of monkeypox was recorded in the Democratic Republic of Congo (DRC) in 1971 [1]. The first case outside of Africa, however, was discovered in the United States in 2003, and it was connected to contact with infected pet prairie dogs. These animals were housed with Gambian stuffed rats and dormice brought from West Africa (Ghana) [3].

One of the four orthopox virus species that can infect humans is the human monkeypox virus (MPXV), a double-stranded DNA virus that is a

member of the Poxviridae family and the orthopoxvirus genus [4]. The other three are the cowpox virus, variola minor virus, and variola major virus (VARV), which together cause smallpox, which is currently eradicated [5]. The monkeypox virus has been divided into two genetic clades: West African and Central African [5]. Geographical differences between these two clades are accompanied by distinct epidemiological and clinical traits. The West African clade has a case mortality rate (CMR) of less than 1% and no evidence of human-to-human transmission, whereas the Congo Basin clade (also known as the Central African clade) has a CMR of approximately 11% with a recorded human-to-human transmission [5,6]. Monkeypox has a symptomatic appearance similar to smallpox, but the presence of swollen lymph nodes at the onset of fever distinguishes MPX from smallpox [7]. The specific method by which MPXV is transmitted to humans is unknown. Although the

Abbreviations: Abs, Antibodies; ACIP, Advisory committee on immunization practices; CDC, Centers for Disease Control and Prevention; CEV, Cell-associated enveloped virus; CFR, Case fatality rate; CPXV, Cowpox virus; DRC, Democratic Republic of the Congo; EEV, Extracellular enveloped virus; HSV, Herpes simplex virus; IEV, Intracellular enveloped virus; IFN- γ , Interferon; IMV, Internal mature virus; MHC, Major histocompatibility complex; MPXV, Human monkeypox virus; NK, Natural killer; OPXVs, Orthopoxviruses; PCR, Polymerase chain reaction; PFU, Plaque-forming units; PPE, Personal protective equipment; PrEP, Pre-exposure prophylaxis; Th, T-helper; TLRs, Toll-like receptors; TNF- α , Tumor necrotic factor; VACV, Vaccinia virus; VARV, Smallpox virus; VARV, Variola major virus; VZV, Varicella-zoster virus; WHO, World Health Organization.

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actual mechanism(s) of primary animal-to-human infection are unknown, it is believed that it happens when people handle animals that have the monkey pox either directly (by touching, biting, or scratching them) or indirectly. The respiratory tract, mucous membranes, or broken skin are thought to be entry points for the virus (eyes, nose, or mouth) [5]. It takes 6–13 days for the symptoms of monkeypox to develop. When it comes to clinical presentation, smallpox and monkeypox patients share similar symptoms and lesions [5]. Even though it can be severe in some people, such as newborns, pregnant women, and those with impaired immune systems, monkeypox often has a self-limiting course [3]. On May 7, 2022, the world learned that there may have been a monkeypox in the United Kingdom after several years with no verified cases of the disease in non-endemic nations. Since then, cases have been reported from Sweden and Australia to the United States and Canada. As of May 21, 2022, the World Health Organization (WHO) discovered 92 documented (and 28 suspected) incidences of monkeypox in 12 nations where the disease is uncommon [8]. Polymerase chain reaction (PCR) testing has been used to identify all infected individuals to present, and they have all been connected to the West African clade [8]. The monkeypox virus responsible for the current outbreak has been connected to cases shipped from Nigeria to the United Kingdom, Israel, and Singapore in 2018 and 2019 [8]. Nations are still dealing with the COVID-19 pandemic, so the potential of another outbreak is worrisome. The fact of the matter is that, unlike COVID-19 in early 2020, scientists already have a lot of information regarding monkeypox. This review seeks to discuss current knowledge on monkeypox, including preventive, immunisation, and treatment options, as well as create awareness on possible preventive measures and suggest future targets for drug discovery and development.

A literature search was conducted on various scientific databases including web of science, PubMed, and Scopus using the keyword monkeypox infection. A total of 1926 articles were found using MeSH words like antiviral, vaccine, and biomarkers coupled with Boolean operators, which were relevant to monkeypox infection. From that 58 articles were on the pathophysiology, treatment, epidemiology, and transmission prevention of monkeypox.

2. Pathophysiology

Viruses are obligate parasites and the MPXV has two strains: the Congo Basin, commonly known as Central Africa, and the West Africa clades. According to reports, the Congo Basin clade (Central Africa clade) is more deadly than the ones in West Africa and allows more human-to-human virus transmission [9]. It multiplies within the host and compromises immunity against infections. Several investigations on the pathophysiology of MPXV have been conducted; however, the involvement of innate and adaptive immunity remained unclear. The most crucial element of innate immunity is natural killer (NK) cells, which directly eliminate virus-infected cells with the aid of T cells and dendritic cells [10]. During the early stages of infection, the contact of NK cells with their ligands, such as the major histocompatibility complex (MHC) I molecule, begins suppression or activation of NK cells. NK cells cause an inflammatory response by producing interferon ($\text{IFN-}\gamma$) and tumor necrotic factor ($\text{TNF-}\alpha$), these cytokines then activate T-helper (Th) cells with the help of dendritic cells [10]. McFadden described three types of viral tropisms including, cellular, host, and tissue. Because virus dispersion and propagation occur primarily in infected hosts, host and tissue tropism are significantly affected in MPXV. Histopathology revealed that MPXV antigen was present in the ovary, kidney, heart, brain, pancreas, liver, and lung tissues. Since ovarian tissues showed higher virus titers than other tissues, it was established that ovarian tissue is most affected by the MPXV [11]. In the histopathology of *Macaca fascicularis* (cynomolgus monkey), According to Zaucha et al., lymphoid tissues are an excellent host for MPXV, and the viral antigen was also found in many other tissues, including the salivary gland and the sebaceous tissues of the lips [12]. Monkeypox develops

with dermis infection from infected animals or the respiratory mucosa of an infected individual. The virus causes primary viremia and systemic infection by spreading through the lymphatic system [13].

In addition to that, MPXV belongs to orthopoxvirus family, and its mechanism is similar to that of poxviruses. The pox virus replicates within the cytoplasm, and the process begins with the virus attaching to the cell surface of mammalian cells. The virus is divided into two parts: internal mature virus (IMV) and extracellular enveloped virus (EEV) [14]. It has different surface proteins and distinct numbers of wrapping membranes, and both parts enter the cell through different mechanisms. The virion then binds to the host cell membrane, and fusion takes place. Virion penetration causes immediate release of virion's core structure into the cytoplasm. There is no need for a particular receptor for viral entry; entry happens through quick signalling mechanisms in various host protein kinase networks, and this signalling controls subsequent replication stages [15]. The activation of signalling pathways enhances the expression of cell receptors including toll-like receptors (TLRs), which activate antiviral pathways like the release of cytokines and chemokines; however, some pox viruses have the potential to inhibit TLRs [16].

With the help of RNA polymerase, which generates viral mRNA under the direction of viral early promoters, virus core material is released into the cytoplasm, initiating the initial cascade of gene expression. Then, in the second step, core uncoating takes place, unknown host and viral mechanisms cause the core structure to dissolve [17]. The uncoating of the virus core structure leads to the entry of viral DNA into the cytoplasm, which produces early and late DNA transcription processes and serves as a template for DNA replication. The subsequent intermediate and late transcription steps necessitate coordination with transcription factors produced from the host, which increases the effectiveness of viral gene expression [18]. IMV, an infectious virus produced by the accumulation of late viral genes, travels through microtubule-mediated trafficking and wraps in the golgi-derived membrane to produce IEV [19]. The cell-associated enveloped virus (CEV), which is formed when the IEV formed fuses with the cell membrane and loses one of its outer membrane wrappings is either directed towards neighboring cells by actin tail polymerization or released directly as free EEV particles [20]. While the IMV form is expected to contribute to virus transmission only after late-stage cell death and membrane rupture, the CEV and EEV forms are thought to be particularly important for rapid cell–cell propagation in vivo Fig. 1 [20].

Furthermore, to prevent viral infection, the host body responds to numerous antiviral pathways to alter the extracellular and intracellular environment of infected cells. The host body's antiviral mechanisms include interferon release, cellular apoptotic pathways, MHC-restricted antigen presentation, stress-induced signaling cascades, and pro-inflammatory pathways [21].

3. Monkeypox virus genome

The orthopox genus of the Poxviridae family contains the enormous, double-stranded DNA virus known as the monkeypox virus [22]. The virus is still active in the environment in reservoir rodents like squirrels. These viruses have a 200 kb genome, with highly conserved genes for replication and assembly machinery in the middle and more variable genes for pathogenicity and host range determination in the terminal ends [23]. As per MPXV's morphology, which is similar to that of other OPXVs, virions are ovoid or brick-shaped particles encased in a geometrically corrugated lipoprotein outer membrane [10]. The outer membrane protects the double-stranded DNA genome and transcription factors. The core's biconcave shape and the presence of lateral entities on both sides are described as fixation artifacts from electron imaging. Despite being a DNA virus, MPXV completes its whole life cycle in the cytoplasm of infected cells. All of the proteins required for viral DNA replication, transcription, virion assembly, and emigration are encoded by the MPXV genome [22].

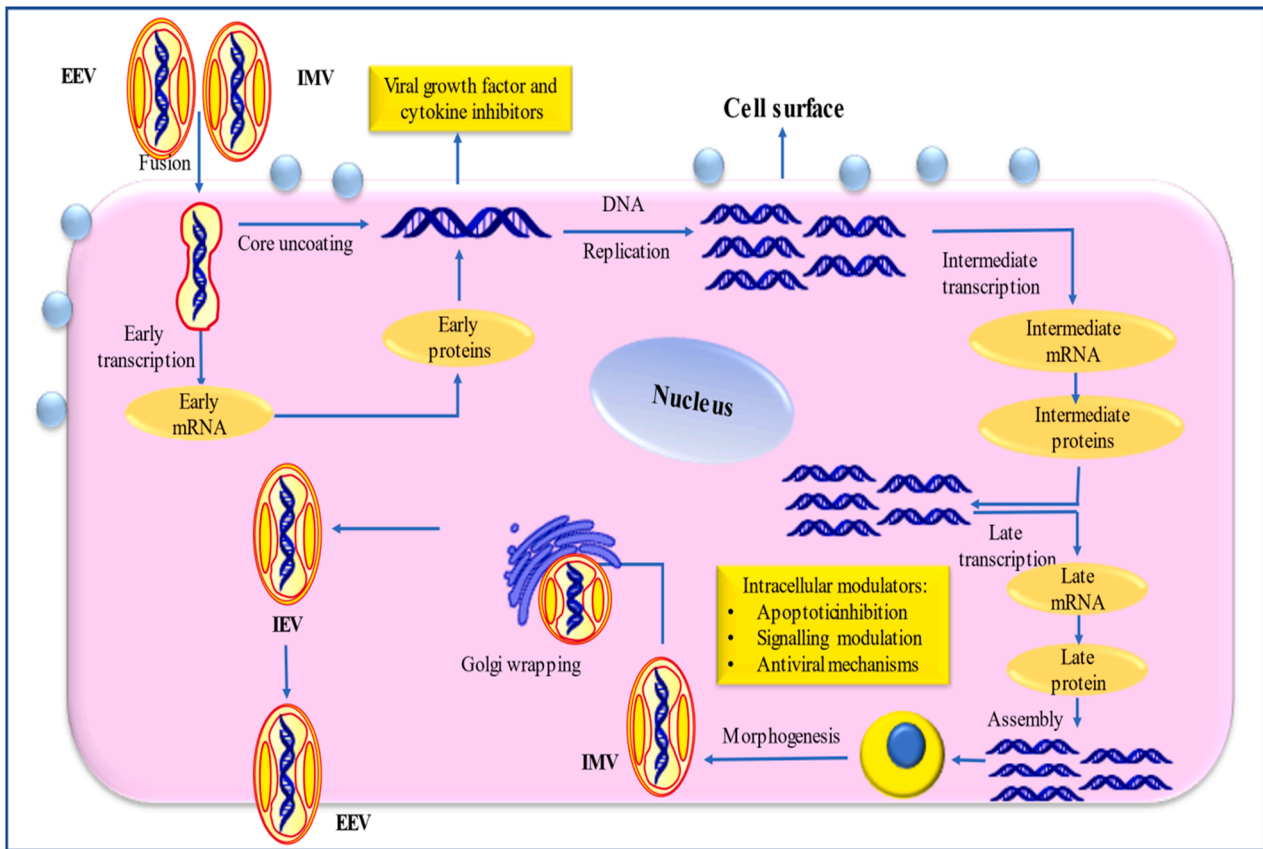


Fig. 1. Pathophysiology of monkeypox virus, briefly, the monkeypox virus multiplies within the host and compromises immunity against infections. The replication of the pox virus occurs within the cytoplasm, and the entire process begins by binding the virus to the host membrane and fusion occurs. The virus is divided into two parts: internal mature virus (IMV) and extracellular enveloped virus (EEV). Then virion releases its core structure into the cytoplasm and the first cascade of gene expression occurs with the assistance of RNA polymerase, which synthesizes viral mRNA under the control of viral early promoters. Then in the second step of core uncoating takes place. The uncoating of the virus core structure released viral DNA into the cytoplasm, which served as a template for DNA replication and resulted in early and late DNA transcription processes. The aggregation of late viral genes results in the formation of infectious virus particles known as IMV virions. Which travel through microtubule-mediated trafficking and wrap in golgi-derived membrane to produce intracellular enveloped virus (IEV). The IEV form loses one of its outer membrane wrappings as it fuses with the cell membrane to create the cell-associated enveloped virus (CEV), which is discharged as free EEV particles.

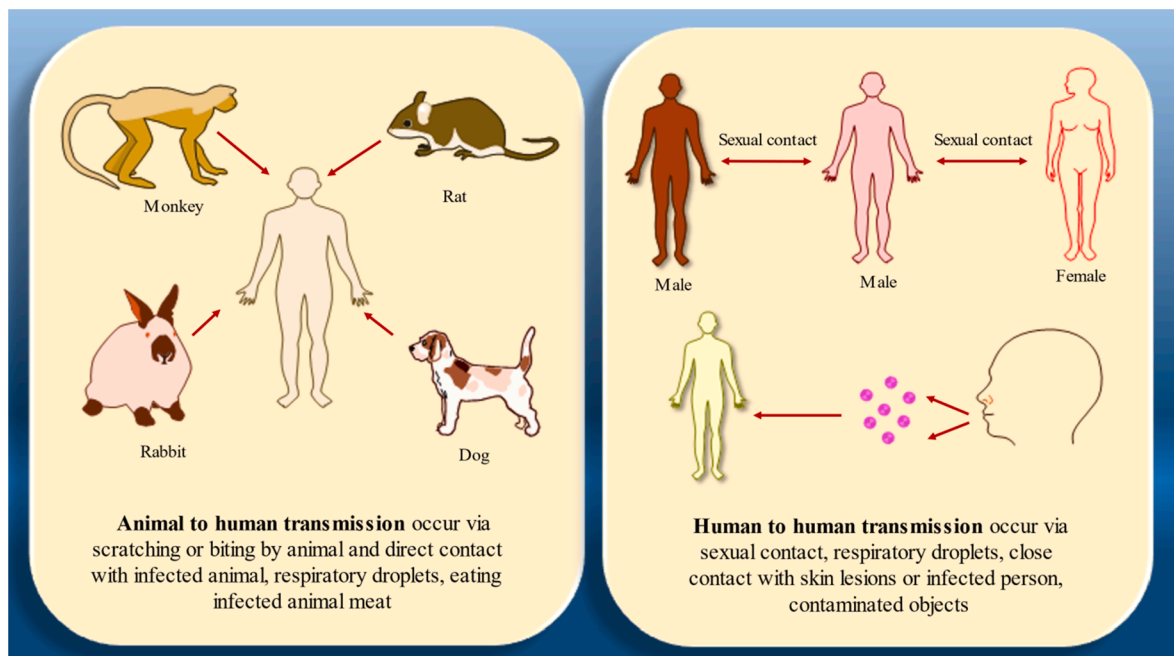


Fig. 2. Mode of transmission for monkeypox virus.

4. Mode of transmission

A viral zoonosis called monkeypox primarily prevalent in the tropical forest regions of Central and West Africa, while it can occasionally spread to other places. With symptoms lasting 2–4 weeks, MPXV is mainly a self-limiting condition. Case reports provided fragments of evidence that MPXV can be transmitted to physically fit people. MPXV is primarily spread when a person comes into touch with infected animals or people who have lesions from the virus on their skin [24]. The MPXV spreads through intimate interaction with body fluid, respiratory secretions, and contaminated materials. This can also be spread whenever a human comes into contact with bedding, clothes, and accessories that have the virus on the skin rash of an infected person [4]. At this time, it is unclear what exact mechanism the virus spreads by. Monkeypox typically takes 6 to 13 days to incubate, although it can sometimes take up to 21 days [4].

According to the Centers for Disease Control and Prevention (CDC), MPXV can be spread when persons are directly exposed to infectious sores, scabs, or body fluids [25]. The transmission of MPXV is more from intimate contact between people, including sex, kissing, cuddling, or touching parts of the body with monkeypox sores. No evidence is available that elaborates the spread of MPXV through semen or vaginal fluids Fig. 2 [26].

Earlier traveler transmission was first reported in 2003 when a UK healthcare worker was infected with monkeypox outside Africa. Similarly, the sporadic condition was seen in the USA when a person was exposed to rodents imported from Ghana [27].

A recently published case report suggests that MPXV is transmitted during sexual contact. Two white British men were infected with MPXV after 24 h of sexual contact. Both individuals suffer from prodromal symptoms such as lymphadenopathy, fever, headache, diarrhea, and skin lesions at the point of sexual contact, after a few hours of sexual contact both exhibit severe herpes simplex virus (HSV) or varicella-zoster virus (VZV) infection with a bacterial infection overlaid [28].

The respiratory transmission of MPXV is more in West Africa. Therefore, the previous study utilized the rodent MPXV model to study the transmission of the virus to naive animals. Their findings revealed minimal transmission of the virus through the respiratory route [29,30]. Recently in 2022 between 7 and 25 May, a total of 86 MPXV cases were reported in the UK, in which 66 cases were transmitted due to being gay, bisexual, and men who have sex with men [31].

5. Preventions

A smallpox vaccine protects against monkeypox, although it is presently only used in clinical trials. To prevent infection with the monkeypox virus, several steps can be followed such as (1) Avoiding animal contact that may carry the virus, including sick or dead animals found in monkeypox-infected areas, (2) Avoid direct contact with any objects that have been in contact with an infected animal, (3) Separate sick individuals from those who could be at risk, (4) Use proper hand sanitation after coming into contact with infectious humans or animals, (5) during care of an infected person use personal protective equipment (PPE) [32,33], (6) Cook all items containing animal meat or components thoroughly, (7) Make use of condoms and barrier methods during intercourse [34]. If a person is found positive for MPXV, he or she should be housed in a separate room and not allowed to move outside. The patient should keep the door shut and wear a medical mask when coming out of the room. Rooms and floors where patients have been kept should be cleaned and disinfected thoroughly. Isolation will be terminated after proper consultation with a doctor/physician [35]. The primary control strategy for monkeypox is to enhance public knowledge of risk factors and teach people how to reduce their exposure to the virus. Currently, a scientific study is being performed to assess the feasibility and appropriateness of vaccination for monkeypox prevention and management. Some governments have programs in place to administer

vaccines to persons who may be at risk, such as laboratory staff, rapid response teams, and health workers. Captive animals that may be infected with monkeypox should be separated from other animals and quarantined immediately [4,36].

6. Role of antivirals in the treatment of monkeypox

Even though smallpox was eradicated 30 years ago, orthopoxviruses (OPXVs) still infect people. The smallpox virus (VARV), which causes the disease, is still a potential biological weapon of grave concern [37]. The MPXV, which is prevalent in parts of Africa, is responsible for the epidemic of human disease in the United States after being introduced to North American prairie dogs through the importation of species from a shipment of infected African animals and subsequent cohabitation with those species [37]. Whereas human OPXV infection can cause serious illness, supportive care is currently the cornerstone of majority of the treatment strategies. Due to several vaccine contraindications, which put some recipients at risk for harmful vaccine reactions, vaccination is nevertheless restricted. Those with compromised immune systems shouldn't receive the vaccine. MPXV belongs to orthopoxvirus families that cause similar pathogenic conditions as smallpox. The monkeypox infection spreads over time since there is no cure. Therefore, researchers tested antiviral drugs against monkeypox viral infection and their outcomes revealed that antiviral has a protective mechanism against orthopoxvirus species [38]. Cidofovir, Brincidofovir, and Tecovirimat are commonly utilized by researchers against orthopoxvirus infection [39].

A broad-spectrum antiviral drug called cidofovir is effective against virtually all DNA viruses. In the treatment of vaccinia virus infection with severe combined immunodeficiency, which is comparable to MPXV, cidofovir has proven to be incredibly effective. The topical and intravenous administration of cidofovir in immunocompromised patients shows potential effectiveness against the monkeypox virus [39]. Cidofovir is already used effectively in humans against a wide range of diseases and viral diseases other than the poxvirus. Cidofovir treatment reduced lesions formation on the animal's body and decreases the mortality rate. It also diminished cytokines and chemokines production in monkeypox-infected rodents [40]. A previous study on monkeypox indicated that cidofovir treatment reversed monkeypox virus infection in experimental animals [39]. Additionally, it has been demonstrated that cidofovir works well in treating experimental monkeypox viral infection. Researchers have found that cidofovir administration limited mortality and the severity of epidermal monkeypox lesions in experimental animals [41].

Brincidofovir is a cidofovir diphosphate prodrug that prevents orthopoxvirus DNA polymerase-mediated viral DNA synthesis. Brincidofovir diminished the intensity of lesion formation related to immunization, considering the vaccination's immunological response. However, the administration of Brincidofovir concurrently with vaccination had no impact on the extent to which protective immunity developed [42]. In the UK seven patients with monkeypox were reported from 2018 to 2021 and were treated with Brincidofovir. It was found that Brincidofovir-treated patients completely recovered from monkeypox infection, although three patients reported elevated alanine transaminase with no severe side effects [3]. Besides that, Cidofovir protects against the MPXV by suppressing viral DNA polymerase from replicating the viral vector in experimental animals [43].

In 2005, tecovirimat was proposed as an antiviral therapy for orthopoxvirus infection. Tecovirimat was licensed by the US Food and Drug Administration in July 2018 for the treatment of symptomatic smallpox. Numerous animal studies have demonstrated the high efficacy of tecovirimat in preventing human orthopoxvirus infection [44]. Tecovirimat was found to be safe and well-tolerated in animal studies at the human dose, or its equivalent. In experimental animals that have already received ACAM2000™ live attenuated smallpox vaccine, tecovirimat administration reduced vaccine-elicited humoral immunity

[44]. Previous studies found that Tecovirimat treatment reduced virus replication as well as reduced viral replication against the experimental model of monkeypox [45]. Additionally, tecovirimat showed protective action against monkeypox animal models which reversed the pox lesions and delayed the onset of viral infection [46]. The previous study on non-human primates indicates that treatment with tecovirimat diminishes viral load as well as lesion counts against monkeypox-infected animals [47]. Further study showed that tecovirimat has the potential to reduce mortality along with diminishing the clinical signs of monkeypox [48]. Altogether, these findings reveal that antiviral could have the potential to show protective action against monkeypox. The action of antiviral is still not clearly understood. But available outcomes revealed that antiviral treatment could be used in the treatment of monkeypox virus Table 1.

7. Vaccines in monkeypox

The CDC currently advises post-exposure smallpox vaccination for those within 4 days of initial direct monkeypox exposure and consideration of vaccination for those within 2 weeks of exposure, although smallpox immunization after monkeypox exposure is effective in preventing or alleviating monkeypox disease [54]. In a different experiment, a monkey model was used to compare the licensed Dryvax vaccine and the attenuated vaccination against the vaccinia virus Ankara (MVA). Following the concurrent administration of two doses of MVA or one dosage of MVA plus Dryvax, T-cell responses and antibody binding and neutralizing titers were equal or higher. After being exposed to the monkeypox virus, non-vaccinated animals experienced more than 500 pustular skin lesions, became critically ill, or perished, whereas animals that had received vaccinations were healthy and asymptomatic, with the exception of a small number of transient skin lesions in animals that had received MVA vaccinations alone [55]. Rhesus macaques were immunized using intradermal and intramuscular methods using plasmid DNA producing the monkeypox orthologs of the VACV L1R, A27L, A33R, and B5R proteins. The same as with placebo controls, animals receiving only DNA failed to produce high titer antibodies (Abs), developed numerous skin ulcers, and eventually died. On the other hand, animals that received protein vaccinations experienced mild to severe sickness (20–155 skin lesions), yet they still survived [52]. Individuals who were injected with DNA and later augmented with proteins, on the other hand, had a mild illness or few lesions that resolved in a few days. The reactions and Abs titer interaction to all four proteins were provoked by DNA/protein immunization, and these were associated negatively with the overall number of lesions. The inoculated macaques' serum recognized a small number of linear B cell epitopes which are highly

conserved among OPXVs [52]. Researchers have shown that vaccinia-specific B-cell responses are required for macaque immunity against MPXV. Antibody-mediated B cell depletion diminished vaccine-induced protection against lethal intravenous MPXV dose, and not CD4+ or CD8+ T cell depletion. Furthermore, nonimmunized macaques were protected against severe sickness via passively transferring human vaccinia-neutralizing antibodies. This demonstrates that B lymphocytes help to defend against vaccinia-induced weight loss and death [56].

A novel vaccine based on the Ankara strain of the modified attenuated vaccinia virus was proposed in 2019 for the prevention of monkeypox. This two-dose vaccine is scarcely available. Due to the cross-protection provided by the immune response to OPXVs, formulations for smallpox and monkeypox vaccines based on the vaccinia virus have been created [4]. The advisory committee on immunization practices (ACIP) suggested that jobs where people may expose to OPXVs, such as monkeypox, should get either ACAM2000 or JYNNEOS vaccination. This is called pre-exposure prophylaxis (PrEP). People who work in laboratories and are involved in the diagnosis and culturing of MPXV should obtain PrEP[57].

8. Future predictive therapy for monkeypox

8.1. Biomarkers-based therapy

There is an urgent need to find potential target-related therapy to prevent the progression and development of monkeypox. As per the current scenario researchers could trust biomarkers-based therapy as biomarkers offer a flexible and effective approach to comprehending the spectrum of viral disease with application in screening, diagnosis, and prognosis and could respond to the therapy. The incorporation of biomarkers with a mechanistic link to monkeypox could lead to the development of new non-addictive treatments. Further continued evaluation of monkeypox suggests its vulnerable relation with smallpox, indicating various clinical presentation similarities [58] with considerable differences between the genome [59,60]. The next wave of developments in monkeypox therapy is being driven by the search for novel biomarkers, innovative designs, and delivery strategies for targeted drugs. Furthermore, the evaluation of some biomarkers could play the main driving force to shape new predictive targets related to monkeypox. In addition, several studies have concluded that some biomarkers such as deoxythymidylate kinase [61], actin beta [62], calpastatin [63], SH3 domain binding protein 4 [64], T cell receptor beta variable 20/OR9-2 [65], cyclin dependent kinase 5 regulatory subunits 1, cell division cycle associated 5, interleukin 12A, ficolin 2, GTP cyclohydrolase I feedback regulator, uroplakin 3B, annexin A1,

Table 1
Various studies on possible treatment options for monkeypox.

S. No.	Drug	Dose	Route of Administration	Study type	Mechanism of Action	Reference
1	ACAM2000 and Tecovirimat	2.5–12.5 × 10 ⁵ PFU/dose ACAM100 and 10 mg/kg Tecovirimat for 14 days	Intrascapular administration	In vivo (Cynomolgus macaques and Indian Rhesus macaques)	Live attenuated small pox vaccine	[49]
2	Cidofovir and Elstree-RIVM	5 mg/kg Cidofovir and 2.5 × 10 ⁵ TCID50	Intraperitoneal	In vivo (Cynomolgus macaques)	Nucleotide analog	[50]
3	CMX001	20 mg/kg	Intracutaneously Intranasal	In vivo (Rabbit)	Nucleotide analog and a DNA polymerase inhibitor	[51]
4	ACAM2000 and Tecovirimat	2.5 µL/2.5 × 10 ⁵ to 12.5 × 10 ⁵ PFU ACAM2000 and 10 mg/kg Tecovirimat	Percutaneous scarification for ACAM2000 and	In vivo (Cynomolgus macaques)	vaccinia virus F13L gene inhibitor	[46]
5	ST246	30 mg/kg	Oral	In vivo (<i>Cynomys ludovicianus</i>)	Antiviral	[37]
6	Subunit recombinant vaccine (VACV L1R, A27L, A33R, and B5R)	(4,3,2,1) mg/kg	Intramuscular	In vivo	Immunomodulation	[52]
7	RNA interference (siA6-a and siE8-d)	(100 and 200) nM	–	In vitro (cultured LLC-MK2 cells)	Inhibition of viral replication	[53]

MNAT1 component of CDK activating kinase [66], signal transducer and activator of transcription 3 [67], retinoid X receptor alpha [68], interferon gamma [69], ubiquitin specific peptidase 9 X-linked [70], interleukin 15 [71], membrane associated ring-CH-type finger 1 [72], tumor necrosis factor [73], WASP actin nucleation promoting factor [74], makorin ring finger protein 3 [75], tyrosinase [76], major histocompatibility complex, class I, A [76], having remarkable association with smallpox virus could act as a future target in monkey pox as both having same pathogenesis in human. This should serve as a reminder to the scientific community to work on smallpox-focused biomarkers as a potential target of therapy for the MPXV in the future.

8.2. Silver nanoparticles-based therapy

Despite repeated attempts to develop treatments and vaccines to combat re-emerging viruses, scientists are currently actively attempting to develop novel, inexpensive, and broad-spectrum antiviral medicines that can not only combat viruses but also function as a shield against pathogen attacks. By altering materials at the nanoscale to have extraordinary physicochemical features, a high surface area-to-volume ratio, and improved reactivity, current advances in nanotechnology offer a fresh platform for the production of potentially effective drugs [77]. Silver nanoparticles have been reported to target cellular viral propagation processes, altering the host immune system, and enhancing the effectiveness of existing antiviral medications [78,79]. In addition, Rogers et al. investigated the therapeutic potential of Ag-nanoparticles against monkeypox virus infection and found that it had a significant, dose-dependent inhibition effect. Silver nitrate inhibits plaque-forming units (PFU) while having no cytotoxic effects on Vero cells at concentrations between 12.5 and 50 µg/ml. Although the exact mechanism of PFU suppression is unknown, however, host cell binding and metabolic pathways may play a role. Overall, research helped to understand that cellular contact, concentration, and nanoparticle size would be important for the creation of nanoparticles in the future to create nanoscale-based treatments for monkeypox infection [80,81].

9. Conclusion

Monkeypox is a severe pathogenic condition that occurs when humans come into contact with infected animals or humans. The pathophysiology of monkeypox is still not clear, but the case report revealed that it can be transmitted from animals to humans or through contact with monkeypox infectious sores, scabs, and body fluids. Monkeypox infection can be prevented by avoiding contact with infected animals, and adhering to proper hygiene after coming into contact with infected humans or animals. The smallpox vaccine (Dryvax, ACAM2000, and JYNNEOS vaccine) and some antiviral drugs (Cidofovir, Brincidofovir, and Tecovirimat) have been used in the management of monkeypox whilst scientists run around to find a definitive cure. Despite various reports on possible treatment options for monkeypox, we propose from our review the need to delve into target-based therapy including futuristic (biomarkers and silver nanoparticles) based therapy that could be used in the treatment of monkeypox infection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Author contribution

Shubham Upadhayay, Richmond Arthur: Data acquisition, concept design, and final approval of the manuscript.

Divya Soni, Poonam Yadav: Drafting manuscript, Correction of Draft Manuscript, and final approval of the manuscript.

UmaShanker Navik, Randhir Singh, Thakur Gurjeet Singh: Proofread of reviewed manuscript, Data Interpretation, and final approval of the manuscript.

Puneet Kumar: Concept design, supervision, review, edit, and final approval of the manuscript.

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