Review Article

Bioactive phytochemicals for Human Monkeypox outbreak

Abstract

Monkeypox is a viral disease caused by the monkeypox virus that occurs primarily in central and western Africa. Nonetheless, it has recently spread internationally, garnering the attention of the scientific community to its own.For many years, medicinal plants and natural substances have been utilised to treat smallpox and chicken pox. They may also have anti-monkeypox viral properties.Therefore, we attempted to group all of the related information so that researchers could quickly access it and conduct studies to identify therapeutic approaches for the outbreak.This review article discusses the present global state of the monkeypox virus, including epidemiology, transmission, clinical manifestations, and prophylaxis, as well as phytochemicals that have been studied computationally as possibly active ingredients against the virus.Studies showed that around 56 plant compounds were evaluated for antimonkeypox capability with top four candidates having higher binding affinity. Curcumin had the highest binding affinity, measuring -37.43 kcal/mol, followed by gedunin (-34.89 kcal/mol), piperine (-34.58 kcal/mol), and coumadin (-34.14 kcal/mol).Additionally, this study highlighted potential therapeutic targets for the monkeypox virus such as DdRp and AF2R profilin like protein. In its entirety, this article may help scientists find and analyse bioactive phytochemicals as well as drug targets for monkeypox virus pharmacotherapy.

Keywords: monkeypox, outbreak, phytochemicals, antivirals, drugs, vaccines

1. Introduction

Global health experts are concerned that the Monkeypox epidemic may pose a new threat when the world continues to cope with the COVID-19 pandemic of 2019.The resurgence of monkeypox in an undervaccinated population is a global health issue requiring immediate attention from the scientific community. There are currently no identified MPXV-specific drugs and vaccines discovered. Because monkeypox is identical to smallpox, it has been given treatment with the smallpox vaccine. The authors revealed that numerous naturally occurring plant-based metabolites can be utilised to develop novel therapies against MPXV. This article discussed different bioactive phytochemicals and drugs that target monkeypox virus.

The monkeypox virus (MPXV) causes a zoonotic disease called monkeypox. The virus is a double-stranded DNA (dsDNA) from the *Orthopoxvirus* (OPXV) genus of the *Poxviridae* family, with *Chordopoxvirinae* as its subfamily (Alakunle*et al.,* 2020). This genus additionally includes *Variolavirus* (VARV), *Cowpox virus* (CPXV), *Vaccinia virus* (VACV), *Camelpox virus* (CMLV), *Taterapox virus* (TATV), and *Ectromelia virus.* MPXV is split into Clade I and Clade II, with Clade IIa and IIbsubclassifications (Happi *et al.,* 2022). All *Orthopoxviridae* viruses elicit cellular immune responses as well as cross-reactive humoral reactions. Poxvirus mature particles feature a distinctive dumbbell-shaped nucleoprotein core that carries a large double-stranded linear DNA genome (Reed *et al.,* 2004). MPXV virions include about 30 structural and membrane viral proteins, in addition to DNA-dependent RNA polymerases and transcriptional enzymes (Resch *et al.,* 2007; Manes *et al.,* 2008). The virus has two infectious forms: intracellular mature virus (IMV) and extracellular enveloped virus (Eboth with distinctive surface glycoproteins and cell-infecting mechanisms (McFadden, 2005).Poxviruses have the requisite assembly, replication, transcription, and egress proteins in their genome, however their mRNA translation relies on host ribosomes (Kugelman *et al.,* 2014; Alakunle*et al.,* 2020).The genome of MPXV is 197 kb linear DNA and contains 190 non-overlapping open reading frames greater than 180 nt. The primary coding region sequence (CRS) of MPXV, which is located between nucleotide positions 56,000 and 120,000, is highly conserved, similar to other *orthopoxviruses*. It is circumscribed by inverted terminal repeats (ITRs) and variable ends (Isidro *et al.,* 2022). EVs have a weak outer membrane and spread throughout the host, but MVs have a more stable membrane. They are believed to enhance transmission among host animals (Moss, 2012). According to McFadden (2005), several species have been shown to harbour MPXV, but it is yet unknown which of these serves as the primary animal reservoir. The spread of the virus within infected hosts and between hosts is significantly influenced by tissue and host tropism. Although rodents and non-human primates have been discovered to be potential natural reservoirs and incidental hosts, there is currently no identified reservoir or natural host for MPXV (Keasey *et al.,* 2010; Falendysz*et al.,* 2017; Reynolds *et al.,* 2019; Yinka-Ogunleye *et al.,* 2019).

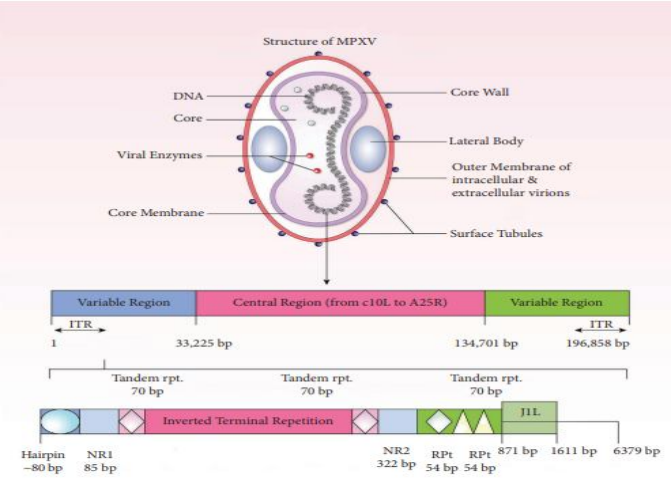

Fig 1: Structure of Mpox virus (Araf et al., 2024).

The monkeypox genome's 5′ and 3′ ends have inverted terminal repetitions, resulting in hairpin-like structures. Early proteins, including polymerases and immunological modulators, are partially translated from double-stranded DNA before replication in the cytoplasm. The resulting DNA partially transcribes into RNA, while the remainder translates into intermediate proteins that become late transcription factors. Viral proteins are translated from cytoplasmic RNA and replicated DNA to form nucleocapsid proteins, which are then processed into MVs and EVs for exocytosis (Niu*et al.*, 2023).

1.1 Transmission and Clinical Manifestations

Regardless of its name, MPXV did not originate from monkeys. Rodents are believed to be the primary reservoirs, with humans and monkeys serving as inadvertent hosts (Nolen *et al.*, 2015). MPXV is commonly transmitted from animals to humans by bodily fluids or bites (Reynolds *et al.*, 2007). Patients with invasive bites from infected animals were more likely to acquire systemic disease than those with noninvasive exposures. Human-to-human transmission usually requires large respiratory droplets, extended face-to-face contact, and close contact with infectious skin lesions or bodily fluids. Contaminated goods and surfaces, such as sharing a home, sleeping in the same bed, or eating from the same dishes as an infected individual, can contribute to viral transmission (Centers for Disease Control and Prevention, 2021). Monkeypox poses specific risks to children and can result in complications such as congenital mpox or stillbirth during pregnancy (Mbala *et al.*, 2017; Kisalu&Mokili, 2017). Although the majority of mpox cases are caused by cutaneous lesions rather than sexual transmission, some seminal fluid samples tested positive for MPXV (Sklenovská & Van Ranst, 2018). The global outbreak was defined by specific patterns of transmission among sexual networks involving men who have sex with men (MSM) (Low *et al.*, 2023). Kumari *et al.* (2024) later said that, in addition to homosexuals, bisexuals, and non-vegetarians, it also affects heterosexuals who have no history of travel. In the 2022 human mpox outbreak in non-endemic locations, skin lesions (95%) were the most prevalent symptoms, followed by pyrexia (58%), lymphadenopathy (53%), fatigue (39%), myalgia (31%), and headache (30%). MPXV infection has an incubation period of 5-21 days (Liu *et*

al., 2023). The most prevalent skin lesions were anogenital (66%), followed by those on the trunk/torso (48%), face/head (39%), and extremities (30%) (Liu *et al.*, 2023).

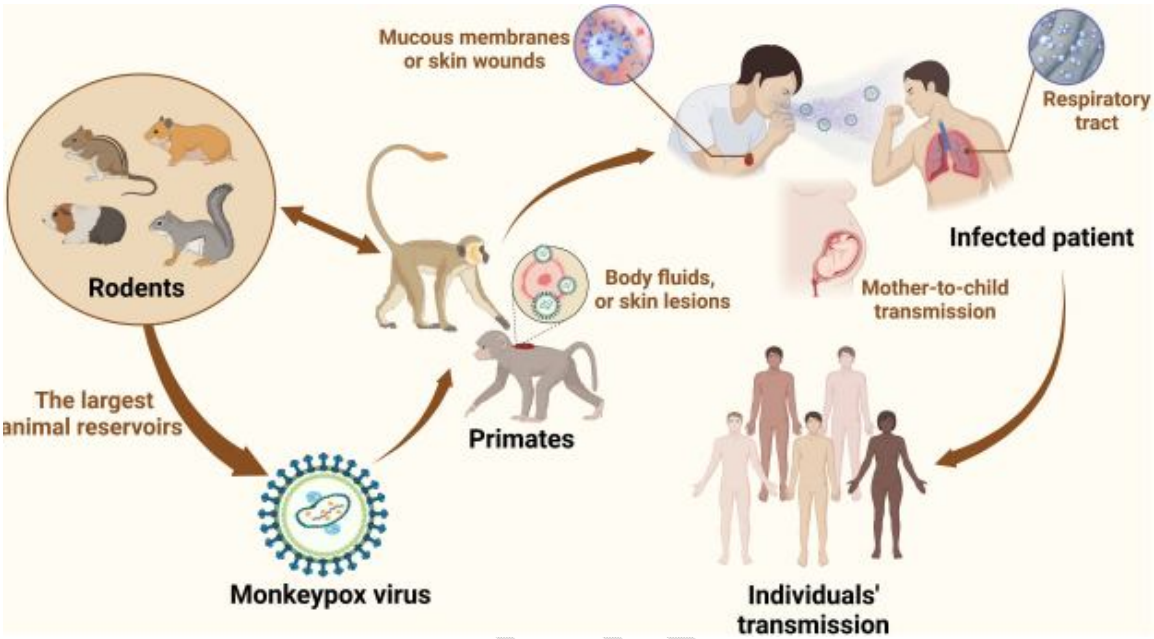

Fig 2: Transmission of Mpox virus (Niu et al., 2023).

1.2 Epidemiology

Human Mpox has historically garnered little attention until 2022, when we noticed a resurgence beyond endemic nations (Thornhill *et al.*,2022; WHO, 2023). The WHO Director-General declared on August 14, 2024, that the outbreak of mpox in the Democratic Republic of the Congo and an increasing number of other African nations is a Public Health Emergency of International Concern (WHO, 2024).Until 1970, there were no documented instances of human MPXV infection, however the virus had formerly infected monkeys and apes (Arita and Henderson, 1968). Infections in monkeys were initially identified in laboratory/captive animals in 1958, after they were discovered in captive monkeys in Denmark. In August 1970 in the Democratic Republic of the Congo (DRC), a 9-month-old boy became the first documented human mpox case (Ladnyj*et al.,* 1972).Subsequently, in Liberia, Sierra Leone, and Nigeria, six more instances of mpox were discovered between September 1970 and April 1971 (Lourie *et al.*, 1972).For almost a decade, the Democratic Republic of Congo has been the source of reports of mpox, with an annual increase in cases observed throughout that time. According to WHO (2024), the number of cases reported rose dramatically than that of previous year, and as of now, this year's total is more than 15,600 cases and 537 deaths which has surpassed the previous year's record.Total laboratory verified cases of Mpox virus are 95,226, including 185 deaths in 117 countries from January 2022 to March 2024 (WHO, 2024). India was the very first country in Southeast Asia to report mpox in an adult male who had travelled to the Middle East. The patient had close interaction with an mpox positive patient in the United Arab Emirates (Chakraborty *et al.*,

2022).According to latest WHO reports, from January 2022 to July 2024, India had 27 mpox positive cases, with 1 death. According to WHO's latest data results, as of March 31, 2024, 96.4% (85,328 / 88,513) of patients with accessible data are male, with a median age of 34 years.According to WHO (2024), sexual contacts were the most common transmission in the worldwide outbreak (18,420 / 22,096; 83.4%), followed by non-sexual contact between individuals. In the past six months, 95.7% (692/723) of new cases reported sexual contact (WHO, 2024).Out of 35,997 recorded cases, the most prevalent clinical manifestation was any rash (89.8%), followed by pyrexia (58.3%) and systemic and genital rash (54.7% and 49.6%, respectively) (WHO, 2024).

WHO Region	Total confirmed cases	Total confirmed deaths	Cases in last month	Monthly change in cases (%)
Region of the Americas	61 264	139	118	-53
European Region	27 179	10	123	-42
African Region	2 920	23	181	-22
Western Pacific Region	2 897	10	32	28
South-East Asia Region	871	2	12	-54
Eastern Mediterranean Region	95	1	0	-
Total	95 226	185	466	-37

Table 1: Number of cumulative confirmed mpox cases and deaths reported to WHO, by WHO Region, from January 1, 2022 toMarch 31, 2024 (WHO, 2024).

According to the report by WHO, the continents with the most confirmed cases were South and North America, followed by Africa, Asia, and Europe. Australia had the lowest positive cases.

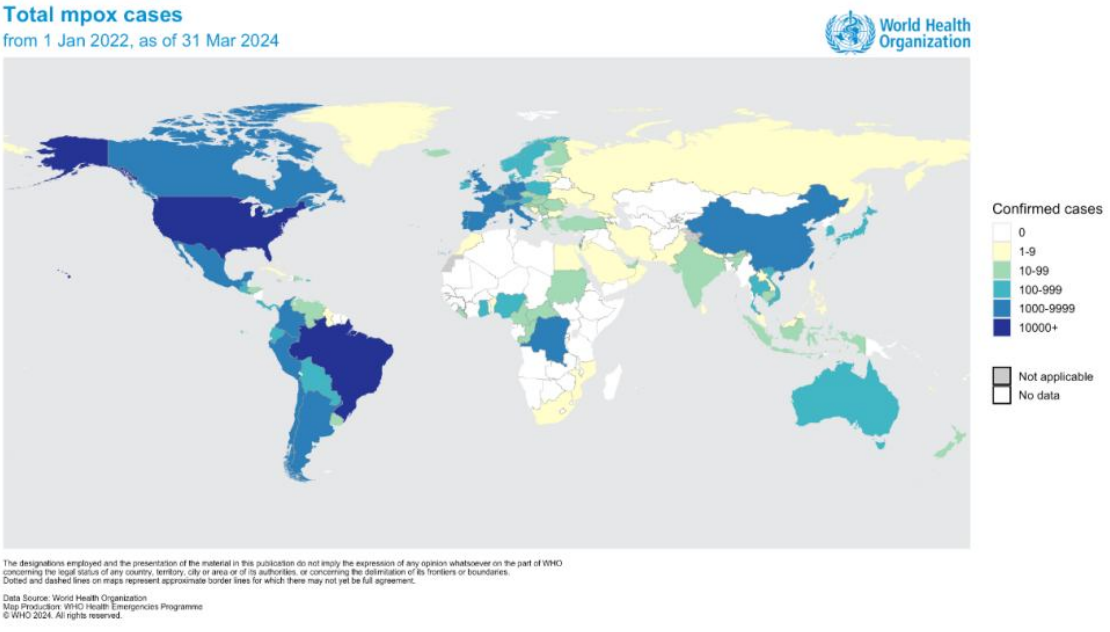

Fig 3: Geographic distribution of confirmed cases of mpox reported to or detected by WHO from official public sources from January 1, 2022 to March 31, 2024 (WHO, 2024).

2. Prophylaxis: Vaccines, Antiviral drugs, and othertherapeutic measures against the virus

Preventive measures are crucial in halting the spread of infections because there is a lack of conclusive evidence for successful treatment of mpox virus (Moore *et al.*, 2022). Avoiding close contact with infected individuals is one way to prevent infection, especially when it comes to their blisters and clothing. As a result, patients with monkeypox should be kept isolated in individual rooms, have their blisters covered until the lesions heal and a new skin layer forms after the lesion crusts fall off. Surgical masks should also be worn. Healthcare professionals who treat infected patients should always use masks, gowns, gloves, and eye protection to ensure their safety (Guarner*et al.*, 2022; Moore *et al.*, 2022).

2.1 Vaccines

2.1.1. Smallpox vaccine

It has been proposed that the rise in monkeypox incidence following the cessation of smallpox vaccine is related to an expanding immunologically naive populations (Bunge *et al.*, 2022). The United States now has two licensed smallpox vaccinations. The US Food and Drug Administration (FDA) licensed ACAM2000, a second-generation smallpox vaccine based on vaccinia virus, in 2007. The vaccine is generated from a Dryvax clone. Individuals at high risk for smallpox virus infection should receive active immunisation against smallpox, not monkeypox illness (Food and Drug Administration). JYNNEOS is the vaccination that the US FDA has approved currently, whereas ACAM2000 is intended for usage off-label (Adalja & Inglesby, 2022). Regarding the efficiency of these two vaccines against the current outbreak, there is a lack of conclusive information. However, in earlier smallpox outbreaks, these immunisations proved to be successful.The vaccinations can be given as post-exposure prophylaxis to prevent disease onset in those who have been exposed to the virus within a few days. Exposure to patients with broken skin, mucosal membranes, bodily fluids, respiratory droplets, or scabs frequently needs post-exposure immunization (Moore *et al.*, 2022). Aventis Pasteur Smallpox Vaccine (APSV), the third vaccine, may be administered for smallpox in accordance with an investigational new drug (IND) protocol. For the purpose of preventing monkeypox, a novel vaccine based on the modified attenuated Vaccinia virus (Ankara strain) was approved in 2019 (Saxena *et al.*, 2023).Immunocompromised and atopic dermatitis patients experienced some adverse reactions from the ACAM2000 vaccine, but those patients can safely utilise the modified vaccinia Ankara (MVA) vaccine (Gong *et al.*, 2022). As of yet, none of these vaccinations are authorised for clinical use in humans (Martin-Delgado *et al.*, 2022). A virus derived from the Lister strain used in first-generation vaccines is present in LC16m8, another third-generation vaccine. The LC16m8 strain was produced through several tissue culture passages and selection for an attenuated phenotype; this strain lacks a functioning, full-length B5 membrane protein (Kidokoro*et al.*, 2005). The vaccine is presently manufactured by Kaketsuken (Kumamoto, Japan), which was granted a full licence by Japanese regulatory authorities in 1980. The FDA has not yet received a biological licence application for LC16m8, however VaxGen is the company with marketing rights in the USA (WHO, 2005).

2.1.2. Novel mRNA vaccines

Conventional vaccinations have been shown over decades to be effective prophylactics against a wide range of illnesses, including influenza, chickenpox, hepatitis, and several more (Hussein, 2015). These conventional vaccinations were developed using attenuated viruses or viral proteins until recently. Although these vaccines are thought to be highly effective in stopping the spread of many viral diseases, developing vaccinations against some viral infections that elicit an adaptive immune response may be challenging (Adesokan*et al.*, 2022). Another vaccination strategy that arose in the 1990s is to use nucleic acid components as vaccines instead of attenuated viruses or viral portions. This notion is based on the injection of messenger RNA (mRNA) molecules that encode specific key viral proteins (Pal *et al.*, 2021). Following injection, these mRNA molecules ought to be translated into encoded proteins, and the human body will recognise these viral proteins and begin to build antibodies against them. This will guard against future viral infections after viral exposure (Hussain *et al.*, 2022; Pantelić*et al.*, 2022). Therefore, the discovery of successful mRNA vaccines was founded on the effective utilisation of nanotechnology drug carriers, which help in overcoming the majority of the nucleic acid constraints (Benamar *et al.*, 2016). This technique is based on employing a carrier to load the mRNA molecules. This will safeguard these mRNA molecules and minimise their quick elimination, resulting in an increase in their half-life and transportation to the target cells (Gregoriadis, 2021). Several pharmaceutical companies were focussing on developing such vaccines, which relied on delivering mRNA molecules that encoded for the virus's viral spike protein, which is the protein that allows the virus to enter human cells. The translation of such mRNA molecules onto the viral spike protein may assist in initiating an immune response by creating antibodies against this protein, which can offer immune responses against the subsequent viral exposures (Du *et al.*, 2022). This has resulted in the rapid creation and urgent clearance of two mRNA-based vaccines created by Pfizer and Moderna. Both vaccines rely on the utilisation of nanoparticles of lipids to encapsulate and transfer mRNA molecules into target cells following immunization (Szabó*et al.*, 2022).

2.2 Antiviral drugs

Certain antiviral drugs (tecovirimat, cidofovir, brincidofovir) have been investigated even if there are no particular antivirals for mpox (Riopelle *et al.*, 2022).

2.2.1. Tecovirimat (TPOXX, ST-246)

Tecovirimat (previously ST-246, now TPOXX®) blocks the p37 Orthopoxvirus protein, which causes virions and spreads the virus within infected hosts (Russo *et al.*, 2021). However, only the EMA has authorisedTecovirimat for treating monkeypox.Tecovirimat has been shown effective in combating smallpox in models involving humans and animals (Grosenbach *et al.*, 2018). Although tecovirimat's efficacy against monkeypox among humans has not been established, studies conducted on animals administered the medication at different stages of infection have demonstrated greater resilience against deadly monkeypox virus infections in comparison to animals given a placebo (Quenelle *et al.*, 2007; Grosenbach *et al.*, 2018).Tecovirimat's in vitro antiviral activity-based concentration showed

potential against various orthopoxviruses (Variola = 0.016–0.067; Monkeypox = 0.014–0.039; Rabbitpox = 0.015; Vaccinia = 0.009), as it was able to suppress the virus-induced cytopathic effect (CPE) by 50% (EC_{50} in µmol/L). It had minimal influence on the intracellular vaccinia virus generation, but it totally inhibited the CPE of the the wild-type strain cowpox virus and the extracellular vaccinia virus development (Hoy, 2018). It is reported that Tecovirimat works efficiently inthe non-human primate mpox model that uses cynomolgus monkeys infected with MPX strain Zaire 79 (V79-I-005) (Jordan *et al.*, 2009; Grosenbach *et al.*, 2018). Tecovirimat is a VP37 protein inhibitor that is specific to the orthopoxvirus and prevents the virus from spreading to other cells systemically (Grosenbach *et al.*, 2018; Hoy, 2018). As reported by Gosenbach*et al.* (2018), the genomic mapping of Tecovirimat-resistant mutant viruses identified the VP37 protein as a target of Tecovirimat.The orthopoxvirus-specific VP37 protein forms an envelope around MPXV, which is similar to an orthopoxvirus. The virus needs to leave the cell and propagate to other cells, so it must form an envelope.

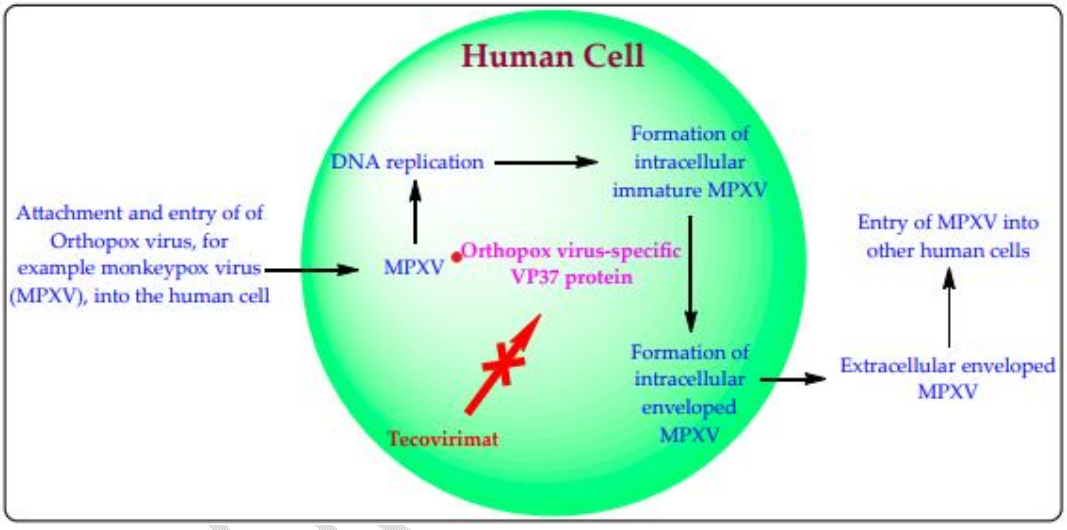

Fig 4. Tecovirimat: Mechanism of Action (Almehmadi et al., 2022).

2.2.2. Cidofovir

The nucleotide analogue cidofovir can inhibit monkeypox and smallpox from progressing (Huggins *et al.*, 2003). The FDA has approved this antiviral drug for use in treating AIDS patients' cytomegalovirus (CMV) retinitis. It is unclear if cidofovir is beneficial in treating human monkeypox. Nonetheless, studies conducted in vitro and on animals have demonstrated its efficacy against OPVs (Rice *et al.*, 2011). Patients with severe monkeypox infection may be administered cidofovir, albeit it is unclear if this will be beneficial for them. Since This drug can have major side effects, including renal dysfunction, it may not be as safe as Brincidofovir (Chittick*et al.*, 2017).

2.2.3. Brincidofovir (CMX001 or Tembexa)

Brincidofovir (BCV) is a phosphonate ester prodrug of Cidofovir (CDV), an injectable drug (Rizk *et al.*, 2022).The lipid moiety of BCV affects oral absorption, distribution, pharmacokinetics, and intracellular concentrations. BCV's lipophilic side chain mimics lysophosphatidylcholine, allowing it to get into cells through natural lipid absorption

pathways. BCV's lipid side chain hydrolyses in cells, releasing CDV, which is then phosphorylated to form CDV-diphosphate (CDV-DP) (Hutson *et al.,* 2022).Brincidofovir, an oral alternative to cidofovir, may have a reduced likelihood of renal damage than cidofovir, which is administered intravenously (Chittick *et al.,* 2017). These drugs function by blocking the virus's DNA polymerase (Lanier *et al.,* 2010). The FDA has approved brincidofovir for the treatment of smallpox, commencing in June 2021 (FDA, 2022). Only a few trials have shown its usefulness in treating Mpox infection. Animal studies indicate that brincidofovir effectively treats orthopoxvirus infections (Hutson *et al.*, 2021). Three Mpox patients who received brincidofovir (200 mg taken orally once weekly) reported elevated liver enzyme values, leading to therapy cessation (Sherawat *et al.,* 2022). While techniques for using these medications in endemic areas are needed, natural materials and extracts could be an intriguing option for antiviral treatments (Vora *et al.,* 2008; Alandijany*et al.*, 2021; Khalid *et al.,* 2021).

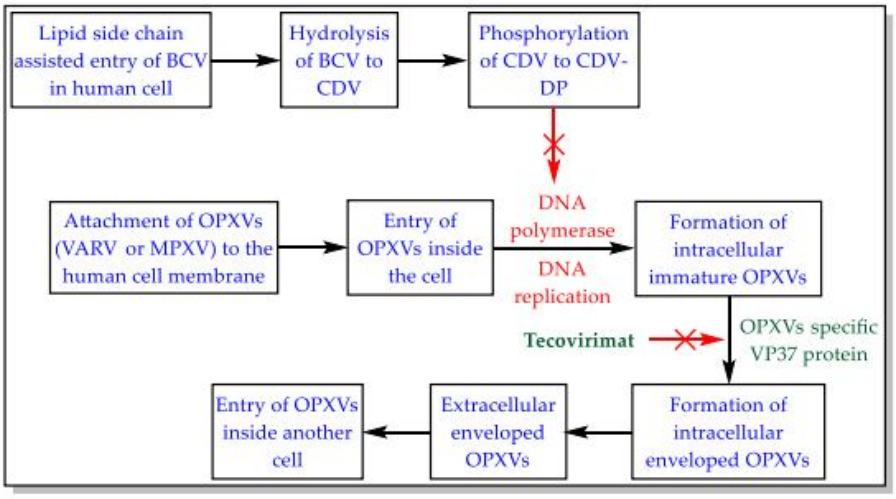

Fig 5. Brincidofovir: Mechanism of Action (Imran et al., 2023).

2.3 Antibodies as MPXV therapeutics

The global MPXV outbreaks in 2022 and the rise in human-to-human transmission highlight the need for prophylactics and therapeutics to stop the virus's spread and to protect and treat those who are allergic to the current MPXV vaccine or who are not able to mount a defence against vaccination. Antibody interventions are effective against poxviruses. Vaccinia immune globulin (VIG) is an approved treatment for complications after vaccinia virus immunisation, demonstrating the efficacy of antibodies towards this kind of virus. Poxviruses, including variola virus and monkeypox virus, are antigenically identical, hence antibodies against vaccinia virus provide protection against monkeypox (Edghill-Smith *et al.*, 2005). Although single monoclonal antibodies have not been clinically proven to be effective in humans, they are protective in certain animal models (Gu *et al.,* 2022). In order to potentially combat the present MPVX outbreak, Esqueda *et al.* (2023) reported the production of glycovariants of 7D11, a neutralising monoclonal IgG antibody (mAb) targeted to the L1 transmembrane protein of the associated vaccinia virus, in a plant-based system.

3. Potential drug targets for anti-viral therapy

Previous research indicates that the Mpox genome matches 96.3% of its DNA with the smallpox genome, that includes crucial enzymes and proteins for survival (Shchelkunov *et al.*, 2001).

3.1 Inosine mononphosphate (IMP) dehydrogenase

Ribavirin and tiazofurin, both IMP dehydrogenase inhibitors, inhibited the replication of all orthopoxviruses examined. Variola and monkeypox were more responsive compared to other types of viruses to both medications (Baker *et al.,* 2003). The rate-limiting enzyme in GMP biosynthesis, inosine monophosphate dehydrogenase, is inhibited by ribavirin and tiazofurin, which leads to decreased intracellular guanosine pools, interference with viral messenger RNA transcription, and disruption of 5′ cap formation (Jordan *et al.*, 1999).

3.2 Thymidylate Kinase

There are currently no known medicines targeting this enzyme, making it a novel target of interest. A48R is crucial for converting thymidine monophosphate and 50 halogenated deoxyuridine monophosphate analogues into their diphosphates (Prichard & Kern, 2012). Human thymidylate kinase's active site differs significantly from its structurally related analogue, making it a potential target for developing thymidine analogues without limiting the function of the human analogue (Caillat *et al.*, 2008).

3.3 DNA-dependent RNA polymerase (DdRp)

The multi-chain complex known as DNA-dependent RNA polymerase (DdRp) of the poxvirus is similar to its eukaryotic equivalent, particularly the RNA polymerase of yeast (Mirzakhanyan & Gershon, 2017). For the development of novel chemotherapeutic antiviral drugs targeting DNA viruses, the poxvirus's DNA-dependent RNA polymerase (DdRp) presents a prospective therapeutic target (Abduljalil&Elfiky, 2022).

3.4 Profilin-like protein A42R

The first known structure of an MPXV-encoded protein, the profilin-like A42R protein, was generated using X-ray crystallisation and has a resolution of 1.52 Å (Minasov*et al.*, 2022). A42R shares structural homology with profilin, a cytoskeletal protein known for its involvement in controlling actin cytoskeleton assembly. The A42R protein, encoded by the MPXV gp153 gene, has a striking amino acid sequence resemblance to eukaryotic cell profilin proteins (Van Vilet *et al.,* 2009). Since the Protein Data Bank (PDB) only contains A42R's structural characterisation of the proteins encoded by the MPXV genome, computational structural modelling has been primarily used to identify potential inhibitors against any target enzyme for the prevention of MPXV (Thai *et al.*, 2024).

3.5 E8 Ectodomain protein

The MPXV E8 protein is divided into two sections: domain I, which includes residues 1–235, and domain II, which is composed of residues 249–304 and consists of two opposing α-helices. A linkage of 13 residues connects these domains (Lam *et al.*, 2022). The MPXV E8 protein, which is equivalent to the VACV D8 protein, interacts with chondroitin sulphate (CS), the most common glycosaminoglycan (GAG), and aids in the entry of the virus (Gong *et al.*, 2022; Lam *et al.*, 2022). The capacity of the mature virus to bind to glycosaminoglycans (GAGs) is significantly affected by the ablation of the E8 protein,

suggesting that the E8 protein may be a viable target for therapeutic intervention against MPXV (Lam *et al.,* 2022).

4. Potential medicinal plants for monkeypox therapeutics

Research on traditional medicinal plants is crucial for developing novel drugs that target different pharmacological targets. Numerous phytochemicals obtained from medicinal plants have been thoroughly studied for their potential antiviral activity (Saifulazmi*et al.,* 2022). Bajrai*et al.* (2022) found that five compounds extracted from *Plantago lanceolata* had a strong capacity to bind to the active site of A42R of monkeypox virus and prevent natural substrate binding.Ginseng, in conjunction with other medications and vaccinations, could be utilised as an adaptogenic agent that may prevent MPXV infection (Das *et al.,* 2023). The phytoconstituents found in *Vernonia amygdalina del.* leaves exhibit beneficial properties and a potent record against the monkeypox virus (Jha *et al.,* 2023).According to a study by Bansal *et al.* (2022), bioactive phytochemicals in *Allophylus serratus* may serve as template molecules for future experiments to assess their efficacy against the monkeypox virus.*Nigella sativa* could be administered as an adjuvant therapy together with repurposed/investigated antivirals and supportive therapy in management of individuals with monkeypox infection in its initial stages to prevent inflammatory disorders and subsequent bacterial infections (Maideen*et al.,* 2024). The phytocompounds contained in *Phyllanthusacidus* control pathways connected to viral infection symptoms, which may aid in maintaining homeostasis. The plant also has antiviral activity and therapeutic potential against monkeypox infection. The efficacy of *P. Acidus* derived phytocompound against MPV was established using functional annotation, PASS prediction, and network pharmacology analysis (Datta*et al.,* 2023).Phytochemicals from *Moringa oleifera* may block monkeypox DNA polymerase, leading to potential ways for combating the disease (Yousaf *et al.,* 2024). Akash *et al.* (2023) suggested curcumin derivatives as promising antiviral medicines for managing monkeypox and smallpox virus.

5.Antiviral activity of phytochemicals through *in-silico* approach

Phytochemicals have been found as potential treatment agents for MPXV, inhibiting viral replication and enhancing immune response (Gulati *et al.,* 2023; Patel *et al.,* 2023). The potential of phytochemicals as a treatment for viral infections like SARS-CoV-2, HIV, herpes simplex virus, and influenza has been thoroughly researched making it promising for monkeypox virus therapeutics.

Sr no	Phytochemicals	Target	Key findings	Citation

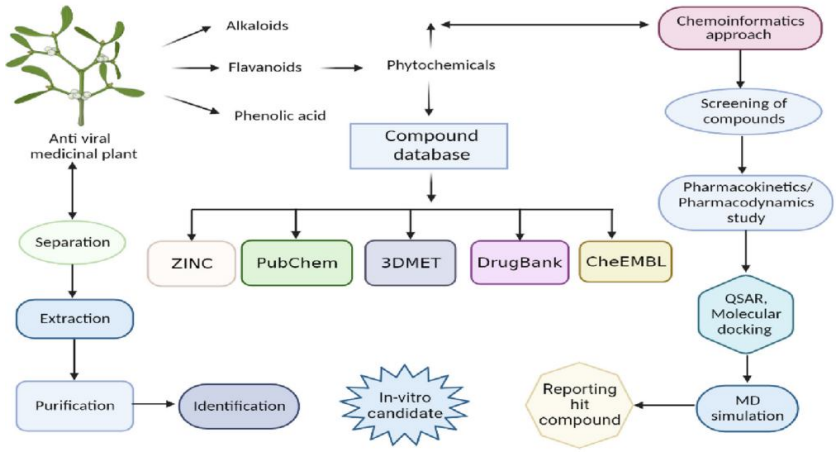

Fig 6: Flow diagram for identifying compounds using in silico technique (Kharwar et al., 2024).

1.	Salpichrolide J (Comp 441),Comp289 (CNP0158693), GTP, Hydroxytubocapsanolide A (Comp 449), and Anabsinthin (Comp 295)	DNA-dependent RNA polymerase (DdRp).	Four compounds (comp289, comp295, comp441, and comp449) were shown to bind the hMPXVDdRp active site with comparable binding affinity (−17.06 ± 2.96, −11.6 ± 5.34, −14.85 ± 2.66, and −10.79 ± 4.49 kcal/mol) with GTP (−21.03 ± 7.55 kcal/mol).	Abduljalil *et al.*, 2023.
2.	Salsoline derivative, Genistein, the semi-synthetic derivative of kojic acid, and Naringenin	Profilin-like protein A42R from the Monkeypox Zaire-96-I-16 virus.	Molecular docking showed that Salsoline derivatives, Genistein, Semisynthetic derivative of kojic acid, and Naringenin had a stronger affinity (−8.9 to −10 kcal/mol) to 4QWO than the FDA-approved Tecovirimat. Molecular dynamics simulation confirmed their high binding stability.	Chebaibi*et al.*, 2024.
3.	Betulin	Papain-like protease and Spike proteins from the SARS-CoV-2 virus and Profilin-like protein A42R from the Monkeypox Zaire-96-I-16 virus.	Betulin is effective against all the applied proteins of SARS-CoV-2 and monkeypox.	Burkhanova*et al.*, 2022.

4.	Punicalagin	MPXV E8 ectodomain protein.	It showed a greater affinity for the target protein (-9.1 kcal/mol).	Tamang *et al.*, 2023
5.	Riboflavin, Curcumin, and Quercetin	D8L protein in the Monkeypox virus.	D8L protein illustrated the best docking score (−7.6 kcal/mol) in relation to the Rib and displayed good docking scores in relation to the Cur (−7.0 kcal/mol) and Qct (−7.5 kcal/mol).	Pourhajibagher&Bahador, 2023
6.	Ascorbic acid, vanillic acid, Flavinoids (Catechin; Epicatechin; Hyperoside; Luteolin; Taxifolin and Quercetin)	Vaccinia virus thymidylate kinase (VTK), the viral profilin-like protein (VPP), and the viral RNA polymerase (VRP).	Flavonoids are potent to VTK, VPP and effectively block the VRP channel with energy values ranging from −7.0 to −9.3 kcal/mol.	Linani*et al.*, 2023
7.	Triterpenes	DNA-dependent RNA polymerase (DdRp)	α-amyrin, β-sitosterol, and β-amyrin were among the top-ranked molecules with strong binding affinities towards DNA-dependent RNA polymerase of the virus	Fidan&Mujwar, 2024
8.	Luteolin 7,3'-Diglucuronide, Luteolin 7-Glucuronide-30 – Glucoside, Plantagoside, Narcissoside, (AlphaE,8S,9R)-N-(3,4-Dihydroxyphenethyl)-8-[(3,4-Dihydroxyphenethyl)Carbamoyl]-9-(1,3-	A42R profilin-like protein of MPXV	MD simulation and post-simulation analysis show that plantagoside and narcissoside have significant stability in the viral protein binding pocket due to hydrogen and hydrophobic	Bajrai*et al.*, 2022

	Benzodioxole-5-Yl)-3aalpha,7aalpha-Ethano-1,3-Benzodioxole-5-Acrylamide		interactions.	
9.	Curcumin, Gedunin, Piperine, and Coumadin	A42R profilin-like protein of MPXV	Curcumin had the highest binding affinity, measuring -37.43 kcal/mol, followed by gedunin (-34.89 kcal/mol), piperine (-34.58 kcal/mol), and coumadin (-34.14 kcal/mol). According to ADME and toxicity assessments, the top four drugs had no detrimental effects.	Banik *et al.*, 2023
10.	Dictamnine, Amentoflavone, Citral, and Naringin	Thymidine kinase of Mpox replication cycle	Phytochemicals dictamnine, amentoflavone (-7.5), citral (-7.8), and naringin (-6.6) from various plants had the highest affinity (-18).	Adil *et al.*, 2023
11.	Kaempferol and Piperine	A42R profilin-like protein of MPXV	The best-pose ligandbinding energies of the A42R profilin-like protein were determined by *in silico analysis* of the interactions between kaempferol (C-1) and piperine (C-4). These values were –6.98 and –5.57 kcal/mol, respectively. C-1's estimated IC_{50} was 7.63lM, while C-4's was 82lM. Kaempferol and piperine are not mutagenic, according to toxicity data, while piperine (5.25) and piperlongumine (5.92) showed higher log P values than the other	Mohapatra *et al.*, 2023

			chemicals analysed in the QSAR data.	
12.	(N-(2-Allylcarbamoyl-4-chloro-phenyl)-3,4-dimethoxy-benzamide, 6-Dimethylaminonaphthene-1-sulfonicacid amide, Oleic Acid and dipentyl ester	Core viral cysteine proteases from Mpox virus	The selected ligands have an affinity for the target viral protein that ranges from -5.0 to -6.7 kcal/mol. With a binding affinity of -6.7 kcal/mol, N-(2-Allylcarbamoyl-4-chloro-phenyl)-3,4-dimethoxy-benzamide had the highest value.	Bansal *et al.*, 2022
13.	Baicalein, Luteolin and Olivil	BR203 and BR209 gene	The phytochemical Baicalein, Luteolin, olivil shows significant interactions with BR203 and BR209 with a high docking score.	Paul *et al.*, 2023
14.	Curcumin derivatives	4QWO viral protein of Mpox and 3IGC viral protein of Smallpox	The molecular docking analysis confirmed the antiviral activity against monkeypox and smallpox viruses. The docking score is around -7.7 kcal/mol to -8.9 kcal/mol against monkeypox	Akash *et al.*, 2023

			virus and -7.3 kcal/mol to -8.8 kcal/mol against smallpox virus.	
15.	Tetrahydroxycurcumin, Procyanidin, Rutin, Vicenin-2, and Kaempferol	*Var*TMPK (1MNR)	Tetrahydroxycurcumin had the highest binding energy (~9.7 kcal/mol) and demonstrated a stable protein-ligand complex throughout MD tests.	Alagarsamy *et al.*, 2023
16.	Gossypetin, Riboflavin, and Ellagic acid	DNA Polymerase	Gossypetin had the highest binding affinity (−7.8 kcal/mol), followed by riboflavin (−7.6 kcal/mol) and ellagic acid. The control drugs Cidofovir and Brincidofovir had lower binding energies of -6.0 kcal/mol and -5.1 kcal/mol, respectively.	Yousaf *et al.*, 2024
17.	Luteolin, Luteolin-7-o- β-glucoside, Vernodalol, Vernolepin, and Vernodalin phytoconstituents	PDB Id (6LUT) receptor	The compounds Luteolin (-3.244), Luteolin-7-o-βglucoside (-2.357), Vernodalol (-2.089), Vernolepin (-1.757), and Vernodalin (-1.534) have lower docking scores than the antiviral drug Tecovirimat (-0.162). These compounds could potentially inhibit Monkeypox infection.	Jha *et al.*, 2023
18.	Limonoids, Triterpenoids, and Polyphenols	DNA Polymerase	Molecular dynamics simulations of the phytochemicals glycyrrhizinic acid and apigenin-7-O-glucuronide	Vardhan & Sahoo, 2023

			demonstrated their capacity to inhibit the monkeypox virus's DNA polymerase activity.	

Fig 7: Tabular representation of phytochemicals as potential antivirals for monkeypox virus.

According to a related study by Maurya*et al.* (2024), curcumin primarily suppresses host inflammatory pathways like TNF, NF-κB, and MAPK signalling during Mpox infection by targeting Mpox DNA polymerase holoenzyme, Methyltransferase VP39, A42R profilin-like protein, envelope protein E8, TNF, MAPK, NFKB1, and PTGS2. Furthermore, in contrast to Cidofovir, a DNA polymerase inhibitor, curcumin has a considerable binding affinity for the MPXV DNA polymerase. Curcumin might be useful as a multi-targeted antiviral agent against newly emerging Mpox. This suggests that curcumin could be used as a broad-spectrum antiviral drug during viral outbreaks, and it encourages further research that gives the molecular foundation for our study.

6. Conclusion

Several phytocompounds have been investigated through molecular docking, MD modelling, and pharmacokinetic studies, with curcumin and luteolin derivatives being the most studied. Amongst the phytocompounds studied curcumin derivatives had the highest binding affinity against the monkeypox virus. Several research focused on several targets, the most prominent of which were DNA dependent RNA polymerase and the A42R profilin-like protein of the mpox virus. These phytocompounds and receptor targets may serve as future therapeutic leads in *in-vivo* research. The latest monkeypox outbreak brings much-needed attention to diseases that are currently neglected or understudied, hence motivating much-needed research.

7. Future prospects

Although the results are promising and provide need for future studies of phytochemicals as therapeutic approaches for monkeypox outbreak. Further in vivo research are required to corroborate these findings. Well-designed and controlled clinical trials must be planned to determine the therapeutic value of phytochemicals and their role in monkeypox pharmacotherapy.

Abbreviations

1. APSV: Aventis Pasteur Smallpox Vaccine
2. BCV: Brincidofovir
3. CDV: Cidofovir
4. CMLV: Camelpox virus
5. CPXV: Cowpox virus
6. CS: Chondroitin Sulphate
7. Cur: Curcumin
8. DdRp: DNA-dependent RNA polymerase

9. DRC: Democratic Republic of Congo
10. FDA: Food and Drug Organisation
11. GAG: Glycosaminoglycan
12. IMP: Inosine Monophosphate
13. MD: Molecular Docking
14. MPOX: Monkeypox
15. MPXV: Monkeypox virus
16. MSM: Men who have sex with men
17. OPXV: Orthopoxvirus
18. PDB: Protein Data Bank
19. Qct: Quercetin
20. QSAR: Quantitative Structure Activity Relationship
21. Rib: Riboflavin
22. TATV: Taterapox virus
23. VACV: Vaccinia virus
24. VARV: Variola virus
25. VIG: Vaccinia Immune Globulin
26. VPP: Viral Profilin like Protein
27. VRP: Viral RNA Polymerase
28. VTK: Vaccinia virus Thymidylate Kinase
29. WHO: World Health Organisation

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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