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Harnessing nature's arsenal: A comprehensive review of phytomedicine approaches in Monkeypox treatment

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Abstract

The recent global outbreak of monkeypox has highlighted the urgent need for effective treatments against this emerging viral threat. Despite the limitations of conventional antiviral therapies, phytomedicine presents a promising avenue for further exploration. This review examines the potential of plant-derived compounds in addressing monkeypox, focusing on recent advancements in phytochemical research and traditional medicine approaches. We analysed key phytochemicals, including curcumin derivatives, flavonoids, triterpenes, and alkaloids, discussing their mechanisms of action and potential efficacy against the monkeypox virus. The review also explores insights from traditional Chinese medicine and other traditional healing systems. Challenges in phytomedicine development, including bioavailability issues and standardisation, are addressed, along with future research directions. This comprehensive analysis provides a foundation for harnessing nature's arsenal in the fight against monkeypox, offering insights into potential phytomedicine-based strategies for prevention and treatment.

1. Introduction

Following COVID-19, a new infectious disease outbreak in 2022 brought on by the monkeypox virus, has raised serious concerns for global health. The zoonotic disease known as mpox is caused by the Monkeypox virus (MPXV), a species of the genus Orthopox virus (Lum *et al*., 2022). The WHO report states that 121 countries worldwide have recorded 102,977 confirmed cases of Mpox caused by MPXV clade I and clade II, including 219 fatalities, since the start of Mpox surveillance in 2022 and up to July 31, 2024. Common symptoms of Mpox include fever, headache, back discomfort, muscle aches, low energy, swollen lymph nodes, and a skin rash or mucosal lesions that can last for two to four weeks (Rong *et al*., 2023; Jiao *et al*., 2023).

In India, Kerala reported its first confirmed case of Mpox (monkeypox) on 38-year-old man, who returned from Dubai on September 13, 2024, had a high fever accompanied by visible blisters, prompting the authorities to send his samples for testing Mpox. The second confirmed case on the 27th of September 2024, a 26-year-old man who recently returned from the UAE, has been hospitalised, and his samples have been sent for genomic sequencing at the National Institute of Virology in Pune to determine, if he is infected with the newer Clade 1b strain or the previously known Clade IIb strain, and in both cases, the samples were tested positive for Mpox.

The virus's genome, ranging from 130 to 360 kbp, encodes numerous proteins involved in viral replication and host interaction (Okyay *et al*., 2022). Transmission of MPXV can occur through various routes, including direct contact with infected animals, close contact with infected individuals, and potentially through fomites. The clinical presentation of monkeypox in humans is similar to smallpox, but generally less severe, characterised by fever, lymphadenopathy, and a distinctive rash progression (Adler *et al*., 2022). Given the limitations of current treatment options and the potential for future outbreaks, exploring alternative therapeutic approaches are crucial. Phytomedicine, with rich history of its use against viral diseases, offers a promising avenue for investigation.

Originally endemic to regions of Central and West Africa, the virus has recently demonstrated its potential for widespread transmission, with outbreaks occurring in multiple countries across several continents (Thornhill *et al*., 2022). The limited availability of specific antiviral treatments for monkeypox underscores the urgent need for alternative therapeutic approaches. Two types of smallpox vaccines have been discovered to be effective against monkeypox, but the most effective strategies to prevent and cure this potentially dangerous illness are yet unknown (Adler *et al*., 2022). The most popular

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vaccination, ACAM2000, is authorised in the United States to prevent smallpox that could be used to treat monkeypox currently. However, because of the possible side effects, it should not be given to vulnerable populations, including pregnant or lactating women and people with weakened immune systems (Kerna *et al*., 2024). As the generation and re-emergence of highly contagious viruses continue to pose a threat to global health. Study into the antiviral properties of medicinal plants has significantly increased, assisted by the expanding availability of sophisticated instruments.

Monkeypox presents with fever, an extensive characteristic rash, and usually swollen lymph nodes (Adler *et al*., 2022; Orviz *et al*., 2022; Tarín-Vicente *et al*., 2022). It is important to distinguish monkeypox from other contagious pox-like viral diseases such as varicella, measles, bacterial skin infections, scabies, syphilis, and medication-associated allergies. However, we can explore ways to prevent and treat monkeypox from human experience in fighting against other contagious pox like viral diseases. Throughout the 3000-year history of China, Chinese medicine (CM) has been used as the routine treatment regime for acute infectious diseases (Wu *et al*., 2021). For example, when severe acute respiratory syndrome (SARS) was the most serious infectious disease outbreak in China in 2003, Chinese herbal formulas played a significant role in the prevention and treatment of SARS (Masi Malaiyan *et al*., 2023). In 2022, facing the outbreak of monkeypox around the world, the National Health Commission of China issued a CM treatment program in the Guidelines for the Diagnosis and Treatment of Monkeypox (2022 Version) (Interpretation of guidelines for diagnosis, 2022), which included six Chinese herbal formulas based on different clinical symptoms (Rong *et al*., 2023).

Plant-based medicines have demonstrated efficacy against various viral pathogens, including coronaviruses, poxviruses, and influenza viruses, suggesting potential applications in monkeypox treatment (Nupur and Jadhav, 2020). The present review aims to comprehensively explore the potential of phytomedicine in the treatment of monkeypox. We exemplified promising plant-derived compounds with potential anti-MPXV activity, discuss insights from traditional medicine systems, and address the challenges and opportunities in translating phytomedicinal research into clinical applications.

2. Phytochemicals with potential anti-monkeypox activity

Recent research has identified numerous phytochemicals with potential efficacy against various viral pathogens, including coronaviruses, poxviruses, and influenza viruses, offering promising avenues for the development of novel antiviral therapies (Nupur and Jadhav, 2020).

2.1 Curcumin and its derivatives

Curcumin, derived from *Curcuma longa* L. (turmeric), has been extensively studied for its broad-spectrum antiviral activities. Its efficacy has been demonstrated against a range of viruses, including influenza, respiratory syncytial virus (RSV), hepatitis B and C viruses (HBV, HCV), and Zika virus (ZIKV) (Alakunle *et al*., 2020; Sivakumar *et al*., 2022). Recent research has unveiled the potential of curcumin derivatives as potent antiviral agents against monkeypox and smallpox viruses.

A comprehensive *in silico* study evaluated fifty curcumin derivatives from natural sources for their antiviral capabilities against MPXV. Twelve derivatives exhibited exceptional binding scores (-8.00 to -8.90 kcal/mol) and showed better standard medications. These compounds showed favourable absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, indicating their potential as orally active drugs with good bioavailability and minimal toxicity (Akash *et al*., 2023). The antiviral mechanisms of curcumin and its derivatives include the inhibition of viral entry by suppression of viral replication, modulation of cellular signaling pathways, and enhancement of the host immune response. Table 1 shows the curcumin derivatives with potential anti-monkeypox activity based on molecular docking studies conducted by Akash *et al*. (2023) and further validated through *in vitro* experiments by Liu *et al*. (2023).

Table 1: Curcumin derivatives with potential anti-monkeypox activity

Compounds	Binding score (kcal/mol)	Potential mechanism
Demethoxy curcumin	-8.90	Viral entry inhibition
Bisdemethoxy curcumin	-8.75	Replication suppression
Cyclocurcumin	-8.60	Immune modulation
Tetrahydro curcumin	-8.45	Cellular signalling modulation

2.2 Flavonoids and phenolic compounds

Flavonoids and phenolic compounds represent a diverse group of plant secondary metabolites with well-documented antiviral properties. Several of these compounds have shown significant binding affinities to monkeypox virus proteins in computational and experimental studies, suggesting their potential as anti-monkeypox agents (Zhang *et al*., 2023; Wang *et al*., 2024). Recent molecular docking analyses combined with *in vitro* validation have identified specific flavonoids that demonstrate promising inhibitory effects against MPXV proteins.

2.2.1 Verbascoside

Verbascoside, a phenylpropanoid glycoside found in various plants, including *Verbascum* species (mullein) and *Plantago major* (common plantain), exhibited a particularly strong affinity for monkeypox thymidine kinase at -10.0 kcal/mol (Patel *et al*., 2023). This compound has previously demonstrated activity against herpes simplex viruses, suggesting a broad-spectrum antiviral potential.

2.2.2 Other promising flavonoids

Other promising flavonoids (Johnson *et al*., 2023; Kumar *et al*., 2024) have demonstrated significant potential through both computational and experimental studies:

2.2.2.1 Tiliroside

Found in *Tilia* species (linden) and *Rosa canina* (dog rose), with binding affinities of -8.8 kcal/mol (B12R) and -9.3 kcal/mol against thymidine kinase enzyme.

2.2.2.2 Rutin

Present in *Ruta graveolens* (rue) and *Sophora japonica* (Japanese pagoda tree), with affinities of -9.0 kcal/mol (B12R) and -9.1 kcal/mol against thymidine kinase.

2.2.2.3 Isorhamnetin-3-O-rutinoside

Derived from *Calendula officinalis* (marigold) and *Hippophae rhamnoides* (sea buckthorn), with affinities of -8.2 kcal/mol (B12R) and -9.3 kcal/mol against thymidine kinase. These compounds have previously shown antiviral activities against various viruses, including HIV-1 and HSV-1, suggesting their potential broad-spectrum antiviral properties (Ahn *et al*., 2023). Table 2 showed the list of flavonoids and phenolic compounds with potential anti-monkeypox activity.

2.3 Triterpenes

Triterpenes are a class of natural compounds that have demonstrated significant antiviral potential across various studies. In the context of monkeypox, several triterpenes have shown exceptional binding affinities to key MPXV enzymes in computational studies.

Table 2: List of flavonoids and phenolic compounds with potential anti-monkeypox activity

Compounds	Plant sources	Binding affinity (kcal/mol)	Known antiviral activity
Verbascoside	*Verbascum* spp.	-10.0 (TK)	HSV-1, HSV-2
Tiliroside	*Tilia* spp., *Rosa canina*	-9.3 (TK)	HIV-1
Rutin	*Ruta graveolens, Sophora japonica*	-9.1 (TK)	HIV-1
Isorhamnetin-3-O-rutinoside	*Calendula officinalis, Hippophae rhamnoides*	-9.3 (TK)	HSV-
Quercetin	*Allium cepa, Camellia sinensis*	-7.7 (TK) |	HSV-1, Poliovirus-1, RSV
Kaempferol	*Kaempferia galanga, Moringa oleifera*	-8.0 (TK)	HCV, HCMV
Myricetin	*Myrica rubra, Vitis vinifera*	-7.9 (TK)	HIV
Apigenin	*Petroselinum crispum, Matricaria chamomilla*	-8.1 (TK)	HSV-2
Luteolin	*Reseda luteola, Achillea millefolium*	-8.2 (TK)	HPV-16

2.3.1 Oleanolic acid

Oleanolic acid, found in plants such as *Olea europaea* (olive) and *Phytolacca americana* (pokeweed), exhibited the strongest binding to MPXV thymidine kinase with an affinity of -10.2 kcal/mol. It also showed strong affinity to B12R serine/threonine kinase at -9.8 kcal/mol (Patel *et al*., 2023). This compound is known for its activity against the hepatitis C virus, suggesting potential broad-spectrum antiviral properties.

2.3.2 Ursolic acid

Ursolic acid, present in *Rosmarinus officinalis* (rosemary) and *Malus domestica* (apple) peel, displayed high binding affinities of -9.3 and -9.4 kcal/mol to B12R and thymidine kinase, respectively (Patel *et al*., 2023). This triterpene has established activity against HPV-18 and HCV, further supporting its potential as an anti-monkeypox virus agent.

2.3.3 Other triterpenes

Other triterpenes, such as pomolic acid derived from *Chryso balanusicaco* (coco plum) and *Syzygium claviflorum*, have also shown promising binding affinities to MPXV enzymes and warrant further investigation. Table 3 shows the list of triterpenes with potential anti-monkeypox activity, as identified through comprehensive molecular docking studies and preliminary *in vitro* screening assays (Smith *et al*., 2023a; Chen *et al*., 2024).

Table 3: Triterpenes with potential anti-monkeypox virus activity

Compounds	Plant sources	Binding affinity (kcal/mol)	Known antiviral activity
Oleanolic acid	*Olea europaea, Phytolacca americana*	– 10.2 (TK), – 9.8 (B12R)	HCV
Ursolic acid	*Rosmarinus officinalis, Malus domestica*	– 9.4 (TK), – 9.3 (B12R)	HPV-18, HCV
Pomolic acid	*Chryso balanusicaco, Syzygium claviflorum*	– 9.2 (TK), – 9.4 (B12R)	HIV-1

2.4 Alkaloids

Alkaloids represent another important class of plant-derived compounds with potential anti-monkeypox activity. Several alkaloids have demonstrated notable binding affinities to MPXV proteins in computational studies, suggesting their potential as antiviral agents against monkeypox.

2.4.1 Homolycorine

Homolycorine, found in the Amaryllidaceae family, exhibited notable binding affinities to both B12R and thymidine kinase proteins, with values of -8.6 kcal/mol for each target (Patel *et al*., 2023). This alkaloid has previously shown activity against HIV-1, indicating its potential broad-spectrum antiviral properties.

2.4.2 Other promising alkaloids

2.4.2.1 Galantamine

Derived from *Galanthus* (snowdrop) and *Narcissus* (daffodil) species, galantamine showed binding affinities of -7.6 kcal/mol (B12R) and -7.9 kcal/mol against thymidine kinase. It has demonstrated activity against poliovirus (Patel *et al*., 2023).

Table 4: Alkaloids with potential anti-monkeypox virus activity

Compounds	Plant sources	Binding affinity (kcal/mol)	Known antiviral activity
Homolycorine	Amaryllidaceae family	-8.6 (TK), -8.6 (B12R)	HIV-1
Galantamine	*Galanthus* spp., *Narcissus* spp.	-7.9 (TK), -7.6 (B12R)	Poliovirus
Lycorine	Amaryllidaceae family	-8.1 (TK), -7.5 (B12R)	Poliovirus, SARS-CoV
Thalimonine	*Thalictrum* spp.	-7.7 (TK),-8.4 (B12R)	Influenza, HSV-1

2.4.2.2 Lycorine

Present in various Amaryllidaceae plants, lycorine exhibited binding affinities of -7.5 kcal/mol (B12R) and -8.1 kcal/mol against thymidine kinase. It has shown antiviral activity against poliovirus and SARS-CoV (Patel *et al*., 2023).

2.4.2.3 Thalimonine

Derived from *Thalictrum* species (meadow-rue), thalimonine showed binding affinities of -8.4 kcal/mol (B12R) and -7.7 kcal/mol on thymidine kinase. It has demonstrated activity against influenza and HSV-1 (Patel *et al*., 2023). The Table 4 showed the list of alkaloids with potential anti-monkeypox activity.

3. Traditional medicine approaches

Traditional medicine systems offer a wealth of knowledge accumulated over centuries of practice. In the context of monkeypox treatment, insights from these systems, particularly traditional chinese medicine (TCM), provide valuable leads for phytomedicine research. A comprehensive study of 2,344 pox-related prescriptions in TCM literature conducted by Li *et al*. (2023), identified 19 frequently used herbs, 61 associated bio-functional modules, and 29 lead compounds with potent anti-inflammatory, antimicrobial, and antiviral properties. This groundbreaking research provides a robust scientific framework for understanding TCM's potential efficacy against poxviruses.

- Immunoregulation, particularly $CD4^+T$ cell regulation, emerged as the primary mechanism of action for these remedies.
- The identified compounds showed potential to inhibit critical stages of the poxvirus life cycle, including DNA synthesis, RNA capping, and mature virus particle formation.
- Many of the compounds exhibited immunosuppressive properties, aligning with the complex pathophysiology of poxvirus infections.

3.1 Ginseng: A potential ally in monkeypox prevention

Ginseng, a renowned herbal remedy with a history spanning thousands of years, has demonstrated promising antiviral effects in numerous studies (Ratan *et al*., 2021; Kim *et al*., 2022). Its potential as an adaptogenic agent in MPXV prevention is of particular interest, given its historical use in treating infectious diseases and its well-documented immune-modulating properties (Park *et al*., 2022). While conventional approaches such as antivirals, vaccinia immune globulin, and smallpox vaccines are being utilised, the integration of ginseng as a complementary therapy could potentially enhance prevention strategies.

3.2 Phytomedicinal plant species in the treatment of monkeypox

3.2.1 *Acacia nilotica* (Mimosaceae)

Acacia nilotica, locally known as Bagaruwa or Scented Thorn, has been traditionally used to treat various viral diseases, includes monkeypox, hepatitis, smallpox, and meningitis. The plant's leaves and stem are commonly prepared as a decoction or mixed with pap for oral administration. *A. nilotica* contains several bioactive compounds, including tannins (such as gallic acid and ellagic acid) and flavonoid sand phenolic compounds, which contribute to its antiviral properties. These compounds have demonstrated the ability to inhibit viral replication and modulate the host immune response. A study by Hussein *et al*. (2000) showed that *A. nilotica* extracts exhibited significant antiviral activity against HIV-1 protease, with an IC_{50} value of 0.9 ig/ml. Additionally, Ellithey *et al*. (2014), found that *A. nilotica* bark extract showed potent antiviral activity against the hepatitis C virus, inhibiting viral replication by targeting the NS3 protease. While specific studies on *A. nilotica*'s efficacy against monkeypox are lacking, its demonstrated antiviral properties and traditional use in treating smallpox suggest potential applications in monkeypox treatment. Further research is needed to elucidate its mechanisms of action against poxviruses and evaluate its clinical efficacy. Figure 1 show the various traditional plants used in the treatment of monkeypox virus.

3.2.2 *Adansonia digitata* (Bombacaceae)

Adansonia digitata, commonly known as Baobab, has been used in traditional medicine to treat monkeypox, poliomyelitis, smallpox, yellow fever, and hepatitis. The stem bark is typically prepared as a decoction for oral administration. The stem bark of *A. digitata* contains various bioactive compounds, including flavonoids (such as quercetin and kaempferol), tannins, and terpenoids, which contribute to its antiviral properties. These compounds have shown the ability to interfere with viral attachment and replication processes. Vimalanathan and Hudson (2009). found that *A. digitata* leaf extracts exhibited significant antiviral activity against herpes simplex virus type 1 (HSV-1), with an IC_{50} value of 48 µg/ml. The extract was found to inhibit viral attachment and penetration into host cells. Another study by Anani *et al*. (2000), demonstrated the antiviral activity of *A. digitata* extracts against poliovirus and coxsackie virus. The broad-spectrum antiviral activity of *A. digitata*, coupled with its traditional use in treating poxviruses, makes it a promising candidate for further investigation in monkeypox treatment.

3.2.3 *Aframomum melegueta* (Zingiberaceae)

Aframomum melegueta, commonly known as Alligator pepper or grains of paradise, has been traditionally used to treat monkeypox, hepatitis, COVID-19, poliomyelitis, and yellow fever. The whole plant is typically prepared as a decoction for oral administration.

Figure 1: Traditional plants used in the treatment of monkeypox virus.

A. melegueta contains various bioactive compounds, including phenolic acids, flavonoids, and terpenoids, which contribute to its antiviral properties. A study by Mahoney *et al*. (2022) found that *A. melegueta* seed extracts exhibited significant antiviral activity against measles and yellow fever viruses. However, the same study reported no activity against poliovirus, highlighting the specificity of its antiviral effects. While direct studies on *A. melegueta*'s efficacy against monkeypox are not available, its demonstrated activity against other viruses and its traditional use in treating poxviruses warrant further investigation. Future research should focus on isolating and characterising the specific compounds responsible for its antiviral activity and evaluating their potential against poxviruses.

3.2.4 *Allium sativum* (Amaryllidaceae)

Allium sativum, commonly known as garlic, has been used globally to treat various viral infections, including monkeypox, COVID-19, meningitis, and hepatitis. The whole plant is typically crushed and mixed with other ingredients or prepared as a concoction for oral administration. Garlic contains several sulphur compounds, including allicin, diallyl trisulfide, and ajoene, which are responsible for its antiviral properties. These compounds have shown activity against a wide range of viruses by inhibiting viral entry, replication, and spread. Weber *et al*. (1992), demonstrated that ajoene, a compound derived from garlic, inhibited HIV-induced destruction of $CD4^+$ cells. A more recent study by Mehrbod *et al*. (2009), showed that garlic extract exhibited significant antiviral activity against influenza A virus (H1N1) in cell culture, reducing virus titers by up to 90%. The broad-spectrum antiviral activity of *A. sativum*, coupled with its long history of use in traditional medicine, makes it a promising candidate for monkeypox treatment. Future research should focus on evaluating its efficacy against poxviruses and developing standardised preparations for clinical use.

3.2.5 *Guiera senegalensis* (Combretaceae)

Guiera senegalensis, locally known as Sabara or Moshi medicine, has been traditionally used to treat monkeypox, poliomyelitis, yellow fever, smallpox, COVID-19, meningitis, and hepatitis. The leaves are typically prepared as a decoction or mixed with pap for oral administration. *G. senegalensis* contains various bioactive compounds, including tannins, flavonoids, Silva *et al*. (2012), demonstrated that *G. senegalensis* leaf extracts exhibited significant antiviral activity against herpes simplex virus type 1 (HSV-1) and poliovirus type 1 and alkaloids, which contribute to its antiviral properties (Fiot *et al*., 2006). A study by Silva *et al*. (2012), demonstrated that *G. senegalensis* leaf extracts exhibited significant antiviral activity against herpes simplex virus type 1 (HSV-1) and a monkeypox virus type 1. The extracts were found to inhibit viral replication and reduce viral titers in cell culture. While specific studies on *G. senegalensis*'s efficacy against the monkeypox are lacking, its demonstrated antiviral properties and traditional use in treating various viral diseases, including smallpox, suggested potential applications in monkeypox treatment.

3.2.6 *Vernonia amygdalina* (Compositae)

Vernonia amygdalina, commonly known as bitter leaf, has been traditionally used to treat monkeypox, yellow fever, smallpox, COVID-19, meningitis, and poliomyelitis. The leaves are typically prepared as a decoction for oral administration. *V. amygdalina* contains various bioactive compounds, including sesquiterpene lactones, flavonoids, and steroidal saponins, which contribute to its antiviral properties (Yeap *et al*., 2010). A study by Vlietinck *et al*. (1995) demonstrated that *V. amygdalina* leaf extracts exhibited significant antiviral activity against herpes simplex virus type 1 (HSV-1) and poliovirus. Another study by Adetunji *et al*. (2018), showed that *V. amygdalina* leaf extracts had potent antiviral activity against Newcastle disease virus, a paramyxovirus. The broad-spectrum antiviral activity of *V. amygdalina*, coupled with its traditional use in treating poxviruses, makes it a promising candidate for further investigation in monkeypox treatment. Future research should focus on isolating and characterising the specific compounds responsible for its antiviral activity and evaluating their potential against poxviruses.

3.2.7 *Momordica charantia* (Cucurbitaceae)

Momordica charantia, commonly known as bitter melon or balsam pear, had been traditionally used to treat monkeypox, poliomyelitis, smallpox, yellow fever, meningitis, COVID-19, and hepatitis. The leaves are typically prepared as a concoction, or the powder is boiled with tea for oral administration. *M. charantia* contains various bioactive compounds, including triterpenoids, proteins, and lectins, which contribute to its antiviral properties. A study by Pongthanapisith *et al*. (2013), demonstrated that *M. charantia* leaf extracts exhibited significant antiviral activity against hepatitis B virus (HBV) by inhibiting viral replication. Another study by Fang *et al*. (2012), showed that *M. charantia* lectin had potent antiviral activity against influenza viruses by inhibiting viral neuraminidase. While specific studies on *M. charantia* efficacy against monkeypox are lacking, its demonstrated antiviral properties and traditional use in treating various viral diseases, including smallpox, suggest potential applications in monkeypox treatment. Further research is needed to elucidate its mechanisms of action against poxviruses and evaluate its clinical efficacy.

Table 5: Traditional medicinal plants used in the treatment of monkeypox and related diseases (Ahmed *et al*., 2022; Ibrahim *et al*., 2022; Oladele *et al*., 2023)

Plant species	Family	Common name	Disease treated	Parts used
Acacia nilotica	Mimosaceae	Scented thorn	Monkeypox, hepatitis, meningitis, smallpox, poliomyelitis, COVID-19	Leaf/stem
Adansonia digitata	Bombacaceae	Baobab	Monkeypox, poliomyelitis, smallpox, yellow fever, meningitis, hepatitis	Stem bark
Aframomum melegueta	Zingiberaceae	Alligator pepper	Monkeypox, hepatitis, COVID-19, poliomyelitis, yellow fever	Whole plant
Allium sativum	Amaryllidaceae	Garlic	Monkeypox, poliomyelitis, COVID-19, meningitis, hepatitis	Whole plant

Guiera senegalensis	Combretaceae	Moshi medicine	Monkeypox, poliomyelitis, yellow fever, smallpox, COVID-19, meningitis, hepatitis	Leaf
Vernonia amygdalina	Compositae	Bitter leaf	Monkeypox, yellow fever, smallpox, COVID-19, meningitis, poliomyelitis	Leaf
Lawsonia inermis	Lythraceae	Henna	Monkeypox, meningitis, COVID-19, yellow fever	Leaf
Momordica charantia	Cucurbitaceae	Bitter gourd	Monkeypox, poliomyelitis, smallpox, yellow fever, meningitis, COVID-19, hepatitis	Leaf
Lagenaria breviflora	Cucurbitaceae	Bottle gourd	Monkeypox, smallpox	Leaf
Balanites aegyptiaca	Zygophyllaceae	Desert date	Monkeypox	Bark
Eleusine coracana	Poaceae	Finger millet	Monkeypox	Whole plant
Combretum micranthum	Combretaceae	Kinkeliba	Monkeypox, smallpox	Leaf
Detarium senegalense	Fabaceae	Tallow tree	Monkeypox, skin infections	Bark/fruit
Tamarindus indica	Fabaceae	Tamarind	Monkeypox, smallpox, skin diseases	Fruit
Calotropis procera	Apocynaceae	Sodom apple	Monkeypox, boils, skin infections	Whole plant
Sterculia setigera	Malvaceae	Karaya gum	Monkeypox, measles, chickenpox	Bark
Vitellaria paradoxa	Sapotaceae	Shea tree	Monkeypox, chickenpox, skin diseases	Bark, seed

3.3 Comparison with known antiviral drugs

When compared to known antiviral drugs suggested by the Centre for Disease Control and Prevention for monkeypox treatment, many of the plant-derived compounds discussed above, particularly the triterpenes and some flavonoids, show binding affinities comparable to or even stronger binding affinities to MPXV proteins (Smith *et al*., 2023b; Chen et al., 2024).

i. **Cidofovir**: A nucleotide analogue with binding affinities to B12R (-6.5 kcal/mol) and TK (-6.9 kcal/mol).

ii. **Ribavirin**: A nucleoside analogue with binding affinities to B12R (-5.9 kcal/mol) and TK (-6.8 kcal/mol).

iii. **Tecovirimat**: A viral egress inhibitor with strong binding affinities to B12R (-8.7 kcal/mol) and TK (-9.5 kcal/mol).

3.4 Computational studies on monkeypox virus

Recent research has demonstrated promising results in combining phytomedicinal compounds with conventional antiviral treatments to enhance therapeutic outcomes. Notable among these studies is the synergistic combination of allicin and tecovirimat, which showed a remarkable 47% increase in viral inhibition compared to tecovirimat monotherapy. This combination not only reduced the effective dose requirements for both compounds, but also demonstrated a lower incidence of resistance development. Similarly, the combination of momordicin with cidofovir has yielded encouraging results, showing a 35% enhancement in antiviral activity. This particular combination also exhibited improved host cell protection while simultaneously reducing the adverse effects typically associated with cidofovir administration.

3.5 Computational studies on monkeypox virus

Using molecular docking-based techniques, Banik *et al.* (2023), evaluated the efficiency of different bioactive chemicals obtained from plants against the monkeypox virus. A total of 56 plant compounds were evaluated for anti-monekypox capabilities, with the top four candidates having a higher binding affinity than the control. The authors also targeted the monkeypox profilin-like protein, which plays a key role in viral replication and assembly. Among the metabolites, curcumin showed the strongest binding affinity with a value of -37.43 kcal/mol, followed by gedunin (-34.89 kcal/mol), piperine (-34.58 kcal/mol), and coumadin (-34.14 kcal/mol). Furthermore, the study discovered that wortmannin, a gedunin analogue, can behave as an orthopox virus. Their study found that these bioactive natural drug candidates could potentially work as monkeypox virus inhibitors.

Khan *et al.* (2023), used molecular screening and simulation approaches to target I7L protease from monkeypox virus from the traditional Chinese medicines (TCM) database. Using molecular screening, only four hits: *viz*., TCM27763, TCM33057, TCM34450, and TCM31564, demonstrated better pharmacological potential than TTP6171 (control). Binding of these molecules targeted Trp168, Asn171, Arg196, Cys237, Ser240, Trp242, Glu325, Ser326 and Cys328 residues and may affect the function of I7L protease in an *in vitro* assay. The binding energy results revealed -62.60 ± 0.65 for the control I7L complex, for the TCM27763 I7L complex -71.92 ± 0.70 kcal/mol, for the TCM33057 I7L complex -70.94 ± 0.70 kcal/mol, for the TCM34450 I7L was -69.94 ± 0.85 kcal/mol, while for the TCM31564 I7L complex the binding energy was calculated to be -69.16 ± 0.80 kcal/mol.

Traditional Chinese Medicine (TCM) has been extensively employed in the treatment of monkeypox virus (MPXV) infections, and it has historically played a significant role in combating diseases like contagious pox-like viral diseases in China. Various traditional Chinese medicine (TCM) therapies have been recommended for patients with the monkeypox virus (MPXV). However, as far as we know, there is no comprehensive database dedicated to preserving and coordinating TCM remedies for combating MPXV. To address this gap, Xin *et al.* (2024) introduced TCM@MPXV, which is a carefully curated repository of research materials focusing on formulations with anti-MPXV properties. Importantly, TCM@MPXV extends its scope

beyond herbal remedies, encompassing mineral-based medicines as well. The TCM@MPXV includes documenting over 42 types of TCM herbs, with more than 27 unique herbs; recording over 285 bioactivity compounds within these herbs; launching a user-friendly web server for the docking, analysis, and visualisation of 2D or 3D molecular structures; and providing 3D structures of proteins of MPXV.

The study by Jiao *et al*. (2023), systematically explored the interactions between the bioactive compounds of XBCQD and the monkeypox-specific XBCQD targets using network pharmacological methods, bioinformatics analyses, and molecular simulations, suggesting that XBCQD could have a beneficial therapeutic effect on monkeypox by reducing the inflammatory damage and viral replication *via* multiple pathways. The use of XBCQD on monkeypox disease was confirmed to be best worked through the oestrone-target AR interaction.

Li *et al*. (2023), did a combined association rule mining analysis; Gancao (*Glycyrrhiza uralensis* Fisch.), Renshen (*Panax ginseng* C. A. Mey.), Danggui (*Angelica sinensis* (Oliv.) Diels), Shengma (*Cimicifuga foetida* L.), and Zicao (*Lithospermum erythrorhizon* Siebold and Zucc.) were selected as the core CM-pair for further investigation. Network pharmacology analysis yielded 131 active components and 348 candidate targets for the core CM-pair. Quercetin and celabenzine were chosen as ligands for molecular docking. GO and KEGG enrichment analyses revealed that the core CM-pair could interact with targets involved in immune, inflammatory, and infectious diseases. Moreover, key mpox virus targets, F8-A22-E4 DNA polymerase holoenzyme and profilin-like protein A42R, were docked well with the selected core components. And molecular dynamic simulation indicated that the component (quercetin) could stably bind to the target (profilin-like protein A42R).

A review study by Rong *et al*. (2023), on Chinese herbal formulas, including modified *Yinqiao* powder, modified *Xijiao dihaung* decoction, modified *Qingjie toubiao* decoction, and modified *Shengma gegen* decoction, were frequently applied to treat pox-like viral diseases and also showed significant effects in shortening the time of fever clearance, rash/pox extinction, and rash/pox scabs. Compared with Western medicine (placental globulin) or no intervention, eight non-randomised trials and observational studies on the prevention of contagious pox-like viral diseases showed a significant preventive effect of *Leiji* powder among high-risk populations.

4. Conclusion

This comprehensive review highlights the significant potential of phytomedicine in addressing the urgent need for effective treatments against monkeypox virus infection. The exploration of plant-derived compounds, including curcumin derivatives, flavonoids, triterpenes, and alkaloids, reported promising antiviral properties and strong binding affinities to key MPXV enzymes. The integration of traditional Chinese medicine knowledge and the potential of ginseng as an adaptogenic agent further expand the repertoire of possible phytomedicine-based interventions. However, the path from promising computational and preliminary studies to effective clinical treatments is fraught with challenges, including the need for rigorous *in vitro* and *in vivo* validation, addressing bioavailability issues, standardising herbal preparations, and navigating potential drug interactions. Future research should focus on validating computational predictions through robust experimental studies, exploring synergistic effects between phytochemicals, developing novel plant-based formulations with enhanced bioavailability, and addressing regulatory hurdles. By pursuing these research priorities and overcoming the identified challenges, the scientific community can work towards harnessing the full potential of phytomedicine in combating monkeypox and other emerging viral threats. This review serves as a base for future investigations, emphasising the importance of bridging traditional knowledge with modern pharmacological approaches in the face of global health challenges.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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