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Research Article

MONKEYPOX : A DISTURBING VIRAL OUTBREAK IN NON-ENDEMIC REGION IN 2022 : HERBAL TREATMENT OPTIONS

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ABSTRACT

Monkeypox is an emerging **zoonotic viral disease** infecting both animal and human. Monkeypox is a large double **stranded DNA virus**, and always infection has been considered as rare and self-limiting. However, recent sporadic reports of monkeypox outbreak in non-endemic region in 2022 is very disturbing. Therefore, **monkeypox virus** is considered as a high threat pathogen causing a disease of public health importance. WHO has considered monkeypox outbreak represents a public **health emergency** of international concern. This is the highest level of warning issued by the UN agency, which currently applies only to the COVID-19 pandemic and polio. The outbreak of monkeypox viral disease in non-endemic region (31 countries) in 2022 outside of Africa could be disastrous. The clinical features of monkeypox are very similar to those of smallpox. Routine smallpox vaccination ended decades ago, there is growing concern that monkeypox may become the next emerging poxvirus to plague humankind. Therefore, there is an urgent need to focus on building surveillance capacities which will provide valuable information for designing appropriate prevention, preparedness and response activities. This literature review paper also discussed about **the herbal treatment** options for controlling monkeypox virus and antiviral activities of the plants have been listed.

Keywords: Africa, antivirals, herbal medicine, Indian Pitcher Plant, monkeypox, Sarracenia purpurea, viral outbreak, vaccine.

INTRODUCTION

Monkeypox is a zoonotic viral disease infecting both animal and human (1-17). Monkeypox is a large double stranded DNA virus. The name monkeypox originates from the initial discovery of the virus in monkeys in a Copenhagen, Danish laboratory in 1958 (1-33, 35-45, 103). The facility received a continual supply of Asian monkeys (mostly M. fascicularis) and rhesus macaques (Macaca mulatta), which were used for polio vaccine research (103-104). The outbreaks occurred in M. fascicularis that had arrived from Singapore (103). The monkeypox disease was first found in colonies of monkeys in animal facility when two outbreaks occurred in monkeys kept for research (1-45, 103). First discovered in 1958, monkeypox is a rare disease caused by a virus that belongs to the same family as the one that causes smallpox (1-33, 103). The **first human** case of monkeypox was identified in a child in the Democratic Republic of the Congo (DRC) in August 1970, in Bokenda, a remote village in the Equatorial province of the Democratic Republic of the Congo (DRC) (called Zaire at the time), exactly two years after smallpox had been eradicated in the region (1-45). However, the virus did not jump from monkeys to humans, nor are monkeys major carriers of the disease (1-17). The first 20 human cases were described by the WHO (1-32) in 1972 and 1976, and 15 newly reported cases were included in the update of 1978 (1-32). Later, WHO reported 54 cases between 1970–1979 (1-32).

Since 13 May 2022, and as of 25 June 2022, **1500 laboratory confirmed cases of monkeypox** have been reported to or identified by WHO from 31 Member States across four WHO regions that are not endemic for monkeypox virus (117). The World Health Organisation (WHO) called the Monkeypox outbreak is unusual and concerning after reports confirmed that over 1500 cases of the infection have been registered globally. The global outbreak of monkeypox is "clearly unusual and concerning" and this outbreak represents a **public health emergency** of international concern (117). Epidemiological investigations are ongoing in 31 countries. Most reported cases so far in have been presented through sexual health or other health services in primary or secondary health care facilities and have involved mainly, but not exclusively, **men who have sex with men** (MSM). Although monkeypox virus is less fatal and not as transmissible as variola virus, the causative agent of smallpox, there is a growing concern is that monkeypox virus could become a more efficient human pathogen (103-104). The reason for this is the virus' genetic makeup, ecological changes, changes in host behaviour, and the fact that with the eradication of variola virus, routine smallpox vaccination is no longer carried out (103-104).

Human-to-human transmission of monkeypox is well described, including nosocomial and household transmission (1-45). However, human-to-human chains of transmission have historically been less well recognized (1-33). Monkeypox is an emerging global health threat, which is capable of cross-border spread and onward transmission (1-45). However, optimum infection control and treatment strategies for this potentially dangerous pathogen are not well established (1-46). The clinical features of monkeypox closely resemble **smallpox**, it makes it difficult to clinically distinguish one infection from the other unless specific diagnostic tests are performed (103). There are also concerns that in the current setting of limited smallpox vaccination, monkeypox could become a more efficient human pathogen.

Monkeypox **probably originated** from smallpox itself, sometime after smallpox was eradicated (1-45). In general, monkeypox was detected in communities where there is often a high background prevalence of malnutrition, parasitic infections, and other

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significant heath-compromising conditions, any of which could impact the prognosis of a patient with monkeypox (1-32, 33-45). The clinical picture of monkeypox closely resembles the one of smallpox but the major difference distinguishing monkeypox from smallpox is the **lymph node enlargement** that occurs early, often at the onset of fever (1-45).

According to The US Centers for Disease Control and Prevention (CDC) has released a new statement regarding the human-to-human transmission of monkeypox (116-119). Monkeypox virus is a completely **different virus than the viruses that cause COVID-19 or measles**. It is not known to linger in the air and is not transmitted during short periods of shared airspace (116-119). The monkeypox cases have been reported mainly, "but not only" among men who have **sexual intercourse with men**. Unlike SARS-CoV-2, which spreads through tiny airborne droplets called aerosols, monkeypox is thought to spread from close contact with bodily fluids, such as saliva from coughing (1-45). Therefore, a person with monkeypox is likely to infect many fewer close contacts than is someone with SARS-CoV-2 (1-45, 46-55). Both viruses can cause influenza-like symptoms, but monkeypox also triggers **enlarged lymph nodes** and eventually causes distinctive **fluid-filled lesions** on the face, hands and feet (1-33, 34-45). Therefore, subsequent outbreaks, field surveys and experimental studies have revealed that the monkeypox virus has the capacity to infect and cause high levels of mortality and morbidity in a broad spectrum of hosts from across the globe (103-104).

Monkeypox has always been considered as a rare sporadic disease with a limited capacity to spread between humans (1-45). It is a life-threatening disease in **the Democratic Republic of the Congo (DRC**) and other countries of western and central Africa (1-32) and possibly worldwide (1-45). The threat would increase if there would be a virulence increase both naturally (1-32) or through genetic engineering (22), a virus spill into more widely distributed taxa (1-32) or an introduction in other continents (1-55). Consequently, monkeypox belongs to the **"Biosafety Level 3" category**, the "high threat" biodefence category in the EU (1-32) and is on the list of select agents in the USA (1-45). Experimentally, monkeypox can infect animals via a variety of multiple different inoculation routes. However, the **natural route of transmission is unknown** and is likely to be somewhat species specific (1-45, 103). Monkeypox likely circulates in many species in Africa. However, squirrels appear to be the most likely reservoir of the virus. Over 40 species have been documented to have been naturally or experimentally infected with monkeypox (103). Infected species have originated from North America, South America, Africa and Asia (1-45, 103).

Airborne transmission occurs when small virus particles become suspended in the air and can stay there for periods of time (119). These particles can spread on air currents, or sometimes even infect people who enter a room after the infected person has left." However, monkeypox may be found in droplets like saliva or respiratory secretions that drop out of the air quickly (116-119). This means airborne transmission of monkeypox is less likely (117-119). The World Health Organization (WHO) is looking into reports that the monkeypox virus is present in the semen of patients, exploring the possibility that the disease could be **sexually transmitted**. However, the agency reiterated that virus is mainly transmitted via close interpersonal contact. Many of the monkeypox cases confirmed in the current outbreak largely centered in Europe are among sexual partners who have had such close contact. In recent days, scientists have detected **viral DNA in the semen** of a handful of monkeypox patients in Italy and Germany, including a lab-tested sample that suggested the virus found in the semen of a single patient was capable of infecting another person and replicating.

Monkeypox: Origin in Africa

Monkeypox is a **viral zoonosis** (a virus transmitted to humans from animals) with symptoms very similar to those seen in the past in smallpox patients, although it is clinically less virulent (1-45). Monkeypox has originated from animals in the rainforest area of Central and West Africa, from squirrels, rats and some monkeys, therefore it is called monkeypox (1-45). Monkeypox is a viral zoonotic illness that is endemic in Central and West Africa's tropical rainforests and is occasionally transported to other parts of the world (1-55). The virus is assumed to have originated among rodents in Central and West Africa and has since spread to humans on several occasions (1-45). Outside of Africa, monkeypox viral infections are very uncommon and have been linked to infected people or imported animals (1-45). The natural reservoir for monkeypox virus or primary host of the virus is still unknown (1-45). Monkeypox is a virus which is from the same family as smallpox and also vaccinia, which was used for making a smallpox vaccine (1-45). **Molluscum contagiosum**, which is commonly noticed in sexually transmitted diseases (STD), is also from the same pox variety family (1-45).

Monkeypox is always confused with **Molluscum contagiosum,** which is an infection caused by a poxvirus (Molluscum contagiosum virus). The result of the infection is usually a benign, mild skin disease characterized by lesions (growths) that may appear anywhere on the body. Within 6-12 months, Molluscum contagiosum typically resolves without scarring but may take as long as 4 years. The lesions, known as Mollusca, are small, raised, and usually white, pink, or flesh-colourd with a dimple or pit in the center. They often have a pearly appearance. They're usually smooth and firm. In most people, the lesions range from about the size of a pinhead to as large as a pencil eraser (2 to 5 millimeters in diameter). They may become itchy, sore, red, and/or swollen. Mollusca may occur anywhere on the body including the face, neck, arms, legs, abdomen, and genital area, alone or in groups. The lesions are rarely found on the palms of the hands or the soles of the feet. Someone with molluscum can spread it to other parts of their body by touching or scratching a lesion and then touching their body somewhere else. This is called autoinoculation. Shaving and electrolysis can also spread mollusca to other parts of the body. Molluscum can spread from one person to another by sexual contact. Many, but not all, cases of molluscum in adults are caused by sexual contact. The **molluscum contagiosum** virus remains in the top layer of skin (epidermis) and does not circulate throughout the body; therefore, it cannot spread through coughing or sneezing. Since the virus lives only in the top layer of skin, once the lesions are gone the virus is gone and cannot spread it to others. Molluscum contagiosum is not like herpes viruses, which can remain dormant ("sleeping") in patients body for long periods and then reappear (CDC Report).

Monkeypox has already occurred in 10 African countries and is known to be **endemic** in the **Democratic Republic of the Congo (DRC)** (1-45). It has once crossed the borders of the African continent when it was imported into the **USA in 2003**, before which it was assumed that the disease was geographically limited (1-45). Most people recover from monkeypox in a few weeks, without treatment. In an average year, a few thousand cases occur in Africa, typically in the western and central parts of the continent (1-45). There have been a few monkeypox outbreaks since then. **The Democratic Republic of the Congo**, for example, has been grappling with the virus for decades, and Nigeria has been experiencing a large outbreak, with over 500 suspected and more than 200 confirmed cases, since 2017, when the country reported its first case in some 40 years (1-36, 37-45).

Monkeypox: A Wakeup Call

The monkeypox cases outside Africa have previously been limited to a handful that were associated with travel to Africa or with the importation of infected animals (1-45). The number of cases detected outside of Africa in the past few weeks in May 2022 alone has already surpassed the total number detected outside the continent since 1970, when the virus was first found to cause disease in humans (1-55). Monkeypox virus does not transmit from person to person as readily, and because it is related to the smallpox virus, there are already treatments and vaccines on hand to curb its spread (1-55). The current outbreaks of monkeypox in non-endemic region in 2022 (May-June) probably will not necessitate containment beyond ring vaccination since monkeypox is still considered as a relatively rare infection (1-45).

This should be a wakeup call to the research community for more engagement, follow-up and research on monkeypox disease. Despite being **discovered in 1958 and for the first time described in a human in 1970, there are no** standard guidelines for clinical management, nor therapeutics or vaccines (1-45). Monkeypox is a significant health concern for people living in endemic regions such as Democratic Republic of the Congo (DRC), and other African countries where circulation of the monkeypox virus is confirmed, but it is also a global health security concern as demonstrated during the USA outbreak in 2003 and now in non-endemic region (Europe, USA, Singapore, Canada, UK) in 2022 (1-45). Appropriate and effective interventions and active surveillance activities are urgently needed to prevent increased transmission efficiency or virulence (1-45). Monkeypox is the most important **orthopoxvirus** in humans, certainly in the endemic areas and perhaps globally (1-32). Therefore, monkeypox is not a rare disease anymore, monkeypox needs more attention (1-45).

Monkeypox: Classification

Monkeypox is caused by monkeypox virus, a member of the Orthopoxvirus genus in the Poxviridae family (1-17). Monkeypox is one of the four Orthopoxvirus species pathogenic for humans, together with **variola virus**, the causative agent of smallpox, largely eradicated in nature; **cowpox virus**, and **vaccinia virus** (1-45). Monkeypox can infect a wide range of mammalian species but the natural host is unknown (1-45). The virus has only been isolated twice from a wild animal, a rope squirrel in the Democratic Republic of Congo (DRC) and a sooty mangabey in Ivory Coast (1-10). The range of animal species known to be susceptible to monkeypox virus infection includes multiple species that are utilized as priority or supplemental protein sources in rural, forested communities of the Democratic Republic of the Congo (DRC), where human monkeypox cases occur most frequently (1-45).

Monkeypox virus is **endemic** in heavily forested regions of rural West and Central Africa, including Cameroon, Central African Republic, Republic of the Congo, and Sierra Leone (1-17). While an animal reservoir for monkeypox virus is still unknown, African rodents are suspected to play a part in transmission (1-45). The monkeypox virus has only been isolated twice from an animal in nature (1-45). Monkeypox is rarely exported from the African continent. In 2003, there was a zoonotic outbreak in the USA causing 47 confirmed or suspected cases (1-45). This outbreak was linked to the importation of Gambian giant rats, squirrels, and dormice, which had transmitted the virus to prairie dogs that were then sold as pets (1-45). Only 14 patients were hospitalized and there were no confirmed cases of person-to-person transmission. Imported monkeypox infections in humans following travel have been reported in the UK, Israel, Singapore, and **USA in 2021** (1-45).

Monkeypox : A Tale of Two Clades

There are two principal genetic clades of monkeypox virus, one of which occurs in the **Congo Basin** (Central African) Clade, the other in **West Africa Clade** (1-45). These two **clades** are geographically separated and have defined epidemiological and clinical differences (1-32). Monkeypox virus in the West African genetic Clade are thought to be **less virulent**, but relatively few instances of human infection with the West African variant of monkeypox have been documented (1-45). The **West African clade** demonstrates a case fatality rate (CFR) <1%, and no human-to-human transmission was ever documented (1-45).

On the other hand monkeypox virus in the Congo Basin (Central African) **genetic Clade** are found to be more virulent and infectious (1-17). In comparison, the Congo Basin Clade (also known as the Central African clade) showed a CFR up to 11% (1-20), and documented human-to-human transmission up to 6 sequential events was observed (1-32). The isolates from the West African Clade originated from outbreaks in Nigeria, Liberia, Ivory Coast, Sierra Leone, and USA (imported from Ghana) (1-45). The isolates belonging to the Central African Clade came from Gabon, Cameroon, the Democratic Republic of the Congo (DRC), Central African Republic (CAR), Sudan, and the Democratic Republic of Congo (DRC) (1-32). According to available data, the Congo Basin clade is more common than the West African clade given it is endemic in the Democratic Republic of the Congo (DRC) where more than 2,000 suspected cases are reported every year (1-32). However, monkeypox is not part of mandatory reporting in other African countries than the Democratic Republic of the Congo (DRC) (1-32).

In Cameroon, they have both Clades in their monkeypox cases (1-17). Monkeypox is usually self-limiting but may be severe in some individuals, such as children, pregnant women or persons with immune suppression due to other health conditions (1-17). Human infections with the West African Clade appear to cause less severe disease compared to the Congo Basin clade (Central Africa), with a case fatality rate of 3.6% compared to 10.6% for the Congo Basin clade (Central Africa)(1-17).

Various animal species have been identified as susceptible to the **monkeypox virus** (1-17). Uncertainty remains on the natural history of the monkeypox virus (1-45). Identification of the exact reservoir(s) and how monkeypox virus circulation is maintained in nature is still unknown (1-45). Eating inadequately cooked meat and other animal products of infected animals is a possible risk factor (1-17).

Monkeypox: Endemic region of Africa

Monkeypox endemic countries in Africa are: Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo (DRC), Gabon, Ghana (identified in animals only), Côte d'Ivoire, Liberia, Nigeria, the Republic of the Congo, and Sierra Leone (1-45). Benin and South Sudan have documented importations in the past. Countries currently reporting cases of the West African clade are Cameroon and Nigeria (1-45).

Monkeypox outbreak: Non-endemic region

According to the **WHO report**, epidemiological investigations are ongoing. The vast majority of reported cases so far have no established travel links to an endemic area and have presented through primary care or sexual health services. The identification of confirmed and suspected cases of **monkeypox** with no direct travel links to an endemic area is atypical. Early epidemiology of initial cases notified to WHO by countries showed that cases have been mainly reported amongst **men who have sex with men (MSM).** One case of monkeypox in a non-endemic country

is considered an outbreak. The sudden appearance of monkeypox simultaneously in several non-endemic countries suggests that there may have been undetected transmission for some time as well as recent amplifying events (WHO Report).

Non-endemic region-Argentina, Canada, French Guiana, USA, United Arab Emirates (UAE), Sudan, Austria, Belgium, Czechia, Denmark, Finland, France, Germany, Italy, The Netherlands, Israel, Portugal, Slovenia, Spain, Sweden, Switzerland, UK, Northern Ireland, Australia.

Monkeypox outbreak in 2022

However, the new cases of monkeypox outbreak in **2022** is a major current health issue in non-endemic region (1-17). Since the first report of monkeypox in 1970, cases of monkeypox in humans have rarely occurred outside of the African continent (1-55). However, since early May 2022, several cases have emerged in Europe, Australia, Canada, and the United States (1-55). A growing number of countries, including Canada, the U.S., Spain, Portugal, and the U.K, are reporting an unusual outbreak of monkeypox (1-55). Therefore, these monkeypox cases in 31 countries are notable as the disease is relatively rare and there are no clear links between some of the infections, raising concerns about community spread and undetected cases (1-55). According to the first hand information from Public Health Canada, the U.S. Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO), monkeypox virus is behaving similarly to previous outbreaks. Further **monkeypox** is rare and usually non-fatal, one version of the disease kills around 1% of infected people. The form of the virus currently circulating is thought to be milder, with a fatality rate of less than 1% (1-55). In UK, monkeypox is classified as a High Consequence Infectious Disease (HCID), and patients are managed in designated HCID treatment centres coordinated by a national network (1-34). Since 2018, four patients were diagnosed with travel-associated monkeypox in the UK, with onward transmission to three people**,** including the first reported household cluster outside Africa (34). The public health management of people infected with monkeypox and their contacts have been reported previously (1-34**). Monkeypox** outbreaks will continue to occur in West and Central Africa, and health-care workers around the world must remain vigilant to the possibility of monkeypox in travellers presenting with fever and rash (1-34. 36-55).

Monkeypox detected in Non-endemic region in 2022

As of 25th of June 2022, Canada has 159 confirmed cases of monkeypox, with 132 in Quebec, 21 in Ontario, four in Alberta, and two in British Columbia, Vancouver (46-49, 60, 120). The monkeypox cases in Canada are currently among men who have had sexual contact with other men, though the virus can spread to anyone who had contact with an infected person (113, 120). Globally, there are 1500 laboratory confirmed cases in 31 non-endemic countries (USA, UK, Belgium, France, Germany, Italy, Netherlands, Portugal, Spain, Sweden, Australia, Canada, Austria, Canary Islands, Israel, and Switzerland) where the virus has not usually been found (40-49, 60, 120). According to the Canadian health officials, Monkeypox cases in Canada are suspected to have originated from a local sauna in Montreal, Quebec, Canada. Quebec province of Canada appears to be an epicentre of monkeypox outbreak in the first week of June, 2022 (46, 47, 48, 60, 120). These are the first cases of monkeypox in Canada. The Quebec province of Canada has started vaccinating the close contacts of infected people a so-called "ring vaccination" approach to prevent a wider outbreak and administered 813 vaccine doses in Canada (46-48, 60, 120). Public Health Agency, Canada (PHAC) recommends consulting with a health-care professional or visiting a travel health clinic at least six weeks before travelling (46-48, 60, 120). Wearing a face mask, frequent hand washing and avoiding close physical contact with people who are sick is also recommended (46-49, 60). Canada's public health agency has also issued a travel notice as the monkeypox virus continues to spread around the world. Clusters of monkeypox cases have been reported in several countries internationally, outside of areas in Central and West Africa where cases are normally found (Global News, Canada, 6th June, 2022) (46, 47, 60). **The Public Health Agency of Canada (PHAC)** is working with provinces, territories and international partners, including the World Health Organization, to actively monitor the situation. Global efforts are focused on containment of the monkeypox outbreak and the prevention of further spread. Canada's National Microbiology Laboratory is performing diagnostic testing for the virus that causes monkeypox. In addition, the laboratory is also conducting whole genome sequencing, an enhanced fingerprint analysis, on Canadian samples of monkeypox. This sequencing will help the experts to understand the chains of transmission occurring in Canada. The laboratory is working in close collaboration with provincial and territorial public health laboratories to provide testing guidance and to increase testing capacity for monkeypox.

According to Health official, anyone, no matter their gender or sexual orientation, could get infected and spread the virus if they come into close contact, including intimate sexual **contact** with an infected person or a contaminated object (Global News Canada, 3rd June 2022). As the climate change contributes to rapidly changing weather conditions like drought, animals and human are changing their food-seeking behaviour (46-49, 60). As a result, diseases that typically circulate in animals are increasingly jumping into humans (46-49, 60). The World Health Organization (WHO) does not believe the monkeypox outbreak outside Africa will turn into another pandemic. The WHO Health Emergencies Programme said that while WHO is "not concerned," the outbreak will lead to a pandemic, there are worries that individuals may acquire the infection through high-risk exposure if they do not have the information they need to protect themselves (46-49, 60). The U.S. Centers for Disease Control and Prevention (CDC) also advised people who have been exposed to monitor for symptoms, which can present between five and 21 days after exposure (46-49). People should also limit close contact, including sexual contact, with others (46-49, 60). Public health officials are struggling to trace contacts of monkeypox cases because many had sexual contact with unknown partners in cruising grounds, sex clubs and during chemsex sessions, it has emerged (114). According to World Health Organization's emergencies department, men attending rave parties in Spain and Belgium "amplified" the outbreak — apparently through kissing and rubbing skin (114). After that, the monkeyvirus accompanied travelers on planes heading for countries far and wide. By June 15, 2022, the WHO had tallied **1500 monkeypox cases in 31** countries.

Furthermore, UK has reported 383 cases of monkeypox. Monkeypox is endemic in certain areas of Central and West Africa, but limited cases have been identified in other regions in the past, such as the United Kingdom, United States, Israel and Singapore. Human-to-human transmission of monkeypox is uncommon. According to UK Health and Security Agency (UKHSA) the interviews had "highlighted challenges" in controlling the monkeypox outbreak (114). Traditional contact tracing as a primary control intervention in this specific group will be challenging as most cases reported having sexual contact with new or casual partners, sometimes in the context of cruising grounds or during chemsex, frequently where contact details were unavailable for tracing (114). The larger of the current monkeypox outbreaks began in early May, 2022 apparently triggered by a U.K. traveler's exposure to an infected person or animal in Nigeria. Hitching a ride to Europe, the monkey virus spread quickly through close physical contact.

The US Centers for Disease Control and Prevention (CDC) has already confirmed more than 1500 global cases of monkeypox, including 21 in the United States, with investigations now suggesting it is spreading inside the country. Another concern is that monkeypox to be detected in people with no apparent connection to one another suggests that the virus might have been spreading silently (33). Unlike SARS-CoV-2, monkeypox rarely goes unnoticed when it infects a person, in part because of the skin lesions it causes (33). If monkeypox could spread asymptomatically, it would be especially troubling, because that would make the virus harder to track (33). National Advisory Committee on Immunization is recommending that people who may be at high risk of exposure have a vaccine.

Monkeypox: DNA virus and mutation

Genomic sequencing of viral deoxyribonucleic acid (DNA) of the monkeypox virus, where available, is being undertaken. Several European countries (Belgium, France, Germany, Israel, Italy, the Netherlands, Portugal, Slovenia, Spain, Switzerland and the United States of America) have published full-length or partial genome sequences of the monkeypox virus found in the current outbreak. While investigations are ongoing, preliminary data from PCR assays indicate that the monkeypox virus genes detected belong to the West African clade.

According to the preliminary genetic data, the strain of the monkeypox virus detected so far is related to a viral strain predominantly found in West Africa. This strain causes milder disease and has a lower death rate about 1% in poor rural populations compared with the one that circulates in Central Africa (which can have a death rate of up to 10%) (33). But exactly how the strain causing the current outbreaks differs from the one in West Africa and whether the cases popping up in various countries are linked to one another remains unknown (33). Another information is that sudden rise in monkeypox cases in non-endemic region in 2022 stems from a **mutation** that allows monkeypox to transmit more readily than it did in the past, and whether each of the outbreaks traces back to a single origin (33). Furthermore, Unlike SARS-CoV-2, a rapidly evolving RNA virus whose variants have regularly eluded immunity from vaccines and previous infection. Monkeypox is caused by a relatively **large DNA virus** (33). DNA viruses are better at detecting and repairing mutations than are RNA viruses, which means it is unlikely that the monkeypox virus has suddenly mutated to become adept at human-to-human transmission (33).

Monkeypox: Not yet detected in India

As of 25th June, 2022**, no monkeypox** case have been detected in India. However, India has reported cases of cow and buffalo pox virus in humans indicating an animal to human transmission. A 5-year-old boy from **Uttar Pradesh's Ghaziabad** has become the first suspected case of the deadly Monkeypox virus in India (115). Furthermore, Ghaziabad case is suspected and under observation, samples have been sent to ICMR NIV Pune, Maharashtra state, India (115). India being the top vaccine producer in the world is closely tracking the global rise in monkeypox cases particularly in non-endemic region (Europe, Canada, USA) in 2022. India with a current population of 1.4 billion is also known as the land of pharmacy, has many innovations in dealing with viral outbreaks including Covid-19. As a precaution, India has increased surveillance, imposed travel restrictions as monkeypox reaches multiple nations in the first week of June, 2022. India is prepared for the monkeypox infections as it is rapidly spreading in non-endemic countries like Europe, USA and others in 2022. **However, no cases have been reported in India so far**. The Indian government is keeping an eye on the global rise in monkeypox cases. Recently, the World Health Organisation Country Office for India has requested the Indian Council of Medical Research (ICMR), and National Institute of Virology, Pune, Maharashtra state, India to help to test the suspected cases of monkeypox for the South-East Asian Region (SEAR) member-states in the first week of June, 2022. Fortunately, there have been no cases of monkeypox in India yet, however, the Indian government has levelled up its preparedness to tackle the monkeypox virus with an adequate number of Bio-safety Level-3 (BSL) facilities. Monkeypox is less contagious than smallpox and can cause less severe illness. The mortality rate is also considered low as no deaths have been reported as of now (33).

Monkeypox: Symptoms

Symptoms of monkeypox usually do not appear until one to two weeks after infection (1-45, 103, 104). **Monkeypox produces smallpox-like skin lesions**, but symptoms are usually milder than those of smallpox (1-45, 102, 103, 104). Flu-like symptoms are common initially, ranging from fever and headache to shortness of breath (1-33, 35-45, 103, 104). One to 10 days later, a rash can appear on the extremities, head or torso that eventually turns into blisters filled with pus (1-33, 35-45, 103, 104). Overall, symptoms usually last for two to four weeks, while skin lesions usually scab over in 14 to 21 days (1-33, 34-45). Monkeypox, like smallpox, begins with a brief (2–3 day) febrile prodrome period prior to the appearance of enanthem and then exanthema, the latter with centrifugal distribution (1-33, 35-45). The total lesion burden at the apex of rash can be quite high (>500 lesions) or relatively slight (<25) (1-33, 35-45). Patients suffering from monkeypox viral disease has a range of complications that can include secondary infection of the integument, bronchopneumonia, sepsis, encephalitis, and infection of the cornea with ensuing loss of vision (1-33, 35-45). **The hallmark feature of monkeypox** is disseminated vesiculo-pustular rash (1-33). In instances of severe illnesses with high rash burden, this alone can create a substantial vulnerability for an infected individual (1-33, 35-45). The most exhibited oral lesions, suggesting that many patients will have extensive injury to the skin and to mucosal surfaces resulting in the partial thickness wounds (1-17 19-33, 35-45). The use of moist, occlusive dressings could be contemplated for patients with extensive facial coverage of rash lesions (1-33). A notable but poorly characterized complication of monkeypox and before that, smallpox—is bronchopneumonia (1-33, 35-45). Monkeypox can have significant impacts on multiple organ systems in the host, compromising the protective barriers of skin and mucosal surfaces, provoking a robust focal inflammatory response in the lymphatics, and congestion in the lungs (1-17). Serious inflammation and bronchopneumonia can restrict air intake and diminish a patient's willingness and/or ability to ingest food and fluids (1-17, 18-33, 34-45). Indeed, many persons with monkeypox experiences only mild to moderate symptoms of illness, but these individuals still constitute a transmission risk until their **skin lesions** resolve (1-35-45). **Monkeypox is an inexact surrogate for smallpox,** nonetheless, it is the best extant model for understanding clinical implications of smallpox in a modern context (1-33, 35-45).

The common symptoms like fever, intense headache, skin rashes and more on the face and extremities that appears in the one to three days of the fever (1-33). Lymphadenopathy (**swelling of the lymph nodes**) is a distinctive feature compared to other diseases like smallpox, chickenpox or measles (1-45). **A rash** usually appears 1–3 days after the onset of fever and lymphadenopathy, with lesions appearing simultaneously, and evolving at a similar rate (1-33). Their distribution is mainly peripheral but can cover the whole body during a severe illness (1-45). The infection can last up to 4 weeks until the lesion desquamate (1-33). Patients can suffer from a range of

complications including secondary bacterial infections, respiratory distress, bronchopneumonia, gastrointestinal involvement, dehydration, sepsis, encephalitis, and corneal infection with ensuing loss of vision (1-45). No specific treatment for a monkeypox virus infection currently exists, and patients are managed with supportive care and symptomatic treatment (1-33, 35-45).

The most prominent symptoms of monkeypox, are people with monkeypox have **pockmarks or vesicles or postules on the face**, palms and soles (1-45). The palms and soles are affected in 80% to 90% of cases. Therefore during travelling, airport authorities can ask to travellers to display their palms and soles, and their face in case somebody's covering their face. Secondly**, lymph node enlargement in the neck area** is again a symptom in 100% of monkeypox cases. So it will make more sense to be vigilant and check for lymph node enlargement, pockmarks or vesicles, and also persons with fever and travelling from affected areas. However, currently, monkeypox is spreading in individuals without any travel history and has become a problem as it is out of its endemic zone (1-45, 103, 104).

Monkeypox: Transmission

Monkeypox virus is transmitted from one person to another by close contact with skin lesions of an infected person or recently contaminated objects like bedding, body fluids, respiratory droplets, respiratory secretions and contaminated materials such as bedding (1-33 34-45, 103, 104). The incubation period of monkeypox is usually from **6 to 13 days but can range from 5 to 21 days** (1-45). Monkeypox can be passed on by direct contact though sex, but is not considered to be a sexually transmitted infection. It can also be spread through touching clothing, bedding or towels used by someone with the monkeypox rash, and through the coughs and sneezes of somebody with the infection (1-45).

Transmission is believed to occur via saliva/respiratory excretions or contact with lesion exudate or crust material (1-30, 32-45). Viral shedding via feces may represent another exposure source (1-30). A good example is Ghana where monkeypox circulates in animals, but the country never reported human cases of monkeypox (1-33, 35-45). The importation of monkeypox-infected rodents to the USA, however, did lead to a human outbreak of monkeypox (1-33, 35-45**). A droplet means surface transmission from bushmeat, from rodents, to dogs and cats and from there to domestic animals to human beings**. So, monkeypox is also transmitted from forest animal to domestic animal to human being, and now even human being to human being (1-45). Monkeypox can spread through close contact in the family, skin to skin contact, therefore it is also grouped under **STDs** (1-33).

The World Health Organization (WHO) issued a public health advice to gay, bisexual and other men who have sex with men last week, urging the community to be on the lookout for certain symptoms like a rash leaving blisters on the face, hands, feet, eyes and mouth, fever, swollen lymph nodes, headaches, muscle aches and a lack of energy (1-33, 45-55). The risk of exposure is not exclusively related to any group or setting. No matter of the gender or sexual orientation, anyone could get infected and spread the monkeypox virus if they come into close contact including intimate **sexual contact** with an infected person or their contaminated objects (1-33).

Furthermore, according to the recent **WHO** report, Sixteen of the first 17 monkeypox cases were among people who identified as **men who have sex with men**. Monkeypox can spread during intimate contact between people, including during sex, as well as activities like hugging, massage, kissing, cuddling, talking closely or touching parts of the body with monkeypox sores. **Oral, anal, and vaginal sex or touching the genitals or anus of a person with** monkeypox. Touching fabrics and objects during sex that were used by a person with monkeypox, such as **bedding, towels and sex toys**. At this time, it is not known if monkeypox can spread through semen or vaginal fluids. According to a new Centers for Disease Control and Prevention (CDC) report, and 14 were thought to be travel associated. All patients are in recovery or have recovered, and no cases have been fatal. After the virus enters the body, it starts to replicate and spread through the body via the bloodstream.

Another puzzle is that almost all of the case clusters include men aged 20–50, many of whom are men who have sex with men (**MSM)** (33). Although monkeypox is not known to be sexually transmitted, sexual activity certainly constitutes close contact (33). The most likely explanation for this unexpected pattern of transmission is that the virus was coincidentally introduced into an MSM community, and has continued circulating between men (33). Some of the health officials also believed that monkeypox outbreak started spreading from rave parties in Spain and Belgium. Rave parties are followed by sex parties, thus, sexual transmission was thought of as the cause earlier and it is being considered more dangerous than earlier thought. Although the monkeypox virus might be spread by sharing swimming pools, baths, saunas, or other wet and warm environments, this has not been proven. Researchers who have investigated this idea thinks that, it is more likely the virus is spread by sharing towels and other items around a pool or sauna than through water.

The monkeypox virus can be transmitted through contact with an infected person or animal or contaminated surfaces (1-33). Typically, the virus enters the body through broken skin, inhalation or the mucous membranes in the eyes, nose or mouth (1-33). Researchers believed that human-to-human transmission is mostly through inhalation of large respiratory droplets rather than direct contact with bodily fluids or indirect contact through clothes (1-33). Human-to-human transmission rates for monkeypox have been limited (1-33). Health officials are worried that virus may currently be spreading undetected through community transmission, possibly through a new mechanism or route (1-33). **Monkeypox** outbreak leading to new infections are still under investigation. The first reported cases of monkeypox in the U.S. was in 2003, from an outbreak in Texas linked to a shipment of animals from Ghana (1-33, 35-45). There were also travel-associated cases in November and July 2021 in Maryland. Because monkeypox is closely related to smallpox. The smallpox vaccine can provide protection against infection from both viruses (1-33). Since smallpox was officially eradicated, however, routine smallpox vaccinations for the U.S. general population were stopped in 1972. Because of this, monkeypox has been appearing increasingly in unvaccinated people (1-33, 35-45).

Monkeypox: Viral detection methods

Monkeypoxvirus (MPXV) is a **double-stranded DNA virus**, a member of the orthopoxvirus genus within the Poxviridae family (1-35, 36-45, 107-112). Poxviruses cause disease in humans and many other animals; infection typically resulted in the formation of lesions, skin nodules or disseminated rash (1-33, 35-45, 107-112).

The recommended specimen type for laboratory confirmation of monkeypox is skin lesion material, including swabs of lesion surface and/or exudate, roofs from more than one lesion, or lesion crusts (107-112). **Swab the lesion** vigorously, to ensure adequate viral DNA is collected (107-112). In addition to a **lesion specimen,** the collection of an oropharyngeal swab is encouraged. However, data on the accuracy of this specimen type for diagnosis is limited for monkeypox, therefore a negative throat swab specimen should be interpreted with caution (107-112).

Confirmation of monkeypox infection is based on **Nucleic Acid Amplification Testing (NAAT),** using real-time or conventional polymerase chain reaction (PCR), for detection of unique sequences of viral DNA (107-112). PCR can be used alone, or in combination with sequencing. This can then be followed by a second step, which can be PCR-based or utilize sequencing, to specifically detect monkeypox virus (107-112). PCR kits detecting OPXV or specifically monkeypox are under development, but no commercial validated PCR kits are currently available widely as of June, 2022 (107-112).

Pan American Health Organization (PAHO) is working to support all WHO Member States, through the national reference laboratories to implement capacity to perform molecular testing for monkeypox (107-112).

Monkeypox: Vaccine

Evidence suggests that the smallpox vaccine can help to prevent monkeypox infections and decrease the severity of the symptoms (1-45). No cure or treatment for smallpox exists. A vaccine can prevent smallpox, but the risk of the vaccine's side effects is too high to justify routine vaccination for people at low risk of exposure to the smallpox virus (1-33, 35-45). **ACAM200 and JYNNEOS™** (also known as Imvamune or Imvanex) are the two currently licensed vaccines in the United States to prevent **smallpox** (1-45). One vaccine known as **JYNNEOS™ Imvamune or Imvanex** is licensed in the U.S. to prevent monkeypox and smallpox. Because monkeypox virus is closely related to the virus that causes smallpox (1-45). **Smallpox vaccine can also protect people from getting monkeypox** (1-45).

There are two types of smallpox vaccine. Both types are based on the vaccinia virus. An older type of smallpox vaccine contains the "live" vaccinia virus (1-45). The main one in this group is **ACAM2000**, which is approved in the US for protecting people against smallpox. Smallpox was eradicated all over the world around 1979-80. Therefore, smallpox vaccination also stopped at that time. There are hardly any manufacturers of smallpox vaccines today, but there is one company, Bavarian Nordic which produces the vaccine (1-45). A second vaccine, a modified vaccinia **Ankara vaccine (Jynneos)**, has been found to be safe, and it can be used in people who are not able to **take ACAM2000**, who have weakened immune systems or who have skin disorders. Center for Disease Control and Preventation (CDC) recommends that the vaccine be given within 4 days from the date of exposure in order to prevent onset of the disease. If given between 4–14 days after the date of exposure, vaccination may reduce the symptoms of disease, but may not prevent the disease. **ACAM-2000 and MVA-BN vaccines** are being deployed by some WHO Member States to manage close contacts. Others may hold supplies of LC16 vaccines (1-45).

Because Monkeypox virus is closely related to the virus that causes smallpox, the smallpox vaccine can protect people from getting monkeypox (1-45). Past data from Africa suggests that the smallpox vaccine is at least 85% effective in preventing monkeypox. The effectiveness of **JYNNEOS™ against monkeypox** was concluded from a clinical study on the immunogenicity of JYNNEOS and efficacy data from animal studies (1-45). Smallpox and monkeypox vaccines are effective at protecting people against monkeypox when given before exposure to monkeypox (1-45). Experts also believe that vaccination after a monkeypox exposure may help to prevent the disease or make it less severe.

Vaccination after exposure to the virus may also help to decrease chances of severe illness. The CDC currently recommends smallpox vaccination only in people who have been or are likely to be exposed to **monkeypox**. However, Immunocompromised people are at high risk. According to the health officials, medicines are not normally needed to treat monkeypox (1-45). The illness is usually mild and most people infected will recover within a few weeks without needing treatment. But there are vaccines that can be used to control monkeypox outbreaks, which some countries are already using and treatments do exist for those who become quite ill from the monkeypox virus (1-45, 45-55).

Diagnostic testing for monkeypox is currently available at Laboratory Response Network labs in the U.S. and globally. Monkeypox is unlikely to cause another pandemic, but with COVID-19 top of mind, fear of another major outbreak is understandable. Though rare and usually mild, monkeypox can still potentially cause severe illness. Health officials and WHO are concerned that more cases will arise with increased travel (1-33, 35-45).

The European Union (EU) will be using **Bavarian Nordic's** smallpox vaccine to mitigate the current monkeypox outbreak in the region (116-119). An agreement has been signed between the European Health Emergency Preparedness and Response Authority (HERA) and the **Danish manufacturer Bavarian Nordic** for the purchase of 110,000 doses of the vaccine. **The vaccine is marketed as IMVANEX in Europe, JYNNEOS in the U.S. and IMVAMUNE in Canada** (116).

Monkeypox: Antiviral drugs

According to the **UK Health** officials, human monkeypox poses unique challenges, even to well resourced health-care systems with High Consequence Infectious Disease (HCID) networks in UK as defined by the UK Health Security Agency (34). Further prolonged upper respiratory tract viral DNA shedding after skin lesion resolution caused by monkeypox also challenged current infection prevention and control guidance (34). There is an urgent need for prospective studies of antivirals for monkeypox viral disease. Cases of human monkeypox are rarely seen outside of west and central Africa (1-45). There are few data regarding viral kinetics or the duration of viral shedding and no licensed treatments (1-45). Currently there are no licensed treatments for human monkeypox; two oral drugs, **brincidofovir** and **tecovirimat**, have been approved for treatment of smallpox in USA, UK and have demonstrated efficacy against monkeypox in animals (34).

Apart from vaccines, there are some medicines that could be used for treating monkeypox. One such drug is **tecovirimat** which stops the spread of infection by interfering with a protein found on the surface of *Orthopoxviruses* (1-45). **Tecovirimat** is approved in the US for treating smallpox only. It has been tested in healthy humans and shown to stop the smallpox virus in the lab. However, it has not been tested in people with smallpox or other *Orthopoxviruses* (1-45). In Europe, **tecovitimat** has been authorised for treating smallpox, monkeypox and cowpox under exceptional circumstances.

Another antiviral that might be used is **cidofovir** – an injectable drug licensed in the UK to treat a serious viral eye infection in people with AIDS. In the body, cidofovir is converted into the antiviral ingredient cidofovir diphosphate. Because cidofovir stops smallpox in the laboratory, it could be authorised for emergency use in smallpox or monkeypox outbreaks. However, cidofovir is quite a potent medicine and can damage the kidneys, so a better alternative might be the closely related drug is brincidofovir, which has been approved in the US for treating smallpox. Brincidofovir (brand name Tembexa) is given by mouth and can be prescribed to people of any age. Its special design helps to get the right amount of the drug into cells to release the cidofovir component and also makes it less damaging to the kidneys. **Brincidofovir** has been tested in humans for other viral conditions. Its approval for use in smallpox in the US comes from laboratory studies showing that it works against ***Orthopoxviruses*.** For this reason, **brincidofovir** is also listed as a potential drug for treating monkeypox.

However, data and clinical study of how effective cidofovir, brincidofovir and tecovitimat will be in treating monkeypox infections in humans is lacking and not sufficient (34). A recent paper, published in The Lancet Infectious Diseases investigated the effectiveness of brincidofovir (three patients) and **tecovirima**t (one patient) in monkeypox cases between 2018 to 2021 in the UK (34). The researchers reported poor efficacy for **brincidofovir** and called for more studies of tecovirimat in human monkeypox infection (1-45).

Neither of these drugs has been studied in human efficacy trials; however, both drugs demonstrated efficacy against other orthopoxviruses (including monkey-pox) in animal models (34). There are reports of compassionate use of tecovirimat for complicated vaccinia and cowpox, with no concerning safety signals identified (1-45). An expanded access programme for **tecovirimat** is in preparation in the Central African Republic, where monkeypox outbreaks are common (34).

Monkeypox: Herbal Treatment options

Viral disease pandemics have shaped the history of mankind, and plants were usually the first available therapeutic choice (59). In a traditional **Indian *Ayurvedic*** system of medicine, plants and plant-based constituents have been extensively used for the treatment and management of different types of viral and other diseases (61-102). ***Ayurveda*** is a holistic approach to health and wellness that emphasizes balance between body, mind, and spirit. It's one of the oldest and the most respected Indian herbal medicinal traditions in the world (61-102**). *Ayurveda* means 'Science of life'**. It provides a complete system to have a long and healthy life (98-101).

The Indian Traditional System of Medicine is one of the oldest systems of medical practice in the world and has played an essential role in providing health care service to human civilization, right from its inception (61--102). India has the exclusive distinction of its own recognized traditional medicine; **Ayurveda, Yoga, Unani, Siddha, and Homoeopathy (AYUSH)** (98-102). Many safe traditional formulations of **AYUSH**, which are well known immunity modulators, have been used for centuries to control the viral disease, respiratory disorders and in allergic conditions (98-102). The use of plant-based traditional medicine is experiencing a revival, as it is seen as safer and healthier than synthetic drugs (61-102). Indeed, one advantage of traditional remedies over modern drugs is that their effects and margin of safety have been known for long (59, 61-102). The rich secondary metabolism that characterizes plants make them a source of compounds that may have a yet unknown therapeutic potential, only limited by the availability of resources to perform clinical trials. It is claimed that natural products (mostly from plant origin) will be the most important source of new drugs in the future (59, 61-102).

Smallpox outbreaks have occurred within the human population for thousands of years, but the natural disease is now considered eradicated after a successful worldwide vaccination program (50-59). In recent years there has been a heightened concern that **variola virus** might be used as an agent of bioterrorism (50-59). In addition, the related **monkeypox virus** represents an emerging threat to the human population (1-48). Though the vaccine provides effective protection against poxvirus infection, side effects and risks associated with the smallpox vaccine are reasonably common and can be quite severe (50-55). The increasing threat of **Orthopoxvirus**-related infections highlights the need to discover effective poxvirus countermeasures (50-55). Following is the list of plants used as antiviral agents during the outbreak of viral diseases and wound healing agents.

1. Sarracenia purpurea (Indian Pitcher Plant)

In the late 1800's, the Micmac Indians of Nova Scotia proclaimed the existence of a botanical-based remedy for smallpox (50-59). This botanical infusion was later described as being derived from the carnivorous plant, Sarracenia purpurea (Family Sarraceniaceae) (50-59, 105, 106). In the nineteenth century, smallpox ravaged through the United States and Canada (50-59). At this time, a botanical preparation, derived from the carnivorous plant **Sarracenia purpurea**, was proclaimed as being a successful therapy for smallpox infections (50-59, 105, 106). Sarracenia purpurea also known as Huntsman's Cup, Side-saddle flower or **Indian Pitcher Plant,** was widely distributed ranging from Labrador to Florida along the Atlantic seacoast of North America and westward to Wisconsin and Minnesota (50-59, 105, 106).

Sarracenia purpurea is an insectivorous bog plant, the leaves of which form cups and become filled with water to capture insects (50-55, 105, 106). The antipoxvirus activity associated with this botanical extract of Sarracenia purpurea against vaccinia virus, monkeypox virus and variola virus, the causative agent of smallpox has long been confirmed (50-59, 105, 106). The research work demonstrated the in vitro characterization of **Sarracenia purpurea** as the first effective inhibitor of poxvirus replication at the level of early viral transcription (50-59, 105, 106). With the renewed threat of poxvirus-related infections, these results indicated Sarracenia purpurea may act as another defensive measure against Orthopoxvirus infections (50-59, 105, 106).

The advent of vaccination put forward the botanical remedy, but the antiviral properties of Sarracenia purpurea have been later demonstrated in vitro. These experiments showed that the plant extract of Sarracenia purpurea was not only active against smallpox, but also against other poxviruses, papovirus SV-40 and various herpes viruses, including papillomavirus and Epstein-Barr virus-associated carcinomas, usually by inhibiting the virus replication at the level of early transcription (55-59). Therefore 'rediscovery' and characterization of Sarracenia purpurea as an effective inhibitor of Orthopoxvirus replication has been reconfirmed (50-55, 105, 106).

In India only known pitcher plant species is **Nepenthes khasiana** (Family-Nepenthaceae) Hook. f., which is an evergreen shrub considered endemic to Meghalaya. Nepenthes khasiana is an endangered tropical pitcher plant of the genus Nepenthes. It is the only Nepenthes species native to India. It is thought to attract prey by means of blue fluorescence. The species has a very localised distribution and is rare in the wild.

2. Resveratrol is a small, natural compound in many plants like grapes, cocoa beans, peanuts and blueberries. One of the recent study found that high concentrations of resveratrol higher than anything may find in food naturally prevent poxviruses from replicating in human cells." **Resveratrol** can be chemically synthesized or extracted from fruits. This research may be a steppingstone to using resveratrol as a complementary treatment for viruses during a time of growing concern over drug resistance. Poxvirus, which produces a green fluorescent protein, can replicate quickly in human cells unless resveratrol, a compound found naturally in many foods, is present, according to a study by researchers at **Kansas State University** USA and Centers for Disease Control and Prevention (CDCP).

The ***Azadirachta indica*** leaf extract was found to be active against a number of viruses such as smallpox (DNA), chicken pox (DNA), poxvirus (DNA), poliomyelitis (RNA) and herpes viruses (DNA). An extract of the **Cactus plant *Opuntia streptacantha*** inhibited intracellular DNA and RNA virus replication and inactivated extracellular virus, such as HSV, equine herpes virus, pseudorabies virus and influenza virus. The *Bergenia ligulata*, *Nerium indicum* and *Holoptelia integrifolia* plants exhibited considerable antiviral activities against influenza virus (RNA), HSV (DNA), and poxvirus.

Triphala (Sanskrit; Tri = three and Phala = fruits) is defined as a well known tri-herbal Indian *Ayurvedic* formulation consisting of

dried fruits of the three plant species, *Emblica officinalis* (Amalaki or the Indian Gooseberry) (Family-*Euphorbiaceae*), *Terminalia bellirica* (Bibhitaki or Karitaki) (Family-*Combretaceae*), and *Terminalia chebula* (Haritaki) (Family-*Combretaceae*) that are native to the Indian subcontinent (81). The major constituents of the Triphala formulations are the tannins, gallic acid, ellagic acid, and chebulinic acid, chebulagic acid which are potent antioxidants and therefore, resulted in the immunomodulatory activity without any side effects (81). Triphala has a proven viral inhibitory activity in clinical trials in animal modesl against many viruses, SARS-CoV-2, dengue fever and small pox too (81). One of the evidence to support Triphala alone inhibited the RNA viruses including human coronavirus (81). Triphala herbal formulation can reduce the production of progeny of human coronavirus, HCoV-NL63 particles and have an antiviral effect under in vitro conditions (81). In India, **Triphala herbal** formulation with an additional supplementation of pumpkin seeds, coconut water, sugar cane juice, *Aloe vera* juice, neem (*Azardirachta indica*) leaf juice, and **melatonin** rich diet has played an important role in controlling coronavirus disease than Triphala alone (81). However, **there no clinical evidence to support Triphala inhibiting monkeypox virus**. A study should be conducted, and will help in developing new antiviral drug for monkeypox virus.

3) Turmeric (*Curcuma longa*) (*Zingiberaceae*) Rhizomes. **4**) Liquorice or Mulethi (*Glycyrrhiza glabra*) (*Fabaceae*) Roots. **5**) Neem (*Azadirachta indica*) (M*eliacaee*) All the parts of plant were used. **6**) **Centella** (*Centella asiatica*) (*Apiaceae*) Leaves. **7**) Carbonal (Mimosa tenuiflora) (Fabaceae) Leaf and stem parts used **8**) Costus speciosus (Zingiberaceae) Rhizome used. **9) Forest Champa** (Spermadictyon suaveolens (Rubiaceae): Roots used **10)** Chlorophytum borivillianum (Liliaceae): Rhizome parts. **11)** Sesame (Sesamum indicum L) (Pedaliaceae) seeds were used. **12)** Calendula officinalis (Asteraceae): Flowers and leaves used. **13)** Trumpet tree (Cecropia peltata): Leaves. **14)** Kencur (Kaempferia galanga) (Zingiberaceae) Rhizomes. **15) Jhand tree** Druce (Prosopis cineraria) (Fabaceae) Leaves. **16)** Maidenhair (Ginkgo biloba) (Ginkgoaceae**)** Leaves and seeds. **17)** Madagascar periwinkle (Vinca rosea or **Catharanthus roseus**) (Apocynaceae) Leaves and flowers. **18)** Asthma Weed (Euphorbia hirta) (Euphorbiaceae) Leaves. **19)** Red sandalwood (Pterocarpus santalinus) (Fabaceae) Bark wood. **20) Lawsonia alba** (Lawsonia inermis) (Lythraceae) Leaves and roots. **21)** Jandi or Ghaf (Prosopis cineraria) (Fabaceae) Leaves and pods. **22)** Aloe (Aloe vera) (Liliaceae) Leaves. **23)** Bay (Sphagneticola trilobata) (Asteraceae) Leaves. **24)** Adusa (Adhatoda vasica) (Acanthaceae) Leaves. **25)** Humble plant (Mimosa pudica) (Leguminosae) Whole plant is used for wound healing. **26)** Papaya (Carica papaya) (Caricaceae) Latex, fruit. **27)** Jungle flame (Ixora coccinea) (Rubiaceae) Roots and leaves. **28)** Betle Piper (Piper betle L) (Piperaceae) Leaves. **29)** Common wireweed (Sida acuta) (Malvaceae) whole plant. **30**) Drumstick tree (Moringa oleifera) (Moringiaceae) Leaves. **31**) Indian olive (Olea europaea) (Oliaceae) Leaves and oil. **32) Burdock** (Arctium lappa) (Asteraceae) Root extract used treatment of sore throats and skin pathologies boils, rashes, and acne in North America, Europe, and Asia. **33)** Ginseng (Panax ginseng) (Araliaceae) Root or Rhizome part is used wound healing in China, Japan, Korea, and Eastern Siberia. **34)** German chamomile (Chamomilla recutita) (Asteraceae) Apigenin is the rarest flavonoid in chamomile flora and has a remarkable effect on the wound healing process. **35**) Pinus pinaster (Leaf and stem part). **36**) *Lavandula angstiforia* (Lamiaceae), **37**) *Argania spinosa* (Sapotaceae), **38**) *Bursera morelensis* (Burseraceae) **39**) *Hypericum patulum* and *H. perforatum* (Hypericaceae) **40**) *Copaifera paupera* (Fabaceae) **41**) *Avicennia schaueriana* (Verbenaceae) **42)** *Cucurbita pepo* (Cucurbitaceae) **43**) *Euphorbia hirta* (Euphorbiaceae) **44)** *Cydonia oblonga* (Rosaceae) **45)** *Chrozophora tinctoria* (Euphorbiaceae) **46**) *Nigella sativa* (Ranunculaceae) **47**) *Elaeis guineensi* (Arecaceae) **48**) *Ficus racemose* (Moraceae), **49)** *Artocarpus communis* (Moraceae), **50**) *Aegle marmelos* (Rutaceae), **51**) *Ephedra alata* (Ephedraceae), **52**) ***Ficus racemose*** (Moraceae), **53)** *Calotropis procera* (Apocynaceae) **54**) Salvia miltiorrhiza (Lamiaceae), **55)** Alchemilla vulgaris (Rose family) **56)** Phyllanthus muellerianus (Euphorbiaceae), **57)** *Andrographis paniculata* (Acantheaceae), **58**) *Angelica sinensis* (Apiaceae) in wound healing. **59**) *Boswellia sacra* (*Bursaraceae*) Frankincense, a resinous extract from *Boswellia sacra*, is valued in Africa, India, and the Middle East for the treatment of trauma and inflammatory diseases such as rheumatoid arthritis, and wound healing. **60**) *Celosia argentea (*Amaranthaceae*)*. *Celosia argentea*, also known as silver cock's comb, is used in traditional medicine to treat skin sores, eruptions, ulcers, mouth ulcers, and other skin diseases. **61)** *Cinnamomum camphor* (Lauraceae), **62**) *Commiphora myrrha* (Burseraceae), **63**) ***Terminalia chebula*** (Combretaceae), **64)** *Terminalia arjuna* (Combretaceae), **65**) Kutaja (*Holarrhena antidysenterica*) (Apocynaceae) Bark and leaf.

CONCLUSION

Monkeypox is not anymore a rare disease that is caused by an infection with monkeypox virus. Recently since **May 2022,** monkeypox viral disease cases in people have occurred outside of Africa linked to international travel or imported animals, and sex with infected person, in the non-endemic region (Europe, United States, Canada, Israel, Singapore, UK). Monkeypox virus represents an emerging threat to the human population (1-48). The natural reservoir of monkeypox remains still unknown. However, African rodents and **non-human primates (like monkeys**) may harbour the virus and infect people. Monkeypox spreads between people primarily through direct contact with infectious sores, scabs, or body fluids. It can also be spread by respiratory secretions during prolonged, face-to-face contact. Monkeypox virus can spread when a person comes into contact with the virus from an infected animal, infected person, or materials contaminated with the virus. The virus can also cross the placenta from the mother to her fetus. **Monkeypox *virus*** may spread from animals to people through the bite or scratch of an infected animal, by handling wild game, or through the use of products made from infected animals. The virus may also spread through direct contact with **body fluids or sores, sex with an infected person** or with materials that have touched body fluids or sores, such as clothing or linens.

The outbreak of monkeypox viral disease in non-endemic region (31 countries) is very disturbing and challenges the present health care system. There are many factors governing the outbreak of monkeypox viral disease. Therefore, there is an urgent need and emergency wake up call to seriously consider this on-going issue and address the monkeypox viral disease. Though the vaccine provides effective protection against poxvirus infection, side effects and risks associated with the smallpox vaccine are reasonably common and can be quite severe.

Therefore, **plant based remedy** for controlling monkeypox viral disease would be an added advantage in terms of low cost, and no side effects on the health. As per the literature survey ***Sarracenia purpurea*** **or Indian pitcher plant** as the first effective inhibitor of poxvirus replication at the level of early viral transcription under in **vitro conditions in animal model** (105-106). **Resveratrol** higher than anything in food naturally prevent poxviruses from replicating in human cells. In addition to this, there are many plants as listed in this review paper which showed viral inhibitory activity under in vitro experimental animal studies.

Large number **of plants** has been shown to be active in vitro against a variety of human pathogenic viruses. A number of pure compounds have demonstrated activity against several viral

infections. For example, glycyrrhizin and its analogues against herpes, hepatitis (including clinical trial), influenza, respiratory syncytial, SARS and vesicular stomatitis viruses. **Glycyrrhizin** perhaps has the widest spectrum of antiviral activity among the natural products so far investigated. Adequate clinical evaluation is necessary to assess its role in treatment of viral disorders particularly monkeypox viral disease. ***Azadirachta indica*** (Neem) also is a promising plant, even though most of the studies have used its extract. It has a variety of compounds and also has a long history of use in traditional medicine in many countries of the world. Detailed studies against some of these viruses, specially poxvirus and monkeypox are strongly warranted. **There are no experimental evidence to support these herbal extracts inhibiting monkeypox virus**.

In several cases, the active compounds have been isolated and characterized. Very few of them, however, have been investigated in detail in vivo or taken to the clinic. Pure compounds like andrographolide, curcumin and glycyrrhizic acid as well as extracts of Azadirachta indica have shown activity against several viruses and should be investigated further for their therapeutic potential. An analysis of available data from several hundred species indicated that antiviral activity is more likely to be found in **plants** belonging to certain families. Adequate attention has not been paid to use them as basic templates to optimize the activity in synthetic or semi-synthetic derivatives. Activity has also been reported in certain compounds which have undergone extensive clinical evaluation in non-viral diseases. Their available safety and dosage regimen data would help in initiating clinical evaluation in viral infection where in vitro or in vivo activity data is available.

However, there is a deep gap **between laboratory scale research**, **clinical scale and even commercialization**. Most of the experiments were conducted on animal model. Another problem is that much of the evidence comes from animal and in vitro studies and overall clinical Evidence-Based Complementary and Alternative Medicine evidence to support these herbal interventions remains weak and lacking. **Phytotoxicity** is another major problem with applications of **plant based extracts** in controlling viral and other diseases. Therefore, detailed phytochemical study should be conducted before the application of plant based remedies in controlling viral diseases specially **monkeypox** are strongly warranted. Future epidemiological and clinical studies are required to further assess the benefits of herbal medicines in the prevention of monkeypox. This will help in developing new antiviral drugs for controlling monkeypox viral outbreak.

Herbal folk medicines neither can avoid the virus infection but may alleviate symptoms and potentially improve the general wellbeing of patients. For successful and effective development of a drug, the basic requirement is the correct identification of the source of biologically active compound, its availability and processing. **In conclusion**, it may be stated that the rich and valuable resource of plants needs to be more extensively exploited to provide new drugs for the treatment of viral disorders particularly **monkeypox**.

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