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Cannabis sativa: 2023-Outbreak and Re-emergence of Nipah virus (NiV) in India: Role of Hemp oil

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Abstract

This review paper highlights and updates the outbreak of Nipah virus (NiV), an emerging zoonotic bat borne virus that can cause severe respiratory illness and deadly encephalitis in humans. Nipah virus (NiV) outbreak was first reported in 1998 from Malaysia and then recorded in Bangladesh, India, Philippines, Singapore and Thailand. A recent fifth outbreak of Nipah virus (NiV) during August-September 2023 in Kerala State, India brought this emerging-re-emerging virus into the spotlight again. Due to the lack of vaccines and drugs with proven effectiveness against Nipah virus (NiV), treatment of patients is limited to supportive and prophylactic. Fruit bats are the main reservoir for this virus, which can cause disease in humans and animals. Nipah virus (NiV) can be transmitted from bats or livestock to humans, typically via contaminated food (fruit or raw date palm sap), and person-to-person through respiratory secretions. Hemp seed oil has gained remarkable popularity due to its perceived therapeutic properties, particularly antiviral properties for potential health benefits. During the recent outbreak of Nipah virus (NiV), the local traditional healers in India used hemp oil as the mouth wash for controlling throat infections, head ache, vomiting and suggested for the consumption of hemp seeds and oil as the functional food. However, clinical trials and scientific data supporting antiviral activity of Cannabis oil (CBD oil) against Nipah virus (NiV) is lacking. Therefore, further research should focus on exploring the molecular mechanisms of hemp oil against Nipah virus (NiV) is warranted. Multicenter clinical trials should be performed to validate the efficacy of hemp oil alone or in the form of formulations for the treatment of viral infections.

Keywords: Bats; Cannabis sativa; CBD oil; Hemp; Herbal medicine; India; Nipah virus (NiV)

1. Introduction

Cannabis sativa is a flowering plant from the *Cannabaceae* family and genus *Cannabis*. Cannabis is a plant notorious for its psychoactive effect, but when used correctly, it provides a plethora of medicinal benefits [1-20,93]. Cannabis has been used for thousands of years for recreational, medicinal, or religious purposes. Cannabis is also a wild noxious weed with notorious psychoactive principle, Δ9-tetrahydrocannabinol (THC) found growing in India, China, Bhutan, Nepal, Pakistan, Afghanistan, Iran, and Morocco[1-25]. Cannabis has a long history in India, recorded in legends and religion. It was found in various habitats ranging from sea level to the temperate and alpine foothills of the Indian Himalaya Region from where it was probably spread over the last 10,000 years [1-25]. Many historians believed that Indian Himalayan Region was the centre of origin of *Cannabis sativa* L. and *Cannabis indica* L. [1-24, 93]. Tribal people in the Himalayan region used Cannabis as a home made herbal medicine for many diseases. During, Covid-19, the infusion of Cannabis flower with a morning cup of tea has saved the life of many people [1-23]. Cannabis oil was used as dengue mosquito repellent for controlling dengue viral fever [26-37], bacterial infections and fungal diseases [20-37].

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Cannabis sativa L., is classified into two types as Industrial *Cannabis sativa*, hemp or Medical *Cannabis sativa* L.(drug or marijuana) based on its THC content[1-25, 93]. Medical *Cannabis sativa* (drug or marijuana) contains a very high levels of THC (above 0.3 to 38% of dry weight) [1-23, 93]. On the other hand Industrial *Cannabis sativa* L. (Hemp) contains very low levels of THC (0 to 0.3% of dry weight) [1-25, 93]. However, due to the presence of psychoactive molecules, Λ9-tetrahydrocannabinol (Λ9-THC) and Λ8-tetrahydrocannabinol (Λ8-THC), Cannabis cultivation and its use is restricted/regulated in many countries [1-25]. Industrial hemp, as a diverse plant, can be a revolutionary crop for a better future and for upcoming generations[1-25]. It is an eco-friendly and worthwhile crop that complements a sustainable growth system. Industrial hemp farming has the potential to dramatically minimize the amount of carbon impact on the environment and can be cultivated with a little or no usage of chemical pesticides or fertilizers [1-25]. The stalks, seeds, and leaves are converted into various construction materials, textiles, paper, food, furniture, cosmetics, and healthcare products [1-25]. Biochar, bioplastics, biofuels, and biopesticides are some of the innovative applications of the hemp plant, which are subjects of research and debate at present time [1-25].

In addition to fiber and essential oils, the hemp plant produces hundreds of secondary metabolites including flavonoids, diterpenes, triterpenes, and Cannabinoids [1-25]. Unlike primary metabolites such as proteins, nucleic acids, lipids, and carbohydrates that are essential for life, secondary metabolites benefit plants in other ways such as deterring predators, attracting pollinators, or preventing infection [1-25]. Several secondary metabolites that are unique to Cannabis sativa L. include some Cannflavins (flavonoids), Cannabisins (lignans), and Cannabinoids [1-25]. Hemp produces over 100 Cannabinoids including Cannabidiol (CBD), Cannabidiolic acid (CBDA), the psychotropic Cannabinoid, Λ9-tetrahydrocannabinol (Λ9-THC), Λ9-tetrahydrocannabinolic acid-A (Λ9-THCA-A), Cannabigerol (CBG), Cannabigerolic acid (CBGA), and Λ9-tetrahydrocannabutol [1-25]. Despite legal restrictions, Cannabinoids and other compounds from hemp have a long and extensive history of safe use in humans. These products have been administered orally, sublingually, dermally, and by inhalation. As a class of natural products, Cannabinoids have been shown to have suitable oral bioavailability, metabolism, blood–brain barrier permeability, and safety for use as therapeutic agents [1-25]. Based on the established therapeutic efficacy of Cannabidiol (CBD) and Λ9-tetrahydrocannabutol (Λ9- THC), these and other cannabinoids are under investigation for additional pharmacological activities, including activity as antiviral agents [1-25]. Among the vast range of compounds, multiple research papers have shown that Cannabinoids, such as Cannabidiol and Λ-9-tetrahydrocannabinol, have antiviral effects. There is limited evidence that demonstrates the therapeutic effects of Cannabinoids in viral infections [1-25]. Some scientists believed that Λ9-tetrahydrocannabutol (Λ9- THC), may be advantageous in viral illnesses, when the inflammatory response of the host is pathogenic. The anti-inflammatory properties of Cannabinoids were found to be associated with the treatment of COVID-19 [1-25].

Nipah virus (NiV) is an emerging virus that can cause severe respiratory illness and deadly encephalitis in humans [38-72]. Nipah virus (NiV) was discovered in 1998 during the first reported outbreak in the Sungai Nipah, a village in Malaysia, where humans contracted Nipah virus (NiV) from pigs, the intermediate hosts of the virus. Nipah viral (NiV) outbreak has been reported from Malaysia, Bangladesh, India, Singapore, Thailand and Philippines [38-72]. A fifth outbreak of Nipah virus (NiV) during August-September 2023 in Kerala State, India brought this emerging-re-emerging virus into the spotlight again [58]. In 2023, a Nipah virus outbreak was declared in the Indian state of Kerala with a total of 6 confirmed cases, 2 which resulted in death [38-72]. Fruit bats are the major reservoirs of the Nipah virus and it is the contact with such bats (infected) or intermediate hosts like pigs which are responsible for infection in man [38-72]. Bats serve as reservoir hosts for several high risk pathogens, including Nipah, rabies and Marbug viruses. Such viruses are not associated with any significant pathological changes in the bat population [38-72].

In the following section, the major scientific advances in Nipah virus (NiV) epidemiology and biology has been updated and discussed effectively to prevent Nipah virus (NiV) infections and deaths. High pathogenicity of Nipah virus (NiV) in humans, and lack of vaccines or therapeutics to counter this disease have attracted attention of researchers worldwide for developing effective Nipah virus (NiV) vaccine and herbal medicine treatment regimens.

1.1. Nipah virus (NiV)

Nipah virus (NiV) is a zoonotic bat borne pathogen, which causes lethal encephalitis in humans has been reported from Malaysia, Bangladesh, India, Singapore, Philippines, and Thailand [38-72]. Nipah virus (NiV) is a Paramyxovirus (Henipavirus genus, Paramyxovirinae subfamily, Paramyxoviridae family, order Mononegavirales). Viruses are the cause of diseases that pose a serious threat to public health [38-72]. Nipah viral outbreaks documented in various parts of the South East Asia pose a substantial threat to the global community. Nipha virus (NiV) is one of the major public health challenges in South and South East Asia [38-72]. Nipah virus (NiV) is an enveloped pleomorphic virus known to cause encephalitis, with cases of acute respiratory distress turning fatal [38-72]. Due to its high mortality in humans, its zoonotic nature, the possibility of human-to-human transmission, and the lack of an available vaccine, the World Health Organization (WHO) has recognized Nipah virus (NiV) as a global health problem. Therefore, since 2015, the World

Health Organization has listed Nipah virus (NiV) as one of the most dangerous emerging viruses, due to its large capacity to transmit from person to person [38-72]. Consumption of contaminated food, contact with animals, and "human-to-human" direct contact were identified as Nipah virus (NiV) transmission routes. Due to the lack of vaccines and drugs with proven effectiveness against Nipah virus (NiV), treatment of patients is limited to supportive and prophylactic. Nipah virus (NiV) belongs to the group of zoonotic viruses whose source and vector enabling transmission and multiplication are wild and domesticated animals [38-72]. Nipah virus (NiV) is an emerging zoonotic pathogen that causes severe febrile encephalitis resulting in death in 40% to 75% of human cases. Nipha virus (NiV) is considered as a biosafety level-4 pathogen and listed as a select agent with high risk for public health and security due to its high mortality rate in people and the lack of effective vaccines or therapies [38-72].

Nipha virus (NiV) is a negative sense, single stranded, non segmented, enveloped RNA virus possessing helical symmetry [38-72]. The genome is approximately 18.2 kb long which encodes six structural proteins: nucleocapsid (N), phosphoprotein (P), matrix protein (M), fusion protein (F), glycoprotein (G) and RNA polymerase (L). The N, P and L along with the viral RNA forms the ribonucleoprotein complex, an indispensable complex that regulates transcription and viral RNA synthesis [38-72]. Nipah virus (NiV) is a zoonotic virus (it is transmitted from animals to humans) and can also be transmitted through contaminated food or directly between people. In infected people, it causes a range of illnesses from asymptomatic (subclinical) infection to acute respiratory illness and fatal encephalitis [38-72]. The virus can also cause severe disease in animals such as pigs, resulting in significant economic losses for farmers. Other regions may be at risk for infection, as evidence of the virus has been found in the known natural reservoir (*Pteropus* bat species) [38-72]. Several other bat species in a number of countries, including Cambodia, Ghana, Indonesia, Madagascar, the Philippines, and Thailand has been reported [38-72]. There are currently no drugs or vaccines specific for Nipah virus (NiV) infection although WHO has identified Nipah as a priority viral disease for the WHO Research and Development Blueprint [38-72]. Intensive supportive care has been recommended for the treatment of severe respiratory and neurologic complications caused by Nipah virus (NiV) [38-72].

1.2. First outbreak of Nipah virus (NiV) in Malaysia

The name 'Nipah' comes from a Malaysian village, where the first outbreak was reported in 1998-1999 [38-72]. The disease was reported for the first time from the Kampung Sungai Nipah village of Malaysia in 1998. Pteropus fruit bats are considered as the natural reservoirs of the Nipah virus [38-72]. The outbreak of Nipah virus (NiV) disease in Malaysia involved more than 250 cases of febrile encephalitis in farm and abattoir workers. In Malaysia, humans contracted the disease through NiV-infected pigs, the intermediate hosts of the virus [38-72]. Spill-over of the virus from bats to pigs are due to the consumption of fruits partially eaten or contaminated by bats infected with Nipah virus (NiV). Transmission of the virus from pig to human occurred through direct contact with the infected pigs, and human-to-human infection could be through direct [38-72]. Nipah virus (NiV) was first detected more than two decades ago, following an outbreak among pig farmers in Malaysia. Within months, it had spread to Singapore through infected pigs. The outbreak resulted in nearly 300 cases and more than 100 deaths. The strain circulating in India and Bangladesh is different from the one that surfaced in Malaysia [38-72].

Outbreaks of the Nipah virus (NiV) in pigs and other domestic animals such as horses, goats, sheep, cats and dogs were first reported during the initial Malaysian outbreak in 1999 [38-72]. The virus is highly contagious in pigs. Pigs are infectious during the incubation period, which lasts from 4 to 14 days [38-72]. An infected pig can exhibit no symptoms, but some pigs develop acute feverish illness, labored breathing, and neurological symptoms such as trembling, twitching and muscle spasms. Generally, mortality is low except in young piglets [38-72]. These symptoms are not dramatically different from other respiratory and neurological illnesses of pigs. Nipah virus (NiV) should be suspected if pigs also have an unusual barking cough or if human cases of encephalitis are present [38-72]. Crop raising and fruit trees in close proximities to traditionally designed pig sties have contributed to the spill-over of Nipah virus (NiV) to pigs via bat-bitten fruits. Drought in the regions could reflect in a reduced availability of natural fruit forcing the bats to resort to fruiting trees in gardens and orchards existing in dense human habitats [38-72]. Although pig farming has been a major source of income for farmers, the NiV outbreak in Malaysia roots from pigs and pig sties [38-72]. Massive culling of pigs as a result of the outbreak lead to poverty and rehabilitation in the areas affected. Similarly, date palm sap consumers, which are major villages in Bangladesh have a high toll of Nipah virus (NiV) infection periodically [38-72].

1.3. Outbreak of Nipah virus (NiV) in India

Nipah virus (NiV) is a lethal emerging zoonotic disease that has been neglected since its characterization in 1999 until recently [38-72]. Nipah virus (NiV) infection occurs predominantly in isolated regions of Malaysia, Bangladesh, and India in small outbreaks. Factors that affect animal–human disease transmission include viral mutation, direct contact, amplifying reservoirs, food, close contact, and host cell mutations [38-72]. There are different strains of Nipah virus, and small outbreaks in humans limit known research and surveillance on this pathogen [38-72]. The small size of

outbreaks in rural areas is suggestive of low transmission. Person-to-person transmission may occur. Whereas the Malaysia strain spread from animals to humans, there was little transmission between people [38-72]. People-to-people contacts are favored by the growth of the human population globalization, trade, or contemporary travel patterns [38-72]. But the version that was behind the latest outbreak in Kerala, India can be passed from person to person, and is much deadlier [38-72].

The outbreak of Nipah virus (NiV) in Kerala State, India and West Bengal State India has been reported in 2001, 2007, 2018, 2019 and 2023 [38-72]. India is no stranger to Nipah virus (NiV) with 4 previous outbreaks occurred between the years of 2001-2021 and the most recent outbreak bringing the number to 5 [38-72]. In India, the first outbreak occurred in Siliguri, West Bengal State in 2001 with mostly nosocomial or person-to-person close contact, and second repeated outbreak in 2007 was reported in Nadia in West Bengal State, India [38-72]. A third outbreak of Nipah virus (NiV) was recorded in 2018 in the Kozhikode district of Kerala, a South Indian State where the index patient was reported to have contracted Nipah virus (NiV) from fruit-eating bats [38-72]. However, no clinical or statistical evidence was available to prove the incidence, though the spread was mostly through nosocomial infection [38-72]. All the outbreaks have recorded high rates of fatality including the 91% mortality rate during the recent Kerala, India outbreak [38-72]. In 2019, a recurring incidence of Nepah virus (NiV) was reported where one patient tested positive for Nepah virus (NiV) at the Ernakulam district of Kerala, India [38-72].

A fifth outbreak of Nipah virus (NiV) during August-September 2023 in Kerala State, India brought this emerging-re-emerging virus into the spotlight again [38-72]. In 2023 a Nipah virus (NiV) outbreak was declared in the Indian state of Kerala with a total of 6 confirmed cases, 2 which resulted in death [38-72]. A 39-year-old man in Kerala has tested positive for the Nipah virus, bringing the total number of infections to six. All of the cases have been reported from Kozhikode District in Northern Kerala State, India during September 2023 [38-72]. The man contracted the virus after coming into contact with a previously infected patient who later died. The Nipah virus (NiV) is highly pathogenic and often fatal, causing brain swelling and respiratory distress. There is currently no cure or vaccine for the virus [38-72]. More than 700 people, including health-care workers, have been tested for infection over the past week. Kerala State authorities have closed some schools, offices and public-transport networks [58-72]. The Nipah virus (NiV) outbreak is the fourth to hit Kerala in five years — the most recent one was in 2021, and 2023 [38-72]. Although such outbreaks usually affect a relatively small geographical area, they can be deadly, and some scientists worry that increased spread among people could lead to the virus becoming more contagious [38-72]. Nipah virus (NiV) has a fatality rate between 40% and 75% depending on the strain [38-72]. The authorities in the Kozhikode district, Kerala State, India where the outbreak occurred, have instituted “containment zones” in the area and schools have been closed [38-72]. Seventy-six people who came into contact with the infected are being closely monitored for signs of the disease [38-72].

The Indian government is working to evaluate preventive measures to tackle the outbreak. Nipah virus (NiV) is emerged as a new virus exactly 20 years ago, causing severe morbidity and mortality in both humans and animals and destroyed the pig-farming industry in Malaysia, and it continues to cause outbreaks in Bangladesh and India [38-72]. As the reservoir host *Pteropus* bat is widespread, and Nipah virus (NiV) has been found in bats in various countries, the potential for outbreaks to occur in new regions remains significant [38-72]. India has adopted guidelines for the clinical management of Nipah virus (NiV) disease, using the One Health approach [38-72]. Moreover, the Indian Council of Medical Research **(**ICMR**)** and Integrated Disease Surveillance Programme has partnered with veterinary divisions, such as the National Centre for Disease Control in India.

1.4. Nipah virus (NiV) outbreak in Bangladesh

Nipah virus (NiV) has been a major cause of encephalitis outbreaks with high mortality, primarily in the Indo-Bangladesh regions [38-72]. Recurring Nipah virus (NiV) outbreaks have been reported annually in different parts of Bangladesh from 2001, where the infection occurred due to the consumption of raw date palm sap contaminated with saliva and excreta of the bats [38-72]. Five outbreaks of human Nipah virus (NiV) infection have been recognized in Bangladesh between 2001 and 2005 [38-72]. Except for the first outbreak in Malaysia-Singapore, which was related to contact with pigs and the outbreak in Philippines was associated with horse slaughter, most other outbreaks have affected the Indo-Bangladesh regions [38-72]. The Indo-Bangladesh outbreaks were associated with consumption of raw date palm sap contaminated by fruit bats and had a very high secondary attack rate [38-72]. The patient usually presents with fever, encephalitis and/or respiratory involvement with or without thrombocytopenia, leukopenia and transaminitis. Malaysia had no more cases since 1999, but outbreaks continue to occur in Bangladesh and India [38-72]. In the Malaysia-Singapore outbreak, transmission occurred primarily through contact with pigs, whereas in Bangladesh and India, it is associated with ingestion of contaminated date palm sap and human-to-human transmission [38-72]. Bats are the main reservoir for this virus, which can cause disease in humans and animals. There are currently no effective therapeutics, and supportive care and prevention are the mainstays of management [38-72]. The wide

distribution of Nipah virus (NiV) antibodies in *Pteropus* fruit bats across South and Southeast Asia suggests that these bats harbor Nipah or related viruses across their range [38-72]. Some of these viruses are likely to be highly lethal and able to transmit from human to human, as seems to have occurred in Bangladesh [38-72].

1.5. Nipah virus (NiV) Outbreak in Philippines

The epidemic in the southern part of the Philippines occurred in 2014 and included 17 cases [38-72]. It was characterized by high mortality, exceeding 80%. The infections were mainly associated with exposure to or consumption of horse meat, and the responsible strain was closely related to the Malaysian strain [38-72]. In 2014, the Philippines National Epidemiology Center received a report of human deaths in 2 villages on Mindanao, an island in the Philippines [38-72]. An outbreak investigation revealed additional human deaths and nonfatal infections with concurrent neurologic disease, and sudden deaths in several horses [38-72]. It was thought that virus transmission to humans was from direct exposure to infected horses, contact with contaminated body fluids during slaughtering of sick horses, and/or consumption of undercooked meat from infected horses [38-72]. While the overall fatality rate was 53%, it was 82% for those with acute encephalitis [38-72].

1.6. Nipah virus (NiV) Strains

Genomic sequencing have identified two strains of Nipah virus (NiV): NiV-B and NiV-M [38-72]. Genetic characterization of the two strains demonstrated that NiV-B has a genome size of 18,252 nucleotides which is longer than NiV-M by six nucleotides [38-72]. Even though both the strains share 91.8% similarity in nucleotide homology, NiV-B is considered to have higher fatality rates [38-72]. The two Nipah virus (NiV) strains are responsible for the outbreaks in various geographical areas [38-72]. Bangladesh and Indian outbreaks have reported the source of the virus to be NiV-B while the Malaysian outbreaks were reported to be from NiV-M [38-72]. NiV-B has a shorter incubation period compared to NiV-M [38-72]. The majority of NiV-B cases had respiratory symptoms as well as lethal encephalitis while NiV-M predominantly caused encephalitis with few signs of respiratory diseases [38-72]. In addition, NiV-B infection resulted in a higher mortality rate compared to NiV-M [38-72]. The major clinical presenting features of Nipah virus (NiV) include acute encephalitis with fever, head ache, vomiting and respiratory discomfort [38-72]. Some patients also developed pneumonia, behavioural changes, disorientations with uncontrolled gait and low levels of consciousness [38-72]. During the Kerala outbreak, fever, myalgia, respiratory difficulties, headache, vomiting, cough, altered sensorium and encephalitis with seizures were reported in infected persons [38-72]. Outbreaks in Bangladesh and India showed a higher number of cases with respiratory distresses [38-72].

1.7. Primary hosts of Nipah virus (NiV)

The reservoir host of Nipah virus (NiV) is fruit bats specifically flying foxes, and the virus is related to another virus, Hendra virus, which causes fatal disease in horses [38-72]. Fruit bats of the family *Pteropodidae* – particularly species belonging to the *Pteropus* genus – are the natural hosts for Nipah virus (NiV) [38-72]. There is no apparent disease in fruit bats [38-72]. This zoonotic virus can be transmitted from bats or livestock to humans, typically via contaminated food (fruit or raw date palm sap), and person-to-person through respiratory secretions [38-72]. Fruit bats of the genus Pteropus (flying foxes) are the natural reservoirs for Nipah virus (NiV) [38-72]. They feed on fruits and nectar and are found predominantly in areas around farms and orchards, limiting the barrier of spill-over of the viruses [38-72]. The bats are endemic to tropical and subtropical regions of Asia, East Africa, Australian continents and some oceanic islands and are proved to be associated with the Nipah virus (NiV) outbreaks reported in different parts of the world [38-72]. Being the natural hosts for Nipah virus (NiV), bats are symptomless carriers but they shed the viruses in their saliva, urine, semen and excreta [38-72]. The route of transmission occurs via contact with excretions or secretions of infected animals, ingestion of fruit contaminated with Nipah virus (NiV) or close contact with infected human bodily fluids [38-72]. It is assumed that the geographic distribution of *Henipaviruses* overlaps with that of *Pteropus* category. This hypothesis was reinforced with the evidence of *Henipavirus* infection in *Pteropus* bats from Australia, Bangladesh, Cambodia, China, India, Indonesia, Madagascar, Malaysia, Papua New Guinea, Thailand and Timor-Leste [38-72]. African fruit bats of the genus *Eidolon*, family *Pteropodidae,* were found positive for antibodies against Nipah and Hendra viruses, indicating that these viruses might be present within the geographic distribution of *Pteropodidae* bats in Africa [38-72].

Deforestation accounts for the major loss in bat habitats. Pteropus bats are frugivorous and nectarivorous and are known to reside in tropical forests across continents [38-72]. They help disperse seeds of native and agro-economically important plants and crops. They are the sole pollinators in many oceanic islands apart from restoring the genetic diversity in intervened forest lands [38-72]. Fruit collection, deforestation and tourism have contributed heavily to habitat loss [38-72]. Spill-over in Bangladesh may have occurred from people eating fruit from trees or drinking date palm juice also utilized by bats [38-72]. In Malaysia, deforestation, planting of fruit orchards and the development of

intensive pig farms created the right conditions for a sustained Nipah virus (NiV) outbreak [38-72]. Therefore, understanding of the conditions and mechanisms of transmission of Nipah virus (NiV) may provide the basis for these intervention strategies to protect human and animal health. In Bangladesh, there is evidence of person-to-person transmission of Nipah virus (NiV) [38-72].

1.8. Nipah virus (NiV): Incubation Period

Nipah virus (NiV) can survive for up to 3 days in some fruit juices or mango fruit, and for at least 7 days in artificial date palm sap (13% sucrose and 0.21% BSA in water, pH 7.0) kept at 22° C [38-72]. The Nipah virus (NiV) has a half life of 18 h in the urine of fruit bats. Nipah virus (NiV) is relatively stable in the environment, and remains viable at 70° C for 1 h (only the viral concentration will be reduced). It can be completely inactivated by heating at 100° C for more than 15 min. However, the viability of the Nipah virus (NiV) in its natural environment may vary depending on the different conditions [48-72]. Nipah virus (NiV) can be prevented by avoiding ingestion of fallen fruit and raw date palm sap, avoiding contact with sick animals, practicing regular hand hygiene, and using proper barrier and respiratory protection if caring for a presumed or confirmed case of Nipah virus (NiV) infection. Nipah virus (NiV) can be readily inactivated by soaps, detergents and commercially available disinfectants such as sodium hypochlorite [38-72].

1.9. Nipah virus (NiV): Symptoms

Disease symptoms typically appear in 2-14 days following exposure to the Nipah virus (NiV). The incubation period in humans ranged from 4 days to 2 months with more than 0% at 2 weeks or less [38-72]. The illness initially presents as 3-14 days of fever and headache, dizziness, and often includes signs of respiratory illness, such as cough, sore throat, and difficulty breathing. A phase of brain swelling (encephalitis) may follow, where symptoms can include drowsiness, disorientation, and mental confusion, which can rapidly progress to coma within 24-48 hours [38-72]. Fever, headache, cough, sore throat, difficulty breathing, and vomiting [38-72]. **Severe symptoms may follow such as:** disorientation, drowsiness, or confusion, seizures, coma, brain swelling (encephalitis). Death may occur in 40-75% of cases [38-72]. Long-term side effects in survivors of Nipah virus (NiV) infection have been noted, including persistent convulsions and personality changes [38-72]. Many patients had a reduced level of consciousness and prominent signs of brainstem dysfunction, including abnormal doll's eye reflex, pupillary reflexes, vasomotor changes, seizures, and myoclonic jerks [38-72]. Neurological involvement was diverse and multifocal, including aseptic meningitis, diffuse encephalitis, and focal brainstem involvement [38-72]. Nipah virus (NiV) infection can affect many major organs, including the brain, lungs, heart, kidneys, and spleen. Infections that lead to symptoms and sometimes death much later after exposure (known as dormant or latent infections) have also been reported months and even years after exposure [38-72].

1.10. Nipah virus (NiV): Diagnosis

The pathogenesis of Nipah virus (NiV) in humans remains poorly understood. Initial signs and symptoms of Nipah virus (NiV) infection are nonspecific, and the diagnosis is often not suspected at the time of presentation [38-72]. Despite commitments to vaccine development, many basic facts about Nipah virus (NiV) epidemiology, biology, and ecology remain unknown. Nipah virus (NiV) infection needs high attention as there are no specific antivirals or antibodies presently effective against the infection. Nipah virus (NiV) infection can be diagnosed during illness or after recovery [38-72]. Disease progression is rapid, and delays in seeking care coupled with lack of rapid diagnostics means that only rarely are patients diagnosed with Nipah virus (NiV) infection before death, severely limiting opportunities to collect biological samples. Furthermore, outbreaks have occurred in areas where diagnostic autopsy is not the standard of care, due to religious and cultural concerns or to limited capacity, further limiting samples available for analysis [38-72]. This can hinder accurate diagnosis and creates challenges in outbreak detection, effective and timely infection control measures, and outbreak response activities [38-72]. Therefore, early diagnosis of Nipah virus (NiV) infection can be challenging due to the non-specific early symptoms of the illness. However, early detection and diagnosis are critical to increase chances of survival among infected individuals, to prevent transmission to other people, and to manage outbreak response efforts [38-72]. Nipah virus (NiV) should be considered for people with symptoms consistent with Nipah virus (NiV) infection who have been in areas where Nipah is more common, such as Bangladesh or India—particularly if they have a known exposure. Different tests are available to diagnose Nipah virus (NiV) infection [38-72].

Nipah virus (NiV) infection can be diagnosed with clinical history during the acute and convalescent phase of the disease [38-72]. An official diagnosis of Nipah virus (NiV) will be the result of laboratory tests confirming virus from a suspected person. In addition, the quality, quantity, type, timing of clinical sample collection and the time needed to transfer samples to the laboratory can affect the accuracy of laboratory results [38-72]. Early diagnosis is very critical for Nipah virus (NiV) infection as serious case fatalities are a hallmark of the disease [38-72]. Various samples are collected from infected individuals and animals for diagnostic purposes. Specimens collected from humans include nasal swab, throat swab, urine, blood and cerebrospinal fluid (CSF) whereas lung, spleen, and kidneys from dead animals are used to

diagnose and isolate Nipah virus (NiV) [38-72]. Diagnosis is performed in enhanced BSL3 (BSL3+) or BSL4 facilities [38-72]. Diagnostic tests for detection of Nipah virus (NiV) include molecular and serological assays, immunohistochemistry, histopathology, virus isolation and neutralisation. Vero cells are used to culture Nipah virus (NiV) with observable cytopathic effects in three days [38-72]. The main tests used are real time polymerase chain reaction (RT-PCR) from bodily fluids and antibody detection via enzyme-linked immunosorbent assay (ELISA) [26-37, 38-72]. ELISA is often followed by a serum neutralisation test or PCR [26-37, 38-72]. Virus isolation and neutralisation methods are also used for diagnosis but are constrained to BSL-4 facilities. Other tests used include polymerase chain reaction (PCR) assay, and virus isolation by cell culture [26-37, 38-72]. Next generation sequencing is an alternative method aiding in effective identification of viral strain, however the method is not frequently used in diagnosis and when considering expenses [26-37, 38-72].

1.11. How to control Nipah virus (NiV) disease: Treatment

Currently, there are no vaccines available against Nipah virus (NiV). Hence there are no licensed treatments available for Nipah virus (NiV) infection [38-72]. There is a need for novel therapeutic and vaccine strategies against Nipah and related viruses to limit future epidemics[38-72]. Treatment is limited to supportive care, including rest, hydration, and treatment of symptoms as they occur [38-72]. There are, however, immunotherapeutic treatments (monoclonal antibody therapies) that are currently under development and evaluation for treatment of Nipah virus (NiV) infections. One such monoclonal antibody, m102.4, has completed phase 1 clinical trials and has been used on a compassionate use basis [38-72]. Ribavirin and Acyclovir are two drugs used during the earlier outbreaks of Nipah virus (NiV) in Malaysia and Singapore [38-72]. Although Ribavirin reduced the death toll by 36% during the open label trial against Malaysian NiV outbreaks, subsequent studies in animal models failed to prove its efficacy. Favipiravir (T-705), a purine analogue inhibiting RNA-dependent RNA polymerase progressed to clinical trials for Ebola and various types of influenza antivirals have also shown efficacy against Nipah virus (NiV) in Syrian hamster animal models [38-72]. In addition, the antiviral treatment Remdesivir has been effective in non-human primates when given as post-exposure prophylaxis, and may be complementary to immunotherapeutic treatments [38-72]. The drug Ribavirin was used to treat a small number of patients in the initial Malaysian Nipah virus (NiV) outbreak, but its efficacy in people is unclear [38-72]. Based on the experience gained during the outbreak of Nipah virus (NiV) involving pig farms in 1999, routine and thorough cleaning and disinfection of pig farms with appropriate detergents may be effective in preventing infection [38-72]. The risk of international transmission via fruits or fruit products (such as raw date palm juice) contaminated with urine or saliva from infected fruit bats can be prevented by washing them thoroughly and peeling them before consumption. Fruit with signs of bat bites should be discarded [38-72]. During early stages of the illness, laboratory testing can be conducted using real time polymerase chain reaction (RT-PCR) from throat and nasal swabs, cerebrospinal fluid, urine, and blood [38-72]. Later in the course of illness and after recovery, testing for antibodies is conducted using an enzyme-linked immunosorbent assay (ELISA) [42-72]. In the absence of a vaccine, the only way to reduce or prevent infection in people is by raising awareness of the risk factors and educating people about the measures they can take to reduce exposure to the Nipah virus (NiV) [38-72].

South Asian and South East Asian countries should increase awareness of the Nipah virus (NiV) risk factors and educate their people on measures to reduce Nipah virus (NiV) exposure and risk of infection [38-72]. By applying the strategies listed in public health educational programmes should focus on reducing the following risk factors: bat-to-human transmission, animal-to-human transmission and human-to-human transmission [38-72]. Healthcare workers should be aware of this risk while caring for suspected or confirmed patients or handling specimens, and should strictly follow the universal standard infection prevention guidelines (i.e., wearing personal protective equipment, an N95 mask, goggles and a face shield) at all times [38-72].

1.12. Role of Cannabis sativa in controlling Nipah virus (NiV): Hemp

In recent years, hemp seed oil has gained remarkable popularity as a natural health supplement due to its perceived therapeutic properties and potential health benefits. Cannabis seed oil is nutritious [1-25]. The seeds are rich in essential fatty acids: the omega-3 fatty acids, alpha-linolenic acids (ALA) and the omega-6 fatty acid gamma-linolenic acid (GLA). The oil, derived from the seeds of the *Cannabis sativa* L. plant, is rich in essential fatty acids, antioxidants, and other bioactive compounds that have garnered considerable attention from consumers seeking alternative remedies [1-25]. As its usage continues to rise, a growing number of individuals are incorporating hemp seed oil into their daily routines alongside conventional pharmaceutical drugs to address various health concerns [1-25]. Hemp has historically been attractive for its top-quality fiber and edible oil [1-25]. The nutritional value of hemp is attracting special attention since hemp seed protein and oil is used in treatment of several human diseases [1-25].

However, many drugs that are available for the treatment of viral diseases possess serious side effects and drugs are active only in the acute phase of the disease [73-78]. However, these drug-related treatments remain mostly ineffective,

expensive, and long treatment, as well as causing side effects and leading to the development of resistance [73-78]. Therefore, there is an urgent need to search for cheaper, more effective, easily available. and less toxic chemotherapeutic agents for combating Nipah virus (NiV). Therefore, herbal medicines without any side effects play an important role in controlling human health disorders and infectious diseases [32-72, 73-78]. A broad spectrum of medicinal plants was used as traditional remedies for various infectious diseases. Indian traditional herbal medicine is very famous since India is leading in the medicinal systems of Ayurveda and Sidha [73-78]. Herbal medicines are becoming popular due to their perceived effectiveness, safety and affordability. Scientific studies have started providing evidence and support for the use of herbal medicines against viral infections [73-78].

Plant essential oils are valuable natural products, and used as a raw materials in aromatherapy, phytotherapy, perfumery, cosmetics, spices and nutrition [21, 73-76]. Essential oils are odorous and volatile compounds found in plants and are stored in special fragile secretary structures, such as glands, secretary hairs, secretary ducts, secretary cavities or resin ducts [73-78]. Aromatic plants produced a diversity of chemical constituents with the potential to inhibit viral replication [21, 73-76]. Essential oils have the ability to hamper the growth of a diverse range of pathogens because of the presence of natural compounds produced by the organs of plants [21, 73-76]. Importantly, the unique aroma and other bioactive properties of an essential oil depends on its chemical constituents [21, 73-78]. Essential oils have several biological properties such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, wound-healing and anti-cancer effects in *in vitro* and *in vivo* [21, 73-76]. Therefore, essential oils have been analyzed and described as good antiviral agents against respiratory tract viral infections, hence are excellent prospective candidate against dengue virus [26-37, 73-76]. Thus, essential oils and their constituents can hopefully be considered in near future for more clinical assessment and possible applications in controlling the viral pandemic [73-76]. Essential oils are among the plant-derived antiviral molecules that are being employed in phytomedicine, and are considered as prospective drug candidate against many viral pathogens [21, 73-76].

During the recent outbreak of Nipah virus (NiV), the local traditional healers in India used hemp oil as the mouth wash for controlling throat infections, head ache, vomiting and suggested all the patients for the consumption of hemp seeds and oil as the functional food [1-76]. The consumption of hemp seed and oil has drastically reduced the fever. Therefore, there is a growing evidence that hemp oil might inactivate the Nipah virus (NiV). Hemp plants produced a diversity of chemical constituents with the potential to inhibit viral replication [1-76]. However, clinical trials and scientific data supporting antiviral activity of Cannabis oil against Nipah virus (NiV) is lacking. Therefore, further research should focus on exploring the molecular mechanisms of essential oils particularly hemp oil and their individual chemical compounds against Nipah virus (NiV) is warranted. Local traditional healers in the rural part of India used Cannabis oil as the dengue mosquito, ***Aedes aegypti*** repellent [26-37]. Cannabis oil was used as dengue mosquito repellent for controlling **dengue viral fever**, bacterial infections and fungal diseases [26-37, 38-82]. Tribal people in the Indian Himalayan region used Cannabis as a home made herbal medicine for many diseases. During, Covid-19, the infusion of Cannabis flower with a morning cup of tea has saved the life of many people [1-37]. In India during the recent outbreak of Monkeypox, Cannabis oil was used for the external body applications as a preventive measures to control the monkeypox viral disease [1-82]. But the no of monkeypox cases in India were very low and preventive measures were adopted by the local traditional healers [77-82]. Hemp oil was also used for controlling the monkeypox disease [77-78]. However, the clinical trials and scientific evidence is lacking.

After years of legal restriction, research on hemp has recently demonstrated antiviral activities in silico, in vitro, and in vivo for cannabidiol (CBD), Λ9-tetrahydrocannabinol (Λ9-THC), Cannabidiolic acid (CBDA), Cannabigerolic acid (CBGA), and several other Cannabinoids against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), human immunodeficiency virus (HIV), and γ-herpes viruses [21, 38-92]. Mechanisms of action include inhibition of viral cell entry, inhibition of viral proteases, and stimulation of cellular innate immune responses [21, 70-92]. The anti-inflammatory properties of Cannabinoids are also under investigation for mitigating the cytokine storm of COVID-19 and controlling chronic inflammation in people living with HIV [21, 70-92]. Retrospective clinical studies supported antiviral activities of CBD, Λ9-THC, and cannabinoid mixtures as do some prospective clinical trials, but appropriately designed clinical trials of safety and efficacy of antiviral cannabinoids are urgently needed [21, 26-82].

With more than 400 active compounds that have therapeutic properties, Cannabis has been accepted widely as a medical treatment and for recreational purposes in several countries [1-82]. Cannabinoids have been shown to have activity against herpes viruses, which are DNA-type viruses, as well as the RNA-type viruses SARS-COV-2 and HIV/SIV [37-92]. The most studied antiviral cannabinoids to date have been CBD and Λ9-THC, which have been approved as drugs by the FDA for unrelated pharmacological activities [75-82]. These two cannabinoids function as antiviral agents through multiple mechanisms of action, some of which overlap such as inhibition of the SARS-CoV-2 main protease 3CL-pro and inhibition of ACE2, which is the human cell receptor for SARS-CoV-2. One of the study reported that Cannabidiol (CBD) inhibits infection of SARS-CoV-2 in cells and mice [65-82]. CBD and its metabolite 7-OH-CBD, but not THC or other

congeneric cannabinoids tested, potently block SARS-CoV-2 replication in lung epithelial cells. CBD and Λ 9-THC also have anti-inflammatory activities that can help suppress the proinflammatory effects of SARS-CoV-2 and HIV/SIV [70-92]. Other cannabinoids have recently been shown to have antiviral activities that include some unique mechanisms of action [75-82]. For example, CBDA and CBGA can prevent cell entry and infection by SARS-CoV-2 [1-25, 70-82]. Research on the antiviral activities of the more than 100 less abundant cannabinoids is just beginning, and there is potential to discover even more potent antiviral agents among these unique chemical structures. Importantly, clinical trials are needed to explore the safety and efficacy of antiviral cannabinoids [1-25, 68-82]. Based on the multiplicity of active cannabinoids acting by different mechanisms of action, combinations of cannabinoids should be explored for activity. Combination therapy has become the mainstay of HIV antiretroviral therapy due to the superior activity of drug mixtures that act by complementary mechanisms of action [1-25, 75-82].

Although most antiviral cannabinoids have shown individual activities in the low micromolar range, combinations of cannabinoids acting through complementary mechanisms of action might show synergistic effects that might be efficacious at lower concentrations [1-25, 75-82]. Studies of the antiviral activities of the more than 100 less abundant cannabinoids are still needed as are carefully designed clinical trials [1-25, 75-82]. Based on the preclinical evidence of antiviral activity as well as oral bioavailability and long history of safe human use of cannabinoids individually or as mixtures, multiple clinical studies of antiviral cannabinoid safety and efficacy are in progress worldwide using CBD and Λ9-THC [1-25, 75-82].

Another major problem is increasing trend of combining hemp seed oil with pharmaceutical medications has raised concerns among healthcare professionals and researchers about the possibility of drug-drug interactions [22]. Drug interactions occur when the effects of one medication are altered by the presence of another substance, potentially leading to adverse effects, diminished drug efficacy, delivery, metabolism, or other unexpected outcomes [22]. Given that hemp seed oil and pharmaceutical drugs can be metabolized and interact with common cellular pathways and enzymes, the potential for drug-drug interactions demands careful investigation [21, 22].

There is very limited in vivo investigation of the antiviral effect of these compounds. Despite the therapeutic effect, cannabis is an illicit drug that can be consumed in a harmful and abusive manner. Thus, preclinical and clinical trials in humans are very restricted due to the legalization of cannabis compounds in a few countries [1-25, 75-82]. Studies on the effects of the compound containing both CBD and THC are also limited. Besides, there is still a gap in revealing the exact mechanism of how cannabinoids and terpenes help in reducing replication of various viruses [75-82]. Moreover, due to the wide range of activities of Cannabinoids and terpenes, further in vivo and clinical studies are essential to determine the effective dose of the cannabis compounds to maximize their therapeutic benefits in viral infections [1-25, 75-82]. In short, we are still very far from the level of evidence required to consider cannabis compounds as a regimen for viral illnesses [1-25, 75-82].

2. Conclusion

Nipah virus (NiV) is an enveloped pleomorphic zoonotic virus known to cause encephalitis, with cases of acute respiratory distress turning fatal. Due to its high mortality in humans, the possibility of human-to-human transmission, and the lack of an available vaccine, the World Health Organization (WHO) has recognized Nipah virus (NiV) as a global health problem. During the recent outbreak of Nipah virus (NiV), the local traditional healers in India used hemp oil as the mouth wash for controlling throat infections, head ache, vomiting and suggested all the patients for the consumption of hemp seeds and oil as the functional food. The consumption of hemp seed and oil has drastically reduced the fever. Therefore, there is a growing evidence that hemp oil might inactivate the Nipah virus (NiV). Hemp plants produced a diversity of chemical constituents with the potential to inhibit viral replication. Antiviral activities of some of the most abundant cannabinoids have been documented in silico, in vitro, and in vivo. However, clinical trials supporting antiviral activity of Cannabis oil against Nipah virus (NiV) is lacking. Therefore, further research should focus on exploring the molecular mechanisms of essential oils particularly hemp oil and their individual chemical compounds against Nipah virus (NiV) is warranted.

About 400 chemical substances found in Cannabis plants are terpenes and phenolic compounds. Recently, scientists found that both compounds can reduce severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral infection by down regulating ACE2 transcript levels and by exerting anti-inflammatory properties. These compounds also act as the SARS-CoV-2 main protease inhibitors that block viral replication. Apart from cannabinoids, terpenes in Cannabis plants have also been widely explored for their antiviral properties. Hence, it is necessary to explore further the mechanisms of cannabinoids and terpenes in viral infection. Further research studies need to be conducted to provide sufficient scientific evidence on the antiviral effects of cannabis described in this review.

Compliance with ethical standards

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No conflict of interest to be disclosed.

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