Nipah virus (NiV) is a highly pathogenic zoonotic virus that has caused several outbreaks with high fatality rates in humans and animals, thus, requiring a “One Health” approach. No specific treatment or vaccine is available for NiV infection, making the development of effective antiviral agents against this virus a critical research priority. In recent years, significant efforts have been made to identify and develop antiviral agents targeting the various stages of NiV pathogenesis. This review comprehensively discusses current research on antiviral agents against NiV. The promising results obtained with several compounds, including repurposed drugs, nucleoside analogs, phytochemicals, and multi-target inhibitors, are also highlighted. Developing effective antiviral agents against NiV remains a major challenge; however, recent advances in understanding the mechanisms of NiV pathogenesis and identifying potential targets for antiviral agents have provided hope for the future. Further research is required to identify and optimize antiviral agents with broad-spectrum activity against NiV and other related viruses.

**Keywords:** antiviral agents, Nipah virus, paramyxovirus, zoonotic pathogen.

### Introduction

Nipah virus (NiV) is a zoonotic pathogen requiring a “One Health” approach in which multiple sectors coordinate and work together to protect global public health. NiV virus belongs to the genus *Henipavirus* within the family *Paramyxoviridae* [1]. The virus was first identified during an outbreak of respiratory and neurological diseases in pigs and, subsequently, encephalitis in humans in Malaysia and Singapore in 1998–1999 [2]. Although the outbreak was initially attributed to the Japanese B encephalitis virus (JEV) because of its association with infected pigs and JEV-specific immunoglobulin M in patient sera, further investigations have revealed that a paramyxovirus is the causative agent. The virus was named NiV, where it was first isolated [3]. NiV virus is closely related to Hendra virus (HeV), and its genome shares 80% sequence identity [4]. These two viruses were subsequently classified into the *Henipavirus* genus, which also includes other related viruses, such as the Cedar virus [5], Ghanian bat virus [6], and Mojiang virus [7].

Following the first report of a NiV outbreak in Malaysia in 1998, there have been sporadic reports of NiV outbreaks in various Asian countries, including Singapore, the Philippines, Bangladesh, and India [8] (Table-1). Given its potential for pandemics, high pathogenicity, and ability to infect a broad range of mammalian species, NiV is a significant public health concern. Between 1998 and 2018, over 600 human cases of NiV infection were reported, with mortality rates of 39.6% in Malaysia and 25%–100% in India and Bangladesh [9].

NiV virus is classified as a biosafety level 4 pathogen because of its high case fatality rate following infection and the lack of effective therapeutics or vaccines [10]. Despite the use of ribavirin as a first-line treatment for acute NiV encephalitis, no approved drugs are available for efficient use in humans and animals [11]. Nevertheless, unwanted pharmacokinetics and numerous side effects of synthetic compounds have driven specific interest in the use of compounds of natural origin, such as phytochemicals, to overcome these side effects. Therefore, there is a strong need to discover novel compounds with potential therapeutic value and fewer or no side effects from NiV treatment [12].

This review aims to comprehensively discuss the different synthetic and natural antiviral agents that have shown antiviral potential against NiV.

### Nipah Virus: An Overview

Nipah virus is a member of the *Henipavirus* genus belonging to the *Paramyxoviridae* family and *Orthoparamyxovirinae* subfamily [8]. The only other pathogenic and zoonotic member of this genus is HeV [13], which was discovered in Australia in the 1990s after the death of several individuals who had contact with infected equines [14]. *Henipavirus*
disease spillover in humans has only been observed in Southeast Asia [15]. However, with the expansion of surveillance efforts, these viruses have also been identified in Chiropteran sera in sub-Saharan Africa [16] and Brazil [17]. In a recent study of human and bat sera in Cameroon, approximately 3%–4% of human samples from individuals involved in butchering bat meat were seropositive [18].

Paramyxoviruses are pleomorphic enveloped viruses with a non-segmented single-stranded negative-sense RNA genome that codes for six structural and three accessory proteins [19]. The genome encodes nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), adhesion glycoprotein (G), and large protein (L) or RNA polymerase in the order of 3′-N-P-M-F-G-L-5′ [20]. Some Paramyxoviridae viruses encode cell attachment proteins that perform hemagglutination (H) and neuraminidase (N) functions. The G protein of NiV plays a role in the adsorption phase but does not display H functions. The P gene uses mRNA editing mechanisms and alternative open reading frames to produce the three non-structural proteins V, W, and C (Figure-1) [21].

The wide range of host susceptibilities to henipaviruses is a key biological trait that highlights their potential to cause diseases in various species [22]. Pteropus species of fruit bats, commonly known as flying foxes, are the primary natural hosts of NiV, which can cause diseases in humans, pigs, horses, dogs, and cats [23]. The loss of natural habitats caused by deforestation in various parts of Southeast Asia forces bat colonies to migrate to urban areas [24], leading to increased contact with humans and, thus, the risk of disease transmission [25]. Recently, NiV and Henipa-like viruses were detected in Pteropus bats in Asian and African countries [26]. The worldwide distribution of these bat species poses a threat to potential NiV pandemics [27] and requires more rigorous global surveillance.

The transmission of NiV from bats to humans occurs through the consumption of raw date palm juice or fruits contaminated with bat saliva or urine, as shown in a previous study by Luby et al. [28]. The virus remained viable for up to 3 days in some fruits and for at least 7 days in date, sap maintained at 22°C. In addition,

<table>
<thead>
<tr>
<th>Outbreak No.</th>
<th>Year/month</th>
<th>Country</th>
<th>Location</th>
<th>No. of cases</th>
<th>No. of deaths</th>
<th>Case fatality rate, %</th>
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<tbody>
<tr>
<td>1</td>
<td>September 1998-April 1999</td>
<td>Malaysia</td>
<td>Perak, Selangor, Negeri Sembilan states</td>
<td>265</td>
<td>105</td>
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<td>2</td>
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<td>3</td>
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<td>Meherpur</td>
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<td>January-April 2004</td>
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<td>74.6</td>
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<td>Kushtia, Naogaon, Natore, Pabna, Thakurgaon</td>
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<td>April 2007</td>
<td>India</td>
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<td>February-April 2008</td>
<td>Bangladesh</td>
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<td>Bangladesh</td>
<td>Gaibandha, Manikganj, Naogaon, Natore, Pabna,</td>
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<td>March-May 2014</td>
<td>Philippines</td>
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<td>9</td>
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<tr>
<td>18</td>
<td>January-February 2015</td>
<td>Bangladesh</td>
<td>Faridpur, Magura, Naogaon, Nilphamari, Porchoghor, Rajbari</td>
<td>9</td>
<td>6</td>
<td>66.7</td>
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<tr>
<td>19</td>
<td>May 2018</td>
<td>India</td>
<td>Kozhikode and Malappuram</td>
<td>18</td>
<td>17</td>
<td>94.4</td>
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<td>Total</td>
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<td>643</td>
<td>380</td>
<td>59</td>
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</table>

**Table-1:** Mortality and morbidity in humans after NiV outbreaks [8].
it can persist for approximately 18 h in the urine of the reservoir bats. The pathogen is relatively stable in the environment and can withstand temperatures up to 70°C for 1 h; however, it can be completely inactivated by heating at 100°C for longer than 15 min [29]. It can also be inactivated by common disinfectants such as sodium hypochlorite, soaps, and detergents [30].

**Clinical Symptoms and Pathogenesis of NiV**

Nipah virus is a highly virulent zoonotic virus that causes severe respiratory diseases and encephalitis in humans and animals [31]. Upon infection, NiV-infected individuals present with initial flu-like symptoms such as fever, headache, dizziness, and vomiting, which rapidly develop into severe encephalitis. The symptoms of NiV infection include reduced consciousness, seizures, areflexia, hypotonia, and myoclonic jerks [4]. Nipah virus pathogenesis is systemic and affects several organs, including the brain, lungs, heart, kidneys, and spleen (Figure-2) [32]. The virus has an incubation period of 4 days–2 months, and in some cases, a clinically silent period can occur, followed by recrudescence of the latent infection and late-onset encephalitis, which can develop months or even years after acute infection [4, 32].

Recent studies have demonstrated the persistence of NiV RNA in various bodily fluids and excretions, including the semen of surviving patients in India, highlighting the potential for prolonged viral shedding and disease transmission [33]. Similar observations have been reported for other viruses, such as Ebola [34] and Zika virus [35]. Survivors of NiV infection may experience long-term neurological sequelae, and late-onset encephalitis has been observed in some patients following a mild or asymptomatic initial infection [36]. In addition, relapse encephalitis has been reported in some cases, occurring several months to years after the initial symptomatic infection [37], including cases in which encephalitis occurred up to 11 years after the primary infection [38].

The pathogenesis of NiV begins with the oronasal route of entry into the host, wherein the virus infects epithelial cells along the respiratory tract [31]. Subsequently, viral antigens are detected at high concentrations in the respiratory and lymphoid tissues [39]. Subsequent secondary replication occurs in the endothelium, and the virus spreads to other body parts through initial viremia [40]. The viral glycoprotein (G protein) binds to the cellular receptors ephrin-B2 [41] and -B3 [42] to initiate NiV infection in host cells [43]. The virus then rapidly disseminates to different organs within the 1st week of infection, including the liver, heart, spleen, and kidneys [44]. Both ephrin-B2 and -B3 are expressed in various cell types, including endothelial cells, epithelial cells, and neurons. These cellular receptors are highly conserved across animal species, explaining the broad tissue and species tropism of NiV [45, 46].

**Figure-2:** Clinical signs and symptoms of NiV infection. Colored boxes indicate the prominence and severity of the infection.

- **Brain:** Fever, headache, dizziness, encephalitis, brainstem dysfunction, reduced consciousness, ataxia, coma, convulsions, epilepsy, hemorrhage, brain damage, aseptic meningitis
- **Lungs:** Acute respiratory difficulty in breathing
- **Spleen/Lymph Nodes:** Acute necrotizing lesions in periarterial sheaths, lymphoid depletion, syncytia with intranuclear inclusions in spleen and lymph nodes
- **KIDNEYS:** Focal glomerular fibrinoid necrosis, syncytia with intranuclear lesions
- **Liver:** Viral RNA detected in liver
- **Heart:** Tachycardia, endothelial cells, smooth muscle cell vasculitic lesions, inflammation
- **Sera/Blood:** Hypertension, thrombocytopenia
- **Throat/Nose:** Nausea, vomiting, fever, cough, abnormal doll’s eye reflex, viral RNA detected in throat and nose swabs
- **Urine:** Viral RNA detected in urine

Blue = primary site of severe pathology and causes of symptoms; Green = evidence of pathology distal from main sites; Orange = no pathology but evidence of viral RNA/antigen [32].
Nipah virus can also enter and infect the central nervous system (CNS) through the circulation of immune cells, specifically immature dendritic and monoeytic cells [47]. These immune cells, infected by NiV, have been observed to migrate across the in vitro blood-brain barrier and infect susceptible cells [48], similar to the observed pattern of neuronal infection and the presence of focal lesions in the brains of both NiV-infected humans and animals [49].

Several mammalian species have been experimentally infected with NiV, including hamsters, ferrets, cats, horses, pigs, and non-human primates, to develop potential therapeutics [50]. Hamsters infected with NiV or HeV develop acute fatal encephalitis with a pathology similar to that of humans [51], making them an important model for studying the pathogenesis and potential treatments [52]. Moreover, Pteropus fruit bats, the natural reservoirs of the virus, have been experimentally infected with NiV to study their susceptibility to infection, distribution, and pathogenesis [29]. Although no clinical signs were observed in flying foxes, this has piqued the scientific community’s interest in understanding fruit bat-NiV interactions and their ability to control NiV infections [53, 54].

Pigs, the amplifying host during the NiV outbreak in Malaysia, have also been used as a model for NiV infection [55]. Nipah virus was found to infect certain populations of swine lymphocytes and invade the CNS [55], resulting in viral shedding and a mortality rate of 10%–15% in infected animals [56]. Interestingly, the NiV Malaysia strain showed higher replication and clinical signs in pigs than the NiV Bangladeshi strain, as observed in a hamster model [57]. However, both strains showed similar pathogenicity in the ferret model, although more viral RNA was recovered from ferrets infected with NiV Bangladesh [58].

**Nipah Virus Antiviral Compounds**

**Ribavirin and chloroquine**

The first antiviral drug to be used against NiV was ribavirin, which was administered during the 1998 Malaysian outbreak. A limited non-randomized trial involving 140 NiV-infected patients demonstrated that ribavirin therapy reduces mortality associated with acute NiV encephalitis [59]. In vitro studies have also revealed the efficacy of ribavirin against HeV, with a more than 50-fold reduction in viral yield [60]. Moreover, a study using a hamster model for NiV infection showed that treatment with ribavirin delayed death from viral disease by 2 days, although it could not prevent death [10, 61].

Furthermore, in vitro studies have shown that chloroquine, an antimalarial drug, exhibits potent antiviral activity against HeV and NiV infections [62]. Considering these results, a combination of intravenous ribavirin and oral chloroquine was used to treat four individuals during the recent HeV outbreak in Queensland [10]. However, subsequent in vivo experiments showed that the ribavirin-chloroquine combination did not provide protection against viral spread. In addition, although ribavirin delayed death in NiV-infected hamsters, it had no significant effect on HeV-infected hamsters, and chloroquine was ineffective in protecting hamsters when administered individually or in combination with ribavirin [10].

**Remdesivir (GS-5734)**

Remdesivir (GS-5734) is a prodrug that acts as a nucleotide analog with a wide range of antiviral activities against filovirus, coronavirus, and paramyxovirus replication [63]. It is undergoing a Phase 2 clinical trial for the treatment of male Ebola virus disease survivors who continue to have viral RNA in their semen [64]. In addition, Remdesivir has been assessed in a randomized and controlled trial of the current Ebola virus outbreak in the Democratic Republic of the Congo [65].

In vitro experiments have shown that it can also inhibit NiV replication by more than four orders of magnitude in primary human lung microvascular endothelial cells [63]. Moreover, a study was conducted to evaluate the efficacy of remdesivir against NiV infection in African green monkeys (AGM), in which mild respiratory symptoms developed in two of four AGM treated with remdesivir, all of which developed severe respiratory symptoms, demonstrating that remdesivir is a promising antiviral drug against NiV [66]. Recently, the Food and Drug Administration approved the use of remdesivir to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and it has been authorized for emergency use in multiple countries, including Bangladesh, Singapore, Taiwan, India, Japan, and Australia [67].

**Favipiravir (T-705)**

Favipiravir (T-705; 6-flouro-3-hydroxy-2 pyrazinecarboxamine; [Avigan]) is a viral RNA-dependent RNA polymerase (RdRp) inhibitor originally developed by Toyama Chemical Company (Tokyo, Japan) [68] as an antiviral agent against influenza [69]. This drug has demonstrated efficacy against several RNA viruses, including Ebola, Lassa, and rabies [68]. Favipiravir is licensed in Japan for treating novel or re-emerging influenza and has undergone several Phase 3 clinical trials in the United States and Europe for use against influenza (www.clinicaltrials.gov) [70].

Completed Phase 2 clinical trials have suggested that favipiravir treatment may result in reduced mortality when administered to patients with moderate viral loads infected with Ebola virus [71]. Its antiviral activity against several viruses has been established both in vitro, including respiratory syncytial virus (RSV), measles virus, human metapneumovirus (hMPV), human parainfluenza virus 3, Newcastle
Defective interfering particles (DIP)

Defective interfering particles are viral particles containing incomplete viral genetic material that can interfere with the standard replication process while still possessing the necessary viral proteins for cellular entry [90]. Defective interfering particles have been observed in various RNA virus species, and recent technological advances have facilitated the exploration of the significance of DIPs in vitro and in vivo. In viral pathogenesis, DIPs contribute to viral interference, persistence, and immune stimulation [91]. Their ability to modulate virulence has stimulated interest in the therapeutic application of DIPs. Studies have shown that the accumulation of DIPs in vivo reduces disease severity [92] and their inclusion in vaccines enhances immunogenicity [93]. Several NiV DIP...
candidates have recently been demonstrated to reduce NiV titers by up to four logs \textit{in vitro} \cite{94}, reduce clinical signs, and protect hamsters from lethal NiV disease \cite{95}.

\textbf{In silico NiV inhibitors}

The use of \textit{in silico} methods to study molecular interactions (Figure-3) has proven valuable in the development of natural therapeutic ligands and receptor complexes \cite{96}. In particular, these methods have demonstrated their importance during the outbreak of COVID-19, a universal crisis caused by SARS-CoV-2, which emerged in Wuhan, China in 2019 \cite{97}. Since the onset of this pandemic, numerous research efforts have been dedicated to studying the different structures of the virus using molecular modeling to better understand the viral structures and develop preventive and therapeutic agents to combat SARS-CoV-2 \cite{98}.

Researchers specializing in \textit{in silico} studies have made significant contributions to the healthcare sector by examining the efficacy of candidate drugs against various targets of COVID-19 \cite{99}. Moreover, they analyzed the therapeutic potential of natural products and enhanced the efficiency of synthesized therapeutics, including antimicrobial peptides, and developed novel agents such as peptidomimetics to combat this life-threatening condition \cite{100}. These approaches are currently employed to identify prospective inhibitors of NiV, as detailed in the following sections.

\textbf{Synthetic NiV inhibitors}

To identify potential NiV inhibitors, researchers have turned to computational techniques that specifically focus on synthetic drugs and drug-like compounds. Computational researchers and chemi-informaticians have identified NiV-G as the primary target for inhibiting viral entry \cite{21}. Utilizing topological analysis of the chemical-protein interaction network, these researchers identified three novel leads for NiV inhibition: Nilotinib, deslanoside, and acetyldigitoxin. These compounds were identified by integrating the drug-target network, NiV-human interaction network, and human protein-protein interaction network \cite{101}. A separate study targeting NiV-G identified the top three ligands after molecular docking as MMV020537, MMV688888, and MMV019838. The dissociation constants of these ligands were calculated to be 0.03 nM, 2.18 nM, and 31.61 nM, respectively. Molecular dynamics (MD) study has confirmed that these compounds display stable binding modes at the protein’s active site \cite{102}.

The gold and platinum Asinex library, which contains 211620 drug-like compounds, was screened to identify potential NiV-G inhibitors. Molecular docking, density functional theory, and MD simulation studies were performed, leading to the identification of 5-(1,3-benzodioxol-5-yl)-2-[(3-fluorobenzyl)sulfanyl]-5,8-dihydropyrido[2,3-d]pyrimidine-4,7(1H,6H)-dione and 7,7-dimethyl-1-(4-methylphenyl)-3-(4-morpholinylcarbonyl)-7,8-dihydro-2,5(1H,H)-quinolinedione as potential candidates for the prevention and treatment of NiV-related diseases \cite{103}.

In addition to synthetic drugs and drug-like compounds, nucleoside analog inhibitors have been extensively explored as potential antiviral agents \cite{104}. Nucleoside analogs, chemically modified nucleosides, mimic endogenous nucleosides and block cellular division or viral replication by inhibiting DNA/RNA synthesis or blocking enzymes involved in nucleoside metabolism \cite{105}. The first antiviral analogs were developed in the late 1960s, and over 25 approved therapeutic nucleosides are currently used for the treatment of viral infections such as HIV/AIDS (tenofovir) \cite{106}, hepatitis B (lamivudine/entecavir) \cite{107}, hepatitis C (sofosbuvir) \cite{108}, and herpes infections (acyclovir) \cite{109}. Nucleoside analogs have also been explored as potential

\begin{figure}
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\includegraphics[width=\textwidth]{Figure-3.png}
\caption{General workflow for \textit{in silico} discovery of Nipah virus inhibitors \cite{96}.}
\end{figure}
inhibitors of NiV RdRp. Among these compounds, Galidesivir, AT-9010, and Norov-29 were identified as the top nucleoside analogs with the highest affinity for binding to RdRp. The binding free energies of these compounds, calculated using molecular mechanics/generalized born surface area, ranged from $-31.01 \pm 3.9$ to $-38.37 \pm 4.8$ kcal/mol, with Norov-29 ranking as the best candidate for a NiV RdRp inhibitor [110].

Natural source-derived NiV inhibitors

The significant pharmacokinetic properties and side effects associated with synthesized compounds (i.e., Ribavirin) have generated interest in exploring natural compounds for potential antiviral activities with fewer adverse effects. Two studies examined the antiviral potential of phytochemicals derived from medicinal plants against NiV-G to prevent viral entry. These studies identified the potential NiV-G ligands serpentinine [111] and neoandrographolide [112] as their top candidates.

Serpentinine, an alkaloid obtained from *Rauvolfia verticillata* (Lour.) Baill root, is known for their hypertensive effects (https://www.biocrick.com/Serpentinine-BCN5325.html) and anticancer potential through their interaction with poly (ADP-ribose) polymerase-1 [113]. Serpentinine was identified as the most potent antiviral agent against SARS-CoV-2 main protease and non-structural protein 16 among the 1916 compounds screened [114]. In contrast, neoandrographolide, a major antiviral component of *Andrographis alata* [115], exhibits antiviral activity against various viruses, including SARS-CoV-2 [116, 117], Zika virus [118], and herpes simplex virus-1 [119]. Neoandrographolide also possesses anti-inflammatory, anticancer, hepatoprotective, and antiradical properties [120].

In contrast to targeting a single viral enzyme, researchers have employed a multi-target drug discovery approach to identify phytochemicals that can modulate the effects of multiple targets. Multi-target drugs have been approved for clinical use, and complex diseases such as neurodegenerative diseases, cardiovascular diseases, and cancers are often treated with multidrug therapy or a combination of drugs. RASE0125 (17-O-Acetyl-nortetraphylline) and CARS0358 (NA) have been identified as distinct multi-target inhibitors of NiV-G, NiV-F, and NiV-N [12]. RASE0125 (17-O-Acetyl-nortetraphylline) and CARS 0358 are indole alkaloids derived from *Rauvolfia serpentina* and *Catharanthus roseus*, respectively. The previous study by Randhawa et al. [12] has shown that indole alkaloid derivatives can inhibit dengue and Zika infections by modulating the viral replication complex. However, these molecules have never been considered for in vitro and in vivo antiviral drug discovery.

Conclusion

The emergence of NiV as a deadly zoonotic pathogen has highlighted the urgent need for effective antiviral drugs. The availability of new technologies, such as high-throughput screening and structure-based drug design, has facilitated the discovery of novel compounds with potent antiviral activity. In this review, several promising antiviral agents against NiV are highlighted, including repurposed drugs, natural products, and synthetic compounds, targeting different stages of the viral life cycle.

Although some promising preclinical results have been reported, clinical trials are needed to evaluate the safety and efficacy of these compounds in humans and animals. Moreover, the emergence of new NiV strains and the potential for viral escape mutations highlight the need for continued efforts to discover and develop new antiviral agents. Given the zoonotic nature of NiV, it is also crucial to explore the potential of these compounds against other closely related viruses, such as the HeV, to develop broad-spectrum antiviral agents.

Developing effective antiviral drugs against the NiV remains a critical public health priority requiring a “One Health” approach. Continued efforts to discover and develop new agents in combination with other therapeutic approaches are essential for the fight against this deadly virus.

Authors’ Contributions

FLO: Conception and design of the study and drafted and revised the manuscript.

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Competing Interests

The author declares that he has no competing interests.

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