REVIEW ARTICLE
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Breaking the chains: Advancements in antiviral strategies to combat Nipah virus infections

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Abstract

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. Nipah 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 Nipah, where it was first isolated [3]. Nipah 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], Ghanaian 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].

Nipah 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 discusses 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*

Table-1: Mortality and morbidity in humans after NiV outbreaks [8].

Outbreak No.	Year/month	Country	Location	No. of cases	No. of deaths	Case fatality rate, %
1	September 1998-April 1999	Malaysia	Perak, Selangor, Negeri Sembilan states	265	105	39.6
2	March-1999	Singapore	Singapore	11	1	9
3	January-February 2001	India	Siliguri	66	45	68.2
4	April-May 2001	Bangladesh	Meherpur	13	9	69.2
5	January 2003	Bangladesh	Naogaon	12	8	66.7
6	January-April 2004	Bangladesh	Rajbari, Faridpur	67	50	74.6
7	January-March 2005	Bangladesh	Tangail	12	11	91.7
8	January-April 2007	Bangladesh	Kushtia, Naogaon, Natore, Pabna, Thakurgaon	18	9	50
9	April 2007	India	Nadia	5	5	100
10	February-April 2008	Bangladesh	Manikganj, Rajbari	11	9	81.8
11	January 2009	Bangladesh	Gaibandha, Nilphamari, Rangpur, Rajbari	4	1	25
12	February-March 2010	Bangladesh	Faridpur, Gopalganj, Kurigram, Rajbari	17	15	88.2
13	January-February 2011	Bangladesh	Comilla, Dinajpur, Faridpur, Lalmohirhat, Nilphamari,	44	40	90.9
14	January 2012	Bangladesh	Joypurhat	12	10	83.3
15	January-April 2013	Bangladesh	Gaibandha, Manikganj, Naogaon, Natore, Pabna,	24	21	87.5
16	January-February 2014	Bangladesh	13 districts	18	9	50
17	March-May 2014	Philippines	Philippines	17	9	52.9
18	January-February 2015	Bangladesh	Faridpur, Magura, Naogaon, Nilphamari, Ponchoghor, Rajbari	9	6	66.7
19	May 2018	India	Kozhikode and Malappuram	18	17	94.4
	Total			643	380	59

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

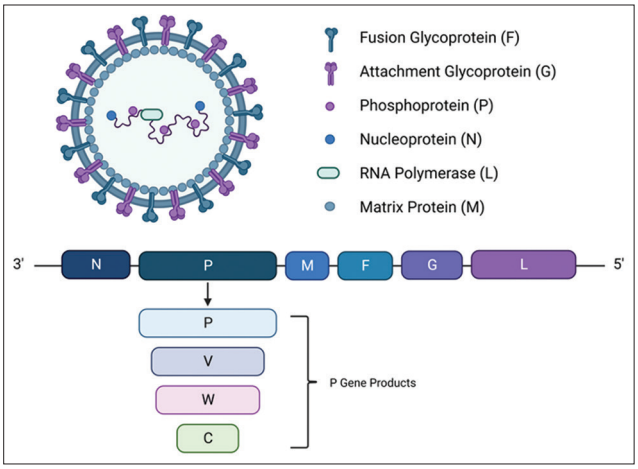

Figure-1: Genome organization and schematic structure of Nipah virus [21].

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,

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].

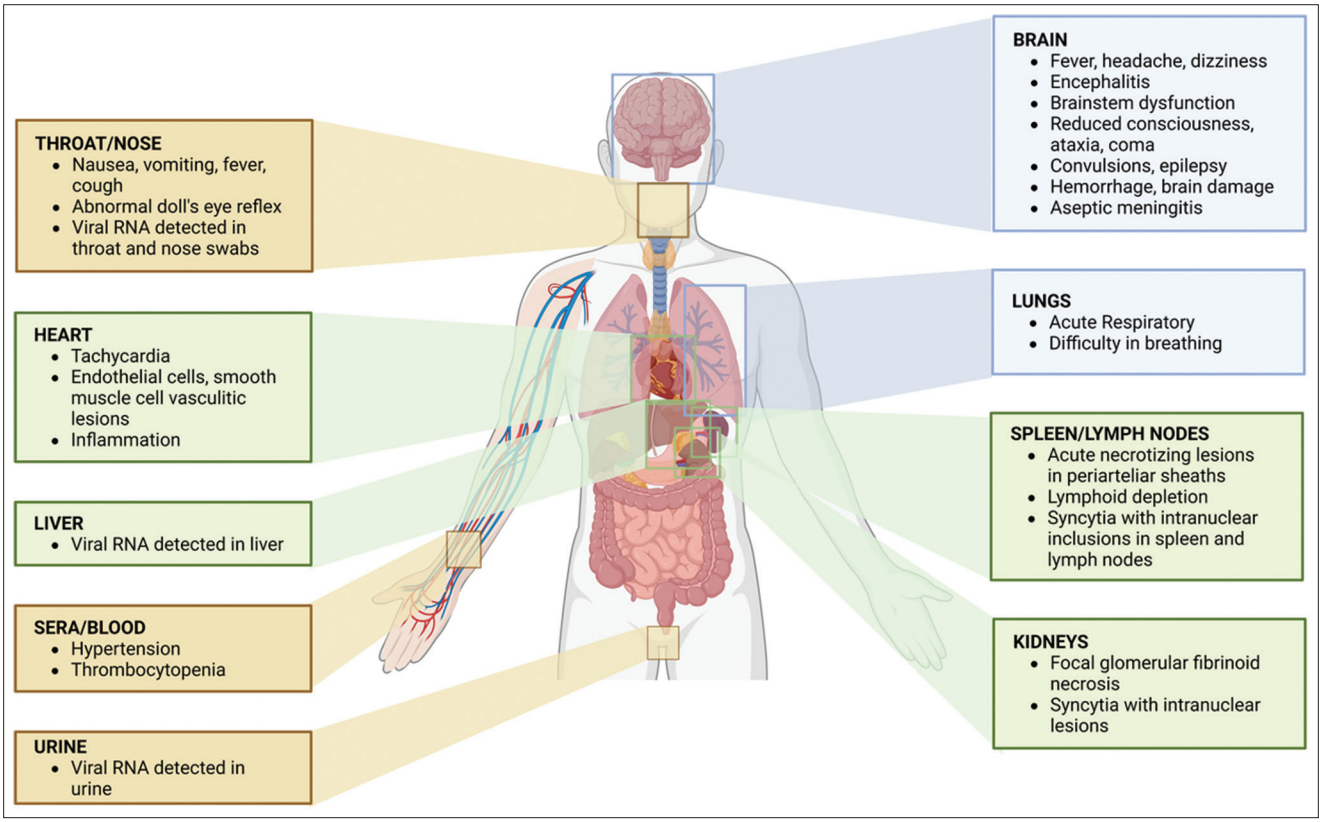

Figure-2: Clinical signs and symptoms of NiV infection. Colored boxes indicate the prominence and severity of the infection. Blue = primary site of severe pathology and causes of symptoms; Green = evidence of pathology distal from main sites; Orange = no pathology but evidence of viral RNA/antigen [32].

Nipah virus can also enter and infect the central nervous system (CNS) through the circulation of immune cells, specifically immature dendritic and monocytic 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]. Furthermore, 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

disease virus, and avian metapneumovirus, and *in vivo*, against hMPV in a hamster model [69, 72].

In addition, favipiravir has been found to possess potent antiviral activity against henipaviruses by inhibiting the replication and transcription of Nipah and Hendra at micromolar concentrations *in vitro*. In a Syrian hamster model, animals challenged with a lethal dose of NiV were fully protected by either twice-daily oral or once-daily subcutaneous administration of favipiravir for 14 days [73].

4′-Azidocytidine (R1479)

4′-Azidocytidine is a tri-isobutyl ester prodrug of balapiravir and is the main circulating form in the plasma [74]. It was first identified as a potent inhibitor of the hepatitis C virus (HCV) replicon *in vitro* in the mid-2000s, with an EC_{50} of 1.28 μM [75]. Further studies revealed that R1479 could also inhibit the RdRp activities of dengue virus with an EC_{50} of 1.9–11 μM [76] and RSV with an EC_{50} of 0.24 μM [77]. In addition, screening for compounds structurally similar to R1479 yielded potential inhibitors of both HCV [78] and RSV [74, 79].

Remarkably, R1479 has been shown to exhibit antiviral activity against members of the *Paramyxoviridae* family, regardless of the virus genus, suggesting that it may have broad-spectrum antiviral activity across both positive- and negative-sense RNA virus families. These findings have implications for developing 4′-modified nucleoside analogs as potential therapeutics for a wide range of viral infections [80].

β-D-4′-chloromethyl-2′-deoxy-2′-fluorocytidine (ALS-8112)

4′-chloromethyl-2′-deoxy-2′-fluorocytidine is the parent nucleoside of the orally bioavailable methyl propionate derivative lumicitabine (ALS-008176, JNJ-64041575). Janssen Biopharmaceuticals developed it for the treatment of RSV infection and has been evaluated in multiple clinical trials (www.clinicaltrials.gov) [74]. A recent *in vitro* study demonstrated that ALS-8112 can significantly reduce the infectious wild-type NiV yield by over six orders of magnitude in two human lung epithelial cell lines with no apparent cytotoxicity. However, cytotoxicity was observed at higher concentrations of ALS-8112 in primary cells and bone marrow progenitor cells, indicating the need for further evaluation of lumicitabine against NiV infection in relevant animal models [81].

Griffithsin (GRFT)

Griffithsin is a lectin with a high affinity for binding to high-mannose oligosaccharides [82]. It is a 121-amino-acid homodimeric protein originally derived from the marine red alga *Griffithsia* spp. GRFT has shown promising results in clinical trials as a topical microbicide to prevent HIV-1 infection [83]. It has also demonstrated broad-spectrum antiviral activity against various viruses such as HCV, severe acute respiratory syndrome coronavirus, and JEV [84]. Although its EC_{50} values are higher for coronaviruses, GRFT is a promising candidate for treating NiV infections. In addition, GRFT has low immunogenicity and excellent safety profiles, as demonstrated in multiple studies in animal models [82].

A recent study [85] investigated the efficacy of GRFT and its synthetic trimeric tandemer (3mG) against NiV *in vitro*. The results showed that 3 mG was more effective than GRFT against NiV, due to its enhanced ability to block syncytia formation induced by the glycoprotein of the virus. In addition, an oxidation-resistant variant of GRFT, known as Q-GRFT, was evaluated *in vivo* and offered significant protection against lethal NiV challenge in Syrian golden hamsters as a prophylactic measure [85].

Fusion-inhibitory lipopeptides

The entry of NiV into host cells is initiated by the fusion of viral and cellular membranes, which is mediated by the viral envelope glycoproteins G and F [21]. The F protein of NiV plays a key role in viral entry by facilitating the fusion of viral and cellular membranes [86]. Therefore, fusion-inhibitory peptides that block the formation of the 6-helix bundle, a key step in F-mediated viral entry, can be used to specifically target the initial step of NiV entry [87]. These peptides have been conjugated to lipid moieties through a flexible linker to create fusion-inhibitory peptide entry inhibitors that are highly effective against NiV infection in the CNS [88].

To improve the efficacy of lipopeptides as antiviral agents, a recent study designed a new set of lipopeptides that exhibited enhanced stability against protease degradation and improved efficacy both *in vitro* and *in vivo*. Lipopeptides have been designed to target peptide retention in the respiratory tract for prophylaxis against NiV infection. This study demonstrated that respiratory delivery of lipopeptides prevents lethal NiV infection in hamsters and non-human primates. This approach avoids systemic delivery in individuals who require only prophylaxis, thus increasing the safety of treatment and improving the effectiveness of the intervention [89].

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 *in vitro* [94], reduce clinical signs, and protect hamsters from lethal NiV disease [95].

***In silico* NiV inhibitors**

The use of *in silico* methods to study molecular interactions (Figure-3) has proven valuable in the development of natural therapeutic ligands and receptor complexes [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 [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 [98].

Researchers specializing in *in silico* studies have made significant contributions to the healthcare sector by examining the efficacy of candidate drugs against various targets of COVID-19 [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 [100]. These approaches are currently employed to identify prospective inhibitors of NiV, as detailed in the following sections.

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 [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 [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 [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 [103].

In addition to synthetic drugs and drug-like compounds, nucleoside analog inhibitors have been extensively explored as potential antiviral agents [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 [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) [106], hepatitis B (lamivudine/entecavir) [107], hepatitis C (sofosbuvir) [108], and herpes infections (acyclovir) [109]. Nucleoside analogs have also been explored as potential

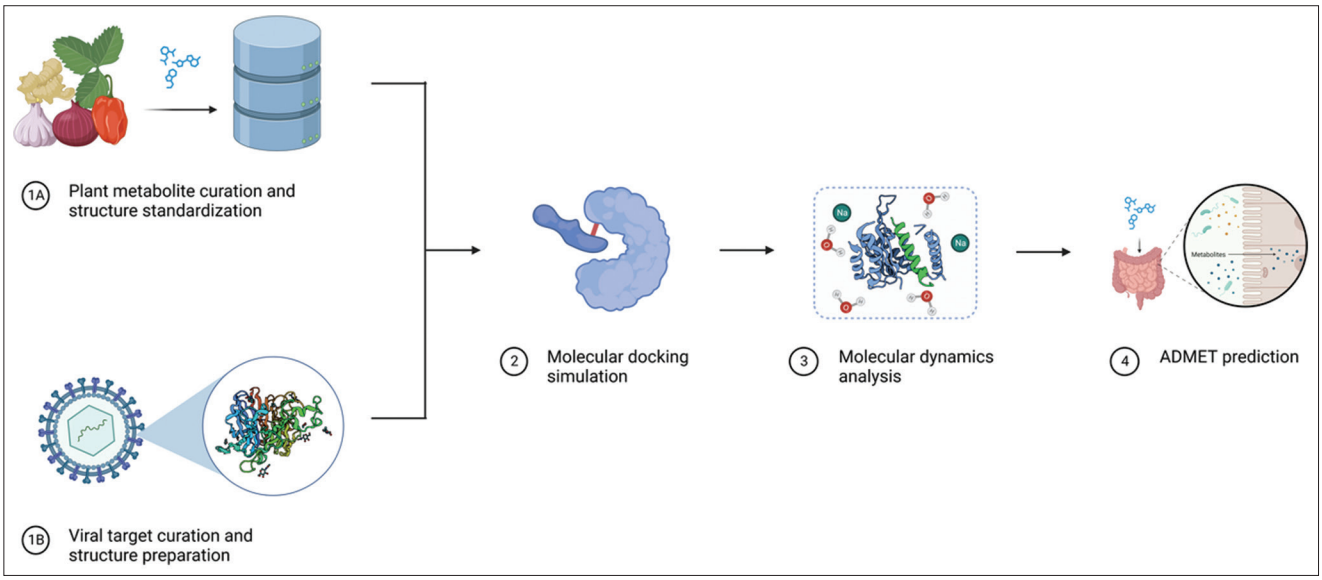

Figure-3: General workflow for *in silico* discovery of Nipah virus inhibitors [96].

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 ± 3.9 to −38.37 ± 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 synthetic 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-Acetylnortetraphyllicine) and CARS0358 (NA) have been identified as distinct multi-target inhibitors of NiV-G, NiV-F, and NiV-N [12]. RASE0125 (17-O-Acetylnortetraphyllicine) 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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