Exploring The Nipah Virus: Insights Into Pathogenesis And Therapeutic Approaches

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Abstract
Nipah virus (NiV), classified as a biosafety level-4 (BSL-4) pathogen, poses a significant challenge in the field of infectious diseases, as its capacity to move between animals and humans raises serious global health concerns. This analysis explores the historical progression of NiV outbreaks, examining its effects on communities globally. This study investigates the emergence and epidemiology of the virus, focussing on its transmission dynamics and the significant impact it has had on affected regions. The neurological sequelae observed in survivors highlight the critical need for thorough care strategies. The exploration of molecular targets for antiviral drug development and current vaccine initiatives is undertaken, in conjunction with computational strategies in drug design. Targeting Ephrin-B2 and Ephrin-B3 presents a promising approach in NiV therapeutics, providing specificity and the potential for broad-spectrum activity.

Keywords: *Nipah virus, BSL-4 pathogen, Antiviral drugs, Vaccines, computational approaches, molecular targets*

Introduction

Nipah virus (NiV) emerged in peninsular Malaysia in 1998, causing fatal encephalitis in humans and respiratory disease in pigs. NiV is closely related to the Hendra virus (HeV) founding Australia in 1994[1–7]. It is proposed that HeV and NiV represent a new genus within the family Paramyxoviridae[8–12]. NiV is notable in the realm of infectious diseases impacting both humans and animals since its emergence in the late 20th century. The capacity for transmission from animals to humans raises significant concerns. Environmental changes and human intrusion into wildlife habitats have resulted in increasingly frequent and severe outbreaks, positioning NiV as a significant global health issue. This review examines the history of NiV outbreaks, their effects on societies globally, the pressing need for care strategies, and the importance of continuous investigation and readiness to address this emerging infectious disease. From its enigmatic origins in the forests of Southeast Asia to its unforeseen occurrences in urban areas, NiV has presented considerable challenges for experts, health authorities, and the communities they serve.

Emergence and Epidemiology of NiV outbreaks

NiV is a high-lethality RNA virus from the family of Paramyxoviridae and genus Henipavirus (HeV)[8,9,13–15]. The polymerase gene (L) of NiV is anticipated to comprise 2244 amino acids, featuring six domains characteristic of non-segmented, negative stranded (NNS) RNA viruses, along with a distinctive GDNE motif. The NiV genome is 18,246 nucleotides long, the largest within its family, and shares sequence homology with HeV and other Paramyxovirinae members[3]. This pathogen is categorised as biosafety level-4 (BSL-4) because of its high pathogenicity and the absence of effective medications and vaccines. The transmission of the virus occurs mainly through direct contact with infected animals or their bodily fluids. The Pteropodidae family, particularly the Pteropus bat species, is recognised as the main reservoir for NiV.

NiV can be transmitted from bats to human, pigs, sick pigs, or contaminated tissue of pigs to humans[2,6,7,16–19]. Transmission may also take place between individuals and through the ingestion of tainted food. The fatality rate of NiV can vary between 40% and 75%, with transmission and mortality rates influenced by the specifics of the outbreak and the effectiveness of clinical management. From 1999 to 2023, Southeast Asian nations including Malaysia, Singapore, Bangladesh, India, and the Philippines have experienced outbreaks of NiV. In 1999, Malaysia faced 265 cases, leading to 105 deaths. In that year, Singapore documented 11 cases, resulting in one fatality. In 2001, Malaysia encountered 11 cases, all resulting in fatalities, highlighting the critical nature of the outbreak. In 2004, Bangladesh faced a severe outbreak, recording 45 cases and a case fatality rate of 75%. In 2008, India reported 5 cases, all of which resulted in fatalities, highlighting the deadly characteristics of the virus. In 2014, the Philippines encountered a significant challenge, recording 18 cases with a case fatality rate of 50%. In 2018, India faced another outbreak, recording 90 cases and a 90% case fatality rate, highlighting the persistent danger posed by NiV.

Finally in 2023, Bangladesh reported 11 cases resulting in 8 deaths and India reported 6 cases resulting in 2 deaths[20]. Figures 1a and 1b illustrate the annual data on NiV-infected cases from different regions around the

globe, along with the associated fatality rates. These episodes highlight the ongoing threat of NiV in the region, stressing the necessity for continuous investigation and readiness to address this emerging infectious disease. Survivors of NiV often face a range of neurological and cognitive difficulties, including encephalitis, muscle weakness, coordination problems, deficits in memory and attention, language and communication challenges, as well as behavioural and emotional variations such as mood swings and anxiety. Furthermore, there exists a potential for the onset of post-traumatic stress disorder, accompanied by manifestations like sleep disturbances and sensory deficits.

Effective management of these difficulties hinges on comprehensive rehabilitation and supportive care, involving physical therapy, occupational therapy, speech therapy and psychological support to aid survivors in navigating and adapting to these challenges[1,2,4–7,21–23].

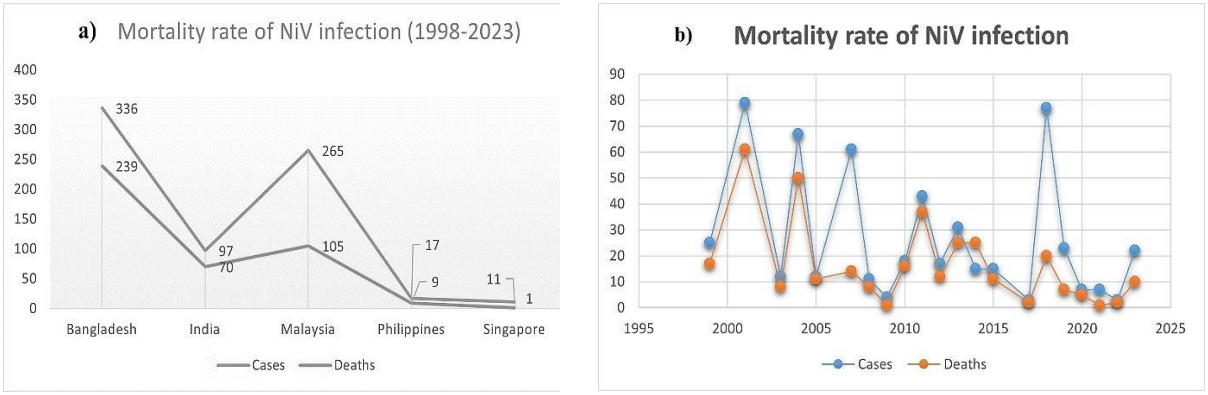

Figure 1: a) Mortality rate of NiV infection worldwide b) Mortality rate of NiV infection year wise.

Molecular Targets for Antiviral Drug Development

The Nipah virus poses a significant threat to human health, with outbreaks occurring sporadically in various regions since its initial identification. To combat this lethal pathogen, it is essential to comprehend its mode of infection and replication within host cells. A detailed analysis reveals several key protein targets essential for the various stages of the Nipah virus life cycle[8,11–13,15,20,24–33]. The glycoprotein (NiV-G)[29,34], situated on the surface of virus serves as a crucial facilitator of virus to infiltrate into host cells. Alongside NiV-G, the fusion protein (NiV-F) plays a pivotal role by mediating the fusion of the viral envelope with the host cell membrane, facilitating viral entry into the cell[22].

The matrix protein (NiV-M) plays a crucial role in the assembly and budding of new virus particles, which is vital for the replication cycle of the virus. The phosphoprotein (NiV-P) plays a crucial role in viral RNA synthesis and the regulation of virus gene expression, particularly in conjunction with NiV-M. The nucleoprotein (NiV-N) also establishes a protective complex with the viral RNA genome, which is essential for both viral replication and transcription. Additionally, the large protein or RNA polymerase protein (NiV-L) is crucial for viral RNA replication and transcription, serving a key function in the virus's replication cycle.

Targeting the inhibition of these crucial proteins offers a compelling approach to hinder the Nipah virus's capacity to infect and replicate in host cells. Furthermore, focussing on human protein receptors associated with NiV infection opens up new pathways for drug discovery and development. Ephrin-B2 and Ephrin-B3, which are cell surface receptors utilised by NiV for viral entry, can be inhibited to block viral infection. In a similar vein, focussing on importing alpha 3 (Imp3), which is employed by NiV to facilitate the transport of viral proteins and replication machinery into the host cell nucleus, can hinder virus replication and dissemination. Additionally, inhibiting Heparan sulphate proteoglycans (HSPG), utilised by NiV attachment the receptors present a viable strategy for preventing viral attachment and substituent infection[22]. Figure 2 lists out various protein targets for drug discovery for NiV infection.

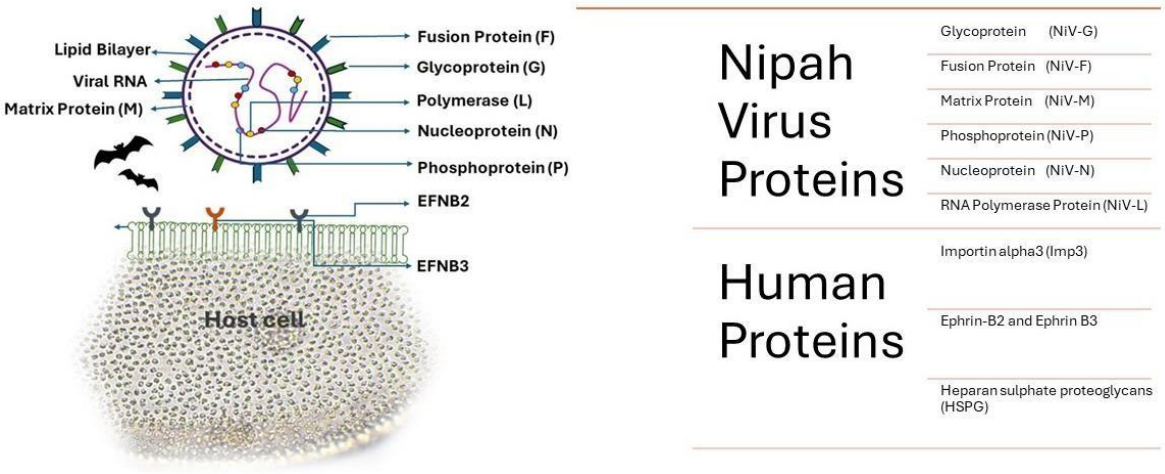

Figure 2: Protein Targets for drug discovery for NiV infection

NiV interacts with the Ephrin-B2 and Ephrin-B3 through its attachment glycoprotein, NiV-G[35–39]. The interaction interface between NiV and Ephrin B2 and Ephrin B3 is mainly facilitated by the G-H loop of the NiV-G protein, along with the adjacent residues on Ephrin B2 and Ephrin B3. The interaction patterns of Ephrin B2 and Ephrin B3 with NiV exhibit notable similarities, with only a minor variation in the relative orientation of the EFN domain. The interface comprises numerous hydrogen bonds, salt bridges, and hydrophobic interactions. Key residues Ephrin B2 and Ephrin B3, including Leu124 and Trp125, establish van der Waals interactions with specific residues on NiV-G, such as Phe458 and Trp504. The binding interface is highly conserved, suggesting a potential target for antiviral drug development[39]. Figure 3 provides a detailed examination of the NiV-G – EphrinB2 structure. (https://www.rcsb.org/structure/2VSM).

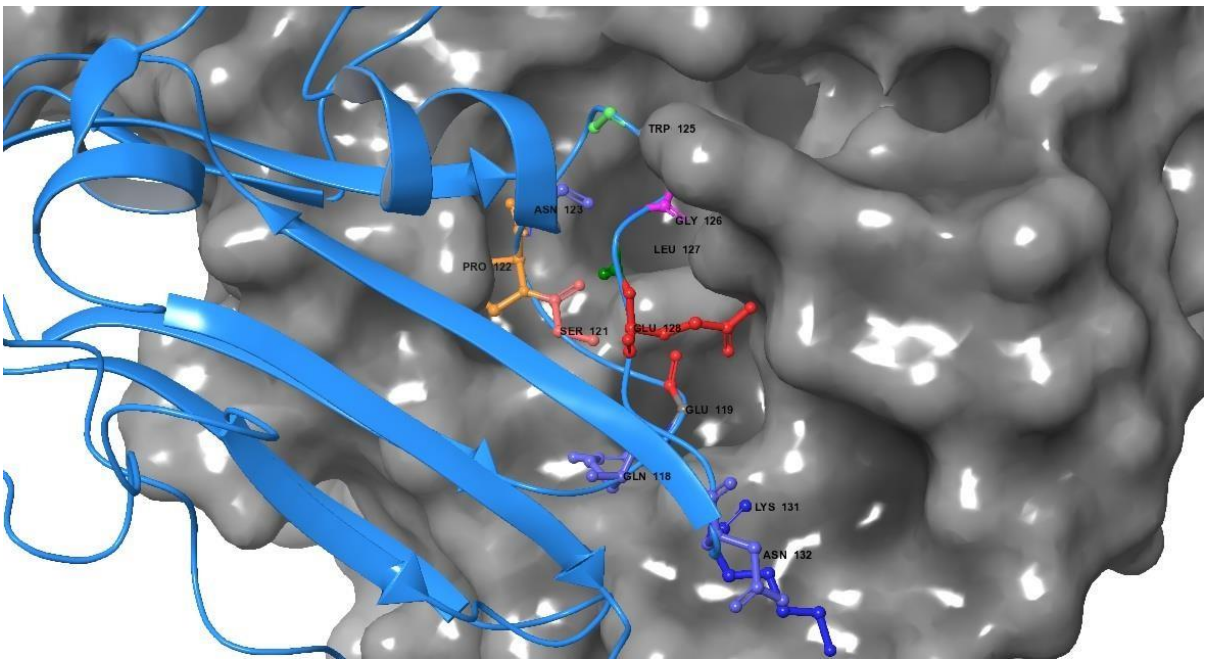

Figure 3: Crystal structure of Nipah virus attachment glycoprotein in complex with human cell surface receptor ephrinB2 (PDB ID: 2VSM). Blue ribbon-like structure represents the Ephrin-B2 and solid surface depicts NiV-G protein. Ephrin-B2 residues in the binding site are marked in the figure[40][Schrodinger Release 2024-2].

Vaccine Development Efforts and Progress

Three strains of NiV, namely NiV-Malaysia (NiVM), NiV Bangladesh (NiVB), and NiV India (NiVI), have been observed circulating in South Asian countries. NiV has disseminated to the African and Australian continents via reservoir bats. Several potential vaccine candidates have been developed and tested in animal model some

of these candidates have injured clinical trial research on therapeutic monoclonal antibodies (mAbs) has identified a few candidates capable of neutralising virus[9,11,44–48,25–27,33,40–43]. Nonetheless, advancements in the identification of possible antiviral medications have been constrained. NiV infection in humans is characterised by severe encephalitis and acute respiratory symptoms. Some patients may experience neurological symptoms, relapses, and late-onset encephalitis. A range of animal models such as golden hamsters, ferrets, African green monkeys, Guinea pigs, pigs, cats, and mice have been employed to investigate NiV pathology. The models have contributed to a deeper understanding of the clinical signs, symptoms, and pathogenesis associated with NiV infection. NiV outbreak have been recorded in Southeast Asian countries, including Malaysia, Singapore, Bangladesh, India and Philippines since 1999[49].

Antibodies derived from NiV41, such as 41-6, demonstrate cross-neutralizing activities against both NiV and HeV, whereas antibodies derived from NiV42 specifically neutralise NiV. Antibody 41-6 has demonstrated protective effects against the Nipah virus infection, and the cryo-EM structure of the NiV-RBP in complex with 41-6 has been elucidated, offering valuable insights into the neutralisation mechanism. Antibodies that have reverted to their germline form have been produced to investigate the impact of somatic hypermutation on antibody affinity and antigen recognition.

These findings contribute to the development of broad-spectrum vaccines against henipaviruses[50]. The investigation conducted by Mohamad Aljofan and colleagues assessed different cell lines for their effectiveness in replicating Nipah virus (NiV) and Hendra virus (HeV). The results indicated that Vero and BSR cells were the most favourable, whereas BAEC, MMEC, A549, and ECV304 cells exhibited reduced levels of virus infection. Ribavirin, known for its broad-spectrum antiviral properties, effectively inhibits NiV replication in all tested cell lines, with ECV304 and BAEC cells showing sensitivity. Nine novel antivirals were identified, each demonstrating varying levels of effectiveness across different cell lines. The results indicate that utilising Vero cells for screening might produce lead molecules with partial effectiveness, whereas employing additional cell lines could improve antiviral detection and provide a more accurate prediction of in vivo efficacy. The study underscores the urgent need for effective therapeutics again NiV and HeV infections, given the lack of available treatment or vaccines[51].

Several promising vaccine candidates have been created for NiV infection. The candidates under consideration comprise recombinant measles virus, recombinant vaccinia virus, rVSV (recombinant vesicular stomatitis virus), recombinant rabies virus, AAV (adeno-associated virus), ChAdOx1-vectored vaccine, Newcastle disease virus, and Canarypox virus-based vaccine. Among these candidates, the mRNA vaccine (mRNA-1215) has advanced to phase-1 clinical trials. Furthermore, various vaccine candidates, including subunit vaccines, viral vector-based vaccines, mRNA vaccines, and virus-like particle (VLP) vaccines, have demonstrated potential in preclinical studies and are currently undergoing evaluation in clinical trials. Continued research and the development efforts are necessary to advance the development of effective NiV vaccines and combat this deadly disease[49].

Computational Approaches in Drug Design and Discovery

Computer-aided drug design (CADD) plays a significant role in the discovery of drug molecules for the Nipah virus. CADD serves as an essential instrument for identifying NiV drug molecules, facilitating the efficient examination of extensive chemical databases, conducting virtual screenings of potential lead compounds, optimising these lead compounds, and integrating with experimental analyses. By utilising CADD, the team can expedite the drug discovery process and enhance the likelihood of identifying effective treatments for NiV. Diverse research groups globally have undertaken studies in computer-aided drug design, focussing specifically on the NiV-G and NiV-F proteins.

In their in-silico study, Maryam Ebrahimi and Mahdi Alijanianzadeh employed simulated annealing to assess interactions between potential inhibitors and the Nipah virus glycoprotein and receptors, successfully identifying promising antiviral compounds. The investigation utilised molecular docking simulation, pharmacophore modelling, and molecular dynamics to evaluate the stability and interactions of these complexes, emphasising the importance of multi-target drugs in the realm of drug discovery. Remedesivir (GS-5734) showed strong antiviral effects against the Malaysian and Bangladesh genotypes of the Nipah virus, leading to a significant decrease in viral replication. The study identified molecules including Pemirolast, Nitrofurantoin, and Eriodictyol as potential inhibitors for Ephrin B2 and B3, while Cepharanthine, Ergoloid, and Hypericin showed promise for targeting the NiV glycoprotein. Figure 4 illustrates the structures of Remedesivir, Pemirolast, Nitrofurantoin, Eriodictyol, Cepharanthine, and Hypericin.

Another study based on *in silico* study provided guidelines for synthetic chemists in developing new drugs for the treatment of Nipah virus using piperazine-substituted favipiravir[52]. Favipiravir shows strong inhibition of NiV glycoprotein in vitro. In silico studies were performed on derivatives featuring piperazine substitutions, evaluating their interactions with the virus and employing Density Functional Theory calculations to analyse their geometrical characteristics. Furthermore, an analysis of chemical reactivity descriptors has been utilised to gain insights into reactivity parameters. Molecular docking studies (PDB ID: 3D11) indicate that the designed

inhibitors demonstrate enhanced binding capabilities relative to the known molecule, highlighting their potential for Nipah virus treatment.

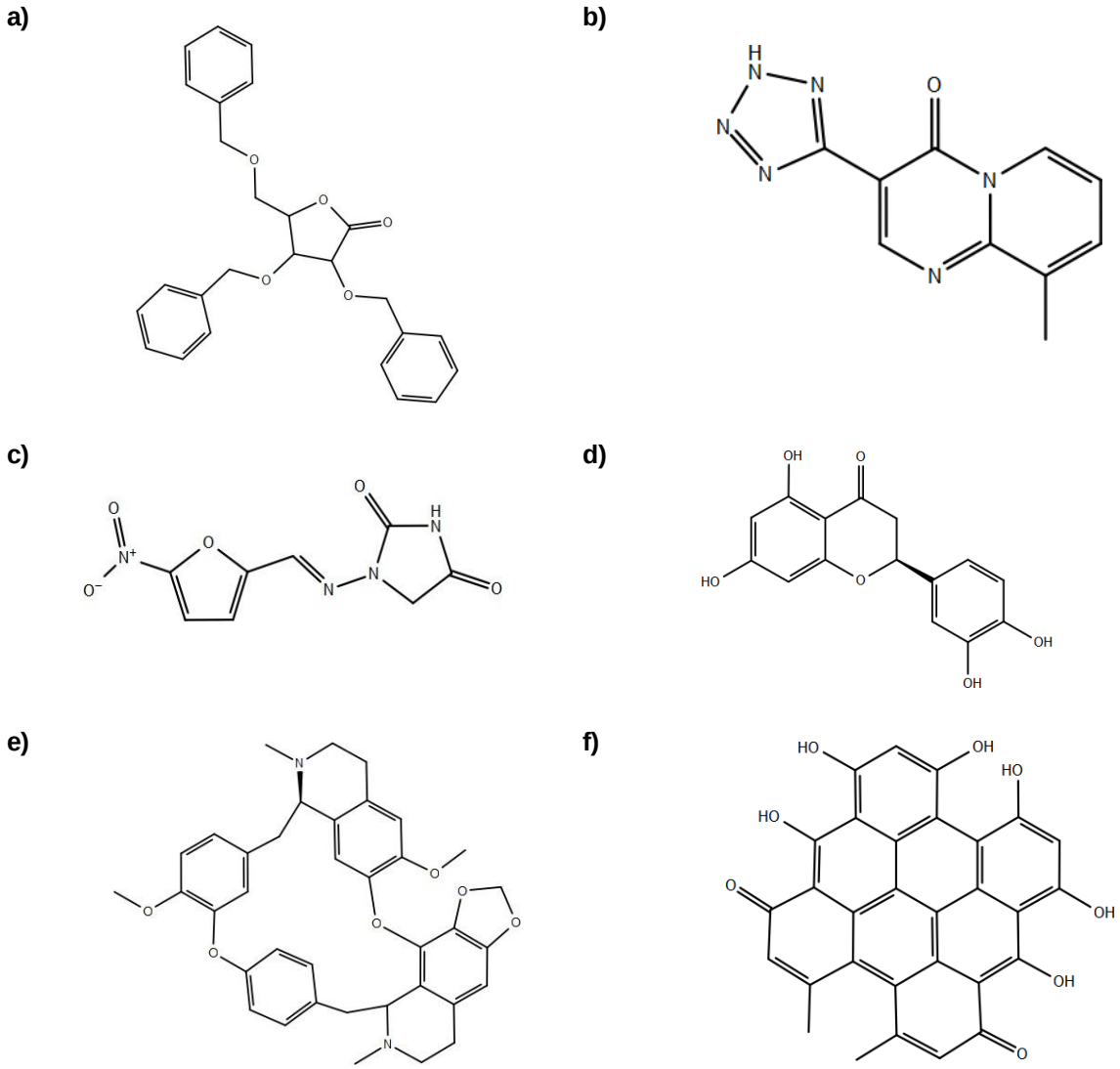

Figure 4: Structures of a) Remedesivir b) Pemirolast, c) Nitrofurantoin d) Eriodictyol e) Cepharanthine, f) Hypericin

In the study conducted by Akansha Rajput, Archit Kumar, and Manoj Kumar, the team aimed to explore potential anti-Nipah agents by compiling existing data from PubMed and patents. A QSAR-based regression predictor was subsequently developed to identify inhibitors. The findings culminated in the creation of a user-friendly interface called “anti-Nipah”, designed to assist researchers in predicting effective anti-Nipah agents[53]. The study utilised quinolone derivatives due to their previously demonstrated antiviral activity against various viruses and their structural similarity to other viral fusion inhibitors. Another study indicated that quinolone derivatives likely interact with the NiV fusion protein, inhibiting the fusion process between the virus and host cell membranes. The NiV fusion protein is essential for the virus's entry into host cells.

It undergoes confirmational changes upon binding to its cellular receptor, Ephrin-B2 or Ephrin-B3 leading to the fusion of the viral envelope with the host cell membrane[54]. This fusion process enables the virus to penetrate the host cell and commence the infection. The active compound under development as potential fusion inhibitors may disrupt the conformational changes of the NiV fusion protein. There is a possibility that they may attach to areas of the fusion protein, obstructing its correct folding or hindering its engagement with the cellular receptor.

This interference would hinder the fusion of the viral envelope with the host cell membrane, thereby blocking viral entry and subsequent infection[55]. Through computational analysis of compounds from the Pathogen Box, three potent inhibitors of NiV-G were identified which exhibits interaction with the residues Cys240 and Arg236

in the NiV-G receptor[56]. Small molecule inhibitors of cathepsin L-mediated cleavage and viral entry were also identified through a high throughput screening assay of 5000 molecules by their inhibitory effect on the cleavage of viral peptides from various viruses including SARS-CoV, EBOV, HeV and NiV. Among these 12 small molecules demonstrated broad-spectrum inhibition of viral peptide cleavage without affecting the cleavage of host-derived peptides[57].

A recent investigation indicates that β-D-4 chloromethyl-2´-deoxy-2´-fluorotidine (ALS-8112) probably functions as a nucleoside analogue targeting Nipah virus, thereby hindering its replication. Nucleoside analogues imitate natural nucleosides, interfering with viral replication by either halting RNA synthesis or causing errors in the viral genome.

ALS-8112's effectiveness in significantly reducing Nipha virus yield indicates its potential incorporation into the viral genome leading to inhibitor RNA synthesis and reduced replication[58].

In their in-silico study, Neeladri Sen and his colleagues explored potential treatments for NiV through computational methods. Partial models were constructed for five NiV proteins, and the post-fusion confirmation of the F protein was modelled for the first time, enhancing the structural coverage of the NiV proteome by 90%. Utilising molecular docking and dynamics simulations, the team identified 13 promising small molecule inhibitors aimed at the N, P, G, and M proteins, informed by their docking scores and binding poses. Furthermore, they developed peptide inhibitors aimed at the F, M, and G proteins to interfere with viral fusion, dimerisation, and the attachment to host cells. The study highlights the promise of both peptide and small molecule inhibitors in targeting specific NiV proteins with the need for further experimental validation to confirm their therapeutic potential[28].

In the context of NiV infection, inhibitors that target Ephrin-B2 and Ephrin-B3 work by obstructing the essential interaction between the viral G envelope glycoprotein and the receptors present on host cells.

By obstructing this interaction these inhibitors effectively prevent viral attachment and subsequent entry into host cells, thereby thwarting the progression of the infection[59].

The decision to focus on Ephrin-B2 and Ephrin-B3 as potential drug targets for NiV infection is supported by several advantages. Firstly, these inhibitors demonstrate a high level of specificity, targeting the precise molecular interactions that play a role in viral entry. Moreover, their potential for broad spectrum activity against NiV presents a promising avenue for addressing the virus across different strains. Furthermore, the possibility of a synergistic effect arises when these inhibitors are utilised in combination therapy regimens.

The interaction between NiV-G protein and Ephrin-B2 and Ephrin-B3 is dependent on amino acid residues. In the case of Ephrin-B2, specific residues including Trp125, Leu124, Pro122, and Tyr/Phe120 located in the G-H loop of the protein engage with hydrophobic pockets found within the central cavity of the NiV--G protein. Additionally, Glu533 in NiV-G establishes essential salt-bridges with Arg57 and Lys116 in Ephrin-B2, strengthening the interaction. In a similar manner, Ephrin-B3 interacts with the NiV-G protein via comparable residues such as Trp125, Leu124, Pro122, and Tyr/Phe120 located in its G-H loop. The interactions are additionally stabilised by Glu533 in NiV-G, which forms salt bridges with Arg57 and Lys116. In Ephrin-B3. These specific amino acid residues serve as key players in the binding affinity and stability of the NiV-G protein with Ephrin-B2 and Ephrin-B3, facilitating the intricate process of viral attachment and entry into host cells[34–38,59–61].

Conclusion

In conclusion, the Nipah virus (NiV), classified as a biosafety level-4 (BSL-4) pathogen, continues to represent a significant threat to global health. Its capacity to transfer from animals to humans leads to severe outbreaks and presents considerable challenges to public health systems across the globe. Since its emergence in the late 20th century, NiV has affected Southeast Asian nations, resulting in numerous fatalities and neurological complications. The epidemiology of NiV outbreaks highlights the critical necessity for continuous investigation and readiness to address this emerging infectious disease. The elevated fatality rate and diverse transmission dynamics of NiV highlight the intricate challenges associated with its management and control. Moreover, individuals who have survived NiV infection encounter persistent neurological and cognitive difficulties, underscoring the necessity for thorough rehabilitation and supportive care. Progress has been made in the development of antiviral drugs and vaccines against NiV, yet challenges persist in converting these advancements into effective clinical applications. Focussing on essential molecular elements involved in the viral life cycle, including glycoproteins and host cell receptors, presents promising opportunities for therapeutic strategies. Furthermore, computational methods in drug discovery and design have enabled the identification of new drug candidates and inhibitors, offering optimism for future treatment possibilities. Specifically, focussing on Ephrin-B2 and Ephrin-B3 as potential drug targets demonstrates potential in obstructing viral attachment and entry into host cells, thus hindering the advancement of NiV infection. The unique characteristics and potential wide-ranging effectiveness of these inhibitors underscore their significance in addressing NiV across different strains.

In summary, collaborative initiatives in investigation, vaccine innovation, and treatment strategies are crucial for addressing the persistent challenge presented by NiV and ensuring global health safety against new infectious threats.

Declaration of interests

The authors declare that they have no known competing financial interests that could have appeared to influence the work reported in this paper.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGpt to rewrite the manuscript for removing grammatical errors and reframing sentences. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Acknowledgements

We are thankful to Dr Pritesh Bhat and Schrodinger Software Team, Bangalore for their technical assistance using Schrodinger Software Package.

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