Community Acquired Infection

REVIEW

A mini review of antiviral compounds against dengue virus

Arif Nur Muhammad Ansori[1,2,3,*]

[1]Postgraduate School, Universitas Airlangga, Surabaya 60286, Indonesia
[2]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun 248007, India
[3]Virtual Research Center for Bioinformatics and Biotechnology, Surabaya 60493, Indonesia

ABSTRACT

This manuscript presents a comprehensive review of current research and potential future prospects in the development of antiviral compounds against the dengue virus (DENV). Despite ongoing research, dengue fever (DF), caused by DENV, remains a significant global public health problem, with no specific antiviral treatment available. In this study, an exhaustive survey of literature to provide a detailed overview of the promising antiviral agents, their modes of action, efficacy, and current status in clinical trials. Key areas of focus include small molecule inhibitors that target various stages of the DENV lifecycle, host-targeted agents, and broad-spectrum antivirals. In addition, the challenges associated with the development of effective antivirals, such as the viral diversity of four DENV serotypes and the phenomenon of antibody-dependent enhancement (ADE). This review also explores potential strategies for overcoming these challenges and emphasizes the need for a combination of approaches for effective therapy. In this age of rapidly emerging and re-emerging infectious diseases, a deep understanding of DENV biology and the development of effective antiviral compounds is essential. Our analysis will guide future studies and contribute to ongoing efforts to combat dengue fever.

Key words: antiviral compounds, dengue fever, dengue virus, medicine

INTRODUCTION

Dengue fever (DF), a mosquito-borne disease caused by the dengue virus (DENV), is a significant global health issue, with approximately 390 million infections occurring annually.[1–5] The virus is primarily transmitted by *Aedes aegypti* or *Aedes albopictus* mosquitoes and exists as four distinct serotypes: DENV1, DENV2, DENV3, and DENV4 (Figure 1).[6–10] Infection with one serotype provides lifelong immunity to that serotype but only short-term protection against the others. Furthermore, secondary infection with a different serotype may increase the risk of severe dengue due to a phenomenon known as antibody-dependent enhancement (ADE).[11–13]

Dengue disease presents a spectrum of clinical symptoms ranging from mild DF to severe dengue, encompassing dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[14–16] Despite its considerable impact on global health, no specific antiviral treatment is currently available for dengue. However, Dengvaxia was approved in the United States as the first vaccine approved for the prevention of dengue disease caused by all DENV serotypes (1, 2, 3 and 4). Management of the disease is primarily symptomatic, with fluid therapy used for severe cases.[17–19]

Development of effective antiviral therapy against DENV has been challenging due to factors such as viral diversity, the complexity of the dengue disease process,

***Corresponding Author:**
Arif Nur Muhammad Ansori, Postgraduate School, Universitas Airlangga, Jl. Airlangga 4-6, Surabaya 60286, Indonesia.
E-mail: ansori.anm@gmail.com; https://orcid.org/0000-0002-1279-3904
Received: 12 July 2023; Revised: 9 August 2023; Accepted: 3 April 2024
https://doi.org/10.54844/cai.2023.0425

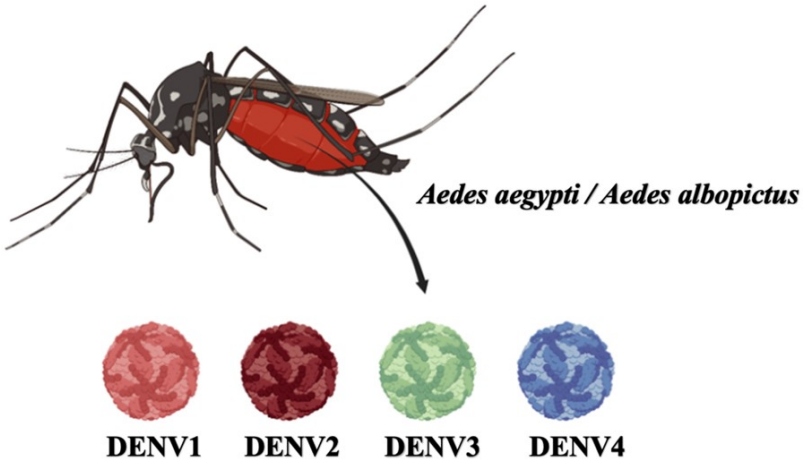

Figure 1. *Aedes aegypti* or *Aedes albopictus* mosquitoes and exists as four distinct serotypes (DENV1, DENV2, DENV3, and DENV4). DENV, dengue virus.

and the phenomenon of ADE.[20–22] However, a deeper understanding of the DENV lifecycle and the host-virus interactions has enabled the identification of several potential targets for antiviral intervention.[23–25] This manuscript aims to provide a comprehensive review of these potential antiviral compounds, discussing their mechanisms of action, efficacy, and current stages in development.

ANTIVIRAL STRATEGIES AND CANDIDATE COMPOUNDS

The development of antiviral compounds against DENV encompasses two primary strategies, targeting viral components and interfering with host factors essential for the viral lifecycle.

Viral-targeted agents

These agents primarily focus on crucial viral proteins such as the envelope (E) protein, nonstructural protein 3 (NS3) protease/helicase, and nonstructural protein 5 (NS5) RNA-dependent RNA polymerase (RdRp).[26,27]

Envelope protein inhibitors

The DENV E protein plays a crucial role in viral attachment and fusion to the host cell membrane during entry. Several compounds have demonstrated potential inhibitory activity against the E protein, hindering viral entry.[28,29]

NS3 protease/helicase inhibitors

The NS3 protein has protease and helicase activities, both of which are vital for viral replication. A small molecule inhibitor targeting the protease activity of NS3, has demonstrated significant antiviral activity *in vitro* and is currently under further investigation.[30,31]

NS5 RdRp inhibitors

The NS5 protein is essential for the replication of the DENV genome. Several nucleoside analogs have shown inhibitory effects on NS5's function, potentially hindering viral replication.[32]

Host-targeted agents

By targeting host factors utilized by DENV during its lifecycle, the likelihood of the development of drug-resistant viral strains may be reduced.[33]

Inhibitors of endocytosis

DENV enters host cells through receptor-mediated endocytosis. Certain compounds that inhibit this process, several compounds have been found to restrict DENV infection and are currently under investigation.[34,35]

Inhibitors of intracellular signal transduction

DENV infection activates various host cell signaling pathways. Some compounds inhibitors of specific signal transduction pathways, have shown promising results in reducing DENV infection.[36,37]

A range of antiviral compounds targeting either viral components or host factors required for DENV lifecycle have shown promise in preclinical studies. However, the translation of these findings into effective clinical therapies requires further research and testing.

CLINICAL TRIALS OF ANTIVIRAL COMPOUNDS AGAINST DENV

Several compounds have been examined for their potential efficacy, as following.

Balapiravir (R1626)

This is an orally bioavailable prodrug of a nucleoside analogue that was originally developed for the treatment of hepatitis C. It inhibits the RNA-dependent RNA polymerase (RdRp) of DENV. A randomized, double-blind, placebo-controlled trial of balapiravir in adult dengue patients was carried out but unfortunately, the trial found no significant difference in viremia or fever clearance time between the treatment and placebo groups.[38,39]

Celgosivir

This is an alpha-glucosidase I inhibitor that disrupts the folding and assembly of viral proteins. A phase 1b randomized controlled trial was carried out to assess the antiviral efficacy, safety, and pharmacokinetics of celgosivir in patients with DF. The results showed that while celgosivir was safe and well-tolerated, it did not significantly reduce viral load or fever burden in patients.[40,41]

Chloroquine

An old antimalarial drug, has been tested as an antiviral for dengue. A randomized, double-blind, placebo-controlled trial found no effect on the duration of dengue illness or viremia.[42,43]

Lovastatin

This is a cholesterol-lowering drug that has been tested for its antiviral properties against dengue. In a clinical trial, it was found to be safe but without significant clinical benefit.[44,45]

In addition to these, there are several other compounds that have shown promise in preclinical studies, and these may be the subject of future clinical trials.

CHALLENGES AND FUTURE DIRECTIONS IN ANTIVIRAL DEVELOPMENT

Challenges

Developing antivirals against DENV is complex due to several challenges.

Viral diversity

The existence of four DENV serotypes with distinct antigenic profiles complicates the development of a universally effective antiviral.[46]

ADE

Secondary infection with a different DENV serotype can potentially lead to severe dengue due to ADE, a process that complicates therapeutic interventions.[47]

Drug resistance

The rapid mutation rate of DENV raises concerns about the development of drug resistance, particularly for antivirals targeting viral proteins.[48]

Future directions

Overcoming these challenges will require innovative approaches.

Broad-spectrum antivirals

Antiviral compounds targeting conserved viral structures or host factors necessary for the virus lifecycle could potentially inhibit all DENV serotypes and other flaviviruses.[49]

Combination therapy

Using a combination of antiviral compounds targeting different aspects of the DENV lifecycle might help reduce the risk of drug resistance and potentially improve therapeutic outcomes.[50]

Antiviral peptides

Antiviral peptides, mimicking essential components of the immune response, may provide a novel route to combat DENV. These could be designed to inhibit viral entry, replication, or interfere with the host's immune response to the virus.[51]

The advancement in understanding of DENV biology and host-virus interactions, coupled with technological advancements in drug discovery and delivery, promises a hopeful future in the development of effective antiviral compounds against DENV.[52,53]

CONCLUSION

Dengue, caused by the DENV, is a global public health challenge with no specific antiviral treatments. Current strategies, including viral-targeted and host-targeted agents, show promise in preclinical studies. However, challenges like viral diversity, ADE, and drug resistance exist. Future directions include broad-spectrum antivirals, combination therapy, and antiviral peptides.

DECLARATIONS

Acknowledgement

We thank Jalan Tengah, Indonesia (www.jalantengah.site) for editing the manuscript.

Author contributions

Ansori ANM: Conceptualization, Data curation, Writing—Original draft, Writing—Review and Editing. The author has read and approved the final version of the manuscript.

Funding

This study funded by Postgraduate School, Universitas

Airlangga, Indonesia.

Ethics approval
Not applicable.

Conflict of interest
The author has no conflicts of interest to declare.

Data availability statement
No additional data.

REFERENCES

1. Gubler DJ. Dengue, Urbanization and Globalization: The Unholy Trinity of the 21(st) Century. *Trop Med Health*. 2011;39(4 Suppl):3–11.
2. Bhatt S, Gething PW, Brady OJ, *et al*. The global distribution and burden of dengue. *Nature*. 2013;496(7446):504–507.
3. Halstead SB. Dengue. *Lancet*. 2007;370(9599):1644–1652.
4. Katzelnick LC, Gresh L, Halloran ME, *et al*. Antibody-dependent enhancement of severe dengue disease in humans. *Science*. 2017;358(6365):929–932.
5. Perera R, Kuhn RJ. Structural proteomics of dengue virus. *Curr Opin Microbiol*. 2008;11(4):369–377.
6. Noble CG, Chen YL, Dong H, *et al*. Strategies for development of Dengue virus inhibitors. *Antiviral Res*. 2010;85(3):450–462.
7. Lim SP, Wang QY, Noble CG, *et al*. Ten years of dengue drug discovery: progress and prospects. *Antiviral Res*. 2013;100(2):500–519.
8. Yap LJ, Luo D, Chung KY, *et al*. Crystal structure of the Dengue virus methyltransferase bound to a 5'-capped octameric RNA. *PLoS One*. 2010;5(9):e12836.
9. Clyde K, Kyle JL, Harris E. Recent advances in deciphering viral and host determinants of Dengue virus replication and pathogenesis. *J Virol*. 2006;80(23):11418–11431.
10. Zhao R, Wang M, Cao J, *et al*. Flavivirus: From structure to therapeutics development. *Life*. 2021;11(7):615.
11. Colón-González FJ, Gibb R, Khan K, Watts A, Lowe R, Brady OJ. Projecting the future incidence and burden of dengue in Southeast Asia. *Nat Commun*. 2023;14(1):5439.
12. Huang Q, Gavor E, Tulsian NK, *et al*. Sivaraman J. Structural and functional characterization of *Aedes aegypti* pupal cuticle protein that controls Dengue virus infection. *Protein Sci*. 2023;32(10):e4761.
13. Akter R, Tasneem F, Das S, *et al*. Approaches of Dengue control: Vaccine strategies and future aspects. *Front Immunol*. 2024;15:1362780.
14. Obi JO, Gutiérrez-Barbosa H, Chua JV, Deredge DJ. Current trends and limitations in Dengue antiviral research. *Trop Med Infect Dis*. 2021;6(4):180.
15. Klema VJ, Ye M, Hindupur A, *et al*. Dengue virus nonstructural protein 5 (NS5) assembles into a dimer with a unique methyltransferase and polymerase interface. *PLoS Pathog*. 2016;12(2):e1005451.
16. Murugesan A, Manoharan M. Dengue virus. *Emerging and Reemerging Viral Pathogens*. 2020:281–359.
17. Mukhopadhyay S, Kuhn RJ, Rossmann MG. A structural perspective of the Flavivirus life cycle. *Nat Rev Microbiol*. 2005;3(1):13–22.
18. Screaton G, Mongkolsapaya J. Which Dengue vaccine approach is the most promising, and should we be concerned about enhanced disease after vaccination? The challenges of a Dengue vaccine. *Cold Spring Harb Perspect Biol*. 2018;10(6):a029520.
19. Dejnirattisai W, Jumnainsong A, Onsirisakul N. Cross-reacting antibodies enhance dengue virus infection in humans. *Science*. 2010;328(5979):745–748.
20. Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a Dengue virus vaccine. *Nat Rev Microbiol*. 2007;5(7):518–528.
21. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. *Nat Rev Immunol*. 2011;11(8):532–543.
22. Kuhn RJ, Zhang W, Rossmann MG, *et al*. Structure of Dengue virus: Implications for flavivirus organization, maturation, and fusion. *Cell*. 2002;108(5):717–725.
23. Sampath A, Padmanabhan R. Molecular targets for Flavivirus drug discovery. *Antiviral Res*. 2009;81(1):6–15.
24. Lin K, Gallay P. Curing a viral infection by targeting the host: The example of cyclophilin inhibitors. *Antiviral Res*. 2013;99(1):68–77.
25. Noble CG, Shi PY. Structural biology of dengue virus enzymes: Towards rational design of therapeutics. *Antiviral Res*. 2012;96(2):115–126.
26. Patkar CG, Kuhn RJ. Yellow Fever Virus NS3 plays an essential role in virus assembly independent of its known enzymatic functions. *J Virol*. 2008;82(7):3342–3352.
27. Yin Z, Chen YL, Schul W. An adenosine nucleoside inhibitor of Dengue virus. *Proc Natl Acad Sci USA*. 2009;106(48):20435–20439.
28. Lescar J, Luo D, Xu T, *et al*. Towards the design of antiviral inhibitors against flaviviruses: the case for the multifunctional NS3 protein from Dengue virus as a target. *Antiviral Res*. 2008;80(2):94–101.
29. Mastrangelo E, Pezzullo M, De Burghgraeve T, *et al*. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *J Antimicrob Chemother*. 2012;67(8):1884–1894.
30. Gu B, Mason P, Wang L, *et al*. Antiviral profiles of novel iminocyclitol compounds against bovine viral diarrhea virus, West Nile virus, dengue virus and hepatitis B virus. *Antivir Chem Chemother*. 2007;18(1):49–59.
31. Falgout B, Pethel M, Zhang YM, Lai CJ. Both nonstructural proteins NS2B and NS3 are required for the proteolytic processing of Dengue virus nonstructural proteins. *J Virol*. 1991;65(5):2467–2475.
32. Chan JF, Yip CC, Tsang JO, *et al*. Differential cell line susceptibility to the emerging Zika virus: implications for disease pathogenesis, non-vector-borne human transmission and animal reservoirs. *Emerg Microbes Infect*. 2016;5(8):e93.
33. De Clercq E. Antiviral drugs in current clinical use. *J Clin Virol*. 2004;30(2):115–133.
34. Kaur P, Thiruchelvan M, Lee RC, *et al*. Inhibition of chikungunya virus replication by harringtonine, a novel antiviral that suppresses viral protein expression. *Antimicrob Agents Chemother*. 2013;57(1):155–167.
35. Ng CY, Gu F, Phong WY, *et al*. Construction and characterization of a stable subgenomic Dengue virus type 2 replicon system for antiviral compound and siRNA testing. *Antiviral Res*. 2007;76(3):222–231.
36. Chen YL, Yin Z, Lakshminarayana SB, *et al*. Inhibition of Dengue virus by an ester prodrug of an adenosine analog. *Antimicrob Agents Chemother*. 2010;54(8):3255–3261.
37. Wu SF, Lee CJ, Liao CL, Dwek RA, Zitzmann N, Lin YL. Antiviral effects of an iminosugar derivative on Flavivirus infections. *J Virol*. 2002;76(8):3596–3604.
38. Noble CG, Seh CC, Chao AT, Shi PY. Ligand-bound structures of the Dengue virus protease reveal the active conformation. *J Virol*. 2012;86(1):438–446.
39. Nguyen NM, Tran CN, Phung LK. A randomized, double-blind placebo controlled trial of balapiravir, a polymerase inhibitor, in adult dengue patients. *J Infect Dis*. 2013;207(9):1442–1450.
40. Tomlinson SM, Watowich SJ. Use of parallel validation high-throughput screens to reduce false positives and identify novel Dengue NS2B-NS3 protease inhibitors. *Antiviral Res*. 2012;93(2):245–252.
41. Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ. Update on Dengue: epidemiology, virus evolution, antiviral drugs, and vaccine development. *Curr Infect Dis Rep*. 2010;12(3):157–164.
42. Samrat SK, Xu J, Li Z, Zhou J, Li H. Antiviral Agents against Flavivirus Protease: Prospect and Future Direction. *Pathogens*. 2022;11(3):293.
43. Lee MF, Anasir MI, Poh CL. Development of novel antiviral peptides against dengue serotypes 1–4. *Virology*. 2023;580:10–27.
44. Sreekanth GP. Perspectives on the current antiviral developments towards RNA-dependent RNA polymerase (RdRp) and

methyltransferase (MTase) domains of dengue virus non-structural protein 5 (DENV-NS5). *Eur J Med Chem*. 2023;256:115416.

45. Brand YM, Roa-Linares V, Santiago-Dugarte C, *et al*. A new host-targeted antiviral cyclolignan (SAU-22.107) for Dengue virus infection in cell cultures. Potential action mechanisms based on cell imaging. *Virus Res*. 2023;323:198995.
46. Thisyakorn U, Thisyakorn C. Latest developments and future directions in dengue vaccines. *Ther Adv Vaccines*. 2014;2(1):3–9.
47. Lee MF, Wu YS, Poh CL. Molecular mechanisms of antiviral agents against Dengue virus. *Viruses*. 2023;15(3):705.
48. Low JGH, Ooi EE, Vasudevan SG. Current status of Dengue therapeutics research and development. *J Infect Dis*. 2017;215(suppl_2):S96–S102.
49. Goethals O, Kaptein SJF, Kesteleyn B. Blocking NS3-NS4B interaction inhibits dengue virus in non-human primates. *Nature*. 2023;615(7953):678–686.
50. Hu M, Li WF, Wu T. Identification of an arylnaphthalene lignan derivative as an inhibitor against Dengue virus serotypes 1 to 4 (DENV-1 to -4) Using a newly developed DENV-3 infectious clone and replicon. *Microbiol Spectr*. 2023;11(4):e0042323.
51. Pintado Silva J, Fernandez-Sesma A. Challenges on the development of a Dengue vaccine: a comprehensive review of the state of the art. *J Gen Virol*. 2023;104(3):001831.
52. Lim SP. Dengue drug discovery: Progress, challenges and outlook. *Antiviral Res*. 2019;163:156–178.
53. Ansori ANM, Fadholly A, Proboningrat A, *et al*. Novel antiviral investigation of Annona squamosa leaf extract against the dengue virus type-2: *In vitro* study. *Pharmacogn J*. 2021;13(2):456–462.