

REVIEW

A mini review of antiviral compounds against dengue virus

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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,

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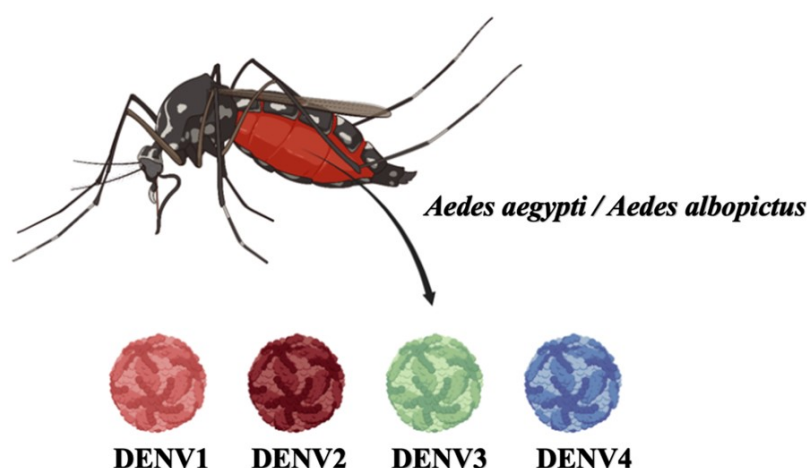


Figure 1. *Aedes aegypti* or *Aedes albopictus* mosquitoes and exists as four distinct serotypes (DENV1, DENV2, DENV3, and DENV4). DENV, dengue virus.

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

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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.

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Conflict of interest

The author has no conflicts of interest to declare.

Data availability statement

No additional data.

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