“A Review in the Field of Anti-viral Treatment for Dengue Virus Infection”

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Declaration

I have completed this project report independently as part of the requirements for obtaining a Bachelor of Pharmacy (B.Pharm) degree at Daffodil International University. This work was conducted under the guidance of Ms. Aklima Akter, Assistant Professor, Department of Pharmacy, Faculty of Allied Health Sciences. I confirm that I am the sole author of this work and that neither this project nor any part of it has been previously submitted to any other university for a Bachelor's or other degree.

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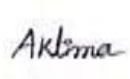

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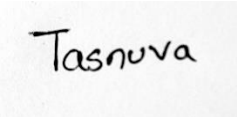

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Abstract

Each year, dengue virus infection imposes a significant global health burden, with approximately 390 million cases of dengue fever and thousands of reported annually, affecting millions of people who exhibit dengue virus symptoms (Tully & Griffiths, 2021). Despite extensive research, no specific antiviral treatment is currently approved for dengue virus infection. This review offers a comprehensive overview of the current landscape of antiviral medications for dengue virus infection, focusing on approved drugs and investigational therapies.

The review delves into each treatment's mechanisms of action, efficacy, safety profiles, and limitations, including small molecule inhibitors, immunomodulators, and therapeutic antibodies. Furthermore, emerging strategies such as host-targeted therapies and combination regimens are explored to enhance treatment effectiveness and mitigate the risk of drug resistance.

In conclusion, the article discusses the challenges and future directions in developing effective antiviral therapies against dengue virus infection, underscoring the importance of sustained research efforts to address this pressing unmet medical need.

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1. Introduction

Dengue virus infections have become a significant concern in recent years, with the virus being transmitted by Aedes mosquitos and causing dengue fever, a tropical disease characterized by symptoms like high fever, headaches, vomiting, muscle and joint pain, and rash. Severe cases can lead to complications like hemorrhagic fever or shock syndrome, posing a serious health risk. The virus has four serotypes, and infection with one type provides immunity to that specific serotype but only short-term immunity to others, increasing the risk of severe outcomes with subsequent infections.

Preventing dengue infections involves mosquito control measures and vaccination. However, currently available vaccines like Dengvaxia have limitations, and no specific antiviral treatment is approved for dengue fever. Treatment mainly focuses on symptom management and supportive care, with various small-molecule anti-DENV drugs like chloroquine and celgosivir undergoing clinical trials to assess their efficacy and safety. Overall, dengue fever remains a significant public health concern, and there is a need for continued research and development efforts to address this global health challenge. (Byrnes et al., 2020).

1.1 Life Cycle of Dengue Virus

When an infected Aedes mosquito bites a human, the virus is transmitted. While DENV can proliferate in various tissues and organs in the body, it infects D.C, macrophages for infection. DENV life cycle comprises several stages. First, they enter the body, replicate inside it, and release further. These stages are interconnected, starting with the attachment of DENV virus particles to host cells using the surface protein.

Domain II protein of the Dengue virus is mainly responsible for the Dengue virus entering into a host cell. Alternatively, DENV can directly enter host cells through membrane fusion between the virus and the host cell. Domain III, present in the Dengue virus E protein, is responsible for the conformational change and further responsible for the viral release into cytoplasm.

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Once released, the viral RNA is translated into a polyprotein within the host cytoplasm, which is then cleaved by both viral and host proteases to generate structural and non-structural proteins. Non-structural proteins play a crucial role in viral replication by mediating further rounds of transcription, leading to the synthesis of additional viral genomes and proteins.

The assembly of viruses occurs in the endoplasmic reticulum (ER) and undergo further processing in the trans-Golgi network (TGN), and is cleaved by host furin proteases to produce mature DENV particles. These particles are exocytosed from host cells upon maturation, completing the DENV life cycle. (Juliet et al., 2021).

1.2 Pathophysiology of dengue fever

Dengue fever is transmitted by female Aedes aegypti mosquitoes, which carry the flavivirus responsible for the disease. After being bitten by an infected mosquito, the virus can remain dormant in the body for three to fourteen days before symptoms appear. Early symptoms of dengue fever include fever, headache, rash, nausea, and joint and muscle pain.

Classic dengue fever typically lasts for about five to seven days, during which the body temperature may rise to 39 to 40 degrees Celsius. At this stage, the virus may enter the peripheral bloodstream. Without proper treatment, the virus can cause damage to lymph nodes and blood vessels, leading to dengue hemorrhagic fever (DHF). DHF is characterized by symptoms such as bleeding from the gums, nose, or under the skin, as well as difficulty breathing, which can progress to dengue shock syndrome (DSS) if severe and untreated, potentially resulting in death.

Female Aedes mosquitoes have distinctive white patterns on their bodies and legs and require blood meals to develop viable eggs. The eggs take approximately two to three days to mature, and the transmission of DENV from one human to another occurs through infected domestic mosquitoes. The onset of an outbreak typically begins when a mosquito bites a person infected with dengue fever or dengue hemorrhagic fever, allowing the virus to be transmitted to a new host. Once inside the new host, the virus replicates in the lymph nodes before spreading to other tissues via the lymphatic and circulatory systems. Understanding the virus's life cycle is crucial for developing potential antiviral treatments for dengue fever.

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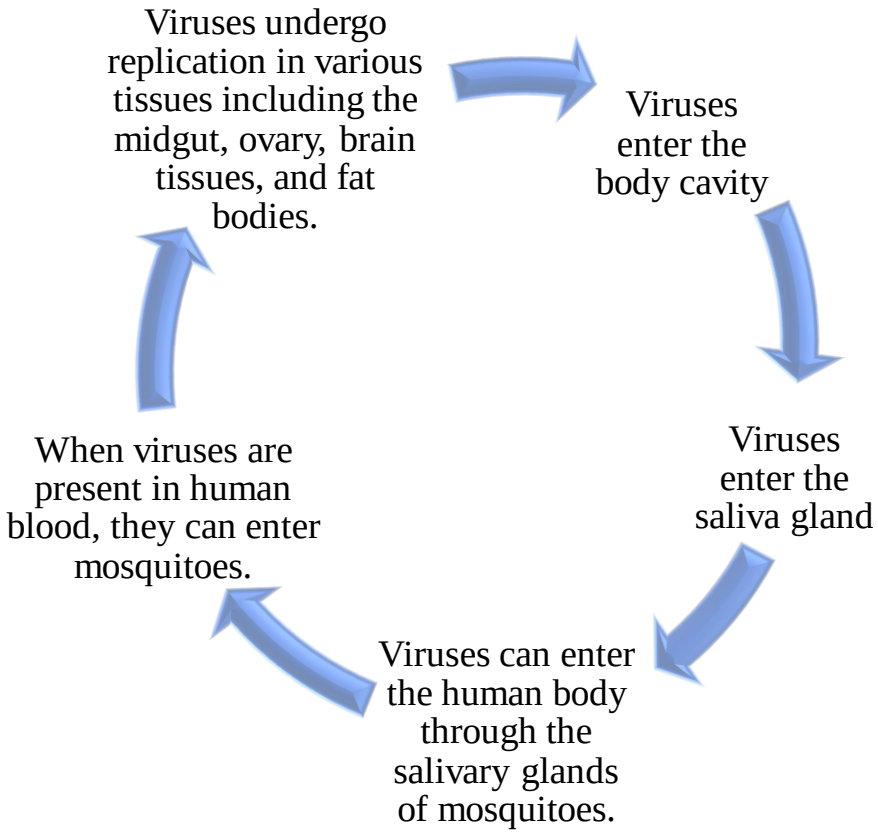

Fig. 1: *Transmission and Life Cycle of Dengue Virus (Mukherjee et al., 2019b)*

Within the dengue virion, a positive single-stranded RNA genome exists, encapsulated by a small particle enveloped in lipoprotein and structured with an icosahedral nucleocapsid. The initial step of virus infection involves binding to the host cell's surface. The cell membrane forms a vesicle-like structure through receptor-mediated endocytosis, allowing the virus to enter the cell. This structure, an endosome, facilitates the virus's penetration into the cell and its traversal deeper into the cellular environment. Subsequently, as the endosome's membrane acquires a negative charge, it enables the fusion of the virus with the endosome membrane, releasing genetic material. This initiates viral replication within the cell's cytoplasm. The viral journey through the secretory pathway is significantly influenced by changes in the pH, impacting the virus's progression and development. (Hassan et al., 2021) (Fig. 2).

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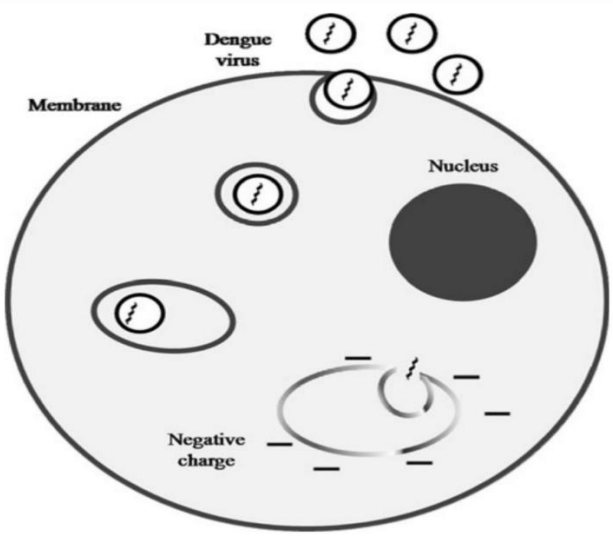

Fig. 2: *Dengue virus infection cycle in cells*

1.3 Potential Mechanisms and Pathways in Dengue Treatment

Currently, there is no specific treatment available for dengue fever. The standard approach involves supportive care, focusing on nursing care, maintaining fluid balance and electrolyte levels, and addressing any issues related to blood clotting. Symptomatic treatment alleviates symptoms, such as acetaminophen for fever reduction, sponging, bed rest, and oral rehydration therapy. Hospitalization may be required for patients showing signs of dehydration or bleeding. Aspirin should be avoided due to the risk of inducing bleeding, and patients' platelet count and hematocrit should be monitored daily until one to two days after the fever subsides.

Prevention of dengue fever primarily relies on prospective vaccination and vector control measures, which are considered highly cost-effective. Mosquito control programs are crucial preventive measures, although they can be challenging to implement and sustain. Developing a vaccine for dengue is complex due to the antigenic differences among the four closely related virus serotypes. Immunity to one serotype does not guarantee protection against the others, posing challenges for vaccine development. Chimeric tetravalent vaccines capable of inducing neutralizing antibodies against all dengue serotypes or strains represent a potential therapeutic approach. (Komarasamy et al., 2022).

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1.4 Preclinical and Clinical Status of Antivirals Against DENV Worldwide

No single animal model can recreate the clinical symptoms of dengue infections in humans. Several nonhuman primate models have produced dengue vaccinations or antibody-based therapies. Animal models, including AG129, BALB/c, and mice, have been extensively used to assess the efficacy of DENV-fighting drugs in wild organisms (Zompì & Harris, 2012).

To determine if antiviral medications are effective against DENV in vivo, viremia reduction against death in AG129 mice can be evaluated (Lee et al., 2023c). Although several antiviral medicines were shown to have antiviral activity in vitro, not all of them had been investigated in vivo using an appropriate animal model. Geraniin, PG545, and HS-1 have all been evaluated for their efficacy against DENV in vivo. Furthermore, in vivo evaluations may have a role in the absence of DENV antivirals that are now being investigated in clinical trials. Only a few DENV antivirals are now in clinical trials (Lee et al., 2023d). Table 1 includes the DENV antivirals that are currently being investigated in clinical studies around the world.

Table 1: Some of Dengue Virus's antivirals are undergoing clinical trials (Lee et al., 2023f).

Drug	Clinical Trial Phase	Status	Clinical Trials-gov Identification
JNJ-64281802 Melatonin	II	Recruiting Not yet recruiting	NCT05048875 NCT05034809
AT-752 Zanamivir	I	Recruiting Not yet recruiting	NCT05366439 NCTO4597437

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1.5 Antiviral drugs and their modes of action

Various approaches have been explored to create antiviral treatments for DENV. Some are Host attachment factors, cell receptors, etc. Additionally, researchers have focused on different stages of the viral lifecycle, including replication, maturation, and assembly post-infection. Conversely, targeting DENV's structural proteins with antivirals may hinder viral binding to host cells, effectively blocking viral penetration. Antiviral strategies focusing on DENV's non-structural proteins can potentially disrupt viral replication, given their integral role in the replication process.

1.5.1 Antivirals that the host directs

DENV infections can be limited by blocking attachment in host cells, which prevents the virus from attaching to and entering host cells. Various molecules have been identified as potential host cellular receptors for Dengue virus (see Figure 3). Table 2 provides a summary of host-directed antivirals specifically identified for DENV. The potential DENV host receptors that could serve as antiviral targets are illustrated in Figure 3, with some chemicals identified as potential host cellular receptors or attachment factors, including heparan sulfate, mannose, DC-SIGN, laminin, HSP90/HSP70, and TIM and TAM proteins.

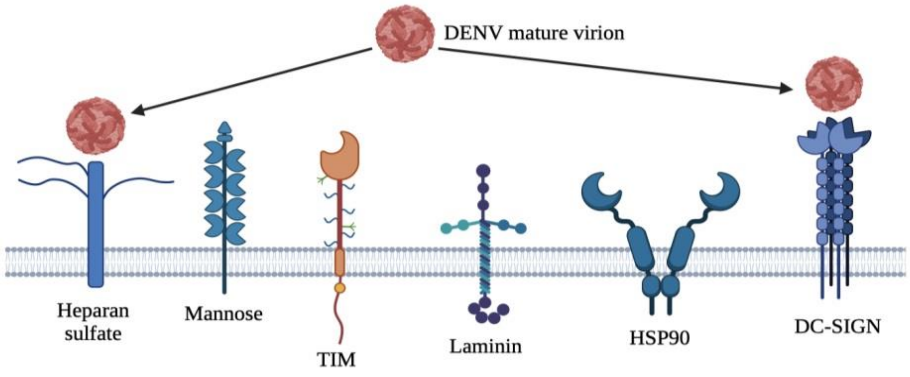

Figure 3: *Potential antiviral targets include DENV host receptors. Several molecules, such as heparan sulfate, mannose, DC-SIGN, laminin, HSP90/HSP70, and TIM and TAM proteins, were potential host receptors for DENV binding.*

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Inhibitors of virus-host receptor interactions:

- PD1 CD44
- Bovine lactoferrin
- Fucoidan
- Hippeastrum hybrid
- PI-88
- Galanthus nivalis
- Urtica dioica
- Chondroitin sulfate E

1.5.2 Heparan Sulphate

Heparan sulfate, alternatively known as CD44, is a member of the glycosaminoglycan (GAG) family. Notably, critical residues such as Lys291 and Lys295 play indispensable roles in these interactions, suggesting a potential avenue for preventing DENV infection by impeding the binding of DENV to heparan sulfate.

Research by Chen et al. (2017) demonstrated the protective effect of bovine lactoferrin against DENV-2 infection in CHO-K1 cells expressing heparan sulfate. Significantly higher infection rates were observed in cells expressing heparan sulfate compared to heparan sulfate-deficient cells. Treatment with bovine lactoferrin resulted in a dose-dependent reduction in DENV-2 infection rates in heparan sulfate-expressing cells, indicating its potential as an inhibitor of DENV infection by disrupting viral interactions with the heparan sulfate receptor.

Furthermore, PG545, a heparan sulfate mimic, exhibited potent inhibition of DENV-2 with an IC50 value of 25 nM. It prevented viral-induced cellular activation and endothelial monolayer integrity destruction mediated by NS1 and improved survival rates in AG129 mice, accompanied by reduced viremia, serum TNF-α, circulating NS1, and systemic vascular leakage.

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1.5.3 Other Receptors

Integrins, comprised of α and β heterodimeric subunits, are pivotal regulators of cellular motility, adhesion, and extracellular matrix protein recognition

Peptides P4 and P7, derived from the c domain of the DENV E protein, demonstrated efficacy in preventing Dengue virus 2 in human endothelial cells, as evidenced by Cui et al. (2018).

Despite these insights, no antiviral agents have been identified to inhibit DENV infection by disrupting interactions with TIM and TAM receptors. Nonetheless, inhibiting host receptors presents a promising avenue for developing DENV inhibitors, with a reduced likelihood of resistance development compared to direct viral targeting.

1.6 The Direct-Acting Antiviral Drugs

Direct-acting antiviral agents are drugs that directly interact with viral proteins to inhibit viral replication. This targeted approach offers advantages over host-directed antiviral drugs, potentially providing broad-spectrum antiviral activity with reduced toxicity. However, a significant concern with direct-acting antivirals is the risk of developing drug resistance over time. In the realm of dengue virus (DENV) research, while the E protein has been extensively studied among structural proteins, attention has also been directed toward the NS3 and NS5 proteins among non-structural proteins. These proteins represent promising targets for developing direct-acting antiviral therapies against DENV.

1.6.1 Targeting DENV E Protein

The DENV E protein is critical for viral entry, with domains facilitating fusion and receptor binding. Antivirals like EF and compound 1662G07 target the E protein, inhibiting viral entry by preventing dimer-to-trimer transition and binding to specific pockets. NITD448 disrupts fusion by binding to the E protein's β-OG pocket, showing efficacy against DENV-2 entry. These findings highlight the potential of targeting the DENV E protein for antiviral development.

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Table 2: DENV Structural Protein-Targeting DAAs: Advancements in Antiviral Therapy

Drug	Target	Mechanism of Action	Inhibitory Action ($IC_{50}/EC_{50}/EC_{90}$)
1662G07 and analogs, DN59, NITD448	E protein	Fusion inhibitor	IC90: D2-0.89-2.0 μM, D4-1.3-2.3 μM; IC50 against DENV-2: -10 μM; EC50 against DENV-2: 9.8 μM
DV2419-177, DN57opt, 1OAN1, Rolitetracycline, Doxycycline, A5, Compound 6	E protein	Viral entry and binding inhibitor	IC90: D1-01 1C50 against DENV-2: 8± 1uM, 7 ± 4 μM, 671 μM, 556 μM, 12± 0.7 uM; 1C50 against DENV-2: 77 and 91 pmol
PO2, 9g-ww,EF Geraniin, DETZ, DET4, Peptide 1	E protein, C protein	Various mechanisms including inhibition of virus entry and inter I ns between	L'*(plaque assay and RT-PCR); IC_{50} against DENV-2: 96 uM, >500 uM; EC50 against DENV-2: 1.75 μM, 0.016

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		DENV C protein and Host	hM, 112 nM, 25 μM
Rolitetracycline, Doxycycline, A5, Compound 6		binding and entry	1 μM, 7 ± 4 μM , 671 μM, 55.6 μM, 12+ 0.7 μM; EC50

1.6.2 Targeting DENV Non-Structural Proteins

Inhibiting DENV's non-structural proteins can slow down post-infection processes like viral replication, assembly, and maturation due to their crucial roles in DENV's replication mechanism. Among these proteins, NS3 and NS5 are deemed crucial targets for developing DENV antivirals, given their significant role as replication enzymes. NS1, ranging from 46 to 55 kDa, exists in various forms and cellular locations, playing a role in viral RNA replication. It is highly immunogenic, making it a vaccine candidate. Several inhibitors targeting NS1 have been studied for their anti-DENV effects.

Targeting NS3 protein

The NS3 protein, the second-largest in DENV with a molecular weight of 69 kilodaltons, harbors multiple enzymes. It plays a pivotal role in viral RNA replication by cleaving the viral polyprotein. NS3's protease domain requires the NS2B cofactor for proper protein folding. Its RNA helicase domain also collaborates with other DENV non-structural proteins, like NS5, to facilitate viral RNA replication. The helicase activity of NS3 unwinds secondary structures at the UTRs and dsRNA intermediates formed during DENV RNA synthesis. For instance, ivermectin effectively blocks DENV-2 NS3 helicase. Studies suggest that ST-610's mechanism of action occurs post-entry and involves the zA26T mutation in the NS3 helicase domain, making it resistant to ST-610. Moreover, protegrin-1 and retrocyclin-1 demonstrate promising inhibition of DENV protease

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activity, while nelfinavir, a repurposed medicine, exhibits potent anti-DENV action by targeting the NS2B-NS3 protease active site through various molecular interactions.

Targeting the NS4 protein

The NS4A protein rearranges membranes, which is essential for DENV to replicate efficiently. It works alongside other viral and host proteins in this process. Researchers have found specific regions within NS4A that are important for its function. For instance, residues 1–49 are necessary for NS3-protein activity, while residues 50-73, 76-89, and 101-127 are hydrophobic areas linked with membranes.

On the other hand, the NS4B protein, which is highly hydrophobic, plays a role in inhibiting the phosphorylation of STAT1, hindering the interferon-α/β signaling cascade. NS4B also influences the function of the NS3 helicase domain and collaborates with NS4A during viral replication.

Several inhibitors have been developed to target the NS4 protein, aiming to disrupt DENV replication. For instance, AM404, a paracetamol metabolite, has shown promising inhibitory effects on DENV replication by targeting NS4B. Similarly, a spiropyrazolopyridone molecule, compound 1a, selectively suppressed DENV-2 and DENV-3 by inhibiting viral transmission via NS4B. Another molecule, NITD-618, exhibited specific inhibition of DENV-1 to 4 by blocking viral RNA synthesis. These findings suggest the potential of targeting NS4 proteins as a strategy for developing anti-DENV therapeutics. Further research is needed to fully understand the interactions between these inhibitors and the NS4 proteins.

Targeting NS5 Protein

The distribution of homologous sequences among DENV serotypes is primarily influenced by a 100 kDa protein crucial for viral replication. NS5, containing RNA polymerase and methyltransferase domains, is pivotal in interacting with cellular proteins to facilitate viral RNA replication. Compounds such as I-OMe-AG238 and suramin hexasodium inhibit NS5, disrupting

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viral replication. Importin and IMPß1 assist in NS5's nuclear localization during infection. Cordycepin inhibits DENV replication by targeting NS5. Extracts from Myrtopsis corymbosa exhibit significant inhibition of NS5 RdRp, though compounds isolated from these extracts have limited antiviral activity. RK-0404678 displays broad inhibition of NS5 RdRp across DENV serotypes, binding to specific sites crucial for viral replication. These findings present promising targets for DENV therapeutics, underscoring the importance of NS5 as a drug target. Further research is warranted to enhance the efficacy of natural compounds and synthetic inhibitors targeting NS5, ultimately offering hope in combating DENV infections. Collaboration between researchers and pharmaceutical companies is essential for accelerating drug discovery efforts in this field.

1.7 Antiviral Role of Phenolic Compounds against Dengue Virus

Geraniin

Geraniin, an ellagitannin found in several Asian plants like Geranium thunbergia and Nephelium lappaceum, serves as a significant polyphenolic compound. Its versatile nature is evident through its association with multiple biological effects. These include stimulating the immune system by activating NF-kB, suppressing ovarian cancer growth by reducing Mcl-1 expression, protecting against radiation-induced cell damage, boosting antioxidant enzymes, hindering Hps90 ATPase, and demonstrating anti-malarial activity against Plasmodium falciparum in laboratory settings. Moreover, Geraniin displays promising antiviral properties, inhibiting viruses such as enterovirus 71, herpes simplex type 2, through various mechanisms.

Geraniin's Anti-DENV Properties

The research investigated Geraniin's efficacy against DENV-2 infection. A mixture of Malaysian plant extracts was tested using different treatment methods on VERO cell monolayers. Antiviral

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effects were observed in both pre-treatment and trans-treatment approaches. Protein profiling revealed alterations in cellular proteins associated with viral processes. Geraniin, abundant in the extract, displayed significant antiviral activity. In VERO cells, Geraniin showed dose-dependent virucidal activity against DENV-2. Molecular docking suggested that Geraniin binds to the viral envelope protein. Competitive binding assays confirmed Geraniin's interaction with viral proteins. In vivo studies on BALB/c mice confirmed Geraniin's anti-DENV action. Geraniin administration reduced virus presence in blood and prevented liver damage.

Flavonoids

Flavanols such as catechin, EGCG, and compounds like delphinidin, naringin, quercetin, and fisetin. Flavonoids have garnered extensive research attention due to their diverse health benefits. Their pharmacological effects include anti-inflammatory, antiallergic, neuroprotective, hepatoprotective, nephroprotective, anticancer, and antimicrobial properties. Moreover, numerous flavonoids exhibit antiviral activity against various viruses, encompassing HIV, HSV, influenza virus, RSV, SARS-CoV, measles, and rotavirus. Quercetin, for instance, inhibits HBV replication and shows activity against influenza A virus. EGCG demonstrates inhibition against multiple viruses, including HBV, HCV, IAV, HSV-1, HSV-2, and VSV. Overall, flavonoids possess promising antiviral potential, making them valuable candidates for combating viral infections across diverse viral families. (Colpitts & Schang, 2014).

Anti-DENV Effects of flavonoids

Flavonoids exhibit potent antiviral effects, particularly against flaviviruses like DENV, WNV, and ZIKV. Studies reveal that flavonoids such as quercetin, fisetin, catechin, delphinidin, and EGCG inhibit DENV infection through various mechanisms. Quercetin and fisetin modulate immune responses and generate type 1 interferon. Molecular docking suggests flavonoids interact with viral proteins, hindering multiple stages of the viral replicative cycle. EGCG and delphinidin demonstrate antiviral activity against DENV, WNV, and ZIKV, possibly by altering viral internalization or endosomal pH. Other flavonoids like naringin and naringenin show direct virucidal activity against DENV. Baicalein exhibits virucidal and anti-adsorption effects against

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Japanese encephalitis and DENV. Flavonoids are promising candidates for combating flavivirus infections through diverse antiviral mechanisms.

Resveratrol

Resveratrol, a phytoalexin in various plant sources, including grapes and berries, acts as an antioxidant and anti-inflammatory agent, protecting the body from stress and infection. It can exist in trans- or cis-forms, with exposure to ultraviolet light leading to transformation between them. Its mechanisms of action include post-entry inhibition, virucidal activity, and adsorption inhibition. However, its efficacy against HCV remains uncertain, with some studies suggesting increased replication.

The Effect of Resveratrol on the Anti-DENV

Low MOI infection exhibits dose-dependent effects, with EC50 measured at 11.37 μM, contrasting with a less apparent effect at a higher MOI of 2 (EC50: 24.37 μM). Resveratrol in Huh7 cells inhibits DENV-2 infection by upregulating nuclear HMGB1 and enhancing ISG gene synthesis, bolstering the innate immune response. Structural analogs PNR-4-44 and PNR-5-02 also reduce viral cytopathic effects in Huh7 cells. These findings suggest resveratrol and its analogs as promising candidates for DENV therapy, warranting further investigation into their mechanisms of action and therapeutic potential. (Loaiza-Cano et al., 2020d).

1.8 Advances in antiviral medicines for the treatment of illnesses caused by the dengue virus

Balapiravir

Balapiravir, also known as R1626, exhibits potent antiviral activity against the hepatitis C virus (HCV) by inhibiting its replication in laboratory settings. It acts as a prodrug of the nucleoside analog 4'-azacytidine, phosphorylated within host cells to produce its active metabolite, hindering viral RdRp function. While initially considered a potential treatment for chronic HCV infection,

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its clinical development was terminated due to unsatisfactory benefit-to-risk ratios. However, its efficacy against HCV prompted an investigation into its potential effectiveness against the dengue virus (DENV). In laboratory studies, balapiravir demonstrated EC50 values ranging from 1.9 to 11 uM in human hepatoma cells and between 1.3 and 6.0 hM in primary human macrophages and dendritic cells. It effectively inhibited DENV replication in various serotypes and strains, with EC50 values ranging from 0.10 to 0.25 kM in peripheral blood mononuclear cells (PBMCs). Despite promising in vitro results, clinical trials administering balapiravir orally at 1500 and 3000 mg twice daily failed to significantly impact viral load, viremia kinetics, cytokine expression, or hematological parameters in dengue-infected patients. Several factors may contribute to this lack of efficacy, including reduced effectiveness when administered after infection, cell-type specificity, and cytokine-mediated alterations in balapiravir metabolism. Increasing the dose or frequency of administration to achieve higher plasma exposures is not feasible due to the risk of adverse effects observed in HCV patients treated with higher doses of favipiravir. Additionally, balapiravir showed no efficacy in a mouse model of DENV infection, indicating its unsuitability for DENV treatment.

Chloroquine

Chloroquine, identified by its PubChem CID number 2719, works by increasing the pH levels in acidic cell compartments like endosomes and lysosomes, which prevents dengue viruses from entering cells and disrupts their maturation process. It also has anti-inflammatory properties, reducing the release of inflammatory substances. In lab tests, chloroquine effectively inhibited the growth of DENV-2 in certain cell types without causing cell death. However, it did not show the same effect in other cell types. Additionally, chloroquine reduced levels of pro-inflammatory substances in infected cells, suggesting it could modulate the body's response to the virus. Despite promising lab results, clinical trials administering chloroquine to dengue patients did not significantly improve their symptoms or reduce the severity of the disease. Although patients reported feeling better, the treatment did not significantly impact the course of the illness.

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Lovastatin

Statins, like lovastatin (identified by its (PubChem CID: 53232), hinder various biological processes, one of which is cholesterol production, essential for the replication cycle of many viruses, including those from the Flaviviridae family like DENV. Lovastatin specifically targets the final stages of the DENV replication process, hindering the maturation and release of infectious viral particles. It has shown efficacy in suppressing DENV replication in different cell types and preventing the spread of viable viruses. When administered to DENV-infected mice, lovastatin delayed virus-induced mortality by approximately two days, regardless of whether treatment was initiated before or after infection. However, this delay in mortality did not correspond to a significant reduction in viral RNA levels; in some cases, viral titers even increased. Despite these findings, lovastatin's widespread use, favorable safety profile, and beneficial effects on endothelial function prompted researchers to explore its potential in clinical studies for DENV infections. In a study involving adult patients with confirmed dengue, lovastatin treatment (80 mg once daily for five days) did not significantly impact viral RNA levels, clearance, or symptom relief. Although there was a slight tendency towards lower viremia in patients infected with DENV-2 and faster viral clearance in those with secondary infections, these trends were deemed insignificant.

Celgosivir

Celgosivir, also known as 6-O-butenyl castanospermine (identified by its PubChem CID: 60734), exhibits efficacy against various viruses, including DENV. Studies have shown that celgosivir inhibits the growth of DENV1-4 clinical isolates in laboratory settings, with EC50 values in the sub-hM range, significantly lower than its cytotoxic concentration. Its anti-DENV action involves two main processes: inhibiting endoplasmic reticulum (ER) a-glucosidases, thereby disrupting the processing of DENV proteins, and modulating the host's unfolded protein response (UPR) pathway, which affects cell survival and death. In animal studies involving DENV-infected mice, celgosivir treatment substantially reduced viral RNA load and provided complete protection against virus-induced mortality. However, despite promising preclinical results, celgosivir did not demonstrate significant antiviral effects in a phase 1b clinical trial (CELADEN), although lower levels of viral RNA and NS1 were observed in patients treated with celgosivir compared to those who received a placebo, especially in cases of secondary DENV infection. This discrepancy between preclinical and clinical outcomes may be attributed to various factors, including

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differences in virus strains, cell types, and dosing regimens. Further optimization of dosing schedules may enhance the therapeutic efficacy of celgosivir in DENV-infected individuals. (Kelesidis & Landovitz, 2011).

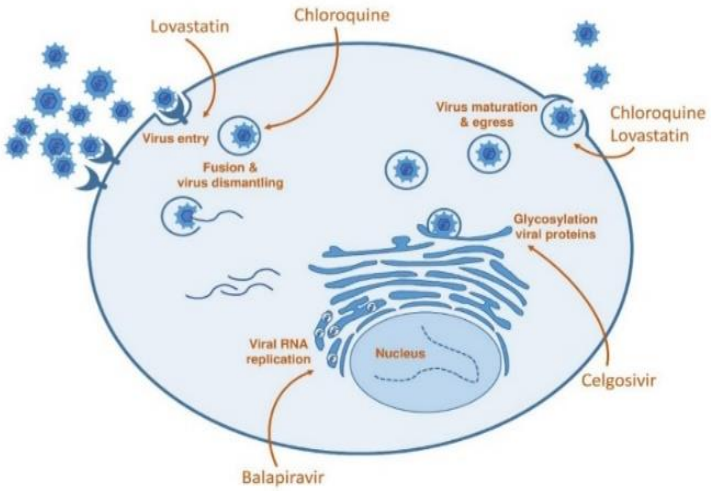

Figure 4: *Schematic representation of the DENV Life Cycle*

1.9 Approaches to Handling Dengue Infections

No specific antiviral medication has yet gained approval for treating dengue fever. Nonetheless, several treatment modalities have been proposed and are utilized to mitigate the disease's impact. s. Various seaweed-derived polysaccharide compounds have demonstrated efficacy against all pathogenic dengue virus serotypes. (Juliet et al., 2021b).

Moreover, the investigational antiviral drug ribavirin has been explored in combination therapy regimens and has shown potential in reducing dengue virus activity in certain cells. Upon metabolism, ribavirin mimics purine RNA nucleotides, impeding RNA degradation necessary for viral replication. Various strategies involving ribavirin have been investigated to assess its effectiveness as a prodrug against dengue.

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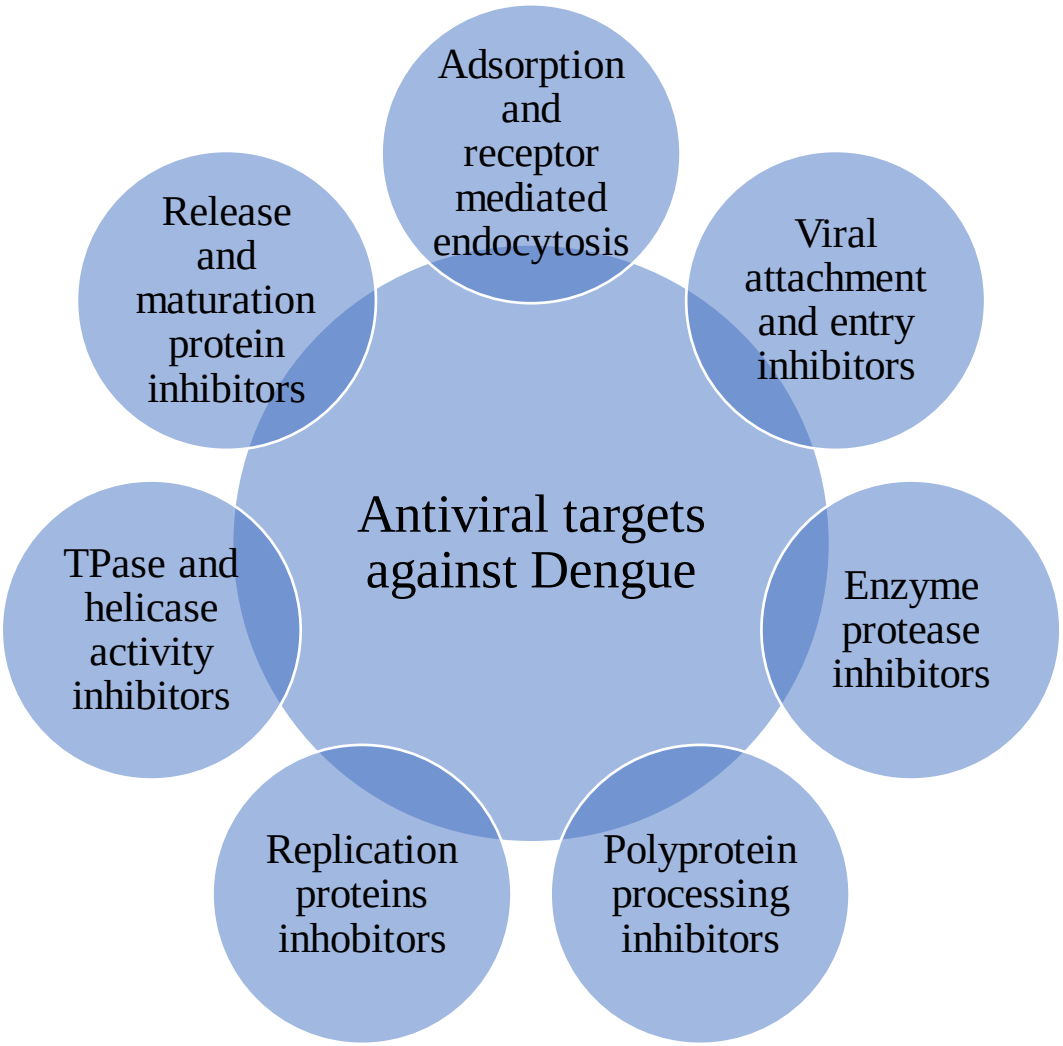

***Figure 5**: Antiviral and therapeutic targets Against DENV (Malik et al., 2023)*

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1.10 Advancements in Developing Dengue Virus Vaccines

The pressing need to address the challenges posed by the Dengue virus (DENV) and its associated diseases has spurred efforts towards developing anti-Dengue vaccines. Alongside this, vector population control and preventive public health measures play crucial roles in combating the spread of these infections. However, obstacles such as genomic mutations within the viral genome and the emergence of drug resistance pose significant challenges to vaccine development. The rapid mutation rates observed during DENV outbreaks, notably in 2006 and 2011, contribute to the development of drug resistance, posing a considerable threat to healthcare systems. Consequently, efforts to develop vaccines and medications must keep pace with these evolving threats.

Table 3: Exploring Noble Therapeutic Approaches Combatting Dengue Virus (Malik et al., 2023)

Sl. no.	Therapeutic Strategy	Explanation	Candidates under Trials
1.	The development of nanobodies targeting proteins of the dengue virus	Some existing nanobodies are being repurposed to treat dengue fever. These nanostructures are engineered to deliver drug adjuvants specifically targeting infectious viral agents within the body. Additionally, nano assemblies are increasingly utilized for diagnostic purposes to detect viruses in patients.	
2.	Gold nanoparticle-based subunit vaccine	Gold nanoparticles join unique underlying parts of DENV, for example, encompassed glycoproteins, through half-breed technology. The outcomes have shown that AUNP-E initiated an undeniable immune response intervention against DENV.	• AUNP-E subunit vaccines. • Tetravalent AuNP-based Subunit dengue vaccine.
3.	Polymerase inhibitor-based drugs	It inhibits the viral RNA-dependent RNA polymerase without inducing harmful effects on mammalian cells.	• T-705

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1.11 Antibody-Dependent Enhancement (ADE)

The primary obstacle in developing effective dengue vaccines is Antibody-Dependent Enhancement (ADE), wherein certain antibodies facilitate its entry into target cells and enhance its replication instead of neutralizing the virus. This occurs when non-neutralizing antibodies occur during a subsequent infection with a different virus serotype. Dengue virus comprises four distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), and initial infection with one serotype typically provides immunity against that specific serotype. However, ADE can lead to more severe disease during subsequent infections with a different serotype.

The molecular mechanisms underlying ADE involve antibodies interacting with the primary infecting virus neutralizing it completely, and facilitating its entry into immune cells through Fc receptors. This results in enhanced viral replication and can exacerbate the disease. Several factors contribute to ADE, including the presence of non-neutralizing or cross-reactive antibodies,

In conclusion, overcoming ADE is crucial for developing safe and effective dengue vaccines. Extensive research efforts are underway to address this challenge and develop vaccines to prevent viral entry without exacerbating the disease through ADE.

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Chapter Two
Purpose of the Study

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2. Purpose of the Study

This research aims to gather the most positive data on the investigation of several chemical compounds for treating the dengue virus.

- To understand the dengue fever's pathogenesis.
- To gain knowledge about antiviral drugs in dengue disease cases.
- To gain knowledge about chemical compounds' effects against dengue virus.
- Collect information about antiviral medicines for treating illnesses.
- To gain knowledge about the Development of Vaccines against Dengue.

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Chapter Three
Literature Review

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3. Literature Review

Title: Exploring the Antiviral Properties of Phenolic Compounds against Dengue Virus: A Comprehensive Review

Phenolic compounds have garnered attention for their diverse biological activities, including antiviral effects. This review focuses on elucidating the potential of phenolic compounds against the dengue virus, which has caused numerous epidemic outbreaks, particularly in recent years. We discuss twenty phenolic compounds known for their anti-DENV activity, highlighting the diverse mechanisms of action they employ. These mechanisms include targeting viral particles or proteins essential for viral replication and infection dissemination. (Loaiza-Cano et al., 2020)

Title: Exploring the Molecular Mechanisms of Antiviral Agents Against Dengue Virus

Dengue poses a significant global health threat, with millions of infections and thousands of deaths reported annually. This review discusses the development of host-targeted antivirals that focus on receptors and direct-acting antivirals that target both structural and non-structural proteins of DENV. Additionally, the review explores the development of antivirals targeting various stages of the viral lifecycle, including viral replication, assembly, and maturation. Furthermore, evaluating combinations of antiviral drugs with different mechanisms of action may lead to the development of synergistic drug combinations for treating dengue at various stages of infection.

Title: Advancements Toward Antiviral Therapies for Treating Dengue Virus Infections

Dengue infection presents a significant global health challenge, infecting approximately 390 million individuals annually, with a quarter experiencing clinical symptoms. Despite progress in understanding dengue pathogenesis, there remains a lack of licensed vaccines or antiviral treatments for this virus. Current patient management primarily involves symptomatic relief and supportive care. Therefore, the development of therapeutics for dengue is of utmost importance.

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This review focuses on the molecules evaluated in dengue virus-infected patients, including balapiravir, chloroquine, lovastatin, prednisolone, and celgosivir. Insights gained from these clinical trials can inform the design of future trials for the next generation of dengue virus inhibitors. (Kaptein & Neyts, 2016)

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Chapter Four
Methodology

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4. Methodology

4.1 Method of searching

The exploration of conventional books and databases, including PubMed, SciFinder, Elsevier, Springer Scopus, Science Direct, Google Scholar, and Web of Science, was conducted to analyze natural compounds against dengue fever from 2010 to 2023.

4.2 Criteria

- Pathophysiology of Dengue fever.
- Molecular mechanism of dengue immunotherapy
- Current prospects for antiviral compounds against dengue fever
- Current treatment available against dengue fever
- Future perspective of dengue fever treatment using chemical compounds,

4.3 Data Analysis

Data analysis was done to synthesize the gathered data and derive significant insights; the study's objectives guided the thematic organization of the literature, resulting in discrete sections that tackled every facet of stress.

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Chapter Five
Results and Discussion

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5. Results and Discussion

5.1 Result

Table 4: lists drugs with the mode of action, advantages, and disadvantages.

Drug	Mode of action	Advantage	Disadvantage
Balapiravir	Inhibits the replication of various DENV serotypes and strains in human hepatoma (Huh-7) cells and primary human macrophages (Kaptein & Neyts, 2016b)	Proven safe at administered doses (Kaptein & Neyts, 2016b)	Adverse reactions include headaches, dizziness, vomiting, nausea, diarrhea, abdominal pain, back pain, and neck pain (Kaptein & Neyts, 2016c)
Chloroquine	Possible antiviral effect, anti-inflammatory properties . (Borges et al., 2013)	Reduction in pain and improved well-being of patients (Borges et al., 2013)	No alteration in disease duration or intensity and days of fever compared to placebo. (Borges et al., 2013)
Lovastatin	Reduces dengue virion assembly, possibly possessing antiviral properties. (Whitehorn et al., 2015)	It is safely tolaretated (Whitehorn et al., 2015b)	

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5.2 Discussion

In my review, several drugs have shown promise in combating Dengue virus infection. Balapiravir, for example, has demonstrated effectiveness in limiting DENV replication and has been deemed safe at various doses. However, despite its efficacy, it has been associated with adverse side effects such as headaches, dizziness, vomiting, nausea, diarrhea, abdominal pain, back pain, and neck discomfort.

Chloroquine is another drug utilized in dengue patients due to its anti-inflammatory properties, potential antiviral activity, low cost, widespread availability, safety, and global public health significance. While it effectively relieves pain and improves the overall well-being of patients, it does not significantly alter disease duration or body temperature.

Similarly, Lovastatin has shown promise by reducing dengue virion assembly, indicating potential antiviral activity. Additionally, it has been found to lower endothelial inflammation, making it a safe and well-tolerated option for dengue-infected adults.Celgosivir therapy misfolds the dengue virus NS1 protein, promotes pro-survival genes, and protects against lethal challenge mice models. However, it does not directly affect dengue patients' viral load or fever burden.

In the past few years, there has been a growing concern among mainstream researchers about infectious diseases. As a result, there has been a significant increase in research focusing on viral infections. Researchers are exploring modern therapeutic approaches, including nanotechnology, to develop innovative vaccination and drug development solutions.

In regions with limited resources, there is a critical need to adopt adaptable strategies to address dengue infection. Exploring plant-based natural compounds and nanomedical applications to enhance vaccination and drug development efforts is essential.

Looking ahead, traditional vaccination methods will continue to evolve, incorporating advancements in assembly techniques, genetic engineering, and nanobiotechnology. These advancements promise to improve vaccine efficacy, dosing, safety profiles, and clinical trial outcomes compared to previous drug protocols. (Villarreal et al., 2013).

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Chapter Six
Conclusion

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6. Conclusion

This review underscores the intricate landscape of antiviral treatments for dengue virus infection, emphasizing the pressing need for a specific approved treatment despite significant research endeavors. While various approaches have demonstrated promise in preclinical and clinical studies, challenges such as limited efficacy, safety concerns, and the emergence of drug resistance underscore the necessity for ongoing innovation.

In the future, developing effective antiviral therapies against dengue virus infection will necessitate collaborative efforts among researchers, clinicians, and pharmaceutical companies, as well as sustained investment in basic and translational research. Additionally, integrating new technologies, such as structure-based drug design and high-throughput screening, holds the potential to identify novel therapeutic targets and expedite the drug discovery process.

Ultimately, addressing the unmet medical need for antiviral treatments for dengue virus infection remains a critical public health priority, and concerted efforts are required to minimize the impact of this debilitating disease on global health.

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Chapter Seven
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