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Synthetic And Natural Medicines To Combat Dengue Virus

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Abstract
Dengue virus (DENV) infection starts through female anopheles mosquito vector. This virus belongs to flaviviridae family. If a carrier mosquito (Aedes gypti) attacks a human, the virus is transmitted. There are four serotypes such as DENV-1, DENV-2, DENV-3, and DENV-4 of the virus. The infection affects the 50-100 million people worldwide. No specific dengue antiviral medicament has been produced yet to combat dengue; The only Dengvaxia vaccine was authorized to fight DENV. It has recently become a global health worry and threat. After 2-3 weeks of infection, severe signs such as an elevated fever, nausea, pain in the body, inflammation of the skin, discomfort, and head motion occur. The present review updates the synthetic and natural medicines which can control the dengue fever.
Keywords: *Dengue virus (DENV), synthetic drugs, natural treatment*

INTRODUCTION

Dengue is a viral disease caused by *Aedes aegypti*. Dengue is an endemic disease. It is caused by dengue virus from the genus Flavivirus. It produces dengue fever that has become among the biggest risks to public health in hot and humid areas of the world [1]. Nearly 400 million people are attacked by the virus each year, with over 96 million people exhibiting sickness that is medically noticeable [2,3]. DENV exists in four distinct but closely related DENV-1 to DENV-4 subtype, as well as infection with single variants confers long-term defense mechanism only against the particular variants, leaving individuals vulnerable to subsequent infections by alternatives [4]. This characteristic increases the risk of severe manifestations, For example, a condition called dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) may develop into significant morbidity and mortality if not promptly managed [1,5]. The principal vector for dengue transmission is the female *Aedes aegypti* mosquito, although *Aedes albopictus* can also serve as a competent carrier [6]. With a strong affinity for human hosts and the ability to develop in damp conditions, these mosquitoes flourish in metropolitan settings. If an infected mosquito strikes a person, the virus is disseminated initiating the replication chain within the human host that targets immune cells and disseminates rapidly [7]. Once in circulation, DENV can compromise vascular integrity, trigger immune over activation, and severe bleeding, leaks of plasma, and in extreme situations, multiple organ malfunction [7,8].

Globally, dengue imposes a substantial health burden. According to figures from the World Health Organization's (WHO), over fifty percent of the world's population currently lives in regions where dengue is a threat. Morbidity rates are highest in densely populated and poorly resourced urban areas of Parts of the Americas, the Western Pacific, and South-east Asia, where recurring outbreaks overwhelm healthcare systems [9]. Although the overall case fatality rate for dengue remains below 1% with proper clinical management, it can rise dramatically up to 20% or more in severe cases without timely intervention [10]. The disease disproportionately impacts children in endemic regions, where repeated exposure to different serotypes is common. Currently there is no particular antiviral properties drug approved regarding viral treatment. The mainstay of healthcare measures is rehabilitation, which includes hydration replenishment and keeping an eye out for any indications of a serious illness [3].Although one licensed vaccine (CYD-TDV, Dengvaxia®) is available, its use is restricted to individuals with prior DENV exposure due to safety concerns in seronegative recipients [11,12]. These limitations highlight the urgent need for effective, targeted antiviral therapies that can inhibit viral replication and reduce disease severity.Two critical enzymes in the DENV life cycle methyltransferase and RNA-dependent RNA polymerase have emerged as promising drug targets [13]. MTase is essential in capping contagious RNA, RdRp is in charge of viral RNA production, while it ensures its stability and avoidance of host immunological responses [14]. Structural studies of these enzymes, including

co-crystallization with small-molecule ligands, provide valuable insights into their active sites, substrate specificity, and conformational dynamics [15]. Structure-based drug design leveraging co-crystallized inhibitors offers a rational approach to developing potent molecules that can block these enzymatic functions, thereby halting viral replication.In this context, exploring the structure-guided design of inhibitors against DENV MTase and RdRp represents a promising strategy to address the unmet need for specific antiviral agents, possibly lowering the burden of dengue disease morbidity and mortality worldwide

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a) Life Cycle of DENV

The mosquito-borne flavivirus known as dengue virus has a complicated stage of life that affects both human hosts and Aedes mosquitoes that transmit it [3]. Following these bite of an infected mosquito, the virus uses receptors to allow it to enter human cells. This virus is transmitted by the help of infected female Aedes mosquito.at first the mosquito transfers the viral genome into a normal human by the biting. Then this virus assembles into the infected cell and divides to form the colony. Releasing the infected cell into the extracellular matrix, then the viruses attach to the host cell surface and penetrate the host cell, then uncoated the viral genome into the host cell and uncoated viral genome attach to the host cell and attach to the nucleus of the host cell n where the replicate themselves. The positive-sense single-stranded RNA genome is released into the cytoplasm once the viral envelope and endosomal membrane fuse together within [16]. The NS5 protein's methyltransferase (MTase) and RNA-dependent RNA polymerase (RdRp) domains are among the structural and nonstructural proteins that are produced when the entire genome is translated into only one polyprotein. MTase caps these viral RNA to protect it from host degradation and ensure efficient translation, while RdRp catalyzes RNA genome replication. Newly synthesized viral RNA is packaged with structural proteins to form immature virions in the endoplasmic reticulum. These virions undergo maturation in the Golgi and are released from the host cell via exocytosis [17]. In mosquitoes; ingestion of viremic blood initiates a similar replication cycle, enabling further transmission [18].

SYNTHETIC MEDICINES AVAILABLE AGAINST DENGUE

Currently, there isn't fully accepted, specific virus-inhibiting drug for dengue infection. Management primarily relies founded on rehydration and supportive therapy, fever control, and keeping an eye out for warning signs of harsh disease. The antipyretic paracetamol is given along with fluid administration. Doxycycline is a broad spectrum tetracycline derivative having potent NS2B-NS3 DENV protease inhibitory activity. DENV can attack the host platelet and sudden reduction may cause death of the patient. The thrombopoietin receptor agonist eltrombopag has been shown to increase the platelet count significantly. However, several antiviral strategies are under investigation to target key viral enzymes such as the NS1, NS5, methyltransferase (MTase) and RNA-dependent RNA polymerase (RdRp). The neuraminidase inhibitor Zanamivir was shown as potent DENV NS1 inhibitor. The antiparasitic drug ivermectin has been shown as potent DENV NS5 inhibitory action [19].

Nucleoside analogues, such as sofosbuvir and favipiravir, have shown promising in vitro inhibition of DENV RdRp by joining the viral RNA chain and resulting in an early termination. Non-nucleoside inhibitors (NNIs) are also being designed to bind allosteric pockets of RdRp [20], disrupting polymerase function without competing with natural nucleotides. For MTase, S-adenosylmethionine (SAM) analogues and small molecules mimicking the cap structure have been explored to block methylation of the viral RNA cap, thus impairing immune evasion [21]. Structure-based drug design, supported by crystallographic data of co-crystallized enzyme-inhibitor complexes, allows precise optimization of molecular interactions within the active site. This approach has accelerated the discovery of lead compounds with high specificity and reduced host toxicity. Several such inhibitors are in pre-clinical or early clinical stages, with some broad-spectrum antivirals demonstrating cross-reactivity against other flaviviruses like Zika and West Nile virus [22, 23]. While vaccines, such as Dengvaxia, offer partial protection, targeted antiviral drugs remain crucial for effective dengue therapy, especially in acute infections [11,24]. Continued research into structure-based design of MTase and

RdRp inhibitors holds significant possibility of creating effective, safe, and targeted anti-dengue medications [19, 25].

VACCINATION AGAINST DENGUE

In tropical and subtropical areas, dengue fever, which is brought on by the dengue virus (DENV), continues to pose a serious threat to public health. Vaccination offers a proactive approach to prevent infection, but its effectiveness is limited by the presence of four antigenic distinct serotypes, the danger of antibody-dependent enhancement (ADE) and variants (DENV-1 to DENV-4). Current vaccines, such as CYD-TDV (Dengvaxia®), provide partial protection and are recommended selectively, underscoring the need for complementary therapeutic strategies.

Dengvaxia is a tetravalent dengue vaccine developed by Sanofi Pasteur. It was approved in 2019 for the prevention of dengue fever caused by serotypes 1-4 in people ages nine through 16 who have laboratory-confirmed previous dengue infection and who live in endemic areas [26]. Dengvaxia is a chimeric vaccine formulated by recombinant DNA technology by replacing the PrM (pre-membrane) and E (envelope) structural genes of the yellow fever attenuated 17D strain vaccine with those from the four dengue serotypes [27].

Thus, while vaccination remains a cornerstone in dengue prevention, the rational design of MTase and RdRp inhibitors represents a crucial parallel strategy in achieving comprehensive dengue control and reducing the global disease burden.

NATURAL TREATMENT TO COMBAT DENGUE

Even though medical science has conducted a great deal of research and development, no effective anti-dengue viral medication has been discovered to date. As a result, people are becoming more probable to use natural remedies in conjunction with general but non-specific or unconventional medicine to help dengue patients survive. Natural medications are recognized to be less harmful and to have fewer resistance problems, which strengthens patients' immune systems [28]. Mother Nature has many medicinal properties. *Andrographis paniculata* (Kalmegh), *Euphorbia hirta*, *Cissampelos pareira* (velvet leaf), *Carica papaya* (Papaya), Azadirachta indica (Neem), and goat milk are among the ancient Indian treatments used to fight the terrible dengue virus onslaught [29]. In recent years, natural compounds have emerged as promising candidates in the structure-based design of inhibitors against viral enzymes such as Dengue virus (DENV) [30,31]. Many plant-derived phytochemicals, alkaloids, flavonoids, terpenoids, and polyphenols exhibit strong antiviral activity by targeting essential viral replication proteins [32]. Through structure-based drug design, these bioactive molecules can be optimized to fit into the active sites of MTase and RdRp, potentially disrupting their catalytic functions [30]. Co-crystallization studies allow researchers to visualize the precise binding interactions between natural compounds and target proteins, enabling rational modification for improved potency, selectivity, and stability. For instance, flavonoids like quercetin and catechins have shown inhibitory effects on viral polymerases, while certain alkaloids exhibit MTase suppression. Natural treatment approaches also offer advantages such as reduced toxicity, biocompatibility, and diverse structural scaffolds for drug development [33]. By integrating computational modeling, crystallography, and biochemical assays, researchers can develop co-crystallized natural inhibitors with high efficacy against DENV replication machinery. This strategy bridges traditional medicinal knowledge with modern molecular design, paving the way for safer, plant-based antiviral therapeutics that may complement or replace synthetic drugs in dengue treatment.

CONCLUSION

There is no specific antiviral drug developed to combat dengue. The symptom management treatments are given by synthetic medicines such as paracetamol, zanamivir, invermectin, doxycycline, and multi vitamins and minerals to combat dengue. Several remedies found in Mother Nature are given along with synthetic drugs. Ancient Indian remedies such as the plant *Andrographis paniculata* (Kalmegh), *Euphorbia hirta*, *Cissampelos pareira* (velvet leaf), *Carica papaya* (Papaya), Azadirachta indica (Neem), and goat milk have been

used to treat dengue fever and increase the immunity. Further, design of anti dengue drugs taking small molecule co-crystal ligand which are co-crystallized at the active site of various DENV targets such as structural proteins of Capsid(C), Envelope (E), and pre-membrane/membrane (prM/M) and the non-structural proteins are NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5 utilizing ligand and structure based design tools provides a viable approach to the creation of efficient antiviral therapeutics.

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