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Features Evaluation and Treatment of Dengue

Gaikwad Akash Sarjerao, Prof. M. V. Vanve, Dr. Survase K. P.
Aditya Institute of Pharmaceutical, Beed, India

Abstract: *Dengue is a viral infection that impacts a large number of people in over 125 countries and is linked to considerable illness and death. Due to the lack of a specific antiviral treatment, supportive and alternative therapies are being investigated. One such option is the juice derived from the leaves of Carica papaya, a plant from the Caricaceae family, which is believed to aid in raising platelet levels in dengue patients. This review summarizes findings from relevant research conducted over the past ten years. Two authors independently performed a literature search using PubMed, Google, and a library database to locate applicable studies. In total, seven studies were included: one animal study, one case report, three case series, and two randomized controlled trials.Although many of the reviewed studies have limitations, such as small sample sizes and weak methodologies, early evidence suggests that Carica papaya leaf extract may offer therapeutic benefits. Nonetheless, further well-designed, large-scale clinical trials are necessary to confirm its effectiveness and safety.*

Keywords: Dengue Fever, Dengue Hemorrhagic Fever

I. INTRODUCTION

The term "dengue" originates from the Swahili phrase "ka-dinga pepo," which translates to "cramp-like seizure." The first recorded outbreaks of dengue occurred in the 1780s across North America, Africa, and Asia. In the early 1970s, only nine countries reported severe dengue epidemics. However, today, with dengue cases present in over 100 countries, it is now considered an endemic disease.

The dengue virus (DENV) is a positive-sense RNA virus belonging to the Flaviviridae family. There are four primary serotypes of the virus: DENV-1, DENV-2, DENV-3, and DENV-4. In 2007, a fifth serotype (DENV-5) was identified in Sarawak, Malaysia, after it was found in patients' blood samples. Dengue infection can result in illness ranging from mild dengue fever (DF) to severe dengue hemorrhagic fever (DHF).

Dengue and DHF are mainly spread by Aedes mosquitoes, which breed in peridomestic settings and thrive in tropical and subtropical climates. Warmer temperatures accelerate the replication of the virus within the mosquito's body, enabling faster transmission to humans. Additionally, climate warming expands the range of Aedes mosquitoes, allowing them to survive in more regions, including higher altitudes and latitudes.

This review will examine the methods and materials used in dengue research, explore the differential diagnosis, distinguish the clinical features, assess the impact of co-infections, and recommend treatment approaches, including strategies for prevention and control.

(Bennett et al., 2020)

AIM:

To evaluate the clinical, laboratory, and epidemiological features of dengue disease and to assess effective treatment strategies for improving patient outcomes, minimizing complications, and guiding preventive care.

OBJECTIVE:

1] To identify and analyze key clinical features of dengue for early diagnosis and classification of disease severity (DF, DHF, DSS).

2] To differentiate dengue from other febrile illnesses through the evaluation of specific signs, symptoms, and laboratory markers.

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3] To assess the effectiveness of current treatment protocols, including supportive care, fluid management, and symptom relief.
4] To explore the potential of alternative treatments, such as Carica papaya leaf extract, in improving platelet count and clinical recovery.
5] To understand the impact of dengue on different populations (e.g., children, elderly, immunocompromised) for better risk stratification.
6] To recommend prevention and control strategies, including patient education, vector control, and early

LITERATURE REVIEW:

1] Gubler (1998): highlighted the epidemiology and clinical spectrum, emphasizing classic symptoms like high-grade fever, retro-orbital pain, myalgia, arthralgia, and rash. Severe forms involve hemorrhagic manifestations and plasma leakage.
2] Halstead (2007): elaborated on pathogenesis, noting that antibody-dependent enhancement (ADE) contributes to severe disease upon secondary infection with a different serotype.
3] World Health Organization (WHO, 2009): categorized dengue into dengue without warning signs, dengue with warning signs, and severe dengue, improving clinical recognition and triage.
4] Martina et al. (2009): also described neurological and hepatic involvement, underlining the multi-systemic nature of severe dengue.
5] Peeling et al. (2010): reviewed diagnostic methods, including NS1 antigen detection, IgM/IgG ELISA, and RT-PCR. NS1 antigen is particularly useful in the early phase of infection.
6] Rathore and St. John (2020): emphasized point-of-care diagnostics as vital tools in resource-limited settings. They also pointed out the need for diagnostics that distinguish between serotypes.
7] WHO guidelines (2009, 2022): provide diagnostic algorithms that recommend laboratory confirmation during outbreaks and the use of clinical diagnosis in endemic settings when laboratory access is limited.
8] Wills et al. (2005): demonstrated the role of fluid management in avoiding shock and complications in severe dengue. Careful fluid therapy is the cornerstone of treatment.
9] Simmons et al. (2012): outlined standard treatment protocols, including isotonic crystalloid solutions and monitoring for warning signs such as hematocrit changes and persistent vomiting.
10] Srikiatkhachorn et al. (2011) :reviewed biomarkers for severity, suggesting that individualized care may improve outcomes when integrated with laboratory findings.
11] Shepard et al. (2016): discussed the economic burden of dengue and the cost- effectiveness of interventions, including vector control and vaccination.
12] Hadinegoro et al. (2015): evaluated Dengvaxia (CYD-TDV), the first licensed dengue vaccine. The study showed good efficacy in previously infected individuals but raised safety concerns in seronegative recipients.
13] Biswal et al. (2019): reviewed TAK-003, a tetravalent dengue vaccine candidate showing promise in ongoing trials.
14] Sabchareon et al. (2012): stressed that age and serostatus significantly influence vaccine effectiveness and safety, calling for targeted vaccination strategies
15] Bowman et al. (2016): conducted a systematic review of vector control strategies, highlighting that community-based integrated vector management is most effective.
16] Erlanger et al. (2008): noted that environmental control, insecticide-treated materials, and public education are key to reducing mosquito populations.

MATERIALS AND METHOD:

Four studies were reviewed, focusing on their methodologies and materials. Most of these studies concentrated on planning, execution, data analysis, and conceptual definitions. All adhered to the WHO's 1997 classification framework for dengue infections.

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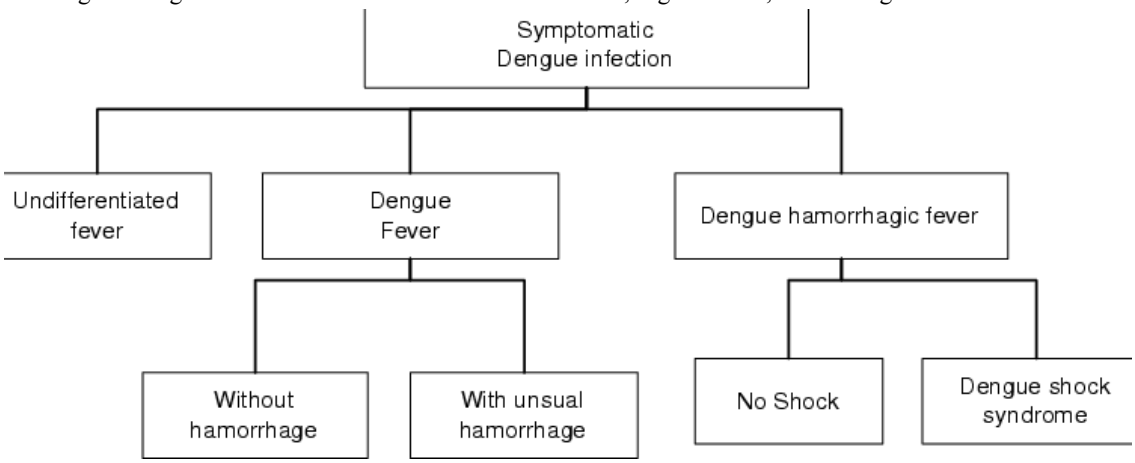
The WHO's 1997 classification system categorizes dengue infections into: 1]Undifferentiated Fever: Fever without specific signs.

2] Dengue Fever (DF): Fever with two or more of the following: headache, retro- orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, leucopenia, and positive tourniquet test.

3] Dengue Hemorrhagic Fever (DHF): Dengue fever with hemorrhagic manifestations and evidence of plasma leakage.

Severe Dengue: Dengue with severe manifestations such as shock, organ failure, or bleeding.



These classifications aid in diagnosing and managing dengue infections.

The reviewed studies also highlighted the impact of environmental factors on dengue transmission. Warmer temperatures enhance the replication of the dengue virus within Aedes mosquitoes, leading to faster spread of the infection. Additionally, climate change affects the distribution of Aedes mosquitoes, allowing them to survive in more regions and at higher altitudes.

In summary, the studies underscore the importance of understanding the clinical features, classification, and environmental factors associated with dengue to improve diagnosis, treatment, and prevention strategies.

DATA ANALYSIS:

In contrast to the other three studies, the first study utilized two distinct methodologies in its data analysis. These included polygenic risk scores (PRS) and core analysis with validation cohorts representing various ancestries. The PRS approach was employed to assess the potential genetic risk associated with dengue virus (DENV) infection outcomes. Additionally, the study examined the effect of applying a PRS to a validation cohort comprising individuals from multiple ancestries and compared these findings with other syndromes .

The remaining three studies collected data through coding and entered it into worksheets. Subsequently, IBM SPSS Statistics 25 was used to analyze and interpret the data. Descriptive statistics were employed to summarize primary characteristics and clinical features, assigning frequencies and percentages to each group. To analyze the relationships between variables, the Chi-square test was utilized .

DIAGNOSIS:

All four studies reviewed consistently demonstrated that polygenic risk scores (PRS) for dengue virus (DENV) infection outcomes—specifically, comparing dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) to dengue fever (DF), and both to healthy controls—yielded comparable effect sizes across different ancestries. For instance, a study by Wang et al. (2020) reported an odds ratio (OR) of 1.31 per standard deviation increase in PRS for DHF/DSS versus DF, and 1.89 for DHF/DSS versus controls, indicating a significant genetic predisposition to severe dengue outcomes .

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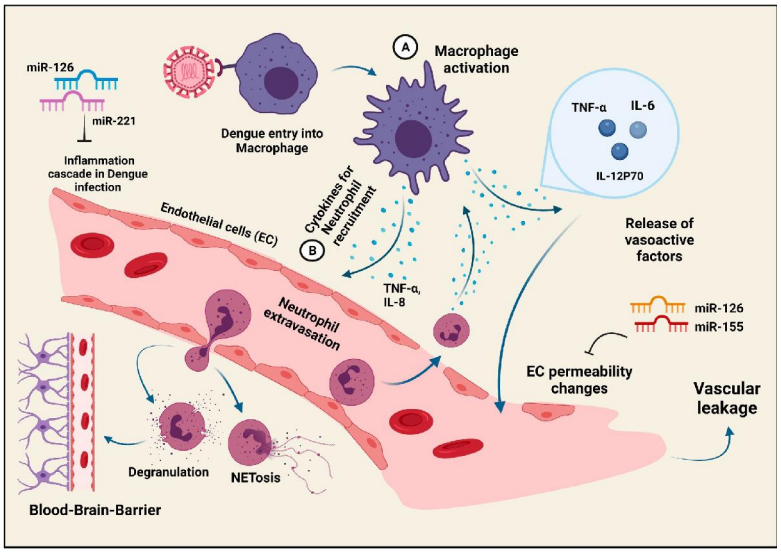

The pathogenesis of DHF involves several factors: changes in viral pathogenicity, genetic predisposition, cytokine storms, lipid profile alterations, and immune enhancement. Notably, some DHF patients have never been exposed to DENV, while the majority have been infected with two different serotypes. This secondary heterotypic infection is associated with antibody-dependent enhancement (ADE), where pre-existing antibodies facilitate viral entry into host cells, leading to increased viral replication and more severe disease manifestations .

Cytokine profiles play a crucial role in dengue pathogenesis. In patients with symptomatic DENV infections, peripheral blood mononuclear cells (PBMCs) produce elevated levels of IL-15, MCP-1, and IL-6. In contrast, patients with mild or non-dengue syndromes exhibit increased secretion of IL-12, IL-2R, MIP-1α, RANTES, GM-CSF, and TNF-α. These cytokines contribute to inflammation and vascular permeability, leading to plasma leakage—a hallmark of severe dengue .

Lipid profiles also influence dengue severity. Patients with severe dengue (DWWS) have lower levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol compared to those with mild dengue (DNWS). These alterations in lipid metabolism may affect immune responses and contribute to disease progression .

Collectively, these findings underscore the multifactorial nature of dengue pathogenesis, highlighting the interplay between genetic factors, immune responses, and lipid metabolism in determining disease severity.

CLINICAL FEATURES:

According to the World Health Organization (WHO) criteria, 43.05% of patients were diagnosed with dengue fever (DF), while 56.95% had dengue hemorrhagic fever (DHF). The highest incidence of dengue occurred among adolescents aged 12–21 years, followed by young adults aged 21–45 years, and children aged 2–12 years .

In the DHF group, a higher proportion of male patients (55.9%) was observed compared to the DF group (46.9%). Common symptoms among dengue patients included fever, nausea/vomiting (66.97%), headache, and abdominal pain (21.7%). Notably, DHF patients exhibited significantly higher rates of nausea/vomiting and abdominal pain compared to DF patients. Conversely, fatigue was more prevalent in the DF group than in the DHF group.

Regarding compliance with the PSN 3M Plus program, no significant correlation was found between gender, age, education, or occupation. However, theoretical models suggest that elderly individuals may have higher compliance and adherence levels. Interestingly, individuals with higher education levels were found to be less compliant with DHF prevention practices. Additionally, working respondents demonstrated lower compliance with DHF prevention practices compared to non- working respondents and housewives. This aligns with previous studies indicating that economically inactive individuals are more likely to engage in DHF prevention measures .

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TREATMENT:

As of 2019, there is no specific antiviral treatment or authorized vaccine for dengue virus (DENV) infections . Dengue fever (DF) and dengue hemorrhagic fever (DHF) continue to pose significant global health threats, with recent outbreaks leading to increased mortality rates .

The cornerstone of dengue management remains supportive care. This includes the administration of paracetamol (acetaminophen) to manage fever and pain, as nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are contraindicated due to their potential to exacerbate bleeding risks . Adequate fluid intake is essential; oral rehydration solutions (ORS), fruit juices, or electrolyte solutions are preferred over plain water to prevent dehydration .

For patients unable to maintain oral hydration, intravenous (IV) fluids are administered. The critical phase of the illness typically occurs between days 3 and 7, transitioning from the febrile phase to the afebrile phase. During this period, close monitoring is crucial, including daily hematocrit measurements to assess plasma leakage and determine the need for IV fluid therapy .

In severe cases, such as DHF, hospitalization is mandatory. Management involves aggressive fluid resuscitation, blood product transfusions if necessary, and continuous monitoring for signs of shock or organ failure .

Preventive measures focus on vector control and minimizing mosquito exposure. While vaccines like Dengvaxia and Qdenga have been developed, their use is currently limited and subject to specific guidelines and approvals .

PREVENTION AND CONTROL STRATEGIES:

Physical Control Methods:

Community-based programs play a pivotal role in educating the public about eliminating mosquito breeding sites. These initiatives involve activities such as cleaning environments, removing containers that collect water, and raising awareness about practices to prevent mosquito breeding. By engaging communities, these programs aim to reduce mosquito populations and prevent the spread of dengue fever.

Biological Control Methods:

Biological control involves using natural organisms to manage mosquito populations. One approach is the introduction of Wolbachia bacteria into mosquitoes, which interferes with their reproductive capabilities, thereby reducing mosquito numbers. Additionally, the Sterile Insect Technique (SIT) involves releasing sterilized male mosquitoes into the wild; these males mate with females, leading to a decline in mosquito reproduction. Furthermore, introducing larvivorous fish species, such as Poecilia reticulata (guppy), Aplocheilus spp. (nalahandaya), and juvenile stages of Tilapia spp. (Oreochromis mossambicus and O. niloticus), into water bodies can effectively reduce mosquito larvae populations.

Chemical Control Methods:

Chemical control involves the use of insecticides to eliminate mosquito larvae and adult mosquitoes. While effective, the continuous use of chemical insecticides can lead to resistance among mosquito populations and may have adverse environmental impacts. Therefore, integrating chemical control with other methods is recommended to enhance efficacy and sustainability.

PAPAYA LEAFS USAGE IN TREATING DENGUE:

Chemical control methods are among the most straightforward approaches to managing dengue vector populations. Insecticides, such as temephos (Abate) and methoprene (Altosid), are commonly used to target Aedes mosquito larvae in water containers. When applied correctly, these chemical agents have minimal environmental impact. It's important to note that while there is no specific antiviral treatment for dengue fever, research indicates that live attenuated dengue vaccines can offer protection against subsequent infections. These vaccines have shown up to 84% efficacy in preventing severe dengue and 82% in reducing symptomatic cases in individuals previously exposed to the virus. Therefore, maintaining environmental hygiene, minimizing mosquito breeding sites, and considering vaccination are crucial steps in dengue prevention.

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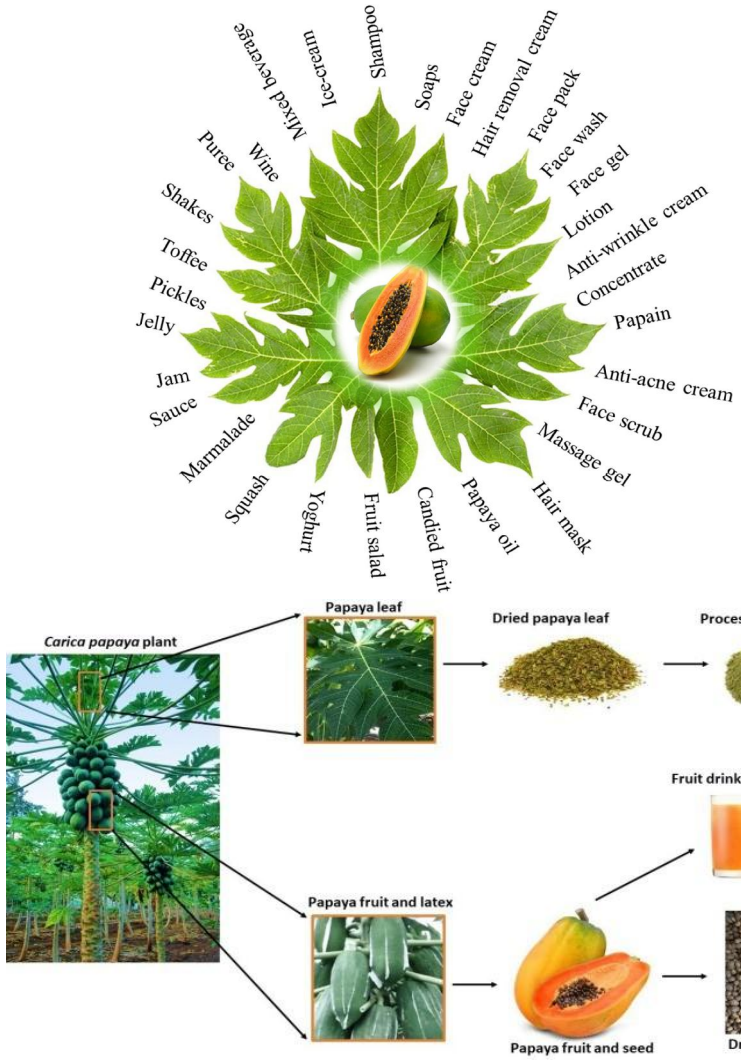

Dengue fever, transmitted by Aedes mosquitoes, has become a significant global health concern. The disease is now endemic in over 100 countries, with an estimated 390 million infections annually. The Americas, Southeast Asia, and the Western Pacific regions are particularly affected, with Asia accounting for approximately 70% of the global disease burden. Factors such as climate change, urbanization, and increased international travel have contributed to the spread of dengue. In countries like India, underreporting of cases exacerbates the situation, with actual numbers potentially being much higher than official statistics .

MECHANISM OF THROMBOCYTOPENIA IN DENGUE:

Dengue hemorrhagic fever (DHF) is characterized by a significant decrease in platelet count, often falling below 100,000 cells/mm³. This thrombocytopenia arises from two primary mechanisms: impaired platelet production (thrombopoiesis) and increased platelet destruction.

Impaired Platelet Production

During the early stages of dengue infection, there is evidence of reduced megakaryocyte production in the bone marrow. This suppression may result from the virus directly infecting megakaryocytes or disrupting stromal cells that regulate cytokine release and megakaryocyte development. Additionally, dengue infection can lead to hypocellularity in

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the bone marrow and inhibition of megakaryocyte maturation. Studies have shown that dengue virus can infect human megakaryocytes in vitro, ex vivo, and in vivo, leading to a reduction in mature megakaryocytes, which are essential for platelet production.

Increased Platelet Destruction

Increased platelet destruction in the bloodstream contributes significantly to thrombocytopenia in DHF. Activated platelets are more prone to aggregation and clot formation, leading to their depletion from circulation. Dengue virus infection can activate platelets through interactions with surface receptors such as FcγRII, DC-SIGN, and heparan sulfate proteoglycans. This activation results in platelet aggregation, attachment to endothelial cells, and subsequent phagocytosis by immune cells. Furthermore, the dengue nonstructural protein 1 (NS1) has been implicated in platelet activation and destruction. NS1 induces immune cell and platelet activation via Toll-like receptor 4 (TLR4), leading to increased vascular permeability and hemorrhaging during dengue infection.

STUDIES IN ANIMALS:

In a study involving mice, administration of 15 mg of powdered Carica papaya leaf per kilogram of body weight resulted in a significant increase in platelet count within 1 to 12 hours post-administration. This suggests that papaya leaf extract may have a rapid effect on platelet production.

Another investigation demonstrated that aqueous extracts of Carica papaya leaves, at doses of 400 mg/kg and 800 mg/kg, significantly boosted platelet levels in rats with cyclophosphamide-induced thrombocytopenia. Additionally, the extract was found to shorten clotting time in the treated rats.

MEDICINAL USES OF THE PAPAYA PLANTS:

Carica papaya, commonly known as the papaya plant, has been utilized since ancient times to treat a variety of health conditions. Scientific research has highlighted the therapeutic potential of its leaves, fruits, and seeds. Leaf extracts containing enzymes like chymopapain and papain are particularly helpful in managing digestive disorders, while the fruit and seed extracts possess antibacterial properties. Both the fruit juice and leaf extract have been shown to offer numerous health benefits, including anticancer, antioxidant, anti-inflammatory, antibacterial, kidney- and liver-protective, blood sugar- and lipid-lowering, and anti-sickling effects for sickle cell disease. Traditionally, ripe papaya has been used to treat ringworm, and unripe fruit has been applied to lower blood pressure, serve as an aphrodisiac, and even induce abortion. Additionally, papaya leaf extract has demonstrated larvicidal activity against Aedes aegypti, the mosquito responsible for transmitting the dengue virus.

POSSIBLE MECHANISM OF ACTION OF PAPAYA EXTRACT IN DENGUE:

Carica papaya leaf extract (CPLE) has garnered attention for its potential in managing thrombocytopenia associated with dengue fever. Several studies have explored its efficacy, particularly in increasing platelet counts and reducing hospital stays.

Scientific Insights

Research indicates that CPLE may exert its effects through multiple mechanisms: Membrane Stabilization: In vitro studies have shown that CPLE can stabilize red blood cell membranes, preventing hemolysis induced by heat and osmotic stress. This property may help protect platelets from damage during dengue infection.

Platelet Augmentation: Animal studies have demonstrated that CPLE administration leads to increased platelet counts in thrombocytopenic rats. This effect is accompanied by elevated levels of thrombopoietin (TPO) and interleukin-6 (IL-6), suggesting a role in hematopoiesis and immune modulation

RESULT:

The risk of developing severe dengue increases with prior exposure to the virus. After an initial infection with one of the four dengue virus serotypes, individuals acquire temporary immunity to that specific serotype. Over time, this

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immunity diminishes, leaving them susceptible to reinfection with a different serotype. Such secondary infections can lead to more severe manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), primarily due to a phenomenon known as antibody-dependent enhancement (ADE).

ADE occurs when non-neutralizing antibodies from a previous infection bind to the new virus, facilitating its entry into immune cells via Fc receptors. This process enhances viral replication and increases the viral load, which is associated with more severe disease outcomes. Additionally, the immune response triggered by ADE can lead to the release of pro-inflammatory cytokines, contributing to vascular leakage and shock .

Epidemiological studies have consistently shown that secondary dengue infections are a significant risk factor for severe disease. For instance, a study involving over 8,000 Nicaraguan children found that those with specific levels of dengue antibodies were 7.64 times more likely to develop severe illness upon reinfection .

Understanding the role of ADE in dengue pathogenesis is crucial for developing effective vaccines and therapeutic strategies. Current research focuses on designing vaccines that can induce a balanced immune response, minimizing the risk of ADE while providing broad protection against all four dengue serotypes.

II. CONCLUSION

While several studies have investigated the use of Carica papaya leaf extract (CPLE) in treating dengue-related thrombocytopenia, it's essential to approach the findings with caution due to certain limitations.

While preliminary studies suggest that CPLE may have a role in managing thrombocytopenia associated with dengue, the existing evidence is not robust enough to make definitive clinical recommendations. Further well-designed, large-scale studies with confirmed diagnoses are necessary to establish the efficacy and safety of CPLE in treating dengue. Healthcare providers should exercise caution and consider the limitations of current research when evaluating CPLE as a treatment option.

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