

EFFECT OF CARICA PAPAYA LEAF EXTRACT ON HAEMORRHAGIC MANIFESTATIONS IN DENGUE FEVER: A RANDOMISED CONTROLLED TRIAL

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Abstract

Background: Dengue fever, a mosquito-borne viral illness, affects millions of people globally and can lead to severe complications, such as haemorrhage and shock, if untreated. While traditional remedies, such as papaya leaf extract, are used for managing dengue, their clinical efficacy remains inconsistent and requires further study. This study aimed to evaluate the effects of CPLE on the haemorrhagic manifestations in patients with dengue fever. **Materials and Methods:** A randomized controlled trial involving 200 patients was conducted at the Tertiary Care Centre between August 2017 and August 2019. Participants were randomly assigned to receive either CPLE (1100 mg thrice daily) or a placebo, along with standard supportive care. Daily monitoring included platelet counts, signs of clinical bleeding, and adverse events, with documented hospital stay duration and treatment adherence. Follow-up ensured that all participants completed the five-day course. **Result:** Dehydration (54%) was the most common adverse event, followed by tachycardia (43%), and petechiae (6%). Most patients had dengue fever (87.5%) and 12% had dengue haemorrhagic fever. Bleeding manifestations occurred in 14 of the 200 patients, primarily melena (40%), gum bleeding, and petechiae (26%). No significant difference was found in the incidence or severity of haemorrhagic manifestations between the treatment and control groups. Platelet counts showed a similar trend of recovery in both groups, with no statistically significant improvement in the CPLE group. In addition, no adverse effects were directly attributed to CPLE. **Conclusion:** CPLE did not significantly affect haemorrhagic manifestations in patients with dengue fever. While the extract was well tolerated, its use did not confer additional benefits in reducing haemorrhagic symptoms compared to placebo.

INTRODUCTION

Dengue fever (DF) is a viral illness that spreads through the bite of an infected female Aedes mosquito. Although it is commonly observed in infants and young children, it can affect individuals of all ages. The disease presents with symptoms such as high-grade fever, intense headaches, muscle and joint pain (myalgia and arthralgia), skin rashes, and episodes of bleeding from the nose and the gastrointestinal tract. If not treated promptly, these symptoms can escalate to severe complications, including extensive haemorrhaging, shock, and potentially death. Dengue haemorrhagic fever, when

untreated, has a mortality rate of 10–20%, and this risk increases significantly if the condition advances to dengue shock syndrome (DSS).^[1]

Globally, dengue affects approximately 2.5 billion people, with 975 million residing in tropical and subtropical regions, particularly in Southeast Asia, the Pacific, and the Americas.^[2] Dengue fever not only has a profound impact on morbidity and mortality but also poses a substantial economic burden.^[3] A study conducted by Edillo et al. (2015) estimated that the direct medical costs of clinically diagnosed dengue cases in the Philippines amounted to USD 345 million annually (based on 2012 US dollars). Dengue appears to have surpassed malaria in terms of its economic toll on the country.^[4]

Dengue virus infection can occur as either a primary or secondary infection. Primary infection leads to an acute febrile illness, commonly referred to as dengue fever, which typically resolves within a week and is driven by a complex immune response. It is characterised by a fever lasting three to five days, often accompanied by headaches, skin rashes, thrombocytopenia (low platelet count), and relative leukopenia (low white blood cell count). Additional symptoms may include severe muscle and joint pain (commonly known as breakbone fever), nausea, vomiting, and pain behind the eyes (retroorbital pain). In contrast, secondary infections tend to be more severe, potentially leading to dengue haemorrhagic fever or dengue shock syndrome (DSS). This complication is marked by increased vascular permeability and plasma leakage, causing haemorrhagic manifestations and severe thrombocytopenia. However, the exact mechanisms underlying these severe manifestations remain unclear.^[5]

In a local study assessing knowledge, attitudes, and practices concerning dengue, herbal remedies such as "tawa-tawa" and papaya were often employed as alternative supportive treatments because of their availability and low cost.^[6] In traditional medicine, papaya latex is believed to aid in the treatment of dyspepsia and is applied externally to the burns and scalds. Papaya seeds and fruits have also been recognized for their anthelmintic and anti-amoebic properties.^[7] Various parts of the *Carica papaya* plant, including latex, ripe and unripe fruits, seeds, seed juice, roots, leaves, flowers, and stem bark, have been reported to possess antimicrobial, anthelmintic, antimalarial, antifungal, anti-amoebic, hepatoprotective, immunomodulatory, and anti-allergic properties.^[8] Animal studies have suggested that papaya leaf extracts may have therapeutic potential in stabilizing biological membranes and inhibiting haemolysis *in vitro*.^[9] However, research on human subjects is limited, findings are often inconsistent, and consistent data on haemorrhagic manifestations have not been reported previously.

Aim

This study aimed to evaluate the effect of CPLP on haemorrhagic manifestations in adult patients with dengue.

MATERIALS AND METHODS

This randomised controlled trial was conducted on 200 patients at a tertiary care center from August 2017 to August 2019.

Inclusion Criteria

- Adult patients aged 18 years and older
- Diagnosed with dengue fever based on clinical and laboratory findings
- Platelet counts were < 150,000/ μ L at the time of enrolment

Exclusion Criteria

- Pregnant and lactating women

- Patients with pre-existing haematological disorders, such as aplastic anaemia or haemophilia.
- Anticoagulant therapy or other medications that affect platelet function
- Individuals with chronic liver disease, renal failure, or other significant comorbidities
- Patients who received platelet transfusions before enrolment in the study.
- The patients were unwilling or unable to provide informed consent.

Methods

Participants were randomly assigned to either the treatment group receiving CPLP (1100 mg thrice daily for five days) or the control group receiving a placebo. Both groups received standard supportive care. Platelet counts were monitored daily for five days, while clinical bleeding events were assessed for signs such as melena, hematemesis, gum bleeding, petechiae, and menorrhagia. Adverse events were recorded and closely monitored throughout the study with strict compliance measures in place to ensure adherence to the treatment regimen. The duration of hospital stay was documented for each participant, and follow-up was conducted to ensure that all participants completed the full five-day treatment course. Outcome data were analysed using statistical methods to compare platelet counts, bleeding episodes, and other haemorrhagic symptoms between the two groups. The findings are presented in pie charts and graphs.

Ethical approval

The study protocol was reviewed and approved by the Institutional Ethics Committee of the Tertiary Care Center. Written informed consent was obtained from all participants before enrolment. This study adhered to the ethical guidelines outlined in the Declaration of Helsinki, ensuring patient confidentiality, safety, and the right to withdraw from the study at any point without repercussions.

RESULTS

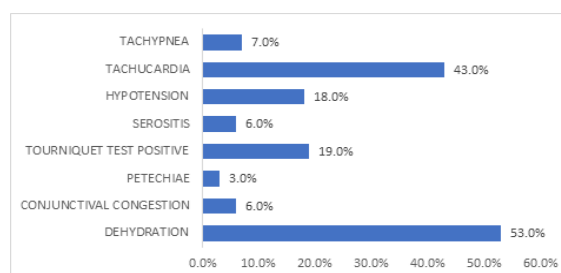


Figure 1: Clinical signs on admission

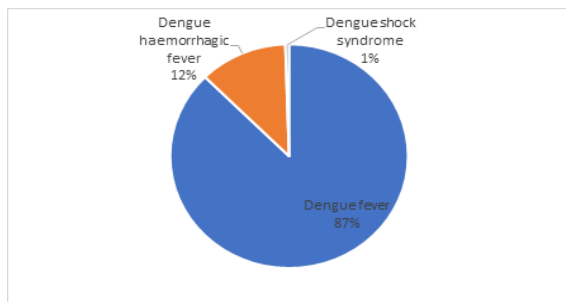


Figure 2: Category of dengue

Dehydration was more common (54%), followed by tachycardia (43%) and petechiae (6%) [Figure 1]. Most of the patients admitted were classified under the category of dengue fever (87.5%), whereas 12% of the patients had dengue haemorrhagic fever [Figure 2].

Manifestations of bleeding

In our study, bleeding manifestations were seen in 14 of 200 patients, most of whom were Malena (40%), followed by gum bleed and petechiae (26%) [Figure 3].

The occurrence of clinical bleeding was similar in both groups (4% in the CPLE group and 3% in the placebo group). There were no data available in other studies on the effect of *Carica papaya* leaf extract capsule (CPLE) on clinical bleeding, as they excluded patients with bleeding manifestations.

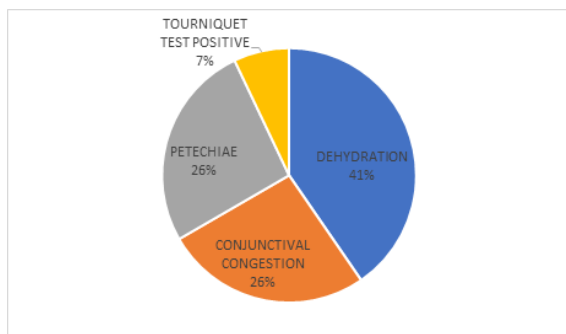


Figure 3: Bleeding manifestations

The study showed no significant reduction in haemorrhagic manifestations or duration of hospital stay among patients treated with CPLE. Adverse effects including nausea and vomiting were more commonly reported in the CPLE group. Haematocrit and haemoglobin levels, as well as the need for platelet transfusions, were similar across both groups.

DISCUSSION

In this study, dehydration was the most common clinical sign on admission, observed in over half of the patients (54%), followed by tachycardia (43%), and petechiae (6%). These findings align with the typical presentation of dengue, where dehydration occurs due to high fever and reduced fluid intake, exacerbating clinical symptoms, such as tachycardia and petechiae.

Most patients (87.5%) were diagnosed with classic dengue fever, with a smaller proportion (12%) presenting with more severe dengue haemorrhagic fever (DHF). This distribution highlights that while most dengue cases remain uncomplicated, a notable percentage progress to DHF, which carries a higher risk of complications, such as plasma leakage and bleeding. In terms of bleeding manifestations, 14 of 200 patients (7%) exhibited symptoms, with melena being the most frequent (40%), followed by gum bleeding and petechiae (26%). These findings are consistent with the haemorrhagic tendencies observed in dengue infections, in which thrombocytopenia increases the risk of bleeding. The similar incidence of clinical bleeding between the CPLE group (4%) and the placebo group (3%) suggests that *Carica papaya* leaf extract does not significantly impact bleeding risk in dengue patients, a finding supported by the lack of previous studies addressing the effect of CPLE on clinical bleeding. Bleeding of varying severity is primarily associated with severe manifestation of dengue, specifically dengue haemorrhagic fever. The underlying pathophysiology of bleeding involves plasma leakage from the blood vessels. This phenomenon is thought to result from platelet destruction mediated by the complement system, bone marrow suppression caused by dengue virus, or possibly a combination of both. Additionally, it has been noted that the platelets that survive the destructive process often exhibit reduced or impaired functionality.^[11,12] Numerous studies have established a direct relationship between platelet count and clinical outcomes in patients with dengue.^[10-13]

The study did not show a significant reduction in haemorrhagic manifestations or hospital stay duration among the patients treated with CPLE. This suggests that while CPLE may have theoretical benefits, its clinical effectiveness in reducing severe complications such as bleeding or shortening hospital stay remains unproven. Additionally, adverse effects such as nausea and vomiting were more frequently reported in the CPLE group, raising concerns regarding the tolerability of this treatment. Key laboratory parameters, including haematocrit and haemoglobin levels, as well as the need for platelet transfusions, showed no differences between the CPLE and placebo groups, further supporting the conclusion that CPLE does not offer significant clinical benefits in managing dengue-associated complications. Given these findings, more extensive research is needed to fully evaluate the efficacy and safety of CPLE in the treatment of dengue fever, particularly in populations at a higher risk of severe disease. Amid the recent dengue outbreak in India, there has been a notable surge in the demand for papaya leaf juice across the country. This rise in interest has been fueled by opinion pieces, news reports, and blogs in print, social, and national media, all of which promote the use of papaya as a treatment for dengue due to its perceived ability to boost platelet counts.^[14] Scientific literature highlights the

potential therapeutic benefits of the aqueous extract of papaya (*Carica papaya*) leaves, attributing these effects to various active compounds, such as flavonoids, alkaloids, enzymes, and minerals, which may exert antioxidant and immunomodulatory actions.^[15-18] A bioinformatics study revealed that flavonoids present in the leaf extract of *Carica papaya* can inhibit proteases crucial for viral assembly.^[17] Additionally, *C. papaya* leaf extract possesses antioxidant properties and scavenges free radicals, which may contribute to the prevention of haemolysis and bleeding.^[19]

A systematic review conducted by Charan et al., including four clinical trials, reported the potent activity of *Carica papaya* leaf extract in the management of DSS, where a reduction in hospital stays and an increase in platelet count were reported. Bioactive compounds in *Carica papaya* have been suggested to enhance the stability of platelet membranes, thereby reducing platelet destruction. These compounds include flavonoids, which exhibit antioxidant properties and scavenge free radicals, contributing to the stabilization of erythrocyte membranes and mitigating lysis under stress conditions, such as infections. Research indicates that administration of the extract may also lead to an increase in the white blood cell count and stabilization of haematocrit levels. A potential mechanism underlying these effects is genetic modulation by certain *C. papaya* constituents, such as the upregulation of arachidonate 12-lipoxygenase (ALOX 12), which promotes megakaryocyte production, and the platelet-activating factor receptor (PTAFR) gene, which enhances megakaryocyte expression and subsequently boosts platelet production.^[20]

In a 2008 study, Hettige S. investigated 12 consecutive dengue patients treated with *Carica papaya* leaf extract (CPLE) and observed a rapid increase in white blood cell (WBC) and platelet (PLT) counts, with all patients recovering without requiring hospital admission.^[21] Subsequent clinical trials, including randomised controlled trials (RCTs), have reported similar outcomes.^[22,23]

In 2010, Otsuki N. and colleagues examined the anti-tumour and immunomodulatory effects of CPLE. In vitro studies have revealed that CPLE enhances Th1-type immunity. It is known that the progression from dengue fever (DF) to dengue haemorrhagic fever (DHF) is associated with a shift from Th1 to Th2-type immune responses.^[24] The study suggested that CPLE might mitigate this shift, potentially reducing the incidence of DHF. Additionally, Norahmed and others have highlighted the immunomodulatory effects of CPLE in DENV-infected rats.^[25]

Our study revealed that dehydration was the most prevalent clinical sign among dengue patients, followed by tachycardia and petechiae. Most patients were classified as having dengue fever, with a small percentage of patients diagnosed with dengue haemorrhagic fever. Although bleeding manifestations were observed in a subset of patients,

including malena, gum bleeding, and petechiae, the incidence of clinical bleeding was comparable between the *Carica papaya* leaf extract (CPLE) and placebo groups. Despite this, treatment with CPLE did not result in a significant reduction in haemorrhagic manifestations or length of hospital stay. Adverse effects such as nausea and vomiting were more frequently reported in the CPLE group. Overall, CPLE did not demonstrate a substantial benefit in terms of clinical outcomes or hematologic parameters compared with placebo.

CONCLUSION

Carica papaya leaf extract did not significantly affect platelet count, haemorrhagic manifestations, or adverse reactions. These findings suggest that CPLE may not be a reliable treatment option for managing thrombocytopenia or reducing haemorrhagic risks in dengue fever. Further studies are necessary to explore alternative therapeutic options.

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