Section: General Medicine

Original Research Article

# EXPLORING THE THERAPEUTIC POTENTIAL OF CARICA PAPAYA LEAF EXTRACT IN DENGUE: A DOUBLE-BLIND, RANDOMIZED TRIAL ON PLATELET ENHANCEMENT AND CLINICAL RECOVERY

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## Abstract

**Background:** Dengue fever, a mosquito-borne viral infection, poses significant global health risks, particularly in tropical regions. CPLE is traditionally used to manage dengue-related thrombocytopenia; however, its clinical efficacy remains unclear. This study aimed to evaluate the efficacy of CPLE on platelet counts and clinical outcomes in patients with dengue through a double-blind randomised controlled trial. **Materials and Methods:** This double-blind, stratified, randomised controlled trial was conducted at the Tertiary Care Center from August 2017 to August 2019. 200 patients were randomised to receive either CPLE (1100 mg thrice daily) or placebo for 5 days, stratified by platelet count (<75,000 or ≥75,000 cells/μL). Platelet counts were monitored daily, with subgroup analysis comparing outcomes based on the initial counts. Adverse effects were recorded, and data were presented using pie charts and graphs. **Result:** Most patients presented on day 5 of fever (28.5%). No significant difference in mean platelet counts was observed between the CPLE and placebo groups, with the maximum difference observed on day 5 (1,06,800±52,447 vs. 1,00,197±54,788, p=0.454). Most patients were discharged after five days (46 in the CPLE group vs. 38 in the placebo group). CPLE did not significantly improve platelet counts, reduce hospital stay, or affect haematocrit and haemoglobin levels. Platelet transfusion requirements were similar, with nausea and vomiting being reported as common adverse effects in the CPLE group. **Conclusion:** Administration of CPLE did not result in significant improvements in platelet counts or clinical outcomes in dengue patients. These findings suggest that CPLE may not provide a therapeutic benefit for managing dengue-associated thrombocytopenia.

## INTRODUCTION

Dengue fever is a significant public health concern, particularly in tropical and subtropical regions. Dengue fever is caused by the dengue virus belonging to the flavivirus family, which is transmitted by the vector mosquito Aedes aegypti. Both Aedes aegypti and Aedes albopictus were the main competent vectors of dengue virus. The disease is characterised by fever, thrombocytopenia, and risk of haemorrhagic manifestations. Currently, there is no specific treatment for dengue, and its management includes supportive care. Mortality in dengue is most often due to shock, intractable multiorgan dysfunction, or uncontrollable bleeding.[1,2]

Carica papaya, an herbaceous plant resembling a tree, belongs to the family Caricaceae.[3] Commonly referred to as papaya, this evergreen species features broad, spirally arranged leaves measuring 50-70 cm and bears fruit throughout the year.[4] Native to Southern Mexico, C. papaya has been widely distributed across tropical regions globally. The fruit of C. papaya is regarded as a quasi-drug, and numerous studies have confirmed the bioactivity of its various components, including leaves, fruits, shoots, roots, rinds, latex, and seeds.[5] Notably, C.


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papaya leaves exhibit several therapeutic properties, including high concentrations of fat-soluble vitamins (A, D, E, and K), vitamins B and C, and essential minerals such as iron, sodium, and magnesium.[6] Additionally, plants absorb significant amounts of potassium, nitrogen, and calcium during growth, whereas phosphorus is extracted to a lesser extent.[7] In some Asian countries, young C. papaya leaves are steamed and consumed as spinach because of their health benefits. C. papaya leaf juice is known for its role in liver repair and the normalization of clotting, particularly by increasing platelet and white blood cell counts. Various studies have demonstrated the efficacy of C. papaya leaves in mitigating thrombocytopenia complications, which is attributed to their rich phytochemical profile.[8]

Dengue is a viral infection transmitted by mosquitoes, characterized by its acute onset and is significantly associated with morbidity and mortality.[9] Currently, approximately half of the global population resides in regions where dengue transmission is endemic, with approximately 125 countries affected.[10] Annually, there are estimated 50-200 million dengue infections worldwide, including 500,000 cases of severe dengue and 20,000 deaths related to the disease.[11] Future projections suggest an increase in dengue incidence and prevalence owing to factors such as climate change, increased travel, socioeconomic shifts, global trade, and viral evolution.[11] For individuals living in endemic areas, the risk of contracting dengue is approximately 40%, with a 0.5% chance of progressing to severe disease. Clinically, dengue presents with symptoms such as moderately high fever, rash, and intense body aches, particularly back and retroorbital pain. This was often followed by a period of clinical improvement. In more severe cases, the symptoms may include vomiting, abdominal pain, petechiae, reduced urine output, altered mental status, and bleeding. The hallmark of severe dengue is the leakage of fluid from blood vessels and capillaries, which can occur in areas such as the nose, gums, skin, lungs, and abdominal cavity, signifying life-threatening progression of the disease.[12]

Excessive fluid therapy also contributes to mortality in patients with plasma leakage due to the development of pulmonary oedema during the recovery phase. Traditional medicine has proposed the use of Carica Papaya Leaf Extract (CPLE) as a potential treatment to increase platelet counts and reduce bleeding risks in dengue patients. However, the clinical efficacy of CPLE remains controversial and requires rigorous scientific evaluation.[11,12]

**Aim**

This study was aimed to assess the effect of CPLE on platelet counts and clinical outcomes in patients with dengue.

## MATERIALS AND METHODS

This double-blind, stratified, randomised controlled trial was conducted at the Tertiary Care Center from August 2017 to August 2019. A total of 200 adult patients diagnosed with dengue fever and with a platelet count below 150,000 were enrolled in the study.

**Inclusion criteria**

- Patients aged 18-65 years were diagnosed with dengue fever based on the clinical and laboratory criteria.
- The platelet count was < 150,000 cells/µL at the time of enrolment.
- Onset of fever within the last 7 days.
- Patients willing to provide informed consent.
- Hemodynamically stable patients (i.e., without shock).

Exclusion criteria

- History of chronic platelet disorders or preexisting haematological conditions.
- Pregnant and lactating women.
- Patients on anticoagulant therapy or those with other significant comorbid conditions such as chronic liver disease, renal failure, or malignancy.
- Patients with evidence of bleeding diathesis or ongoing major bleeding.
- Patients with known allergies to Carica papaya or extracts.
- Patients who had previously received platelet-enhancing treatment within the last 7 days.

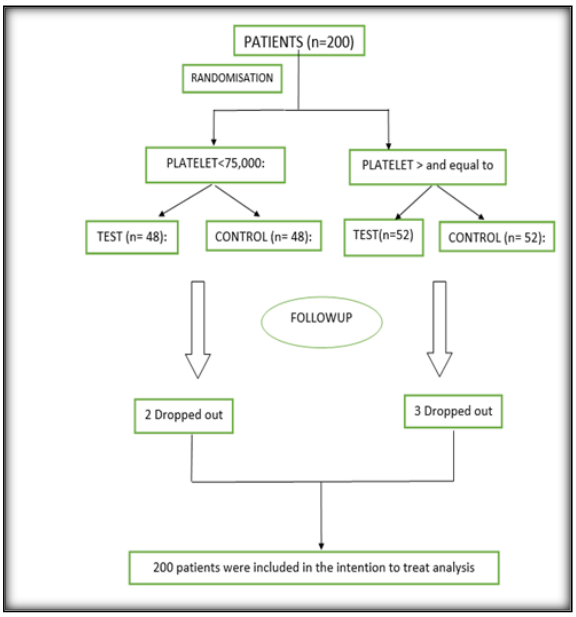


**Figure 1: Requirement of the study participants and follow-up**

Ethical approval: Ethical approval for this study was obtained from the Institutional Ethics Committee of the Tertiary Care Center. Written informed consent was obtained from all participants before enrolment, and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Randomisation and data collection: A total of 200 patients were randomly assigned using a computer-generated stratified randomisation process to either the intervention group (n=100), which received standardised doses of CPLE (1100 mg three times


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daily for 5 days), or the control group (n=100), which received a placebo. Randomisation was stratified based on the initial platelet counts (< 75,000 and ≥ 75,000 cells/µL). Compliance was monitored through daily follow-ups, and all patients completed the full 5-day treatment course.

Platelet counts were recorded daily for five days in both groups, and a subgroup analysis was performed to compare outcomes between patients with platelet counts < 75,000 and those with platelet counts ≥ 75,000. Adverse effects were recorded during the study period.

Statistical analysis

Data were collected, entered, and double-checked using a Microsoft Excel spreadsheet. Data were compared using an independent-sample t-test. Statistical significance was set at $p<0.05$. Data are presented as pie charts and graphs, summarising the mean platelet count, subgroup outcomes, and reported adverse effects.

## RESULTS

In our study, most patients presented on day 5 of fever (28.5%) [Figure 2].

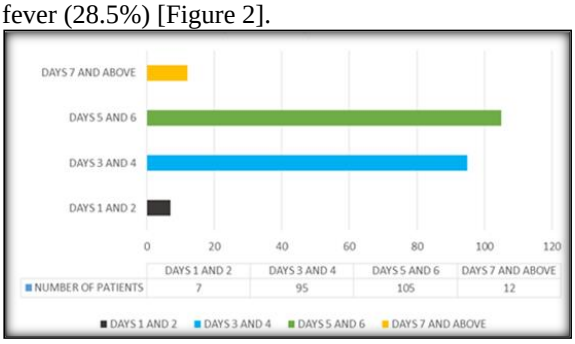


**Figure 2: Day of fever**

### Mean platelet difference between the two groups over 5 days

There was no statistically significant difference between the two groups in terms of mean platelet counts, and the maximum difference was seen on 5th day (1,06,800±52,447 in the CARIPILL group vs. 1,00,197±54,788 in the placebo group, p=0.454) [Figure 3 and 4].

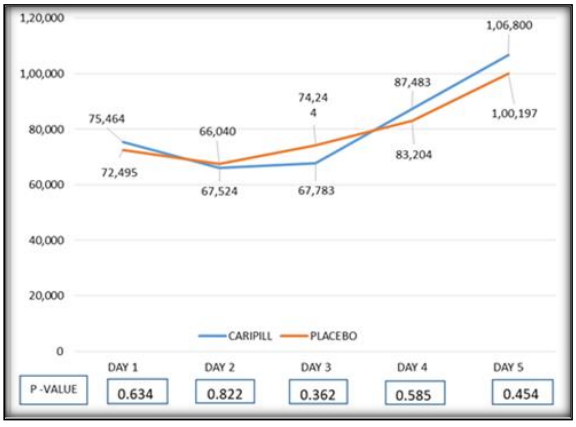


**Figure 3: Mean platelet count in 5 days**

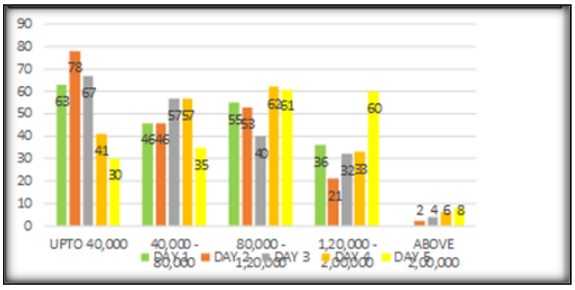


**Figure 4: Platelet distribution in 5 days**

### Duration of hospital stay

Most patients were discharged after five days. 46 of the 100 patients and 38 of the 100 patients were discharged on the 5th day in the CPLE and placebo groups, respectively [Figure 5].

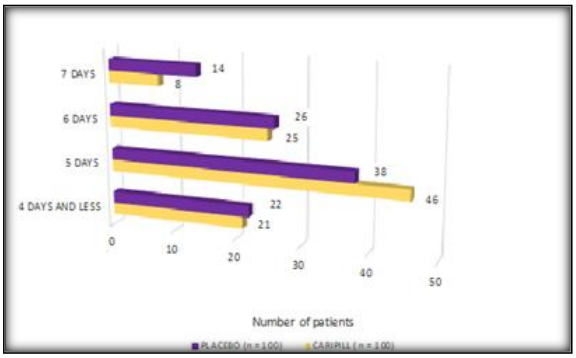


**Figure 5: Hospital stay**

The study found no significant improvement in the mean platelet counts in the CPLE group compared to the placebo group. Additionally, there was no reduction in the duration of hospital stay among patients who underwent CPLE. Haematocrit and haemoglobin levels remained unaffected by CPLE, and the requirement for platelet transfusions was similar in both groups. The common adverse effects reported in the CPLE group included nausea and vomiting.

## DISCUSSION

Thrombocytopenia leading to bleeding is a dengue complication. Thrombocytopenia is characterized by petechiae, gum bleeding, melena, hematemesis, and bruising. Causes of thrombocytopenia in DF include bone marrow suppression in the early stages, disseminated intravascular coagulation, peripheral sequestration of platelets, and destruction of platelets (antiplatelet antibodies). Severe thrombocytopenia is associated with DHF and DSS and, if untreated, leads to morbidity and mortality. Only a few studies have been conducted in adult patients. Hence, there is a lack of evidence to claim that Carica papaya leaf extract capsule (CPLE) is useful in the treatment of thrombocytopenia in adult patients with dengue. Therefore, this study aimed to evaluate the efficacy of Carica papaya leaf extract capsules (CPLE) in adults with dengue fever and thrombocytopenia.[12]


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In this study, we investigated the effects of Carica papaya leaf extract (CPLE) on platelet counts and clinical outcomes in patients with dengue fever. Most patients (28.5%) presented on the 5th day of fever, indicating that most participants sought medical attention in the critical phase of dengue, when thrombocytopenia typically manifests [Figure 2]. This timing aligns with the natural progression of the disease, in which platelet levels tend to decline during later stages of infection. Our findings revealed no statistically significant difference in the mean platelet counts between the CPLE and placebo groups over the 5-day treatment period. The maximum observed difference in platelet counts occurred on the 5th day, with a mean platelet count of 106,800±52,447 in the CPLE group compared to 100,197±54,788 in the placebo group (p=0.454) (Figures 3 and 4). Despite this numerical difference, the lack of statistical significance suggests that CPLE does not confer a meaningful clinical advantage in boosting platelet levels during the acute phase of dengue fever.

Data were extracted from four clinical trials comprising 377 participants.[13-16] A comparison between the Carica papaya and control groups showed a statistically significant increase in platelet count, with a mean difference (MD) of 20.27 (95% CI: 6.21–34.73; p=0.005). Moderate heterogeneity was observed across the studies ($I^2$ = 50%). Similar findings were observed after excluding the trial conducted by Yunita et al., with a standardised mean difference (SMD) of 0.46 (95% CI: 0.13–0.78; p=0.006) and heterogeneity slightly reduced ($I^2$ = 45%).[14]

Moreover, the duration of hospital stay was comparable between the two groups. Most patients were discharged by the 5th day, with 46% in the CPLE group and 38% in the placebo group, leaving the hospital after 5 days. This finding further supports the conclusion that CPLE does not significantly alter the clinical course of dengue in terms of recovery time or hospitalization duration. Data for this outcome was available from a single study that included a total of 80 participants.[14] The systematic review conducted by Charan J et al., reported that treatment with Carica papaya was significantly linked to a reduction in the duration of hospitalization compared to the control group, with a mean difference (MD) of 1.90 days (95% CI: 1.62–2.18; p < 0.00001).[17]

C. papaya leaf extract (CPLE) has been shown to increase the activity of genes such as arachidonate 12-lipoxygenase (ALOX12) and platelet-activating factor receptor (PTAFR), which influence platelet production and platelet aggregation. The hypothesized mechanism of action is the increased activity of ALOX-12, which increases the production of platelets through its active metabolite 12-hydroxy eicosatetraenoic acid (HETE) and increases the platelet-activating factor receptor (PTAFR), but there are no proven studies. There is limited research available on the exact mechanisms underlying the beneficial effects of Carica papaya leaf extract on dengue. An in vitro study conducted by Ranasinghe et al. demonstrated that C. papaya leaf extract is associated with enhanced erythrocyte membrane stabilisation.[18] Additionally, a bioinformatics study revealed that the flavonoids in C. papaya leaf extract may inhibit a protease involved in viral assembly.[19] Moreover, the extract exhibited antioxidant and free radical-scavenging properties, which may contribute to the prevention of haemolysis and bleeding.[20]

The findings of this study suggest that Carica papaya leaf extract does not significantly affect platelet counts or reduce clinical outcomes in patients with dengue fever. Despite the traditional use of CPLE for this purpose, the results indicate that its efficacy is comparable to that of placebo. This study highlights the need for further research into alternative treatments for thrombocytopenia in dengue patients, given the lack of significant benefits of CPLE.

## CONCLUSION

Carica papaya leaf extract did not demonstrate a significant effect on platelet count or hospital stay duration in adult patients with dengue fever. Carica Papaya leaf extract capsule (CPLE), though shown to improve platelet counts in previous studies, has not been shown to have any beneficial effect in this randomized control trial on patients with Dengue fever. A meta-analysis of high-quality RCTs is necessary to obtain more clarity and reasons for heterogeneity in the results of the Carica Papaya effect in the treatment of dengue fever.

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