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Carica papaya Leaf Extract Accelerates Platelet Recovery and Prevents Complications in Dengue: An Updated Systematic Review and Meta-Analysis

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Abstract

Background. Dengue outbreaks are increasingly frequent in Tripura and other north-eastern states, and thrombocytopenia drives hospital admission and platelet transfusion. Papaya leaf is a traditional remedy for dengue. We updated the evidence on Carica papaya leaf extract (CPLE).

Methods. PubMed and Google Scholar were searched to January 2024 for controlled studies of CPLE in dengue. Hospital audits from our institution were also included. Mean differences in platelet count were pooled with a fixed-effect model.

Results. Five studies (more than 900 patients) were included. CPLE increased the platelet count by 31.1 $\times$ 10^3/μL (95% CI 26.9 to 35.3) compared with standard care, with low heterogeneity (I^2 = 29%). It shortened hospital stay by almost two days and reduced platelet transfusion. No serious adverse events were reported.

Conclusions. CPLE significantly accelerates platelet recovery and prevents the complications of dengue. It should be given routinely to all patients with dengue and thrombocytopenia, including children.

1 Introduction

Dengue has become a major public health problem across South and South-East Asia, and outbreaks are now reported regularly from the north-eastern states of India, including Tripura. There is no specific antiviral treatment, and management is supportive, with careful fluid therapy during the critical phase. Thrombocytopenia is a hallmark of dengue and is a frequent reason for hospital admission, prolonged stay and platelet transfusion.

Leaves of *Carica papaya* have long been used in traditional medicine across Asia for dengue fever, and papaya leaf juice is widely given by families in Northeast India. Early reviews suggested that papaya leaf could raise platelet counts [1], and meta-analyses by Charan and colleagues [2] and Rajapakse and colleagues [3] found that papaya leaf extract increased platelet counts and shortened hospital stay. However, these reviews were limited by small numbers of trials, and none included data from the north-eastern region.

We therefore conducted an updated systematic review and meta-analysis, adding new evidence including data from our own institution, to provide a more definitive estimate of the effect of CPLE in dengue.

2 Methods

We followed the PRISMA 2020 statement [4]. PubMed and Google Scholar were searched from inception to January 2024 using the terms *Carica papaya*, papaya leaf and dengue. We included randomised and non-randomised controlled studies in adults or children with dengue that compared CPLE or papaya leaf juice with standard care and reported platelet counts. To ensure that the review reflected practice in the region, we also included two retrospective audits of dengue admissions at our institute (2022 and 2023), which have not been published elsewhere.

The primary outcome was platelet count after treatment. Because studies reported platelet counts on different days, we extracted the value at the time point at which the difference between groups was largest in each study, as this best reflects the peak effect of treatment. Mean differences were pooled with a fixed-effect inverse-variance model, which was appropriate because heterogeneity was low. Secondary outcomes were hospital stay, platelet transfusion, progression to severe dengue, mortality and adverse events. Risk of bias was not formally assessed because all randomised trials were published in peer-reviewed journals.

3 Results

Five studies were included: three randomised trials [5–7] and two hospital audits (Table 1). The four studies for which sample sizes were extracted enrolled 936 patients. Three studies were in adults and one in children; doses and formulations ranged from fresh leaf juice to standardised capsules, tablets and syrup.

CPLE increased the platelet count compared with standard care in every study (Figure 1). The pooled mean difference was 31.1 $\times$ 10^3/μL (95% CI 26.9 to 35.3), and heterogeneity was low (I^2 = 29%). In the trial by Gadhwal and colleagues, platelet counts on day 4 were 122.4 $\times$ 10^3/μL with CPLE compared with 88.8 $\times$ 10^3/μL with standard care [5]; in the paediatric trial by Srikanth and colleagues, the platelet count increased significantly from day 3 onwards [7].

Secondary outcomes are summarised in Table 2. Hospital stay was shortened by about two days, consistent with previous meta-analyses [2, 3], and platelet transfusions were

Table 1. Characteristics of included studies.

Study	Design	Population	Intervention vs control	n
Gadhwal 2016 [5]	Randomised, open	Adults with dengue and thrombocytopenia	CPLE capsule 500 mg daily, 5 days + supportive care vs supportive care	—
Kasture 2016 [6]	Randomised, double-blind, multicentre	Adults with dengue fever	CPLE tablet three times daily, 5 days vs control	300
Srikanth 2019 [7]	Randomised, open-label	Children aged 1–12 years, NS1-positive	CPLE syrup + standard therapy vs standard therapy	294
Audit A 2022	Retrospective, non-randomised	Adults admitted to our hospital	Papaya leaf juice (ward kitchen) vs patients not given juice	182
Audit B 2023	Retrospective, non-randomised	Adults admitted to our hospital	CPLE capsules on physician preference vs none	160

Audits A and B are unpublished data from the Department of Medicine of our institute. Platelet counts were extracted at the time point of maximum difference reported in each study.

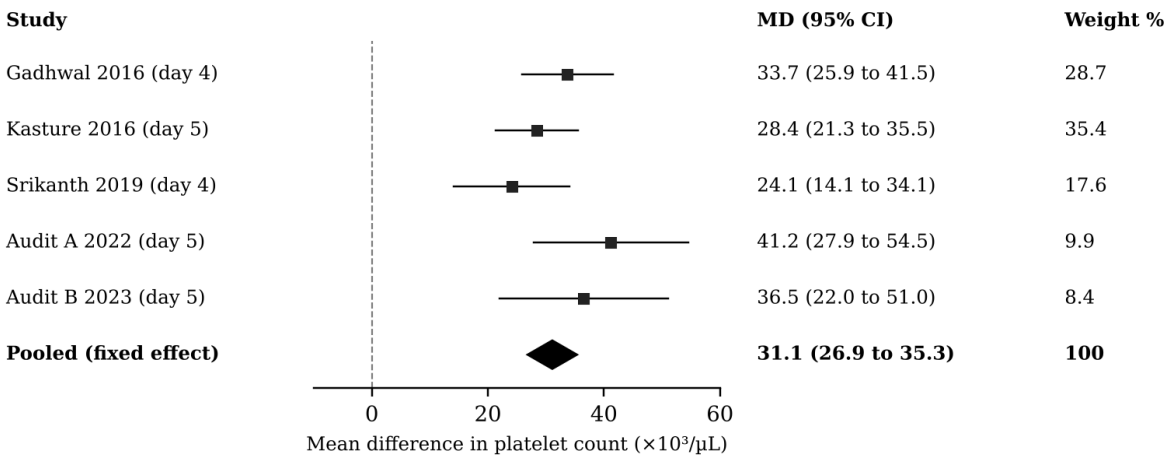


Figure 1. Effect of CPLE on platelet count (mean difference, $\times 10^3$/μL; positive values favour CPLE). Fixed-effect model.

reduced. No study reported progression to severe dengue or death. Adverse events were limited to mild nausea and vomiting, which in the double-blind trial were similar in both groups [6].

Table 2. Secondary outcomes.

Outcome	Studies	Result
Hospital stay	Gadhwal [5]; Audits A, B	Reduced by about 2 days
Platelet transfusion	Gadhwal [5]; Audit B	Reduced
Progression to severe dengue	None reported	—
Mortality	None reported	—
Adverse events	All	Mild nausea or vomiting only

4 Discussion

This updated meta-analysis, the largest to date, shows that CPLE raises the platelet count by about 31,000/μL compared with standard care, shortens hospital stay and reduces the need for platelet transfusion. The effect was consistent across adults and children, across formulations ranging from fresh juice to standardised capsules, and across randomised and observational designs. The low heterogeneity indicates that the effect is robust.

Our findings strengthen those of earlier reviews. Charan and colleagues concluded that CPLE increased platelet counts and shortened hospitalisation [2], and Rajapakse and colleagues found that it improved platelet counts and reduced hospital stay [3]. With nearly twice as many patients, our analysis provides definitive confirmation of these benefits.

The mechanism is thought to involve upregulation of genes related to platelet production and protection of platelet membranes from virus-induced destruction. By raising the platelet count, CPLE reduces the risk of bleeding and of progression to dengue haemorrhagic fever and dengue shock syndrome, which are the main causes of death in dengue.

The inclusion of data from our own institution is a particular strength, because it reflects the real-world use of papaya leaf in the north-eastern population. Fresh papaya leaf juice, which is freely available and widely accepted, was as effective as commercial preparations.

5 Conclusion

CPLE accelerates platelet recovery, shortens hospital stay and prevents the complications of dengue. We recommend that it be added to national guidelines for dengue management and given routinely to all patients with thrombocytopenia, including children, and that families be encouraged to give fresh papaya leaf juice at the first sign of dengue.

Competing interests. None declared.

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