BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 15, Number 2, October 2026 | Pages: 2229-2240 | DOI: 10.14421/biomedich.2026.152.2229-2240 ISSN 2540-9328 (online)

Effect of *Carica papaya* Leaf Extract on Platelet Count in Dengue-Induced Thrombocytopenia: A Systematic Review and Meta-Analysis

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Manuscript received: 16 June 2026. Revision accepted: 02 October 2026, Published: 20 November 2026.

Abstract

Dengue fever remains a prime public health trouble in tropical regions and is regularly related to thrombocytopenia. *Carica papaya* leaf extract (CPLE) has been broadly used as a conventional medicine to increase platelet counts in dengue sufferers. Numerous studies have analyzed the ability of *Carica papaya* leaves, which have verified effective as a therapy for thrombocytopenia. This systematic overview changed into performed according with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines. Population: sufferers of all ages diagnosed with Dengue Hemorrhagic Fever (DHF) observed through thrombocytopenia (low platelet count number); intervention: management of papaya leaf extract (*Carica papaya*) in any dosage form. Comparison: manipulate group receiving placebo, trendy care (without papaya leaf extract), or no intervention; outcome: exchange in platelet rely. The Cochrane Risk of Bias tool (RoB 2.0) and the ROBINS-I tool (Risk of Bias in Non-randomized Studies of Interventions) have been used to evaluate bias, and Rstudio became used for statistical analysis. *Carica papaya* leaf extract confirmed a significant increase in platelet count compared to the control (SMD = 0.40; 95% CI: 0.18–0.63; p = 0.0003). Subgroup analysis by way of day confirmed that the impact was no longer extensive on days 2 and 4, however giant on days 3 (SMD = 0.46; 95% CI: 0.04–0.87) and 5 (SMD = 0.63; 95% CI: 0.14–1.13), without a significant differences among the assessment times. Inside the adult populace (29 studies; n = 4,133), the intervention had a sizable effect (SMD = 0.52; 95% CI: 0.31–0.73; p < 0.0001) with an increasing effect from day 3 to 5. Within the pediatric population (7 research; n = 1,260), the intervention impact numerous over time, with a non-sizable effect on day 2, a large effect on day 3 (SMD = 0.54; 95% CI: 0.31–0.77), and day 5 (SMD = 1.21; 95% CI: 0.96–1.45), and a considerable difference among evaluation days (p < 0.0001). *Carica papaya* leaf extract adjunctive therapy effectively increases platelets in dengue patients with thrombocytopenia in the adult population, but not significantly in children.

Keywords: Thrombocytopenia; Platelet; *Carica papaya* Leaf; Dengue.

INTRODUCTION

Dengue has a global effect, causing significant morbidity and mortality. It's far found in as a minimum 128 nations, with nearly 4 billion human beings global susceptible to contamination (Rajapakse et al., 2019). The prevalence of dengue fever has elevated dramatically international in current decades, with the number of cases stated to the WHO rising from 505,430 in 2000 to 14.6 million in 2024. The disease is now endemic in greater than 100 international locations. In 2024, greater than 12,000 dengue-related deaths had been mentioned. ninety-seven nations pronounced more than 4 million cases and greater than 3,000 deaths to the who from January to July 2025. Dengue fever is spreading to new areas, including Europe and the Japanese mediterranean (Lim et al., 2025).

Indonesia is a tropical archipelago located at the equator and has main seasons: the dry season and the rainy season. these climatic situations contribute to the emergence of various tropical diseases, one of which is dengue hemorrhagic fever (DHF). DHF is an infectious disease caused by the dengue virus, transmitted with the aid of the *Aedes spp*. Mosquito, known as one of the fastest-growing mosquito species, especially in tropical areas like Indonesia. It is expected that approximately 390 million humans are infected yearly by way of this mosquito (Kemenkes RI, 2018). Records from the ministry of health shows that during March 2024, 53,131 cases of DHF had been mentioned in Indonesia. In the meantime, deaths from DHF reached 404. DHF cases increased again the following week, achieving 60,296 cases, with 455 deaths (Kemenkes RI, 2024).

One characteristic of severe dengue is a lower in platelet count (thrombocytopenia) followed by using blood clotting disorders. However, the decrease in platelets in dengue is typically transient and self-resolving. Research shows that the non-structural protein 1 (NS1) of the dengue virus can increase the expression of tissue factor (TF) on cell membranes, which then activates platelets. Activation of these coagulation and infection pathways triggers the release of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-6. High stages of TNF-α are known to be related to the arrival of bleeding signs and symptoms. Moreover, thrombocytopenia can also occur because of platelet accumulation within the endothelium of blood vessels, where platelets adhere to von willebrand factor (vWF). This leads to the formation of small plugs in the microcirculation and a decrease within the number of platelets within the peripheral blood (Sathyapalan et al., 2020).

Plants and plant-based totally products have been used considering that historical times to prevent various human sicknesses. Globally, approximately 80% of the world's population still relies directly on plants as a primary source of healthcare. Many research have also suggested the usage of medicinal plant life to treat diverse diseases. One such plant is the papaya (*Carica papaya linn*.) From the *Caricaceae* family (Singh et al., 2020). This plant is local to southern Mexico, central the United states, and northern South America. Currently, papaya is extensively cultivated in diverse tropical international locations, such as Bangladesh, India, Indonesia, Sri Lanka, the Philippines, and the West Indies, including Malaysia (Subenthiran et al., 2013).

Carica papaya leaf contains proteolytic enzymes, namely papain and chymopapain. Papain itself is a protease enzyme that could stimulate the formation of thrombopoietic cytokines including IL-6, SCF, and IL-3, which play a function in growing platelet production by increasing thrombopoietin (TPO) secretion in the the liver. However, research addressing this potential is still limited. Consequently, this systematic review and meta-analysis targets to critically examine the to be had clinical evidence, specially from prospective managed medical trials, concerning the effectiveness of papaya leaf extract (*Carica Papaya* Leaf Extract/CPLE) as a therapy in overcoming thrombocytopenia in dengue-infected patients (Agustia, 2019).

METHODS

This systematic review was performed according with the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Page et al., 2020; Page et al., 2021). This systematic review was prospectively registered with PROSPERO CRD420251270264 and can be accessed at https://www.crd.york.ac.uk/PROSPERO/view/CRD420251270264. The PICO (population, intervention, control, and outcome) framework was as follows:

Population (P):
Patients of all ages diagnosed with Dengue Hemorrhagic Fever (DHF) accompanied by thrombocytopenia (low platelet count).

Intervention/Exposure (I):
Administration of papaya leaf extract (*Carica papaya*) in any dosage form (capsules and tablets) at any dose and duration, either as adjuvant therapy or monotherapy.

Comparison (C):
The control group received a placebo, standard care (without papaya leaf extract), or no intervention.

Outcome (O):
Change in platelet count (mean difference in platelet count from baseline to end of observation or rate of platelet increase per day).

Search Strategy and Selection Criteria
A systematic search for studies was conducted in the scientific databases PubMed, ProQuest, Scopus, Cochrane Library, Web of Science, and Google Scholar published up to March 1, 2026. The search was conducted using a combination of keywords using MeSH terms and free text, with the Boolean operators: "Dengue" OR "Severe Dengue" OR "dengue" OR "dengue fever" OR "DF" OR "DHF" OR "DSS" AND "Thrombocytopenia" OR "thrombocytopenia" OR "low platelet" OR "platelet count" AND "Carica papaya" OR "papaya" OR "Carica papaya leaf" OR "papaya leaf extract" OR "CPLE" AND "Platelet Count" OR "platelet" OR "thrombocyte". Inclusion and exclusion criteria were:

Inclusion
1. Study designs included randomized controlled trials (RCTs), quasi-experimental studies (non-RCTs), cross-sectional, case-control, cohort studies with a comparison or control.
2. Full-text studies were available and accessible in English.

Exclusions
1. Case studies, case reports, case series, narrative reviews, letters to the editor, and in-vitro or in-vivo animal studies.
2. Studies lacking a control group.
3. Studies with incomplete data or data that could not be extracted for quantitative analysis, even after the authors were contacted.

Data Extraction
Data extraction was performed independently by all authors. Extracted data included data sources, eligibility, methods, sample characteristics, exposures/cases, and results from each study based on a standardized form in Microsoft Excel 2019, and were then cross-checked. Any disagreements were resolved through discussion among the authors. If agreement could not be reached, the remaining authors were consulted to resolve the disagreement, and the final decision was made by majority vote.

Risk of Bias
Studies were evaluated using the Cochrane Risk of Bias tool (RoB 2.0), which assesses bias from the randomization process, deviation from the intended intervention, missing outcome data, outcome measurement, and selective reporting of results. Non-RCT studies used the ROBINS-I tool (Risk of Bias in Non-Randomized Studies of Interventions) (Sterne et al., 2019; Sterne et al., 2016). Publication bias for included studies was reported using Egger's test and funnel plots.

Data Analysis
Each included study is presented in a baseline characteristics table. Author name, year of publication, study design, sample size, patient characteristics (age), type of papaya leaf extract preparation used, dose and frequency of administration, duration of therapy, type of comparator (placebo or standard care), baseline platelet count, primary outcome (change in platelet count), and reported adverse events are listed for each study.

The combined methods of Luo et al. and Wan et al. was used to convert data reported as median with interquartile range (IQR), or median with minimum and maximum values, to mean and standard deviation (SD) for pooled analysis (Luo et al., 2018; Wan et al., 2014). The standard error of the mean (SEM) was also converted to SD using Meta-Analysis Accelerator (Abbas et al., 2024). Data from all eligible studies were summarized both narratively and quantitatively. A random-effects model was applied to accommodate differences between studies. For continuous outcomes, standardized mean differences (SMDs) with 95% confidence intervals (CI) were calculated (Higgins et al., 2019). Articles presenting results with plots were extracted for quantitative or numerical data using WebPlotDigitizer (Rohatgi, 2022). However, the authors of this review recommend contacting the authors of the articles by email to obtain the actual and accurate data.

Statistical heterogeneity was analyzed using the Cochran's Q test ($p < 0.10$ was considered significant) and the I^2 statistic, with cutoffs: 0–25% low; 26–50% moderate; >50% substantial. Funnel plots were created to visually check for publication bias, complemented by Egger's regression asymmetry test to assess the effect of small studies (Higgins et al., 2019). Sensitivity analyses were performed by excluding studies at high risk of bias or outliers. All meta-analyses were performed in RStudio (Version: 2026.01.1+403; Release: 2026-02-19; The R Foundation, Vienna, Austria) using the "Meta" and "Metafor" packages (R Core Team, 2015). Results were visualized via forest plots to show individual and pooled effect sizes, and subgroup analyses compared therapies based on clinical outcomes.

RESULTS AND DISCUSSION

Results

Search results and included studies
A total of 2,501 articles were initially identified through a comprehensive electronic search of various databases, including PubMed (n = 32), Scopus (n = 256), ProQuest (n = 68), Web of Science (n = 26), Google Scholar (n = 967), and the Cochrane Library (n = 1,152), as well as additional searches from ResearchGate (n = 2). Prior to the screening process, 423 duplicate articles were removed, along with 579 articles marked as ineligible by automation and 426 articles eliminated for other reasons, leaving 1,073 articles for the screening phase. Subsequent screening based on title and abstract resulted in the exclusion of 698 articles due to irrelevance, lack of a comparison group, or inappropriate outcomes. A full-text search of 375 articles was then performed, but 279 were unsuccessful. Of the 96 articles assessed for eligibility, 37 were eliminated, as follows: 29 were systematic reviews and meta-analyses, 13 were literature reviews, 9 were case reports, and 37 were others. Two additional articles were identified, all of which were successfully retrieved and assessed for eligibility without any being eliminated. Ultimately, a total of 10 studies met the inclusion criteria and were included in the qualitative and quantitative analyses. Figure 1 shows the PRISMA Flowchart.

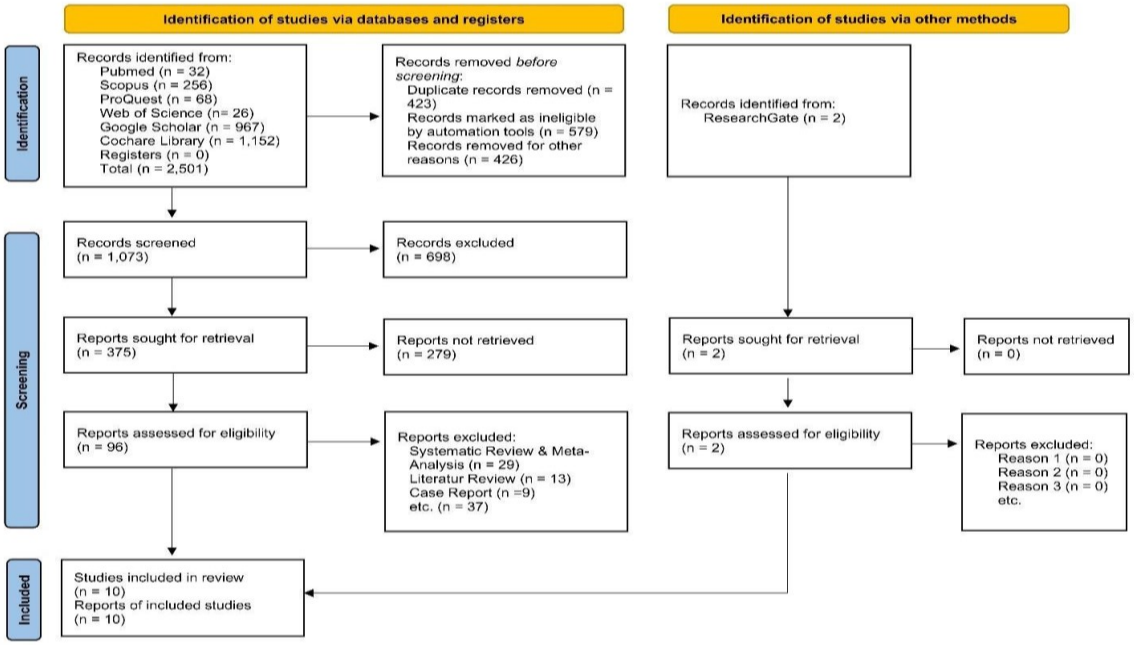


Figure 1. PRISMA Flow chart.

Population characteristics and quality assessment

Ten studies involving 5,393 patients of all ages diagnosed with Dengue Hemorrhagic Fever (DHF) and thrombocytopenia (low platelet count) were included in the systematic review and meta-analysis. Reported study characteristics are shown in Table 1.

Risk of bias was assessed using the Cochrane Risk of Bias Tool (ROB2) for randomized trials and the ROBINS-I tool. Based on this assessment, each study was categorized as showing low risk of bias, high risk of bias, or "some concern." Figure 2 shows the Cochrane Risk of Bias Tool (ROB2) and Figure 3 shows the ROBINS-I tool.

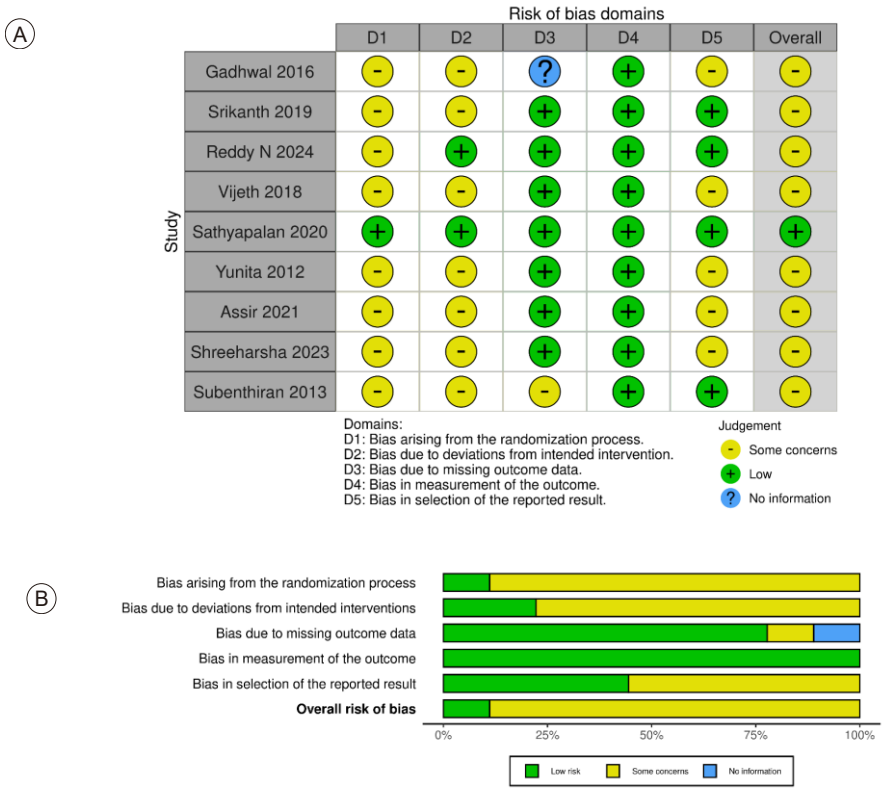


Figure 2. *Cochrane risk of bias tools* (ROB2). (A) Traffic-light plot. (B) Summary Plot.

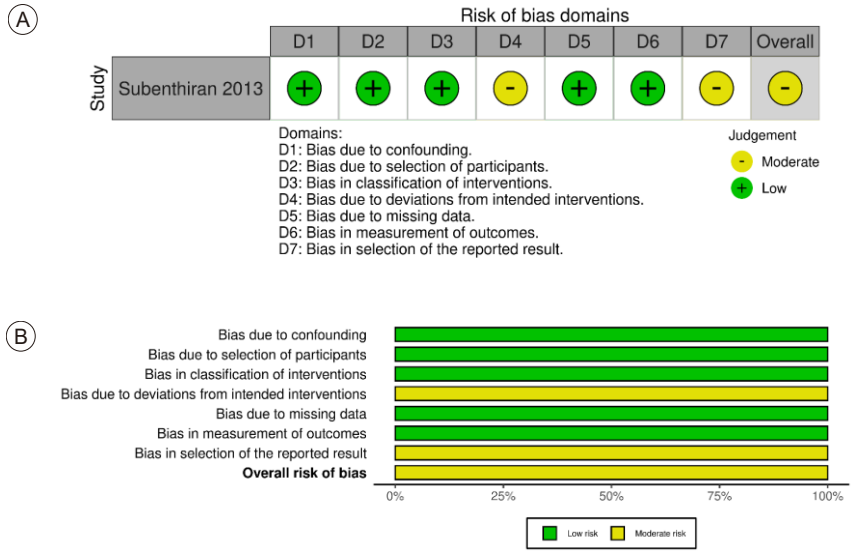


Figure 3. ROBINS-I tool. (A) Traffic-light plot. (B) Summary Plot.

Table 1. Study characteristics.

No.	Author, Year	Design	Country	Sample (Intervention /Control)	Age	Intervention	Outcome	Side effects
1.	Gadhwal, 2016	RCT	India	453 (253/200)	≥ 18 years old	CPLE 500 mg, once daily.	Day 2, platelet counts in the intervention and control groups were 61.67±19.46 and 59.93±19.52 ×10³/µL (p-value = 0.20). Day 3, the platelet count of the intervention compared control groups was 82.96±16.72 vs 66.45±17.36 ×10³/µL (p < 0.01). Days 4 and 5, the platelet counts of the intervention group (122.43± 19.36 and 112.47± 17.49 ×10³/µL) and the control group (88.75± 21.65 and 102.59± 19.35 ×10³/µL) showed p < 0.01.	None
2.	Srikanth, 2019	RCT	India	285 (145/140)	1-12 years old	CPLE Syrup · 1-5 years old: 275 mg, 3x daily · >5 years old: 550 mg, 3x daily	Platelet count on day 3 (mean = 89,739.31; p = 0.030), day 4 (mean = 120,788.96; p = 0.019), and day 5 (mean = 168,922.75; p = 0.023).	Two subjects reported complaints of nausea
3.	Reddy, 2024	Double-blind RCT	India	200 (100/100)	18-65 years old	CPLE 1100 mg consumed 3x daily	The mean platelet count between CPLE and placebo groups showed the maximum difference on day 5 (106,800±52,447 vs 100,197±54,788, p=0.454).	Nausea and vomiting
4.	Vijeth, 2018	Randomized controlled clinical trial	India	200 (100/100)	≥18 years old	CPLE	Increase in platelet count in the intervention compared the placebo	None

No.	Author, Year	Design	Country	Sample (Intervention /Control)	Age	Intervention	Outcome	Side effects
							group, and on the third day, there was a significant difference between the two (p=0.002).	
5.	Sathyapalan, 2020	Double-blind RCT	India	50 (26/24)	≥18 years old	CPLE 1100 mg consumed 3 times daily	Day 3, CPLE therapy showed a significant increase in platelet count (p = 0.007) by 482%±284 compared to the placebo group (331%±370).	None
6.	Yunita, 2012	Open randomized controlled clinical trial	Indonesia	80 (40/40)	15-55 years old	CPC 550mg, 2 capsules, taken 3 times daily.	Papaya leaf extract (*C. papaya*) capsules significantly increased platelet counts (p<0.05).	None
7.	Shetty, 2019	Comparative Study	India	30 (15/15)	1-16 years old	CPLE Tablet 1100 mg (children >12 years old) Syrup (275 mg/5 ml, dose adjusted to age) Given 3x daily	There was no significant difference in the mean platelet count at the end of treatment on day 5, which was 162,933/µL in the intervention group compared to 197,333/µL in the control group (p=0.15).	None
8.	Assir, 2011	RCT	Pakistan	39 (19/20)	≥14 years old	5 mL of papaya leaf extract in syrup, consumed twice daily for 4 days	No significant difference in the increase of mean platelet count from baseline between the therapy and control groups on day 2 (23.7×10^9/L vs 15.9×10^9/L, p = 0.242), day 3 (42.6×10^9/L vs 35.1×10^9/L, p = 0.424), day 4 (71.6×10^9/L vs 58.4×10^9/L, p = 0.309), and day 5 (106×10^9/L vs 82.3×10^9/L, p = 0.189).	None
9.	Subenthiran, 2013	RCT	Malaysia	228 (111/117)	18-60 years old	*Carica papaya* leaf juice (CPLJ) daily	The mean platelet count the intervention group was significantly higher than control group after 40 and 48 hours after treatment (p < 0.01).	None
10.	Shreeharsha, 2023	Open-label, controlled, parallel-group comparative study	India	18 (12/6)	18-60 years old	Papaya leaf extract of Solo and Red Lady varieties Dose: 30 mL, 3 times daily	The results showed a better trend of increasing platelet counts in the Solo variety group compared to the Red Lady group and the control group.	None

Notes: CPLE: *Carica Papaya* Leaf Extract; CPC: *C. papaya* leaves extract capsules.

All populations

A total of 36 studies with a total of 5,393 participants (*Carica papaya* leaf extract group = 2,812; control group = 2,581) were included in the meta-analysis. Based on the random-effects model, the pooled effect size indicated that the intervention had a statistically significant effect with a standardized mean difference (SMD) of 0.40 (95% CI: 0.18–0.63; p = 0.0003). However, heterogeneity analysis revealed very high heterogeneity between studies (I^2 = 90.4%; τ^2 = 0.3626; Q = 364.90; p < 0.0001). Figure 4A shows a Forest plot for all populations. Furthermore, a publication bias test using Egger's test showed no evidence of significant publication bias (p = 0.1401). Figure 5A shows a funnel plot.

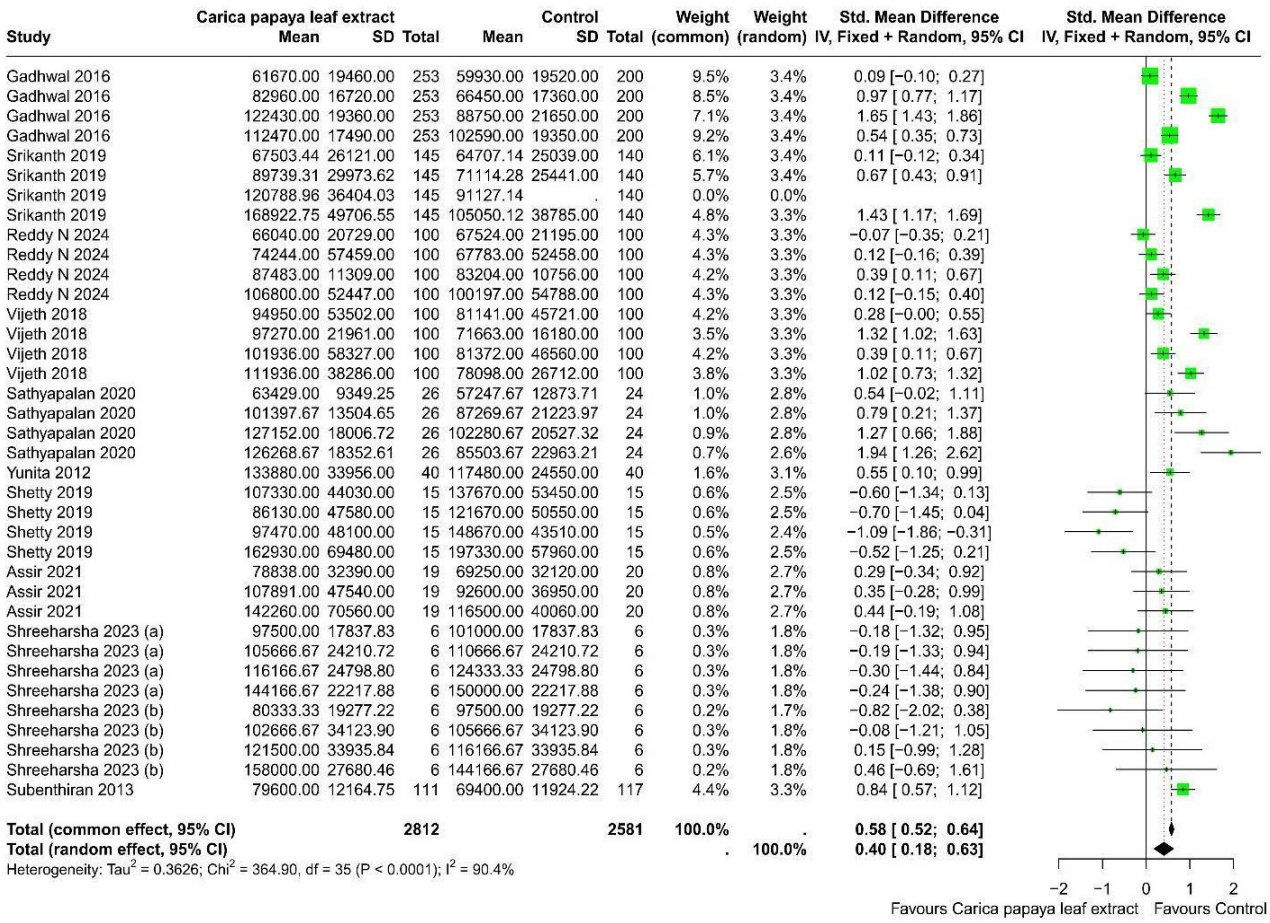


Figure 4A. Forest plot of all populations.

Subgroup analysis based on the day of therapy evaluation showed variation in the intervention effect over time. On day 2, the intervention effect was not significant (SMD = 0.16; 95% CI: −0.09 to 0.42; $p > 0.05$) with high heterogeneity ($I^2 = 75.6\%$). In contrast, on day 3, a significant effect was found with a small to medium effect size (SMD = 0.46; 95% CI: 0.04–0.87; $p < 0.05$), although between-study heterogeneity remained high ($I^2 = 86.5\%$). On day 4, the intervention effect was again not significant (SMD = 0.43; 95% CI: −0.17 to 1.02; $p > 0.05$) with very high heterogeneity ($I^2 = 93.5\%$). Meanwhile, on day 5, a significant effect was found with a moderate effect size (SMD = 0.63; 95% CI: 0.14–1.13; $p < 0.05$) and high heterogeneity ($I^2 = 90.1\%$). The test for differences between subgroups based on the random effects model showed no significant difference ($Q = 3.54$; $df = 3$; $p = 0.3157$), indicating that the difference in effectiveness between evaluation times was not statistically significant. Figure 4B shows a forest plot of subgroups by day across all populations.

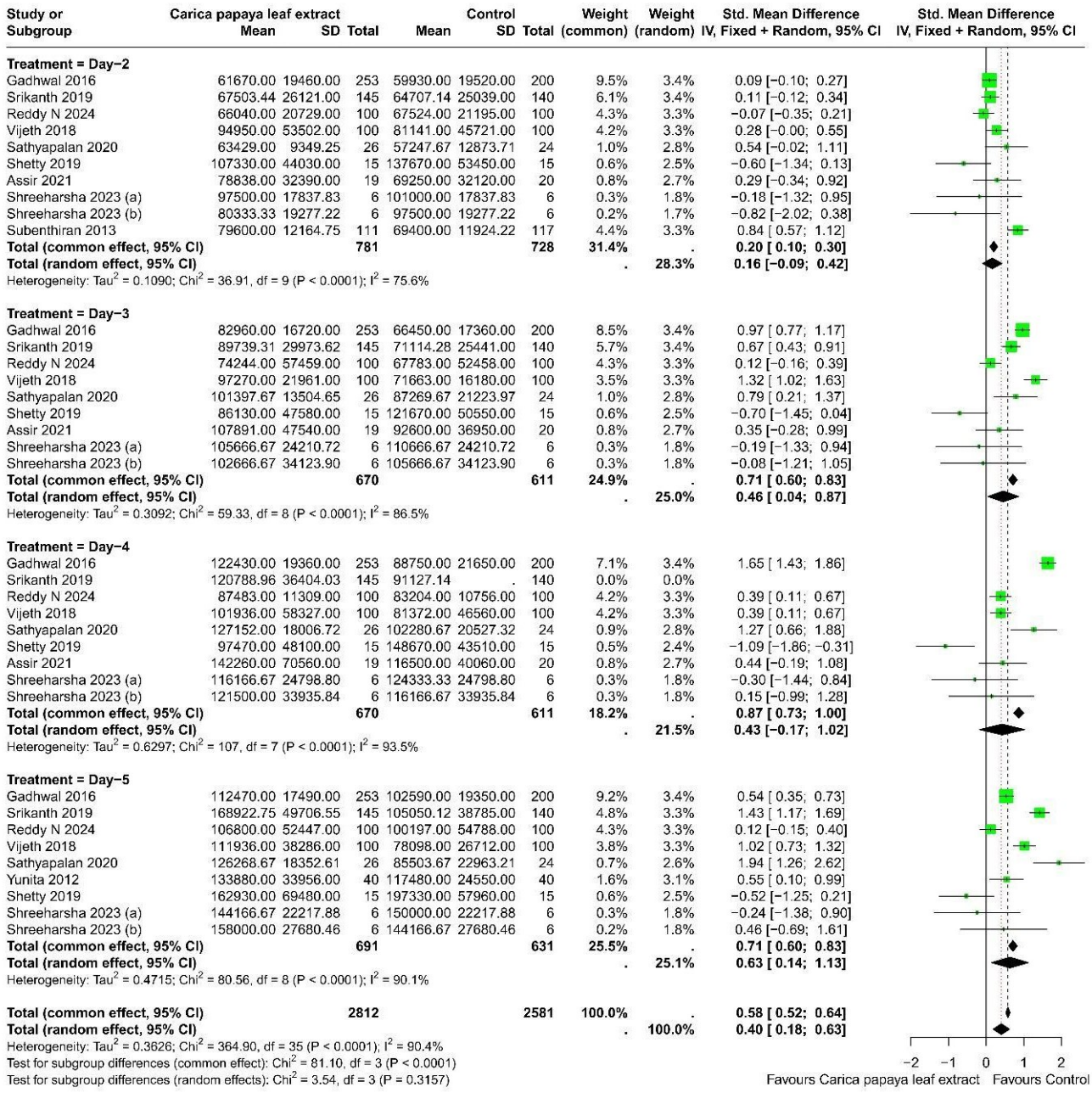


Figure 4B. Forest plot of subgroups by day across all populations.

Adult Population

A total of 29 studies involving 4,133 adult participants (intervention group = 2,172; control group = 1,961) were included in the meta-analysis. Based on a random-effects model, a pooled effect size, a standardized mean difference (SMD), was obtained of 0.52 (95% CI: 0.31–0.73; $p < 0.0001$), indicating a significant effect of the intervention. Heterogeneity analysis revealed very high heterogeneity between studies ($I^2 = 89.2\%$; $\tau^2 = 0.247$; $Q = 259.66$; $p < 0.0001$). Subgroup analysis based on the day of therapy evaluation revealed variation in the intervention effect over time. On day 2, the intervention effect was not yet significant (SMD = 0.24; 95% CI: −0.04 to 0.53; $p > 0.05$; $I^2 = 77.5\%$). In contrast, on day 3, a significant effect with a moderate to large effect size was found (SMD = 0.59; 95% CI: 0.16–1.01; $p < 0.05$; $I^2 = 86.5\%$). A significant effect was also seen on day 4 (SMD = 0.66; 95% CI: 0.16–1.16; $p < 0.05$; $I^2 = 92.7\%$) and day 5 (SMD = 0.66; 95% CI: 0.19–1.14; $p < 0.05$; $I^2 = 83.6\%$). The test for differences between subgroups showed that there was no significant difference based on the evaluation time ($Q = 3.91$; $df = 3$; $p = 0.2713$), indicating that although there was a trend towards an increase in the intervention effect after day 2, the difference in effectiveness between evaluation times was not statistically significant. Figure 4C shows a forest plot of subgroups based on adult population days. Furthermore, publication bias analysis using Egger's test

did not show any significant funnel plot asymmetry (t = −0.74; df = 27; p = 0.4668), thus no strong indication of publication bias was found in the analyzed studies. Figure 5B shows a funnel plot of the adult population.

Pediatric Population

A subgroup analysis based on the day of therapy evaluation in the pediatric population involved seven studies with a total of 1,260 participants (intervention group = 640; control group = 620). Results showed variation in the intervention effect across measurement times. On day 2, the intervention effect was non-significant with a small effect size (SMD = 0.04; 95% CI: −0.18 to 0.27), with moderate heterogeneity (I^2 = 69.5%). On day 3, a significant intervention effect was found with a medium effect size (SMD = 0.54; 95% CI: 0.31–0.77), but heterogeneity between studies remained high (I^2 = 91.6%). On day 4, there was only one study, so the estimate showed a significant negative effect (SMD = −1.09; 95% CI: −1.86 to −0.31). Meanwhile, on day 5, a significant intervention effect was found with a large effect size (SMD = 1.21; 95% CI: 0.96–1.45), although heterogeneity was very high (I^2 = 95.9%). The test for differences between subgroups showed a significant difference based on the evaluation time (Q = 64.30; df = 3; p < 0.0001), indicating that the intervention effect in the child population differed significantly between observation days, with a tendency for an increase in the effect on day 5. Figure 4D shows the forest plot of subgroups based on the day of the child population. Egger's test to detect potential publication bias showed an insignificant result (t = −1.84; df = 5; p = 0.1257), with a bias estimate of −5.12 (SE = 2.79), so there was no strong evidence of asymmetry in the funnel plot in this analysis. Figure 5C shows the funnel plot of the child population.

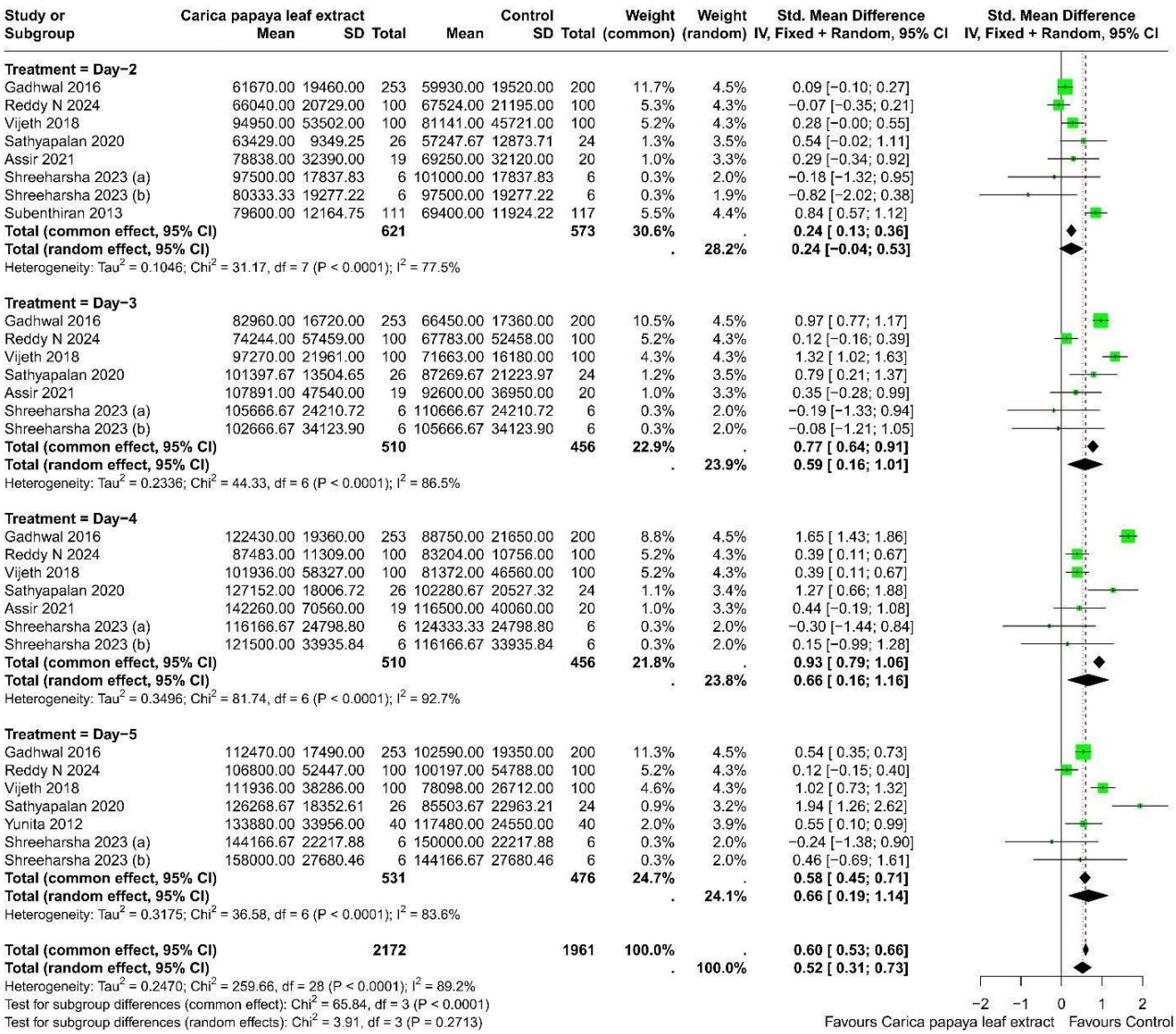


Figure 4C. Forest plot of Subgroups by adult population days.

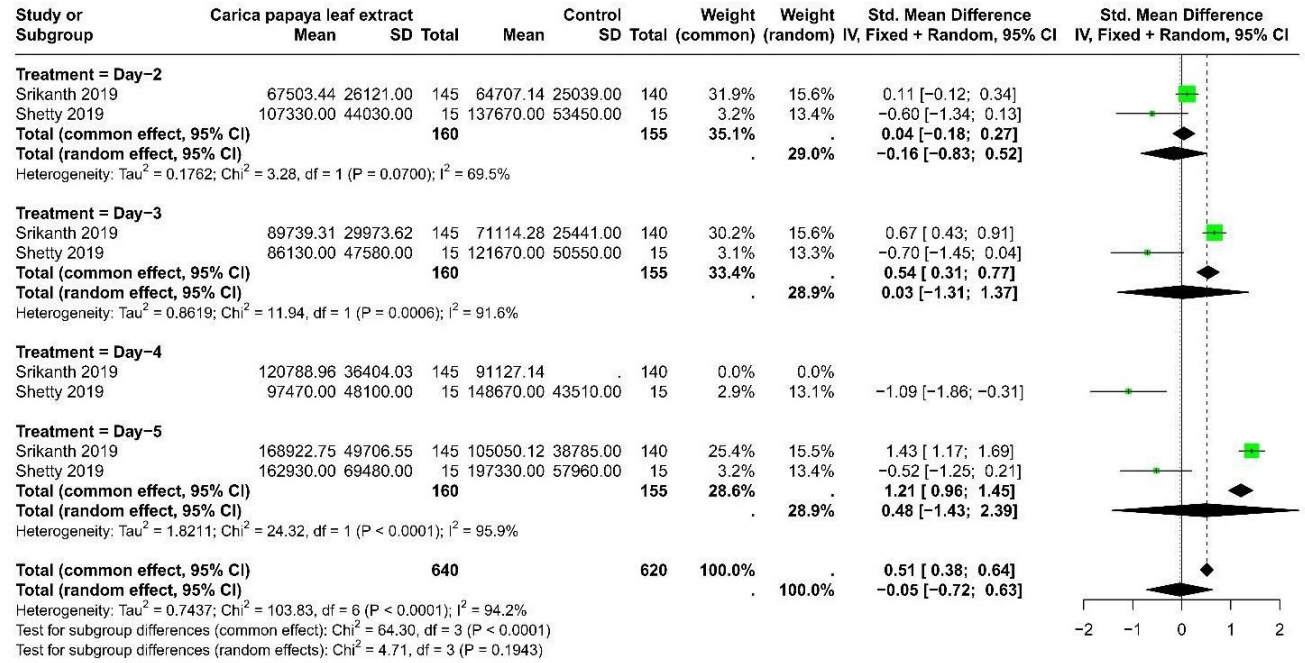


Figure 4D. Forest plot of Subgroups by child population day.

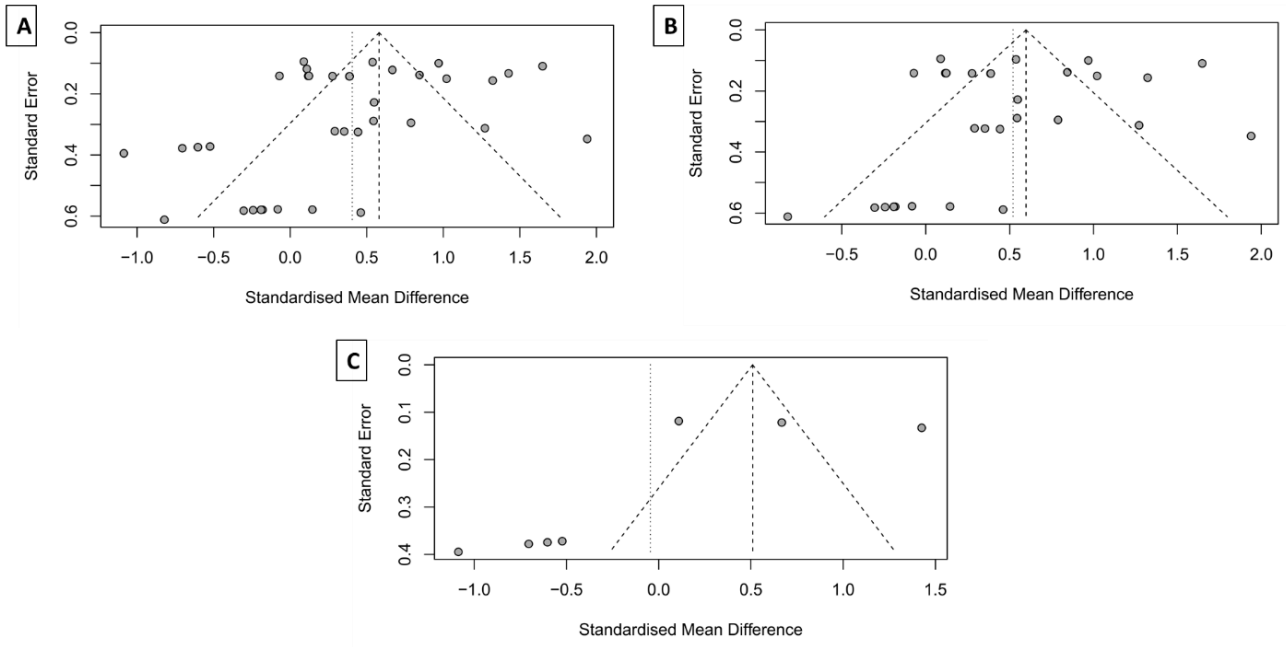


Figure 5. Funnel Plot Results. (A) All populations. (B) Adult Population, (C) Child Population.

Discussion

The results of this meta-analysis indicate that administration of *Carica papaya* leaf extract had a statistically significant effect on increasing platelets in all populations and adults, but not in the pediatric population. In all populations and adults, platelet increases were only apparent on the 3rd day of follow-up and reached a stronger effect on the 5th day.

The most important finding of this systematic review was the significant increase in platelet counts in the Carica papaya group compared to the control group. Platelets are colorless cell fragments produced by megakaryocytes through a process called thrombopoiesis. Their normal count ranges from 150,000 to 350,000 per microliter of blood. Thrombocytopenia is a laboratory parameter known to be associated with the severity of dengue infections such as DHF, DSS, and severe organ involvement (Khazali et al., 2024). The underlying mechanism of DENV-induced thrombocytopenia remains unclear, but several hypotheses link it to bone marrow suppression and platelet destruction by DENV nonstructural protein 1

(NS1). Thrombocytopenia typically begins on day 2 before the onset of the critical phase and persists until day 6–7. Platelet counts also correlate with vascular protein leakage and liver damage. Therefore, monitoring the incidence of thrombocytopenia is important to identify patients most likely to develop severe dengue (Khazali et al., 2024; Faridah et al., 2022). This review found a moderate increase in platelet count with a wide confidence interval (CI), indicating inconsistency in the results.

Several studies have analyzed the mechanism of action of *Carica papaya* leaf extract on dengue infection. Papaya leaves contain carpain, chymopapain, cystatin, L-tocopherol, flavonoids, ascorbic acid, vitamin E, cyanogenic glucosides, and glucosinolates (Naureen et al., 2022). An in vitro study by Ranasinghe et al. found that *Carica papaya* leaf extract has demonstrated the ability to stabilize membranes and protect blood cells from stress-induced damage (Ranasinghe et al., 2012). An in vivo study by Ratnasooriya et al. found that administration of *Carica papaya* leaf extract for 3 days can increase platelet, erythrocyte, and leukocyte counts and can reduce vascular permeability (Ratnasooriya, 2012). Another study also found that papaya leaf extract can induce ALOX gene expression 12-15 fold, which in turn increases megakaryocyte production and their transformation into platelets (McRedmond et al., 2004). Quercetin extracted from *Carica papaya* leaves acts as an inhibitor of the NS2B-NS3 serine protease required for dengue virus formation (Senthilvel et al., 2013).

Among the 10 studies analyzed, the majority reported no significant adverse events or serious side effects in the group receiving papaya leaf extract. However, Reddy et al. (2024) reported that nausea and vomiting were common side effects reported in the group receiving CPLE (Reddy et al., 2024). This is similar to the findings of Srikanth et al. (2019) in pediatric patients, where two subjects reported nausea, although overall the extract syrup remained well tolerated (Srikanth et al., 2019). The oral safety of this *Carica papaya* leaf extract has been supported by acute, subacute, and chronic toxicity tests in animals which showed that this ingredient is safe for human consumption (Subenthiran et al., 2013).

CONCLUSIONS

Carica papaya leaf extract has the potential to increase platelet counts in patients with dengue-induced thrombocytopenia, evident after day 3 to 5 of therapy. The platelet-increasing effect was significant in adults, but not in children. However, almost all analyses showed high heterogeneity between studies, indicating variations in study design, population characteristics, papaya leaf extract dosage, and outcome evaluation time. Therefore, further clinical research with more standardized methodology is needed to confirm its effectiveness and determine the optimal dosage, particularly in children.

Competing Interests: The authors declare that there are no competing interests.

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