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Efficacy and Safety of a Plant-based Nutraceutical Formulation in Dengue-Associated Thrombocytopenia: A Randomized, Open-label, Parallel-group Study

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Abstract

Background: Febrile illnesses associated with thrombocytopenia, particularly dengue, malaria, and typhoid fever, pose a significant public health burden in India with limited targeted therapeutic options. This study evaluated the efficacy and safety of a new plant-based nutraceutical formulation efficacy and safety.

Methods: In this randomized, open-label study (CTRI/2024/04/065599), 50 dengue patients received either plant-based nutraceuticals (Group 1) or Carica papaya leaf extract (Group 2) for 7–10 days. Clinical and lab parameters, including fever, associated symptoms, platelet count, clotting, bleeding, and biochemical markers, were monitored at intervals. Safety was assessed through adverse event tracking.

Results: Both groups improved in clinical and lab parameters; Group 1 showed superior and earlier outcomes. Platelet recovery was higher in Group 1 by Day 5 (65,000 vs 58,450 cells/mm^3; p = 0.044). Similarly, a greater reduction in arthralgia was observed in Group 1 by Day 10 (0.05 Vs 0.14; p=0.0001) along with improved myalgia scores. Group 1 had consistently lower clotting time, better bleeding control early on, greater leukocyte recovery, and higher post-treatment sodium levels. SGOT, SGPT and renal parameters remained within normal ranges throughout the study, indicating renal and hepatic safety in both the groups. Both treatments were well tolerated with comparable safety profiles.

Conclusion: The plant-based nutraceutical formulation showed superior efficacy in clinical and lab outcomes, confirming its role as an effective adjunct therapy for dengue-associated thrombocytopenia.

Keywords: Dengue, Thrombocytopenia, Plant-based nutraceutical formulation, Carica papaya leaf extract, Tinospora cordiflolia stem extract, Curcuma longa extract, Ocimum sanctum leaf Extract, Platelet recovery

Introduction

Dengue has shown a sharp rise over the past few decades, with the World Health Organization reporting over 14 million cases and more than 9,000 deaths globally in 2024 [1]. India mirrors this increasing trend, with cases rising from approximately 28,000 in 2010 [2] to over 200,000 in 2024 [3], and projections estimating 309,836 cases (95% CI: 240,337–379,334) and 533 deaths (95% CI: 285–781) in 2026 [4]. In 2025, over 263,000 suspected and approximately 181,000 confirmed cases were reported globally, with India contributing over 30,000 suspected cases in early 2025 [5]. Similarly, influenza continues to impose

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a substantial global burden, accounting for approximately 1 billion cases annually, including 3–5 million severe cases and an estimated 290,000–650,000 deaths each year [6]. Pneumonia remains a leading cause of mortality, particularly among children, with over 808,000 deaths reported in children under five years of age in 2017 [7]. Typhoid fever also contributes significantly, with approximately 9 million cases and 110,000 deaths annually worldwide [8]. In addition, India accounts for nearly 66% of malaria cases in the South-East Asia region, further highlighting the substantial regional burden [9]. Febrile illnesses associated with thrombocytopenia, such as dengue, malaria, chikungunya, influenza, pneumonia, and typhoid fever, constitute a significant and growing public health burden in India. Thrombocytopenia is particularly common in vector-borne infections, occurring in a substantial proportion of cases, including dengue (reported in ≈79% of patients) [10], malaria (≈63-77%) [11], typhoid (26%) [12], and chikungunya (≈56.9% [13], often milder compared to dengue. Approximately 60% of patients with tropical febrile illness present with thrombocytopenia [14], of which nearly 88% are infection-related, primarily due to dengue, malaria, and enteric fever [15]. Thrombocytopenia in these conditions, along with myalgia, arthralgia, and headache, not only reflects disease severity but also contributes to complications such as bleeding tendencies, delayed recovery, and increased healthcare utilization, thereby amplifying the overall burden.

Despite this high disease burden, treatment options remain limited due to the lack of specific antiviral therapy for dengue, rising antimicrobial resistance, and the persistent challenge of thrombocytopenia. Current management is largely supportive and often involves symptomatic treatments such as analgesics for fever-associated manifestations, including myalgia, arthralgia, and headache. However, these approaches may be associated with adverse drug reactions, increased cost burden, and limited accessibility, particularly in resource-constrained settings. This has led to a growing interest in adjunctive, non-invasive, and non-synthetic alternatives, including nutraceutical and plant-based interventions, which may offer safer and more accessible options [16]. Medicinal plants have long been used globally to manage vector-borne illnesses such as malaria and dengue, and their demand continues to increase due to their safety and non-toxic nature compared to synthetic drugs. Recent studies indicate that adverse events associated with herbal medicines are generally low, with a pooled incidence of approximately 1.42%, although variability exists depending on formulation, quality, and usage patterns [17]. Several plant-based agents have demonstrated notable efficacy in conditions associated with fever and thrombocytopenia, including dengue, malaria, and typhoid. Carica papaya leaf extract (CPLE), derived from the leaves of the papaya plant (family Caricaceae), has been shown to increase platelet production by stimulating megakaryocytes, exhibit anti-dengue viral activity through flavonoids such as quercetin, and demonstrate efficacy in dengue- and malaria-associated thrombocytopenia [17, 18]. In addition, *Tinospora cordifolia* exhibits immunomodulatory properties with significant platelet improvement, particularly when used in combination with Carica papaya leaf extract [18, 19], while *Curcuma longa* (curcumin) exerts potent anti-inflammatory effects by reducing key biomarkers such as TNF-α, IL-6, and CRP [20]. Similarly, *Ocimum sanctum* (Tulsi) contributes to inflammation control through suppression of pro-inflammatory cytokines, including TNF-α and IL-6 [21], and piperine enhances the bioavailability of curcumin by approximately 2000%, thereby amplifying its therapeutic effects [22]. Collectively, these findings support a synergistic, multi-targeted approach involving platelet enhancement, immune modulation, and inflammation control, resulting in faster clinical recovery compared to single-agent therapy.

In this context, *Carica papaya* extract and plant-based nutraceutical formulations offer a rational, plant-based adjunctive strategy in febrile illnesses with thrombocytopenia, supporting platelet recovery, improving symptoms such as myalgia, fever, and arthralgia, and enhancing overall clinical outcomes. The synergistic interplay among the multiple ingredients of Plant-based Nutraceutical formulation appears particularly promising, as each component demonstrates complementary mechanisms such as anti-inflammatory effects via suppression of pro-inflammatory cytokines, stimulation of megakaryocytes to enhance platelet production, and immunomodulatory activity, collectively contributing to faster clinical recovery compared to single-agent therapy. Considering the available evidence, the present study aims to assess the efficacy and safety profile of the test formulation sachet in febrile conditions, particularly dengue, which is commonly associated with thrombocytopenia.

Methods

Study Design

This was a randomized, open-label, parallel-group clinical trial conducted in patients diagnosed with dengue fever, confirmed by a positive NS1 antigen test, between 18th April 2024 to 13th September 2024. Written informed consent was obtained from all participants prior to enrolment in the study. A total of 50 patients were randomized in a 1:1 ratio into two groups, with 25 patients in each group, in an open-label design. Patients in the test group (Group 1) diagnosed with dengue viral fever, with or without thrombocytopenia, received plant-based nutraceutical formulation sachet twice daily for a duration of 7–10 days. Patients in the comparator group (Group 2) diagnosed with dengue viral fever, with or without thrombocytopenia, received Carica papaya extract tablets twice daily for a duration of 7–10 days. This study method is demonstrated in Figure 1.

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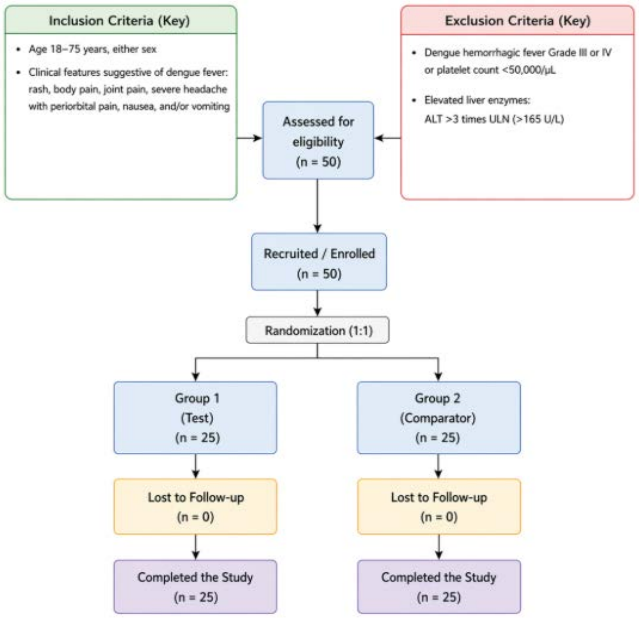

Figure 1: CONSORT diagram

Abbreviations

ALT; alanine transaminase, ULN; upper-limit of normal

Investigational product

Test Group (plant-based nutraceutical formulation sachet):

Participants in the test group received a plant-based nutraceutical formulations sachet (8 g) containing key plant-based extracts with known therapeutic benefits in dengue, including Carica papaya leaf extract (1100 mg), Tinospora cordifolia extract (167 mg), Ocimum sanctum extract, Curcuma longa extract, and Piper nigrum extract, along with supportive micronutrients such as selenium and electrolytes (sodium and potassium). The formulation was designed to target platelet enhancement, reduction in inflammation, and symptomatic relief (myalgia and arthralgia), which are clinically relevant in acute dengue infection. The sachet was administered orally after dissolving in water, typically after meals, and was used alongside standard supportive care (e.g., paracetamol as required). Patients received 1 sachet 2 times daily for 7–10 days, as per the physician's discretion

Comparator:

Each film-coated tablet contains Carica papaya (Eranda Karkati) leaf extract (1100 mg). Participants in the comparator group received Carica papaya extract tablets, administered orally twice daily for a duration of 7–10 days. At screening, demographic data, including age, height, weight, and body mass index (BMI), were recorded. A detailed personal history, including a history of cardiovascular disease, along with relevant medical history, was obtained. Vital signs and a comprehensive systemic examination were performed for all participants. Blood samples were collected for laboratory investigations, including complete blood count (CBC) with platelet count, non-structural protein 1 (NS1) antigen test, bleeding time, clotting time, blood urea, serum creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum electrolytes. Clinical parameters, including temperature, fever score and fever symptoms like arthralgia, myalgia, headache, and loss of appetite, were assessed at the time of screening.

Ethical approval

The study was registered with CTRI (CTRI/2024/04/065599), and ethical approval was obtained from the Ethics Committee of the Ethique de la Nature Association.

Eligibility criteria

Inclusion criteria

Patients of either sex aged 18–75 years with an oral temperature ≥38.0°C (100.4°F) at presentation were included in the study. Eligible patients presented with clinical features suggestive of dengue fever, including rash, body pain, joint pain, severe headache with periorbital pain, nausea, and/or vomiting. All patients had laboratory-confirmed dengue viral infection, as evidenced by a positive NS1 antigen test, along with thrombocytopenia, defined as a platelet count between 50,000/µL and 150,000/µL. Only hemodynamically stable patients, with stable vital parameters such as pulse and blood pressure, were included. Additionally, patients who had not participated in any other clinical trial within the past 3 months and who provided written informed consent were eligible for inclusion.

Exclusion criteria

Patients with dengue hemorrhagic fever Grade III or IV or with a platelet count <50,000/µL were excluded from the study. Pregnant or lactating women and patients who had received blood or blood product transfusions during the current illness were also excluded. Patients with a history or presence of hematological disorders, including immune thrombocytopenic purpura (ITP), leukemia, or hemophilia, were not eligible. Patients with elevated liver enzymes, defined as serum ALT >3 times the upper limit of normal (>165 U/L), or impaired renal function, defined as serum creatinine >1.5 mg/dL in males and >1.4 mg/dL in females, were excluded. Additionally, patients with known hypersensitivity to any component of the study formulations or with any other condition that, in the opinion of the investigator, could render them unsuitable for participation were excluded from the study.

Endpoints

The primary endpoint of the study was to evaluate efficacy

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based on changes in hematological parameters, including platelet count, bleeding time, clotting time, and hematocrit, assessed at baseline and on Days 1, 3, 5, 7, and 10. Electrolyte levels and hydration status were evaluated at baseline and at the end of the study period. Other laboratory parameters, including complete blood count (CBC), urea, creatinine, bilirubin, AST, ALT, and electrolytes, were evaluated at baseline and at the end of the study. Clinical parameters such as temperature, fever score, arthralgia, myalgia, headache, hydration status, and loss of appetite were assessed at baseline and on days 1, 3, 5, 7, and 10. Fever was scored on a scale of 0 to 3 (0 ≤ 99°F, 1 = 99–100°F, 2 = 101–102°F, 3 ≥ 102°F); other symptoms were evaluated using a 5-point Likert scale, and headache was assessed using the Visual Analogue Scale (VAS). Additionally, changes in quality of life from baseline to day 10 were measured using the Short Form Health-12 questionnaire. The secondary endpoint was to assess the safety of the interventions by monitoring adverse events throughout the study period. Additionally, laboratory parameters were compared between baseline and post-study assessments.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, including age and sex, as well as adverse events and tolerability profiles. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparative analyses between the test and comparator groups, as well as between baseline and post-study assessments, were performed using the student's *t*-test for continuous variables and the chi-square test for categorical variables. Statistical analysis was conducted using SPSS software (version 23.0), and a *p*-value <0.05 was considered statistically significant.

Results

Demographic characteristics of patients

A total of 50 participants were enrolled and allocated to the test group (plant-based nutraceutical formulation; Group 1, *n = 25*) and comparator group (Carica papaya extract; Group 2, *n = 25*). The mean age of participants in Group 1 was 34.0 ± 15.1 years, compared to 38.71 ± 9.89 years in Group 2. Regarding sex distribution, Group 1 comprised 18 males (72%) and 7 females (28%), while Group 2 included 16 males (64%) and 9 females (36%). These demographics are summarized in Table 1.

Table 1: Demographic characteristics of patients

Demographics	TEST- plant-based formulation	Comparator- Carica papaya extract
Age (Years)	34.0 ± 15.1	38.71 ± 9.89
BMI (kg/m2)	22.2 ± 4.8	23.71 ± 3.41
Sex		
Male	18 (72.0)	16 (64.0)
Female	7 (28.0)	9 (36.0)

Symptom outcomes

Temperature (°F)

A progressive and consistent improvement in clinical symptoms was observed across both groups over the 10-day study period. For temperature, Group 1 showed a reduction from a baseline of 101.6 ± 1.12 to 101.1 ± 1.11 (0.5%) on Day 1, 100.2 ± 1.07 (1.4%) on Day 3, 99.7 ± 0.41 (1.9%) on Day 5, 98.3 ± 0.50 (3.3%) on Day 7, and 98.1 ± 0.47 (3.4%) on Day 10. Similarly, the comparator group showed a reduction from 102.5 ± 1.12 at baseline to 101.5 ± 1.20 (1.0%) on Day 1, 100.3 ± 0.58 (2.1%) on Day 3, 99.6 ± 0.68 (2.8%) on Day 5, 98.5 ± 0.33 (3.9%) on Day 7, and 98.4 ± 0.51 (4.0%) on Day 10, with a statistically significant difference between groups at Day 10 (p = 0.0356). This change in temperature is demonstrated in Table 2.

Fever score

For fever score, Group 1 demonstrated a reduction from 3.0 ± 0.40 at baseline to 2.79 ± 0.54 (7.0%) on Day 1, 2.11 ± 0.20 (29.7%) on Day 3, 1.46 ± 0.26 (51.3%) on Day 5, 0.41 ± 0.10 (86.3%) on Day 7, and 0.19 ± 0.12 (93.7%) on Day 10. The comparator group showed similar reductions from 3.0 ± 0.25 at baseline to 2.65 ± 0.48 (11.7%) on Day 1, 2.12 ± 0.85 (29.3%) on Day 3, 1.45 ± 0.21 (51.7%) on Day 5, 0.39 ± 0.20 (87.0%) on Day 7, and 0.20 ± 0.45 (93.3%) on Day 10, with no significant differences between groups at any time point. This change in fever score is demonstrated in Table 2.

Arthralgia Score

The mean arthralgia score at baseline was higher in Group 1 (0.45) compared to Group 2 (0.41), indicating comparable but slightly greater initial severity in Group 1. On Day 1, a reduction in mean scores was observed in both groups, with Group 1 decreasing to 0.41 (8.9% reduction) and Group 2 to 0.39 (4.9%), reflecting an early but modest improvement, with slightly greater reduction in Group 1. By Day 3, further improvement was noted, with Group 1 reducing to 0.34 (24.4%) and Group 2 to 0.37 (9.8%), indicating a more pronounced reduction in Group 1. A substantial decline in arthralgia scores was observed on Day 5, with Group 1 decreasing to 0.22 (51.1%) and Group 2 to 0.25 (39.0%), demonstrating a marked and clinically meaningful improvement, particularly in Group 1. The downward trend continued on Day 7, with Group 1 reaching 0.19 (68.9%) and Group 2 reaching 0.14 (53.7%), showing significant improvement in both groups, with Group 1 maintaining a higher percentage reduction. By Day 10, near-complete resolution of symptoms was

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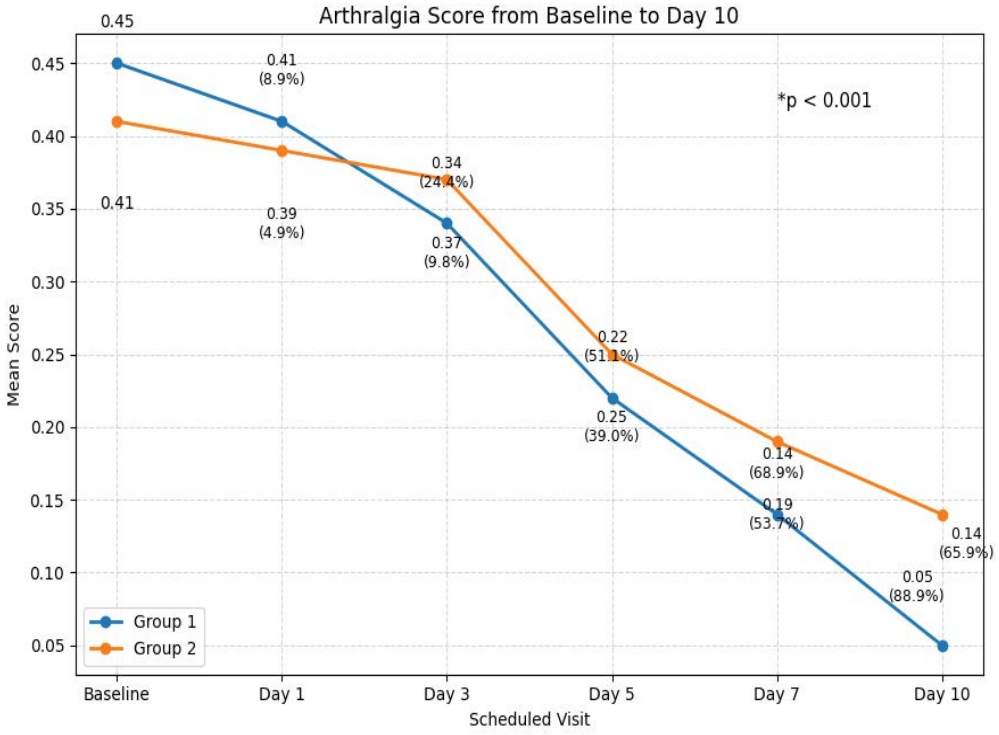
observed, with Group 1 demonstrating a marked reduction to 0.05 (88.9%) and Group 2 to 0.14 (65.9%), with consistently greater reduction observed in Group 1 across all time points. This reduction is demonstrated in Figure 2.

Myalgia score

The mean myalgia score at baseline was slightly higher in Group 1 (2.35) compared to Group 2 (2.26), indicating



Note: Values are presented as mean (% reduction from baseline).

Figure 2: Arthralgia Score from Baseline to Day 10

comparable initial severity between the groups. On Day 1, a minimal reduction was observed in both groups, with scores decreasing to 2.19 (6.8% reduction) in Group 1 and 2.11 (6.6%) in Group 2, reflecting early but modest improvement. By Day 3, a marked reduction was evident, with Group 1 decreasing to 1.02 (56.6%) and Group 2 to 1.54 (31.9%), indicating a substantially greater improvement in Group 1. Further decline in scores was observed on Day 5, with Group 1 reducing to 0.69 (69.5%) and Group 2 to 0.58 (75.3%), showing pronounced improvement in both groups, with slightly greater reduction in Group 2 at this time point. On Day 7, the downward trend continued, with Group 1 reaching 0.25 (80.4%) and Group 2 reaching 0.44 (78.3%), demonstrating comparable reductions. By Day 10, near-complete resolution of myalgia was observed, with Group 1 decreasing to 0.14 (94.0%) and Group 2 to 0.30 (86.7%), indicating progressive improvement in both groups, with a greater overall reduction in Group 1. This change in myalgia score is shown in Figure 3.

Headache score

For headache score, Group 1 showed a decline from 2.0 ± 1.1 at baseline to 1.46 ± 1.05 (27.0%) on Day 1, 1.12 ± 0.79 (44.0%) on Day 3, 0.88 ± 0.69 (56.0%) on Day 5, 0.42 ± 0.23 (79.0%) on Day 7, and 0.20 ± 0.16 (90.0%) on Day 10. The comparator group showed reductions from 1.67 ± 1.10 at baseline to 1.37 ± 1.10 (18.0%) on Day 1, 1.12 ± 1.04 (32.9%) on Day 3, 0.86 ± 0.35 (48.5%) on Day 5, 0.36 ± 0.10 (78.4%) on Day 7, and 0.19 ± 0.24 (88.6%) on Day 10, with comparable improvements between groups. This change in headache score is demonstrated in Table 2.

Loss of appetite score

Similarly, loss of appetite scores improved over time. In Group 1, scores reduced from 0.45 ± 0.12 at baseline to 0.40 ± 0.11 (11.1%) on Day 1, 0.32 ± 0.18 (28.9%) on Day 3, 0.22 ± 0.07 (51.1%) on Day 5, 0.12 ± 0.05 (73.3%) on Day 7, and 0.05 ± 0.02 (88.9%) on Day 10. The comparator group showed reductions from 0.49 ± 0.20 at baseline to 0.39 ± 0.10 (20.4%) on Day 1, 0.29 ± 0.15 (40.8%) on Day 3, 0.20 ± 0.06 (59.2%) on Day 5, 0.15 ± 0.05 (69.4%) on Day 7, and 0.05 ± 0.02 (89.8%) on Day 10, again demonstrating comparable improvements. This change in loss of appetite score is demonstrated in Table 2.

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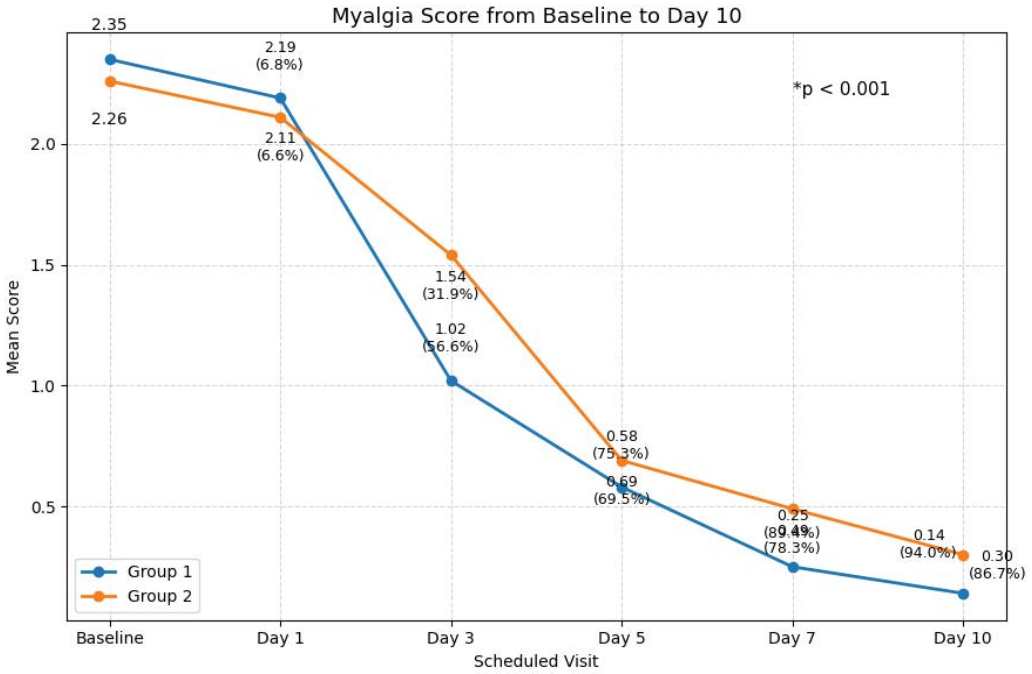

Figure 3: Myalgia Score from Baseline to Day 10

Perceived hydration status

Perceived hydration status improved markedly in both groups over the course of the study, reflecting overall clinical recovery and adequate supportive care. The slightly higher proportion of patients reporting "very satisfied" hydration status in Group 1 (92% vs 88%) suggests a marginally better improvement in fluid balance and symptomatic well-being, which may be attributed to the electrolyte-containing formulation and enhanced recovery profile in this group. This change in hydration score is demonstrated in Table 2.

Assessment of specific efficacy lab parameters

Platelet cells/mm^3

The mean platelet count at baseline was comparable between Group 1 (113,333) and Group 2 (108,000). On Day 1, a decline in platelet count was observed in both groups, with Group 1 reducing to 98,659 (−13.0%) and Group 2 to 92,324 (−14.5%). This downward trend continued on Day 3, with counts decreasing further to 76,667 (−32.4%) in Group 1 and 70,000 (−35.2%) in Group 2. The lowest platelet counts were observed on Day 5, with Group 1 at 65,000 (−42.6%) and Group 2 at 58,450 (−45.9%), indicating a marked decline in both groups. Subsequently, recovery was noted on Day 7, with platelet counts increasing to 81,667 (−28.0%) in Group 1 and 84,636 (−21.6%) in Group 2. By Day 10, a substantial rebound was observed, with platelet counts rising above baseline levels to 182,000 (+60.6%) in Group 1 and 183,500 (+69.9%) in Group 2, indicating significant recovery in both groups. This change in platelet count is shown in Figure 4.

Haematocrit %

Baseline values were comparable (40.35 ± 2.3 vs 43.36 ± 4.17; p = 0.077). Hematocrit increased on Day 1 (43.13 ± 2.48 vs 43.71 ± 3.12; p = 0.470) and peaked on Day 3 (45.37 ± 5.14 vs 47.41 ± 1.21; p = 0.059). It remained elevated on Day 5 (44.68 ± 6.29 vs 45.32 ± 3.86; p = 0.666), followed by a decline on Day 7 (38.26 ± 3.27 vs 41.22 ± 4.59; p = 0.011) and Day 10 (37.0 ± 2.04 vs 39.17 ± 2.37; p < 0.001). Within-group changes were significant (p < 0.001). The rise in hematocrit during Days 1–3 indicates hemoconcentration due to plasma leakage, peaking during the critical phase. The subsequent decline reflects fluid reabsorption and recovery. Lower values in Group 1 during recovery (Day 7–10) suggest better resolution of plasma leakage, though baseline differences may partially reflect randomization variability. This change in haematocrit is shown in Table 3.

Clotting Time (minutes)

Baseline values were comparable (6.11 ± 0.64 vs 7.46 ± 1.27; p = 0.100). Clotting time increased on Day 1 (6.79 ± 0.46 vs 7.90 ± 1.06; p < 0.001) and Day 3 (7.39 ± 0.59 vs 8.15 ± 1.39; p = 0.015), remained elevated on Day 5 (7.51 ± 0.24 vs 7.90 ± 1.17; p = 0.109), and decreased on Day 7

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(6.50 ± 1.02 vs 7.16 ± 1.15; p = 0.036) and Day 10 (6.05 ± 0.67 vs 6.98 ± 0.47; p < 0.001). Within-group changes were significant (p = 0.001). Prolongation during Day 1–5 reflects coagulopathy in dengue, while faster normalization in Group 1 suggests better restoration of coagulation function. This change in clotting time is shown in Table 3.

Bleeding time (minutes)

Baseline values were comparable (2.10 ± 1.06 vs 2.20 ± 1.63; p = 0.798). Bleeding time increased on Day 1 (2.12 ± 0.85 vs 2.93 ± 0.79; p = 0.001) and peaked on Day 3 (3.10 ± 1.05 vs 3.84 ± 1.07; p = 0.017). It remained elevated on Day 5 (3.86 ± 0.84 vs 3.90 ± 1.64; p = 0.914), followed

Table 2: Change in Symptomatic Outcomes

Clinical symtoms	Scheduled visits	Group 1 (n=25)	Reduction (%)	Comparator group (n=25)	Reduction (%)	Comparison between test and comparator P value
	Baseline	101.6 ± 1.12	-	102.5 ± 1.12	-	0.0666
	Day 1	101.1 ± 1.11	0.50%	101.5 ± 1.20	1.00%	0.2271
Temperature	Day 3	100.2 ± 1.07	1.40%	100.3 ± 0.58	2.10%	0.683
	Day 5	99.7 ± 0.41	1.90%	99.6 ± 0.68	2.80%	0.996
	Day 7	98.3 ± 0.50	3.30%	98.5 ± 0.33	3.90%	0.1016
	Day 10	98.1 ± 0.47	3.40%	98.4 ± 0.51	4.00%	0.0356*
Within group comparison P-value		0.0001		0.0001		
	Baseline	3 ± 0.40	-	3 ± 0.25	-	1
Fever score	Day 1	2.79 ± 0.54	7.00%	2.65 ± 0.48	11.70%	0.3375
	Day 3	2.11 ± 0.20	29.70%	2.12 ± 0.85	29.30%	0.9546
	Day 5	1.46 ± 0.26	51.30%	1.45 ± 0.21	51.70%	0.8817
	Day 7	0.41 ± 0.10	86.30%	0.39 ± 0.20	87.00%	0.6567
	Day 10	0.19 ± 0.12	93.70%	0.20 ± 0.45	93.30%	0.915
Within group comparison P-value		0.0001		0.0001		
	Baseline	2.0 ± 1.1	-	1.67 ± 1.10	-	0.2942
	Day 1	1.46± 1.05	27.00%	1.37 ± 1.10	18.00%	0.1738
	Day 3	1.12 ± 0.79	44.00%	1.12 ± 1.04	32.90%	1
Headache score	Day 5	0.88 ± 0.69	56.00%	0.86 ± 0.35	48.50%	0.8977
	Day 7	0.42± 0.23	79.00%	0.36 ± 0.10	78.40%	0.2375
	Day 10	0.20 ± 0.16	90.00%	0.19 ± 0.24	88.60%	0.8631
Within group comparison P-value		0.0001		0.0001		
	Baseline	0.45 ± 0.12	-	0.49 ± 0.20	-	0.3954
Loss of appetite score	Day 1	0.40 ± 0.11	11.10%	0.39 ± 0.10	20.40%	0.7381
	Day 3	0.32± 0.18	28.90%	0.29± 0.15	40.80%	0.6731
	Day 5	0.22 ± 0.07	51.10%	0.20 ± 0.06	59.20%	0.7381
	Day 7	0.12 ± 0.05	73.30%	0.15 ± 0.05	69.40%	0.3475
	Day 10	0.05 ± 0.02	88.90%	0.05 ± 0.02	89.80%	1
Within group comparison P-value		0.021		0.01		
Perceived hydration status	Baseline	Dissatisfied (100%)		Dissatisfied (100%)		
	Post study	Very satisfied (92%)		Very satisfied (88%)		

Citation: Pirthi Pal Singh, M. Sakthi Balan, Bijoy Deb, Purushottam Nagar, Vijay Thakur, Renuka Thakur, Praneeth Immadisetti, Kriti Kaushik, Rachana Bhoite. Efficacy and Safety of a Plant-based Nutraceutical Formulation in Dengue-Associated Thrombocytopenia: A Randomized, Open-label, Parallel-group study. Fortune Journal of Health Sciences. 9 (2026): 223-236.

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by a reduction on Day 7 (2.18 ± 1.41 vs 2.29 ± 0.79; p = 0.735) and Day 10 (2.16 ± 1.32 vs 2.50 ± 1.23; p = 0.350). Within-group changes were significant (p = 0.001). Early rise reflects platelet dysfunction and vascular fragility during acute illness. Lower values in Group 1 during the early days indicate better hemostatic control during the critical phase. This change in bleeding time is shown in Table 3.

Haemoglobin (%)

Baseline hemoglobin levels were comparable between Group 1 and Group 2 (13.3 ± 1.1 vs 13.92 ± 1.7; p = 0.132). At the end of the study, values remained stable in both groups (13.1 ± 0.9 vs 13.76 ± 1.6; p = 0.078), with no statistically significant difference between groups. Within-group comparisons also showed no significant change over time (Group 1: p = 0.485; Group 2: p = 0.733). Hemoglobin levels remained stable throughout the study period, indicating the absence of clinically significant bleeding or hemoconcentration-related complications. This is consistent with the inclusion of mild to moderate dengue cases, where major hemorrhagic manifestations are uncommon, and supports the overall clinical stability of the study population. This change in hemoglobin is shown in Table 3.

Leukocyte Profile and Immune Recovery (cells/mm3)

Baseline total WBC count was comparable between Group 1 and Group 2 (4409.1 ± 1071.9 vs 4533.3 ± 1047.3; p = 0.680), with improvement observed at post-study (5621.6 ± 1910.2 vs 4541.6 ± 1239.9; p = 0.021). Within-group analysis showed a significant increase only in Group 1 (p < 0.001), while no significant change was observed in Group 2 (p = 0.992). Neutrophil counts were similar at baseline (67.5 ± 5.2 vs 66.5 ± 4.1) and decreased at post-study (55.1 ± 5.4 vs 58.5 ± 5.6; p = 0.033), with significant within-group reductions in both groups (p < 0.001). In contrast, lymphocyte counts increased from baseline (33.7 ± 7.3 vs 32.2 ± 3.9; p = 0.369) to post-study (41.6 ± 4.7 vs 40.0 ± 4.4; p = 0.849), with significant within-group improvements (p < 0.001 for both groups). These findings reflect the characteristic hematological evolution of dengue, with leukopenia during the early phase followed by recovery by the end of the study period, along with a shift from neutrophil predominance to lymphocyte predominance. The greater increase in total WBC count in Group 1 suggests better immune recovery and improved resolution of viral suppression, particularly during the recovery phase (Day 7–10), when most patients clinically stabilize. These results are summarized in Table 3.

Liver function test (U/L)

For SGOT (AST), baseline values were comparable between both groups (31.9 ± 5.2 vs 32.2 ± 2.9; p = 0.963). At the end of the study, SGOT levels remained comparable between the two groups (34.0 ± 4.2 vs 34.6 ± 2.4; p = 0.538), with no statistically significant difference. Within-group analysis showed no statistically significant change in the Group (p = 0.091), whereas a significant increase was observed in Group 2 (p = 0.002). For SGPT (ALT), baseline values were comparable between both groups (28.8 ± 5.8 vs 28.7 ± 2.5; p = 0.937). At the end of the study, SGPT levels were significantly higher in Group 2 compared to Group 1 (30.6 ± 3.1 vs 33.0 ± 1.4; p < 0.001). Within-group analysis showed no statistically significant change in Group 1 (p = 0.177), whereas a significant increase was observed in the Group 2 (p < 0.001). Hepatic safety was comparable across both groups. These results are summarized in Table 3.

Kidney function test (mg/dL)

For blood urea, baseline values were comparable between both groups (24.4 ± 3.8 vs 23.8 ± 5.5; p = 0.655). At the end of the study, blood urea levels remained comparable between the two groups (28.8 ± 4.7 vs 29.6 ± 3.2; p = 0.485), with no statistically significant difference. Within-group analysis showed a statistically significant increase in blood urea levels in both Group 1 (p < 0.0001) and Group 2 (p < 0.001). Mild rise in urea likely reflects transient dehydration, with no significant renal impairment. In serum creatinine, baseline values were comparable between Group 1 and Group 2 (0.7 ± 0.09 vs 0.65 ± 0.10; p = 0.069). At the end of the study, serum creatinine levels were identical in both groups (0.9 ± 0.08 vs 0.9 ± 0.10; p = 1.000), with no statistically significant difference. This likely reflects transient physiological changes such as mild dehydration or increased metabolic demand during acute illness, rather than true renal impairment. The absence of significant between-group differences indicates that both interventions were renally safe and did not adversely affect kidney function. For electrolytes (mEq/L), at the end of the study, Serum sodium levels were significantly higher in Group 1 compared to Group 2 (141.5 ± 3.5 vs 138.8 ± 3.9; p = 0.013). Within-group analysis showed a significant increase in serum sodium levels in Group 1 (p = 0.013), while no significant change was observed in Group 2 (p = 0.237). In contrast, serum potassium and serum chloride and chloride levels remained comparable between groups at baseline and post-study, with no statistically significant changes observed either between or within groups, indicating no clinically significant electrolyte imbalance and overall maintenance of electrolyte homeostasis. These results are summarized in Table 3.

Adverse Effects

Adverse events were mild and comparable between the two groups. In Group 1 (n = 25), nausea and vomiting were each reported in 2 patients (8.0% each), while gastritis was reported in 3 patients (12.0%). In Group 2 (n = 25), nausea and vomiting were each reported in 3 patients (12.0% each),

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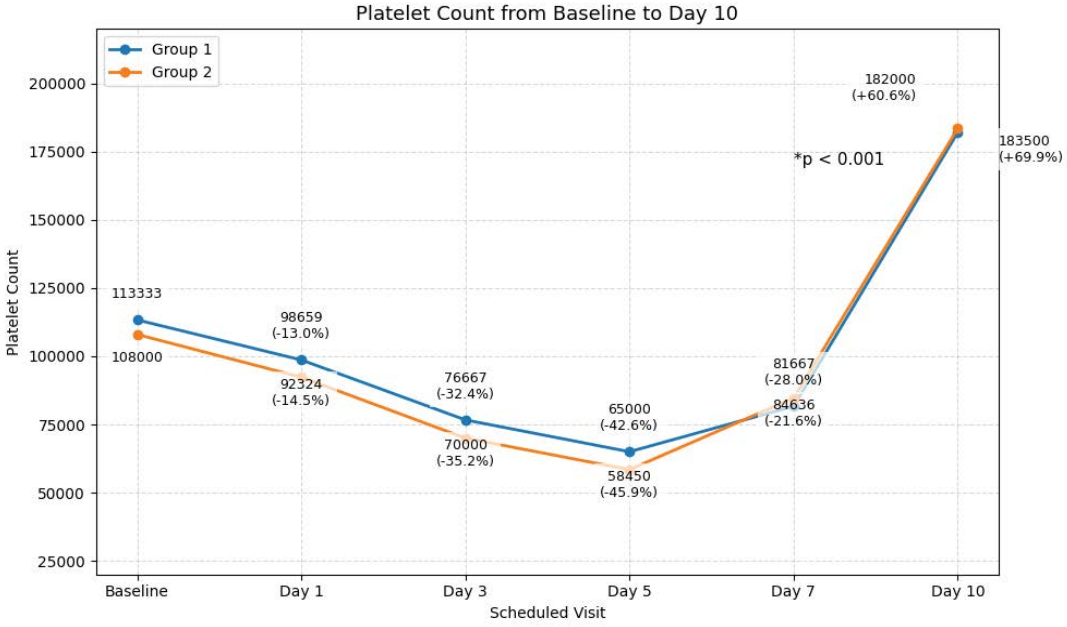
and gastritis in 4 patients (16.0%). No cases of diarrhoea, giddiness, or allergic reactions were reported in either group (0% in both groups). All adverse events (AEs) reported during the study were non-pharmacological in nature and were not related to the investigational product. All events were resolved by the end of the study. These adverse events are shown in Figure 5.

Concomitant medications

In Group 1, paracetamol use was limited to shorter durations, with all patients requiring it for three days or less and none needing it beyond three days. In contrast, in Group 2, a majority of patients (68%) required paracetamol for five days or more, suggesting prolonged symptom persistence. Similarly, the need for additional analgesics was substantially lower in Group 1, where 76% of patients did not require any analgesics at all, compared to only 16% in Group 2. Furthermore, none of the patients in Group 1 required analgesics beyond two days, whereas 24% of patients in Group 2 required them for three days or more. This data is summarized in Table 4.

Overall assessment of the study outcome

The investigator's overall assessment showed comparable outcomes between the two groups. In Group 1 (n = 25), 14 patients (56.0%) were reported as completely cured, 9 (36.0%) showed marked improvement, and 2 (8.0%) showed moderate improvement. In Group 2 (n = 25), 13 patients (52.0%) were reported as completely cured, 9 (36.0%) showed marked improvement, and 3 (12.0%) showed moderate improvement. No patients in either group were reported to have only slight



Note: Values are presented as mean (% change from baseline).

Figure 4: Platelet count from Baseline to Day 10

Table 3: Change in Laboratory parameter

Specific Efficacy Lab parameters	Scheduled visits	TEST Group 1 (n=25)	Comparator Group 2 (n=25)	Comparison between test and comparator P value
	Baseline	40.35 ± 2.3	43.36 ± 4.17	0.077
Hematocrit %	Day 1	43.13 ± 2.48	43.71 ± 3.12	0.4704
	Day 3	45.37± 5.14	47.41 ± 1.21	0.0593
	Day 5	44.68 ± 6.29	45.32 ± 3.86	0.6665
	Day 7	38.26 ± 3.27	41.22 ± 4.59	0.0116*
	Day 10	37.0 ± 2.04	39.17 ± 2.37	0.0001*
Within Group comparison P value		0.001	0.001	
	Baseline	6.11 ± 0.64	7.46 ± 1.27	0.1
	Day 1	6.79 ± 0.46	7.90 ± 1.06	0.0001*

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	Day 3	7.39 ± 0.59	8.15 ± 1.39	0.0152*
	Day 5	7.51 ± 0.24	7.90 ± 1.17	0.1091
Clotting Time (minutes)	Day 7	6.50 ± 1.02	7.16 ± 1.15	0.0369*
	Day 10	6.05 ± 0.67	6.98 ± 0.47	0.0001*
Within Group comparison P value		0.001	0.001	
	Baseline	2.10± 1.06	2.20 ± 1.63	0.7982
	Day 1	2.12 ± 0.85	2.93 ± 0.79	0.0010*
	Day 3	3.10 ± 1.05	3.84 ± 1.07	0.0172*
	Day 5	3.86 ± 0.84	3.90 ± 1.64	0.914
Bleeding Time (minutes)	Day 7	2.18 ± 1.41	2.29 ± 0.79	0.7351
	Day 10	2.16 ± 1.32	2.50 ± 1.23	0.3508
Within Group comparison P value		0.001	0.001	
Hemoglobin (%)	Baseline	13.3 ± 1.1	13.92 ± 1.7	0.1323
	Post study	13.1± 0.9	13.76 ± 1.6	0.0785
Within group comparison P value		0.4851	0.7333	
Total WBC count cells/mm^3	Baseline	4409.1 ± 1071.9	4533.3 ± 1047.3	0.6804
	Post study	5621.6 ± 1910.2	4541.6 ± 1239.9	0.0218*
Within group comparison: P value		0.0001	0.9929	
Neutrophils cells/ mm^3	Baseline	67.5 ± 5.2	66.5 ± 4.1	0.0001
	Post study	55.1 ± 5.4	58.5 ± 5.6	0.0338
Within group comparison: P value		0.001	0.001	
Lymphocytes cells/ mm^3	Baseline	33.7 ± 7.3	32.2 ± 3.9	0.3694
	Post study	41.6 ± 4.7	40 ± 4.4	0.8491
Within group comparison: P value		0.001	0.001	
SGPT (U/L)	Baseline	28.8 ± 5.8	28.7 ± 2.5	0.9372
	Post study	30.6 ± 3.1	33 ± 1.4	0.0009
Within group comparison: P value		0.1775	0.0001	
Blood Urea (mg/dL)	Baseline	24.4 ± 3.8	23.8 ± 5.5	0.6556
	Post study	28.8 ± 4.7	29.6 ± 3.2	0.4851
Within group comparison: P value		0.0007	0.0001	
Serum Creatinine (mg/dL)	Baseline	0.7 ± 0.09	0.65 ± 0.1	0.0693
	Post study	0.9 ± 0.08	0.9 ± 0.1	1
Within group comparison: P value		0.0001	0.0001	

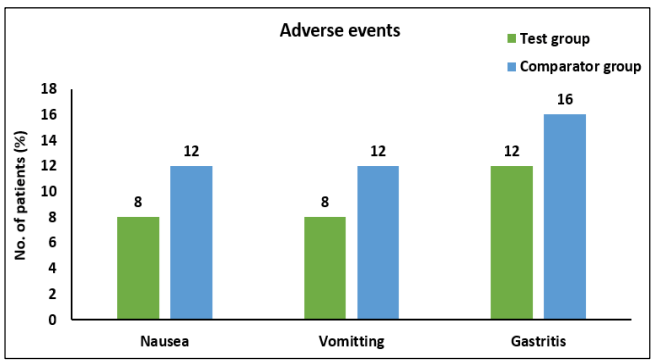

Figure 5: Adverse events

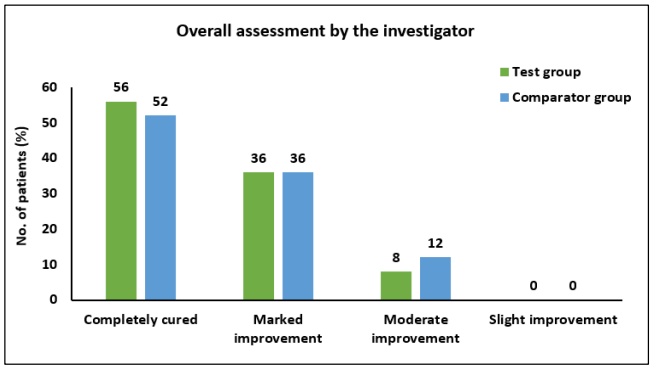

Figure 6: Overall assessment by the investigator

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Table 4: Concomitant medications

Concomitant Drug used and Duration	No. of participants	
	Group 1 (n=25)	Group 2 (n=25)
Paracetamol		
One day alone	4 (16)	0
Two days alone	12 (48)	0
Three days alone	9 (36)	8 (32)
Five days alone	0	0
Analgesics (Ibuprofen, Aceclofenac, Diclofenac)		
Not required	19 (76)	4 (16)
One day alone	3 (12)	8 (32)
Two days alone	3 (12)	7 (28)
Three days alone	0	6 (24)

improvement. These insights are demonstrated in Figure 6.

Discussion

The present study demonstrated that while both the Plant-based nutraceutical formulation and Carica papaya leaf extract improved clinical outcomes in dengue, the Plant-based nutraceutical formulation showed distinct and consistent advantages across multiple clinical and laboratory parameters. In particular, it achieved significantly higher platelet counts by Day 5 (65,000 ± 12,027.76 vs 58,450 ± 10,406.6 cells/mm³; $p = 0.044$), along with consistently lower clotting time ($p < 0.05$) and earlier reduction in bleeding time. Additionally, the Plant-based nutraceutical formulation resulted in greater improvement in myalgia and arthralgia, better recovery from leukopenia ($p < 0.001$), a favorable hepatic profile without a significant rise in liver enzymes, and improved sodium levels at the end of the study (141.5 vs 138.8; $p = 0.013$), suggesting a broader spectrum of clinical and biochemical benefits. Acute febrile illnesses such as dengue, malaria, and typhoid fever commonly present with thrombocytopenia, which is strongly associated with increased morbidity and mortality [21, 22]. The degree of platelet reduction serves as an important prognostic marker, correlating with bleeding risk, disease severity, and clinical outcomes. Therefore, therapeutic approaches that address not only platelet recovery but also associated inflammatory symptoms such as fever, myalgia, and arthralgia are essential for improving overall patient outcomes.

The findings of the present study are consistent with existing literature on Carica papaya leaf extract. A systematic review and meta-analysis involving four trials (n = 439) demonstrated a significant increase in platelet count (MD = 20.27; $p = 0.005$), with a greater effect observed after Day 4 (MD = 28.25; $p < 0.0001$), along with a reduction in duration of hospitalization (MD = 1.90; $p < 0.00001$) [23]. Similarly, pooled estimates from six randomized clinical trials (n = 988) showed significant platelet improvement at Day 3 (MD = 12.18), Day 4 (MD = 31.30), and Day 5 (MD = 13.23) [24]. A case report by Haward *et al.* reported platelet recovery from 27,450/mm³ (Day 5) to 120,320/mm³ (Day 14) along with improvement in symptoms such as fatigue, arthralgia, and myalgia [25]. Furthermore, a study by Ramesh *et al.* demonstrated that a combination of Carica papaya and Tinospora cordifolia resulted in platelet counts of approximately 160,000/µL vs 130,000/µL in the placebo group by Day 15 [19]. In line with these findings, the present study demonstrated that although both groups showed a decline in platelet counts from baseline to Day 5, followed by recovery by Day 10, baseline values were comparable between Group 1 and Group 2 (113,333.3 ± 15,275.25 vs 108,000 ± 14,142.14; $p = 0.206$). By Day 5, Group 1 maintained significantly higher platelet counts compared to Group 2 (65,000 ± 12,027.76 vs 58,450 ± 10,406.6; $p = 0.044$). This enhanced recovery may be attributed to the presence of Carica papaya leaf extract and *Curcuma longa*, which are known to contribute to platelet augmentation and improved hematological outcomes.

Beyond platelet recovery, the additional benefits observed with the Plant-based nutraceutical formulation may be attributed to the complementary mechanisms of its individual components. Carica papaya leaf extract has been shown to modulate inflammatory pathways by reducing pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6, and IL-8, while enhancing immune response through increased levels of IL-12 and IFN-γ [19]. Similarly, Tinospora cordifolia has demonstrated significant anti-inflammatory and analgesic activity, with evidence showing modulation of pro-inflammatory cytokines (TNF-α, IL-6) and inhibition of NF-κB signaling pathways, thereby providing a mechanistic basis for improvement in symptoms such as myalgia, arthralgia, and headache [24, 26]. This is consistent with the present study findings, where greater reductions in pain-related symptoms were observed in Group 1, with significantly lower arthralgia scores at Day 10 (0.05 ± 0.05 vs 0.14 ± 0.08; $p < 0.001$) and myalgia scores at Day 7 (0.25 ± 0.09 vs 0.49 ± 0.20; $p = 0.001$) and Day 10 (0.14 ± 0.10 vs 0.30 ± 0.16; $p = 0.014$).

Furthermore, Curcuma longa (curcumin), in combination with piperine, plays a crucial role in inflammation control. A pilot study by Vajpayee *et al.* demonstrated a significant reduction in hs-CRP levels from 47.53 ± 55.73 mg/dL to 16.96 ± 38.97 mg/dL (mean difference = 30.57; $p = 0.002$) [27]. Additionally, Boonreung *et al.* reported substantial analgesic effects, with reductions in pain-like behavior of up to 63% and 89% with curcumin and piperine, respectively [28]. Piperine further enhances the bioavailability of curcumin by up to 20-fold, with studies also reporting

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increases of up to 154% in systemic bioavailability when co-administered with high-dose curcumin [18,29]. These mechanisms collectively contribute to improved control of inflammatory symptoms and may explain the superior reduction in myalgia and arthralgia observed in Group 1. Consistent with these mechanistic insights, the present study demonstrated significant improvement in both groups across parameters such as temperature (101.6 ± 1.12°F vs 102.5 ± 1.12°F at baseline to 98.1 ± 0.47°F vs 98.4 ± 0.51°F at Day 10; $p < 0.001$), fever score (3 ± 0.40 vs 3 ± 0.25; $p < 0.001$), headache (2.0 ± 1.1 vs 1.67 ± 1.10 to 0.20 ± 0.16 vs 0.19 ± 0.24; $p = 0.001$), and loss of appetite (0.45 ± 0.12 vs 0.49 ± 0.20 to 0.05 ± 0.02; $p = 0.021$ and $p = 0.010$). However, the Plant-based nutraceutical formulation demonstrated superior outcomes in symptom resolution. Perceived hydration status also improved, with 92% of patients in Group 1 vs 88% in Group 2 reporting being very satisfied by the end of the study. Taken together, these findings suggest that while Carica papaya leaf extract plays a central role in platelet recovery, the addition of other bioactive components such as Tinospora cordifolia, Curcuma longa, Ocimum sanctum, and piperine provides a synergistic advantage by targeting multiple pathways, including inflammation, immune modulation, and symptom control, resulting in faster and more comprehensive clinical recovery compared to single-agent therapy.

Limitations

This study has certain limitations that should be considered while interpreting the findings. First, the study included only hemodynamically stable dengue patients with mild to moderate disease severity, excluding patients with severe dengue (e.g., platelet count <50,000/µL, hemorrhagic manifestations, or those requiring ICU care). Therefore, the findings cannot be generalized to severe dengue cases, where standard supportive management, including fluid therapy, platelet transfusion, and intensive care, remains essential, and nutraceutical supplementation alone is unlikely to be sufficient. The study had a small sample size and open-label design, which may introduce potential bias and limit the robustness of conclusions. Finally, the absence of severe clinical endpoints (e.g., progression to severe dengue, hospitalization duration, ICU requirement) restricts comprehensive evaluation of clinical benefit.

Future Scope

Future studies should aim to include larger, multicentric populations to improve generalizability and statistical power. While inclusion of severe dengue patients may enhance clinical applicability, such studies should be carefully designed to evaluate these formulations as adjuncts to standard-of-care management, rather than standalone therapies. Extended follow-up beyond the acute phase may help assess sustained recovery, normalization of laboratory parameters, and safety profile. Additionally, studies exploring time to platelet recovery, reduction in hospitalization duration, and need for supportive interventions (e.g., transfusion, analgesics) would provide more clinically meaningful outcomes.

Conclusion

In this randomized parallel study of patients with mild to moderate Dengue fever, both groups showed clinical improvement over time; however, the plant-based nutraceutical formulation (Group 1) demonstrated superior clinical benefits, particularly in terms of greater reduction in musculoskeletal symptoms (arthralgia and myalgia), improved leukocyte recovery, and reduced need for concomitant medications. Group 1 also showed a lower requirement for rescue analgesics and antipyretics, while paracetamol and supportive interventions were required more frequently in Group 2, suggesting better symptomatic control with the test formulation. Clotting and bleeding time initially worsened during the early phase of illness, consistent with dengue-associated coagulopathy, followed by gradual normalization in both groups. Group 1 demonstrated faster recovery of these parameters, indicating better restoration of hemostatic function during the critical phase. Liver enzyme levels remained stable in Group 1, whereas a rise was observed in Group 2, suggesting comparable hepatic safety profile in both the groups Perceived hydration status improved in both groups over the study period; however, Group 1 showed better hydration recovery with lower need for oral rehydration salt (ORS) supplementation, while ORS intervention was substantially higher in Group 2. This suggests that the plant-based sachet formulation, enriched with electrolytes and herbal extracts with potential antipyretic activity, may have contributed to improved fluid balance and symptomatic well-being. These findings suggest that the plant-based nutraceutical formulation may provide enhanced symptomatic relief, hydration support, and overall recovery compared with Carica papaya extract alone, supporting its role as a more effective supportive adjunct in uncomplicated dengue management. It is important to note that dengue is generally a self-limiting illness, and in severe cases, standard medical management remains essential, with such formulations serving only as adjunctive therapy.

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Author Contributions

Pirthi Pal Singh: Product ideation, Design of medical rationale, product design, and development

M. Sakthi Balan: Clinical study design and execution

Bijoy Deb: Clinical study coordination, and execution

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Purushottam Nagar: Formulation conceptualization and lead formulation development program

Vijay Thakur: Formulation, process development, and stability studies

Renuka Thakur: Analytical method development, validation, and stability studies

Rachana Bhoite: Data validation, writing – review & editing

Praneeth Immadisetti: Data validation, writing – review & editing

Kriti Kaushik: Data validation, writing – review & editing

Conflict of interest: None

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