



Papaya Leaf Extract and Platelet Count: A Review of its Role in Thrombocytopenia

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Abstract:

Thrombocytopenia, characterized by a reduced platelet count, is a critical haematological condition associated with increased risk of bleeding commonly associated with diseases such as dengue fever and chemotherapy-induced bone marrow suppression, posing significant risks of bleeding and morbidity. Carica papaya leaf extract (CPLE) has emerged as a promising natural therapeutic agent due to its potential to elevate platelet counts effectively. This review synthesizes current clinical and experimental evidence regarding the efficacy, mechanisms, and safety of papaya leaf extract in thrombocytopenia management. Studies demonstrate that CPLE administration accelerates platelet recovery by upregulating genes involved in hematopoiesis, including ALOX12 and PTAFR, and enhances megakaryocyte activity, thereby promoting thrombopoiesis. Clinical trials in dengue and chemotherapy-induced thrombocytopenia patients report significant platelet count increases, reduced hospital stays, and fewer transfusion requirements compared to controls. The review synthesizes data on efficacy, optimal dosing, formulation (e.g., juice, tablets, capsules), and safety profile. While clinical evidence, particularly in dengue-induced thrombocytopenia, While findings indicate a beneficial role for CPLE as an accessible, cost-effective adjunct therapy, limitations including variable dosing regimens and small sample sizes highlight the need for large-scale randomized controlled trials to establish standardized protocols and confirm long-term safety. This comprehensive review concludes by summarizing the current scientific consensus, highlighting existing knowledge gaps, and proposing directions for future research to fully establish CPLE as a safe and effective adjunctive therapy for thrombocytopenia and encourages further research to optimize its clinical application.

INTRODUCTION :

Thrombocytopenia may range from mild (100,000–150,000/ μ L) to severe (<50,000/ μ L), with severe cases posing risks such as gastrointestinal bleeding, intracranial hemorrhage, or excessive bleeding post-injury. Clinically, symptoms often appear only when platelet levels fall below 100,000/ μ L [4].

Major Causes, Thrombocytopenia results from three main mechanisms such as decreased platelet production, increased destruction, or abnormal distribution (such as splenic sequestration).

1. Reduced platelet production – Caused by bone marrow suppression due to factors like:

- Certain medications (e.g., valproic acid, linezolid)
- Infections or chronic diseases affecting marrow (HIV, hepatitis C, leukaemia)

- Nutrient deficiencies (vitamin B12, folate, copper)

2. Increased platelet destruction – Caused by:

- Immune thrombocytopenic purpura (ITP): an autoimmune condition wherein antibodies destroy platelets mistakenly; can be acute (self-limiting, often post-viral in children) or chronic (common in adults)
- Drug-induced destruction: triggered by drugs like heparin, quinine, sulfa drugs, or certain NSAIDs
- Disseminated intravascular coagulation (DIC) and sepsis can also consume platelets excessively

Clinically known as Thrombocytes, are small components of blood produced in the bone marrow with a key role in blood clotting. The major function of thrombocytes is to stop bleeding from injured blood vessels. These nucleated cell fragments in mammals are called as platelets [4]. Dysfunction or low levels of platelets predisposes to bleeding, while high levels, although usually asymptomatic, may increase the risk of thrombosis. An abnormality or disease of the platelets is called a thrombocytopathy. Both thrombocytopenia and thrombocytosis may present with coagulation problems. Generally, Low Blood Platelet counts increase bleeding risks (although there are exceptions, e.g. immune heparin-induced thrombocytopenia) and thrombocytosis (high counts) may lead to thrombosis (although this is mainly when the elevated count is due to myeloproliferative disorder). [13]

Specific Conditions and Examples

- Dengue Fever: Thrombocytopenia is a hallmark, arising from platelet destruction and bone marrow suppression by the dengue virus.
- Chemotherapy-related thrombocytopenia: A result of bone marrow toxicity from cytotoxic drugs, often transient.
- Idiopathic (Immune) Thrombocytopenic Purpura (ITP): A primary immune disorder causing isolated platelet destruction in the absence of other underlying diseases.
- Other infections: Malaria, sepsis, and bacterial infections can suppress or destroy platelets directly or indirectly.

Among such herbal remedies, *Carica papaya* (papaya) leaves have gained significant attention due to several clinical and experimental studies suggesting their potential in increasing platelet count and stabilizing hematocrit levels in dengue patients. The leaves are rich in bioactive compounds such as flavonoids, alkaloids (notably carpaine), and antioxidants, which are believed to stimulate bone marrow activity and protect platelets from destruction [15]. Papaya Leaf Papaya leaves are traditionally used in the treatment of thrombocytopenia. The latex contains papain and several other beneficial compounds including chitinases, flavonoids, alkaloids, and tannins that support platelet production [1].

Phytochemical Composition of Papaya leaves:

Overview of papaya plant

Family Name: *caricaceae*

Kingdom- Plantae

Sub Kingdom- Tracheobionta

Class- Magnoliopsida

Subclass- Dilleniidae

Super division- Spermatophyta

Phylum- Streptophyta

Order- Brassicales

Family- Caricaceae

Genus- *Carica*



Fig. : Papaya leaf

Biological Source: Papain is the dried and purified latex of the green fruits and leaves of *Carica papaya* L., belonging to family Caricaceae. The plant is 5–6 m in height bearing fruits of about 30 cm length and a weight up to 5 kg.

Plant Part	Medicinal uses
Ripe fruit	Sinuses, chronic forms of skin indurations in Caribe, Philippines; Chronic skin ulcers in Jamaica Stomachic, digestive, diuretic, expectorant, sedative and tonic, bleeding Piles and dyspepsia in India
Green Fruit	Malaria, hypertension, diabetes mellitus, hypercholesterolemia, jaundice Intestinal helminthiasis in Nigeria
latex	Dermatitis and psoriasis in Africa, Asia, Europe
Leaves	Heart tonic, febrifuge, vermifuge, colic, dengue fever, Thrombocytopenia, beriberi, abortion, asthma India, Stomach troubles, cancer in Australia
Flowers	Jaundice, cough, hoarseness, bronchitis, laryngitis, and trachealis in Asia
Seeds	Anti-fertility. Antimicrobial, fungicidal, carminative, counter irritant

Table 1: Medicinal uses of different part of papaya plant

Papaya leaves are a significant source of potent secondary metabolites, which are largely responsible for their traditional medicinal uses. Key phytochemical classes include:

1. Alkaloids:

The most notable is carpaine, which is often cited for its potential cardiovascular benefits. Other alkaloids include pseudocarpaines and dehydrocarpaine I and II.

2. Phenolic Compounds and Phenolic Acids:

These compounds exhibit strong antioxidant properties. Examples include protocatechuic acid, caffeic acid, coumaric acids, and chlorogenic acid.

3. Flavonoids:

A large group of polyphenols with antioxidant and anti-inflammatory effects. Specific flavonoids identified include quercetin and kaempferol.

4. Terpenoids:

Includes carotenoids (like beta-carotene), which are potent antioxidants, and saponins, known for potential antimicrobial and cholesterol-lowering effects.

5. Other Bioactive Compounds:

Tannins, glycosides, and enzymes such as papain and chymopapain are also present.

MECHANISM OF CARICA PAPAYA LEAF EXTRACT AGAINST THROMBOCYTOPENIA

Numerous studies have demonstrated that *C. papaya* leaf enhances platelet formation through gene expression activities. The effect of *C. papaya* leaf extract boosted the activity of specific genes, such as arachidonic acid 12-lipoxygenase (ALOX-12) and platelet-activating factor Receptor (PTAFR), the high expression of particular gene expression induces the bone marrow to manufacture more megakaryocytes. These megakaryocytes are the stem cells that produce platelets; when they mature, they divide into tiny pieces known as platelets, which increases the number of platelets and their aggregation in the bloodstream. According to a recent experimental investigation, the for this mechanism of action of *C. papaya* leaf is attributed to carpaine. The leaf juice of *C. papaya* helps to express more CD110 receptors on megakaryocytes, which are useful in preventing thrombocytopenia brought on by chemotherapy. *C. papaya* leaf can also be used to treat thrombocytopenia by lessening the breakdown of platelets. Flavonoids found in *C. papaya* leaves bind to the proteases in the viral assembly—the virus's functional and replicating units—to stop viral growth. Procedure maintains normal hematocrit levels while minimizing platelet damage. By raising the activities of ALOX-12 and PTFAR by 15 and 13–14 folds, respectively, these extracts also increase platelet generation.

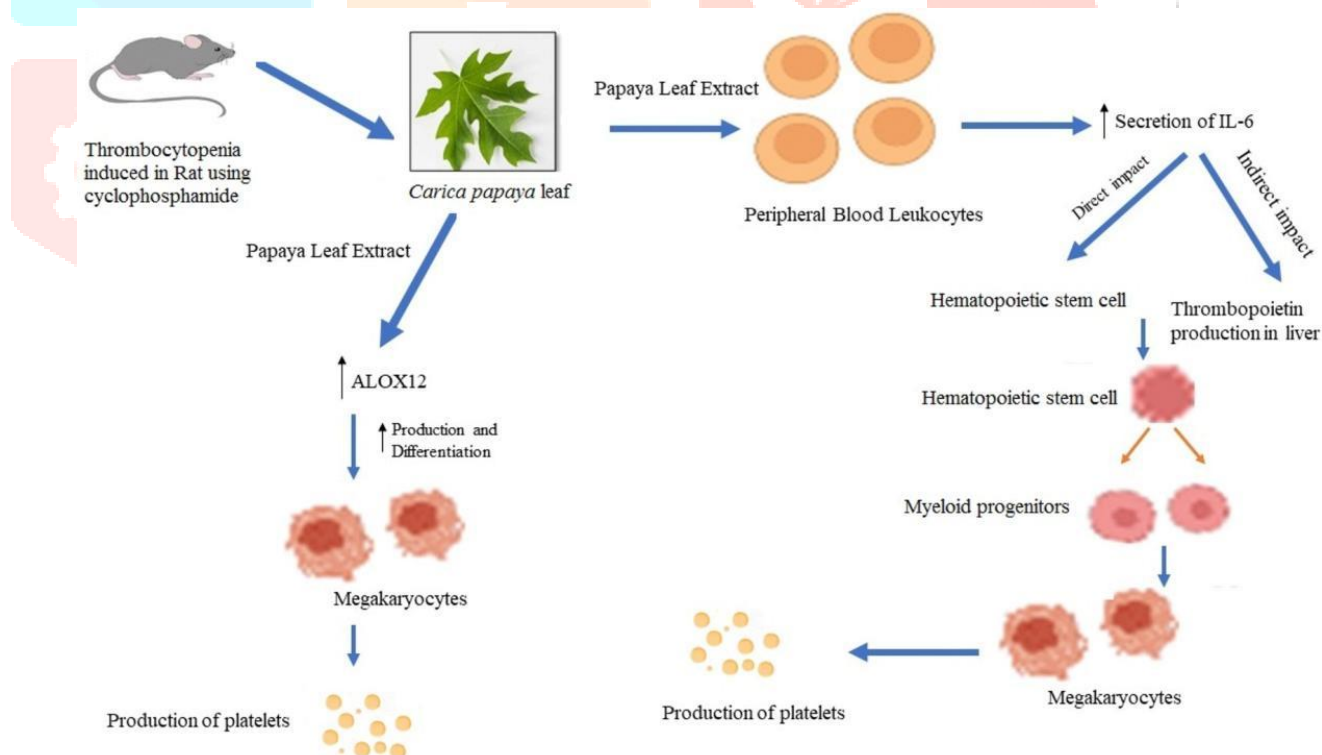


Fig. : Mechanism of carica papaya leaf extract against thrombocytopenia

AIM AND OBJECTIVE

This aim to provide a foundational understanding of how classical herbs can be utilised to enhance platelets count, potentially offering alternative therapeutic option for condition characterised by thrombocytopenia. To investigate the efficacy of selected classical herbs in enhancing platelets count and to identify their active compounds and mechanism of action. Analyse the result statically to determine the significance of any observed effects on platelet count. The main objective of this medication is to enhance the platelet counts during the condition of thrombocytopenia during Dengue and malarial fever. It is the combination of various herbs which is not only for enhancing platelets counts but it also helps in the management of symptoms associated with dengue and malarial fever (*Plasmodium falciparum*) and typhoid. Ayurvedic herbs believed to enhance immune function and platelet production.

MATERIAL AND METHODS

Method of preparation Get fresh healthy mature papaya leaves from a fruit-bearing tree, Wash the leaves thoroughly with running tap water and chop the leaves in to small pieces excluding the main stem (not necessary to remove the small stems in the leaves) after that Weigh 50g of papaya leaves and put it into a mortar and pestle then Add 50ml of boiled cool water and 25g of sugar, Pound the above mixture well for 15 minutes till a uniform pulp is made. Mix this pulp well and keep for about 30 minutes then Squeeze this pulp by hand and get the papaya leaf n extract (do not use a cotton sieve to extract the juice), now you can store this preparation for 24 hours in the lower compartment of the refrigerator. The 20 g powder of dried stems of *Tinospora cordifolia* is placed in thimble holder and about 300 mL of ethanol is filled in the flask. The thimble was clogged with cotton in order to avoid transfer of sample particles to the distillation flask, the drug was extracted with ethanol in Soxhlet apparatus for 3 h. Ethanolic extract is filtered and concentrated on Rota evaporator to give the ethanolic extract. Certified sample of species of wheat *Triticum aestivum*, was acquired from wheat Research Centre. These wheat varieties were grown in plastic trays as per standard procedure described by Wigmore, 1985. Fresh juice of wheat grass was prepared by standard procedure described by Wigmore, 1985. Dried powder of wheatgrass was subjected for extraction with methanol and water using Soxhlet apparatus. Method for extracting aloe vera to increase platelet count: Clean 250 grams of fresh aloe vera leaves with 70% ethanol Remove the rind and cut the gel into 5 cm sections Wash the gel sections with deionized water to remove latex Grind the gel into a liquid Centrifuge the Lliquid at 2500 rpm for 5 minutes to remove fibres. Add the clear supernatant to sterile culture plates and lyophilize at -72°C for 48 hours Refrigerate the concentrated, freeze-dried extract at 4°C . [13]

OTHER CAUSES OF THROMBOCYTOPENIA:

Briefly summarize any findings related to other causes, such as neonatal sepsis or liver cirrhosis.

Evidence regarding papaya leaf extract (*Carica papaya* leaf extract, CPLE) use for thrombocytopenia extends beyond immune causes such as ITP to other conditions like neonatal sepsis, chemotherapy-induced, and liver disease–related thrombocytopenia. However, most evidence remains anecdotal, primarily limited to individual case reports and small preclinical studies rather than controlled clinical trials. Neonatal Sepsis–Associated Thrombocytopenia

A well-documented case report by Pandita et al. (2019) in Clinical Case Reports described a preterm infant with persistent thrombocytopenia secondary to sepsis who failed standard treatments (antibiotics, supportive care, transfusions) but showed a marked platelet count recovery after seven days of oral papaya leaf extract at 20 mg/kg three times daily [1].

- Platelet counts normalized within a week without adverse effects.
- The infant remained healthy at an 18-month follow-up.
- The authors emphasized that this was the first reported neonatal case and that CPLE should be considered experimental and last-resort in refractory cases only.

Liver Cirrhosis and Other Systemic Conditions; Thrombocytopenia in liver disease often stems from splenic sequestration and impaired thrombopoietin synthesis. While direct human reports of CPLE use in cirrhosis are scarce, preclinical studies and reviews suggest its hepatoprotective and thrombopoietic actions could aid platelet recovery indirectly through:

➤ Reduction of oxidative stress and inflammation in hepatocytes [2].

- Upregulation of thrombopoietic cytokines (IL-6, SCF, TPO) implicated in megakaryopoiesis [5].

Thus, future research into the role of CPLE as a hepatoprotective adjunct in cirrhosis-related thrombocytopenia is warranted, but no clinical evidence currently supports its use.

LITERATURE OF RESEARCH:

Moklesur Rahman Sarker et. El. (April 2012)

Therapeutic application of carica papaya leaf and how Papaya leaf help in dengue to increase platelet count. Several Reports have suggested that papaya leaves have the Ability to inhibit destructive effects on platelets by the Dengue virus and increase the expression of ALOX 12 Gene responsible for elevating platelet count. Moreover, Papaya leaves have been found to have a wide Therapeutic range with very few toxic effects. However, Very few investigations were done to explore the Mechanism(s) behind the role of papaya leaves to Improve the platelet count. If the exact mechanisms are Known, papaya leaves extract could be optimized for Better effectiveness as well as therapeutic preparations That could be formulated targeting the same pathway as Papaya leaves. Also, the anti-thrombocytopenic potential Of papaya leaves is not very widely known.[11]

Jaykaran Charan et.al (Oct-Dec 2016)

This study suggest that C. papaya leaf extract has a Definitive role in improving the platelet count in patients Of dengue. Looking at the wider CI, the rise in platelet Count may be very less and may not clinically Significant. There is a statistically significant positive Effect on the rise of platelet count, but whether this rise is Clinically significant or not? That can be explored Further by designing high-quality clinical trials based on Large sample size with all measures to prevent Incorporation of bias. Dengue is an infectious disease Associated with high mortality and morbidity. Being a Viral disease, there is no specific drug available for Treatment. There are some reports that Carica papaya Leaf extract may improve the clinical condition of dengue Patients.[11]

Nandini et.al(2021):-Ethno pharmacological relevance: Carica papaya leaf

Juice/decoction has been in use in folk medicine in Sri Lanka, Malaysia and in few parts of India for enhancing the platelet counts in dengue. In Siddha medicine, a traditional form of Medicine in India, papaya leaf juice has been used for increasing the platelet counts. Papaya, Leaf has been reported to enhance blood volume in ancient Ayurveda books in India. Carica Papaya leaf is well known for its platelet enhancement activity. Although many preclinical And clinical studies have demonstrated the ability of papaya leaf juice for platelet Enhancement, but the underlying mechanisms are still unclear.[2]

Seemal Munir et.al(2022):-

A low platelet count of less than $150 \times 10^3/\mu\text{L}$ in blood is known as thrombocytopenia, a clinical manifestation that causes unbalanced hemostasis and multiple deadly consequences. The underlying causes differ widely, but ultimately they Disrupt the synthesis of platelets and encourage their decomposition, which results in Mortality. Scientific research supports the special therapeutic and medicinal properties of carica papaya leaf against thrombocytopenia. Minerals and secondary metabolites found in Leaves, such as quercetin and

carpaine, encourage the formation of new platelets, prevent the Destruction of existing ones, and preserve the membrane of existing platelets by reducing Viral proteases and promoting the expression of certain genes. [2]

CONCLUSION :

Papaya leaf extract (Carica papaya leaf extract, CPLE) has emerged as a promising natural intervention for managing thrombocytopenia associated with various etiologies, including dengue infection, chemotherapy-induced bone marrow suppression, and idiopathic thrombocytopenic purpura (ITP). Across several case series, animal models, and randomized controlled trials, CPLE has demonstrated the potential to significantly accelerate platelet recovery, improve hematologic parameters, and reduce dependence on transfusions or supportive therapy. The mechanisms attributed to its action include immunomodulation, antioxidant activity, and up regulation of thrombopoietic genes such as ALOX12 and PTAFR, which promote megakaryocyte maturation and platelet formation. Despite these encouraging findings, the current body of evidence remains limited by methodological inconsistencies, small sample sizes, and heterogeneous extract formulations. Most studies emphasize short-term improvement in platelet counts but fall short of assessing key clinical outcomes such as reduced bleeding risk, hospitalization duration, or mortality. Furthermore, the lack of standardized formulations—especially for commercially available or syrup preparations—poses challenges for reproducibility and large-scale clinical translation. For papaya leaf extract to progress from an empirical natural remedy to an evidence-based therapeutic option, future research must focus on well designed, multicentre, randomized, placebo-controlled clinical trials. These should standardize dosing, identify active phytoconstituents, and evaluate both efficacy and long-term safety across different patient populations. Mechanistic studies integrating molecular biology, pharmacokinetics, and toxicology will be vital to clarify its role within hematologic, immune, and hepatic pathways

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