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Therapeutic Potential of *Carica papaya* Linn.: A Comprehensive Review of Its Pharmacological Properties and Health Benefits, with Emphasis on Dengue Fever Healing

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

For thousands of years, people have used various plant products, foods, spices, and herbs to treat and prevent illnesses. Sri Lankans have been using traditional and folk medicine to satisfy their basic health needs from the earliest days. *Carica papaya* Linn. (Caricaceae) is a commercially grown exotic plant in Sri Lanka. The entire plant, including the fruits both ripened and green, leaves, roots, peel, seed, and pulp, was used as medicine in traditional medicinal systems. Plant parts of

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Carica papaya Linn. were frequently used by ancient Sri Lankans to treat diabetes mellitus, hypertension, cancer, dengue fever, skin infections, renal disorders, and infections caused by bacteria, fungi, parasites, and viruses. Dengue fever is the most prevalent and significant arthropod-borne viral disease in humans, and it is extensively spread throughout Sri Lanka. *Carica papaya* Linn. extracts have been used to treat dengue patients to recover from its complications, which include thrombocytopenia, hemolysis, and leukopenia. Studies reveal that the papaya leaf extract can neutralize plasma with the dengue virus, reduce platelet aggregation, and increase the production of the enzyme ALOX12, which promotes platelet production. Moreover, the extract also upregulates the platelet-activating factor receptor (PTAFR) gene and inhibits serine proteases NS2B and NS3 involved in dengue virus replication. In this review, we have discussed extensively the ethnomedicinal and pharmacological properties of *Carica papaya* while highlighting its remarkable potency in healing dengue.

Keywords: Carica papaya; dengue; Thrombocytopenia; dengue hemorrhagic fever; ethnomedicine; phytochemical screening; Sri Lanka.

1. INTRODUCTION

Plants and their products have been used for centuries in complementary medicine to treat various human diseases [1-4]. According to studies, approximately 80% of the world's population relies on plant products for primary medical care [5-9]. These plant-based products possess multiple benefits over synthetic drugs, including being less expensive, more readily available, and having fewer side effects after either brief or prolonged consumption [8-12].

Carica papaya Linn. (Caricaceae) is commonly known as Papaya and Pawpaw, and in Sri Lanka Gas -Labu and Papol. This plant is native to Mexico, USA, and Costa Rica and exotic to Sri Lanka. Papaya is a popular fruit in Sri Lanka, where it is grown as a home garden and a commercial crop for local and export markets. In Sri Lanka, papaya is commercially grown on approximately 8,000 hectares, yielding approximately 32,000 tons annually [13]. Ripe papaya is a popular dessert fruit in Sri Lanka available throughout the year. Fruit salads, jelly, marmalade, refreshing drinks, candies, jam, and crystallized fruit can all be made with it. The unripe fruit is a key ingredient used to make a traditional food called Sinhala pickle.

The papaya tree, or *Carica papaya* Linn., is a tropical plant. Although its ripe fruit is thought to be safe, unripe papaya fruit can harm the digestive tract because it contains papain. Papaya fruits are rich in folate, pantothenic acid, zeaxanthin, lycopene, lutein, magnesium, copper, calcium, and potassium. They are also high in vitamins A, B, C, E, and K. Loaded with fibres, antioxidants, and vitamin C, it lowers blood pressure, lowers the risk of ageing, cancer, macular degeneration, cardiovascular disease, and stress. *Carica papaya* Linn. is a succulent evergreen plant, a tree-like herb that grows 2-10 m tall, is usually unbranched, but can become branched due to injury, and contains white latex in all parts. Spiral-arranged leaves clustered near the trunk's apex and flowers are small, yellow-colored, funnel-shaped, and can be found alone or in clusters in the leaf axils. The fruits exhibit a cylindrical shape with juicy, orange-hued pulp, empty berries, and a slender, yellowish skin upon ripening. Female flowers give rise to fruits that are oblong, spherical, or pear-shaped, while hermaphrodite flowers yield fruits that are elongated, obovoid, or pyriform in structure. The seeds are plentiful, tiny, circular, and enveloped in a gelatinous aril. The tree features petite latex vessels distributed extensively, with a higher concentration observed in fully grown fruit that is yet to commence the maturation process [14]. *Carica papaya* is extensively employed in therapeutic applications globally. Each part of the plant is recognized for its distinct medicinal properties. People often use the plant as a remedy for various conditions such as diabetes mellitus, hypertension, parasitic infections, cancer, and dengue. In addition to these ethnomedicinal uses, scientific studies have confirmed that *Carica papaya* possesses a spectrum of pharmacological properties, including antibacterial, anti-inflammatory, anti-malarial, antioxidant, anti-cancer, anti-dengue activity, and more [13, 14].

Dengue fever is identified as the most prevalent and significant arthropod-borne viral (arboviral) disease among humans. It is spread by mosquitos of the Aedes genus such as *Aedes*

aegypti and *Aedes albopictus*, which have a widespread distribution in Sri Lanka [15]. Dengue transmission follows a seasonal pattern in Sri Lanka, characterized by two peaks coinciding with the monsoon rains in June-July and October-December. The majority of cases are reported during the summer monsoon season, spanning from June to July [16]. Dengue fever gives rise to various hematological manifestations like thrombocytopenia (low blood platelet counts), hemolysis, and leukopenia. Platelet count is also associated with vascular protein leakage and liver damage. Vascular leakage is the primary pathophysiological marker that determines the level of severity of dengue. Thus, thrombocytopenia may be a significant predictor of mortality. *Carica papaya* extracts have been used to treat dengue patients to recover from thrombocytopenia, hemolysis, and leukopenia [16].

This comprehensive investigation looks into the numerous health benefits and therapeutic properties of *Carica papaya*, with an emphasis on how well it could potentially be able to treat dengue fever. The article also explores the traditional uses of papaya in different cultures and looks at the rich composition of bioactive compounds found in different parts of the plant. The plant's incredible ability to lessen dengue symptoms, reduce the disease's severity, and possibly even speed up recovery is highlighted in the paper. The review seeks to determine the precise mechanisms by which *Carica papaya* may aid in dengue healing through the integration of current knowledge.

2. TAXONOMIC HIERARCHY AND OTHER NAMES

Taxonomic Hierarchy show in Table 1.

Table 1. Taxonomic hierarchy of *Carica papaya*

Rank	Scientific Name and Common Name
Kingdom	*Plantae* - Plants
Subkingdom	*Tracheobionta* - Vascular plants
Superdivision	*Spermatophyta* - Seed plants
Division	*Magnoliophyta* - Flowering plants
Class	*Magnoliopsida* - Dicotyledons
Subclass	*Dilleniidae*
Order	*Violales*
Family	*Caricaceae* Dumort. - Papaya family
Genus	*Carica* L. - Papaya plant
Species	*Carica papaya* L. – Papaya P

2.1 Other Names [17]

Arabic: Fafay, Babaya
Bengali: Pappaiya, Papeya
Burmese: Thimbaw
English: Pawpaw Tree, Melon Tree, Papaya
Filipino: Papaya, Lapaya, Kapaya
French: Papailler, Papaye, Papayer
German: Papaya, Melonenbraum
Hindi: Papaya, Papeeta
Indonesian: Gedang, Pepaya.
Malay: Papaya, Betek, Ketalah, Kepaya
Sinhala: Pepol
Spanish: Figuera Del Monte, Fruta Bomba, Papaya, Papaita, Lechosa
Tamil: Pappali, Pappayi
Thai: Ma Kuai Thet, Malakor, Loko
Vietnamese: Du Du

3. GEOGRAPHICAL DISTRIBUTION

Carica papaya thrives across a wide geographical range, from the equatorial tropics to temperate latitudes. Warm and sunny locations, ideally below 1500 meters in elevation, are ideal for growth. Strong winds have a significant negative impact, particularly on soils with limited capacity to compensate for significant transpiration loss. Due to the tree's sensitivity to frost, exposure to cold winds usually results in leaf damage and, as a result, the tree's death. The plant's roots are susceptible to waterlogging, making even brief periods of flooding could be fatal [17,18].

The optimal soil type for papaya cultivation is a well-drained, permeable, and well-aerated fertile loamy soil that is free from root-knot nematodes. Ideally, this soil should be rich in organic matter, promoting a neutral pH range of 6 to 7. Such conditions provide an ideal environment for the growth and development of papaya plants [14].

The plant is documented to be native to the United States of America, Mexico, and Costa Rica. The plant is now distributed almost all over the world [18].

4. BOTANICAL DESCRIPTION AND CULTIVATION

Carica papaya, an evergreen herb with a tree-like appearance, typically reaches 2-10 meters high. While it generally grows as a single unbranched stem, occasional branching may occur as a response to injury. The plant features white latex throughout all its parts. The cylindrical stem measures 10-30 cm in diameter and is characterized by hollowness, prominent leaf scars, and spongy-fibrous tissue. Additionally, *Carica papaya* possesses a comprehensive rooting system [14, 19]. The leaves of *Carica papaya* are spirally arranged and form clusters near the apex of the trunk. The petiole, measuring up to 1 meter in length, is hollow and exhibits a greenish or purplish-green hue. The lamina is orbicular, with a diameter ranging from 25 to 75 cm. It is palmate and deeply divided into seven lobes, presenting a glabrous surface with prominent veins. The lobes themselves are deeply and broadly toothed. The flowers of *Carica papaya* are small, yellow, and funnel-shaped. They can be found either as solitary blooms or in clusters within the leaf axils, categorized into three types [14, 20]. Female flowers, ranging from 3 to 5 cm

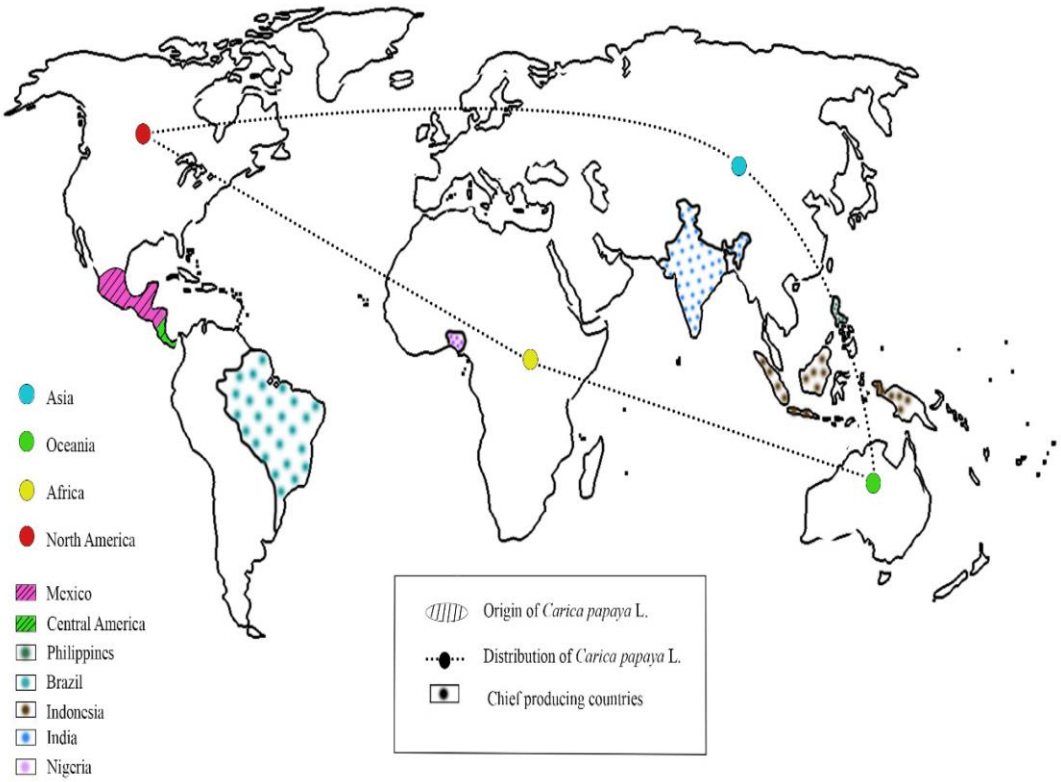


Fig. 1. The origin, distribution, and the chief producing countries of *Carica papaya* Linn. [18]

Fig. 2. A drawing of a papaya plant illustrating the fruit, flowers, leaves, and stem [22]

in length, showcase a substantial functional pistil but lack stamens, featuring an ovate-shaped ovary. Male flowers emerge on extended drooping panicles, each adorned with 10 stamens arranged in two rows. These male flowers lack a gynoecium, except for a pistillode. Hermaphrodite flowers, larger than the males, exhibit a 5-carpellate ovary. The occurrence of these flower types is influenced by the tree's season or age [19, 21]. The fruits of *Carica papaya* are sizable and cylindrical, featuring fleshy orange pulp within a hollow berry. Upon ripening, the slender skin adopts a yellowish tint. The variety in fruit morphology is apparent, as those derived from female flowers exhibit an oblong, spherical, or pear-shaped form, while those originating from hermaphrodite flowers take on a long, obovoid, or pyriform structure. The seeds are plentiful, small, black, and round, enveloped in a gelatinous aril. Across the tree, petite latex vessels are dispersed, particularly abundant in fruits that have attained full size but are still in the process of ripening [14, 19, 20].

Carica papaya typically begins fruiting within 5 months of its growth and has a lifespan of 4-5 years. Typically, male and female flowers are found on separate trees, although some flowers exhibit bisexual characteristics. The pollination process engages a diverse array of insects, encompassing larger bees like Xylocarpa and Trigona, honeybees, long-tongued sphinx moths (Sphingidae), hummingbird moths (Macroglossa), and even the wind. Through open (uncontrolled) pollination, a cultivar has the potential to undergo changes and lose its distinctive traits over several generations [14].

5. NUTRITIONAL VALUE

Papaya is often referred to as the "common man's fruit" due to its affordability and remarkable nutritional value. Phytonutrients can be found in various parts of the papaya plant, including the leaves, unripe, and ripe fruits [23]. Renowned for its richness in thiamine, folate, riboflavin, and niacin, as well as vitamins A, B1,

B2, and C, along with significant fiber content, papaya holds a special place among fruits. It consistently ranks among the top five fruits, alongside kiwi, watermelon, grapefruit, and guava, when evaluated based on nutritional scores [24, 25].

Every component of *Carica papaya* proves valuable in some capacity. It is a potent reservoir of three robust antioxidants: C, A, and E. Additionally, this fruit harbors a digestive enzyme called papanita, renowned for its efficacy in treating sports injuries, trauma, and allergies [27]. Studies reveal that papaya leaves contain numerous active components capable of enhancing overall antioxidant levels in the bloodstream and reducing lipid peroxidation [28]. The papaya leaves and fruit complex yield various proteins and alkaloids with significant applications in both pharmaceutical and industrial settings. One noteworthy proteolytic enzyme, papain, is particularly abundant in the milky latex of green, unripe papaya [29].

This fruit stands out as an exceptional source of beta-carotene, shielding against free radical damage and aiding in preventing diabetic heart disease. *Carica papaya* also significantly lowers elevated cholesterol levels [27]. Moreover, the *Carica papaya* plant synthesizes natural compounds in its leaf, bark, and twig tissues, demonstrating potent anti-tumor and pesticidal properties [28]. With two active components, chymopapain, and papain, *Carica papaya* proves highly advantageous for managing digestive disorders and gastrointestinal disturbances. Importantly, papain retains its efficacy in acidic pH conditions without undergoing denaturation [30].

Carica papaya holds therapeutic potential in ulcer treatment when its unripe fruit is employed. The use of green papaya fruits extends to addressing conditions like amenorrhea, constipation, dyspepsia, expel worms, general debility, high blood pressure, and stimulating reproductive organs [28]. *Carica papaya* constituents exhibit an alkaline combination, akin to borax or potassium carbonate, showcasing promising outcomes in treating various skin conditions such as corns, cutaneous tubercles, eczema, skin hardness, and warts. Furthermore, these constituents, when injected into indolent glandular tumors, facilitate their absorption [29]. The nutritional content of papaya plays a crucial role in inhibiting cholesterol oxidation. Papaya boasts a significant presence of iron and calcium. Extracts from unripe papaya are found to encompass terpenoids, alkaloids, flavonoids, carbohydrates, saponins, and steroids [29].

Table 2. Nutritional content of *Carica papaya*, per 100g [26]

Energy	163KJ
Sodium	3mg
Potassium	257mg
Phosphorus	5mg
Magnesium	10mg
Iron	0.10mg
Calcium	24mg
Vitamin C	61.8mg
Folate	38mg
Vitamin B6	0.1mg
Niacin	0.338mg
Riboflavin	0.05mg
Thiamin	0.04mg
Vitamin A	328IU
Protein	0.61g
Fat	0.14g
Dietary fiber	1.8g
Sugars	5.9g
Carbohydrates	9.81g

Papaya actively contributes to bolstering the immune system, enhancing resistance against coughs and colds, courtesy of its rich vitamin A and C content. The diverse therapeutic properties of papaya make it a valuable addition to promoting overall health and well-being [27].

6. ETHNOMEDICINAL USES OF *Carica papaya* Linn

Carica papaya is prominent in traditional and ethnomedicinal practices, extensively utilized for its diverse therapeutic applications across various nations [31]. Decoctions derived from different parts of the plant exhibit unique curative potency, forming a key component in traditional medicinal practices [32, 33].

Ethnomedicinal surveys carried out in Nigeria document the use of *Carica papaya* in addressing conditions such as diabetes mellitus, intestinal helminthiasis, and hypertension [32]. Additional studies emphasize its application in treating fungal and helminthic infections [34]. The Australian Gold Coast reveals that *Carica papaya* leaf juice is utilized in cancer treatment [35].

In India, *Carica papaya* leaf extracts are employed to alleviate asthma, colic disorders,

and fever. Additionally, *Carica papaya* is utilized for its contraceptive potential in various Asian countries, including India, Pakistan, and Sri Lanka, while countries in Southeast Asia such as Laos, Cambodia, and Vietnam use it for diverse medicinal purposes. The milky latex juice is employed as a remedy for eczema and psoriasis [32]. Moreover, in certain regions, seed extracts are utilized as anthelmintic medicine, thirst quenchers, and pain relief agents. In Cameroon, *Carica papaya* is integrated as an active pharmacological ingredient in antimalarial mixtures [36].

In China, various parts of *Carica papaya*, including leaves, fruits, and seeds, are employed in the treatment of stomach pains, bacterial infections, and inflammations. Lactating mothers in this region consume soup made from nearly ripe fruits with fish to enhance the flow of breast milk [37]. This extensive array of traditional and ethnomedicinal uses underscores the cultural and medicinal significance of *Carica papaya* across diverse regions.

7. MEDICINAL VALUE OF VARIOUS PARTS OF *Carica papaya* Linn

7.1 Leaves

The papaya leaf has demonstrated its efficacy as a valuable nutritive agent, characterized by diverse concentrations of essential nutritional components. These include significant amounts of ascorbic acid (38.6%), carbohydrates (8.3%), iron (0.0064%), minerals such as magnesium (0.035% per 100 g), protein (5.6%), and phosphoric acid (0.225%) within the leaf portion [38].

In the context of Dengue Fever, the juice extracted from *Carica papaya* leaves plays a crucial role in elevating the count of white blood cells (WBCs) and platelets, while also aiding in the normalization of clotting and liver repair [27]. Administering the extract of papaya juice to patients with dengue fever has shown remarkable results, with the counts of platelets and WBCs returning to normal levels within 24 hours [16].

The extracts of *Carica papaya* leaves have exhibited the ability to inhibit the growth of cancer cells [27]. It enhances the production of crucial signaling molecules known as Th1-type cytokines, which play a pivotal role in regulating the immune system [30].

Papaya leaves are commonly utilized to make tea for the treatment of malaria [39]. Some preparations of the plant have been observed to possess antimalarial and anti-plasmodial activity [39], although the underlying mechanism remains unclear and has not been scientifically proven.

Certain compounds are isolated from the leaves including, karpain, a substance known for its ability to eliminate microorganisms that can disrupt digestive function [27].

Other benefits of Papaya Leaves:

- A remedy for acne
- Helps to Increase the appetite
- Easing the menstrual pain
- Acting as a meat tenderizer
- Providing relief from nausea

7.2 Fruits

Papaya fruit stands out as a rich source of essential nutrients, including vitamins, minerals, and dietary fiber [27]. Within papaya, the presence of Danielone, a phytoalexin, exhibits potent antifungal activity [27]. The fruit offers versatile uses, serving as a:

- Laxative
- Cure for indigestion
- Preventive measures against heart attack and stroke

Consuming fresh ripe papaya every morning is recommended to prevent indigestion, constipation, and to enhance appetite [27]. Furthermore, the fruit of *Carica papaya* proves beneficial in the treatment of mouth ulcers, gum disease, and toothaches [28].

7.3 Seeds

Remarkably, papaya seeds exhibit higher medicinal value compared to other parts of the tree.They are noted for their antibacterial properties and prove highly effective against staphylococcus infections. Additionally, the seeds contribute to kidney protection by guarding against toxins and preventing kidney failure. Their beneficial effects extend to aiding in the recovery from piles and typhoid. Dried papaya seeds offer enhanced nutritional value. Grinding these seeds and incorporating them into meals can introduce enzymes to the diet, thereby improving digestive problems [27].

7.4 Peel

Papaya peel finds versatile applications, not only in cosmetics but also in various home remedies [29]. It benefits by functioning as a sunscreen and soothing agent, aiding in the fight against dandruff, and serving as a muscle relaxant [27].

7.5 Roots

Papaya roots offer various therapeutic uses in different parts of Asia. The juice extracted from papaya roots is employed to alleviate urinary troubles. Additionally, dried and cured papaya leaves, shaped like cigars, are smoked by individuals dealing with asthma. Fresh papaya leaves, when infused, are utilized to expel or eliminate intestinal worms. Furthermore, fresh young papayas are employed as a remedy for colic, a specific stomach disorder, or cramps.

In the treatment of dyspepsia, a decoction is prepared by boiling the outer part of the papaya tree's roots, highlighting another application for this versatile plant in promoting digestive health [27, 29].

7.6 Latex

The milky sap extracted from unripe papaya contains two significant enzymes, chymopapain and papain. Chymopapain, in particular, has received approval for intradiscal injection in individuals with confirmed herniated lumbar intervertebral discs who have not shown improvement with conventional treatment. The latex of the unripe papaya also contains vitamins and traces of an alkaloid called Carpaine. Additionally, the seeds of the fruit contain benzyl senevol, carbohydrate, carpasemine, and glucoside. Papain, one of the enzymes found in latex, serves various purposes, including acting as a meat tenderizer, degumming natural silk, production of chewing gums, and for the treatment of commercial beer. Cosmetically, it is used in shampoos and certain face-lifting procedures. Interestingly, Carpaine, when consumed by humans, has a slowing effect on the heart, consequently reducing blood pressure [27].

8. PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITY OF *Carica papaya* Linn

8.1 Phytochemical Constituents of *Carica papaya* Linn

Carica papaya is found to be rich in various phytochemicals and other compounds. The following Table 3 contains the list of phytochemicals in different parts of the papaya plant.

8.2 Pharmacological Properties of *Carica papaya* Linn

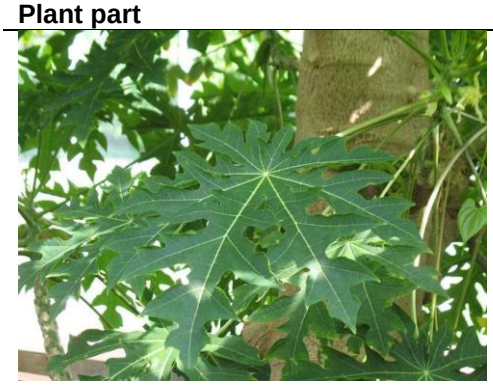
Carica papaya demonstrates remarkable efficacy in treating various ailments, attributed to the abundance of diverse phytoconstituents found in nearly all parts of the plant. Literature review that the plant shows the following pharmacological activities [56],

- Antibacterial activity
- Anticancer activity
- Anti-dengue activity
- Antidiarrheal responses
- Anti-inflammatory and immunomodulatory responses
- Anti-malarial activity
- Antioxidant activity
- Insecticidal and repellent responses
- Wound-healing activity

This review aims to investigate the traditional claim that *Carica papaya* leaf juice enhances platelet count with dengue fever and dengue haemorrhagic fever while highlighting the plant's remarkable ability to reduce dengue symptoms, and the severity of the disease, and potentially aid in the recovery process.

Table 3. Isolated compounds from the papaya plant

Plant part	Isolated compound/ phytochemicals
Leaves	1. Alkaloids 2. Anthraquinone 3. Tannins 4. Saponins 5. Steroids 6. Resins

Plant part	Isolated compound/ phytochemicals
 (40)	7. Flavonoids • Kaempferol • Kaempferol 3-(2G- Rhamnosylrutinoside) • Kaempferol 3-Rutinoside • Myricetin 3-Rhamnoside • Quercetin • Quercetin 3-Rutinoside • Quercetin3-(2G-Rham Nosylrutinoside) 8. Phenolic Compounds • Kaempferol • Protocatechuic Acid • Quercetin • 5,7-Dimethoxy Coumarin • Caffeic Acid • P-Coumaric Acid • Chlorogenic Acid 9. Minerals • Calcium • Ferrous • Magnesium • Potassium • Zinc • Manganese [41-44].
Fruit  (40)	1. Enzymes • Papain • Chymopapain 2. Other phytoconstituents • Carotenoids • Carotenoids – lycopene • Cryptoxanthin • Flavonoids-kaempferol • Myricetin • Quercetin • Violaxanthin • Zeaxanthin • β carotene [41, 45] The identification of phytochemicals in the unripe fruit aqueous extract was conducted using the GC–MS technique, revealing the presence of fifteen components. Among the major phytochemical compounds identified were, • Hexadecenoic acid • Z-11 • Methyl ester • Octadecanoic acid. Minor phytochemical compounds in the unripe fruit aqueous extract were detected within the concentration range of 0.78–5.38% [46].
Seeds	• Papaya oil, derived from the seeds, is known to contain various compounds, including flavonoids, kaempferol, and myricetin [41]. • Benzyl glucosinolate and benzyl isothiocyanate have been identified in the seeds, pulp, and pericarp of the papaya [47, 48].

Plant part	Isolated compound/ phytochemicals
 (40)	Other phytochemicals • Oleic acid [49] • 1,2,3,4-tetrahydropyridin-3-yl-octanoate – An antifertility compound [50]. • Fatty acid, amide, nitriles, sterol, fatty aldehydes, and organic acids [51].
Roots  [40]	• Benzyl isothiocyanate • Glucosinolatescarposide [41].
Latex  [40]	Enzymes • Caricain • Chitinase • Chymopapain • Cysteine endopeptidases • Glutaminyl cyclase • Papain • Protease omega [52, 53]
Flowers  [40]	• 3-O-(6-O-tetradecanoyl-β-D- glucopyranosyl) -β-sitosterol • Benzyl β-D-glucopyranoside • Caffeic acid • Kaempferol 3- O -β -D -glucopyranoside • Kaempferol 3-O -α -L -arabinopyranoside • Kaempferol 3-O -α -L -rhamnopyranoside • Myricetin • Palmitic acid • Quercetin 3-O -β -D -galactopyranoside • Stigmast-4-ene-3-one • Trans-ferulic acid • Uracil • β-sitosterol3-O-β-D-glucopyranoside [54, 55]

9. *Carica papaya* Linn. AND DENGUE

9.1 Dengue Fever

Dengue stands out as a prominent viral disease, emerging as a significant global public health threat in recent decades. It is commonly found in tropical and subtropical regions of the world, primarily within urban and suburban areas [57]. The virus that causes dengue fever is a small structure that can only replicate within a host cell. Dengue viruses are members of the Flavivirus genus and the Flaviviridae family. Dengue infections occur by four closely related viruses (serotypes): (Dengue Virus-1, Dengue Virus-2, Dengue Virus-3, Dengue Virus-4), and are transmitted to people through the bite of an infected mosquito of the Aedes species (*Aedes aegypti* or *Aedes albopictus*). These four viruses are classified as serotypes because they interact differently with antibodies found in human blood. Every year, a maximum of 400 million individuals worldwide get infected with the dengue virus. and approximately 500,000 cases of dengue hemorrhagic fever require hospitalization [58], while 40,000 die from severe dengue. An individual can become infected with dengue on multiple occasions in their lifetime [59, 60]. An infected individual can manifest symptoms in a healthy host within 5 to 7 days. The different serotypes allow for multiple infections in an individual. While each infection provides life-long immunity for the specific serotype, subsequent infections with a different serotype can facilitate the risk of developing the potentially fatal dengue hemorrhagic fever possibly due to antibody-dependent enhancement [61]. It is currently unknown what specific mechanism the dengue virus uses to cause low platelet counts. However, thrombocytopenia is thought to be caused by various processes that this virus mediates in the host system, as summarised.

A patient experiencing dengue fever typically presents with the classic dengue triad- fever, headache, and rash. Alongside these, various non-specific signs and symptoms associated with dengue fever (eye pain, nausea, severe joint and muscle pain, and vomiting), and the conditions can progress into dengue hemorrhagic fever, marked by abdominal pain, bleeding, and potential circulatory collapse. The clinical trajectory of dengue unfolds in three distinct phases: the febrile phase, the critical phase, and the recovery phase. The critical phase is characterized by detectable thrombocytopenia, where the platelet count drops below 100,000/mm^3 from the baseline, and haemoconcentration, identified with a 20% or more elevation in the hematocrit. These clinical manifestations occur before the resolution of fever and the onset of a potential shock [63].

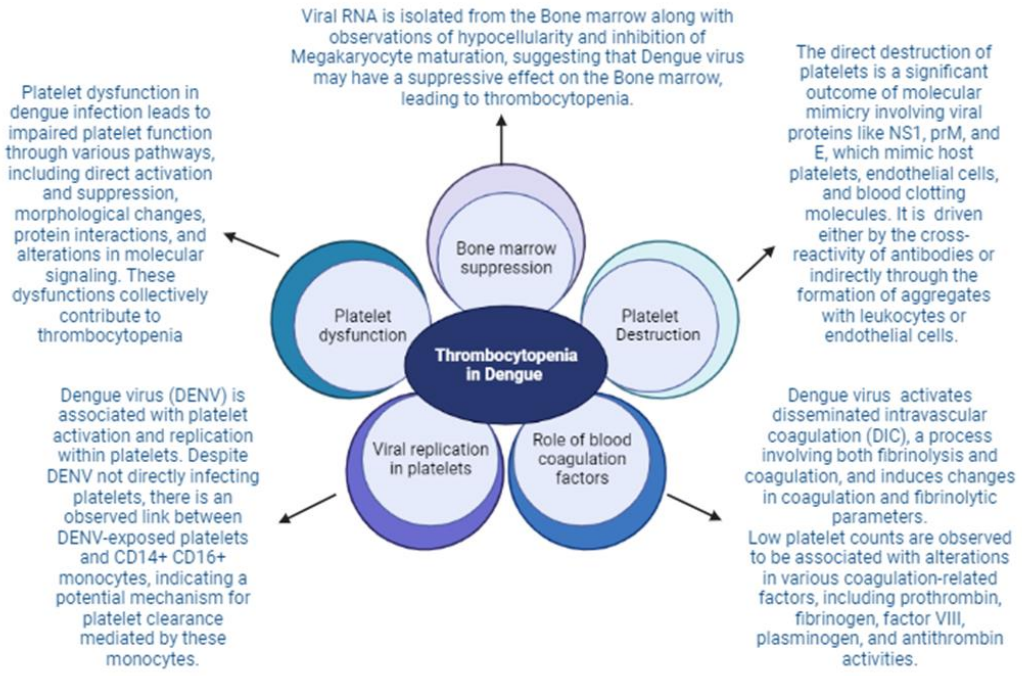


Fig. 3. The development of thrombocytopenia in dengue [62]

Although the disease itself rarely results in death, dengue fever can cause severe pain and weakness and has the potential to spread throughout a population if a new serotype is introduced. Generally, it's self-healing, and only supportive care is needed. Symptomatic fever in patients may be addressed with acetaminophen, while caution is advised against the use of aspirin, brufen, (non-steroidal anti-inflammatory drugs) NSAIDs, antibiotics, and corticosteroids as they not only proven ineffective but may also lead to gastritis and/or bleeding. For those with confirmed or suspected dengue fever, it is crucial to monitor their platelet count a hematocrit daily from the 3rd day of illness till 1-2 days after the fever subsides. Even though there are promising tetravalent vaccines in clinical trials, unfortunately, they are not readily available throughout the world. Therefore, the primary method to prevent getting the disease is to avoid vector bites [57, 58, 64, 65].

9.2 Local Prevalence of Dengue Fever

Dengue fever and most severe Dengue Hemorrhagic fever (DHF) became nationwide reported illnesses in Sri Lanka in 1996, and information before that was based on outbreak reporting. During the early 2000s, the magnitude of Dengue fever and Dengue Hemorrhagic fever (DHF) epidemics in Sri Lanka increased, with two of the largest epidemics occurring in 2002 and 2004, with 8931 cases (incidence of 47 per 100,000 population) and 15463 cases (incidence of 77 per 100,000 population) reported to the national Epidemiological Unit, respectively. Currently, nearly all districts in the country have reported cases. The western province's Colombo, Gampaha, and Kalutara districts had the highest case rate, particularly during the epidemic year [66, 67].

9.3 Mechanism of Action Behind the Anti-Dengue Activity of *Carica papaya* Linn

Safety studies, conducted following Organisation for Economic Co-operation and Development (OECD) guidelines for acute, subacute, and chronic toxicity, have demonstrated that the extracts from *Carica papaya* are safe for human consumption [68].

Specific genes play a role in influencing both the production and aggregation of platelets. Notably, the Arachidonic Acid 12-lipoxygenase (ALOX 12), also recognized as the Platelet-type Lipoxygenase, and the Platelet-Activating Factor Receptor (PTAFR) are implicated in these processes. Increased activity in these genes is essential for both the production and activation of platelets. The ALOX 12 gene is prominently expressed in megakaryocytes (hematological progenitor cells of platelets) and is responsible for the production of 12-Hydroxyeicosatetraenoic acid (12-HETE) in platelets. On the other hand, the PTAFR gene, expressed in megakaryocytes, serves a dual role as a precursor for platelet production and in the well-established function of platelet aggregation [69, 70].

A study was conducted in Malaysia, in 2013 aiming to assess the potential of *Carica papaya* leaf juice in elevating platelet levels among patients diagnosed with dengue fever. An open-label randomized controlled trial was conducted, involving 228 participants diagnosed with dengue fever and dengue hemorrhagic fever. The participants were divided into two groups, with approximately half receiving *Carica papaya* leaf juice for three consecutive days, while the control group underwent standard management. Full blood count monitoring occurred every 8 hours over 48 hours. Gene expression studies focused on ALOX 12 and PTAFR genes. Using repeated measure ANCOVA, the study found a significant increase in mean platelet count in the intervention group ($P < 0.001$), particularly 40 hours after the first dose of *Carica papaya* leaf juice, compared to the control group. Further analysis revealed a significantly higher mean platelet count in the intervention group compared to the control group after 40 and 48 hours of admission ($P < 0.01$). The expression of ALOX 12 and PTAFR genes was notably higher in individuals receiving *Carica papaya* leaf juice. This study concludes that *Carica papaya* leaf juice significantly increases platelet counts in patients with dengue fever and dengue hemorrhagic fever. The observed rise in platelet levels, coupled with the increased expression of ALOX 12 and PTAFR genes, suggests a potential therapeutic benefit of *Carica papaya* leaf juice in managing dengue-related thrombocytopenia [71].

A study was conducted on a 45-year-old patient with dengue to observe the potency of *Carica papaya* leaf juice in curing the disease. The patient was administered with 25ml of leaf juice twice a day, for five days. A blood sample was analysed and compared both before and after administering the leaf juice. The study reveals that the Platelet count (PLT), WBC count, and neutrophil count increased (PLT from $55\times10^3/\mu L$

to 168×10^3/µL, WBC from 3.7×10^3/µL to 7.7×10^3/µL, and neutrophils from 46.0% to 78.3%) after the administration of *Carica papaya* leaf juice. Concerning the study results, the study concludes that *Carica papaya* leaf juice exhibits significant potency in curing dengue [16].

10. CONCLUSION

This literature concluded that *Carica papaya* Linn. leaf extract reduces mortality by increasing platelet count and neutrophil count in treating dengue patients. Due to the abundance of diverse phytoconstituents found in almost every part of the plant, *Carica papaya* is remarkably effective in treating a wide range of ailments. According to review, the plant possesses the pharmacological properties such as protection against bacteria, cancer, dengue, anti-inflammatory and immunomodulatory reactions, anti-malarial activity, antioxidant activity, insecticidal and repulsive reactions, anti-diarrheal responses, and wound healing. Further research is needed to isolate useful phytochemicals and evaluate other medicinal and pharmacological properties of this valuable species.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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