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A REVIEW ON CARICA PAPAYA: IS REALLY RECOMMENED IN THE TREATMENT OF DENGUE FEVER!

More Nikita Nandu*[1], Suryawanshi R. Yashodha[1] and Pawar Abhishek Vijay[2]

[1]B.Pharm Student, Swami Vivekananda Sanstha's, Institute of Pharmacy (B. Pharm), Mungase, Tal. Malegaon, Dist. Nashik-423201.

[2]Assistant Professor (M.Pharm, Dept. Pharmaceutics), Swami Vivekananda Sanstha's, Institute of Pharmacy (B. Pharm), Mungase, Tal. Malegaon, Dist. Nashik-423201.

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***Corresponding Author**
More Nikita Nandu
B. Pharm Student, Swami Vivekananda Sanstha's, Institute of Pharmacy (B. Pharm), Mungase, Tal. Malegaon, Dist. Nashik-423201.

ABSTRACT

The primary goals of this review are to describe the dangerous dengue fever virus and the main problems associated with selling supplements made from Carica papaya leaves. This review primarily focuses on discussing the fatal dengue virus and the key issues surrounding the sale of supplements made from Carica papaya leaves. Supplies and Procedures: Data was gathered from a number of published studies, reviews, websites, and other subject-related online databases. Dengue is a fatal virus that has afflicted 40% of people worldwide. It can spread through mosquitoes. (Aedes aegypti) carrying one of the four serotypes of dengue virus. Because of this intricate viral serotype, there, There isn't a specific therapeutic intervention for dengue. Thus, in spite of dengue's severe and fatal effects, There are no vaccinations on the market. Findings and Discussion: Consequently, the usage of herbal supplements has been extended ver time. Findings and Discussion: Consequently, there has been a gradual rise in the usage of herbal supplements as supplemental medications. Because C. papaya leaves have the ability to increase platelets, their supplements have demonstrated promising potential. However, the production methods applied in a number of commercially available C. papaya formulations for leaves have the ability to break down the active phytochemicals, which will impede the positive effects of the additions. In conclusion, in light of the current situation, it is imperative to refine the traditional herbal remedies. Consequently, the negative aspects of

marketing Supplements containing C. papaya leaves need to be updated for improved patient care.

KEYWORDS: Carica papaya, dengue, formulations, fever.

INTRODUCTION

Worldwide, papaya is widely grown in all tropical and subtropical regions. Among the most lucrative tropical organic products, papaya is thought to stand out because it contains beta-carotene, protein, carbohydrates, and minerals and vitamins. The papaya is a little plant with very little growth. the majority, with a single stem growing to a height of five to ten meters, leaves are broad, 0.5 to 0.7 meters wide, and exhibit pronounced palmate lobedness. Seven forecasts. Common papaya things are green and have smooth skin, however youthfully becoming yellow. The traditional papaya in the Philippines is shaped like a pear upon maturity, roughly 0.1–0.4 m long.[1] Dengue is a serious viral disease spread by arthropods that primarily affects tropical regions and can result in both morbidity and mortality and human mortality. The primary flavivirus vector that transmits dengue to people.[2] According to the World Health Organization survey, Organization (WHO), 40% of people have dengue of the entire world's population. But dengue pandemic has spread to numerous more nations and much increased in the already impacted regions.[3]

The case study

A 45-year-old man who works as a truck driver in a cement mill was brought to the emergency room with a 104°F severe fever. Breathing issues, severe vomiting, red skin, shivering, severe body pain, and elevated blood pressure were among the symptoms. He said he had been operating a vehicle and delivering cement to different parts of Pakistan's KPK province. He would often stop for meals while traveling and it was during one of these stops that he was bitten by a mosquito that had the dengue virus. After a full day, he began to experience intense physical discomfort, fever, and teary eyes. Over the course of the next few hours, these symptoms got worse from time to time and were followed by vomiting. Three to four patients in the vicinity of the indicated location (Figure 1) passed away from dengue fever during the same days. The patient was then admitted to the Abottabad Medical Complex emergency room. He was diagnosed with dengue fever based on the results of a screening blood test.[4]

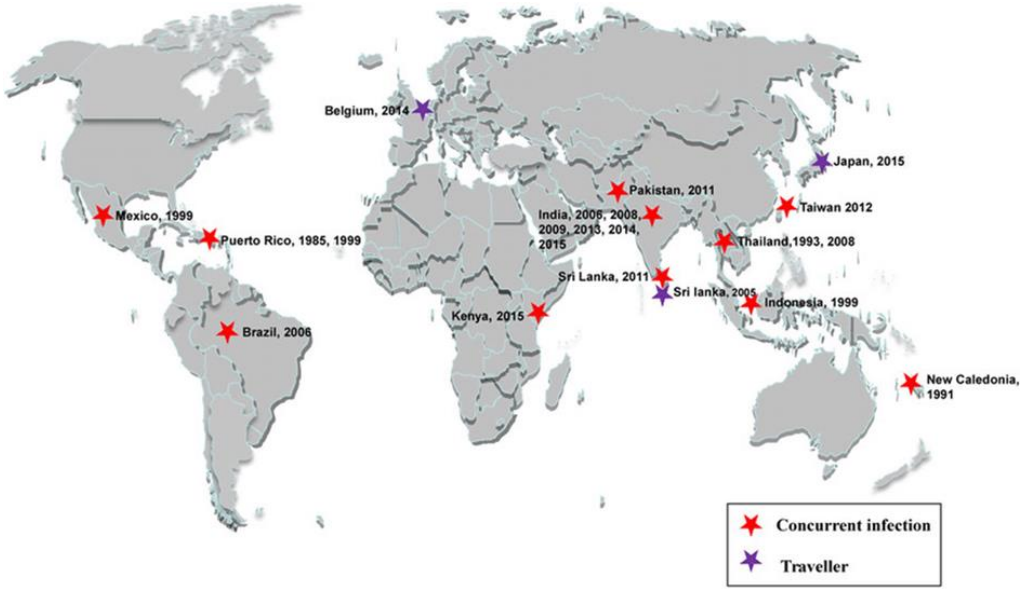


Fig no. 1: Aimed areas of dengue.

The patient's platelet levels abruptly declined, according to the serological investigations. Despite receiving various broad spectrum antibiotics and antimalarial medications, the patient's condition continued to worsen with no signs of improvement. Despite being fed various foods, he regrettably continued to vomit. Our team was investigating C. papaya's biological activity at the same time.[5]

The plant's leaves were gathered and given a thorough water wash in preparation for the patient's treatment. In a fruit juicer, the leaves were ground with water. Since the extract from C. papaya leaves had a very bitter flavor, some sucrose was added to make administration easier. For five days in a row, 25 milliliters of leaf extract were administered orally, twice a day. Every 24 hours, the patient's blood was tested for total platelets before the extract was administered. Five days after the patient's blood was extracted, the platelet counts were checked once more. The patient then begins to improve.[6]

Fig no. 2: Papaya leaves.

Testings

A blood test was performed on the patient prior to the administration of leaf extracts. There was no dedicated lab to detect Dengue virus in patient blood in the patient target area. As a result, it was noted from the test results that PLT, WBC, and NEUT had dropped below normal. The patient experienced fever and exhaustion as soon as the infection, and these symptoms got worse over night. Physicians recommended hospitalization based on patient symptoms and blood reports because the majority of Dengue fever patients died in October 2010. According to the initial blood report, the PLT count was 176 x 103/µL, WBC was 8.1 x 103/µL, and NEUT was 84.0%, in that order. PLT count was 122×103/µL, WBC was 6.6×103/µL, and NEUT was 81.5% in the second report. The PLT counts, WBC, and NEUT were 110×103/µL, 4.4×103/µL, and 71.8%, respectively, according to the third day report. WBC, NEUT, and PLT all dropped quickly. The patient's family was informed by the doctors that the patient might start bleeding and possibly even pass away if the PLT count dropped below 20×103/µL. Doctors at various hospitals advise PLT injections that are separate from donor blood. However, in this instance, the PLT count dropped to 71×103/µL and 55×103/µL on the fourth and fifth days, respectively, while the WBC and NEUT reached 4.0×103/µL, 3.7×103/µL, and 60.0%, 46.0%, respectively. Numerous oral and intravenous antibiotics and antimalarial medications were administered, but with no success.[7]

Table no. 01.

Parameters	1st day	2nd day	3rd day	4th day	5th day
WBC	8.10×10^3/µL	6.60×10^3/µL	4.4×10^3/µL	4.00×10^3/µL	3.70×10^3/µL
RBC	5.28×10^6/µL	4.96×10^6/µL	4.94×10^6/µL	5.23×10^6/µL	5.00×10^6/µL
HGB	14.4 s/dL	13.5 s/dL	14.3s/dL	16.2s/dL	15.2s/dL
HCT	45.6%	43.0%	42.9%	47%	42%
MCV	86.4 fL	86.7 Fl	87.0 fL	90 fL	90 fL
MCH	27.3 Ps	27.2 Ps	28.9 Ps	31.1 Ps	27.1 Ps
MCHC	31.6 s/dL	31.4 s/dL	33.3 s/dL	34.1 s/dL	32.1 s/dL

Sample report

The patient received the water-based extract of C. papaya leaves twice a day. The doctors advised fruits and fruit juices because the patient began throwing up while eating. The patient received 25 milliliters of extract both in the morning and at night. The blood samples were examined for several parameters twice in a row. PLT count, WBC, and NEUT increased to 73×103/µL, 3.8×103/µL, and 56.0% in the first blood report, respectively. After taking extracts at the same dose, the blood report the following day showed that the PLT count had increased to 120×103/µL, while the WBC and NEUT had decreased to 4.4×103/µL and

64.2%, respectively. PLT count (137×103/µL), WBC (5.3×103/µL), and NEUT (71.1%) were found to have increased on the third day. The PLT, WBC, and NEUT reach their normal levels in the fourth blood report (PLT: 159×103/µL, WBC: 5.9×103/µL, and NEUT: 73.0%) and the fifth report (PLT: 168×103/µL, WBC: 7.7×103/µL, and NEUT: 78.3%).[8]

Fig no.03: Methods localy use to prepare papaya leaf extract.

Table no. 02.

Parameters	1st day	2nd day	3rd day	4th day	5th day
WBC	3.80×10^3/µL	4.40×10^3/µL	5.30×10^3/µL	5.90×10^3/µL	7.70×10^3/µL
RBC	4.71×10^6/µL	5.33×10^6/µL	4.99×10^6/µL	5.21×10^6/µL	5.26×10^6/µL
HGB	15.2 s/dL	16.8 s/dL	14.5 s/dL	16.0 s/dL	15.2 s/dL
HCT	42.1%	48.2%	42.9%	46%	46.6%
MCV	89.0 fL	90.0 fL	86.0 fL	84.6 fL	86.6 fL
MCH	32.6 Ps	31.5 Ps	28.9 Ps	29.1 Ps	27.2 Ps
MCHC	36.5 s/dL	34.8 s/dL	34.3 s/dL	34.1 s/dL	35.1 s/dL

DISCUSSION

Investigating the potential of C. papaya leaf extracts against dengue fever is the primary goal of the current study. The secondary metabolites derived from plants are a vast reservoir of substances with a diverse array of biological activities. Several reports have indicated that higher plant extracts have a reasonably good potential for inhibiting viruses (Van Den Berghe, 1978). Aedes aegypti L, the dengue fever vector, has been shown to be susceptible to several plant extracts, including Spilanthes calva, Sterculia guttata, Balanites aegyptiaca, Vitex negundo, Solanum xanthocarpum, Artemisia annua, Fagonia indica, Nerium indicum, and Trigonella foenum, when diluted in various solvents.[9,10] Chymopapain and papain, two significant biologically active substances found in C. papaya, are commonly used to treat digestive disorders.[11] It demonstrated that pepsin degradation and acidic pH conditions can be enhanced by papain, caricain, chymopapain, and glycine endopeptidase derived from papayas. Additional active ingredients in C. papaya include the hydrolase lipase, or CPL, which is firmly bound to the water-insoluble portion of crude papain and is regarded as a biocatalyst that has been "naturally immobilized".[12]

In traditional medicine, papaya latex is used to treat external burns and scalds as well as dyspepsia. Fruits and seeds have strong antihelminthic and anti-amoebic properties.[13] The dried and ground leaves are sold to make tea; the leaf infusion is also used to treat genito-urinary system disorders in horses and is given as a purgative. To induce abortion, unripe and semi-ripe papaya fruits are consumed or applied topically to the uterus. While eating ripe papaya fruits does not pose any risk, consuming unripe or semi-ripe fruits may be hazardous to health during pregnancy.[14]

According to reports, Quercus lusitanica plant extracts exhibit the highest level of activity against Dengue virus DENV-2 Replication.[15] Additionally, it has been reported that plant-derived methyle gallate interacts with the proteins of the herpes simplex virus, changing the

virion's adsorption and penetration.[16] It has been noted that Gastrodia elata B1 affects Dengue virus serotype 2's cycle of multiplication.[17] Aedes aegypti's noval trypsin Kazal-type inhibitor has thrombin coagulant inhibitory activity, and two compounds, 1-beta-D-ribofuranosyl-3-ethynyl-[1,2,4]triazole (ETAR) and 1-beta-Dribofuranosyl-4-ethynyl[1,3]imidazole (IM18), have been shown to significantly reduce dengue virus serotype 2 (DENV-2) replication in cultured Vero cells.[18]

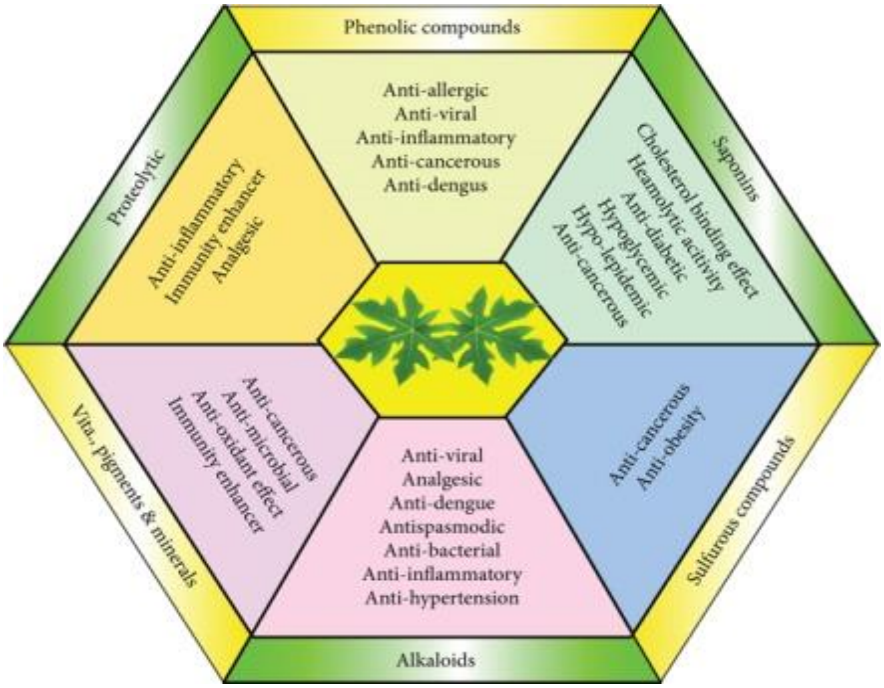
General

The C. papaya plant is used for its latex, ripe and unripe fruits, seeds, juice from the seeds, root, leaves, flower, and stem bark. It is also used as an anthelmentic, antimalarial, antifungal, anti-amoebic, hepatoprotective, immunomodulatory, and anti-histaminergic agent.[19] This case study demonstrates how C. papaya leaf extracts can prevent dengue fever.

In Pakistan, dengue fever outbreaks occur from late summer to early winter. The majority of infected patients are between the ages of 30 and 45. Every year, the dengue fever outbreak recurs and claims many lives. The increase in PLT count from 55×103/µL to 168×103/µL in this instance suggests that the C. papaya leaves extract is active. This research is only preliminary, and additional efforts are required to isolate the active compounds from this valuable species, which could aid in the management of infectious diseases of this kind.

Chemical Compositions

- Proteolytic
- Vitamins, pigments and minerals
- Alkaloids
- Sulphurous compounds
- Phenolic compounds
- Saponins



Compositions

Globally data

Since ancient times, people have used plants and plant-based products to prevent a variety of human diseases. Globally, about 80% of people rely solely on plants for their primary healthcare needs.[20] It has been estimated that 45,000 plant species in India have therapeutic qualities.[21] Natural products or compounds that have been extracted from plants have demonstrated significant advantages over synthetic medications, including being easily accessible, affordable, and having hardly any side effects.[22] The use of medicinal plants for the treatment of a wide range of diseases has been documented in numerous studies. Carica papaya Linn., a member of the Caricaseae family, is native to South America and Central America. It is widely grown in India and is well-known for its medicinal benefits worldwide.[23]

To identify and describe the bioactive components found in papaya leaves, numerous scientific investigations have been conducted.[24] According to the photochemical analysis, young leaves have antibacterial, antiviral, hypoglycemic, anticancer, and many other medicinal qualities because they include alkaloids, saponin, tannin, flavonoids, and glycosides.[25]

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, beriberi, abortion, asthma India, Stomach troubles, cancer in Australia
Flowers	Jaundice, cough, hoarseness, bronchitis, laryngitis, and tracheitis in Asia
Seeds	Anti-fertility. Antimicrobial, fungicidal, carminative, counter irritant
Roots/barks	Digestive, tonic, abortifacient in Australia, sore teeth in India, syphilis in Africa

Medicinal uses of different part of papaya plant[26-29]

Benzyl isothiocyanate, found in papaya fruit seed extract, has bacteriostatic, fungicidal, and bactericidal properties at a single effective dose of 4-5 g seeds (25–30 mg BITC). Papaya has high levels of antioxidant activity, which helps to neutralise the production of free radicals and stop the onset of disease.[30] Papain, glycyl endopeptidase, chymopapain, and caricain are among the most significant components of latex, which varies in quantity depending on the section of the papaya plant Numerous scientific studies have been conducted recently to investigate the potential medicinal benefits of papaya leaf. Papaya leaves have been used as medicine to treat a number of illnesses, including jaundice, fever, asthma, colica, and beriberi. Papaya leaf extract (PLE) is currently prepared using a variety of techniques; however, aqueous extract, ethanol extract, methanol extract, and freeze-dried papaya leaf juice are most frequently used for disease prevention.[31-33] Papaya leaf can be utilised as a nutritional agent because it contains proteins, lipids, vitamins, and carbs. Per 100 g of leaf part, these substances vary in concentration: ascorbic acid is 38.6%, protein is 5.6%, phosphoric acid is 0.225%, carbs are 8.3%, iron is 0.0064%, and minerals like magnesium are 0.035%.[34] Aqueous PLE was found to include 0.001% tannins, 0.022% saponins, 0.013% flavonoids, 0.011% phenolics, 0.019% alkaloids, and 0.004% steroids, according to the quantitative phytochemical study. Furthermore, PLE has a treatment alternative for preventing the viral disease dengue.[35] Otsuki and colleagues recently reported on the impact of PLE on tumour cell proliferation and demonstrated that increased human lymphocyte secretion of TH1 type cytokines.[36] According to recent reports, papaya leaf contains a number of active ingredients, including ascorbic acid, alpha-tocopherol, chymopapain,

cyanogenic glucosides, cystatin, flavonoids, glucosinolates, and papain, that can increase blood antioxidant capacity and lower lipid peroxidation levels.[37] displayed the architectures of bioactive secondary metabolites that were obtained from PLE. Numerous anecdotal examples for osteosarcoma, breast cancer. There have been reports of mesothelioma, lung adenocarcinoma, pancreatic epithelioid carcinoma, hepatocellular carcinoma, Burkitt's lymphoma, and cervical cancer. Even further research on the anticancer qualities of PLE made by Australian aboriginal people has since been published.[38] To identify and describe the bioactive components found in papaya leaves, numerous scientific investigations have been conducted. According to the photochemical analysis, young leaves have antibacterial, antiviral, hypoglycemic, anticancer, and many other medicinal qualities because they include alkaloids, saponin, tannin, flavonoids, and glycosides. The review primarily focuses on the medicinal qualities of Carica papaya leaf in managing and preventing the advancement of illness.[39]

Theraputic application of PLP

Because papaya leaf extract (PLE) is a rich source of vitamins, minerals, and phytochemicals, it can be used medicinally to treat a variety of human diseases. The use of PLE for the prevention and treatment of different diseases has been documented in numerous academic works since antiquity. Moreover, the present scientific studies provide the basis for the possible role of leaves in disease prevention, which is outlined below.

Mechanism of papaya leaf in health management

It is well known that PLE interacts with a wide variety of molecular targets and has anti-disease effects. The key molecular targets in the prevention of anticancer include DNA topoisomerase I/II activity suppression, signal pathway modifications, downregulation of Bcl-2 and Bcl-XL gene expression, upregulation of Bax, Bak, cleaved caspase 3, and upregulation of P53 expression.[40-45] Nitric oxide (NO), costimulatory receptor (CD80), tumor necrosis factor-alpha (TNF-α), IL-12p40, IL-6, IL-12p70, IFN-γ, and IL-2 and IL-4 secretion were all increased and decreased, respectively, by PLE treatment.[40-47]

PLE regulates the release of chemokines CCL7, CCL2, and CCL8, as well as pro-inflammatory cytokines such as IL-1β, IL-6, IL-1α, and IL-8.[48] Through the activation of ALOX 12 and PTAFR gene expression, CPE therapy has been shown to have a positive impact on dengue patient.[49] The molecular processes by which PLE treats different disorders are depicted in Figure 22. Additionally, in dengue virus-infected mice AG129, freeze-dried

Carica papaya leaf modulates the production of inflammatory cytokines CCL6/MRP-1, CCL17/TARC, CCL12/MCP-5, CCL8/MCP-2, IL1RN/IL1Ra, IL1R1, PF4/CXCL4, and NAMPT/PBEF1. In diabetic rats, PLE also controls the β-cells that release insulin.[50]

Anti dengue effect of PLE

An alarming number of people worldwide are afflicted by dengue, which is thought to affect 50–100 million cases annually.[51] The dengue virus (DENV) 1-4, which is a member of the Flaviviridae family, is the cause of dengue and is spread by the bite of an infected Aedesaegypti mosquito.[52] Four to seven days after the dengue virus incubates, the disease's symptoms—which include vomiting, headaches, rash, high fever, and muscle soreness—appear.[53]

One of the primary symptoms of dengue is thrombocytopenia, which is a decrease in platelet count that is used to diagnose dengue patients.[54] According to the World Health Organization (WHO), thrombocytopenia is defined as a sharp decline in platelet count, which is verified by a platelet count of less than 150,000 per microliter of blood.[55] There isn't currently a vaccine or antiviral medication available to treat dengue fever. Blood, blood components, and fluids are only given as supportive therapy to patients in order to prevent disease or provide maintenance therapy. A glimmer of hope exists for a dengue vaccine, as multiple clinical trials are currently underway. As an alternative, more options must be investigated in order to combat the dengue nemesis. Numerous investigations have been conducted to investigate the potential of herbal medicine as a complementary treatment for dengue complications. Numerous studies have recently examined PLE's possible use in the treatment of dengue-related thrombocytopenia.

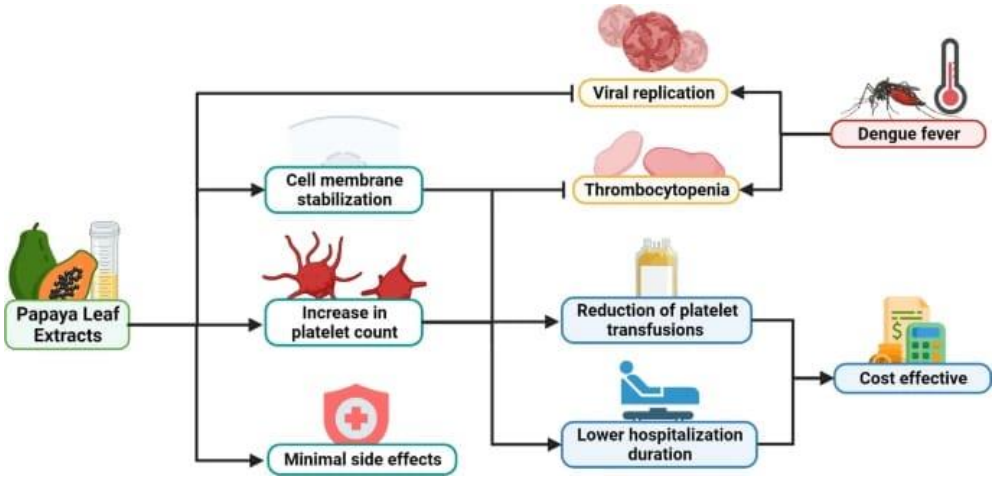
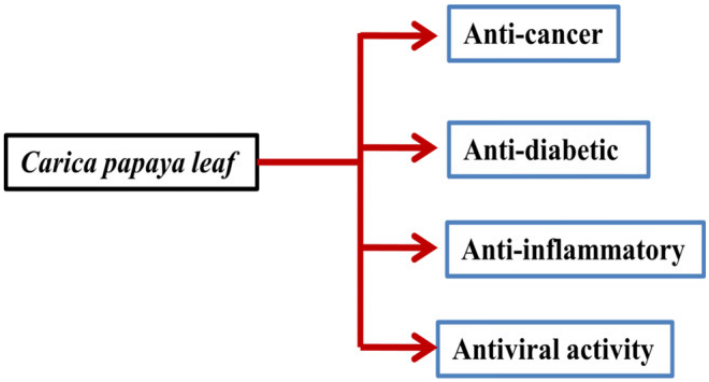


Fig. no.04: Uses of extract.

These investigations showed that administering papaya leaf extract to patients considerably raises their platelet count, which is lowered when they have a dengue infection.[56] Five dengue patients' platelet counts increased within twenty-four hours of receiving PLE treatment, according to a study.[57] In a similar vein, 285 patients participated in a randomized controlled trial which found that papaya leaf syrup raised the mean platelet count relative to control subjects.[58] Comparable outcomes have been noted in a Malaysian study involving 228 patients.[59] According to studies, a lower platelet count is linked to increased vascular permeability and plasma leakage, which are the primary causes of bleeding in dengue patients.[60] It has been documented that the membrane-stabilizing abilities of PLE shield blood cells from damage brought on by stress. In dengue patients, such an action can stop platelet lysis.[61] In dengue virus-infected mice AG129, freeze-dried Carica papaya leaf juice has also been shown to significantly reduce the production of inflammatory cytokines, such as CCL12/MCP-5, CCL8/MCP-2, CCL17/TARC, CCL6/MRP-1, IL1RN/IL1Ra, IL1R1, PF4/CXCL4, and NAMPT/PBEF1. It has been demonstrated that PLE causes an upregulation of IFN-α expression in THP-1 cells and a decrease in the expression of DENV NS1 envelop protein. These findings are promising and indicate that in order to standardize the use of PLE for the prevention and treatment of dengue infection, comprehensive studies involving animal models and clinical trials are required.[62]



In Vitro Discoveries

Three included studies used cells isolated from healthy and dengue patients and healthy rodents, respectively, to examine the effects of C. papaya leaf juice at different maturities. Ranasinghe et al. (2012) state that no discernible variation was discovered on level of hemolysis inhibition ($p > 0.05$) amongst the three leaf maturities on both different heat-induced hemolysis erythrocyte types (dengue: 25.7–32.5%, healthy: 31.8–38.5%), in contrast to the aspirin control group, which had a 45.9% healthy and a 43.6% dengue rate. Testing on

hemolysis erythrocytes induced by hypotonicity revealed that the level of inhibition was likewise not notably different ($p > 0.05$) in the partially mature leaves (intervention-treated group) on Compared to indomethacin, both types of erythrocytes (healthy: 31.57%, dengue: 57.03%) control group (dengue: 65.35%), healthy: 47.67%.[63]

The effectiveness of C. papaya leaf juice on adenosine diphosphate-induced platelet aggregation was examined by Chinnappan et al. (2016) using plasma rich and plasma poor platelets from dengue patients and healthy donors. They discovered that platelet aggregation was considerably reduced ($p < 0.05$) in both healthy and platelets rich in dengue plasma compared to the untreated group. The same thing was noted($p < 0.05$) for healthy plasma-rich platelets that were pre-infected and treated with the interventionwhen compared to the untreated, pre-treated dengue plasma with low platelets collective.[64] Phagocytic activity in peritoneal macrophages treated with an intervention (62.5–1000µg/mL) Interleukin (IL)-10 and interferon (IFN)-γ levels were significantly ($p < 0.05$) higher than those of the media control group, rising by 72.91–189.58% (non-dose dependently). In comparison to the media, there was a dose-dependent, statistically significant increase ($p < 0.05$). Interferon (IFN)-γ and interleukin (IL)-10 levels significantly increased ($p < 0.05$) in a dose-dependent manner relative to the media control group, while phagocytic activity in intervention-treated peritoneal macrophages (62.5–1000 µg/mL) increased by 72.91–189.58% (non-dose dependent manner). Collective.[65] Benefits of C. papaya leaf juice for major dengue infection clinical symptoms were demonstrated by in vitro research by inhibiting erythrocyte hemolysis. similar to medications like aspirin and indomethacin in terms of stabilizing the plasma membrane between patients with dengue. Thus, the possibility of patients experiencing plasma leakage as a result of elevated It is possible to decrease capillary fragility and vascular permeability. The non-structural DENV Protein 1 was able to cause platelet aggregation in addition to activation by Toll-like receptor 4.[66] It's interesting to note that the leaf juice was discovered to have the ability to prevent excessive platelet aggregation, suggesting that dengue infection-related thrombocytopenia and bleeding conditions may be reduced. Impact on the activity of phagocytes. Additionally, cytokine release offers information about the potential benefits of C. papaya leaf juice in regulating the immune system's functional and non-functional reactions, which are brought on when apathogen enters the body of the host.

Ex Vivo and In Vivo Findings

(Table 2) lists the 13 included studies that investigated the potential use of C. papaya leaf juice as a dengue-fighting strategy using mouse and rat models, and the single study that used mosquitoes. Using larvicidal to control vectors is an easy way to method of preventing diseases carried by mosquito vectors. Aedes is the typical dengue vector. aegypti mosquitoes, which have four life stages: larvae, pupae, adults, and eggs. The eggs can develop into adults in as little as 10 days. Thus, it's imperative to prevent adult mosquitoes from emerging as soon as feasible. But based on the article search The C. papaya leaf juice was discovered to have an insecticidal effect on when it was only in juice form. larvae in a single study. Rubio (2016) discovered that Aedes sp. mosquito larvae perished.5 to 30 minutes following the leaf juice's addition to the synthetic trap filled with clean water.[67] Jayasinghe et al. (2017) investigated the effects of leaf juice on healthy Wistar rats in addition to an in vitro investigation. The researchers used bone marrow cells from healthy Wistar rats (which did not contain mitogens) and separated splenocytes. Significantly, both cells multiplied ($p < 0.01$, by 63.2% and 39.62%) in the group that received the intervention (just 31.25 µg/mL). IFN-γ Level significantly ($p < 0.05$) increased from splenocytes (31.25–1000 µg/mL) during the intervention. groups, but the amount of IFN-γ produced by bone marrow cells only rose from a dose of 62.5 µg/mL for treatment. Bone marrow cells' level of IL-10 (only at 62.5 µg/mL) and splenocyte-derived IL-10 (31.25–500 µg/mL) considerably ($p < 0.05$) rose in groups for interventions. Following three days of oral therapy, the platelet count rose by 68%.cells from the bone marrow monocytes (44.67%), lymphocytes (10%), total white blood counts (19%), pro-inflammatory cytokines (tumor necrosis factor (TNF)-alpha (39.09%), IL-6).[68] The majority of the evaluated in vivo evidence in this review involved inducing thrombocytopenia in the animal model, and multiple experiments were conducted using an animal model specifically designed to mimic the primary clinical manifestations of dengue to enhance the reliability of the research findings. An analysis of inflammatory cytokine gene expression profiles and receptors discovered to be connected to dengue infection.[69] Fascinatingly, Because the liver is surrounded by sinusoidal endothelium and during the DENV invasion, it has been suggested that the degree of liver damage is correlated with the infection. Permeability of endothelium rises. As a result, aberrant liver function enzyme levels, histopathological lesions, and dengue antigen traces can all be found in liver tissue. Animal models used in the included were both healthy and infected with dengue research suggests, The pharmacological impact of C. papaya leaf juice on phagocytosis activation

function and cell division) as well as non-functional (immune cell level regulation and release of inflammatory cytokines) immune responses.[70]

Clinical findings: Patients were diagnosed with dengue infection after their blood parameters were examined for the presence of dengue immunoglobulin G, M, and/or non-structural protein 1 antigen. In contrast, some patients were diagnosed based only on low platelet counts (not exceeding 150,000/µL) and clinical symptoms like high fever and body aches without the need for any antigen or antibody tests. Several included studies shared safety-related observations in addition to clinical manifestations related to dengue.[70] Hepatoxicity and nephrotoxicity were not seen in two three-day oral acute toxicity studies involving 0.72 mL C. papaya leaf juice per 100 g body weight of healthy rats. However, cytotoxicity was noted in healthy bone treated with 500 and 1000 µg/mL of leaf juice in marrow cells and splenocytes. Nandiniet al. (2021) observed that leaf juice administered at a dose of 5–2000 mg/kg body weight to healthy rats exhibited a notably reduced alanine aminotransferase level ($p < 0.05$) in contrast to the untreated control group; nonetheless, the liver and kidney in that group had fewer lesions the group receiving intervention.[71-73]

In his subsequent work, he used AG129 mice treated with 500 and 1000 mg/kg body weight of leaf juice for three days. The intervention-treated group did not significantly differ in body weight from the untreated mock infected group ($p > 0.05$).collectives. Additionally, there was no discernible difference ($p > 0.05$) in the mice's spleen sizes between the Untreated mock-infected group and intervention-treated dengue-infected group. Based on the current understanding of dengue pathogenesis, it has been determined that a number of organs and cells, including bone marrow cells, splenocytes, and platelets, are susceptible to infection. The liver and spleen, in particular, are sites where platelets are produced. Considering based on the previously published safety results, using C. papaya leaf juice up to a certain dosages and length of treatment appear to have a preventive effect on dengue's organs.affected individuals.

C. papaya trees are grown for both commercial and food use in Malaysia. In Malaysia, there are two types of papaya that are widely consumed: "eksotika" and "sekaki." There are minor physical differences between the two varieties, but both are typically hermaphrodites. As of right now, just one metabolite profiling analysis has been carried out. on the fruit portion of both types, and it was discovered that the metabolite profiles of the "Sekaki" and "eksotika" .

Comparable in-depth content analysis on the leaf portion Differences between the two varieties are still absent.[74-75]

RESULTS

The papaya plant—fruit, leaves, seeds, bark, latex, and all of their constituents—plays a significant part in controlling the course of illness. The active ingredients in carica papaya leaf—alkaloids, glycosides, tannins, saponins, and flavonoids—are what give it its therapeutic properties. Furthermore, those with dengue fever have higher platelet counts when they consume papaya leaf juice. There are a few limitations on the scoping review's conclusions. First off, the full text of only English articles that were accessible was included. Secondly, C. papaya leaf was only used medicinally in juice form. Lastly, there weren't enough clinical trials that satisfied the requirements for inclusion. Fourthly, a number of the included research offered experimental values in graphical form, making it impossible for the writers to compare the results in one the same parameter was measured in a different study.

CONCLUSION

The use of complementary herbal medicines has grown over time. Because C. papaya leaves have the ability to increase platelets, their supplements have demonstrated promising potential. However, the production methods applied in a number of commercially available C. papayaformulations for leaves have the ability to break down the active phytochemicals, which will impede the positive effects of the additions. In conclusion, in light of the current crisis, it is imperative to refine the traditional herbal remedies. Consequently, the negative aspects of marketing Supplements containing C. papaya leaves need to be updated for improved patient care.

REFERENCE

1. Oliver-Bever B. “Medicinal Plants in Tropical West Africa”, Cambridge University Press; 1986. p. 161.
2. Rajapakse S. Rodrigo C, Rajapakse A, “Treatment of dengue fever,”0 Infect Drug Resist, 2012; 5: 103-12.
3. Balmaseda A, Hammond S.N, Pérez M.A, Cuadra R, Solano S, Rocha J, et al. “Short report: Assessment of the World Health Organization scheme for classification of dengue severity in Nicaragua”, Am J Trop Med Hyg., 2005; 73: 1059-62
4. Pandey V, Agrawal V, Raghavendra K, Dash A.P. “Strong larvicidal activity of three species of Spilanthes (Akarkara) against malaria (Anopheles stephensi Liston, Anopheles

culicifacies, species C) and filaria vector (Culex quinquefasciatus Say)" Parasitol Res., 2007; 102: 171–174.

5. Katade S. R, Pawar P.V, Wakharkar R.D, Deshpande N.R. "Sterculia guttata seeds extractives an effective mosquito larvicide", Ind J Exp Biol., 2006; 44: 662–665.
6. Wiesman Z, Bishnu P, "Chapagain Larvicidal activity of saponin containing extracts and fractions of fruit mesocarp of Balanites aegyptiac"., Fitoterapia, 2006; 77: 420–424.
7. Mohan L, Sharma P, Srivastava C.N, "Comparative efficacy of Solanum xanthocarpum extracts alone and in combination with a synthetic pyrethroid, cypermethrin, against malaria vector, Anopheles stephensi", Southeast Asian J Trop Med & Public Health., 2007; 38: 256–260.
8. Tonk S, Bartarya R, Mahara. K.K, Bhatnagar V.P, Srivastava S.S, "Effective method for extraction of larvicidal component from leaves of Azadirachta indica and Artemisia annua Linn", J Environ Biol., 2006; 27: 103–105.
9. Chaubal R, Pawar P.V, Hebbalkar G.D, Tungikar V.B, Puranik V.G, Deshpande V.H, et al, "Larvicidal activity of Acacia nilotica extracts and isolation of D-pinitol-a bioactive carbohydrate" Chemi Biodivers, 2005; 2: 684–688.
10. Sharma P, Mohan L, Srivastava C.N "Larvicidal potential of Nerium indicum and Thuja oriertelis extracts against malaria and Japanese encephalitis vecto", J Environ Biol., 2005; 26: 657–660.
11. Huet J, Looze Y, Bartik K, Raussens V, Wintjens R, Boussard P "Structural characterization of the papaya cysteine proteinases at low Ph", Biochem Biophys Res Commun, 2006; 341: 620–626.
12. Dominguez de Maria P, Sinisterra J.V, Tsai S.W, Alcantara A, "Carica papaya lipase (CPL): An emerging and versatile biocatalyst", Biotechnol Advances, 2006; 24: 493–499.
13. Okeniyi J.A, Ogunlesi T.A, Oyelami O.A, Adeyemi L.A, "Effectiveness of dried Carica papaya seeds against human intestinal parasitosis: A pilot study". J Med Food, 2007; 10: 194–196.
14. Adebowale A, Garnesan A.P, Prasad R.N.V, "Papaya (Carica papaya) consumption is unsafe in pregnancy: Fact or fable? Scientific evaluation of a common belief in some parts of Asia using a rat model". British J Nutr., 2002; 88: 199–203.
15. Rahmana N.A, Muliawanb H.S, Rashidb N.N, Muhamadb M, Yusofb R, "Studies on Quercus lusitanica extracts on DENV-2 replication", Dengue Bull., 2006; 30: 260–269.

16. Tong X.K, Qiu H, Zhang X, Shi L.P, Wang G.F, Ji F.H, et al, WSS45, "a sulfated alpha-D-glucan, strongly interferes with Dengue 2 virus infection in vitro", Acta Pharmacol Sin., 2010; 31: 585–592.
17. McDowell M, Gonzales S.R, Kumarapperama S.C, Jeselnik M, Arterburn JB, Hanley K.A, "A novel nucleoside analog, 1-beta-D-ribofuranosyl-3-ethyl-[1, 2, 4] triazole (ETAR), exhibits efficacy against a broad range of flaviviruses in vitro", Antiviral Res., 2010; 87: 78–80.
18. Watanabe R.M, Soares T.S, Morais-Zani K, Tanaka-Azevedo A.M, Maciel C, Capurro M.L, et al, "A novel trypsin kazal-type inhibitor from Aedes aegypti with thrombin coagulant inhibitory activity", Biochimie, 2010; 92: 933–939.
19. Karishna K.L, Paridhavi M, Patel J.A "Review on nutritional, medicinal and pharmacological properties of papaya"(carica papaya linn.)Nat prod radiance, 2008; 7: 364-373.
20. Tripathi L, Tripathi J.N, "Role of biotechnology in medicinal plants", Trop J Pharm Res., 2003; 2(2): 243–253.
21. Jain S. K "Ethnobotany and research in medicinal plants in India" Ethnobot Search New Drugs, 1994; 185: 153–168.
22. Wang M.W, Hao X, Chen K "Biological screening of natural products and drug innovation in China", Philos Trans R SocLond B Biol Sci., 2007; 362(1482): 1093–1105.
23. Aravind G, Bhowmik D, Duraivel S, Harish G, "Traditional and medicinal uses of Carica papaya" J Med Plants Stud, 2013; 1(1): 7–15.
24. Wall M.M "Ascorbic acid, vitamin a, and mineral composition of banana (Musa sp.) and papaya (Carica papaya)24 cultivars grown in Hawaii", J Food Compos Anal, 2006; 19(5): 434–445.
25. Leader B, Baca Q.J, Golan D.E "Protein therapeutics: a summary and pharmacological classification", Nat Rev Drug Discov, 2008; 7(1): 21–39.
26. Vij T, Prashar Y "A review on medicinal properties of Carica papaya Linn" Asian Pac J Trop Dis., 2015; 5(1): 1–6.
27. Leader B, Baca Q.J, Golan D.E "Protein therapeutics: a summary and pharmacological classification" Nat Rev Drug Discov, 2008; 7(1): 21–39.
28. Tang C.S "Benzyl isothiocyanate of papaya fruit" Phytochemistry, 1971; 10(1): 117–121.
29. Krishna K.L, Paridhavi M, Patel J.A, "Review on nutritional, medicinal and pharmacological properties of papaya (Carica papaya Linn.)" Nat Prod Radiance, 2008; 7(4): 364–373.

30. Krishna K.L, Paridhavi M, Patel J.A, "Review on nutritional, medicinal and pharmacological properties of papaya (Carica papaya Linn.)" Nat Prod Radiance, 2008; 7(4): 364–374.
31. Patil T, Patil S, Patil A, Patil S, "Carica papaya leaf extracts–an Ethnomedicinal boon", Int J Pharmacogn Phytochem Res., 2014; 6(2): 260–265.
32. Hu T, Guo Y.Y, Zhou Q.F, Zhong X.K, Zhu L, Piao J.H, et al. "Optimization of ultrasonic-assisted extraction of total saponins from Ecliptaprostrasta L. using response surface methodology" J Food Sci., 2012; 77(9): C975–C982.
33. Longdet I.Y, Adoga E.A, "Effect of methanolic leaf extract of Carica papaya on plasmodium berghei infection in albino mice" Eur J Med Plants, 2017; 20(1): 1–7.
34. Saran P.L, Choudhary R, "Drug bioavailability and traditional medicaments of commercially available papaya: a review" Afr J Agric Re., 2013; 8(25): 3216–3223.
35. Bamisaye F.A, Ajani E.O, Minari J.B, "Prospects of ethnobotanical uses of pawpaw (Carica papaya) J Med Plants", 2013; 1(4): 171–177.
36. Otsuki N, Dang N.H, Kumagai E, Kondo A, Iwata S, Morimoto C, "Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects", J Ethnopharmacol, 2010; 127(3): 760–767.
37. Seigler D.S, Pauli G.F, Nahrstedt A, Leen R "Cyanogenicallosides and glucosides from Passifloraedulis and Carica papaya", Phytochemistry, 2002; 60(8): 873–882.
38. Nugroho A, Heryani H, Choi J.S, Park H.J, "Identification and quantification of flavonoids in Carica papaya leaf and peroxynitrite-scavenging activity", Asian Pac J Trop Biomed, 2017; 7(3): 208–213.
39. Otsuki N, Dang N.H, Kumagai E, Kondo A, Iwata S, Morimoto C "Aqueous extract of Carica papaya leaves exhibits anti-tumor activity and immunomodulatory effects" J Ethnopharmacol, 2010; 127(3): 760–767.
40. Seigler D.S, Pauli G.F, Nahrstedt A, Leen R "Cyanogenicallosides and glucosides from Passifloraedulis and Carica papaya," Phytochemistry, 2002; 60(8): 873–882.
41. Hadadi S.A, Li H, Rafie R, Kaseloo P, Witiak S.M, Siddiqui R.A ,"Anti-oxidation properties of leaves, skin, pulp, and seeds extracts from green papaya and their anti-cancer activities in breast cancer cells" J Cancer Metastasis Treat, 2018; 4: 25.
42. Liew S.Y, Stanbridge E.J, Yusoff K, Shafee N "Hypoxia affects cellular responses to plant extracts, J Ethnopharmacol, 2012; 144(2): 453–456.
43. Saranya V, Malathi N "Evidence-based review on anticancer effects of commonly used herbs", J AdvClin Res Insights, 2014; 1(2): 73–77.

44. Webb L.J "The use of plant medicines and poisons by Australian aborigines", Aust J Anthropol, 1969; 7(2): 13146.
45. Nugroho A, Heryani H, Choi J.S, Park H.J "Identification and quantification of flavonoids in Carica papaya leaf and peroxynitrite-scavenging activity", Asian Pac J Trop Biomed, 2017; 7(3): 208–213.
46. Rumiyati S, "Effect of the protein fraction of Carica papaya L. leaves on the expressions of P53 and BCL-2 in breast cancer cells line", Maj Farm Indones, 2006; 17: 170–176.
47. Salim E, Kumolosasi E, Jantan I, "Inhibitory effect of selected medicinal plants on the release of pro-inflammatory cytokines in lipopolysaccharide-stimulated human peripheral blood mononuclear cells", J Nat Med., 2014; 68(3): 647–653.
48. Siddique O, Sundus A, Ibrahim M.F, "Effects of papaya leaves on thrombocyte counts in dengue--a case report", JPMA J Pak Med Assoc., 2014; 64(3): 364–366.
49. Norahmad N.A, Razak M.R, Misnan N.M, Jelas N.H, Sastu U.R, Muhammad A, et al. "Effect of freeze-dried Carica papaya leaf juice on inflammatory cytokines production during dengue virus infection in AG129 mice", BMC Complement Altern Med., 2019; 19(44): 1–10.
50. Ahmad N, Fazal H, Ayaz M, Abbasi B.H, Mohammad I, Fazal L, "Dengue fever treatment with Carica papaya leaves extracts", Asian Pac J Trop Biomed, 2011; 1(4): 330–333.
51. Yunita F, Hanani E, Kristianto J, "The effect of Carica papaya L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient", Int J Med Aromat Plants, 2012; 2(4): 573–578.
52. Subenthiran S, Choon T.C, Cheong K.C, Thayan R, Teck M.B, Muniandy PK, et al, "Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever", Evid Based Complement Alternat Med., 2013; 2013: 1–7.
53. Gammulle A, Ratnasooriya W.D, Jayakody J.R, Fernando C, Kanatiwela C, Udagama P.V "Thrombocytosis and anti-inflammatory properties and toxicological evaluation of Carica papaya mature leaf concentrate in a murine model" Online Int J Med Plant Res., 2012; 1(2): 21–30.
54. Oishi K, Saito M, Mapua C.A, Natividad F.F, "Dengue illness: clinical features and pathogenesis", J Infect Chemother, 2007; 13(3): 125–133.

55. Dharmarathna S.L, Wickramasinghe S, Waduge R.N, Rajapakse R.P, Kularatne S.A " Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model", Asian Pac J Trop Biomed, 2013; 3(9): 720–724.
56. Ahmad N, Fazal H, Ayaz M, Abbasi B.H, Mohammad I, Fazal L, "Dengue fever treatment with Carica papaya leaves extracts", Asian Pac J Trop Biomed, 2011; 1(4): 330–333.
57. Yunita F, Hanani E, Kristianto J, "The effect of Carica papaya L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient", Int J Med Aromat Plants, 2012; 2(4): 573–578.
58. Subenthiran S, Choon T.C, Cheong K.C, Thayan R, Teck M.B, Muniandy PK, et al. "Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever", Evid Based Complement Alternat Med., 2013; 2013: 1–7.
59. Gammulle A, Ratnasooriya W.D, Jayakody J.R, Fernando C, Kanatiwela C, Udagama P.V, "Thrombocytosis and anti-inflammatory properties and toxicological evaluation of Carica papaya mature leaf concentrate in a murine model", Online Int J Med Plant Res., 2012; 1(2): 21–30.
60. Oishi K, Saito M, Mapua C.A, Natividad F.F, "Dengue illness: clinical features and pathogenesis", J Infect Chemother, 2007; 13(3): 125–133.
61. Kala CP. Leaf juice of Carica papaya L. a remedy of dengue fever. Med Aromat Plants, 2012; 1(6): 1–2.
62. Ranasinghe, P.; Ranasinghe, P.; Abeysekera, W.P.; Premakumara, G.A.; Perera, Y.S.; Gurugama, P.; Gunatilake, S.B. In vitro erythrocyte membrane stabilization properties of Carica papaya L. leaf extracts. Pharmacogn. Res., 2012; 4: 196–202.
63. Chinnappan, S.; Ramachandrappa, V.S.; Tamilarasu, K.; Krishnan, U.M.; Pillai, A.K.; Rajendiran, S. Inhibition of platelet aggregation by the leaf extract of Carica papaya during dengue infection: An in vitro study. Viral Immunol, 2016; 29: 164–168.
64. Jayasinghe, C.D.; Gunasekera, D.S.; De Silva, N.; Jayawardena, K.K.M.; Udagama, P.V. Mature leaf concentrate of Sri Lankan wild type Carica papaya Linn. modulates nonfunctional and functional immune responses of rats. BMC Complement. Altern. Med., 2017; 17: 230.
65. Rubio, I.C.S.; Lubos, L.C. Effectiveness of Carica papaya Linnaeus (papaya) and Azadirachta indica A. Jussieu (Neem) crushed leaves as potential larvicides for mosquitoes. Asian J. Health, 2016; 6: 146–162.

66. Rubio, I.C.S.; Lubos, L.C. Effectiveness of Carica papaya Linnaeus (papaya) and Azadirachta indica A. Jussieu (Neem) crushed leaves as potential larvicides for mosquitoes. Asian J. Health, 2016; 6: 146–162.
67. Jayasinghe, C.D.; Gunasekera, D.S.; De Silva, N.; Jayawardena, K.K.M.; Udagama, P.V. Mature leaf concentrate of Sri Lankan wild type Carica papaya Linn. modulates nonfunctional and functional immune responses of rats. BMC Complement. Altern. Med., 2017; 17: 230.
68. Ahmad, N.; Fazal, H.; Ayaz, M.; Abbasi, B.H.; Mohammad, I.; Fazal, L. Dengue fever treatment with Carica papaya leaves extracts. Asian Pac. J. Trop. Biomed, 2011; 1: 330–333. [CrossRef]
69. Deepak, B.S.R.; Girish, K.J.; Jadhav, L.L. Effect of papaya leaf juice on platelet and WBC count in dengue fever: A case report. J. Ayurveda Holist. Med., 2013; 1: 44–47.
70. Ismail, I.S.; Hairon, S.M.; Yaacob, N.M.; Besari, A.M.; Abdullah, S. Usage of traditional and complementary medicine among dengue fever patients in the Northeast Region of Peninsular Malaysia. Malays. J. Med. Sci., 2019; 26: 90–101.
71. Hettige, S. Salutary effects of Carica papaya leaf extract in dengue fever patients–a pilot study. Sri Lankan Fam. Physician, 2008; 29: 17–19.
72. Prakash Kala, C. Leaf juice of Carica papaya L.: A remedy of dengue fever. Med. Aromat. Plants, 2012; 1: 109.
73. Sanimah, S.; Sarip, J. Metabolomic analysis of Carica papaya variety eksotika and sekaki. J. Trop. Agric. Food Sci., 2015; 43: 103–117.
74. Bok, Z.K.; Balakrishnan, M.; Jong, Y.X.; Kong, Y.R.; Khaw, K.Y.; Ong, Y.S. The plausible mechanisms of action of Carica papaya on dengue infection: A comprehensive review. Prog. Drug Discov. Diomedical Sci., 2020; 3: a0000097.