



***Carica papaya*; A Paired and Alternative Therapy of Dengue Fever**

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Abstract

The purpose of the study is to explore the prospective use of *Carica papaya* leaves extracts for Dengue fever that is a painful, debilitating mosquito-borne disease caused by dengue viruses. An estimated 390 million dengue infections occur worldwide each year, with about 96 million resulting in illness. It has been found at height in developing nations like India, Pakistan, Sri Lanka and Bangladesh. Mostly tropical areas have been reported infected. The disease is transmitted by an Aedes mosquito infected with a dengue virus; interestingly it is not transferred from person to person. Symptoms are mild to serious including hemorrhagic fever; a rare complication characterized by high fever, damage to lymph and blood vessels, bleeding from the nose and gums, enlargement of the liver, and failure of the circulatory system and it can cause the death. All the symptoms of disease are due to low platelets count that may become very low if not managed. Consequently, the research reveals that juice of the leaves of the *Carica papaya* plant from the family Caricaceae help to increase the platelet levels. The present review is done to enlighten the theory of the management of dengue through this alternative therapy that can be implement along with conventional treatment. The covered researches in present study would raise and support the possibility of being, the remedy and significant alternative in the prospect.

Key words: Dengue, Alternative Therapy, Carica Papaya, Leaf Extract, Viral Fever.

Subject Classification: Biotechnology

Language: English

Date of Submission: 2017-01-05

Date of Acceptance: 2018-02-20

Date of Publication: 2018-03-10

ISSN: 2348-6201

Volume: 07 Issue: 01

Journal: Journal of Advances in Biotechnology

Publisher: CIRWORLD

Website: <https://cirworld.com>



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Introduction

Dengue is a mosquito-borne single positive-stranded RNA virus of the family *Flaviviridae*; genus *Flavivirus*, and causative agents of dengue fever [1]. In recent decades the disease due to its high epidemiology and mortality rate has become a major public health concern internationally. Dengue is found in tropical and sub-tropical regions around the world, predominantly in urban and semi-urban area and about 500, 000 cases of dengue hemorrhagic fever (DHF) each year require hospitalization [2, 3].

The World Health Organization (WHO) estimates there may be 50-100 million dengue infections globally every year, with two-fifths of the world population, or 2.5 billion people, at risk of this mosquito-borne infectious disease [4]. Unfortunately, due to lack of adequate surveillance programme in the underdeveloped and developing countries, the management of the disease is not known [5]. *Carica papaya*, an alternative herbal medicine being investigated to control the massive problem of dengue. Although there are certain conflicting views on the effectiveness of the treatment in dengue. The present article covers a brief overview and literature regarding the use of the papaya leaf extract for the treatment of dengue. This alternate way of treatment is being widely followed in many countries interestingly with no reported adverse effects and further toxicology studies ruled out any toxic effects even at higher doses [6-8].



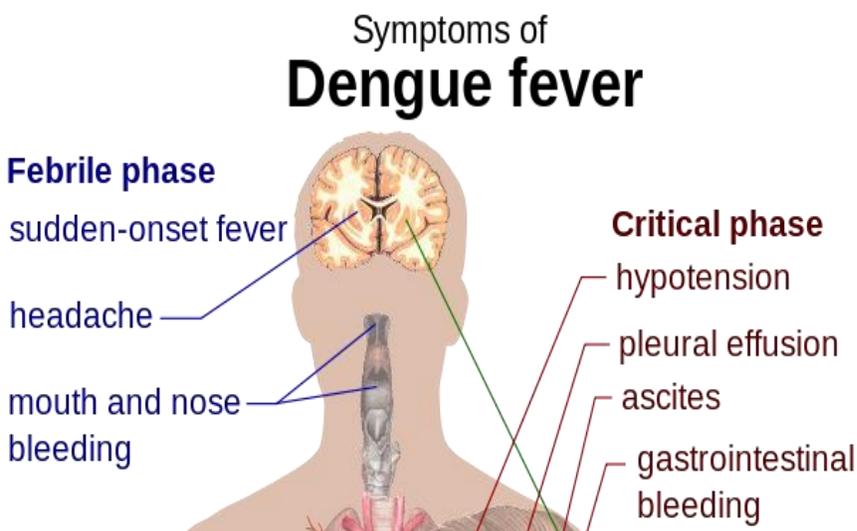
Materials and Methods

The literature search was carried out by using the most renown research engines PubMed, Google and the library database. The keywords used for the literature search included dengue, treatment of dengue, herbal treatment of dengue, dengue papaya leaf extract, dengue *Carica papaya* and dengue fever. A search in PubMed was conducted for relevant articles over the last 9 years, from 2008 to 2016. A Google search was done using the same keywords to identify articles that related to alternative treatment of dengue fever. Additionally, with a detailed search in the library database for relevant articles. A total of 12 studies were selected for this review included animal study, case reports, case series and randomized controlled trials. The studies were published in the years 2008 or later. A brief review of the studies is mentioned in Table 1.



Brief Review of Dengue Fever

Dengue is a mosquito-borne tropical disease caused by four antigenically distinct serotypes of the Flaviviridae family, which are designated as dengue virus (DENV) DENV-1, 2, 3 and DENV-4. Many cases of dengue are asymptomatic in children and in adults with a first infection. In other cases, it may appear as undifferentiated fever or classic dengue fever [3]. An incubation period varying from 3 to 14 days but most often it is 4 to 7 days is followed by a febrile illness consisting of sudden-onset fever, anxiety, muscles pain, joint pain and rash. Thrombocytopenia is main and common feature of the illness [4]. The patient develops hemorrhagic manifestations such as red or purple spot on skin and bleeding through the nose, gastrointestinal tract and gums. Other symptoms have also been reported in the literature, which include encephalitis, encephalopathy, myocarditis, hepatitis and cholecystitis [5].



Deaths due to dengue fever are commonly a consequence of patients developing complications like hemorrhagic fever and dengue shock syndrome [6]. Dengue hemorrhagic fever occurs due to progression of thrombocytopenia and development of increased vascular permeability and plasma leakage. It progresses to dengue shock syndrome, which is again associated with high mortality [4].

There are no specific antiviral drugs for dengue. Treatment for dengue is usually symptomatic. Some cases require platelet transfusions and proper fluid management [3]. Though symptomatic treatment works in most mild cases, some cases progress to complications very fast and this often make it difficult to save the life of the patient.

Attempts to develop an antiviral agent for dengue have met several hurdles. Dengue is caused by four distinct serotypes which often undergo mutations [7]. Like in other ribonucleic acid (RNA) viruses, these mutations are due to the error-prone nature of RNA polymerase, which results in the formation of quasispecies. It is currently unclear which viral genome results in a higher viral titre [8]. An antiviral would have to be effective against all the serotypes. The current mouse model for dengue (AG129) is inefficient due to low viral load and short period of viremia [7].



There are ongoing efforts to develop effective vaccines that would be used to treat attacks of dengue fever and prevent severe complications, many of which are undergoing clinical trials [2]. In addition to vaccines, every other possible treatment including alternative medicines are being investigated to test their usefulness in controlling this problem. Lee and his co-investigators demonstrated the effectiveness of cocktail extracts prepared from four species of *phyllanthus* against the DENV [9].

Mechanism of Dengue Induced Thrombocytopenia

Hemorrhagic dengue is characterized by less than 100,000 cells/mm³ thrombocyte counts [3]. Two mechanisms have been suggested that could be responsible for dengue-induced thrombocytopenia—impaired thrombopoiesis and peripheral platelet destruction. In support of the theory of impaired thrombopoiesis, studies have suggested reduced megakaryopoiesis at the onset of infection, which is normal at the time of clinical recovery. This effect could be due to a direct effect of the virus on the megakaryocytes, or an effect on the stromal cells which are responsible for the release of cytokines and control of megakaryopoiesis. Studies have also indicated altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis as possible mechanisms of thrombocytopenia.

The other main mechanism proposed for thrombocytopenia is the increased peripheral platelet destruction by the DENV. This could be due to an autoimmune reaction, where antibodies produced by the host against the DENV bring about activation and destruction of platelets. Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction. Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the destruction. Recent studies indicate a direct infection of the platelets by the DENV. Increased levels of mediators like tumor necrosis factor- α and interleukin-1 β were associated with the thrombocytopenia [10].

Medicinal Use of *Carica Papaya* Plant

The *Carica papaya* has been used since antiquity for the treatment of different disease conditions. Different medicinal effects of *Carica papaya* extracts (from the leaves, fruit and seeds) have been suggested through scientific studies. The chymopapain and papain extracts of the leaves are useful in the treatment of digestive disorders. The extracts from fruits and seeds have bactericidal properties [11]. The fruit juice and leaf extract have been demonstrated to have a wide variety of properties including anticancer, antioxidative, anti-inflammatory, anti-bacterial, nephroprotective, hepatoprotective, hypoglycemic and hypolipidemic effects, and anti-sickling effect in sickle cell disease. The ripe fruit has been used against ringworm, whereas the green fruit has been used to lower blood pressure, as an aphrodisiac and to induce abortion [12]. The leaf extract has also been shown to have larvicidal properties against the *Aedes aegypti* mosquito, the vector of the DENV [11].

Possible Mechanism of Action of *C. Papaya* Leaf Extract in Dengue Infection

The papaya plant possibly brings about its effect in dengue fever by treating the thrombocytopenia. A study has reported membrane stabilizing properties of *C. Papaya* L. leaf extracts in *in-vitro* studies. The study found that *C. Papaya* L. leaf extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue infection; the effect was observed at the lower concentrations of the extracts. Thus, the extracts are likely to possess membrane-stabilizing properties and protect blood cells against stress-induced destruction. This property may be useful in patients with dengue infection where the leaf extracts could possibly prevent platelet lysis. The authors hypothesize that this effect could be due to the flavonoids and other phenolic compounds present in the papaya leaves [12].



Animal Studies

A study in mice found an increase in thrombocyte counts in mice administered 15 mg of powdered papaya leaves/kg body weight between 1 and 12hrs following dosing [13]. Another study found that the *C. papaya* leaf aqueous extract at concentrations of 400 mg/kg and 800 mg/kg significantly increased the platelet counts in cyclophosphamide-induced thrombocytopenic rat model. It also reduced the clotting time in the treated rats [14]. Another study in mice reported that *C. papaya* substances responsible for the release and/or production of thrombocytes [15].

Reported Studies in Humans

Treatment of dengue using *C. papaya* leaf extract in humans has been reported in very few studies conducted in Asia. A study conducted in 2016 and reported that *C. papaya* leaf extract can directly act on platelet. This study also found that the leaf extract possesses a dengue-specific neutralizing effect on dengue viral-infected plasma that may exert a protective role on platelets [16]. A pilot study was conducted in Sri Lanka on 12 patients suspected of suffering from dengue. The patients had a platelet count of <130,000/cu mm, but only six patients were serologically confirmed to be suffering from dengue. The patients received 2 doses of papaya leaf extract at intervals of 8hrs. They also received standard symptomatic care for dengue. The study found an increase in platelet count and total white blood cell count in patients administered papaya leaf extract within 24hrs of treatment with the extract [17]. Another pilot study conducted on 30 dengue fever patients stated that *Carica papaya* leaf extract (CPL) does significantly increase the platelet count in patients with thrombocytopenia [18].

A case report from Pakistan described the effective treatment of dengue with papaya leaf extract. The patient received 25 mL of papaya leaf extract twice a day for 5 days. A steady increase in the platelet and white blood cell count was observed after 2 days of treatment [19]. A 23-year-old man was administered a calculated dose for five days. Blood samples were tested for complete blood count before and after the administration of the juice. Thrombocyte count had increased from 28000/micro liter to 138000/micro liter at the end of five days [20].

Another study conducted in Indonesia used *C. papaya*, leaves extract capsules (CPC), which contained 70% ethanol extract of *C. papaya* leaves. The 80 patients included in the study had high continuous fever for 2-7 days, thrombocyte count of <150,000/ μ L and hematocrit of 20% or more. They were randomized into two groups; one group received CPC in addition to standard treatment, whereas the other group received only standard treatment for dengue. The study found that platelets in patients with dengue increased faster in those who were administered the CPC. The authors thus conclude that treatment with CPC can hasten recovery of patients and therefore reduce hospitalization. But, there is no clear mention if any of the patients including those in the control group died due to dengue. The study also does not confirm the diagnosis of dengue in these patients [21].

A report in the British Medical Journal website described the rapid recovery of platelet counts in two children suffering from dengue. These cases were proved to be positive for dengue by the demonstration of the dengue antigen in the serum. The boys, aged 10 years and 14 years, were administered a spoonful of ground papaya leaves paste every 4 hourly. A dramatic increase in platelet counts was observed; in one case within 12hrs of initiating treatment, the count increased to 100,000. In the second case, it increased within 2 days to 250,000. The duration of treatment was not mentioned in the report [22].

A study in the journal of Medicinal and Aromatic Plants reported an increase in platelet counts in five patients within 24hrs who had taken papaya leaf extract for dengue. However, no other details have been provided whether the dengue was confirmed in these patients, what other treatment was given and



whether the increase in platelet count is significant. Furthermore, the response in platelet count beyond 24hrs has not been described [23].

A study conducted in Malaysia had a more systematic approach in evaluating the use of papaya leaf juice in the treatment of dengue. The juice was obtained from the papaya leaves under hygienic conditions from trees that were grown without insecticides or pesticides. An open-labeled randomized controlled trial was conducted on 290 patients between the ages of 18 and 60 years with platelet counts $\leq 100,000/\mu\text{L}$. The patients were confirmed to be suffering from dengue using a rapid dengue bedside test. Patients in the intervention group were administered fresh juice from 50g of *C. papaya* leaves once a day 15 min after breakfast for 3 consecutive days. In addition, they received the standard treatment for dengue. The controls only received the standard treatment. The final analysis was conducted on 111 patients from the intervention group and 117 controls. The study found that there was a significant increase in the platelet counts in the intervention group at the end of 40hrs when compared to the counts 8hrs after the intervention began. This significant increase was not observed in the control group. An increase in arachidonate 12-lipoxygenase and the platelet-activating factor receptor gene expression was also observed in the intervention group. These genes are associated with increased platelet production [7].

Discussion

Reports of different studies published in scientific literature *C. Papaya* L. leaf extract have been proved as beneficial remedy for dengue having a rapid increase in platelet count. This could be possibly attributed to its membrane-stabilizing property. The flavonoids and other phenols present in the extract have been suggested to provide the beneficial effects. Another study reveals the rich content of several minerals that may balance the mineral deficiency caused by the virus and strengthen the immune cells against dengue [24].

Although, it is not entirely clear. First of all, there are very few cases reported in literature. Many of the studies have assumed that the patients suffer from dengue due to the presence of thrombocytopenia and have not confirmed the diagnosis. This may have been due to the high cost of the test, which is often unaffordable to people in the underdeveloped and developing countries, where most of these studies were conducted. Thus, it cannot be proved based on these case reports that the extract is conclusively effective in dengue. It is possible that the extract may be beneficial in other cases of thrombocytopenia as well. Therefore, it is first important to diagnose the cases correctly and prove beyond doubt that the patient indeed suffers from dengue infection.

This is the common practice that crude leaves extract prepared by grinding the papaya leaves. The amount of extract given also differed among the studies. Thus, the active principle needs to be identified and the dosage standardized to conduct clinical studies on it to prove its efficacy in dengue beyond doubt. It is also necessary to conduct pharmacokinetic studies to ensure that the active principle is absorbed from the digestive tract.

In addition to its effect against the virus, the papaya plant also appears to be effective against the *Aedes* mosquito. Thus, if proved to be effective, this plant could control dengue at two levels, at the level of transmission as well at the host level.

Papaya extract no doubt offers effective treatment for dengue at low cost. However, the benefits are established but it is also necessary to not to rely entirely on the leaf extract and do not ignore or omit standard treatment for dengue as large scale randomized clinical trials in dengue-confirmed patients is necessary to establish their usefulness.



Table: 1

Authors	Subject/ Animals	Article Type	Article title	Key Message
Chinnappan,S., Ramachandra ndrappa,V.S., Tamilarasu , K., Krishnan, U. M., Pillai, A. K., Rajendiran, S. 2016	n=60	Case report	Inhibition of Platelet Aggregation by the Leaf Extract of Carica papaya During Dengue Infection: An In Vitro Study.	Carica papaya leaf extract exert a protective role on platelets.
Gowda, A C Kumar, N Vijay Kasture, P N Nagabhushan, K H., 2015	n=30	randomized controlled trial	A Pilot Study to Evaluate the Effectiveness of Carica Papaya Leaf Extract in Increasing the Platelet Count in Cases of Dengue with thrombocytopenia.	Carica papaya leaf extract (CPLE) does significantly increase the platelet count in patients with thrombocytopenia associated with dengue
Siddique, O., Sundus, A., Ibrahim, M. F. 2014	n=1	Case report.	Effects of papaya leaves on thrombocyte counts in dengue, a case report.	Oral administration of Carica papaya leaves extract is said to have a positive impact on thrombocyte count.
Patil, Shetty, Bhide, Narayanan 2013	n=24 (4 groups with 6 animals in each)	Placebo controlled	Evaluation of platelet augmentation activity of Carica papaya leaf aqueous extract in rats.	Increased platelet counts and reduced clotting time by Carica papaya leaf aqueous extract in cyclophosphamide- induced thrombocytopenic rat model
Sathasivam, K., Ramanathan, S., Mansor, S. et al 2009	n=10	Clinical trial	Thrombocyte counts in mice after the administration of papaya leaf suspension.	<i>C. papaya</i> substances responsible for the release and/or production of thrombocytes.
Hettige 2008	n=12	Case series	Salutary effects of Carica papaya leaf extract in dengue fever patients-a pilot study.	Papaya leaf juice elevated total white cells and platelets in dengue patients



Ahmad. N., Fazal, H., Ayaz. M., Abbasi, B. H., Mohammad, I., Fazal, L., 2011	n=1	Case report	Dengue fever treatment with Carica papaya leaves extracts.	Carica papaya leaves extracts increased platelets over 5 days
Yunita, Hanani,. 2012	n=80	Randomized clinical trial.	The effect of Carica papaya L. leaves extract capsule on platelet count and hematocrit level in dengue fever patient.	Carica papaya L. leaves extract increased platelets and hastened recovery
Kumar,. 2010	n=2	Case series (rapid response).	Dengue: An escalating problem.	Increase in platelets within 12 hrs and 2 days respectively
Kala,. 2012	n=5	Case series.	Leaf juice of Carica papaya L: A remedy of dengue fever.	Increase in platelets by 24 hrs
Subenthiran,S.,Choon,C heong,Thayan,Teck,Mun iandy, Adlin Afzan, Noor Rain, Abdullah, and Zakiah Ismail et al 2013	n=228	Open labeled randomized control trial	Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue hemorrhagic fever.	Increase in platelets after 40 hrs of the first dose

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