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Review Article

Papaya Leaf Extract To Treat Dengue: A Review

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Abstract: In India over the ancient times people used plants to extract plant actives to make drug formulations. In recent time the less use of herbal formulations due to lack of their standardization. Papaya (*Carica papaya* linn.) is well known for its exceptional nutritional and medicinal properties throughout the world. In present review article, an attempt is made to compile all the strange facts available about this tasty fruit. From the times immemorial, the whole Papaya plant including its leaves, seeds, ripe and unripe fruits and their juice is considered as nutraceutical fruit due to its multifaceted medicinal properties. Phytochemically, the whole plant contains enzymes (Papain), lycopene, carotenoids, alkaloids, monoterpenoids, flavonoids, mineral and vitamins. Dengue is a viral disease that today affects a vast number of people in over 125 countries and is responsible for a sizable number of deaths. In the absence of an effective antiviral drug to treat the disease, various treatments are being investigated. Studies have indicated that the juice of the leaves of the *Carica papaya* plant could help to increase the platelet levels in these patients. The present article reviews the pharmacological uses of *Carica papaya* and side/toxic effects. An herbal medicine being investigated to control the mammoth problem of dengue is the extract of the leaves of the papaya plant, *Carica papaya*. In this article, we present a brief overview of dengue and a review of available literature regarding the use of the papaya leaf extract for the treatment of this condition.
Keywords: *Carica papaya* Linn, Papaya, Nutraceutical, Leaf Extract, Thrombocytopenia, Dengue.

INTRODUCTION:

Papaya (Carica papaya linn.) is well known for its exceptional nutritional and medicinal properties throughout the world. Papaya, a juicy and tasty fruit, belonging to family Caricaceae is scientifically known as Carica papaya Linn. It is grown in various parts of the world, including India, tropical America and Europe. It is commonly known as Papaya melon tree, Pawpaw or papau, Kapaya, Lapaya, Papyas, Papye, Tapayas, Fan mu gua [1]. Papaya is a powerhouse of nutrients and is available throughout the year. From the times immemorial, the whole Papaya plant including its leaves, seeds, ripe and unripe fruits and their juice is used as traditional medicine. Nowadays, Papaya is considered as nutraceutical fruit due to its multifaceted medicinal properties. The prominent medicinal properties of papaya include Anti-fertility, Diuretic, Uretonic, Anti-hypertensive, Hypolipidemic, and Anti-helmintic; Wound healing, Antifungal, Antibacterial, Antitumor and free radical scavenging activities. It is a rich source of threes powerful antioxidant vitamin C, vitamin A and vitamin E; the minerals, magnesium and potassium; the B vitamin pantothenic acid and folate and fiber. In addition to all this, it contains a digestive enzyme-papaintha effectively treats causes of trauma, allergies and sports injuries [2, 3] All the nutrients of papaya as a whole improve cardiovascular system, protect against heart diseases, heart attacks, strokes and prevent colon cancer. The fruit is an excellent source of beta carotene that prevents damage caused by free radicals that may cause some forms of cancer. It is reported that it helps in the prevention of diabetic heart disease. Papaya lowers high cholesterol levels as it is a good source of fiber. Papaya effectively treats and improves all types of digestive and abdominal disorders. It is a medicine for dyspepsia, hyperacidity, dysentery and constipation. Papaya helps in the digestion of proteins as it is a rich source of proteolytic enzymes. Even papain-a digestive enzyme found in papaya is extracted, dried as a powder and used as aid indigestion. Ripe fruit consumed regularly helps in habitual constipation. It is also reported that papaya prevents premature aging. It may be that it works because a poor digestion does not provide enough nutrients to our body. The enzymes papain and chymopapain and antioxidant nutrients found in papaya have been found helpful in lowering inflammation and healing burns [2].

Dengue virus:-

Dengue is an endemic disease. Dengue fever is a borne tropical caused by the dengue virus [4]. It has affected the normal life of people living tropical and subtropical regions. Dengue is the most common human arthropod-borne virus disease and it causes thousands of deaths every year [5]. Symptoms typically begin three to fourteen days after infection. This may include a high fever, headache, vomiting, muscle and joint pains, and a characteristic skin rash. Recovery generally takes two to seven days. In a small proportion of cases, the disease develops into the life-threatening dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs [6].

DV is very unique in structure. It can be transmitted by mosquitoes named Aedes aegypti. Aedes mosquitoes are normally small and black with the white lines on the body and legs. The DV belongs to the Flaviviridae family and it has four different serotypes (DV-1 to DV-4) [7]. The most common virus responsible for dengue is DV- 2 (dengue virus-2). DV-2 inhibits *in vitro* megakaryopoeisis and induces apoptotic cell death in a sub-population of early megakaryocytic progenitors which may contribute to thrombocytopenia in dengue disease [8].

DV is a positive-stranded encapsulated RNA virus and is composed of three structural protein genes, which encode the nucleocapsid or core (C) protein, a membrane-associated (M) protein, an enveloped (E) glycoprotein and seven non-structural (NS) proteins. The non-structural proteins are NS1, NS2a, NS2b, NS3, NS4A, NS4B, and NS5 [9]. Schematic representation of DV is shown in Figure 1. The three structural proteins are united into the developed infective vision. However, the non-structural proteins only help in the replication of the virus.

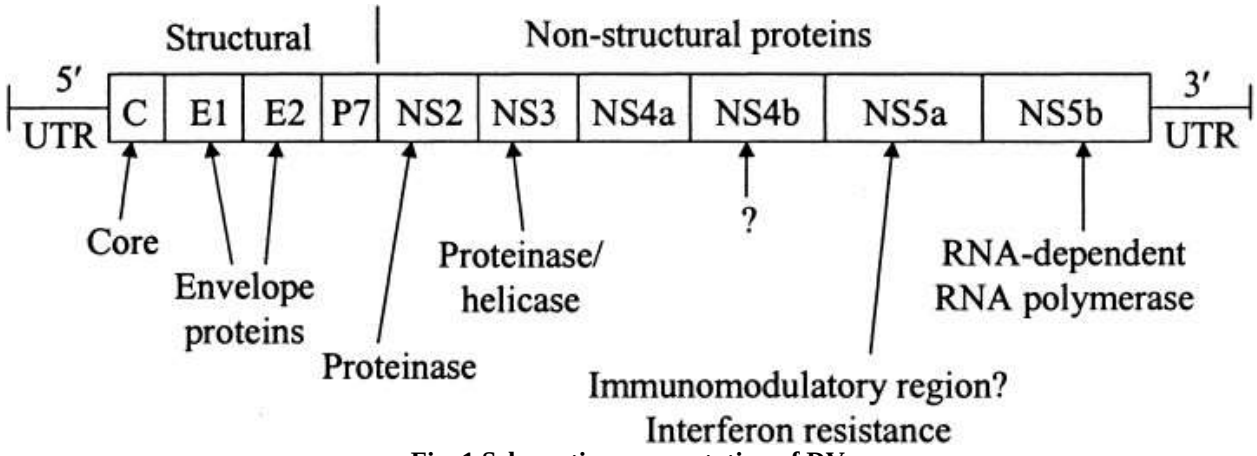
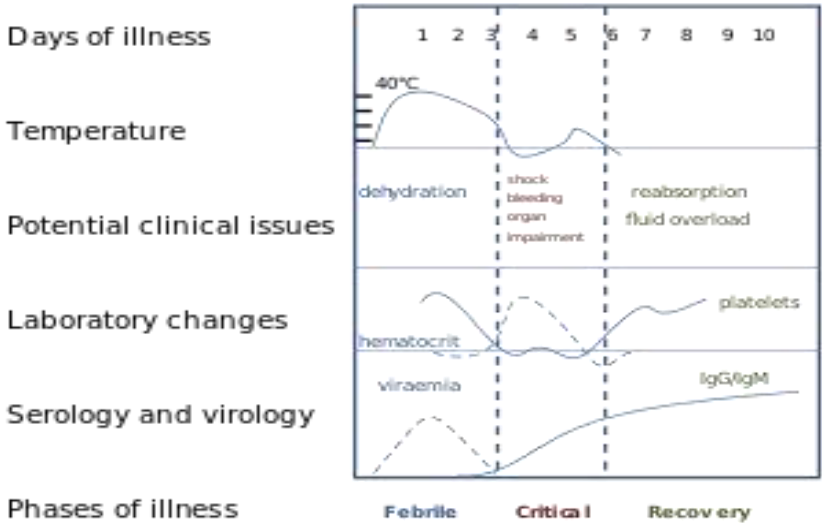


Fig. 1 Schematic representation of DV

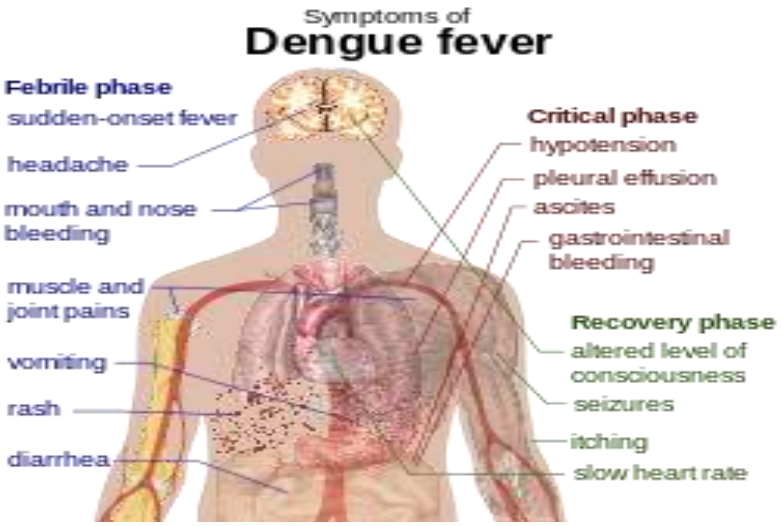
It is transmitted mainly by Aedes aegypti mosquito and also by Ae. Albopictus. All four serotypes can cause the full spectrum of disease from a subclinical infection to a mild self-limiting disease, the dengue fever (DF) and a severe disease that may be fatal, the dengue hemorrhagic fever/dengue shock syndrome (DHF/ DSS). The WHO 2009 classification divides dengue fever into two groups: uncomplicated and severe, though the 1997 WHO classification is still widely used. The 1997 classification divided dengue into undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF) [10]. Four main characteristic manifestations of dengue illness are (i) continuous high fever lasting 2-7 days; (ii) hemorrhagic tendency as shown by a positive tourniquet test, petechiae or epistaxis; (iii) thrombocytopenia (platelet count <100x109/l); and (iv) evidence of plasma leakage manifested by hem concentration (an increase in hematocrit 20% above average for age, sex and population), pleural effusion and ascites, etc [11].

Management of Dengue

The A. aegypti mosquito is the primary vector of dengue. A. aegypti can control Flavivirus transmission. Flavivirus has four separate serotypes, which are DV-1, DV-2, DV-3, and DV-4. However, the DV can transmit in human beings through the bites of infected female mosquitoes. After 4-10 days of virus incubation period, an infected mosquito is capable of transmitting the virus its whole life. The illness started to build up after the incubation period. It followed three main phases-febrile, critical, and recovery. In the febrile phase, suddenly high temperature can be identified as symptoms. In critical phase, the temperature of the patient falls to 37.538°C or less. The afterward platelet count is reduced, and it causes plasma leakage. In the recovery stage of dengue, the patient started to recover, and proper monitoring of symptoms should be done to next following 48-72 h [12, 13]. Schematic outline of different phases of dengue are shown in Figure 2.



Febrile phase in dengue can last for 2-7 days. The main symptoms are a headache, skin erythema, arthralgia, body ache, myalgia, and facial flushing. In the beginning of the critical phase, hematocrit levels may increase. However, in the critical phase platelet count started to lower down and it causes plasma leakage. In dengue patients, shock occurs due to plasma leakage. During 24-48 h of critical phase, the fluid management of the patient is very critical. After 72 h of critical phase, recovery phase started. However, in recovery phase; patient's physical condition started to improve. In this phase, the normal appetite will return, gastrointestinal bleeding will reduce, the platelet count will increase, and blood pressure will stabilize. Bradycardia and electrocardiographic changes can be identified during the recovery stage [14]. Schematic depiction of the symptoms of dengue fever is shown in Figure 3.



According to the guideline of the WHO, dengue management is done using three steps, which are overall assessable of the disease, diagnosing disease phase with severity, and finally, focus on the treatment of dengue. Clinical diagnosis can be done by serological testing in the febrile phase of dengue [13]. In the febrile phase, patients are only encouraged to take paracetamol and oral fluid saline. However, in the critical phase 0.9% saline is given to dengue patients. If the symptoms started to worsen and hematocrit level is rising, the fluid infusion rate needs to be increased.

Thrombocytopenia:-

Platelets are the shape of disc which is 2 - 4 µm, 0.5 µm wideness, colorless, seedless. The average volume is 6 - 10 fL. There are about 150,000 - 450,000/ microL platelet in peripheral circulation of blood. The average life of them is 8 - 10 days. Nearly 2/3 platelet is

in blood and 1/3 is in spleen [15]. Platelets can have a role both in primer and in secondary homeostasis. Platelets are essential for maintaining the integrity of the vascular endothelium and controlling hemorrhage from small-vessel injury through the formation of platelet plugs. More extensive injury and involvement of larger blood vessels requires, in addition to platelets, the participation of the coagulation system to provide a firm, stable, fibrin clot. The average of the platelet counts should be 150,000 - 450,000/microL. If the numbers go down 150,000/microL, it causes thrombocytopenia [16].

Thrombocytopenia separates three stages as numerical. Mild: 100,000 - 150,000/microL, Moderate: 50,000 - 100,000/microL. Severe: < 50,000/microL.

A low platelet count occurs because:

- The body's bone marrow doesn't make enough platelets.
- The bone marrow makes enough platelets, but the body destroys them or uses them up.
- The spleen holds on to too many platelets.

The Bone Marrow Doesn't Make Enough Platelets

Bone marrow is the sponge-like tissue inside the bones. It contains stem cells that develop into red blood cells, white blood cells, and platelets. When stem cells are damaged, they don't grow into healthy blood cells. Many conditions and factors can damage stem cells.

- ***Cancer***
  Cancer, such as leukemia (lu-KE-me-ah) or lymphoma (lim-FO-ma), can damage the bone marrow and destroy blood stem cells. Cancer treatments, such as radiation and chemotherapy, also destroy the stem cells [15].
- ***Aplastic Anemia***
  Aplastic anemia is a rare, serious blood disorder in which the bone marrow stops making enough new blood cells. This lowers the number of platelets in your blood [17, 18].
- ***Toxic Chemicals***

Exposure to toxic chemicals—such as pesticides, arsenic, and benzene—can slow the production of platelets.

- ***Medicines***
  Some medicines, such as diuretics and chloramphenicol, can slow the production of platelets. Chloramphenicol (an antibiotic) rarely is used in the United States.
  Common over-the-counter medicines, such as aspirin or ibuprofen, also can affect platelets [19].
- ***Alcohol***
  Alcohol also slows the production of platelets. A temporary drop in the platelet count is common among heavy drinkers, especially if they're eating foods that are low in iron, vitamin B12, or folate.
- ***Viruses***
  Chickenpox, mumps, rubella, Epstein-Barr virus, or parvovirus can decrease your platelet count for a while. People who have AIDS often develop thrombocytopenia.
- ***Genetic Conditions***
  Some genetic conditions can cause low numbers of platelets in the blood. Examples include Wiskott-Aldrich and May-Hegglin syndromes.

The Body Destroys Its Own Platelets

A low platelet count can occur even if the bone marrow makes enough platelets. The body may destroy its own platelets due to autoimmune diseases, certain medicines, infections, surgery, pregnancy, and some conditions that cause too much blood clotting.

- ***Autoimmune Diseases*** **[20, 21].**

Autoimmune diseases occur if the body's immune system mistakenly attacks healthy cells in the body. If an autoimmune disease destroys the body's platelets, thrombocytopenia can occur. One example of this type of autoimmune disease is immune thrombocytopenia (ITP). ITP is a bleeding disorder in which the blood doesn't clot as it should. An autoimmune response is thought to cause most cases of ITP. Normally, your immune system helps your body fight off infections and diseases. But if you have ITP, your immune system attacks and destroys its own platelets. Why this happens isn't known. (ITP also may occur if the immune system attacks your bone marrow, which makes platelets.) Other autoimmune diseases that destroy platelets include lupus and rheumatoid arthritis.

- ***Medicines***

A reaction to medicine can confuse your body and cause it to destroy its platelets. Examples of medicines that may cause this to happen include quinine; antibiotics that contain sulfa; and some medicines for seizures, such as Dilantin, ®vancomycin, and rifampin. (Quinine is a substance often found in tonic water and nutritional health products.) Heparin is a medicine commonly used to prevent blood clots. But an immune reaction may trigger the medicine to cause blood clots and thrombocytopenia. This condition is called heparin-induced thrombocytopenia (HIT). HIT rarely occurs outside of a hospital. In HIT, the body's immune system attacks a substance formed by heparin and a protein on the surface of the platelets. This attack activates the platelets and they start to form blood clots. Blood clots can form deep in the legs (deep vein thrombosis), or they can break loose and travel to the lungs (pulmonary embolism).

- ***Infection***

A low platelet count can occur after blood poisoning from a widespread bacterial infection. A virus, such as mononucleosis or cytomegalovirus, also can cause a low platelet count [21].

- ***Surgery***

Platelets can be destroyed when they pass through man-made heart valves, blood vessel grafts, or machines and tubing used for blood transfusions or bypass surgery.

- ***Pregnancy***

About 5 percent of pregnant women develop mild thrombocytopenia when they're close to delivery. The exact cause isn't known for sure.

- ***Rare and Serious Conditions That Cause Blood Clots*** [22, 23].

Some rare and serious conditions can cause a low platelet count. Two examples are thrombotic thrombocytopenic Purpura (TTP) and disseminated intravascular coagulation (DIC). TTP is a rare blood condition. It causes blood clots to form in the body's small blood vessels, including vessels in the brains, kidneys, and heart. DIC is a rare complication of pregnancy, severe infections, or severe trauma. Tiny blood clots form suddenly throughout the body. In both conditions, the blood clots use up many of the blood's platelets.

The Spleen Holds On to Too Many Platelets

Usually, one-third of the body's platelets are held in the spleen. If the spleen is enlarged, it will hold on to too many platelets. This means that not enough platelets will circulate in the blood. An enlarged spleen often is due to cancer or severe liver disease, such as cirrhosis (sir-RO-sis).

Dengue and Thrombocytopenia:

The most common virus responsible for dengue is DV2 (dengue virus-2). DV-2 inhibits in vitro megakaryopoeisis and induces apoptotic cell death in a sub-population of early megakaryocytic progenitors which may contribute to thrombocytopenia in dengue disease [8].

Mechanisms of Thrombocytopenia in Dengue:

Two mechanisms have been suggested that could be responsible for dengue-induced thrombocytopenia- impaired thrombopoiesis and peripheral platelet destruction. 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 [24]. Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction [25, 26]. Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the destruction [27, 28]. Increased levels of mediators like tumor necrosis factor-α and interleukin-1β were associated with thrombocytopenia [4].

Currently available treatment for dengue fever associated with thrombocytopenia:-

Treatment is guided by etiology and disease severity. The thrombocytopenia is not addressed till it gets lowered down to levels less than 20000 /µl, where platelet transfusion is advocated. Corticosteroid is advised by some which is supposed to halt further platelet destruction; however, not all prefer. TPO agonists and mimetic like Eltrombopag and Romiplastim are available for increasing the platelet counts however, cost and accessibility factors would hamper larger proportion of people from availing them and also they are associated with adverse effects. Therefore in the current lieu, considerations for alternate therapies to combat the low platelet count, which is relatively free from the toxic side effects of the drugs, should be given [29, 30]. Carica Papaya Leaf Extract in the management of thrombocytopenia associated with dengue is significant as it would be:

- Better & viable option in fever associated with thrombocytopenia.
- Palatable and appropriately formulated.
- Fewer side effects.
- Decreases the cost of hospitalization.
- Cost effective.
- More affordable and accessible.
- Averting the mortalities.

Papaya Leaf Extract in Dengue Treatment

Thrombocytopenia occurs if platelet count reduces and it may cause plasma leakage in dengue patients. Megakaryocyte is responsible for the production of blood platelets, and ALOX 12 genes are strongly expressed in megakaryocytic. ALOX 12, which is also known as platelet activating factor receptor (PTAFR), plays an important role in platelet aggregation. It means that PTAFR gene can be a precursor for platelet production. Carica papaya leaf extract increases the activity of ALOX 12 gene [31].

CONCLUSION:

Carica papaya is a Neutraceutical plant having a wide range of pharmacological activates. The whole plant has its own medicinal value. The wide range of enzymes, vitamins present in Carica papaya makes it a Neutraceutical plant. The present review is about all the prominent pharmacological activity, home remedies and side effects of Carica papaya. Papaya extract no doubt

offers a cheap and possibly effective treatment for dengue. Papaya leaf extract could be used as an additional or as a complementary drug in acute febrile illness patients with thrombocytopenia; it accelerates the increase in the platelet count and shorten the hospitalization thereby reducing the cost of hospitalization significantly.

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