A GLOBAL HUMAN THREAT: DENGUE VIRAL INFECTION AND ITS MANAGEMENT BY CARICA PAPAYA, A CURRENT PERSPECTIVE

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ABSTRACT

Dengue fever is a viral disease that affects a large number of individuals in more than 125 countries and kills a large percentage of the population. Throughout the decades, a lot of work has gone into developing viable treatments for dengue fever. Conversely, scientific trials and evaluations have shown that the majority of therapy approaches are ineffective. Due to the absence of effective treatments for dengue fever, herbal supplements have been popular as a means of relieving suffering, one of which is the use of C.papaya leaf juice. C.papaya Linn is also known as paw-paw and is a member of the Caricaceae family. The medicinal benefits of papaya fruit as well as other plant parts are widely established in conventional healers. Throughout the course of years, significant advancement have been made in terms of papaya's biological functioning as well as medical applications, and it is currently regarded as an important nutritional fruit plant. This review article describes contemporary findings and investigation aimed at elucidating the mode of action of papaya leaf extract in the medication of dengue fever. Till yet, three important pathways for papaya leaf juice extract's anti-thrombocytopenic, immunomodulatory, and anti-viral effects have already been postulated. Despite the fact that many of the information about the research findings reported in the literature missing sufficient knowledge, plenty of the investigations do suggest that this therapy might be a viable alternative in the future. To evaluate whether or not this natural material is effective in the treatment of dengue fever, more large-scale study is required.

Keywords: Carica papaya Linn, Dengue hemorrhagic fever, Thrombocytopenia, Aedes aegypti, Platelet count.

INTRODUCTION

Dengue fever is a viral disease that is spread by the female Aedes aegypti L. mosquito and is triggered by an RNA virus from the Flaviviridae family. Dengue hemorrhagic fever, a serious condition of dengue fever, can result in significant bleeding, a fall in blood pressure (shock),
and mortality. Dengue fever can reach 106 degrees Fahrenheit (41 degrees Celsius), as well as headaches and soreness in the tendons, ligaments, joints, even behind the eyes, as per Mayo Clinic [1]. As a result of dengue fever, an extensive redness may develop, along with nausea and vomiting. Hematological problems associated to platelet and endothelial dysfunction commonly seen in chronic dengue includes thrombocytopenia, coagulopathy, and vasculopathy. Thrombocytopenia is among the WHO's standards for a possible sign of therapeutic aggravation [2-3].

The virus is divided into four serotypes: DV-1, DV-2, DV-3, and DV-4. The nucleocapsid or core (C) protein, a membrane-associated (M) protein, an enveloped (E) glycoprotein, and seven non-structural (NS) proteins make up the DV virus, which is a positive stranded encapsulated RNA virus [4]. DENV-1 was first discovered in French Polynesia and Japan, and its prevalence in Asian locations has steadily expanded throughout period. Likewise, DENV-2 was initially discovered in Indonesia and Papua New Guinea, and has subsequently expanded across Asia, including Malaysia, Thailand, the Philippines, and Singapore. DENV-3 and DENV-4 were first documented in the Philippines and Thailand in 1953 [5]. Researches have been carried out to determine the link among dengue serotypes and their clinical presentations. DENV-1 and DENV-3 infections have minor clinical signs, but DENV-2 infections have major clinical features. The viruses range in severity from mild to severe, including haemorrhagic fever and dengue shock syndrome. Thrombocytopenia, leukopenia, and intermittent neutrophil shortage with coagulation abnormalities are the clinical symptoms of dengue infestations. It's thought that those symptoms are caused by the dengue virus's ability to suppress megakaryocyte proliferation or platelet aggregation [6-7]. Dengue fever (DF), a moderate self-limiting illness caused by all four serotypes, can range from a subclinical infection to a major sickness which can be lethal, dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). Although this 1997 WHO categorization is currently commonly used, the WHO 2009 categorization separates dengue fever into two groups: mild and severe. Dengue fever was split into three types in 1997: undifferentiated fever, dengue fever (DF), and dengue haemorrhagic fever (DHF).

ETIOPATHOGENESIS OF DENGUE FEVER

Dengue fever is spread by female Aedes aegypti mosquitos containing the Flavivirus. This influenza takes 3 to 14 days to incubate just after victim is attacked, whereby the individual may have preliminary indications like fever, headache and stiffness in muscles as well as in skeletons. This legendary Dengue fever generally lasts 5–7 days and has temperatures around 39 and 40 °C. This pathogen may enter the peripheral bloodstream throughout this time and, when remain unattended, affect blood vessels as well as lymphatic system, leading in Dengue haemorrhagic fever (DHF) accompanying manifestations like bleeding from the nose, gums, or beneath the epidermis. The Aedes mosquito is a tiny black mosquito with white stripes on all over the body. Maternal dragonflies require plasma from humans or creature in order to lay fertile embryos. The maturation of an embryo requires 2–3 days. The main dengue parasite (Aedes aegypti) has adapted effectively to the urban atmosphere as well as breeds in sluggish vessels at all times. Embryos require to be kept wet and mature in 24–72 hours. The only method for DENV to propagate is through mosquito attacks.
DENV is commonly transmitted from person to person by household mosquitoes. An infestation begins when an insect feeds on the plasma of a Dengue fever or Dengue haemorrhagic fever sufferer (as shown in Fig 1) [4].

Figure 1: Mechanism of Dengue Virus Spreading

After being introduced to a new human host by contaminated vectors, the pathogen replicates in cardiovascular system and spreads to other tissues via fluids and blood. To find a feasible DENV antiviral therapy, researchers must first study the virus's life span. Dengue virus is a tiny virus with a lipoprotein envelope and an icosahedral nucleocapsid that contains a positive single-stranded RNA genome. Adhesion to the host cell interface is the first step in virus transmission. It reaches the cell through receptor-mediated endocytosis, in which the cell membrane forms an endosome, a sac-like structure. The pathogen enters the endosome and travels extensively within the cytoplasm until the endosome barrier receives an anion, allowing it to combine with the endosomal layer and unlock the channel for genetic material liberation. At this point, the influenza virus in the cell fluid begins to multiply. Throughout this infectious excursion, variations in the secretory pathway's acidity perform a key function in its maturity [4].

TREATMENT OF DENGUE FEVER
Apart from preventive interventions and conservative fluid supplementation, there is no particular medication for dengue. Over the previous 50 years, clinical studies have largely failed to evaluate diverse therapy choices. Dengue fever's danger phase, or so-called "critical period," during which the patient's condition may rapidly deteriorate, is only 48–72 hours long. The chances of a high mortality are negligible unless the sufferer is properly handled throughout this stage. Even so, fluid management must be closely monitored and reviewed on a regular basis [8]. In simple dengue fever, there are no protracted consequences unless the sufferer heals (infrequent complications of dengue, such as orchitis and inflammation of cornea and brain can have a long-term impression in a very small minority of cases). Exposure provides transient resistance against the same serotype of dengue virus, but not against subsequent serotypes. Because it is tough to treat a dengue illness once it has developed, substantial focus is being placed on preventing acquisition by limiting parasite counts. To reduce transmission of pathogens, several vector control strategies have been tried, including physical (elimination of nesting sites), chemical (insecticides and larvicides), as well as biological (use of microbes such as Bacillus thuringiensis) [9].

An outline of dengue fever treatment

1. **Febrile Phase:** High body temperature, cluster headache, joint pain, muscle ache, motion sickness and vomiting distinguish the febrile phase, which normally lasts 5–7 days. At the completion of the febrile episode, assessment can disclose an inflamed oesophagus, lymphadenopathy, and tender hepatomegaly. The febrile episode is often accompanied by the recovery phase, as well as the entire sickness can be mistaken for a normal febrile event in several people. The gradual reduction in platelet frequency may be the initial diagnostic indicator for dengue at this phase. Over the course of 2–3 days, the platelet frequency might decrease quickly from numbers exceeding 250,000/L to less than 100,000/L. If a reduction in platelets is noted in sequential complete blood counts, every participant having fever should be monitored with daily blood counts for the next 3–5 days, notably in endemic regions throughout epidemics. IgM antibodies to the pathogen can be found in the blood 5 days after the beginning of fever [10].

Management of Febrile Phase: Throughout the febrile stage, a large amount of oral fluid should be given, as well as antipyretic prophylaxis with acetaminophen as needed. Nonsteroidal anti-inflammatory medicines (NSAIDs) should be resisted as well. If the patient has easy access to a medical facility, he or she can be treated at home with regular complete blood tests. Prolonged vomiting or dysentery that causes lack of moisture, major prostration, or premature haemorrhage symptoms are all signs that you should be admitted to the hospital and monitored closely.

2. **Critical Phase:** The critical phase might begin anywhere between 3 and 7 days after the onset of the fever. Enhanced capillary permeability with extravasation of fluids is a pathologic feature of the critical stage [11]. As previously stated, the actual process causing capillary leakage is unknown, while immunological pathways are assumed to perform a significant part.
Whereas the greatest reduction in platelet frequency occurs throughout the critical period, it is simply a predictor for the intensity of the sickness. The decline in platelet concentration in some cases might be as low as 5000/L. Only proof of fluid evacuation determines when the crucial stage begins. This comprises pleural effusion or ascites that can be seen clinically or radiologically, as well as indications of hemoconcentration, such as an increase in compact cell content in sequential blood samples.

The critical period lasts between 24 and 48 hours. The hydraulic balance should be precisely managed throughout this period to establish a compromise between maintaining the vascular segment sufficiently occupied inside the face of leakage and preventing hydraulic excess later on. At the start of the critical stage, the temperature usually goes down. As a result, defervescence should not be regarded as a sign of relaxation in the case of dengue fever, but rather as a signal to increase surveillance in the following days. Trauma can happen throughout the critical stage for 2 purposes: excessive water evacuation due to insufficient ingestion and internal bleeding (facilitated by thrombocytopenia and deranged clotting). The sufferer will reach the recovery phase if he or she overcomes the critical period. The extravascular fluids will re-enter the intravascular region at this period (48–72 hours after the critical period), and the patient may acquire cardiovascular disease or pulmonary edema, if fluids were administered too sparingly [12].

Mortality may arise as a result of fluid excess as well as shock from bleeding or leakage. Healing will be evident at the bedside if proper fluid administration has been implemented, as the sufferer will feel well, restore their appetite, and become more energetic. Throughout recovery period, certain sufferers develop an irritating erythematous rash with white speckles in between. The platelet level climbs quickly at this period, frequently crossing the 150,000/L barrier in 2–3 days from lows of less than 50,000/L.

Management of Critical Phase (Fluid resuscitation):

The important challenge here is predicting and identifying when the critical period will begin. When an evacuation or ascites becomes clinically noticeable, the critical period has already begun some hours before. Although a lateral decubitus chest radiograph or an ultrasound screening can be helpful in detecting initial symptoms of fluid collection in the serous cavities, they may not be physically viable for every individual during epidemics.

The beginning of severity can usually be recognized once the packed cell volume begins to rise beyond baseline (Keep in mind that numerous patients are admitted to the hospital while they are in a severe condition, and their "normal" hematocrit is a subject of consternation). A platelet count of less than 100,000/L indicates that the victim is on the verge to reach the critical stage in the coming 24 hours.

Throughout the critical phase, careful fluid administration is the most important therapeutic technique. The volume of fluid that must be supplied, as well as the appropriate variety of fluid, has a restricted data foundation. There have been no trials evaluating intravenous fluid infusion to placebo for apparent moral considerations. Saline water, Hartmann’s solution, 5 % glucose diluted 1:2 or 1:1 in normal saline, plasma or 5 % albumin are some of the fluids utilised for
volume augmentation. There's really presently no proof that colloids are better or worse than crystalloids [8].

3. Recovery Phase: As the patient heals so no requirement to confine fluids. The whole volume of fluid can be ingested orally. Therefore, in adolescents with illnesses such as Angina, congestive heart failure, ischemic heart disease, high blood pressure, and diabetes frequent supervision is essential to detect heart failure or pulmonary edema throughout restoration.

PLANT THAT HAVE TRADITIONALLY BEEN USED TO MANAGE DENGUE FEVER

As per a World Health Organization (WHO) information report from December 2008, because to economic and geographical limitations, 80% of the people in several Asian and American nations rely on traditional therapy as their preventative treatment. Herbal compounds have replaced conventional clinical techniques as the primary supplier of test material throughout the production of antiviral medicines. Antiviral activity has been documented in ancient herbal remedies, but some have been employed to cure growing illnesses in both animals and humans [13].

A DESCRIPTION OF CARICA PAPAYA LINN

Carica papaya Linn, a native of the Caricaceae family, is known as papaya in English, Papita in Hindi, and Erandakarkati in Sanskrit. This species originated in tropical America and was introduced to India in the 16th century. Traditionally, leaves were employed to cure a variety of diseases, including malaria, dengue fever, jaundice, immunomodulatory, and antiviral properties. Flavonoids (kaempferol and myricetin), alkaloids (carpaine, pseudocarpaine, dehydrocarpaine I and II), phenolic compounds (ferulic acid, caffeic acid, chlorogenic acid), and cynogenetic chemicals (benzylglucosinolate) are all abundant in mature stalks. Both the leaf and the fruit of Carica papaya Linn are smaller than mature leaves. Containing carotenoids like β-carotene, lycopene, and anthraquinones glycoside, and hence have pharmacological properties including anti-inflammation, hepatoprotective, wound healing, and more recently, anti-hypertensive and anti-tumor effects.
TAXONOMY OF CARICA PAPAYA LINN

Domain: Flowering Plant
Kingdom: Plantae
Sub Kingdom: Tracheobionta
Class: Magnoliopsida
Subclass: Dilleniidae
Superdivision: Spermatophyta
Phylum: Steptophyta
Order: Brassicales
Family: Caricaceae
Genus: Carica

Botanical Name: Carica papaya Linn

GEOGRAPHICAL DISTRIBUTION

The papaya is said to be native to Tropical America, maybe in Southern Mexico and Central America, whereas its exact origins are unknown. Aside from the broad but lesser development in South Africa and Latin America, profitable economic growth currently is mostly in Hawaii, Tropical Africa, the Philippines, India, Malaysia, and Australia. Maharashtra, Bengal, Bihar, Haryana, Punjab, Delhi, Andhra Pradesh, and Uttar Pradesh are among the states in India where papaya is grown [14].

Table 1- Carica papaya Linn's chemical profile in different segments of plants [15-17].

<table>
<thead>
<tr>
<th>Parts</th>
<th>Chemical Constituents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fruit</td>
<td>Protein, fat, carbohydrates, minerals, calcium etc and volatile substances like linalol, benzylisothiocynate, cis and trans 2, 6-dimethyl-3, 6 expoxy-7 octen-2-ol.</td>
</tr>
<tr>
<td>2. Juice</td>
<td>N-butyric acid, n-hexanoic and n-octanoic acids, lipids; myristic, palmitic, stearic, linoleic and oleic acids.</td>
</tr>
<tr>
<td>3. Seed</td>
<td>Fatty acids, crude proteins and fibre, papaya oil, carpaine, benzylglucosinolate, ß-sitosterol, caricin and an enzyme nyrosin.</td>
</tr>
<tr>
<td>4. Root</td>
<td>Arposide and an enzyme myrosin</td>
</tr>
<tr>
<td>5. Leaves</td>
<td>Alkaloids carpain, pseudocarpaine and dehydrocarpaine I and II, vitamin C and E.</td>
</tr>
</tbody>
</table>
Latex

Proteolytic enzymes, papain and chemopapain, glutamine cyclotransferase, chymopapain A,B and C.

INVOLVEMENT OF CARICA PAPAYA LINN IN DENGUE CHEMOTHERAPY

Regarding the ongoing dengue spread, the usage of papaya leaves as a traditional dengue remedy have attracted the wider public curiosity as well as that of the general media. [18]. Papaya is recognised as a “nutrient powerhouse” and was named “The Fruit of Angels” by Christopher Columbus in the 20th era. Papaya leaf infusions have cellular membranes stability capabilities, which inhibit stress-induced plasma membrane breakdown. The tissue stabilising capability of papaya leaf extracts was attributed to flavonoids and other phenolic chemicals, which prevented intracellular bleeding inside the coronary arteries [19]. Antioxidant vitamins and minerals included in papaya leaf may aid to raise haemoglobin, hematocrit, red blood cells, thrombocytes, and overall protein levels.

Papaya leaf contains xanthine oxidase antagonists, which serve to detoxify superoxide free radicals generated throughout dengue virus transmission. The erythrocyte glutathione peroxidase enzyme is increased by papaya leaf extracts, which also modulates lipid peroxidation efficiency in circulatory system. In human lymphocytes, papaya leaf extract generates Th1 cytokines. Throughout a dengue virus transmission, this feature may have immune-stimulating properties. This seems to be initial findings, and more research is needed to identify the chemicals found in papaya leaf extract (PLE) but also elucidate their medicinal significance in the treatment of dengue fever [20].

PUTATIVE MODE OF ACTION OF CARICA PAPAYA LINN EXTRACT IN DENGUE

The papaya plant may have an anti-dengue impact by addressing the thrombocytopenia connected with the disease. In-vitro investigations of Carica papaya Linn leaf extracts revealed membrane stabilising effects. Carica papaya Linn leaf infusions were demonstrated to reduce heat-induced and hypotonicity-induced hemolysis of erythrocytes taken from both healthy and dengue-infected people; this impact was seen at lesser amounts of the extract. As a result, membrane-stabilising damage is predicted in the extracts and prevents blood vessels from stress-induced cell death. This ability might be beneficial in patients suffering from dengue fever, as the leaf extracts may help to avoid platelet rupture. The existence of flavonoids and other phenolic chemicals in papaya foliage, according to the researchers, could explain this impact [21-22].

MEDICAL APPLICATIONS OF THE CARICA PAPAYA PLANT

The Carica papaya plant has been utilised for the therapy of a range of illnesses throughout prehistoric days. Empirical researches have demonstrated that crude extract from the plant, fruit as well as nuts offer a range of therapeutic benefits. Its plants chymopapain and papain extracts can be used to cure digestive problems. Antibacterial properties are found in fruit and nut extracts. The fruit juice and plant extract were shown to have anti-cancer, anti-oxidative,
anti-inflammatory, and anti-bacterial properties, as well as nephroprotective, hepatoprotective, hypoglycemic and antihyperlipidemic advantages, and anti-sickling effects in sickle cell anaemia. The ripe fruit is often used to elicit miscarriage, reduce blood pressure, and also as an aphrodisiac [22]. The DENV transmission, the Aedes aegypti mosquito, has also been demonstrated to exhibit larvicidal effects in the extract of leaves [23].

**PHARMACOLOGICAL EFFECTS OF CARICA PAPAYA LINN IN THE MANAGEMENT OF DENGUE FEVER**

1. **ANTI-INFLAMMATORY ACTION OF CARICA PAPAYA**- There has been studies available to see if papaya leaf extract can help dengue sufferers by increasing their immune system. According to a survey by Sathyapalan et al (2020), oral dosing of 1100 mg of papaya leaf extract in tablet three times a day for five days in humans stimulated as well as prompted the coagulation and inflammation pathways, resulting in the discharge of pro-inflammatory cytokines like TNG-alpha, IFN-gamma, and IL-6, which further inhibited thrombocytopenia in patients [24].

2. **ANTI-VIRAL ACTION OF CARICA PAPAYA**- Carica papaya extract has been shown to boost platelet count while also having antiviral properties. Chinnappan et al (2016) postulated further method of papaya effect on dengue, in which the papaya extract acts directly on platelets, inhibiting platelet stimulation as well as aggregation while also neutralising dengue viral-infected serum [25].

3. **ANTI-THROMBOCYTOPENIA ACTION OF CARICA PAPAYA**- An rise in platelet number was found in the Wistar rat over 72 hours after oral treatment of 150 mg/kg of aqueous extract of papaya leaf, according to Anjum et al (2017). The papaya leaf aqueous extract may boost and generate thrombopoietic stimulatory behavior or promote splenic rigidity to manufacture thrombocytes, according to the research. The occurrence of high flavonoids and phenolic chemicals in the papaya extract, like Kaempferol, trans-ferulic acid, caffeic acid, and myricetin, is thought to be responsible for the enhancement in platelet mobility [26].

In dengue patients, Siddique et al (2014) found that oral ingestion of papaya leaf juice increased thrombocyte numbers considerably compared to control groups over a five-day period. With the exception of the rise in thrombocytes, the findings also indicated that the anti-haemolytic property of papaya may be responsible for the alleviation of dengue manifestations [27]. This suggests that the Carica papaya leaf extract has the potential to sustain platelet number by promoting platelet creation and might be employed in difficult conditions, making it a viable substitute therapy for dengue patients.

4. **LARVICIDAL ACTION OF CARICA PAPAYA LINN**- Amongst the greatest important approaches in reducing the prevalence of C.papaya seed toxicity in Aedes aegypti is vector management. In exclusion environments, aqueous extracts of the seed basal layer and cotyledon are not larvicidal. Throughout the bioassay, moreover, a composition of 17 μg/ml tegument extract and 27 μg/ml cotyledons extract resulted in 100 percent larval death rates [28].
DENGUE-RELATED THROMBOCYTOPENIA WITH CARICA PAPAYA LINN

Carica papaya Linn is an herb that has the ability to treat dengue fever issues. In highly regarded publications, the potential impact of Carica papaya in the management of dengue fever is regularly noted. However, in India, the management of dengue fever with C. papaya has still not been formally acknowledged as a conventional cure in the AYUSH dengue management recommendations [1]. This could be attributable to a shortage of consistency in clinical reports and sufficient confirmation of C.papaya dose specimens used in the management of dengue haemorrhagic fever.

DISCUSSION AND CONCLUSION

C. papaya has antiviral effect towards dengue virus, according to several studies printed in research journals. Researchers can also utilise C. papaya for prophylaxis because it has larvicidal potential against the dengue virus. And, because preventing dengue is preferable to treating it, additional investigation into C.papaya as natural vector prevention is needed. It has been proven to cause a significant rise in platelet number. This might be attributable to its capacity to stabilise membranes. The extract's flavonoids and other phenols are thought to be responsible for the positive benefits.

This image isn't totally apparent, though. Due to the existence of thrombocytopenia, several investigations assumed that the patients had dengue fever but did not verify the diagnosis [21]. This could be owing to the test's massive cost, which is frequently out of reach for people in undeveloped as well as developing countries, where the majority of such investigations were performed. As a result, depending on such case reports, it is impossible to conclude if the extract is also beneficial in further instances of thrombocytopenia. As a result, it is critical to appropriately evaluate the infections and establish beyond a reasonable dispute that the patient is infected with dengue fever [21]. Throughout the occurrence of C.papaya, exploratory studies have been fragmented. Because the plant is made up of many phytoconstituent rather than a specific chemical institution, proper standardisation of the phytoconstituent is needed for optimal confirmation of the plant as well as investigation of the main phytomolecules that could be responsible for its pharmacological interventions [1]. The papaya plant seems to be efficient towards the Aedes mosquito in contrast to its action against the infection. As a result, if proven to be successful, this plant has the potential to reduce dengue on two concentrations: transmission and host. Therefore, until the advantages of the leaf extract are confirmed, it is also vital not to depend only on it and neglect regular dengue therapy. To prove their effectiveness, large-scale randomised clinical trials in dengue-positive individuals are required.

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CONFLICT OF INTEREST

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