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DENGUE FEVER: ROLE OF CARICA PAPAYA L. A REVIEW

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ABSTRACT

Dengue is spreading in urban area with the lightning speed. Dengue is now endemic in more than 100 countries. Dengue disease creates highly complex patho-physiological, economic and ecologic conditions. Approximately 2.5 billion people live in dengue-risk regions with about 100 million new cases each year worldwide. Dengue is a public health issue with an economic burden that is currently challenged for any substantial medicine or vaccination. Considering, the possible positive effects of papaya leaves in thrombocytopenia occurring in dengue fever, this review highlights the understanding of dengue and remedy for it.

KEYWORDS: Dengue, thrombocytopenia, *Carica papaya* L., alkaloids, Aedes aegypti.

INTRODUCTION

The name dengue originated from the Swahili word for “bone-breaking fever” or the word for “the walk of a dandie” in Spanish. The first probable case of dengue fever (DF) was recorded during the Jin Dynasty (265–420 AD) in China. The first recognized epidemics occurred almost simultaneously in Asia, Africa and North America in the 1780s, shortly after the identification and naming of the disease in 1779 by Benjamin Rosh (Cecilia D 2014).

Dengue is an acute viral infection with potentially fatal complications. Dengue viruses (DV) belong to family *Flaviviridae* and there are four serotypes of the virus (Benazir, 2015; Soonwera M 2015). It is transmitted mainly by *Aedes aegypti* and *Aedes Albopictus.*

mosquito. Aedes mosquitoes are small and black with white markings on the body and legs. Female mosquitoes need blood from biting humans or animals to produce live eggs. It takes 2–3 days for egg development. The principal vector of dengue (*Aedes aegypti*) has adapted well to the urban environment and always breeds in stagnant containers. Eggs need moist conditions, and mature in 24–72 hrs. Mosquito bites are the only route of virus spread. The transmission of virus is often from human to human through domestic mosquitoes. An outbreak starts after a mosquito sucks the blood of a patient with dengue fever/ dengue hemorrhagic fever. After being transmitted to a new human host by infected mosquitoes, the virus replicates in the lymph nodes and spreads through the lymph and blood to other tissues. All four serotypes can cause full spectrum of disease from a subclinical infection to a mild self- limiting disease. The dengue fever (DF) is a severe disease that may be fatal due to dengue hemorrhagic fever or dengue shock syndrome. According to WHO (1997) classification dengue was divided into undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever. The WHO 2009 classification divides dengue fever into two groups: uncomplicated and severe, yet the 1997 WHO classification is still widely used.

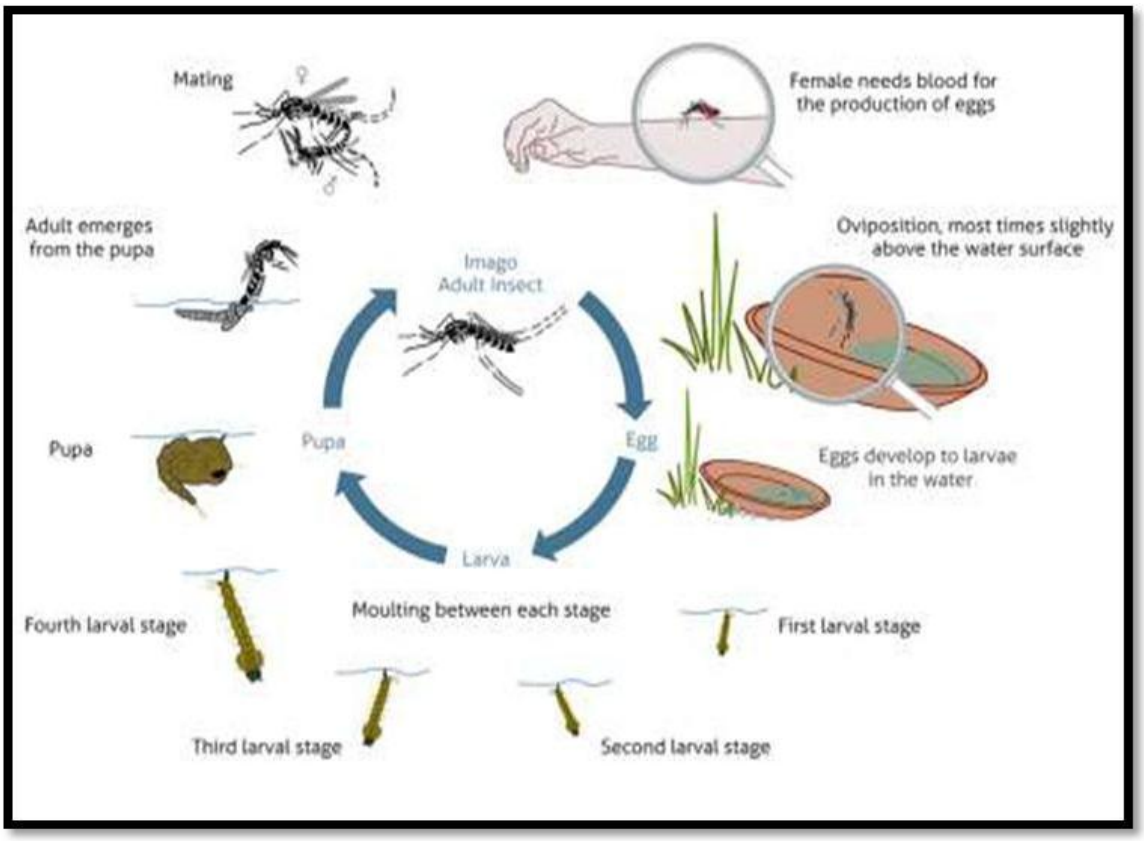
Virology

Dengue virus (DENV) is a positive- strand RNA virus of the family Flaviviridae, genus Flavivirus. It exists as four closely related but anti-genetically distinct serotypes (DENV-1, -2, -3, and -4), all of which have *Aedes aegypti* mosquitoes as their primary vector, with *A. albopictus* as a secondary vector.

The virion comprises a spherical particle, 40–50 nm in diameter, with a lipopolysaccharide envelope. The positive single-strand RNA genome, which is approximately 11 kb in length, has a single open reading frame. Reading frame codes for three structural and seven structural proteins. Structural proteins are capsid, membrane and envelope glycoproteins. Non-structural proteins are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5.

Important biological properties of dengue viruses, including receptor binding, hemagglutination of erythrocytes and the induction of neutralizing antibodies and the protective immune response, are associated with the E glycoprotein.

Life cycle *aedes albopictus* mosquito



Pathophysiology of dengue fever

Dengue infection is caused by bites of the female *Aedes aegypti* mosquito carrying Flavivirus. After a person is bitten, the virus incubation period varies between 3 and 14 days, after which the person may experience early symptoms such as fever, headache, rash, nausea, and joint and musculoskeletal pain. This classic DF records temperatures between 39 and 40^0C and usually last for 5–7 days. During this period, the virus may get into the peripheral bloodstream and, if left untreated, can damage blood vessels and lymph nodes resulting in dengue hemorrhagic fever with symptoms such as bleeding from the nose, gums or under the skin. Dengue hemorrhagic fever patients also have difficulty in breathing and severe development can lead to dengue shock syndrome. Dengue shock syndrome can result in death if proper treatment is not provided.

World-wide frequency

Some 1.8 billion people are at risk for dengue worldwide which accounts at more than 70%. An estimated 50 million dengue infections occur worldwide annually. An estimated 50, 00, 00 people with DHF require hospitalization each year. A very large proportion (approximately 90%) of them are children aged less than five years, and about 2.5% of those

affected die. Dengue and DHF is endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The South-East Asia and Western Pacific regions are the most seriously affected. Epidemics of dengue are increasing in frequency. During epidemics, infection rates among those who have not been previously exposed to the virus are often 40% to 50% but can also reach 80% to 90%. Seasonal variation is also observed. *Aedes (Stegomyia) aegypti* is the primary epidemic vector. Primarily an urban disease, dengue and DHF are now spreading to rural areas worldwide. Imported cases are common. Co-circulation of multiple serotypes/genotypes is evident. (WHO 2011, 2014).

Treatment

Allopathy- benefits and hazards: There is no specific therapy for dengue infections. Good supportive care may be life-saving, but ultimately initiatives aimed at vector control and prevention of mosquito bites may provide the greatest benefit (Singhi S et al 2007).

Management of dengue fever is symptomatic and supportive. Bed rest is advisable during the acute phase. Use cold/tepid sponging to keep temperature below 38.5° C. Antipyretics may be used to lower the body temperature. Aspirin/NSAIDS like Ibuprofen, etc should be avoided since it may cause gastritis, vomiting, acidosis, platelet dysfunction and severe bleeding.

Oral fluid and electrolyte therapy is recommended for patients with excessive sweating or vomiting. Patients should be monitored for 24 to 48 hours after they become a febrile for development of complications (Dengue national guide lines 2015).

Till now there is no licensed vaccine available against dengue viral infection. Several trials are ongoing in the world for the development of tetravalent dengue vaccine. So far phase III trials of a recombinant, live attenuated tetravalent dengue vaccine (CYD-TDV) has completed in Five Asian countries in children which may be promising in preventing dengue infection in near future (Dengue national guide lines 2015).

Effective vector control measures are critical to achieve and sustain reduction of morbidity attributable to dengue. Preventive and vector control interventions aim to reduce dengue transmission, thereby decreasing the incidence of the infection and preventing outbreaks of the disease. Attempt to identify potential antiviral for the treatment of dengue is a global

challenge as all four serotypes are frequently undergoing mutations (WHO 2012).

Studies on herbal medicinal products for platelet augmentation are consistently increasing due to the limited supportive treatments available for thrombocytopenic disorders.

Plants species traditionally used to treat dengue fever

According to a World Health Organization (WHO) 80 % of the population in some Asian and African countries depends on traditional medicine as their primary health care due to economic and geographical constraints. Natural products have become the main source of test material in the development of antiviral drugs based on traditional medical practices. Traditional medicinal plants have been reported to have antiviral activity, and some have been used to treat viral infections in animals and humans. In the Philippines, *Euphorbia hirta*, known locally as tawa- tawa, is used in folk medicine to cure dengue fever by people in rural areas (Naresh Kumar et al 2015) *Andropogon citratum* oil is put in candles and lanterns that can be burnt to repel mosquitoes. Its mosquito repellent qualities have been verified by research, including effectiveness in repelling *Aedes aegypti* (Gadhwal A et al 2016; Ibrahim Jet al, 1998). Also, there are many undocumented uses of *Euphorbia hirta* for platelet augmentation probably owing to its current prominence in the Philippines as an alternative supportive treatment for dengue hemorrhagic fever. This claim is verified by the published report (Johnson et al2010) which demonstrated that there is a significant increase in platelet counts and a decrease in bleeding and clotting times in ethanol- induced thrombocytopenic rats after administration of *Euphorbia hirta* decoction for 14 days. These folkure medicines need a careful review of other evidences regarding the use of *Euphorbia hirta.*

The *in vitro* and *in vivo* inhibitory potential of aqueous extract of *Azidarachta indica* (neem) leaves on the replication of virus was evaluated by Parida et al 2002.

Turmerone obtained from volatile oil of *Curcuma longa* give 100% mosquitocidal activity against *Aedes aegypti* (Roth et al 1998).

The water decoction of leaves from *Euphorbia hirta*, locally known as gatas– gatas, is used in the Philippines as a folk medicine to treat DF.

Efficacy of these species is in following order: *P. longum> P. armentosum Roxb> P ribesoides Wall*. This study conclude that Pepper plant possess activity against *Aedes aegypti* (*U Chaithong* et al *2006*).

Psidium guava is an evergreen shrub or small tree indigenous to Mexico, the Caribbean and Central and South America, has been tested *in vitro* and showed to inhibit the growth of dengue- virus. Water boiled with guava leaves has been used to avoid bleeding in dengue hemorrhagic fever, and to elevate platelet counts. *P. guava* ripe fruit or juice has healing properties in cases of DF by improving the declining levels of platelets (Abouthealt-h.com/dengue-fever-medicine 2011).

*Carica papaya, Ipomea batatas g*reen and violet variety, *Alternanthera Sessilis*, and *Euphorbia hirta* have significant platelet augmentation activity. This is suggestive these plants extracts can be used as supportive treatment for thrombocytopenic disorders and dengue hemorrhagic fever which may be an alternative to platelet transfusions (Allorado et al 2010). The investigation on these plant showed 93.1777% increase in platelet count which corroborated the previous investigation on its effect on blood components. It is recommended that more investigations can be conducted on *Ipomea batatas* and *Alternanthera Sessilis* to further support the cause (Johnson et al *2010*).

Several Ayurvedic herbs have been shown to be effective in treatment of dengue fever.

They include

Amaltas, Chirayata, Datura, Hara dhania, Hermal, Kanghi, Giloy or Amrita.

Carica papaya

India is a country having a wide medicinal history as “Ayurveda”. Many plants and their parts have been explored and exploited for their medicinal importance. Since then, man has been showing interest in the medicinal use of plants. As new discovery and inventions came up, technology grew up to explore the old ideas in a new way.

Carica papaya L. is not an exception. Its leaf extract is now-a-days gaining popularity in many aspects. Considering the folk treatment, papaya has shown remarkably admirable results in many diseases and disorders. The plant is weak, usually un-branched and having soft stem and can grow up to 20m high. *Carica papaya L.* plant bears cluster of large and long stalked leaves (V. Yogiraj 2014). Papaya is known as "A powerhouse of nutrients" and was reputably called the "The fruit of Angels" by Christopher Columbus in the 20th century.

Botanical classification of papaya plant: (USDA)

Kingdom : Plantae
Subkingdom : Tracheobionta
Super division: Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Dilleniidae
Order : Violales
Family : Caricaceae
Genus : Carica L.
Species : papaya L.

Part of plant and its constituents: (The wealth of India 1992; Kirtikar KR 1998; Indian Medicinal Plants 2005; Krishna KL 2008):

Part	Constituent
Fruit	Protein, fat, fibre, carbohydrates, minerals (calcium, phosphorous, iron), Vitamin (vitamin C, thiamine, riboflavin, niacin, and carotene), amino acids, citric and malic acids (green fruits), volatile compounds (linalool, benzyl iso-thiocyanate, cis and trans 2, 6- dimethyl-3,6 epoxy-7 octen-2-ol), Alkaloid (carpaine, benzyl- β -D glucoside, 2-phenylethyl -β-D-glucoside, 4-hydroxy- phenyl-2 ethyl-β-D-glucoside and four isomeric malonate benzyl-β-D-glucosides).
Juice	N-butyric, n-hexanoic and n-octanoic acids, lipids; myristic, palmitic, stearic, linoleic, linolenic and cis - vaccenic and oleic acids.
Bark	B-Sitosterol, glucose, fructose, sucrose, galactose and xylitol
Seed	Fatty acids, crude protein, crude fibres, papaya oil, alkaloid Carpaine, some volatile compounds benzyl iso-thiocyanate, benzyl glucosinolate, glucotropacolin, benzyl thiourea, hentriacontane, β- sitosterol, caricin and myrosin
Root	Carposide and an enzyme myrosin
Leaf	Alkaloids carpain, pseudocarpain and dehydrocarpaine I and II, choline, carposide,vitamin C and E
Latex	Proteolytic enzymes, papain and chemopapain, glutamine cyclotransferase, chymopapains A, B and C, peptidase A and B

The screening of leaves at all three stages (green, yellow and brown) shows richness in vitamins like thiamine, riboflavin, ascorbic acid. Similarly, minerals like calcium, magnesium, sodium, potassium, manganese and iron were also detected at considerable amount. The Phytochemical analysis of the leaves showed that the leaves contained saponins, cardiac glycosides, and alkaloids (Ayoola PB 2010). *Carica papaya* leaves contain various phytoconstituents like saponins, tannins, cardiac glycosides and alkaloids. The alkaloids present include carpaine, pseudo-carpaine and dehydro-carpaine I and II (Patil S

2013). The fruit, seed and leaf were found to be rich in proteins. All the three parts were rich not only in minerals (calcium, magnesium, phosphorous, and iron) but also vitamins (vitamin C, niacin, thiamine, riboflavin, and beta-carotene) (Godson EN2012).

Proximate analysis of the plants showed that all the macronutrients were present, with carbohydrate being the most abundant in *Carica papaya*. Vitamins A, C, B_{12} and Folic acid were present but are void of Vitamin E. Papaya leaf extract contained only magnesium, the other metals tested were not detected (Begum M 2014). The study of the *Carica papaya* leaves of semi-arid zone of Kutch region showed that it is rich in elements like calcium, magnesium, sodium, potassium, chlorine, and lithium with comparison to other reported analysis of other regions. This is in contradiction to above analysis due to nature of soil here (Vyas S 2014). *Carica papaya* leaf has been used traditionally in the treatment of Dengue. The leaf has been investigated for its potential against DF. Anti-dengue virus activity, papaya leaf extract being a strong stimulant of IL-6 and SCF might help to improve thrombocytopenic conditions of the infected patients. Papaya leaves extract, rich in papain, was shown to improve thrombocyte (platelet) count in dengue patients (Aziz Jet al, 2015). The qualitative phytochemical analysis reveals that except steroids and tannins all the phytochemical including glycosides, alkaloids, saponins, flavonoids, proteins are present in leaf of papaya (Sherwani SK 2014). Papaya leaf contains anti-oxidant vitamins and minerals which may help to increase the hemoglobin, hematocrit, Red blood cells, thrombocytes and total protein contents (Halim et al2011.) A study has reported membrane stabilizing properties of *Carica papaya*L. leaf extracts even in lower concentration *in vitro* studies by inhibiting heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue infection. 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 theory postulates that this effect could be due to the presence of flavonoids and other phenolic compounds inthe papaya leaves (Mathews A 2016). Papaya leaf extracts possess biological membrane stabilization properties preventing stress-induced destruction of the plasma membrane. Flavonoids and other phenolic compounds present in papaya leaf extracts were responsible for the observed membrane stabilizing property and thereby prevent the internal bleeding in the blood vessels (Ranasinghe et al 2012).

Vinca-alkaloids have been proven effective against anti-platelet macrophages in patients suffering from Idiopathic Thrombocytopenic Purpura (ITP) (Ahn Y et al1998). Vitamin C may act as anti-oxidant to scavenge the oxygen radical (superoxide, hydroxyl, peroxyl) Sulphur radicals and nitrogen - oxygen radicals (Sebastian et al2003). Magnesium ions in papaya leaves are found to improve erythrocyte hydration. Sodium ions help in maintaining electrolyte balance and prevent hypo-natremia during dengue infection (Jutrat et al2005). Calcium ions helps in the proliferation of lymphocyte cells, play key role in platelet aggregation when combine with Vitamin D and prevents thrombocytopenia (Cabrera-Cortina et al, 2008). Vitamin B_{12} helps in maintaining the normal count of thrombocytes and helps to fight against thrombocytopenia (Betty et al, 2009). A recent study showed that flavonoids, present in *Carica papaya* inhibits NS2B-NS3 protease and thereby prevent the DEN-2 Virus assembly (Senthilvel et al 2013; Subenthiran S et al, 2013 investigated the platelet increasing property of *Carica papaya* leaves juice (CPLJ) in patients with dengue fever (DF). This was clearly demonstrated by the significant increase in the mean platelet count after 40 hours and 48 hours of juice consumption. A suspension of powdered crude *Carica papaya* leaves in palm oil when administered to experimental animal show the consistent rise of the thrombocyte counts in the treated group. The effect of papaya leaf formulations was higher and significant indicating a potential in the treatment of thrombocytopenic purpura (Kathiresan et al 2009). The results of experiments of Zunjar V et al, 2016 suggested that *Carica papaya* leaves decoction has very good anti- thrombocytopenic properties. It is predicted in the study that anti-thrombocytopenic property of *Carica papaya* leaves may be due to carpaine. Additionally, no visible toxicity or any adverse effect was observed in animals treated with carpaine.

The study reiterated that the mature leaf *Carica papaya* concentrate (MLCC), irrespective of whether obtained from mature or immature leaves of *Carica papaya*, has the potential to be developed as a plant based therapeutic agent for thrombocytopenia. It was also observed that the MLCC prepared by the mature leaves of *Carica papaya* can be orally administered, is safe (non-toxic) for a period of 3 days and is orally active, effectively increasing platelet, WBC and RBC counts in normal (non-thrombocytopenic) and thrombocytopenic rats (Gamulle A 2012).

Multiple mechanisms mediated by many active principles in papaya leaf juice may be responsible for increasing the blood cell counts. Papaya leaves contain active compounds

papain, chymopapain, alkaloids, flavonoids, benzyl-glucos-inolate and tannins. These compounds stimulate and / or improve the megakaryocytes to produce sufficient numbers of platelets to maintain a suitable platelet count in mammals, in particular during chemotherapy Enzyme papain and chymo- papain activate enzyme caspase (protease), which in turn regulates pro-platelet, thus this protein digestion increases platelet count. Tannins are large poly-phenolic compounds containing sufficient hydroxyls and other groups (such as carboxyl) to form strong complexes with proteins and other macromolecules. On retraction events to release individual pro-platelets. The complex – forming properties of tannins may contribute to the positive effects on platelet count in blood. Papaya leaf juice prevents reversible thrombocytopenia induced by carboplatin in a dose dependent manner. There is no difference between male and female plants in this respect (Tahir N et al2014).

The RNA was extracted from the blood of the experimental patients and gene expression of two genes, namely, the ALOX 12 and the PTAFR were conducted. There was a 15-fold increase in the ALOX 12 gene activity among the patients which is known to be associated with increased megakaryocyte production. Also, ALOX 12 is linked with conversion of the megakaryocyte to platelets through 12- HETE mediated pathway which in turn leads to increased platelet production. The alkaloids present include carpaine, pseudo- carpaine and dehydro-carpaine I and II. These constituents can act on the bone marrow, prevent its destruction and enhance its ability to produce platelets. Moreover, it can also prevent platelet destruction in the blood and thereby increase the life of the platelet in circulation.

CONCLUSION

Papaya leaf has a great potential to fight against dengue. The review implies that major research is done on crude extract of various solvents basically water and methanol. Various researches suggest various components in the papaya leaf that promote the rise of platelet count. The probable active components include enzymes such aspapain, chymopapain, caspase, alkaloids like carpaine, pseudo- carpaine and dehydro-carpaine I and II, flavonoids, benzyl-glucos-inolate and tannins, Vitamin B_{12}, C, D, minerals such as calcium, magnesium, potassium, sodium. Yet no firm composition responsible to resist the disease is presented. The work in this region is needed in order to explore the exact composition of bio-components responsible to raise the platelet count and counter act dengue.

The isolation and purification of the compounds responsible for platelet augmentation in the plant would play an important role in drug designing for the disease. Also study in elucidating

the potential activity of the most probable compound of plants extracts, in mechanism of action to fight dengue virus at every stage of lifecycle is needed to be established. In this way building immunity towards natural production of platelet instead of transfer can be booster against fight for dengue. Hence, the papaya leaf may be a fruitful for research leading to the development of herbal therapeutic agent for thrombocytopenia and associated inflammatory disease conditions, manifested in disease such as dengue. There is also a need to generate awareness and preventive measures among the people in order to control the disease. Combined efforts of the health care industries, governing bodies and efforts at individual level would help to handle the spread of dengue.

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