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THERAPEUTIC APPROACH FOR DENGUE USING MEDICINAL PLANT *CARICA PAPAYA LINN*

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ABSTRACT

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. Dengue is caused by single stranded RNA virus, belonging to family Flaviviridae having four distinct serotypes DENV-1, DENV-2, DENV-3 and DENV-4 respectively, that spread by the bite of infected *Aedes aegypti* mosquito. 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 from the family Caricaceae could help to increase the platelet levels in these patients. The present article reviews on the medicinal plant *Carica papaya* available for its anti-dengue activity. Some of the studies and case reports published in literature raise the possibility that this treatment could be an important option in the future. Further large-scale studies could establish the usefulness or ineffectiveness of this natural product in the treatment of dengue.

KEYWORDS: Medicinal plant, *Carica papaya*, Dengue, Dengue treatment, Thrombocytopenia.

INTRODUCTION

Dengue is an acute viral infection with potential fatal complications. Dengue viruses (DV) belong to family Flaviviridae and there are four serotypes of the virus referred to as DV-1, DV-2, DV-3 and DV-4. 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. It is transmitted mainly by *Aedes aegypti* mosquito and also by Ae. *albopictus*.

All four serotypes can cause 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 haemorrhagic 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 haemorrhagic fever (DHF).[1]

HISTORY

Dengue virus was isolated in Japan in 1943 by inoculation of serum of patients in suckling mice and at Calcutta (now Kolkata) in 1944 from serum samples of US soldiers. The first epidemic of clinical dengue-like illness was recorded in Madras (now Chennai) in 1780 and the first virologically proved epidemic of DF in India occurred in Calcutta and Eastern Coast of India in 1963-1964. The first major epidemic of the DHF occurred in 1953-1954 in Philippines followed by a quick global spread of epidemics of DF/DHF. The DHF started simmering in various parts of India since 1988. The first major wide spread epidemics of DHF/DSS occurred in India in 1996 involving areas around Delhi and Lucknow and then it spread to all over the country.[1]

DENGUE FEVER/HAEMORRHAGIC FEVER/SHOCK SYNDROME

In most cases asymptomatic or relatively mild disease follows infection with dengue virus. However, to take into account the increasing number of clinical cases, the World Health Organization (WHO) produced guidelines[2] in which they identified the clinical pictures resulting from infection with dengue virus. The first, known as dengue fever (DF), is characterized by an abrupt onset of fever accompanied by frontal headache and retro orbital pain, followed by a variety of possible clinical symptoms such as myalgia, arthralgia, vomiting and weakness. A generalized maculopapular rash appears one or two days after fever defervescence. Minor haemorrhagic manifestations such as petechiae may be observed in some patients. DF is generally self-limiting and rarely fatal. Most patients recover without complications around ten days after the onset of illness. The second clinical picture, dengue haemorrhagic fever (DHF), is a more severe form of the disease and occurs in up to 5% of dengue cases. It is initially characterized by the same variety of clinical symptoms as are seen in DF. The critical period in DHF starts at the moment of defervescence but haemorrhagic manifestations may occur 24 hours earlier. A positive tourniquet test indicates that the patient has increased capillary fragility. Petechiae, bleeding at venepuncture sites, epistaxis, gum

bleeding, and haematemesis may also be observed. High fever, haemorrhagic manifestations, thrombocytopenia (platelet count 100 000/mm3 or less), and haemoconcentration (>20% difference) characterize DHF. Plasma leakage is the most significant pathophysiological event in determining the severity of the disease. Signs of circulatory failure such as irritability, cold clammy extremities, flushed face, and restlessness may be observed. This crisis usually persists for 24–36 hours. Patients progressing to shock (dengue shock syndrome -DSS) show intense abdominal pain or tenderness, persistent vomiting, weak pulse, and hypotension. If increased vascular permeability progresses to vascular collapse the outcome is usually fatal as a result of irreversible DSS. In addition to DF, DHF and DSS, it is now recognized that other clinical manifestations can be associated with infection by dengue virus, for example, encephalitis, myocarditis, hepatitis, cholecystitis, myelitis, and acute colitis.[3-8]

PATHOPHYSIOLOGY OF DENGUE FEVER[9]

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^{o}C and usually lasts 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 DHF with symptoms such as bleeding from the nose, gums or under the skin. DHF patients also have difficulty in breathing and severe development can lead to DSS. DSS can result in death if proper treatment is not provided. *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 (*Ae. aegypti*) has adapted well to the urban environment and always breeds in stagnant containers. Eggs need moist conditions, and mature in 24–72 h. Mosquito bites are the only route of DENV spread. The transmission of DENV is often from human to human through domestic mosquitoes. An outbreak starts after a mosquito sucks the blood of a patient with DF/ DHF (Fig 1). 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. To identify a potential antiviral treatment for DENV, it is necessary to understand the life cycle of the virus. The dengue virion is a small particle with a lipoprotein envelope and an icosahedral nucleocapsid containing a positive single-stranded RNA genome. Virus

infection of the cell begins with binding to the host cell surface. It enters the cell by receptor-mediated endocytosis, with the cell membrane forming a sac-like structure known as an endosome. In the endosome, the virus penetrates deep into the cell until the endosome membrane acquires a negative charge, which allows it to fuse with the endosomal membrane to open a port for release of genetic material. At this point, the virus in the cell fluid starts to reproduce. Changes in the acidity of the secretory pathway during this viral journey travel play an important role in its maturation (Fig. 2).

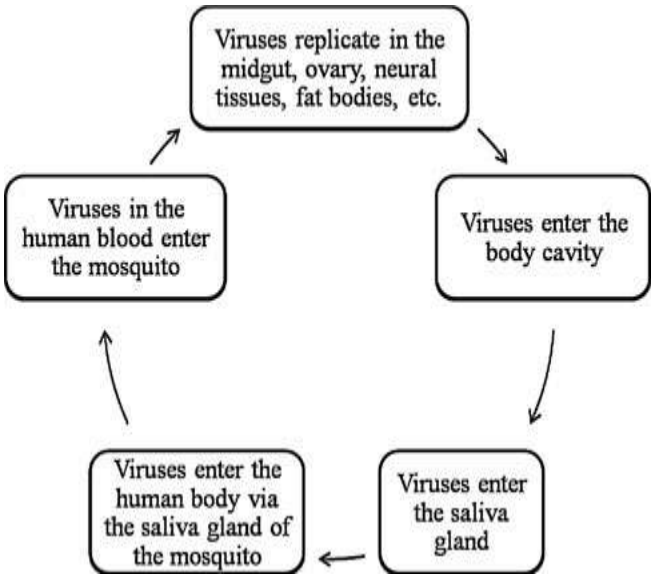

Fig. 1 Dengue virus transmission cycle.

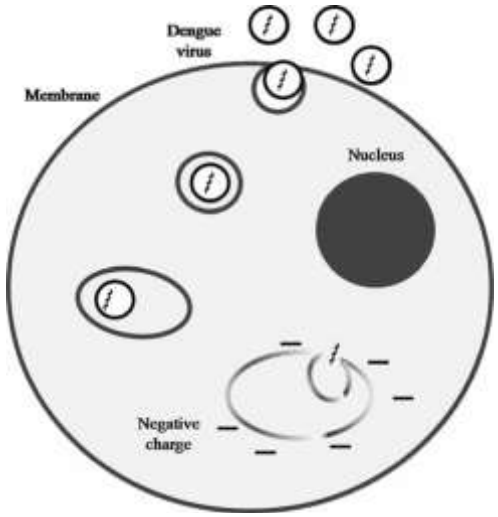

Fig. 2 Dengue virus infection cycle in cells.

THROMBOCYTOPENIA IN DENGUE

Thrombocytopenia has always been one of the criteria used by WHO guidelines as a potential indicator of clinical severity. In the most recent 2009 WHO guidelines, the definitions generally describe a rapid decline in platelet count or a platelet count less than 150,000 per microliter of blood. The mechanisms involved in thrombocytopenia and bleeding during DENV infection are not fully understood. Several hypotheses have been suggested to elucidate the mechanism involved. In this context, DENV could directly or indirectly affect bone marrow progenitor cells by inhibiting their function to reduce the proliferative capacity of hematopoietic cells. Indeed, there is evidence that DENV can induce bone marrow hypoplasia during the acute phase of the disease. Besides platelets counts, the functional disruption of these cells is associated with a significant deregulation of the plasma kinin system and the immunopathogenesis of dengue. In addition, DENV infection induces platelet consumption due to disseminated intravascular coagulation (DIC), platelet destruction due to increased apoptosis, lysis by the complement system and by the involvement of antiplatelet antibodies.[10]

PLANTS TRADITIONALLY USED TO TREAT DENGUE

According to a World Health Organization (WHO) fact sheet dated December 2008, 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 medicines are based on knowledge, experience and practices based on indigenous cultural beliefs and knowledge, and are used to maintain health, prevent, treat and diagnose physical or mental illness. Traditional medicinal plants have been reported to have antiviral activity and some have been used to treat viral infections in animals and humans.[9]

MEDICINAL PLANT - *CARICA PAPAYA*

The evolution of *Carica Papaya* Leaf Extract (Caripill) 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.

Literature search has found several human and animal studies been conducted where extract of *Carica papaya* leaf was used for treating thrombocytopenia associated with dengue. The results of these studies have been encouraging with platelets showing significant rising trend.[11]

BOTANICAL CLASSIFICATION

Domain	:	Flowering plant
Kingdom	:	Plantae
Sub Kingdom	:	Tracheobionta
Class	:	Magnoliopsida
Subclass	:	Dilleniidae
Superdivision	:	Spermatophyta
Phyllum	:	Steptophyta
Order	:	Brassicales
Family	:	Caricaceae
Genus	:	*Carica*
Botanical Name	:	*Carica papaya* Linn.[12]

CONSTITUENTS OF *CARICA PAPAYA* LEAVES

Carica papaya Linn belonging to family Caricaceae is commonly known as papaya in English, Papita in Hindi and Erandakarkati in Sanskrit. The plant is native to tropical America and was introduced to India in 16th century. The plant is recognised by its weak and usually unbranched soft stem yielding copious white latex and crowded by a terminal cluster of large and long stalked leaves, is rapidly growing and can grow up to 20m tall. (Fig 3, fig 4) Traditionally leaves have been used for treatment of a wide range of ailments, like in treatment of malaria, dengue, jaundice, immunomodulatory and antiviral activity. Young leaves are rich in flavonoids (kaempferol and myricetin), alkaloids (carpaine, pseudocarpaine, dehydrocarpaine I and II), phenolic compounds (ferulic acid, caffeic acid, chlorogenic acid), the cynogenetic compounds (benzylglucosinolate) found in leaves. Both leaf and fruit of the *Carica papaya* Linn possess carotenoids namely β- carotene, lycopene, anthraquinones glycoside, as compared to matured leaves and hence possess medicinal properties like anti-

inflammatory hypoglycaemic, anti-fertility, abortifacient, hepatoprotective, wound healing, recently its antihypertensive and antitumor activities have also been established.[13]

Fig 3: *Carica papaya* plant.

Fig 4: Fresh *Carica papaya* leaf.

GEOGRAPHICAL DISTRIBUTION

Though the exact area of origin is unknown, the papaya is believed native to Tropical America, perhaps in Southern Mexico and neighbouring Central America. Successful commercial production today is primarily in Hawaii, Tropical Africa, the Philippines, India, Ceylon, Malaysia and Australia, apart from the widespread but smaller scale production in South Africa, and Latin America. In India, papaya is cultivated in Maharashtra, Bengal, Bihar, Haryana, Punjab, Delhi, Andhra Pradesh and Uttar Pradesh.[14]

ROLE OF *CARICA PAPAYA* IN DENGUE TREATMENT

With the recent dengue outbreak, the use of papaya leaves as natural cure for dengue has received much interest among the public, and in the lay press. Being easily available and affordable, the use of papaya leaves occurs indiscriminately.[15] Various databases were electronically searched for articles focusing on dengue treatment using *Carica papaya* leaf extracts, Followed by which only full text articles were included in this review.

Papaya is known as "A powerhouse of nutrients" and was reputably called the "The fruit of Angels" by Christopher Columbus in the 20th century. 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.[16] A recent study showed that flavonoids present in carica papaya inhibit NS2B-NS3 protease and there by prevent the DEN-2 Virus assembly.[17] Recent studies have also shown that papaya leaf juice significantly increases the platelet count.[18,19] Papaya leaf contains anti-oxidant vitamins and minerals which may help to increase the haemoglobin, hematocrit, Red blood cells, thrombocytes and total protein contents.[20, 21]

Vitamin A keeps bile production normal and Vitamin B9 helps in blood DNA synthesis, cell growth and development. Vitamin B12 helps in maintaining the normal count of thrombocytes and helps to fight against thrombocytopenia.[20, 22] Vitamin C may act as anti-oxidant to scavenge the oxygen radicals (Superoxide, hydroxyl, peroxyl) sulphur radicals and nitrogen - oxygen radicals.[23] Minerals present in papaya leaves play an important role in fighting DENV infection.

Calcium ions helps in the proliferation of lymphocyte cells, play key role in platelet aggregation when combine with Vitamin D and prevents thrombocytopenia.[24, 25] Magnesium ions improve erythrocyte hydration. Sodium ions help in maintaining electrolyte balance and prevent hyponatremia during dengue infection.[26] Potassium ions maintain body potassium level and help to prevent acute hypokalaemic quadriparesis during dengue infection.[27, 28, 29] Manganese ions help in reducing inflammation and joint pains during dengue infection. Iron is the important oxygen carrier material which helps in red blood cell formation. Xanthine oxidase inhibitors present in papaya leaf helps to scavenge superoxide free radicals produced during dengue virus infection. The papaya leaf extracts increases the erythrocyte glutathione perioxidase enzyme and controls the lipid peroxidation activity in blood plasma. Papaya leaf extract induces Th1 type of cytokine in human lymphocytes. This property may do immune stimulating activity during dengue virus infection. This is only a preliminary data and further studies are necessary for identification of the compounds present in papaya leaf extract (PLE) and exploring their therapeutic role in curing dengue infection.[30]

Preliminary Research On Carica Papaya And Dengue Treatment

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 ≤100,000/μL. 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 50 g 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 40 h when compared to the counts 8 h 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.[18]

A study in the journal of Medicinal and Aromatic Plants reported an increase in platelet counts in five patients within 24 h 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 24 h has not been described.[31]

Treatment of dengue using *C. papaya* leaf extract in humans has been reported in very few studies conducted in Asia. 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 8 h. 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 24 h of treatment with the extract.[32]

A study conducted in Indonesia used *C. papaya* L. 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/μL 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. However, 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.[33]

A report in a study conducted in single case showed increase in the initial platelet count of 73×103/µL to 137×103/µL after on three days administration of *C. Papaya* leaf extract twice daily without any medical management. The study also noticed positive effect on in WBC count.[34]

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 12 h 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.[35]

A study was conducted formulating a ready to serve beverage incorporated with papaya leaves and guava against Dengue fever. Papaya leaves contain various nutrients and phytoconstituents like saponins, tannins, cardiac glycosides and alkaloids. These constituents can act on the bone marrow, prevent its destruction and enhance its ability to produce platelets. The guava fruits are rich in vitamin C (ascorbic acid) content. It can be concluded that the papaya leaves induce the rapid increase in platelet count and immunity. It may play a valuable role in the management of dengue fever in the future.[36]

A study investigating the platelet increasing property of *Carica papaya* leaves juice (CPLJ) in patients with dengue fever (DF) was conducted in which an open labeled randomized controlled trial was carried out on 228 patients with DF and dengue hemorrhagic fever (DHF). Approximately half the patients received the juice, for 3 consecutive days while the others remained as controls and received the standard management. Their full blood count was monitored 8 hours for 48 hours. Gene expression studies were conducted on the ALOX 12 and PTAFR genes. The mean increase in platelet counts were compared in both groups using repeated measure ANCOVA. There was a significant increase in mean platelet count observed in the intervention group but not in the control group 40 hours since the first dose of CPLJ. Comparison of mean platelet count between intervention and control group showed that mean platelet count in intervention group was significantly higher than control group after 40 and 48 hours of admission. The ALOX 12 (FC=15.00) and PTAFR (FC=13.42) genes were highly expressed among those on the juice. It was concluded that CPLJ does significantly increase the platelet count in patients with DF and DHF.[18]

A study was conducted investigating the management of thrombocytopenia by drugs and blood products, both of which are costly. Conversely, Sri Lankan traditional medicine use mature leaf concentrate of *Carica papaya* to treat this condition. This claim was scientifically validated. Adult wistar rats (N=6/group) with Hydroxyurea – induced thrombocytopenia (model established for the first time), were orally administered, once daily on 3 consecutive days with three doses of fresh mature leaf concentrate of *Carica papaya* (0.18, 0.36 and 0.72 ml/100g), while controls received water. Standard protocols were used to establish their platelet, WBC and RBC counts. Effects of mature leaf concentrate of *Carica papaya* on carrageenan induced edema in rats, on rat erythrocyte membrane stabilization and on acetic acidinduced vascular permeability in mice, as well as acute toxicity studies were conducted using standard methodology. High doses of mature leaf concentrate of *Carica papaya* in thrombocytopenic rats significantly ($P<0.05$) increased platelets by 76.5%, WBC by 30.51% and RBCs by 9.08%, when compared with controls. High dose of mature leaf concentrate of *Carica papaya* also significantly ($P<0.5$) inhibited carrageenan induced rat paw edema and impaired in vivo vascular permeability in mice (by 82%), while inducing maximum (10.11%) membrane membrane stabilizing activity of rat RBCs at 8mg/ml of mature leaf concentrate of *Carica papaya*, suggestive of effective anti-inflammatory activity. Administration of high dose of mature leaf concentrate of *Carica papaya* on 3 consecutive days neither provoked overt signs of toxicity nor stress, where hepatotoxicity, renotoxicity, hematotoxicity and neurotoxicity were also ruled out. Thus freshly prepared mature leaf concentrate of *Carica papaya* is orally active, effectively increases rat platelet, WBC and RBC counts with no acute toxicity, and possesses potent anti-inflammatory activity, that overly justify claims of traditional medicine.[37]

CONCLUSION

From the various reports published in scientific literature, it appears that the administration of *C. papaya* L. leaf extract does have beneficial properties in dengue. It has been shown to bring about 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. Further experimental studies and clinical trials need to be carried out to establish the effectiveness of papaya leaf juice in this aspect which would definitely prove beneficial to the mankind at large owing to the cost effectiveness and easy availability of papaya plant. Papaya extract no doubt offers a cheap

and possibly effective treatment for dengue. Large scale randomized clinical trials in dengue-confirmed patients is necessary to establish their usefulness.

REFERENCES

1. Nivedita Gupta et al. — Dengue in India; Centenary Review Article; Indian J Med Res., September 2012; 373-390.
2. WHO, Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention and Control, WHO, Geneva, Switzerland, 2nd edition, 1997.
3. L.M. Ling, A. Wilder-Smith and Y. S. Leo, "Fulminant hepatitis in dengue haemorrhagic fever," Journal of Clinical Virology, 2007; 38(3): 265–268.
4. S. Gulati and A. Maheshwari, "Atypical manifestations of dengue," TropicalMedicine and International Health, 2007; 12(9): 1087–1095.
5. R. Kumar, S. Tripathi, J. J. Tambe, V. Arora, A. Srivastava and V. L. Nag, "Dengue encephalopathy in children in Northern India: clinical features and comparison with non dengue," Journal of the Neurological Sciences, 2008; 269(1-2): 41–48.
6. M. Wasay, R. Channa, M. Jumani, G. Shabbir, M. Azeemuddin and A. Zafar, "Encephalitis and myelitis associated with dengue viral infection. Clinical and neuroimaging features," Clinical Neurology and Neurosurgery, 2008; 110(6): 635–640.
7. T. Solomon, N. M. Dung, D. W. Vaughn et al., "Neurological manifestations of dengue infection," The Lancet, 2000; 355: 1053–1059.
8. S. B. Park, S. Y. Ryu, K. B. Jin et al., "Acute colitis associated with dengue fever in a renal transplant recipient," Transplantation Proceedings, 2008; 40(7): 2431–2432.
9. Siti Latifah Abd Kadir, Harisun Yaakob, Razauden Mohamed Zulkifli et al., "Potential anti-dengue medicinal plants: a review", J Nat Med, 2013; 67: 677–689.
10. Elzinandes Leal de Azeredo et al., "Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammator Mediators, a review", Hindawi Publishing Corporation, 2015; 1-16.
11. C. Gowda et al., "A Pilot Study to Evaluate the Effectiveness of Carica Papaya Leaf Extract in Increasing the Platelet Count in Cases of Dengue with Thrombocytopenia", Indian Medical Gazette — MARCH 2015; 109-116.
12. Vijay Yogiraj, et al., Carica papaya Linn: An Overview, International Journal of Herbal Medicine, 2014; 2(5): 01-08.
13. Anjum V, Ansari SH, Naquvi KJ, Arora P, Ahmad A. Development of quality standards of Carica papaya Linn. Leaves, Sch Res Lib, 2013; 5(2): 370-376.

14. Arvind G, et al., Traditional and Medicinal uses of Carica papaya, J Med Car Pap, 2013; 1(1): 2320-3862.
15. NEETU SHARMA, DEVENDRA MISHRA, "Papaya Leaves in Dengue Fever: Is there Scientific Evidence?" Indian pediatrics, April 15 2014; 324(51).
16. Ranasinghe P, Ranasinghe P, Kaushalya M, Abeysekera WP, Sirimal Premakumara GA, et al. In vitro erythrocyte membrane stabilization properties of Carica papaya L. leaf extracts. Phcog Res., 2012; 4: 196-202.
17. Senthivel et Senthilvel P, Lavanya P, Kumar KM, Swetha R, Anitha P, Bag S, Sarveswari S, Vijayakumar V, Ramaiah S, Anbarasu A Flavonoid from Carica papaya inhibits NS2B-NS3 protease and prevents Dengue 2 viral assembly. Bioinformation, 2013; 9(18): 889-895.
18. Subenthiran S, Choon TC, Cheong KC, Thayan R, Teck MB, Muniandy PK, et al. Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic Fever. Evid Based Complement Alternat Med., 2013; 616-737.
19. Dharmarathna SL, Wickramasinghe S, Waduge RN, Rajapakse RP, Kularatne SA. Does Carica papaya leaf extract increase the platelet count? An experimental study in a murine model. Asian Pac J Trop Biomed, 2013; 3: 720-4.
20. Kathiresan S, Surash R, Sharif M, Mas Rosemal N, Walther H Thrombocyte couts in mice after the administration of papaya leaf suspension. Wien. Klin. Wochenschr. 2009; 121(3): 19-22.
21. Halim S, Abdullah R, Afzan A, Abdul R, Jantan I, Ismail Z Acute toxicity study of Carica papaya leaf extract in Sprague Dawley rats. J. Med. Plants Res., 2011; 5: 1867-1872.
22. Betty A, Wu H, Yu T, Hsuen C, Dengue haemorrhage in a mouse model. Ann. NY Acad. Sci., 2009; 1171: E42-E47.
23. Sebastian J, Arie K, Yaohui W, Peter E, Oran K, Je H, Shenglin C, Christopher C, Anand D, Sudhir K, Mark L Vitamin C as an antioxidant: evaluation of its role in disease prevention. J. Am. Coll. Nutr., 2003; 22(1): 18-35.
24. Cabrera-Cortina J, Sanchez-Vakdez E, Cedas-DeLezama D and Ramirez-Gonzalez M Oral calcium administration attenuates thrombocytopenia in patients with dengue fever, Report of a pilot study. Proc. West. Pharmacol. Soc., 2008; 51: 38-41.
25. Emilio S, Melissa D, Jose A, Jose M Clinical response in patients with dengue fever to oral calcium plus vitamin D administration: study of 5 cases. Proc. West. Pharmacol. Soc., 2009; 52: 14-17.

26. Jutrat M, Ausaneya S, Harutai T, Thaworn C, Thamrongprawat C, Chitsanu P, Usa T Serum and urine sodium levels in dengue patients. The Southeast Asian J. Trop. Med. Public Health, 2005; 36: 197-199.
27. Sanjeev J, Ansari M, Dengue infection causing acute hypokalemic quadriparesis. Neurol. India, 2010; 58: 592-594.
28. Amitava R, Anil K, Shailendra PV, Himanshu R, Nirdesh J, Acute hypokalaemic quadriparesis in dengue fever. 2010; BMJ Case Reports. doi:10.1136/bcr.11.2010.3514.
29. Harmanjith S, Amandeep K, Anuj S, Acute neuromuscular weakness associated with dengue infection. J. Neurosci. Rural Pract, 2012; 3(1): 36-39.
30. Saiful M, Parveen J, Azura A, Purification of Xanthine Oxidase Inhibitor from Carica papaya leaves using Reversed Phase Flash Column Chromotography (RPFCC) - High Performance Thin Layer Chromotography (HPTLC) Australian J. Basic Appl. Sci., 2012; 6(1): 117-122.
31. Kala CP. Leaf juice of Carica papaya L.: A remedy of dengue fever. Med Aromat Plants., 2012; 1: 109
32. Hettige S. Salutary effects of Carica papaya leaf extract in dengue fever patients a pilot study. Sri Lankan Fam Physician. 2008; 29: 17–9.
33. Yunita F, Hanani E. The effect of Carica papaya L leaves extract capsule on platelet count and hematocrit level in dengue fever patient. Int J Med Aromat Plants., 2012; 2: 573–8.
34. Ahmad N, Fazal H, Ayaz M, Abbasi BH, and Mohammad I, Fazal L. Dengue fever treatment with Carica papaya leaves extracts. Asian Pac J Trop Biomed., 2011; 1: 330–3.
35. Kumar N. Re: Papaya leaves for speedy rise of platelet count in Dengue. Br Med J., 2010.
36. V Krishna prabha and Freeda Thomas Formulation, nutrient and microbial analysis of papaya leaves and guava incorporated RTS beverage, Int. J. Curr. Microbiol. App. Sci 2014; 3(5): 233-236.
37. Achini Gammulle, Ratnasooriya WD, Jayakody JRAC, Charmain Fernando, Charmini Kanatiwela. Thrombocytosis and Anti-inflammatory properties and toxicological evaluation of Carica papaya mature leaf concentrate in a murine model, Onl Int J Med Pla Res, 2012; 1(2): 21-30.