Dengue Virus Disease: Current Updates on the use of Carica Papaya Leaf Extract as a Potential Herbal Medicine

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Abstract: This review of literature highlights the potentiality of Carica papaya leaf extract in controlling dengue viral disease induced thrombocytopenia-platelet count and discussed most of the published research work on this topic. Epidemic dengue is one of the leading arthropod-borne viral disease causes an acute febrile illness known as dengue fever (DF) followed by dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Dengue induced thrombocytopenia is life threatening and a major health disorder resulted in the lower platelet count in patients with dengue fever (DF). Carica papaya is not only consumed as a nutritious and delicious fruit but also used as a chief and the best herbal medicine for many health disorders. On the basis of experimental studies, clinical data and pilot studies, the Carica papaya leaf extract could help to increase platelet levels in patients suffering from dengue. All these studies strongly confirmed antiviral properties of Carica papaya and supports a strong scientific evidence for the treatment of dengue. Therefore, the use of Carica papaya leaf extract (Caripil) in the management of thrombocytopenia associated with dengue is significant and considered as an alternative herbal medicine for dengue.

Key words: Dengue, botanical medicine, dengvaxia, India, papaya, platelet, thrombocytopenia, viral fever

1. OVERVIEW

Sanofi branded vaccine Dengvaxia (CYD-TDV). Dengvaxia (CYD-TDV) is the first licensed dengue vaccine in Mexico in December 2015 for use in individuals 9–45 years of age living in endemic areas (Mexico dengue vaccine first, Nature biotechnology, 2016; Malabadi et al. 2017; Villar et al. 2015; Vannice et al. 2016; Mahoney, 2014; Thomas, 2015; Gottscham et al. 2016; Pang and Loh, 2017; Skon Campos and Jose Luis, 2017). There are many efforts throughout the world by different research groups using gene delivery method, virus based vectors, and nanoparticle approach for the development of a dengue vaccine (Malabadi et al. 2016a; Khan et al. 2011, 2012).

Dengue fever (DF) is a self limited febrile illness (Jayashree et al. 2011; Azeredo et al. 2015). Dengue viral disease induced thrombocytopenia is one of the major health disorder (WHO, 2009; Jayashree et al. 2011; Palbag et al. 2016; Azeredo et al. 2015). Thrombocytopenia is characterized by lacking enough number of platelet counts in the blood. Platelets are the specialized cells that stick together which helps in clotting of blood. Plasma leakage in dengue patients will hamper the blood clotting and it can cause death (Azeredo et al. 2015). By increasing the platelet count in the dengue patient, the death rate can be reduced. Thrombocytopenia and platelet dysfunction are common in patients suffering from dengue fever (DF) and are related to the clinical outcome and higher mortality (Jayashree et al. 2011; Palbag et al. 2016; Azeredo et al. 2015). The haematological abnormalities of severe dengue are thrombocytopenia, coagulopathy, vasculopathy related to platelet and endothelial dysfunction (WHO, 2009; Jayashree et al. 2011; Azeredo et al. 2015; Palbag et al. 2016). Thrombocytopenia is one of the potential indicator of dengue clinical severity (de Castro et al. 2007; WHO, 2009; Jayashree et al. 2011; Azeredo et al. 2015; Palbag et al. 2016). On the other hand dengue hemorrhagic fever (DHF) is characterized by haemorrhagic manifestations associated with thrombocytopenia, and an increased vascular permeability (Jayashree et al. 2011; Sarangi and Padh, 2014; Azeredo et al. 2015). Further, thrombocytopenia was associated with clinical improvement while further fall in platelet counts was associated with fatality (Jayashree et al. 2011; Hottz et al. 2011; Azeredo et al. 2015). Dengue viral disease affects bone marrow suppression resulting in the decreased platelet synthesis, a criteria of thrombocytopenia in dengue hemorrhagic fever (DHF) (Azeredo et al. 2015; Jayashree et al. 2011; Sarangi and Padh, 2014). Laboratory findings such as thrombocytopenia and a rising hematocrit in dengue hemorrhagic fever (DHF) cases are usually observed by day 3 or 4 of the dengue fever illness (Jayashree et al. 2011; Azeredo et al. 2015).

Therefore, a study was conducted in order to find out the relationship between the platelet counts and severity of the disease in pediatric cases of dengue fever (Jayashree et al. 2011). Platelet counts were found to be predictive as well as recovery parameters of dengue fever (DF), severe form as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Jayashree et al. 2011). In one of the study reported by Jayashree et al. (2011), children below 15 years with seropositivity for dengue fever (DF) admitted to JSS University Hospital, Mysore, Karnataka, India and a tertiary care center between 1st of May and 15th of August 2009 (Jayashree et al. 2011). These children’s were evaluated for platelet count and severity of the dengue disease (Jayashree et al. 2011). During this study period, there were 414 pediatric cases admitted with fever. Of these 105 were found to be seropositive for dengue (Jayashree et al. 2011). Of these seropositive cases, 70% had thrombocytopenia while the remaining 30% had normal platelet counts (Jayashree et al. 2011). Of the patients with thrombocytopenia (platelet count <1 lakh), 36 patients (48.64%) had platelet counts between 51,000 and 1 lakh (mild thrombocytopenia), 31 patients (41.89%) had platelet counts between 21,000 and 50,000 (moderate thrombocytopenia) while the remaining 7 patients (9.45%) had platelet counts >20,000 (severe thrombocytopenia) has been confirmed (Jayashree et al. 2011). This study also noticed a significant association was observed between the severity of thrombocytopenia and the age groups (Jayashree et al. 2011). Thrombocytopenia was found to be more severe in age groups of 6–10 years than in the older age group and this difference was significant (Jayashree et al. 2011). The study conducted by Jayashree et al. (2011) also concluded that the decreasing platelet counts have been found to predict the severity of the dengue disease and is associated with increased hematocrit, increased liver enzymes, altered coagulation profile (Jayashree et al. 2011).

Dengue hemorrhagic fever (DHF) is characterized by a thrombocyte count of <100,000 cells/mm² (Sarala and Paknikar, 2014; Azeredo et al. 2015). Two mechanisms have been suggested that could be responsible for dengue induced thrombocytopenia impaired-thrombopoiesis and peripheral platelet destruction (Hottz et al. 2011; Sarala and Paknikar, 2014; Azeredo et al. 2015). In support of the theory of impaired thrombopoiesis, studies have suggested reduced megakaryopoiesis at the onset of infection, which is normal at the time of clinical recovery (Sarala and Paknikar, 2014; Azeredo et al. 2015). This effect could be due to a direct effect of the virus on the megakaryocytes, or an effect on the stromal cells which are responsible for the release of cytokines and control of megakaryopoiesis (Sarala and Paknikar, 2014; Azeredo et al. 2015). Studies have also indicated altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis as possible mechanisms of thrombocytopenia (Sarala and Paknikar, 2014; Azeredo et al. 2015). Thrombocytopenia is also related with the increased peripheral platelet destruction by the dengue (Hottz et al. 2011; Sarala and Paknikar, 2014; Azeredo et al. 2015). Thrombocytopenia may be due to modulation of endothelial cell by the infection of dengue virus to the cell (Palbag et al. 2016; Azeredo et al. 2015). Another study showed that dengue virus could directly or indirectly affect bone marrow progenitor cells by inhibiting their function (Palbag et al. 2016). This could be due to an autoimmune reaction, where antibodies produced by the host against the
Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients might also be responsible for the destruction (Sarala and Paknikar, 2014; Azeredo et al. 2015). Recent studies also indicated a direct infection of the platelets by the dengue (Hottz et al. 2011; Sarala and Paknikar, 2014; Azeredo et al. 2015). Platelets play a vital role in maintaining the intercellular junctions of endothelium, thrombocytopenia in dengue hemorrhagic fever (DHF) offers no help to the already fragile vascular wall (Ansari, 2016; Azeredo et al. 2015). In the peripheral circulation, premature destruction of platelets is induced by abnormal activation and prevention of normal platelet aggregation and direct infection of the platelets by the dengue virus (Ansari, 2016; Azeredo et al. 2015).

II. DENGUE CONTROL BY CARICA PAPAYA AS A HERBAL MEDICINE

Papaya (Carica papaya L.) belongs to family Caricaceae is one of the economically important fruit crops in many tropical and subtropical countries (Malabadi et al. 2011; Aravind et al. 2013; Sarala and Paknikar, 2014; Vij and Prashar, 2015). Papaya cultivation had its origin in South Mexico and Costa Rica. Papaya (Carica papaya) fruit is known for its high nutritive and medicinal value (Malabadi et al. 2011; Aravind et al. 2013; Sarala and Paknikar, 2014; Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Vyas et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). The papaya fruit is consumed worldwide as a fresh fruit and vegetable or used as processed product which is a rich source of antioxidants vitamin E, vitamin C and vitamin A (Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sarala and Paknikar, 2014; Sudhakar et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). The papaya fruit is very tasty, delicious and all the parts of the plant including fruit, root, bark, peel, seeds and pulp known to have medicinal properties which are rich in minerals magnesium, potassium, vitamin B, pantothenic acid, and folate (Vij and Prashar, 2015; Aravind et al. 2013; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). The ripe fruit has been used against ringworm, whereas the green fruit has been used to lower blood pressure, as an aphrodisiac and to induce abortion (Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). Carica papaya is also known for the digestive enzyme papain which is used for the treatment of liver disorders, trauma, allergies and injuries (Vij and Prashar, 2015; Sarala and Paknikar, 2014; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). Total annual world production of papaya is estimated over 6.8 million tonnes of fruits. Brazil followed by India leads the world in papaya production with an annual output of approximately of about 4.5 million tones. Some of the commercial varieties of Carica papaya grown in Belgaum, and surroundings of Dharwad district in Karnataka state, India are Coorg Honey dew, Washington, Honey dew, Pusa delicious, Pusa nana, Taiwan 786, Taiwan 785, Sunrise, Solo, Co-1, Co-7, and Co-3 (Malabadi et al. 2011).

Papaya is also used in preventing colon cancer and stroke, in the treatment of heart diseases, heart attack, and also found to improve cardiovascular system too (Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Vyas et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). Papaya fruit is also a rich source of beta-carotene which prevents the damage caused by free radicals that may cause cancer (Vij and Prashar, 2015; Aravind et al. 2013; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Vyas et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). High cholesterol levels is also controlled by papaya since it is rich in fiber too (Sarala and Paknikar, 2014; Vij and Prashar, 2015). The chymopapain and papain extracts of the leaves are useful in the treatment of digestive disorders (Aravind et al. 2013; Sarala and Paknikar, 2014; Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Vyas et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). Papain is one of the enzyme abundant in unripe papaya fruits is an excellent aid to digestion, which helps in the digestion of protein food at acidic, alkaline and neutral medium. The extracts from fruits and seeds have bactericidal properties (Aravind et al. 2013; Sarala and Paknikar, 2014; Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Vyas et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). The fruit juice and leaf extract have been demonstrated to have a wide variety of pharmacological properties including anticancer, anti-inflammation, anti-hypertensive, wound healing, hepatoprotective, antimicrobial, antihypertensive, effect on smooth muscles, antimalarial, immunomodulatory activity, anti-ulcer activity, anti-fertility, histaminergic, diuretic, anti-amoebic, anti-tumor, anti-inflammatory, anti-bacterial, antiviral, antifungal, nephroprotective, hepatoprotective, hypoglycemic and hypolipidemic effects, and anti-sickling effect in sickle cell disease (Aravind et al. 2013; Vyas et al. 2014; Sarala and Paknikar, 2014; Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016). Hence papaya has been prescribed for dyspeptic patients, who cannot digest the wheat protein gliadin, can tolerate it, if it is treated with crude papain (Vij and Prashar, 2015; Marfo et al. 1986; Krishna et al. 2008; Macalood et al. 2013; Sudhakar et al. 2014; Yogiraj et al. 2014; Gunde and Amnerkar, 2016).

Plants offers multiple health benefits because of presence of bioactive compounds and have been used for medical treatment is as old as human civilization. The extraction and characterization of bioactive compounds from medicinal plants have resulted in the introduction of new drugs with a high medicinal value (Chalannavar et al. 2011, 2012, 2013a, 2013b, 2015a, 2015b; Narayanaswamy et al. 2013, 2014; Malabadi et al. 2016b, 2016c, 2016d). Therefore, plants are the sources of life saving drugs which are very cheap, affordable, and no side effects with optimum level of consumption. Now a days medicinal plants of pharmaceutical importance have been exploited and in vitro plant techniques have been applied for the micropropagation to meet current commercial demand (Malabadi and Nataraja, 2001, 2002; Malabadi, 2002a, 2002b, 2005; Malabadi et al. 2004, 2005a, 2009, 2011, 2005b; Malabadi and Vijay Kumar, 2005, 2007, 2008; Malabadi et al. 2007, 2010; 2012a, 2012b, 2012c, 2012d; Malabadi et al. 2016b, 2016c, 2016d).

*Carica papaya* L. has recently been in the news for the last few years due to its potential in controlling dengue viral diseases. This review describes some of the published studies on this topic. The search was done by the authors using PubMed, Google and the library database and included relevant articles of the present topic viz. dengue treatment by papaya. Therefore, this paper is the overview of dengue and a review of available literature regarding the use of the papaya leaf extract as one of the cheap, effective and potential herbal medicine against dengue viral disease. The use of *Carica papaya* as a herbal medicine would be the comprehensive strategy in the management of dengue by plant and plant derived medicines particularly in the poor and developing dengue endemic countries. Following are the few clinical, experimental and pilot studies conducted in dengue endemic zones.

1) Treatment of dengue using *C. papaya* leaf extract in humans has been reported in a very few studies conducted in Asia (Hettige, 2008; Sarala and Paknikar, 2014; Mathew et al. 2016). A pilot study was conducted in Sri Lanka on 12 patients suspected of suffering from dengue (Hettige, 2008; Sarala and Paknikar, 2014). The patients had a platelet count of <130,000/cu mm, but only six patients were serologically confirmed to be suffering from dengue (Hettige, 2008; Sarala and Paknikar, 2014). The patients received 2 doses of papaya leaf extract at intervals of 8 h. They also received standard symptomatic care for dengue (Hettige, 2008; Sarala and Paknikar, 2014). This study confirmed an increase in the platelet count and total white blood cell count in patients administered papaya leaf extract within 24 h of treatment with the papaya leaf extract (Hettige, 2008; Sarala and Paknikar, 2014; Mathew et al. 2016).

2) Sathasivam et al. (2009) reported the use of crude leaf preparations of *Carica papaya* for the treatment of dengue infections using a mice as experimental model (Sathasivam et al. 2009). During this study, a suspension of powdered *Carica papaya* leaves in palm oil has been investigated for its effect on thrombocyte counts in mice (Sathasivam et al. 2009). This was done by administering a 15 ng of powdered leaves per kg body weight to 5 mice by a method of gavage (Sathasivam et al. 2009). Equal numbers of mice animals received corresponding volumes of either palm oil alone or physiological saline solution (Sathasivam et al. 2009). Thrombocyte counts before and at 1, 2, 4, 8, 10, 12, 24, 48 and 72 hours after dosing revealed significantly higher mean counts at 1, 2, 4, 8, 10 and 12 after dosing with the *Carica papaya* leaf formulation as compared to the mean count at hour 0 (Sathasivam et al. 2009). Hence there was only a non-significant rise of thrombocyte counts in the group having received saline solution, possibly the expression of a normal circadian rhythm in mice (Sathasivam et al. 2009).
The group having received palm oil only showed a protracted increase of platelet counts that was significant at hours 8 and 48 and obviously the result of a hitherto unknown stimulation of thrombocyte release (Sathasivam et al. 2009). These results called for a dose-response investigation and for extending the studies to the isolation and identification of the Carica papaya substances responsible for the release and/or production of thrombocytes (Sathasivam et al. 2009). Therefore, the leaf extract of Carica papaya has been effectively used for thrombocytopenia (Sathasivam et al. 2009).

3) A report in the British Medical Journal website described the rapid recovery of platelet counts in two children suffering from dengue (Kumar, 2010; Sarala and Paknikar, 2014). These cases were proved to be positive for dengue by the demonstration of the dengue antigen in the serum (Kumar, 2010; Sarala and Paknikar, 2014). The boys, aged 10 years and 14 years, were administered a spoonful of ground papaya leaves paste every 4 hourly (Kumar, 2010; Sarala and Paknikar, 2014). A dramatic increase in platelet counts was observed; in one case within 12 h of initiating treatment, the count increased to 100,000 (Kumar, 2010; Sarala and Paknikar, 2014). In the second case, it increased within 2 days to 250,000 (Kumar, 2010; Sarala and Paknikar, 2014). The duration of treatment was not mentioned in the report (Kumar, 2010; Sarala and Paknikar, 2014).

4) The potentiality of Carica papaya leaf extracts against dengue fever in a 45 year old patient has been reported (Ahmad et al. 2011). During this study, the treatment of dengue fever was carried out by using the water diluted Carica papaya leaf extract (Ahmad et al. 2011). Further, 25 mL of aqueous extract of C. papaya leaves was administered to patient infected with dengue fever (DF) twice daily i.e. morning and evening for five consecutive days (Ahmad et al. 2011). Before the papaya leaf extract administration, the blood samples of the patient was analyzed (Ahmad et al. 2011). During dengue fever (DF), platelets count (PLT), white blood cells (WBC) and neutrophils (NEUT) of a patient decreased from 176 × 10^3/μL, 8.10 × 10^3/μL, 84.0% to 55 × 10^3/μL, 3.7 × 10^3/μL and 46.0% (Ahmad et al. 2011). Subsequently, the blood samples of the patient was rechecked after the administration of papaya leaf extract (Ahmad et al. 2011). It was observed that the platelet count increased from 55 × 10^3/μL to 168 × 10^3/μL, WBC from 3.7 × 10^3/μL to 7.7 × 10^3/μL and NEUT from 46.0% to 78.3% (Ahmad et al. 2011). Therefore, this study confirmed that Carica papaya leaf extract exhibited potential activity against dengue fever and hence Carica papaya could be used as a strong natural candidate against viral diseases (Ahmad et al. 2011).

5) Carica papaya L. fruit juice and leaf extracts are known to have many beneficial medicinal properties (Ranasinghe et al. 2012; Siddique et al. 2014; Sharma and Mishra, 2014). There is a emerging evidence for possible beneficial effects of the extracts of C. papaya L. leaves in the treatment of patients with dengue viral infections (Ranasinghe et al. 2012; Siddique et al. 2014; Sharma and Mishra, 2014). Thrombocytopenia is one of the key clinical manifestations in dengue viral infections and contributes to the plasma leakage and hemorrhage in dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) in the presence of enhanced vascular fragility (Ranasinghe et al. 2012). Thrombocytopenia in dengue is considered to be an immune related, molecular mimicry involving dengue viral particles and the platelet leads to auto-destruction of the platelets by Immunoglobulin M (IgM) antibodies (Ranasinghe et al. 2012). Any compound or drug having a stabilization effect on the plasma membrane may effectively enhance survival of platelets with a potential morbidity and mortality benefits in patients with dengue viral infections (Ranasinghe et al. 2012). Erythrocytes membrane is the model system used for many in vitro investigations of drug and membrane interactions (Ranasinghe et al. 2012).

Therefore, a study reported by Ranasinghe et al. (2012) evaluated the membrane stabilization properties of C. papaya L. leaf extracts using an in vitro hemolytic assay (Ranasinghe et al. 2012). During this study, two milliliters of blood from healthy volunteers and patients with serologically confirmed dengue infection were freshly collected and used in the assays (Ranasinghe et al. 2012). Fresh papaya leaves at three different maturity stages (immature, partly matured, and matured) were cleaned with distilled water, crushed, and the juice was extracted with 10 ml of cold distilled water (Ranasinghe et al. 2012). Freshly prepared cold water extracts of papaya leaves (1 ml containing 30 μl of papaya leaf extracts, 20 μl from 40% erythrocytes suspension, and 950 μl of phosphate buffered saline) were used in the heat-induced and hypotonic-induced hemolytic assays (Ranasinghe et al. 2012). In dose response experiments, six different concentrations (9.375, 18.75, 37.5, 75, 150, and 300 μg/ml) of freeze dried extracts of the partly matured leaves were used. Membrane stabilization properties were investigated with heat-induced and hypotonic-induced hemolytic assays (Ranasinghe et al. 2012). Extracts of papaya leaves of all three maturity levels showed a significant reduction in heat-induced hemolysis compared to controls (P < 0.05) (Ranasinghe et al. 2012). Papaya leaf extracts of all three maturity levels showed more than 25% inhibition at a concentration of 37.5 μg/ml (Ranasinghe et al. 2012). The highest inhibition of heat-induced hemolysis was observed at 37.5 μg/ml (Ranasinghe et al. 2012). Inhibition activity of different maturity levels was not significantly (P < 0.05) different from one another (Ranasinghe et al. 2012). Heat-induced hemolysis inhibition activity did not demonstrate a linear dose response relationship (Ranasinghe et al. 2012). Further at 37.5 μg/ml concentration of the extract, a marked inhibition of hypotonicity-induced hemolysis was observed (Ranasinghe et al. 2012). Therefore, on the basis of this study, it was concluded that C. papaya L. leaf extracts showed a significant inhibition of hemolysis in vitro and could have a potential therapeutic effect on disease processes causing destabilization of biological membranes (Ranasinghe et al. 2012).
This study also demonstrated that *C. papaya* L. leaf extracts inhibit heat-induced and hypotonicity-induced hemolysis of erythrocytes derived from both healthy individuals and patients with dengue viral infections (Ranasinghe et al. 2012). This indicated that *C. papaya* L. leaf extracts possess biological membrane stabilization properties preventing stress-induced destruction of the plasma membrane (Ranasinghe et al. 2012). The exact underlying mechanism for the membrane stabilizing effect of *C. papaya* L. leaf extracts and the chemical constituent(s) responsible for this effect is hitherto not known (Ranasinghe et al. 2012). It has also been shown that *C. papaya* L. leaf extracts contain flavonoids such as kaempferol, quercetin and p-coumaric acid (Ranasinghe et al. 2012). The production of free radicals, such as lipid peroxides and superoxides, are reported to be accountable for cell membrane destabilization (Ranasinghe et al. 2012). Flavonoids and other phenolic compounds are reported to act as effective scavengers of free radicals (Ranasinghe et al. 2012). Thus, it is not unreasonable to postulate that flavonoids and other phenolic compounds in *C. papaya* L. extracts could be responsible for the observed membrane stabilizing effect in this study (Ranasinghe et al. 2012). Furthermore, the reported anti-cancer, anti-inflammatory, and nephro/hepatoprotective properties of *C. papaya* L. extracts could well be due to their membrane stabilizing potential (Ranasinghe et al. 2012). This study confirmed that *C. papaya* L. extracts from partly matured leaves demonstrated a significant inhibition of hemolysis *in vitro* (Ranasinghe et al. 2012). The inhibition effect shown by crude extracts of the *C. papaya* L. leaves at comparatively lower concentrations (37.5 μg/ml) was comparable with that of standard anti-hemolysis compounds such as aspirin and indomethacin (Ranasinghe et al. 2012). This experimental evidence indicated that *C. papaya* L. leaf extracts could have a potential therapeutic efficacy in disease processes causing destabilization of biological membranes (Ranasinghe et al. 2012).

6) A study reported by Yunita et al. (2012) in Indonesia, the use of *Carica papaya* leaf extracts capsules (CPC) increased platelets count in dengue infected patients (Yunita et al. 2012; Sarala and Paknikar, 2014). Treatment with *Carica papaya* leaf extracts capsules (CPC) can hasten recovery of patients suffering from dengue and therefore reduce hospitalization (Yunita et al. 2012; Sarala and Paknikar, 2014).

7) Another study by the journal of Medicinal and Aromatic Plants also reported an increase in platelets count in five patients within 24 h who had taken papaya leaf extract as a herbal medicine for dengue (Kala, 2012; Sarala and Paknikar, 2014). 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 (Kala, 2012; Sarala and Paknikar, 2014). Furthermore, the response in platelet count beyond 24 h has not been described (Kala, 2012; Sarala and Paknikar, 2014).

8) Study found that the *Carica papaya* leaf aqueous extract at a concentrations of 400 mg/kg and 800 mg/kg significantly increased the platelet counts in cyclophosphamide-induced thrombocytopenic rat model (Patil et al. 2013; Sarala and Paknikar, 2014). It has also reduced the clotting time in the treated rats (Patil et al. 2013; Sarala and Paknikar, 2014).

9) Subenthiran et al. (2013) investigated the platelet increasing property of *Carica papaya* leaves juice (CPLJ) in patients with dengue fever (DF) (Subenthiran et al. 2013). An open labeled randomized controlled trial was carried out on 228 patients with dengue fever (DF) and dengue haemorrhagic fever (DHF) (Subenthiran et al. 2013). Approximately half the patients received the juice, for 3 consecutive days while the others remained as controls and received the standard management (Subenthiran et al. 2013). Gene expression studies were conducted on the ALOX 12 and PTAFR genes (Subenthiran et al. 2013). The mean increase in platelet counts were compared in both groups using repeated measure ANCOVA (Subenthiran et al. 2013). There was a significant increase in mean platelet count observed in the intervention group (P < 0.001) but not in the control group 40 hours since the first dose of *Carica papaya* leaves juice (CPLJ) (Subenthiran et al. 2013). 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 (P < 0.01) (Subenthiran et al. 2013). The ALOX 12 (FC = 15.00) and PTAFR (FC = 13.42) genes were highly expressed among those on the papaya juice (Subenthiran et al. 2013). Therefore, this study concluded that *Carica papaya* leaf juice (CPLJ) does significantly increased the platelet count in patients with DF and DHF (Subenthiran et al. 2013). The RNA was extracted from the blood of the patients recruited and gene expression of two genes, namely, the ALOX 12 and the PTAFR were conducted (Subenthiran et al. 2013). There was a 15-fold increase in the ALOX 12 gene activity among the patients in the experimental group as compared to those in the control group at the end of the 3 days (Subenthiran et al. 2013). ALOX 12 is known to be associated with increased megakaryocyte production as well as its conversion to platelets through 12-HETE mediated pathway which in turn leads to increased platelet production (McRedmond et al. 2004; Subenthiran et al. 2013). The Alox 12 gene was highly expressed in platelets and found to be a platelet specific gene (McRedmond et al. 2004; Subenthiran et al. 2013). ALOX12 is a direct target of transcription factor RUNX1 in megakaryocytes and platelets (McRedmond et al. 2004; Subenthiran et al. 2013). RUNX1 is a transcription factor that regulated the expression of haemopoietic–specific genes (McRedmond et al. 2004; Subenthiran et al. 2013). When there is RUNX1 haploinsufficiency, which affected overall haemopoiesis and hence, ALOX 12 expression in platelets is decreased (McRedmond et al. 2004; Subenthiran et al. 2013). There was also an agonist-induced decreased 12-HETE production in platelets with the decrease in ALOX 12
expression (McRedmond et al. 2004; Subenthanin et al. 2013). This provides further evidence that platelet production is associated with ALOX 12 expression (McRedmond et al. 2004; Subenthanin et al. 2013).

10) Dharmarathna et al. (2013) reported the potential role of fresh Carica papaya (C. papaya) leaf extract on haematological and biochemical parameters and toxicological changes in a murine model (Dharmarathna et al. 2013). In this study, a total of 36 mice were used for the trial (Dharmarathna et al. 2013). Fresh C. papaya leaf extract [0.2 mL (2 g/mouse)] was given only to the test group (18 mice) (Dharmarathna et al. 2013). General behaviour, clinical signs and feeding patterns were recorded. Blood and tissue samples were collected at intervals (Dharmarathna et al. 2013). Haematological parameters including platelet, red blood cell (RBC), white blood cell (WBC), packed cell volume (PCV), serum biochemistry including serum creatinine, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) were determined (Dharmarathna et al. 2013). Organs for possible histopathological changes were examined (Dharmarathna et al. 2013). This study confirmed that neither group exhibited alteration of behavior or reduction in food and water intake (Dharmarathna et al. 2013). Similarly, no significant changes in serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and serum creatinine levels were detected in the test group (Dharmarathna et al. 2013). Histopathological organ changes were not observed in either group of mice except in three liver samples of the test group which had a mild focal necrosis (Dharmarathna et al. 2013). The platelet count (11.33±0.35)×10^6/μL (P=0.000 04) and the red blood cell (RBC) count (7.97±0.61)×10^6/μL (P=0.000 03) were significantly increased in the test group compared to that of the controls (Dharmarathna et al. 2013). However, while white blood cell (WBC) count and packed cell volume (PCV) (%) values were not changed significantly in the test group (Dharmarathna et al. 2013). The platelet count in the test group started to increase significantly from day 3 (3.4±0.18×10^6/μL), reached almost a fourfold higher at day 21 (11.3×10^6/μL), while it was 3.8×10^6/μL and 5.5×10^6/μL at day 3 and day 21 respectively in the control (Dharmarathna et al. 2013). Furthermore, the red blood cell (RBC) count in the test group increased from 6×10^6/μL to 9×10^6/μL at day 21 while it remained near constant in the control group (6×10^6/μL) (Dharmarathna et al. 2013). Therefore, fresh C. papaya leaf extract significantly increased the platelet and RBC counts in the test group as compared to controls (Dharmarathna et al. 2013; Wiwanitkit, 2013). Therefore, it is very important to identify those chemicals of Carica papaya leaves as it can be recommended to be used as a medication to boost thrombopoiesis and erythropoiesis in humans and in animals in which these cell lineages have been compromised (Dharmarathna et al. 2013; Siddique et al. 2014; Wiwanitkit, 2013).

11) Another study found that the papaya seed was toxic to the Aedes aegypti mosquito, which is a vector for the etiologic agents of both yellow and dengue fever (Nunes et al. 2013; Manohar, 2013; Ansari, 2016). The identification of tegupain, the enzyme that generates toxicity has been reported (Nunes et al. 2013).

12) One of the study investigated the effect of Carica papaya leaf extract on blood chemistry specifically thrombocyte count of rats (Sheikh et al. 2014). Local syrup of papaya leaf extract was used for experimentation (Sheikh et al. 2014). Six animals were used for experiment, 3 as control and 3 experimental (Sheikh et al. 2014). The dose given to experimental animals was 0.5 ml of papaya leaf extract for 7 consecutive days which were at fasting for 4 hours before dose administration (Sheikh et al. 2014). There was a significant increase in mean platelet count, Mean Cell Haemoglobin (MCH) and Mean Corpuscular Volume (MCV) (p<0.05) of the treated animals as compared to control after seven days treatment with Carica papaya (CP) leaf formulations (Sheikh et al. 2014). Therefore, this study highlighted the need for isolation and identification of the C. papaya substances responsible for the release and/or production of thrombocytes (Sheikh et al. 2014). Hence it was concluded that C. papaya leaf extract is associated with rapid increase of platelet count (Sheikh et al. 2014).

13) A study reported by Joseph et al. (2015) determined the phytochemicals present in Carica papaya L. leaf extracts, as well as their cytotoxic effect and anti-DENV2 activity on the LLC-MK2 cell line (Joseph et al. 2015). Methanolic extracts, containing triterpenoids and flavonoids, showed cytotoxic effects (CC50=0.6156 mg ml^-1), whereas a chloroform extract, rich in alkaloids, tannin and saponin, was non-cytotoxic (CC50= >1 mg ml^-1) to LLC-MK2 cells and it showed inhibitory activity (EC50= >1 mg ml^-1) against DENV2 with a selectivity index value of≥1(Joseph et al. 2015). Hence the crude chloroform extract has a moderate or less inhibitory action against DENV2 growth under in vitro conditions (Joseph et al. 2015). Therefore, this study will help in the future development of new and novel drugs against dengue pathogens with high efficacy (Joseph et al. 2015; Hossain et al. 2016).

14) A pilot study confirmed the platelet increasing property of Carica papaya leaf extract (CPLE) in patients with dengue fever (DF) (Gowda et al. 2015). An open labelled randomized controlled trial was carried out at two centres of Bangalore, Karnataka, India on 30 subjects in patients with thrombocytopenia associated with dengue (Gowda et al. 2015). The subjects were randomized into two groups, as control and intervention group (Gowda et al. 2015). Both the groups were managed by the standard management guidelines for dengue except steroid administration (Gowda et al. 2015). During this study, the intervention group received Carica papaya leaf extract (CPLE) tablet three times a daily for five days (Gowda et al. 2015). Platelet count was monitored (Gowda et al. 2015). These results showed that CPLE had significant increase in the platelet count (p<0.003) over the therapy duration, in dengue fever patients, reiterating that it
accelerates an increase in platelet count compared to the control group (Gowda et al. 2015). There were few adverse events related to GI disturbance like nausea and vomiting which were similar in both groups (Gowda et al. 2015). Therefore, this study concluded that Carica papaya leaf extract (CLE) significantly increased the platelet count in patients with thrombocytopenia associated with dengue with fewer side effects and good tolerability (Gowda et al. 2015). Papaya leaf extract (CLE) no doubt offers a cheap and possibly effective treatment for dengue (Gowda et al. 2015). Various clinical and preclinical reports have demonstrated a positive effect in dengue cases with thrombocytopenia (Gowda et al. 2015). The current pilot study also confirmed the same positive beneficial trend in increasing the platelets significantly (Gowda et al. 2015). The oral consumption of Carica papaya leaf extract tablet (CLE) during the course of dengue infection has the potentiality to induce the rapid production of platelets (Gowda et al. 2015; Hossain et al. 2016). This was clearly demonstrated by the significant increase in the mean platelet count in the intervention group (Gowda et al. 2015). However, large scale randomized clinical trials are necessary to further establish its pivotal role in the management of dengue (Gowda et al. 2015).

15) A new bio-insecticide granules toxin from the extract of Carica papaya seed and leaf modified against Aedes aegypti larvae possess technology, dosage, formulation, and remarkable larvicidal activity (Wahyuni, 2015; Kovendan et al. 2012). Further investigations are needed to elucidate active ingredient responsible for larvicidal activity should be identified and utilized in preparing a commercial product (Wahyuni, 2015; Kovendan et al. 2012).

16) Plant derived compounds remains a significant source for the development of antiviral drug. Extracts from the Carica papaya leaves, are commonly prescribed for the dengue patients but there are no scientific evidences for its activity against dengue (Sajin et al. 2015). Therefore, Sajin et al. (2015) investigated the antiviral activity of compounds present in the leaves of Carica papaya against envelope protein of dengue 2 virus (DENV-2). Molecular docking approach using Autodock 4.2 was used in this study and results confirmed that six compounds showed high inhibitory activity against the E protein (Sajin et al. 2015). Six compounds (Stigmast-5-en-3-ol, (3β,24S) (M-30); D-A-Friedooleanan-7-one, 3-hydroxy (M-28); 5-Heptadecene, 1-bromo (M-26); 2-(4-Chlorophenyl)naphtho[2,3-b]furan-4,9-dione (M-27); Neurosporaxanthin methyl ester (M-25); 3,6-bis(t-Butyl)fluorenone (M-20); 5,11,17,23-Tetrakis(1,1-dimethylethyl) pentacyclo [19.3.1.1(3,7)1 (9,132).1(15,19)] octacosa-1-(25),3,5,7(28),9,11,13(27), 15,17,19(26),20,22-dodecaene-4,12,16-triols-24-one (M-22) showed high inhibitory activity against the β-OG pocket (hydrophobic pocket between the domain I and II) of envelope protein (Sajin et al. 2015). This study was focused on assessment of the inhibitory activity of methanol extract compounds of Carica papaya leaves against dengue virus protein (Sajin et al. 2015). Among the identified thirty compounds, six compounds (M-30, M-28, M-27, M-25, M-20 and M-22) showed better binding affinity towards the β-OG pocket of E protein (Sajin et al. 2015). Different modes of interaction such as hydrogen bonding and other hydrophobic interactions were observed between the ligands and the E protein of dengue virus (Sajin et al. 2015). The information acquired through this study on the binding mode of phytocompounds from Carica papaya and E protein would highly facilitate the synthesis and testing of these compounds as drugs against dengue virus (Sajin et al. 2015). These findings concluded that the selected compounds could serve as antiviral drugs for dengue infections (Sajin et al. 2015). Further in-vitro and in-vivo studies are necessary to confirm their efficacy and to evaluate their drug potency (Sajin et al. 2015).

17) The extracts of Carica papaya leaf have been reported to increase the thrombocyte counts in individuals with dengue fever (DF) (Aziz et al. 2015; DeLCure Life Sciences Ltd, Upcount Knowledge series, Issue-2). A study was conducted in order to analyze the potentiality of Carica papaya to induce thrombopoietic Cytokines [Interleukin-6 and stem cell factor] (Aziz et al. 2015; DeLCure Life Sciences Ltd, Upcount Knowledge series, Issue-2). Stem cells obtained from human exfoliated deciduous teeth and in vitro cultures of peripheral blood leukocytes were exposed to unripe papaya pulp juice (Aziz et al. 2015; DeLCure Life Sciences Ltd, Upcount Knowledge series, Issue-2). The results of this study revealed that a rapid in vitro scratch gap closure was achieved in human exfoliated deciduous tooth culture treated with unripe papaya pulp juice (Aziz et al. 2015; DeLCure Life Sciences Ltd, Upcount Knowledge series, Issue-2). An increase was observed in the concentrations of interleukin-6 in human exfoliated deciduous tooth culture and peripheral blood leukocytes culture supernatant when treated with unripe papaya (Aziz et al. 2015). Moreover, a significant rise in the synthesis of stem cell factor (when treated with unripe papaya) in human exfoliated deciduous tooth culture was also noted (Aziz et al. 2015). The conclusion drawn from this study suggested that unripe papaya possess the potential to induce and upregulate in vitro thrombopoietic cytokines synthesis in cells of hematopoietic and mesenchymal origin (both in Peripheral Blood Leukocytes and human exfoliated deciduous tooth culture) (Aziz et al. 2015; DeLCure Life Sciences Ltd, Upcount Knowledge series, Issue-2).

18) Thrombocytopenia in dengue fever is a common and serious complication (Gadhwal et al. 2016; Arya and Agarwal, 2014; Pangtey et al. 2016). Till today, there is no specific treatment for dengue fever (DF) induced thrombocytopenia (Arya and Agarwal, 2014; Gadhwal et al. 2016). Recently, Gadhwal et al. (2016) reported the effect of Carica papaya leaf extract on platelet count in dengue fever (DF) patients (Gadhwal et al. 2016; Pangtey et al. 2016). During this study, all participants were randomised into two groups, study and control group; the study group was given papaya leaf extract capsule of 500 mg once a daily and routine supportive treatment for consecutive five days (Gadhwal et al. 2016). The controls were given only routine supportive
Treatment (Gadhwal et al. 2016). The platelet count was done for both study and control group (Gadhwal et al. 2016). The platelet count of the study group with papaya leaf extract was found to be higher than control group on 3, 5, 7 days respectively (Gadhwal et al. 2016). It was also concluded that Carica papaya leaf extract increases the platelet count in a dengue fever without any side effects and prevents the complication of thrombocytopenia (Gadhwal et al. 2016). Therefore, Carica papaya leaf extract could be used in dengue fever with thrombocytopenia patients (Sharma and Mishra, 2014; Gadhwal et al. 2016).

19) There are many dengue fever cases and dengue is correlated with platelet activation and thrombocytopenia by a poorly understood mechanism (Chinnappan et al. 2016; Pangtey et al. 2016). Carica papaya leaf extract could recover the platelet count in dengue cases (Chinnappan et al. 2016). However, no studies have attempted to unravel the mechanism of the plant extract in platelet recovery (Chinnappan et al. 2016). Therefore, the study reported by Chinnappan et al. (2016) evaluated the Carica papaya leaf extract exerts its action directly on platelets. Further papaya leaf extract could specifically inhibit the platelet aggregation during dengue viral infection (Chinnappan et al. 2016). During this study, sixty subjects with dengue positive and 60 healthy subjects without dengue fever were recruited in the study (Chinnappan et al. 2016). Platelet-rich plasma (PRP) and platelet-poor plasma were prepared from both the dengue-infected and healthy control blood samples (Chinnappan et al. 2016). Effect of the leaf extract obtained from Carica papaya leaves was assessed on plasma obtained as well as platelets collected from both healthy and dengue-infected individuals (Chinnappan et al. 2016). Platelet aggregation was significantly reduced when leaf extract pre-incubated with dengue plasma was added into control platelet-rich plasma (PRP) (Chinnappan et al. 2016). On the other hand no change in aggregation when leaf extract incubated-control plasma was added into control platelet-rich plasma (PRP) (Chinnappan et al. 2016). Upon direct addition of Carica papaya leaf extract, both dengue platelet-rich plasma (PRP) and control platelet-rich plasma (PRP) showed a significant reduction in platelet aggregation (Chinnappan et al. 2016). Within the dengue group, platelet-rich plasma (PRP) from severe and non-severe cases showed a significant decrease in aggregation without any difference between them (Chinnappan et al. 2016). This study concluded that Carica papaya leaf extract could directly act on platelet and leaf extract possessed a dengue-specific neutralizing effect on dengue viral-infected plasma that may exert a protective role on platelets (Chinnappan et al. 2016; Dhara et al. 2016).

20) It has been noted that two components of a dengue viral serine protease, NS2B and NS3, play a pivotal role in viral replication (Senthivel et al. 2013; Ansari, 2016). Furthermore, screening of the flavonoid components of Carica papaya leaves confirmed that quercetin has significant inhibitory activity against NS2B-NS3 serine protease, particularly against dengue virus serotype 2 and exerts its antiviral property by preventing viral assembly (Senthivel et al. 2013; Ansari, 2016).

21) Oral consumption of Carica papaya L. extract leaves has been found to increase the platelet levels as early as 24 h with a significant increase in the total white blood cell and neutrophil counts as well (Swati et al. 2013; Ansari, 2016; Jayanthi, 2016).

22) In another report by Charan et al. (2016), Carica papaya leaf extract could be considered as one of the potential herbal medicine to increase platelet count in patients suffering from dengue fever (DF) (Charan et al. 2016; Wiwanitkit, 2013). During this study, a total of 439 subjects with dengue fever were analyzed for the Carica papaya leaf extracts. Carica papaya leaf extracts was found to be associated with increase in platelet count in the overall analysis (Charan et al. 2016; Wiwanitkit, 2013; Jayanthi, 2016).

23) The flavonoids and other phenols present in the Carica papaya leaf extract have been confirmed to provide the beneficial effects (Sharma et al. 2013; Sarala and Paknikar, 2014). One study found that the leaves of papaya plants are rich in several minerals. It was also noticed that these minerals might balance the mineral deficiency caused by the virus and strengthen the immune cells against dengue (Sharma et al. 2013; Sarala and Paknikar, 2014).

24) A study evaluated the therapeutic benefits of Carica papaya leaf juice on platelet and hematocrit values in patients with dengue fever (Singhai et al. 2016; Agarwal et al. 2016; Dhara et al. 2016). During this study, a total of 80 patients were enrolled from the tertiary healthcare center in central India (Singhai et al. 2016; Agarwal et al. 2016). Subjects were randomized into two groups, 40 patients were intervention groups who received two Carica papaya leaves extract capsules (CPC) thrice daily and rest 40 were controls (Agarwal et al. 2016; Singhai et al. 2016). The results of this study showed that administration of papaya leaf juice was beneficial in dengue patients in elevating the platelet count (p<0.05) and maintained stability of hematocrit in the normal level in those patients who were subjected to Carica papaya leaves extract capsules (Singhai et al. 2016; Agarwal et al. 2016; Jayanthi, 2016). Therefore, Carica papaya leaf extract could be used as an additional or as a complementary drug in dengue fever patients with thrombocytopenia which accelerates the increase in the platelet count and shorten the hospitalization thereby significantly reducing the cost of hospitalization (Singhai et al. 2016; Agarwal et al. 2016; Jayanthi, 2016).

25) Kasture et al. (2016) reported the administration of Carica papaya leaf extract significantly increased the platelet count in cases of thrombocytopenia associated with dengue, preventing the patient to go in dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) conditions (Kasture et al. 2016; Dhungat and Gore, 2016). During this study, a multi-centric, double blind, placebo controlled, randomized, prospective was conducted in 300 patients across
5 centres in order to evaluate the efficacy and safety of *Carica papaya* leaf extract (CPLE), as an empirical therapy for thrombocytopenia associated with dengue fever (DF) (Kasture *et al.* 2016). Furthermore, the subjects were randomized into two groups, as control and intervention group (Kasture *et al.* 2016). In addition to this, the intervention group received *Carica papaya* leaf extract (CPLE) tablet three times daily for five days followed by platelet count (Kasture *et al.* 2016). The results of this study confirmed that *Carica papaya* leaf extract (CPLE) had significant increase (p<0.01) in the platelet count over the therapy duration, in dengue fever patients (Kasture *et al.* 2016). Hence *Carica papaya* leaf extract (CPLE) accelerates the increase in platelet count compared to the control group (Kasture *et al.* 2016). There were few adverse events related to GI disturbance like nausea and vomiting which were similar in both groups (Kasture *et al.* 2016). Drastic fall of the platelets being one of the concerns in dengue cases, this novel option of *Carica papaya* leaf extract (*Caripill*) could be optimized and exploited for the treatment of dengue. The use of *Carica papaya* leaf extract (*Caripill*) is simple, convenient, cost effective, safe and efficacious adjuvant in the treatment of thrombocytopenia (Kasture *et al.* 2016; Benazir and Abhinayani, 2015). Therefore, this study concluded that *Carica papaya* leaf extract (CPLE) significantly increased the platelet count in patients with thrombocytopenia associated with dengue with fewer side effects and good tolerability (Kasture *et al.* 2016). This study has been registered in the clinical trial registry--India (CTRI - Registration number: CTRI/2015/05/005806) (Kasture *et al.* 2016). *Caripill* is the tablet released by a Bengalure based pharmaceutical company *Micro Labs Bengalure*, Karnataka, India for treating patients suffering from dengue fever (The Times of India, 2015; News Gram, 2015). As per standard dosage, one tablet of *Caripill* (110mg) should be taken three times a day, for five days. For children more than 1 year and less than 5 years: 275mg (5m) three times a day for 5 days. For children more than 5 years and less than 18 years: 50mg (10m) three times a day for 5 days (http://www.caripillmicro.com/caripill.php).

26) Secondary interpretation of a therapeutic trial study evaluated the potentiality of *Carica papaya* leaves extract against dengue fever (DF) by application of chemical kinetic studies (Gamage and Basnayake, 2016). The performed secondary analysis data set was obtained from Ahmad *et al.*, (2011) (Gamage and Basnayake, 2016). According to this study, 25 mL of aqueous extract of *C. papaya* leaves was administered to a patient infected with dengue fever twice daily for 5 consecutive days (Gamage and Basnayake, 2016). Before and after the administration, the blood samples from the patient were analyzed for platelets counts (PLT), White Blood Cells (WBC) and Neutrophils (NEUT) (Gamage and Basnayake, 2016). The effectiveness of *Carica papaya* leaf extract was predicted by the logistic growth equation, first order and Michalis-Menten kinetics (Gamage and Basnayake, 2016). Michalis-Menten analysis of PLT count, WBC and NEUT showed longer time period for recovery and it can be predicted (Gamage and Basnayake, 2016). Application of logistic growth equation to predict the rise of PLT count showed the growth coefficient of \( \alpha = 0.627 \), retardation coefficient \( \beta = 0.0033 \), the peak \( \alpha/\beta = 190 \times 10^3/\mu L \) and the lowest \( X = 50 \times 10^3/\mu L \) (Gamage and Basnayake, 2016). However, a first order equation fits better indicating virus inhibitions. A first order rate reaction allows predictions to be made even after one day’s PLT count. If the slope, \( k \) is \( > 0.2868 \), between the ln values of 1st and 2nd day, the patient is likely to have had an attack of dengue virus (Gamage and Basnayake, 2016). Knowing \( k \), can lead to prediction of hypothetical values for the next five days (Gamage and Basnayake, 2016). Michalis-Menten kinetics can be applied to the hypothetical values so as to make comparisons (Gamage and Basnayake, 2016). In order to validate these findings, it is best to undertake a research involving number of patients suffering from dengue (Gamage and Basnayake, 2016). This study confirmed that it is possible to interpret some of the parameters to make comparisons between patients (Gamage and Basnayake, 2016). The application of Michalis-Menten showed defined inhibitive reactions during the decline phase of PLT, WBC, NEUT and RBC (Gamage and Basnayake, 2016). The recovery phase after administering papaya, although at a slower rate, the kinetic study validates the use of papaya as a treatment (Gamage and Basnayake, 2016). The logistic growth equation can be applied to demonstrate the growth and retardation of PLT counts (Gamage and Basnayake, 2016). The first order too can be applied to predict within a day of the presence of dengue virus in a patient (Gamage and Basnayake, 2016). However, this is only a preliminary study which demonstrated the soundness of the mathematical techniques used and it is recommended to undertake a large scale study to validate the findings (Gamage and Basnayake, 2016).

27) Asghar *et al.* (2016) conducted to test the medicinal profile of all parts of *C. papaya* by extracting secondary metabolites with organic and aqueous solvents (Asghar *et al.* 2016). During this study, a total of 42 extracts of different parts of *C. papaya* were examined using key in vitro biological assay models (Asghar *et al.* 2016; Mathew *et al.* 2016). Methanol and ethanol extracts of roots and bark showed good antioxidant activities in addition to leaves, peel and pulp extracts; however, methanol and ethanol extracts of pulp and leaves showed promising antibacterial activities in addition to antioxidant potential (Asghar *et al.* 2016). Ethanol and methanol both were found to be the best solvents of choice to extract natural products to get maximum medicinal benefits (Asghar *et al.* 2016). The results obtained from this study could be more beneficent if individual or combined extraction of pulp, leaves, bark or peels is carried out with ethanol for preparing ready to use extracts to combat oxidative stress and bacterial infections (Asghar *et al.* 2016; Kovendan *et al.* 2012).

28) The study of Ching *et al.* (2016) demonstrated the complementary and alternative medicine (CAM) use among dengue fever (DF) patients was high in Malaysia.
A higher level of education was known to be the factor associated with Complementary and alternative medicine (CAM) use (Ching et al. 2016). The most common Complementary and alternative medicine (CAM) used among dengue fever (DF) patients were isotonic drinks, crab soup and papaya leaf extract (Ching et al. 2016). This study also suggested for more number of studies should be conducted in near future to identify the active compounds in crab soup, which has an antiviral activity against dengue fever (DF) (Ching et al. 2016). The prevalence of Complementary and alternative medicine (CAM) use was 85.3 % among patients with dengue fever (DF) (Ching et al. 2016). The most popular CAMs were isotonic drinks (85.8 %), crab soup (46.7 %) and papaya leaf extract (22.2 %) (Ching et al. 2016). The most common reason for Complementary and alternative medicine (CAM) use was a good impression of Complementary and alternative medicine (CAM) from other Complementary and alternative medicine (CAM) users (33.3 %) (Ching et al. 2016). The main resource of information on Complementary and alternative medicine (CAM) use among patients with dengue fever was family (54.8 %) (Ching et al. 2016). In multiple logistic regression analysis, dengue fever patients with a tertiary level are more likely to use CAM 5.8 (95 % confidence interval (CI) 1.62–20.45) and 3.8 (95 % CI 1.12–12.93) times than secondary level and primary and below respectively (Ching et al. 2016).

29) A study reported by Mir et al. (2016), different flavonoids (baicalein, fisetin, hesperetin, naringenin/naringin, quercetin and rutin) that possess antidenduge activity were adopted for the molecular docking analysis (Mir et al. 2016). Molecular docking analysis was done to examine the inhibitory effect of flavonoids against envelope protein of DENV-2(Mir et al. 2016). Results confirmed quercetin (flavonoid found in Carica papaya, apple and even in lemon) as the only flavone that can interrupt the fusion process of dengue virus by inhibiting the hinge region movement and by blocking the conformational rearrangement in envelope protein (Mir et al. 2016). These novel findings using computational approach are worth while and will be abridge to check the efficacy of compounds using appropriate animal model under in vivo studies (Mir et al. 2016). This information can be used by new techniques and provided a new way to control dengue virus infection (Mir et al. 2016; Kovendan et al. 2012).

30) Asadullah et al. (2017) also evaluated the medicinal role of papaya seeds on thrombocyte count and hepatic parameter on healthy rabbits (Asadullah et al. 2017). This study showed that there is a rationale behind the use of Carica papaya seeds powder in the treatment of thrombocytopenia (Benazir and Abhinayani, 2015; Asadullah et al. 2017). Therefore, Carica papaya seeds powder was effective in rapidly increasing platelet count in healthy rabbits with a standard dosing regimen and extended dosing regimen once a day with standard diet for 45 days (Asadullah et al. 2017). Total platelet count showed direct proportional incremental response, which was further reinforced with the observed escalation of the dose (Asadullah et al. 2017). Hence these results supported the traditional claim that consumption of papaya product in a dengue fever are beneficial (Asadullah et al. 2017; Mathew et al. 2016; Dhungat and Gore, 2016; Jayanthi, 2016).

III. CONCLUSION

Dengue is a serious public health concern and massive challenge to modern medical science, and a major threat to human population. Herbal medicines are used because of the fact that plants contain bioactive compounds that can promote health and alleviate illness. This review paper discussed the diversified role of Carica papaya, from the prevention to the management of dengue. The role of Carica papaya leaf extract in controlling dengue viral fever has been confirmed. Carica papaya leaf extract increases the platelet count in dengue fever and prevents the complication of thrombocytopenia and significantly reducing the cost and period of hospitalization. Sudden fall of the platelets count being one of the concerns in dengue cases. Therefore, a novel option of Carica papaya leaf extract (Caripill) which is simple, convenient, cost effective, safe and efficacious adjuvant in the treatment of thrombocytopenia. Therefore, Carica papaya leaf extract could be used as an additional or as a complementary botanical drug in acute febrile illness patients with thrombocytopenia since optimum dose of papaya leaf accelerates the increase in the platelet count. Further papaya leaf extract could also be used as a oral First aid treatment for dengue or in near future there is a possibility of development of vaccine from papaya such as papaya vaccine. However, optimum oral dose of Carica papaya leaf extract might be associated with the increase of thrombocytopenia platelet count but oral consumption of papaya leaf extract for longer period could cause hepatotoxicity and risk for cardiovascular disease. However, large scale randomized clinical trials are necessary to further establish papaya leaf extract pivotal role in the management of dengue.

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