

THERAPEUTIC POTENTIAL OF *CARICA PAPAYA* L. LEAF EXTRACT IN TREATMENT OF DENGUE PATIENTS

C.V.M. Naresh Kumar^{1,2}, V. Taranath¹, A. Venkatamuni³, R. Vishnu Vardhan⁴, Y. Siva Prasad¹, U. Ravi³ and D.V.R. Sai Gopal^{1,2*}

¹Department of Virology, College of Sciences, Sri Venkateswara University, Tirupati -517 502, Andhra Pradesh, India

²Department of Science and Technology-Promotion of University Research and Scientific Excellence Centre (DST-PURSE CENTRE), Sri Venkateswara University, Tirupati -517 502, Andhra Pradesh, India

³Vishnu Sri Hospital, Korlagunta Main Road, Tirupati -517 502, Andhra Pradesh, India

⁴Department of Statistics, Pondicherry University, Puducherry - 14, India

*Corresponding author Email: profdvrsaigopal@gmail.com

ABSTRACT: *Carica papaya* leaf extracts are known to have many beneficial medicinal properties. Recent studies have claimed possible beneficial effects of *Carica papaya* leaf extracts in treating patients with dengue infection. The present study aims to evaluate the therapeutic potential of *Carica papaya* leaf extracts in treating dengue patients. *Carica papaya* leaf extracts were given to dengue infected patients and their blood samples were daily monitored. Polyserositis condition of the patients was analysed by ultrasonography before and after the completion of *Carica papaya* leaf extract treatment. Repeated Measures ANOVA and descriptive measures such as mean, standard error values were calculated. Before the administration of *Carica papaya* leaf extracts the patients had a low WBC and platelet counts. After the administration of *Carica papaya* leaf extracts there was a good amount of increase in the counts of WBC and platelets ($p < 0.05$) in all the patients and the patients started recovering from dengue infection. Ultrasonographic findings revealed clearance in pleural ascites, pericardiac effusion and peritoneal ascites. Blood analysis reports, ultrasonographic findings, statistical results and patients recovery from dengue infection clearly shows the therapeutic role of *Carica papaya* leaf extracts in treating dengue infected patients. Further studies are necessary for identification of the compounds present in *Carica papaya* leaf extract and exploring their therapeutic role in curing dengue infection.

Key words: *Carica papaya*, Dengue, Papaya leaf extract (PLE), Phytochemicals, Thrombocytopenia.

INTRODUCTION

Dengue is the most important arboviral disease affecting human beings and is a leading cause of illness and death in the tropics and subtropics. It belongs to *Flaviviridae* family and is transmitted by the mosquitoes *Aedes aegypti* and *Aedes albopictus* respectively. Dengue fever (DF) is caused by any of four closely related but antigenically distinct serotypes of dengue virus designated as DENV 1, 2, 3, 4 respectively. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Today about 2.5 billion people (one-third of the world's population), live in areas where there is a risk of dengue transmission. Dengue is endemic in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean. It is estimated that 50 million infections occur annually of which 500,000 are DHF cases and nearly 22,000 deaths mainly among children (WHO, 2014). There are not yet any vaccines to prevent infection with dengue virus (DENV) and the most effective protective measures are those that avoid mosquito bites.

Dengue symptoms usually begin 4 - 7 days after the mosquito bite and typically last for 3 - 10 days. Infected patients deprived of medication, may develop capillary leakage near or at the end of the febrile phase which progresses to DHF (characterised by polyserositis, pleural effusion and haemoconcentration). At this stage if patients do not receive intravascular fluid resuscitations it progresses to DSS and finally death of the patients (Lei et al., 2001; Martina et al., 2009).

The capillary leakage is mainly due to increase in vascular endothelial cell permeability and thrombocytopenic purpura (Lei et al., 2001; Martina et al., 2009). The mechanism behind the platelet reduction is not yet clear till date due to lack of suitable animal model studies (Martina et al., 2009). There are two mechanisms causing thrombocytopenia. DENV induced bone marrow suppression decreases the platelet synthesis and leads to thrombocytopenia (Lei et al., 2001). Immune-mediated clearance of platelets also causes thrombocytopenia (Lei et al., 2001; Martina et al., 2009). In this mechanism, anti-platelet antibodies clear the virus attached platelets via complement activation and also inhibits ADP-induced platelet aggregation (Lei et al., 2001; Martina et al., 2009; Funahara et al., 1987; Huang et al., 2000; Schexneider and Reddy, 2005; Leong et al., 2007).

Complement activation involves over production of cytokines, including TNF α , interleukins (IL-2, IL-6, and IL-8) and other soluble factors which triggers the death of infected cells as well as the anticoagulation pathway. Dengue virus commonly increases the serum trans-aminases which indicates alteration of liver function (Funahara et al., 1987; Huang et al., 2000; Schexneider and Reddy, 2005; Leong et al., 2007). Treatment of dengue patients usually involves the usage of non steroidal anti-inflammatory drugs (NSAIDs) and intravascular resuscitation. A few drugs (Ribavirin, Amantadine, Carboxyfullerene (C60), have shown promising results in inhibiting DENV in *In vitro* conditions, however there is a pressing need to explore and develop antiviral drugs against dengue virus (Lei et al., 2001; Martina et al., 2009).

Recently the haemostatic property and beneficial effects of papaya leaf extract in curing the dengue infected patients has been reported (Hettige, 2008; Ahmad et al., 2011; Yunita et al., 2012; Patil et al., 2013). Papaya leaves contain active components such as papain, chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides and glucosinolates that increases the total antioxidant power in blood and reduce lipid peroxidation level (Seigler et al., 2002). Papaya leaves also contain vitamins (Vitamin A, Vitamin B9, Vitamin B12, Vitamin C), minerals (Calcium, magnesium, sodium, potassium, manganese, iron), saponins, cardiac glycosides and alkaloids respectively which may play an important role in curing of thrombocytopenia (Imaga et al., 2010; Ayoola et al., 2010).

Carica papaya L. (Family: Caricaceae), a perennial plant have been used in folklore for curing a large number of diseases (Hettige, 2008; Eno et al., 2000). Originally native to southern Mexico, the papaya plant is now being cultivated in many tropical countries including Brazil, India, Indonesia, South Africa, Sri Lanka and Vietnam. It is being cultivated widely for consumption as fresh fruit, dried and crystallised fruit as well as for use in drinks, jams and candies. Green fruit, the leaves and flowers may also be used as a cooked vegetable. Papaya leaves and fruit contain several proteins and alkaloids with important pharmaceutical and industrial applications (ElMoussaoui et al., 2001). Several studies were carried out to evaluate the biological activities of various parts of papaya plant such as fruits, shoots, leaves, rinds, seeds, roots and latex (Kovendan et al., 2012).

Papaya fruit and leaf extract were reported to have anti-cancer, anti-oxidative, anti-inflammatory and anti-bacterial properties (Ranasinghe et al., 2012). In addition to this nephro-protective and hepato-protective activity against toxins, hypoglycemic and hypolipidemic effects and anti-sickling properties in sickle cell disease have also been reported (Ranasinghe et al., 2012).

Keeping this in view, the present study is designed to explore the therapeutic role of papaya leaf extract in treating dengue infected patients.

MATERIALS AND METHODS

Preparation of the Papaya leaf extract

Fresh papaya leaves (partly mature) were collected from papaya fields at Perumallapalli Village, Tirupati and authenticated by department of botany, Sri Venkateswara University, Tirupati. The leaves were cleaned with tap water followed by distilled water. The leafy portion of the papaya leaves were taken and crushed using a blender. Using a clean muslin cloth the aqueous portion of the extract was separated. The presence of saponins gives the papaya leaf extract (PLE) the bitter taste. Hence for easy administration of the extract to the patients, sucrose was added.

Study subjects

Patients admitted to Vishnu Sri Hospital (A Multi speciality Hospital), in Tirupati, Andhra Pradesh during November 2012 were enrolled in the study. Patients fulfilling the following inclusion criteria were admitted as having dengue fever: (1) Fever of ≥ 3 -day duration with symptoms showing strong suspicion of dengue (2) a sharp decline in the platelet count (3) polyserositis diagnosed by ultrasonography (4) Positive by dengue NS1 antigen strip (Standard Diagnostics, South Korea).

Study design

Nine dengue infected patients were orally given 5ml of PLE (3 doses daily at a 6 hour interval) for five consecutive days. Before starting the treatment, the procedure and the possible outcomes were explained to the patients and a written consent form was signed by the patient. The study design and protocol was approved by ethics committee of Sri Venkateswara University, Tirupati. During the course of treatment, the clinical conditions of the patients were daily monitored under the supervision of registered physician. Blood samples were daily obtained and different parameters (Haemoglobin, RBC, PCV, Total WBC count, Platelet count, ESR, Lymphocytes, Neutrophils, Eosinophils, Monocytes, Serum Creatinine, Total Bilirubin, Direct Bilirubin) were determined. Tests were done using an automated system and confirmed manually. In addition, polyserositis condition of the patients was analysed by ultrasonography before and after the completion of PLE treatment. The patients were observed for adverse effects for about one month and were asked to report any abnormal signs/symptoms. The usual management of the patient continued after the administration of papaya leaf extract depending on the patient's clinical condition which was mainly saline, anti emetics and paracetamol in few patients. Drugs which were likely to alter the platelet count (such as blood products, non steroidal antiinflammatory drugs (NSAIDs) were not administered to these patients.

Statistical analysis

Statistical analysis was carried out using IBM SPSS 19.0 version and a p - value of less than 0.05 was considered as statistically significant. Descriptive statistics such as mean and standard error values were calculated for all the parameters. Duration wise comparison was carried out for all the parameters using Repeated measures Analysis of Variance to understand the effect of papaya leaf extract. Further graphical representations were made only for the parameters which were found statistically significant to be using line diagram.

RESULTS AND DISCUSSION

Nine patients (6 females and 3 males) fulfilling the inclusion criteria were enrolled in this study. The median ages were 27 for males and 20 for females respectively. The patients were daily given 3 doses of PLE and the blood analysis was carried out. Gradual recovery of all the patients from lethargy, fatigue and fever were observed and this correlated with clinical findings. Haemoconcentration condition was cured by administration of intravenous fluids for the first two days and then gradual recovery was observed (decreased PCV values). After PLE treatment (i.e after 6 days), clearance in pleural ascites, pericardiac effusion and peritoneal ascites were observed in all the patients.

Descriptive statistics such as mean and standard error values were calculated and found to be significant for Total WBC count and platelet count respectively (Table 1). Further, to depict the influence of the PLE, duration wise comparison was carried out using repeated measures Analysis of Variance. Using this, changes in the parameter values were observed for total WBC count and platelet counts respectively (Table 1). Day wise significance has been indicated with the help of alphabets as the superscripts. Here the interpretation can be given as, the same superscripts do not differ significantly but different superscripts differ significantly. If we observe the platelet count with respect to duration, the day 2 platelet count is found to be statistically significant when compared to day 1, and the day 3 platelet count is also found to be statistically significant from day 2 and so on so forth. Similarly a gradual increase in the WBC counts was also observed in all the patients. This means that on using PLE, there is a good amount of increase in the platelet and WBC counts of all the patients. To explicate the information given in table 2 a graphical representation has been made using line chart constructed on the basis of mean and standard error values by considering all the 6 days (Figure 1). After administration of PLE, the patients were observed for one month and no adverse reactions were observed indicating the non-toxic nature of PLE.

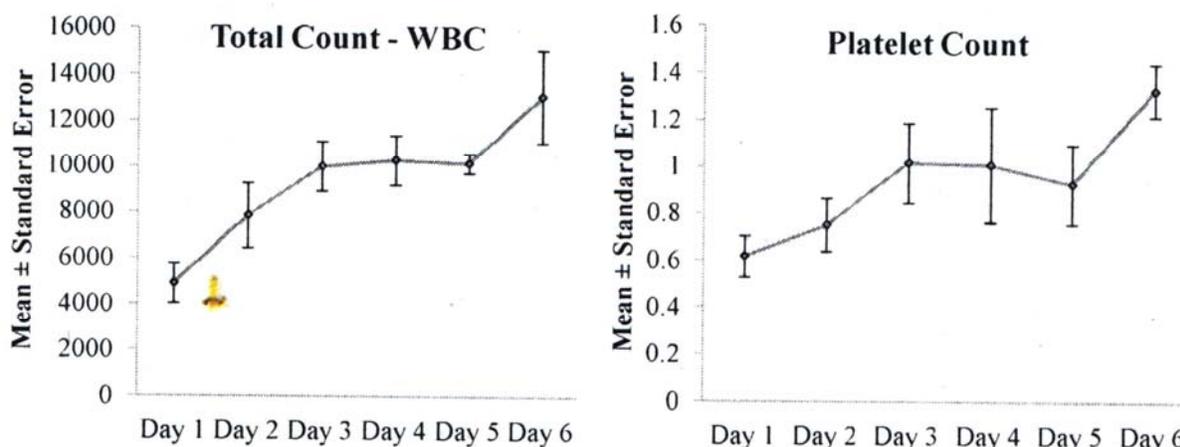
In the present study we found the therapeutic potential of papaya leaf extract (PLE) in curing dengue infection by increasing platelet and WBC counts respectively. Ultrasonographic findings, blood reports, statistical analysis and patient's recovery from dengue infection further supported the culinary effect of papaya leaf extract (PLE) in dengue patients. The nontoxic nature of PLE also supports its use as natural herbal remedy for dengue infection. An earlier study categorized *Carica papaya* leaf as non toxic ($LD_{50} > 15g$ per Kg body weight) (Kardono et al., 2003).

Herbs have been an integral part of society since the beginning of human civilization and are valued for their culinary and medicinal properties. With the development of patented medicines in the early part of the 20th century, herbal medicine lost ground to the new synthetic medicines touted by scientists and physicians to be more effective and reliable. However, plant derived drugs and herbal remedies are considered to be less toxic and are still popular globally (Yunita et al., 2012). Toxicological effect of papaya leaf extract were evaluated in a murine model and were found to be safe (Gammulle et al., 2012).

Table 1: Representation of Mean \pm Std. Error values for statistically significant parameters

Parameters	Duration	*Mean \pm Std. Error
Total WBC Count	Day 1	4911.110 ^a \pm 869.298
	Day 2	7855.560 ^a \pm 1404.270
	Day 3	10025.000 ^b \pm 1080.468
	Day 4	10300.000 ^b \pm 1093.161
	Day 5	10166.670 ^b \pm 425.572
	Day 6	13100.000 ^c \pm 2000.000
Platelet Count	Day 1	0.618 ^a \pm 0.087
	Day 2	0.752 ^b \pm 0.113
	Day 3	1.018 ^c \pm 0.172
	Day 4	1.010 ^c \pm 0.246
	Day 5	0.927 ^c \pm 0.171
	Day 6	1.330 ^d \pm 0.110

* Indicates that same superscripts do not differ significantly but different superscripts differ significantly

**Figure 1: Graphical representation of Mean \pm Std. Error values for statistically significant parameters**

Papaya is known as "A powerhouse of nutrients" and was reputedly 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 (Ranasinghe et al., 2012). Flavonoids and other phenolic compounds present in papaya leaf extracts were responsible for the observed membrane stabilizing property and thereby prevent the internal bleeding in the blood vessels (Ranasinghe et al., 2012). A recent study showed that flavonoids present in carica papaya inhibits NS2B-NS3 protease and thereby prevent the DEN-2 Virus assembly (Senthilvel et al., 2013). Recent studies have also shown that papaya leaf juice significantly increases the platelet count (Subenthiran et al., 2013; Dharmarathna et al., 2013).

Papaya leaf contains anti-oxidant vitamins and minerals which may help to increase the haemoglobin, hematocrit, Red blood cells, thrombocytes and total protein contents (Kathiresan et al., 2009; Halim et al., 2011). 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 (Kathiresan et al., 2009; Betty et al., 2009). Vitamin C may act as anti-oxidant to scavenge the oxygen radicals (superoxide, hydroxyl, peroxy) sulphur radicals and nitrogen - oxygen radicals (Sebastian et al., 2003).

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 (Cabrera-Cortina et al., 2008; Emilio et al., 2009). Magnesium ions improves erythrocyte hydration. Sodium ions helps in maintaining electrolyte balance and prevents hyponatremia during dengue infection (Jutrat et al., 2005). Potassium ions maintains body potassium level and helps to prevent Acute hypokalaemic quadriplegia during dengue infection (Sanjeev and Ansari., 2010; Amitava et al., 2011; Harmanjith et al., 2012).

Manganese ions helps in reducing inflammation and joint pains during dengue infection. Iron is the important oxygen carrier material which helps in red blood cell formation. Papaya leaf contains α -amylase, β -amylase, carbohydrate, protein and essential amino acids (glutamine, proline) which may involve in the important secondary metabolite production. Xanthine oxidase inhibitors present in papaya leaf helps to scavenge superoxide free radicals produced during dengue virus infection (Saiful et al., 2012). The papaya leaf extracts increases the erythrocyte glutathione peroxidase 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.

CONCLUSION

The preliminary data of the present study suggests the therapeutic role of *papaya* leaf extract (PLE) as a cheap and potential herbal therapy for treating the dengue infected patients. Further studies should be carried out for identification of the compounds present in *Carica papaya* leaf extract and exploring their therapeutic role in curing dengue infection.

Conflict of interest statement

We declare that we have no conflict of interest.

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