

EFFECTIVENESS OF CARIPILL DRUG IN THE TREATMENT OF DENGUE FEVER**Dr. Abel Abraham Thomas*¹ and Ms. Aksay Kuruvillia²**

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ABSTRACT

Dengue fever is considered to the most common arthropod borne viral illness which is caused by the infestation of Aedes mosquitoes distributed in subtropical and tropical areas of the world. This disease has its most common clinical manifestation of thrombocytopenia leading to severe bleeding and dengue hemorrhagic fever as its major complication. Treatment for dengue is often based on symptoms and many studies have done to done to treat thrombocytopenia. The administration of Carica papaya leaf extract should significantly increase the platelet count in cases of thrombocytopenia associated with dengue, preventing the patient to go in DHF or DSS conditions. Results: The results indicate that CPLE had significant increase in the platelet count over the therapy duration, in dengue fever patients,

confirming CPLE accelerates the increase in platelet count compared to the control group. There were few adverse events related to GI disturbance like nausea and vomiting which were similar in both groups. This study concluded that Carica papaya leaf extract (CPLE) does significantly increase the platelet count in patients with thrombocytopenia associated with dengue with fewer side effects and good tolerability.

KEYWORDS: Dengue, Caripill, Thrombocytopenia, Platelets.

INTRODUCTION

Dengue is a viral infection caused by four closely related, but antigenic ally distinct serotypes of the Flaviviridae family, which are designated as dengue virus (DENV) DENV-1, DENV-2, DENV-3 and DENV-4.^[2]

Dengue is transmitted by the bite of an *Aedes aegypti* mosquito. *Albopictus* mosquito which in recent decades has become a major international public health problem. Dengue is prevalent in tropical and sub-tropical regions around the world, predominantly in urban and semi urban areas. Total of 18,371 cases of dengue fever (DF) and dengue haemorrhagic fever (DHF) were reported last year and had claimed 33 lives in the same year.^[4]

Many cases of dengue are asymptomatic, especially in children and in adults with a first infection. In other cases, it may appear as self-limited, undifferentiated fever or classic dengue fever.^[6]

Thrombocytopenia in dengue fever is a common and very serious complication. However, no specific treatment is available for dengue fever induced thrombocytopenia.

Dengue fever is often characterised with incubation period varying from 3 to 14 days is followed by a febrile illness consisting of sudden-onset fever, headache, myalgia, arthralgia, rash and thrombocytopenia and even can lead to the damage of organs such as liver and bone.^[10] The patient develops hemorrhagic manifestations such as petechiae and bleeding through the nose, gastrointestinal tract and gums. A number of atypical manifestations have also been reported in many studies, which include encephalitis, encephalopathy, myocarditis, hepatitis and cholecystitis.^[7]

Treatment for dengue is usually symptomatic. One of the most disturbing aspects of the problem of dengue is that there are no effective antiviral agents available to treat dengue complications.^[12] Though symptomatic treatment works in most mild cases, some cases progress to complications very fast and this often make it difficult to save the life of the patient. Some cases require platelet transfusions and fluid management.^[3]

In few countries (Pakistan, Malaysia, Sri Lanka and other Asian countries) the leaf extract of *Carica papaya* has been effectively used for thrombocytopenia. Dengue fever is often characterised with incubation period varying from 3 to 14 days is followed by a febrile illness consisting of sudden-onset fever, headache, myalgia, arthralgia, rash and thrombocytopenia and even can lead to the damage of organs such as liver and bone.^[4] The patient develops hemorrhagic manifestations such as petechiae and bleeding through the nose, gastrointestinal tract and gums. A number of atypical manifestations have also been reported in many studies, which include encephalitis, encephalopathy, myocarditis, hepatitis and cholecystitis.^[5]

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So, the study is planned to make a review of the effect of *Carica papaya* leaf extract on platelet count in dengue fever patients.

DENGUE FEVER

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. **Dengue fever** is a mosquito-borne tropical disease caused by the dengue virus. It is transmitted mainly by *Aedes aegypti* mosquito. ^[1]

EPIDEMIOLOGY

Infections are most commonly acquired in the urban environment. In recent decades, the expansion of villages, towns and cities in the areas in which it is common and the increased mobility of people have increased the number of epidemics and circulating viruses. Dengue fever, which was once confined to Southeast Asia and has now spread to Southern China, countries in the Pacific Ocean and America and might pose a threat to Europe.

Global incidence of dengue has drastically upped in the last few years. According to the World Health Organization (WHO), there are about 390 million cases of dengue fever worldwide, and of the total number of cases, 96 million require medical treatment. India also saw a doubling up of cases of dengue from 2014 to 2015 and the worst hit city was Delhi with over 1800 cases of the fever. 2016 isn't expected to be any better and this has become a cause of concern for the country.

An infection with dengue is second only to malaria as a diagnosed cause of fever among travellers returning from the developing world.^[20] It is the most common viral disease transmitted by arthropods,^[24] The World Health Organization counts dengue as one of seventeen neglected tropical diseases.

Like most arboviruses, dengue virus is maintained in nature in cycles that involve preferred blood-sucking vectors and vertebrate hosts.^[16] The viruses are maintained in the forests of Southeast Asia and Africa by transmission from female *Aedes* mosquitoes—of species other than *A. aegypti*—to their offspring and to lower primates.^[16] In towns and cities, the virus is primarily transmitted by the highly domesticated *A. aegypti*.

In rural settings the virus is transmitted to humans by *A. aegypti* and other species of *Aedes* such as *A. albopictus*.^[16] both these species had expanding ranges in the second half of the 20th century.^[18] In all settings the infected lower primates or humans greatly increase the number of circulating dengue.

ETIOLOGY

Dengue fever virus (DENV) is an RNA virus of the family *Flaviviridae*; genus *Flavivirus*. Most are transmitted by arthropods (mosquitoes), and are therefore also referred to as arboviruses (*arthropod-borne* viruses).

CLINICAL MANIFESTATION

The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. The alternative name for dengue, "break bone fever", comes from the associated muscle and joint pains. The course of infection is divided into three phases: febrile, critical, and recovery.

The febrile phase involves high fever, potentially over 40 °C (104 °F), and is associated with generalized pain and a headache; this usually lasts two to seven days. Nausea and vomiting may also occur. A rash occurs in 50–80% of those with symptoms in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4–7), as a measles-like rash.

A rash described as "islands of white in a sea of red" has also been observed. Some petechiae (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries) can appear at this point, as may some mild bleeding

from the mucous membranes of the mouth and nose. The fever itself is classically biphasic or saddleback in nature, breaking and then returning for one or two days.

In some people, the disease proceeds to a critical phase as fever resolves. During this period, there is leakage of plasma from the blood vessels, typically lasting one to two days. This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and decreased blood supply to vital organs. There may also be organ dysfunction and severe bleeding, typically from the gastrointestinal tract. Shock (dengue shock syndrome) and haemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue; however those who have previously been infected with other serotypes of dengue virus ("secondary infection") are at an increased risk. This critical phase, while rare, occurs relatively more commonly in children and young adults.

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream. This usually lasts two to three days. The improvement is often striking, and can be accompanied with severe itching and a slow heart rate. Another rash may occur with either a maculopapular or a vasculitic appearance, which is followed by peeling of the skin.^[18] During this stage, a fluid overload state may occur; if it affects the brain, it may cause a reduced level of consciousness or seizures. A feeling of fatigue may last for weeks in adults.

PATHOPHYSIOLOGY

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells, and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signalling proteins, such as cytokines and interferons, which are responsible for many of the symptoms, such as the fever, the flu-like symptoms, and the severe pains. In severe infection, the virus production inside the body is greatly increased, and many more organs (such as the liver and the bone marrow) can be affected. Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever.^[39]

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.

The capillary leakage is mainly due to increase in vascular endothelial cell permeability and thrombocytopenia. 4,5 The mechanism behind the platelet reduction is not yet clear till date due to lack of suitable animal model studies.5 There are two mechanisms causing thrombocytopenia. DENV induced bone marrow suppression decreases the platelet synthesis and leads to thrombocytopenia.4 Immune-mediated clearance of platelets also causes thrombocytopenia. In this mechanism, anti -platelet antibodies clears the virus attached platelets via complement activation and also inhibits ADP-induced platelet aggregation.

TREATMENT

Apart from attempts to control the spread of the Aedes mosquito there are ongoing efforts to develop antiviral drugs that would be used to treat attacks of dengue fever and prevent severe complications. There are several plausible targets. The first approach is inhibition of the viral RNA-dependent RNA polymerase (coded by NS5), which copies the viral genetic material, with nucleoside analogy. Secondly, it may be possible to develop specific inhibitors of the viral protease (coded by NS3), which splices viral proteins.^[79] Finally, it may be possible to develop entry inhibitors, which stop the virus entering cells, or inhibitors of the 5' capping process, which is required for viral replication.^[78]

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CURRENTLY AVAILABLE TREATMENT FOR DENGUE

1. The standard treatment protocol for management of Dengue includes symptomatic treatment with fluid management. This is the best option, if detected on time.
2. Drugs like Eltrombopag and Romiplostim are available for increasing the platelet counts, but they are pretty costly options. Again, very much avoidable.

3. Using corticosteroid is advised by some as it is supposed to halt further platelet destruction but generally not preferred. The side-effects are pretty bad enough. Moreover, it is an immunosuppressant; it will "hide" any other secondary infection.
4. Platelet transfusion if the platelet count goes below 20000 / μ l, where such is advocated.

Currently there is no specific treatment for DENV, recent hopeful vaccine candidates have just been deemed ineffective, and there is no prediction of complete vector control. However, rapid diagnosis followed by targeted vector control efforts decrease DENV transmission, and early detection followed by supportive care is reported to potentially decrease mortality rates from 5-20% to less than 1%. 11-13.

There is no specific treatment for dengue; intensive supportive care is the most important aspect of management. The thrombocytopenia which usually happens in the effervescence stage of the illness is the critical phase, and if left unattended or untreated it can lead to mortality.

Till now there is no approved vaccine or drug against dengue virus, therefore there is an urgent need of development of alternative solutions for dengue. Several plants species have been reported with anti-dengue activity. Recently, the use of alternative medicine and the consumption of plant materials have increased in many countries in the world, mostly because plant-derived drugs and herbal formulation are commonly considered to be less toxic and less side effects than the synthetic ones.

NEED FOR CARIPILL

A Bangalore based pharmaceutical company Micro Labs Limited launched a pill known as Caripill which is said to increase the platelet count in patients suffering from dengue.

The drug is a plant medicine manufactured by using carica papaya leaf extract which has received clearance from the department of Ayush. and it underwent clinical trials on 250 dengue patients for two years that has shown decrease in the haemorrhage condition. Caripill works by stimulating the genes responsible for production of platelets. Carica Papaya may have Anti diabetic health benefits Papaya, botanical name *Carica papaya*, is a lozenge tropical fruit seen in orange-red, yellow-green and yellow-orange hues, with a rich orange pulp. The fruit is not just delicious and healthy, but whole plant parts, fruit, roots, bark, peel, seeds and pulp are also known to have medicinal properties. Papaya is a powerhouse of nutrients and is

available throughout the year. It is a rich source of three powerful antioxidant vitamin C, vitamin and vitamin E; the minerals, magnesium and potassium; the B vitamin pantothenic acid and folic acid and fiber. (1)

Different parts of the papaya plants including fruit, dried fruit, leaves, dried leaves, stems, seeds and roots have long been used as ingredients in alternative medicine. For instance, the seeds are used for expelling worms and roots and seeds are used as an abortifacient agent. The leaves (especially fallen ones) are used variously for the treatment of fevers, pyrexia, diabetes, gonorrhoea, syphilis (6).

The Pharmacology of Caripill includes, it possesses membrane stabilizing properties and protect blood cells against stress-induced destruction (3).

In desperation, many people have resorted to use papaya leaf extract covertly. This is applicable even to hospitalized dengue patients. However, recommending *C. papaya* leaf extract for dengue infection is unethical until it is proven by scientific research.

Papaya extract no doubt offers a cheap and possibly effective treatment for dengue. However, currently, it is also necessary not to rely entirely on the leaf extract and ignore standard treatment for dengue until the benefits are established.

DRUG MONOGRAPH OF CARIPILL

Name & Composition

Carica Papaya Leaf Extract; each tablet contains 1100 mg strength & Syrup contains 275 mg / 5 ml

Dosage

- One tablet of Caripill (1100mg) should be taken three times a day, for five days.
- For children more than 1 year and less than 5 years: 275mg (5ml) three times a day for 5 days.
- For children more than 5 years and less than 18 years: 550mg (10ml) three times a day for 5 days

Therapeutic Indications

As an adjuvant for increasing the thrombocytes associated with dengue fever. In thrombocytopenia for treatment and/or prevention of bleeding.

Mechanism of Action

The ALOX 12 gene and PTAFR genes are strongly expressed in megakaryocytes. ALOX-12 has been known to be responsible for the 12-Hydroxyeicosatetraenoic acid (12-HETE) production of platelets. Carica papaya leaf extract has been found to increase the ALOX 12 activity by 15 fold and 13.42 fold increase in PTFAR activity which increases the platelet production.

Contra-indications

Hypersensitivity, Pregnancy.

In males with prostate dysfunction, such as BPH or prostate cancer, C. papaya should be avoided as it increases the iron absorption. Excess iron may increase oxidative stress, especially in the aging male. Iron overload may increase the risk of developing prostate cancer.

Precautions and Interactions

Should be used with caution in individuals with bleeding disorders or those taking blood thinning medications such as aspirin or warfarin. Co administration of extracts of Carica papaya with oral hypoglycaemic may lead to very low blood glucose as observed in one of the experimental animal study. Thus it is important to closely monitor the blood glucose levels regularly to avoid hypoglycaemia.

It has been found to increase the bioavailability of amiodarone and therefore the dose should be adjusted accordingly when co administered with carica papaya leaf extract. In vitro study demonstrated potentiating the action of various antibiotics like penicillin G, ampicillin, amoxycylav, cephalothin, polymyxin B, rifampicin, amikacin, nalidixic acid, gentamycin, cholarmphenicol, ofloxacin when co administered with C. Papaya. The extract of C. papaya with antimicrobial agents possesses synergistic properties which act against the pathogenic organisms.

Adverse effects

Nausea, Vomiting, Abdominal pain, Heartburn, Dyspepsia.

REVIEW OF LITERATURE

Spruthi T did a prospective study on is carica papaya beneficial in dengue patients as platelet elevator. This study was conducted in Medicine department of Viswabarathi Hospital, which are 250 bedded tertiary care teaching hospital providing health care services. The research approach adopted in this study was prospective study in Medicine Department of a tertiary care teaching hospital. This study was conducted from August to November 2015. This study includes hospital In-patients treated for Dengue in Medicine department.

Patient who meets the following criteria was enrolled where, Inclusion criteria was patients of all age groups, both genders. Exclusion criteria were patients with other infectious diseases. The cases which had found in Medicine department, details of cases including patient name, age, sex, past medical history and other relevant information was collected. The collected prescriptions were entered into Microsoft Office Excel sheet according to their age, gender, therapeutic category and prescription. Their result was found that total of 134 patients were analysed. In them 72 (54%) were serologically dengue positive and 62 (46%) were dengue suspected patients. Among the serologically positive patients, male are 44(61%) and females 28(39%). In the same way in dengue suspected patients male are 33(53%) and females 29 (47%). Maximum populations were seen in the age group of 11-20 and the least were seen in the age group of 71-90.

S Hettigedid a pilot study on salutary effects of carica papaya leaf extract in dengue fever patients. This pilot study was undertaken to find out whether *carica papaya* leaf extract had any effect on increasing the lowered platelet count. Twelve patients are under his clinical care, they were given a papaya leaf extract-two 5ml doses at an 8 hour interval for adults and two 2.5 ml doses at an 8 hour interval for children <10 years. Before the treatment, the procedure and the possible outcomes was explained to the patient. The papaya leaf extract was prepared by crushing two (2) tender fresh papaya leaves (not too young – not too mature, using only the leafy part removing the stalks) and squeezing the juice by hand. The juice was given for drinking without diluting. Prior to the intake of papaya leaf juice, a sample of blood was obtained to determine the white cell count, platelet count, alanine aminotransferase (ALT) and packed cell volume. A second sample of blood was obtained, the next day, to determine the white cell count, platelet count, ALT and PCV. Tests were done using an automated system and confirmed manually. This pilot study has shown the effects of papaya leaf juice in dengue patients of elevating the total white cell counts, platelet counts and recovery without hospital admission.

Siddique O et.al did a case study on effect of papaya leaves on thrombocyte counts in dengue. Oral administration of Carica papaya leaves extract is said to have a positive impact on thrombocyte count. A 23-year-old man was administered a calculated dose for five days. Blood samples were tested for complete blood count before and after the administration of the juice. Thrombocyte count had increased from 28000/micro liter to 138000/micro liter at the end of five days. A toxicity study (acute, sub-acute, and chronic toxicity) conducted on

Sprague Dawley rats administered with Carica papaya leaves juice (CPLJ) of the sekaki variant revealed that it was safe for oral consumption.^[12] There are no anti-viral chemotherapeutic agents yet discovered for DF.^[13] They further investigated their role in DF and effects on thrombocyte counts. Their investigation revealed positive findings in the role of C. papaya leaves for the treatment of dengue and for improving platelet counts. This was also observed in another study on a 45-year-old man where counts increased from 55000/micro liter to 168000/micro liter. Their study further depicted the improvement in the symptoms of dengue during and following the administration of the extract. Along with the increasing thrombocyte destabilisation of biological membranes.^[17] The patient's recovery and progressive increase in thrombocyte counts could have been spontaneous since DF is a self-limiting disease with sufficient supportive therapy. This factor can be investigated in a further study using controls.

Their study supports the popular claim of the use of C. papaya leaves in treating DF by increasing platelet counts and alleviating symptoms. The study concluded that C. papaya leaves seems to be a promising solution to treat dengue fever. Dengue fever continues to be a nuisance, causing several deaths every year, and a further detailed study on investigating this topic might help in reducing the associated mortality.

The Bengaluru-based Micro Labs has launched Caripill which helps to increase the platelet count in dengue. The product underwent clinical trials on 300 patients and is already a preferred prescription for dengue specialists. This is the first drug which is backed by adequate scientific data to increase the platelet count in dengue cases.

Caripill in its clinical trials has demonstrated positive results with a dramatic decrease in the haemorrhage condition, besides, none of the patients had to undergo blood transfusion so far, said Dr. A.C. Gowda, Fortis Hospital, Bengaluru and principal investigator, clinical trial for Caripill.

So long, no specific treatment was available for treating dengue, except for some paracetamol tablets, mostly Dolo 650 by Micro Labs to reduce the fever. However immediately post the fever reduces, blood platelets count starts falling leading to serious health consequences. Now Caripill available at all pharmacy outlets has brought immense relief at an affordable price of Rs.25 per tablet with the dosage of administering one pill (1100 mg) three times a day, for

5 days, thus reducing the financial burden and emotional trauma, said Ashok Jain, executive director, Micro Labs Ltd.

YUNITA F et.al did a study on the effect of carica papaya leaves extract capsules on platelet count and haematocrit level in dengue patient. The study was approved by ethics committee of research at and development of Indonesian Ministry of Health. An open randomized controlled clinical trial was conducted at the inpatient medicine ward hospital at Bekasi, West Java Indonesia. Each subject received 24 capsules to be taken twice daily. Eligible clinical trial subjects would receive study material and be monitored everyday to evaluate the outcome. Blood samples were obtained twice daily and the platelet count and haematocrit level were determined in the clinical hospital laboratory, during in the hospitalization period.

The results found that CPC that has been standardised and more comfortable for the patient. CPC also can maintain the haematocrit level of the subjects within the normal level. The study concluded that the CPC could be used as an additional or as a complementary drug in dengue fever patients, accelerates the increased in platelet count, and shorten the hospitalization period.

C V M Nareshkumar did a study on therapeutic of carica papaya leaf extract in treatment of dengue fever. Nine dengue infected patients were orally given 5ml of PLE (3 doses daily at a 6 hour interval) for five consecutive days. 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 and 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 anti Inflammatory drugs (NSAIDs) were not administered to these patients. Results was found to be 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. After PLE treatment, 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 was observed. 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. 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. 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. Toxicological effect of papaya leaf extract were evaluated in a murine model and were found to be safe (Gammulle et al., 2012). the study concluded that 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.

A C Gouda did a prospective study on pilot study to effectiveness of carica papaya leaf extract in increasing the platelet count in cases of dengue with thrombocytopenia. A multi-

centric openlabeled, randomized, comparative pilot study was conducted at two centres of Bengalurumetropolis. The carica papaya leaf extract was formulated in appropriate dosage form of tablet in the strength of 1100mg. A total of 30 subjects diagnosed as dengue cases by NS1 antigen test were enrolled and randomized in this study. The results found that all the 30 subjects enrolled completed the study. These subjects were diagnosed as dengue cases by NS1 antigen test. After administering the tablet *Carica papaya* leaf extract (Caripill) to the study group (n=14) every day platelets of both the groups were monitored from the various reports published in scientific literature, it appears that *C. papaya L.* leaf extract does have beneficial properties in dengue. It has been shown to bring about rapid increase in platelet count. It is shown that the subjects in the intervention group that received CPLE (Caripill) can reach faster and higher increase in platelet count compared to the control group. The finding of this pilot study corroborates the claim that the *Carica Papaya* leaf extract tablet consumption during the course of dengue infection has the potential to induce the rapid production of platelets. The study concluded that Papaya extract no doubt offers a cheap and possibly effective treatment for dengue.

Various clinical and preclinical studies conducted have demonstrated a positive effect in dengue cases with thrombocytopenia. The current pilot study also demonstrates the same positive beneficial trend in increasing the platelets significantly. However, large scale randomized clinical trials are necessary to further establish its pivotal role in the management of dengue.

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 $<150,000/\mu\text{L}$ 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.

Some of the traditional claims of efficacy that have been investigated scientifically using animal models and their efficacy have been proven. Recent studies showed that *C. papaya* leaf extract has potential anti-sickling (inhibition of sickle cell formation) properties. Indran *ET al.* has shown that there is a protective effect against gastric ulcers in rats. Moreover, *C. papaya* flowers are known to have antibacterial activities. The contraceptive efficacy of the seeds of *C. papaya* has been earlier demonstrated in rats, mice and rabbits. Oral administration of *C. papaya* seed extract could induce reversible male infertility and could be used for pharmaceutical development of a male contraceptive.

Waduqe R N did an experimental study on Does *Carica papaya* leaf-extract increase the platelet count? An experimental study in a murine model. The method involved in this study was a male white mice (average body weight 32-33 g) 6 weeks old, obtained from the Medical Research Institute, Sri Lanka were used as the model for haematological and toxicological investigation. Animals were kept in the animal house of the Faculty of Medicine, University of Peradeniya. Three experimental trials were conducted during May 2011 to May 2012 using three sets of mice. Mice were divided into two groups, control and test, in all three trials. For the first and Male second trials, we used 48 mice (for each trial 12 mice/control and 12 mice/test) and for the third trial, 36 mice were used (18 control and 18 test). All mice were given a standard commercial diet with free access to water. All mice in both test and control groups were numbered by ear tattooing. The first trial was a pilot study to plan a proper study where the following variables were considered-dose of *C. papaya* leaf extract, timing of blood sampling and histopathological changes in liver. The second trial refined the methodology and the third provided the results presented. In the first trial, they used 0.5 mL (5 g)/mouse/day and in second and third trial, we used 0.2 mL (2 g)/mouse/day. The first trial was conducted to determine a suitable daily dose per mouse. In the third trial, test group mice were fed with fresh *C. papaya* leaf extract for seven consecutive days (0.2 mL (2 g)/mouse/day), the first of these days being regarded as day one of the trial. Similarly, the control group was given water.

Body weights of all mice were recorded before feeding started and weighing was repeated every second day during the study period. Behavioural activities were recorded once a day.

Blood smears were prepared to evaluate the platelet and red blood cell (RBC) counts from both test and control groups on alternate days and on days of sacrifice (on Days 8, 14 and 21, an equal number of mice were sacrificed from each group for biochemical and histological

examination). The numbers of platelets and RBCs were counted in 10 fields or more under oil immersion ($\times 100$). The procedure was repeated in thin or thick areas of the film if the distribution was uneven. Then, average numbers of platelets and RBCs were determined by dividing the total number by the number of fields viewed. Finally, the average number of platelets and RBCs was multiplied by the established field factor to determine the estimate count.

Six mice from each group (test and control) were sacrificed at Day 8, 14 and 21. Blood was collected. Packed cell volume (PCV) was measured. Serum was separated and stored at -80°C until use. Serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase and creatinine levels were also measured. Furthermore, specimens (liver, lungs, kidney, heart, intestine and spleen) were collected for the histopathological and toxicological investigation.

The average body weight of mice at the start for the third trial was (32.000 ± 0.595) g in the test group and (32.70 ± 0.70) g in the control group. However, it was observed that the average body weight was (36.20 ± 1.63) g and (36.50 ± 1.62) g in the test and control groups respectively by Day 21 after the start of treatment. Neither loss of body weight nor behavioural changes were observed in the test group.

Histopathology

There were no gross pathological changes observed on organs during the post mortem examination of mice from either group. Examination of histological sections of the liver, lung, kidney, spleen, heart and the intestine found no remarkable changes other than mild focal lytic cell necrosis in three liver sections obtained from the test group (3 of 18 samples). However, in the first trial, when high dose of *C. papaya* leaf extract was used, liver histology showed focal lytic necrosis of all test groups indicating that there can be dose dependent toxicity.

Serology

Serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase and creatinine levels were not altered.

Hematological investigation

No significant changes were observed in PCV in the test group compared to that of the control group. Values always remained within the normal range.

Average platelet counts of the test and control groups were $(3.36 \pm 0.16) \times 10^5/\mu\text{L}$ and $(3.67 \pm 0.16) \times 10^5/\mu\text{L}$ respectively before the experiment. There was no significant difference in the platelet counts during the first 3 days in either group. However, platelet counts within the test group started to rise steadily after Day 3 and reached a peak level at Day 13. Subsequently, the platelet count remained relatively constant at a range of 10×10^5 to $11 \times 10^5/\mu\text{L}$. The platelet count of the test group was $(11.33 \pm 0.35) \times 10^5/\mu\text{L}$ at the end of the experiment compared to that of the control group $(5.53 \pm 0.12) \times 10^5/\mu\text{L}$.

Their results clearly indicated that there was a significant increase in average platelet counts in the test group, as against a slight increase in the control group. RBC count was also significantly increased in the test group compared to controls. There were no morphological changes observed in blood cells of mice in test group.

The study concluded that an oral feeding of pure extract of *C. papaya* leaves causes considerable increases in platelet and RBC counts in the murine model without causing any acute/subacute toxicity. Therefore, they suggest that *C. papaya* leaf extract may be used as a medicine to boost haemopoiesis and thrombopoiesis when these have been suppressed by disease.

Abdullah N R did a research on Carica papaya Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever. The method involved in this study were the A total of 145 patients were recruited into the interventional group while 145 patients were recruited into the control group. At the end of the study, 111 patients from the interventional group and 117 controls were included in the statistical analysis. Sixty-two patients were excluded from the analysis as 38 patients were lost to follow-up and 24 patients had incomplete dataC. Papaya leaves of these kaki variant were chosen for the study based on fingerprinting and safety analysis which also contained allowable limit of heavy metals and microbial content. For the purpose of the study, a private plantation certified by the Ministry of Agriculture in Semenyih, Selangor was identified to provide the leaves for the entire duration of the study to ensure similar source of authenticated raw material used. The trees in this plantation were kept free

of herbicides, pesticides and insecticides. Juice was prepared fresh from the leaves that were washed thoroughly with an organic vegetable cleaning agent and reverse osmosis water few times. Juice was extracted from 50 grams of fresh leaves using a juice extractor without any addition of water, under sterile conditions. The fresh juice was aliquoted at a volume of approximately 30 mLs in sterile glass vials and transported daily in an icebox and kept at a temperature of below 4°C to the study site at the male and female dengue wards.

The juice was characterized and standardized using a High Performance Liquid Chromatography Diode Array Detector according to three markers: manghaslin, clitorin and rutin. The chemical fingerprinting of the leaves was consistent throughout the study. This finding supports the claim that the juice consumption during the course of dengue infection has the potential to induce the rapid production of platelets. This was clearly demonstrated by the significant increase in the mean platelet count after 40 hours and 48 hours of juice consumption. The study concluded that the administration of CPLJ in DF and DHF is safe and does induce the rapid increase in platelet count. It may play a valuable role in the management of DF in the near future.

Arunkumar did a prospective study to evaluate the efficacy and safety of carica papaya leaf extract, empirical therapy for thrombocytopenia associated with dengue fever. This prospective study was conducted in 300 patients across 5 centres', to evaluate the Efficacy and Safety of Carica Papaya Leaf extract, as empirical therapy for thrombocytopenia associated with dengue fever. The subjects were randomized into two groups, as control and intervention group. Both the groups were managed by the standard management guidelines for dengue except steroid administration. In addition to this, the intervention group received CPLE tablet three times daily for five days. All of them were followed daily with platelet monitoring. This study has been registered in the clinical trial registry–India (CTRI Registration number: CTRI/2015/05/005806). The results indicate that CPLE had significant increase ($p < 0.01$) in the platelet count over the therapy duration, in dengue fever patients, confirming CPLE accelerates the increase in platelet count compared to the control group. There were few adverse events related to GI disturbance like nausea and vomiting which were similar in both group. Thus this study concluded that *Carica papaya* leaf extract (CPLE) does significantly increase the platelet count in patients with thrombocytopenia associated with dengue with fewer side effects and good tolerability.

Aravind G did a study on Traditional and medicinal use of carica papaya. The study was conducted the research on 70 dengue fever patients, observed that papaya leaf juice helps increase white blood cells and platelets, normalizes clotting, and repairs the liver. Carica papaya constituents exhibit alkaline combination, as with borax or potassium carbonate and they have showed good results in treatment of warts, corns, sinuses, eczema, cutaneous tubercles and other hardness of the skin and also injected into indolent glandular tumors to promote their absorption. Green fruits of papaya are used to treat high blood pressure, dyspepsia, constipation, amenorrhoea, general debility, expel worms and stimulate reproductive organs. Medicinal value of Caricapapaya are:

a.colon cancer

The fiber of papaya is able to bind cancer-causing toxins in the colon and keep them away from the healthy colon cells. These nutrients provide synergistic protection for colon cells from free radical damage to their DNA.

B.ANTI INFLAMMATORY EFFECT

Protein enzymes including papain and chymopapain and antioxidant nutrients found in papaya; including vitamin C, vitamins E, and beta-carotene, reduce the severity of the conditions such as asthma, osteoarthritis, and rheumatoid arthritis.

c. Rheumatoid Arthritis

Vitamin C-rich foods, such as papaya, provide humans with protection against inflammatory polyarthritis, a form of rheumatoid arthritis involving two or more joints.

d. Promote Lung Health

If you are smoker, or if you are frequently exposed to second hand smoke. Eating vitamin A rich foods, such as papaya, help your lung healthy and save your life.

e. Anti-Sickling Activity

Current research proves that papaya is having an anti-sickling activity

f. Prevent Prostate Cancer

Men consuming lycopene-rich fruits and vegetables such as papaya, tomatoes, apricots, pink grapefruit, watermelon and guava were 82% less likely to have prostate cancer compared to those consuming the least lycopene-rich foods.

G. Anticoagulant Effect

Injection of papian extract in a dog increases prothrombin and coagulation threefold. It is also claimed that the enzyme eliminates necrotic tissues in chronic wounds, burns and ulcers. Papain is also of commercial importance in the brewery industry, in the food industry and in the textile industry.

Leaves

Papaya leaf has a numberless of benefits. In some parts of Asia, the young leaves of the papaya are steamed and eaten like spinach.

a. Dengue fever

Commencing on studies of Dr.Sanath Hettige, who conducted the research on 70 dengue fever patients, said papaya leaf juice helps increase white blood cells and platelets, normalizes clotting, *and repairs liver*

b. Cancer Cell Growth Inhibition

Recent research on papaya leaf tea extract has demonstrated cancer cell growth inhibition. It appears to boost the production of key signalling molecules called Th1-type cytokines, which help regulate the immune system.

c. Ant malarial and Antiplasmodial Activity

Papaya leaves are made into tea as a treatment for malaria. Antimalarial and antiplasmodial activity has been noted in some preparations of the plant, but the mechanism is not understood and not scientifically proven.

d. Facilitate Digestion

The leaves of the **papaya plants** contain chemical compounds of karpain, Substance which kills microorganisms that often interfere with the digestive function.

Peel

Papaya peel is often used in cosmetics. The papaya peel can also be used in many home remedies.

a. Sunscreen and Soothing Slave

The presence of vitamin A helps to restore and rebuild damaged skin. Applied papaya peel used as skin lightening agent. When peel mixed with honey and applied it can act as soothe and moisturizers the skin.

b. Fight Dandruff

The papaya vinegar with lemon juice can be applied to the scalp for 20 minutes prior to shampooing to fight dandruff.

c. Muscle Relaxant

Adding papaya oil and vinegar to bath water, along with essential oils like lavender, orange and rosemary can be nourishing, refreshing and relaxing, and can work as a pain reliever and muscle relaxant.

Roots

Juice from papaya roots is used in some countries of Asia to ease urinary troubles. Papaya leaf when dried and cured like a cigar is smoked by asthmatic persons. An infusion of fresh papaya leaves is used by person to expel or destroy intestinal worms. Fresh young papaya is also used to remedy colic, a certain stomach disorder or cramp. A decoction formed by boiling the outer part of the roots of the papaya tree in the cure of dyspepsia.

Prevent Prostate Cancer

Men consuming lycopene-rich fruits and vegetables such as papaya, tomatoes, apricots, pink grapefruit, watermelon and guava were 82% less likely to have prostate cancer compared to those consuming the least lycopene-rich foods.

G. Effect Anticoagulant

Injection of papian extract in a dog increases prothrombin and coagulation threefold. It is also claimed that the enzyme eliminates necrotic tissues in chronic wounds, burns and ulcers. Papain is also of commercial importance in the brewery industry, in the food industry and in the textile industry.

The study concluded that carica papaya is a nutraceutical plant having a wide range of pharmacological activities.

DISCUSSION

The drug Caripill launched by micro labs, Bengaluru, and the clearance was received from Department of Ayush. The principal investigator Dr.A.C.gowda was conducted Clinical trial among 300 hundred patients, showed promise results without the need of blood transfusions. A toxicity study (acute, sub-acute, and chronic toxicity) conducted on Sprague Dawley rats administered with Carica papaya leaves juice (CPLJ) of the sekaki variant revealed that it was safe for oral consumption. There are no anti-viral chemotherapeutic agents yet discovered for DF. The journey to drug discovery through the study of immune-modulatory effects against dengue infection is based on the research of generic compounds and natural products.

C. papaya L. has been used for centuries in ethno-medicine to treat many diseases and symptoms, and mature ripe fruits have been used as an effective remedy against ringworms. Green fruits, on the other hand, have been used to lower blood pressure, and as an aphrodisiac. *C. papaya* Leaves were eaten and used as a heart tonic and analgesic. In traditional medicine, they were used to reduce inflammation and pain due to their analgesic properties. Along with the increasing thrombocyte counts, the anti-haemolytic action of *C. papaya* leaves could have a potential therapeutic efficacy in the disease processes, causing destabilisation of biological membranes. Photochemical analyses have indicated that *C. papaya* leaf extract contains chemical compounds such as alkaloids, tannins, antraquinone, cardenolides, steroids, saponins, phenolics, reducing sugars, flavonoids and cardiac glycosides. These compounds can affect various biological processes in the body in ways that might have harmful or beneficial effects. From the various reports published in scientific literature, It appears that *C. papaya* L. leaf extract does have beneficial properties in dengue. It has been shown to bring about a rapid increase in platelet count.

It is shown that the subjects in the intervention group that received CPLE (Caripill) can reach faster and higher increase in platelet count compared to the control group. However, plant derived drugs and herbal remedies are considered to be less toxic and are still popular globally. Toxicological effect of papaya leaf extract was evaluated in a murine model and was found to be safe.

CONCLUSION

Carica papaya is a nutraceutical plant having a wide range of pharmacological activates. The whole plant has its own medicinal value. The wide range of enzymes, vitamins present in *Carica papaya* makes it a nutraceutical plant. Caripill is a first drug to treat the patient with

dengue fever in view of platelet production. Photochemical analyses have indicated that *C. papaya* leaf extract contains chemical compounds such as alkaloids, tannins, anthraquinone, cardenolides, steroids, saponins, phenolics, reducing sugars, flavonoids and cardiac glycosides. These compounds can affect various biological processes in the body in ways that might have harmful or beneficial effects. Several studies show that the *C. papaya* leaf extract may be used as a medicine to boost haemopoiesis and thrombopoiesis when these have been suppressed by disease. Papaya extract no doubt offers a cheap and possibly effective treatment for dengue. Various clinical and preclinical studies conducted have demonstrated a positive effect in dengue cases with thrombocytopenia. It may play a valuable role in the management of DF in the near future.

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