Caripill

Carica Papaya Leaf Extract 1100 mg Tablets
Carica Papaya Leaf Extract 275 mg/5ml Syrup

Demonstrable Rise in Platelet Count

Proven Action

- Stimulates ALOX 12 gene by 15 folds & PTAFR gene by 13 folds
- Rapidly increases platelets

Rigorously Documented & Published

- 300 patient trial at 5 centers - published in JAPI
- Pilot Study at 2 centers - published in Indian Medical Gazette

Standardised Formulation: Meets the challenging standards of modern medicine

1. Right percentage of glycoside (40%) assures desired treatment outcome
2. Comprehensively clears quality parameters of Microbiological tests & Heavy Metal contents

For the use of Registered Medical Practitioner or Hospital or Laboratory only.

07 / 2015 / Caripill - Monograph / AW-69

Fight against Thrombocytopenia Recognised & Rewarded

Emerging Brand of the Year-2015, Pharma Summit

New Introduction of the Year-2016, AWACS

Excellence in Brand Prescription Drugs - 2016, U B M

MICRO LABS LIMITED

Caripill

First & the Best in Managing Thrombocytopenia

MICRO LABS LIMITED

Taking Leadership in Managing

Dengue & Fever

MICRO LABS

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Caripill

Caripill

PREFACE

Dengue is emerging as a serious public health problem globally, with 2.5 billion people at risk and 50 million dengue infections occurring annually. It is one of the most prevalent mosquito-borne arboviral infection in India. Seventy percent of the 96 million apparent infections occur in Asia, in which India is making upto one third of the total. Despite considerable efforts to control the mosquito populations, dengue fever has emerged, spread and established itself rapidly. The most serious manifestations of the infection are Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).

The rapid fall in the thrombocytes, which puts the dengue patient to the risk of bleeding and death, is one of the concerns which has not been addressed equitably. Options like platelet transfusions, few expensive drugs like Romiplastim, Eltrombopag are available which may not be affordable and accessible to a larger population depriving them of necessary treatment thereby increasing the risk of mortality.

Looking in to the limited current modalities of treatment and its outreach to a fewer sections of population, the search for alternative option was thought about to fill in the gap.

After extensive literature search and feedback from the practicing doctors and patients from the community, it became evident that the Carica papaya leaf extract can be a potential adjuvant cost effective therapeutic option in increasing the platelets significantly. At present people at large are consuming crude juice extracted out of non standardized and unhygienic leaves. This is causing lot of adverse effects, gastric infections leading to non compliance and also because of the non standardization in the dosage, variability in the responses as well.

This led to the development and introduction, of 'CARIPILL' at Micro Labs Ltd, Bangalore, India. Caripill is the standardized form of extract from Carica Papaya leaf and formulated in tablet dosage form with 1100 mg strength and Syrupwith 275mg/5ml strength .Various pre clinical and clinical studies including a pilot study in India have demonstrated significant rise in the levels of platelets in cases of fever with thrombocytopenia. The toxicity study conducted suggests a very large therapeutic safety window and can be consumed in larger quantities of up to 19gms/day. The rapid and significant rise in the patients platelets help in overcoming the precarious hemorrhagic conditions thereby averting the mortalities in dengue cases.

To summarize, Caripill seems to be a viable adjunctive option reaching out to a larger section of needy populations, with affordable cost.

Medical Team of Micro Labs

PRODUCT MONOGRAPH

Caripill

Ingredient: Carica Papaya Leaf Extract

Composition: 1100mg Tablets & 275mg/5ml Syrup

Indication:
Thrombocytopenia associated with Dengue fever.

Caripill

Caripill

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Introduction:

Dengue:

Dengue is an acute viral infection with potential fatal complications. Dengue viruses (DV) belong to **family Flaviviridae** and there are four serotypes of the virus referred to as **DV-1, DV-2, DV-3 and DV-4**. DV is a positive-stranded encapsulated RNA virus and is composed of three structural protein genes, which encode the nucleocapsid or core (C) protein, a membrane-associated (M) protein, an enveloped (E) glycoprotein and seven non-structural (NS) proteins. It is transmitted mainly by **Aedes aegypti** mosquito and also by Ae. Albopictus. [1]

All four serotypes can cause full spectrum of disease from a subclinical infection to a mild self limiting disease, the dengue fever (DF) and a severe disease that may be fatal, the dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). The 1997 WHO classification divided dengue into undifferentiated fever, dengue fever (DF), and dengue haemorrhagic fever (DHF)1. Four main characteristic manifestations of dengue illness are (i) continuous high fever lasting 2-7 days; (ii) haemorrhagic tendency as shown by a positive tourniquet test, petechiae or epistaxis; (iii) thrombocytopoenia (platelet count <100,000/µL); and (iv) evidence of plasma leakage manifested by haemoconcentration (an increase in haematocrit 20% above average for age, sex and population), pleural effusion and ascites, etc.[2]

Warning Signs:

Counts	• **Abdominal pain or tenderness** • **Persistent vomiting** • **Clinical fluid accumulation (Pleural effusion ascites)** • **Mucosal bleed** • **Lethargy, Restlessness** • **Liver enlargement > 2cm**
Laboratory	• **Increase in hematocrit with rapid decrease in platelet counts.**

Adapted from WHO guidelines for Dengue 2012

Caripill

An incubation period varying from 3 to 14 days is followed by a febrile illness consisting of sudden-onset fever, headache, myalgia, arthralgia and rash. **Thrombocytopenia is a common feature of the illness**.[6] The patient develops hemorrhagic manifestations such as petechiae and bleeding through the nose, gastrointestinal tract and gums. After the incubation period,the illness begins abruptly and,in patients with moderate to severe disease, is followed by three phases-febrile,critical and recovery(Figure 1).Due to its dynamic nature, the severity of the disease will usually only be apparent around defervescence i.e during the transition of the febrile to the afebrile phase,which often coincides with the onset of the critical phase.

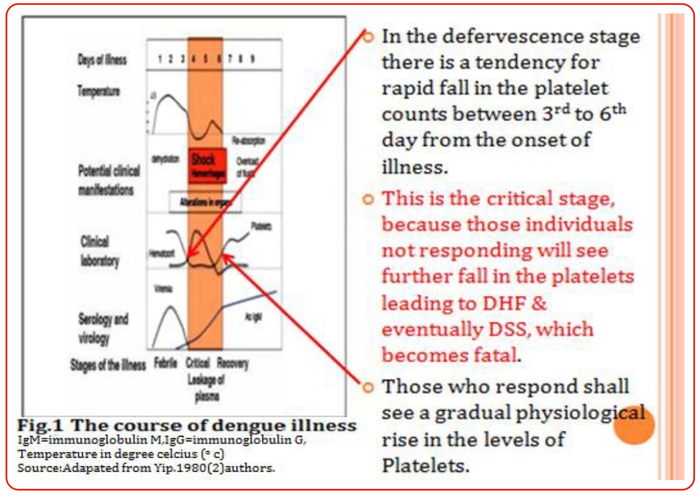


Fig.1 The course of dengue illness
IgM=immunoglobulin M.IgG=immunoglobulin G,
Temperature in degree celcius (° c)
Source:Adapated from Yip.1980(2)authors.

Complications of Dengue fever

Deaths due to dengue are usually a consequence of patients developing complications like dengue hemorrhagic fever and dengue shock syndrome.[8] **Dengue hemorrhagic fever, if untreated, has a mortality rate of 10-20%. It occurs due to progression of thrombocytopenia and development of increased vascular permeability and plasma leakage. It progresses to dengue shock syndrome, which is again associated with high mortality**.[6]

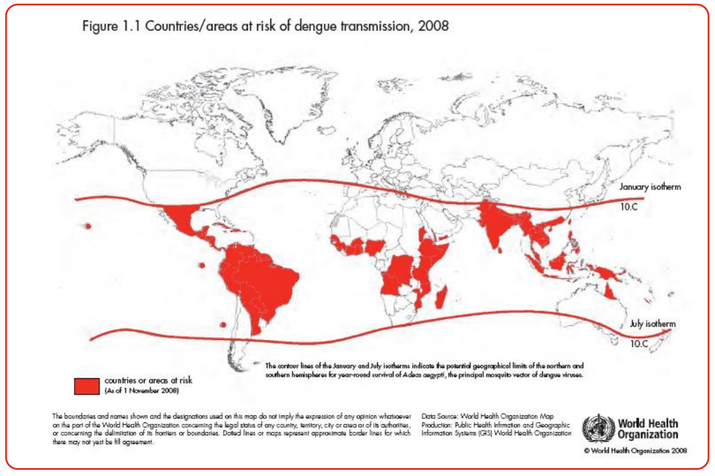
Primary infection is thought to induce lifelong protective immunity to the infecting serotype [9]. Individuals suffering an infection are protected from clinical illness with a different serotype within 2--3 months of the primary infection but with no long-term cross-protective immunity.

Current knowledge about the physiopathology of DHF suggests amplification of the immune response due to the presence of heterotypic antibodies against a serotype of the dengue virus at the time of new infection [10,11] as an explanation for the higher frequency of DHF in repeat dengue infections. The immune system in allergic individuals may be persistently activated with signs of inflammation in tissues and capillaries. [12,13]

Individual risk factors determine the severity of disease and include secondary infection, age, ethnicity and possibly chronic diseases (bronchial asthma, sickle cell anaemia and diabetes mellitus). Young children in particular may be less able than adults to compensate for capillary leakage and are consequently at greater risk of dengue shock.[2]

Treatment for dengue is usually symptomatic. Some cases require platelet transfusions and fluid management.[5] One of the most disturbing aspects of the problem of dengue is that there are no effective antiviral agents available to treat dengue complications. **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.**

The incidence of dengue has grown dramatically around the world in recent decades. Over 2.5 billion people **over 40% of the world's population are now at risk from dengue**. WHO currently estimates there may be 50-100 million dengue infections and half a million DHF worldwide every year, with an average case fatality rate of around 5 %. [2]



Today endemic in over 125 countries and various studies estimated that it infects nearly 50-270 million people every year, resulting in a sizable number of deaths.[3] In fact, dengue appears to be overtaking malaria in terms of morbidity and economic impact of the disease.[4] Unfortunately, due to lack of adequate surveillance systems in the underdeveloped and developing countries, the exact extent of the problem is not known. Travellers from non-endemic areas to the dengue-affected areas are also exposed to the possibility of infection.[5] This makes it an international public health concern, affecting individuals from countries even where the disease is not prevalent.

The epidemiology of dengue fevers in the Indian subcontinent has been very complex and has substantially changed over almost past six decades in terms of prevalent strains, affected geographical locations and severity of disease. The average total economic burden was estimated to be US$27.4 million (US$25.729.1 million). [1,23]

Dengue and Thrombocytopenia:

The most common virus responsible for dengue is DV-2 (dengue virus-2). DV-2 inhibits in vitro megakaryopoiesis and induces apoptotic cell death in a sub-population of early megakaryocytic progenitors which may contribute to thrombocytopenia in dengue disease.[14]

In another study it was shown that DV-2 may directly interact with and activate platelets and thus may be responsible for thrombocytopenia. Significant ultra structural changes in DV infected cells especially endo-membrane re-organization and formation of auto-phagososmes have been shown using whole mount transmission electron microscopy. These changes, taken together with a later study, that showed marked elongation of endothelial cell processes after transfection with the DV-E protein, provided early insights that the replication biology of the virus is coupled closely with the host cell physiology.[15]

Such molecular mimicry occurs between platelets/endothelial cells and dengue virus antigens. Platelets and endothelial cells are bound by the cross-reactive anti-dengue virus antibodies such as anti-NS1 or anti-prM antibodies.[22]

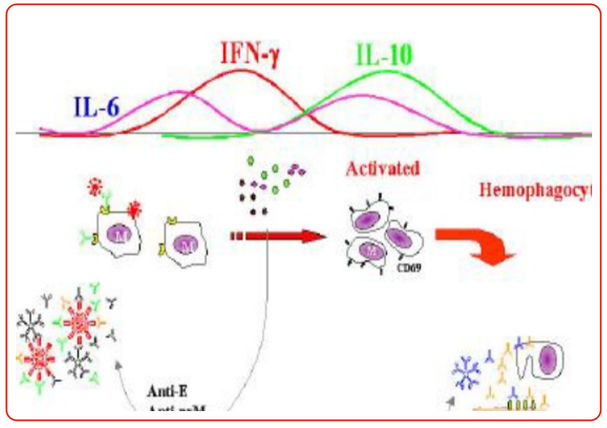


Fig. 1: Autoantibody-associated immunopathogenesis of dengue hemorrhagic fever. Dengue virus infection causes aberrant immune responses including CD4/CD8 ratio inversion, monocytosis, and atypical lymphocytosis, which not only delay virus clearance, but also trigger cytokine overproduction and autoantibodies to platelets and endothelial cells. These autoantibodies would subsequently initiate the dysfunctions of these cells. The IFN-g activated macrophages phagocytosize the autoantibody-coated platelets and endothelial cells, result in thrombocytopenia and endothelial cell damage.

Postulated Mechanisms of Thromocytopenia in Dengue

Two mechanisms have been suggested that could be responsible for dengue-induced thrombocytopenia**- impaired thrombopoiesis** and **peripheral platelet destruction**. 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. [16] 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. Studies have also indicated altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis as possible mechanisms of thrombocytopenia.

The other main mechanism proposed for thrombocytopenia is the **increased peripheral platelet destruction by the DENV**. This could be due to an autoimmune reaction, where antibodies produced by the host against the DENV bring about activation and destruction of platelets.[17] Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction. [18, 19]Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the destruction [20, 21]. Recent studies indicate a direct infection of the platelets by the DENV. Increased levels of mediators like tumor necrosis factor-α and interleukin-1β were associated with thrombocytopenia [97].

Platelets / Thrombocytes:
Introduction

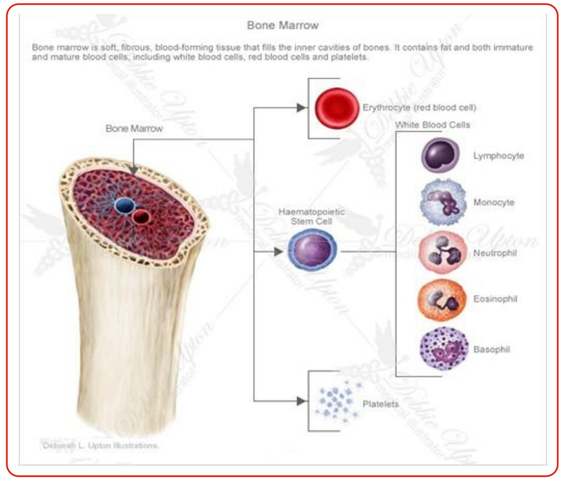
The principal components of blood are: white blood cells (WBCs/leukocytes), red blood cells (RBCs/erythrocytes), and platelets (thrombocytes). Under normal physiological conditions, the count of the blood components are in a specific range and any abnormality in these counts are indicative of an altered physiology.

Platelets are irregularly shaped, colorless bodies present in blood and produced in the bone marrow similar to the other cells in the blood such as, white blood cells and red blood cells. Platelets originate from megakaryocytes; the fragments of these megakaryocytes are released into the blood stream as platelets. The circulating platelets make up about two third of the platelets that are released from the bone marrow. The other one third is typically stored (sequestered) in the spleen.

The function of platelets is very important in the clotting system and they are a part of very complicated pathway. They circulate in the blood vessels and become activated if there is any bleeding or injury in the body. Certain chemicals are released from the injured blood vessels or other structures that signal platelets to become activated and join the other components of the system to stop the bleeding. When activated, the platelets become sticky and adhere to one another and to the blood vessel wall at the site of the injury to slow down and stop the bleeding by plugging up the damaged blood vessel or tissue (homeostasis).

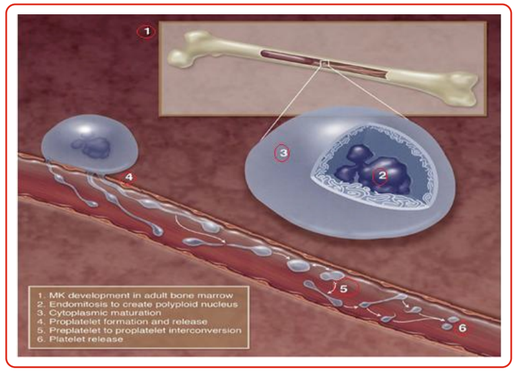
Normally, a healthy individual has platelet count in the range of 150,000 to 450,000 per microlitre (µl) of blood. An increase in the platelet count is referred as thrombocytosis, and results in to formation of clots in the blood, which may obstruct the normal blood to any organ while a decrease is referred to as thrombocytopenia resulting in excessive bleeding leading to hemorrhages.

Physiology of platelet production:



Megakaryopoiesis is tightly regulated by serum factors, such as thrombopoietin [2] which acts in concert with several cytokines (eg, interleukin-3, interleukin-6, and interleukin-11) to maintain differentiation, proliferation, maturation of megakaryocytes, and the release of platelets.[3,4] Megakaryopoiesis involves megakaryocyte lineage commitment from pluripotent hematopoietic stem and progenitor cells, proliferation of megakaryocyte progenitors, complex maturation steps of megakaryocytes and, finally, the release of platelets into the blood.[3,4]. Hematopoietic stem and progenitor cells give rise to a common megakaryocyte/erythroid progenitor.[5]

Differentiating HSC into megakaryocytes:



(1) HSCs in the bone marrow differentiate into MKs in a TPO-dependent manner.
(2) MKs undergo endomitosis and develop nuclei ranging in DNA content from 2n to 128n.
(3) As MKs mature, they develop a highly invaginated membrane throughout their cytoplasm, which is continuous with the external plasma membrane. This membrane serves as a reservoir for proplatelet formation.
(4) MKs migrate to the vascular niche, where they extend proplatelets and release them into vascular sinusoids. The entire MK is converted into pre/proplatelets, and its nucleus is exuded and phagocytosed.
(5) Once in the bloodstream, proplatelets interconvert into preplatelets.
(6) A fission event creates two platelets from a barbell proplatelet.

Gene expression for hematopoiesis:

Core-binding factor subunit alpha- 2 (CBFA2), also known as AML1(Acute Myeloid leukemia 1) and RUNX1(Runt Transcription factor 1), is a transcription factor that regulates the expression of genes involved in hematopoiesis, through highly conserved DNA binding region, called RUNT homology domain (RHD). The study by Kaur et al.(RUNX1/core binding factor A2 regulates platelet 12-lipoxygenase gene (ALOX12): Studies in human RUNX1 haplodeficiency' *Blood*, vol 115, no. 15, pp. 3128-3135.) reported a patient with a mutation (haplodeficiency) in the conserved region of RUNX1/CBFA2 was associated with mild thrombocytopenia and impaired platelet function.[65] Expression profiling of patient platelets revealed 5 fold decreased mRNA expression of 12-lipoxygenase (12-LO, gene ALOX12) .12-LO catalyzes 12-hydroxyeicosatetraenoic acid (12-HETE) production from arachidonic acid (AA) upon platelet activation.[65]

ALOX12 is a direct target of transcription factor RUNX1 in megakaryocytes/platelets. RUNX1 is a transcription factor that regulates the expression of hematopoietic-specific genes and plays a major role in hematopoiesis.[66-69]

Thrombocytopenia:

Thrombocytopenia (Low Platelet Count) often characterized by platelet count less than 150,000 per µl of blood is more prevalent and could be due to a **decreased platelet production and /or increased destruction**. Thrombocytopenia is associated with symptoms as bruising, purpura in forearms, pinpoint hemorrhages, nose bleeds, and bleeding gums.

Clinical manifestations of thrombocytopenia are mild as long as platelet counts are above 20,000/µL and are generally limited to easy bruising. Once the count goes below 10,000/µL the risk of spontaneous mucocutaneous bleeding (gingival bleed, epistaxis, menorrhagia, petechiae and ecchymoses) and life threatening, spontaneous intracranial hemorrhage or gastrointestinal bleeding increases rapidly.[31]

Thrombocytopenia results from one of the following [70]:

a) Decreased production of platelets in the bone marrow

b) Increased destruction of platelets

c) Increased sequestration of platelets in the spleen

Decreased production of platelets

- Bone marrow failure or suppression (e.g., aplastic anemia, from medication, chemotherapy, or irradiation)
- Chronic alcohol abuse
- Congenital macrothrombocytopenias (e.g., Alport syndrome, Bernard-Soulier syndrome, Fanconi anemia, platelet-type or pseudovon Willebrand disease)
- Infection (e.g., cytomegalovirus, dengue virus, Epstein-Barr virus, hepatitis C virus, HIV)
- Myelodysplastic syndrome
- Neoplastic marrow infiltration
- Nutritional deficiencies (vitamin B12 and folate)

Increased destruction of platelets

- Drug-induced thrombocytopenia (Heparin, interferon alpha, digoxin, abciximab, furosemide etc)
- Immune thrombocytopenic purpura
- Infection (e.g., cytomegalovirus, dengue virus, Epstein-Barr virus, hepatitis C virus, HIV)
- Mechanical destruction (e.g., aortic valve, mechanical valve, extracorporeal bypass)
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Sequestration

- Chronic alcohol abuse
- Gestational thrombocytopenia
- Hypersplenism (e.g., distributional thrombocytopenia)
- Liver disease (e.g., cirrhosis, fibrosis, portal hypertension)

Currently available treatment modalities:

Treatment is guided by etiology and disease severity. The main concept in treating thrombocytopenia is to eliminate the underlying problem, whether that means discontinuing suspected drugs that cause thrombocytopenia, or treating underlying sepsis.

Corticosteroids, intravenous immunoglobulin, and splenectomy remain mainstays of treatment; however, newer therapies including rituximab and the thrombopoietin receptor agonists are remodeling conventional treatment algorithms. In severe cases and associated with bleeding platelet transfusion is recommended.

All these above mentioned treatment options have their own advantages and disadvantages.
Corticosteroids are the initial treatment for adults with thrombocytopenia because of their effectiveness for increasing the platelet count, their low cost and convenience[32,33,34].

Steroids may slow platelet destruction and are given along with immunoglobulins or drugs like rituximab to block the immune system and halt the destruction process of platelets.[35]

IVIG exerts immunomodulatory effects that may include antiidiotypic neutralization of antiplatelet antibodies, stimulation of Fcgamma receptor IIB expression, and inhibition of Fc gamma receptor-mediated platelet destruction. Recent work suggests that a large fraction of the benefit provided by IVIG may be the result of competitive inhibition of neonatal Fc receptor (FcRn) and IVIG-induced acceleration of antiplatelet antibody elimination. [36]

Anaphylactic reactions and thromboembolic events have been reported because of IV Ig [37]. It may not be available at all places making it inaccessible to most of the rural population .The estimated cost per treated episode of ITP was $4,269 for IVIg[38].

Corticosteroids are potent anti-inflammatory agents that have a wide range of effects on the immunological processes. Although corticosteroids are not mentioned in the WHO guidelines on the management of dengue, clinicians use corticosteroids empirically, based on the presumed immunological basis of the complications of dengue, particularly in the south east Asian countries [39]. They are thought to be effective for stabilizing the capillary permeability and have been used in addition to the fluid replacement[39].

However there are limited studies in the literature which have assessed the benefits and the risk of the corticosteroid therapy in the thrombocytopenia in the dengue infection. Various steroid regimens have been used and some of them have shown beneficial effects and some have shown no benefits. However, the Cochrane reviews have concluded that there is insufficient evidence on the use of steroids in DSS and DHF and they have advised large randomized trials [40].

The possible risk of the worsening of the dengue illness because of increased viral replication, due to the immunosuppressive property of corticosteroids, was raised in the study which was done by Sam Kularathne and his colleagues[41].

The immunosuppressant effect of corticosteroids might mask the severity of the underlying condition and numerous adverse events have been associated with corticosteroids.

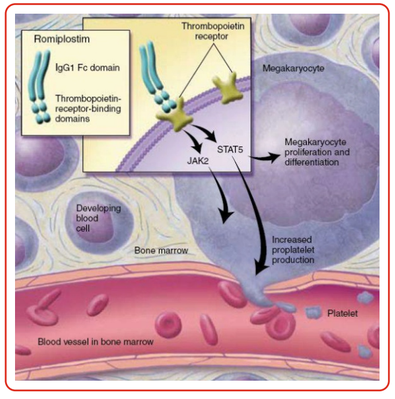
- Corticosteroids halts further destruction of platelets
- Does not have any action on production of platelets
- Insufficient evidence on the use of steroids in DSS and DHF
- Immunosuppressant thereby can increase the Viral replication

The pathogenesis of thrombocytopenia involving antibody-mediated platelet destruction and reduced platelet production, stimulation of platelet production may be an effective treatment for this disorder. Romiplostim and eltrombopag stimulate the thrombopoietin receptor and platelet production without inducing the production of autoantibodies. [44] Romiplostim, a subcutaneous injection, and eltrombopag, an oral small molecule, are second-generation thrombopoietic growth factors.[42]

Romiplostim is a peptibody (a combination of a peptide and an antibody) in a novel class of drugs known as thrombopoietin-receptor mimetic agents.[42]

Romiplostim binds to the thrombopoietin receptor in the same manner as does endogenous thrombopoietin. Activation of the thrombopoietin receptor stimulates the Janus kinase 2 and signal transducers and activators of transcription 5 pathways, leading to megakaryocyte proliferation and differentiation.

Megakaryocytes then extend protrusions (proplatelets) into the bone marrow blood vessels [43]. Sheer stress from blood flow fragments the protrusions, creating platelets. This process increases the number of circulating platelets in the bloodstream as depicted in the figure [44].



Romiplostim has a marketing authorisation 'for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)'. It also states that romiplostim 'may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated [45].

Small-molecule thrombopoietin (TPO)-receptor agonist that interacts with human TPO receptor transmembrane domain of human TPO-receptor & initiates signaling cascades, that induce proliferation & differentiation of megakaryocytes from bone marrow progenitor cells, thereby increasing the number of circulating platelets in the bloodstream[46].

The risks of developing bone marrow fibrosis, malignancy, and thrombosis are reported with romiplostim[47].FDA has required that the manufacturer of romiplostim have a risk-management plan in place to determine the risks associated with long-term use of the drug[47].

Eltrombopag may slow the removal of other drugs from your body, increasing the risk of side effects. These affected drugs include "statin" drugs (such as atorvastatin, fluvastatin, rosuvastatin), methotrexate, repaglinide, rifampin etc. It is known to have interactions with calcium rich foods or supplements containing polyvalent cations and drug interactions with antacids, antibiotics like erythromycin, ciprofloxacin etc, NSAIDs, PPIs, anti psychotics etc. It is also known to cause hepatotoxicity[46].

The disadvantage with these therapies is risk of thrombocytopenia and hemorrhage after discontinuation [48]. More over risk over long term use of these agents are unknown [49].

Both these drugs are very costly and may not be available and affordable to larger population.

The current wholesale price of romiplostim is $1,062.50 for a single-use vial of 250 µg or $2,125.00 for a single-use vial of 500 µg.[50] Most patients who respond to romiplostim will require a dose of < 250 µg, making the extrapolated drug cost for weekly dosing for one year approximately $55,250. This figure does not include pharmacy dispensing fees, nursing administration charges, and physician visits associated with romiplostim therapy [50]. The cost of Eltrombopag therapy per month for the 25-mg per day treatment regimen stands at 27,000 Indian rupees (USD608.12)[51].

If prescribed in dengue cases for shorter duration of time (at least for 5 days averagely) would mean a cost implication of $757 and $101 for romiplostim and eltrombopag respectively.

- **Romiplostim is a peptibody (a combination of a peptide and an antibody) as thrombopoietin-receptor mimetic agents.**
- **Activation of the thrombopoietin receptor stimulates the Janus kinase 2 and signal transducers and activators of transcription 5 pathways, leading to megakaryocyte proliferation and differentiation.**
- **Eltrombopag is (TPO)-receptor agonist that interacts with human TPO receptor transmembrane domain of human TPO-receptor & initiates signaling cascades that induce proliferation & differentiation of megakaryocytes from bone marrow progenitor cells.**
- **Withdrawal thrombocytopenia and risk of hemorrhage is associated with both therapies.**
- **Both are costly (For therapy of 5 days in dengue it may cost $727 & $103 respectively) and may not be affordable to large number of population.**

The antibody-coated platelets are often removed from circulation by the spleen. Theoretically, if the spleen is removed, the platelets will remain in the blood stream. The spleen can also be the site of antibody production. Therefore removing the spleen may reduce the amount of anti-platelet antibodies in addition to removing the antibody-coated platelets.

Although the spleen is often the major site of antibody-coated platelet destruction, platelets may also be removed from circulation by the liver, by a combination of the spleen and liver, or within the blood stream. Therefore, splenectomies are not always successful in raising the platelet count and may fail over time, prompting a return of low platelets .About 10 to 15% have no meaningful splenectomy. The relapse rate in splenectomized patients is approximately 30% to 35%[52].

Further the complication rate from surgery is about 10%. Since the spleen is responsible for making antibodies and removing bacteria, aged, antibody-coated and damaged blood cells, those without a spleen have an impaired immune system. Because of this, splenectomized patients have a more difficult time recovering from infections[53-58].

People who have had a splenectomy have more micro particles in their blood, giving them an increased risk of dementia [59] and heart attacks [60] from blood clots. They are also more prone to blood vessel complications[61].

In severe cases of thrombocytopenia with active bleeding manifestations platelets are transfused. Different options like pooled platelets from multiple donors or apheresis platelets from single donor are available. Apheresis platelets have the advantages of limiting the recipient exposure to a single donor, which potentially reduces the possibility of infection and alloimmunization; however the cost gets escalated as compared to pooled platelets.

Indications for Use of Platelets:

In thrombocytopenia for treatment and/or prevention of bleeding.

Prevention of bleeding:

- Stable patients with normal platelet function: Platelet count < 10,000/µL[62]
- Stable patient with other haemostatic abnormalities (e.g. anticoagulated with warfarin, heparin): Platelet count < 50,000/µL[62]
- Recent history of thrombocytopenia-related life-threatening bleed: Platelet count < 50,000-100,000/µL[62]
- High-risk patients having platelet count < 20,000/cumm and risk of bleeding require urgent platelet transfusion[63].
- Patients with platelet count 21,000-40,000/µL are in moderate risk and require platelet transfusion only if they have any haemorrhagic manifestations and other superadded conditions [63].

Complications associated with Platelet transfusion include blood borne infections, and infection by bacterially contaminated platelets represents a serious hazard of platelet transfusion, Transfusion-related acute lung injury (**TRALI**) ,Transfusion-associated circulatory overload **(TACO)** , Allo immunization, Allergic and anaphylactic reactions ,Febrile non-hemolytic transfusion reactions **(FNHTR)** , Transfusion-associated graft-versus-host disease (**Ta-GVHD**),Post-transfusion purpura[64].

The platelet transfusion needs institutionalization which would incur cost, asks for infrastructure provision which may not be available at all places making it inaccessible and unaffordable to many of the patients. Also transfused platelets can transmit fatal diseases and can elicit an immune response in recipients.

- **High-risk patients having platelet count < 20,000/µL and risk of bleeding require urgent platelet transfusion.**
- **Risk of infections and anaphylactic reactions is associated with platelet transfusion.**
- **Apheresis platelets transfusion has the advantages of potentially reducing the possibility of infection and allo-immunization.**
- **Apheresis transfusion escalates the cost and apheresis unit may not be available everywhere**
- **Accessibility and affordability can keep away the needy from availing it.**

Therefore in the current lieu, considerations for alternate therapies to combat the low platelet count, which is relatively free from the toxic side effects of the drugs, should be given. [24,25]

The evolution of Carica Papaya Leaf Extract (Caripill) in the management of thrombocytopenia associated with dengue is significant as it would be-

- Better & viable option in fever associated with thrombocytopenia.
- Palatable and appropriately formulated.
- Fewer side effects.
- Decreases the cost of hospitalization.
- Cost effective.
- More affordable and accessible
- Averting the mortalities.

Management of dengue fever:

There is no specific treatment for dengue; intensive supportive care is the most important aspect of management. The thrombocytopenia which usually happens in the defervescence 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 formulations are commonly considered to be less toxic and less side effects than the synthetic ones.

Challenges and Obstacles[71]:

Attempts to develop an antiviral agent for dengue have met several hurdles. Dengue is caused by four distinct serotypes which often undergo mutations.[27] Like in other ribonucleic acid (RNA) viruses, these mutations are due to the error-prone nature of RNA polymerase, which results in the formation of quasispecies. It is currently unclear which viral genome results in a higher viral titre.[28] An antiviral would have to be effective against all the serotypes. [27]

A lot of hope rests on the development of effective vaccines, many of which are undergoing clinical trials.[30] Besides vaccines, every other possible treatment including traditional medicines are being investigated to test their usefulness in controlling this problem.[29]

Carica papaya Leaf Extract [Caripill]

Caripill

Introduction:

Carica papaya is a member of the Caricaceae and is a dicotyledonous, polygamous, and diploid species[72]. It originated from Southern Mexico, Central America, and the northern part of South America. It is now cultivated in many tropical countries such as Bangladesh, India, Indonesia, Sri Lanka, the Philippines, West Indies and Malaysia. The papaya fruit is globally consumed either in its fresh form or the form of juices, jams, and crystallized dry fruit. The ripe fruit is said to be a rich source of vitamin A, C, and calcium. There are many commercial products derived from the different parts of the *C. papaya* plant, the most prominent being papain and chymopapain, which is produced from the latex of the young fruit, stem, and the leaves.

C. papaya leaves have been used in folk medicine for centuries. Recent studies have shown its beneficial effect as an anti-inflammatory agent, for its wound healing properties [73], antitumor as well as immune modulatory effects[74] and as an antioxidant[75]. 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[76]. Safety studies based on *OECD guidelines for acute, sub acute, and chronic toxicity were conducted on C. papaya extract and showed that it was found to be safe for human Consumption*[76].

The leaves of papaya have been shown to contain many active components that can increase the total antioxidant activity in blood and reduce lipid peroxidation level, such as papain, chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, cyanogenic-glucosides and glucosinolates[77].

The alkaloids, flavonoids, saponins, tannin, and glycosides are related with anti- inflammatory activity. CP leaves extract also found to have anti-bacterial effect[78], anti tumor, and immunomodulator activities[77]. The leaf of CP is categorized as non toxic because its LD50 > 15 g per kg body weight [79]. The leaves also contain cardiac glycosides, anthraquinones, carpaine, pseudocarpaine, phenolic compounds [80,81].

In addition to the nutritional value of its fruit, the leaves of CP possess medicinal properties and are widely used in traditional medicines. Previous studies on papaya have shown that seed extract of CP possess pharmacological activities, including antIhelminthic, antifertility, contraceptive etc. A hot-water extract of the leaves is taken orally as an antipyretic, and treatment of anemia, appetite stimulation. In other countries the leaves extract of CP had been effectively used for treatment of dengue fever disease (DFD) associated with thrombocytopenia[82].

Mechanism of action:

Certain genes have been shown to influence platelet production and platelet aggregation, namely, the Arachidonate 12-lipoxygenase (ALOX 12) also known as the Platelet-type Lipoxygenase as well as the Platelet-Activating Factor Receptor (PTAFR). An increase in activity of these genes is required for platelet production and activation. The ALOX 12 gene is strongly expressed in megakaryocytes and has been known to be responsible for the 12-Hydroxyeicosatetraenoic acid (12-HETE) production of platelets [65]. The PTAFR gene was been found to be expressed in megakaryocytes indicating that it could be a precursor for platelet production in addition to its well known role in platelet aggregation.

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. The active ingredients of *C.papaya* up regulate the ALOX 12 and PTAFR gene thereby leading to an increased production of megakaryocytes and its conversion into platelets. Clinical evidence shows that C. papaya extract increases ALOX 12 activity 15 fold and PTFAR activity 13.42 fold which is responsible for increased platelet production [83]

Caripill

Key Points on Carica papaya

- CPLE contain many active ingredients as glycosides, Flavonoids, Carpines, Alkaloids which may be responsible for its favourable action.
- The leaves contain many active components that can increase the total antioxidant activity in blood and reduce lipid peroxidation level (Eg: Papain, chymopapain, vitamins C and E etc)
- The leaves also possess antibacterial & antiinflammatory activities
- The ALOX 12 or PTFAR gene is expressed on megakaryocytes
- With *C.papaya* leaf extract there is a **15 fold increase in ALOX 12 activity** and **13.42 fold increase in PTFAR activity** which increases platelet production.

Preclinical Evidence

Caripill

Study #1

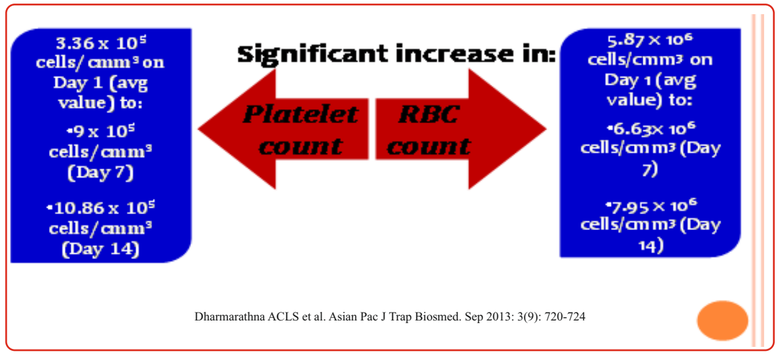
Does *C. papaya* leaf-extract increase the platelet count? An experimental study in a murine model [84]

Dharmarathna ACLS et al. Asian Pac J Trap Biosmed. Sep 2013: 3(9): 720-724

Objective: To investigate the potential role of fresh *C. papaya* leaf extract on haematological and biochemical parameters and toxicological changes in a murine model.

Methods: In total 36 mice were used for the trial. Fresh *C. papaya* leaf extract [0.2 mL (2 g)/ mouse] was given only to the test group (18 mice).General behavior, clinical signs and feeding patterns were recorded. Blood and tissue samples were collected at intervals. Hematological 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 pyruvic transaminase (SGPT) were determined. Organs for possible histopathological changes were examined.

Results: Neither group exhibited alteration of behavior or reduction in food and water intake. Similarly, no significant changes in SGOT, SGPT and serum creatinine levels were detected in the test group. Histopathological organ changes were not observed in either group of mice except the three liver samples of the test group which had a mild focal necrosis. The platelet count (11.33 +_0.35) x 105 /µl (P=0.00004) and the RBC count (7.97 +_0.61) x 106 /µl (P=0.00003) were significantly increased in the test group compared to that of the controls. However, WBC count and PCV (%) values were not changed significantly in the test group. The platelet count in the test group started to increase significantly from day 3(3.4+_0.18x105 /µl , reaching almost fourfold higher at Day 21(11.3)x105 /µl, while it was 3.8 x 105/µl, and 5.5. x105/µl ,at Day 3 and Day 21 respectively in the control. Likewise, the RBC count in the test group increased from 6x106 /µl to 9 x106 /µl, at Day21 while it remained constant in the control group.(6x106 /µl).



Conclusion: Fresh *C. papaya* leaf extract significantly increased the platelet and RBC counts in the test group as compared to the controls. Therefore, it is very important to identify those chemicals of *C. papaya* leaves as it can be recommended to be used as a medication to boost thrombopoeisis and erythropoiesis in humans and in animals in which these cell lineages have been compromised.

Study #2

Repeated Dose 28-Days Oral Toxicity Study of *C. papaya* L. Leaf Extract in Sprague Dawley Rats [85,86]

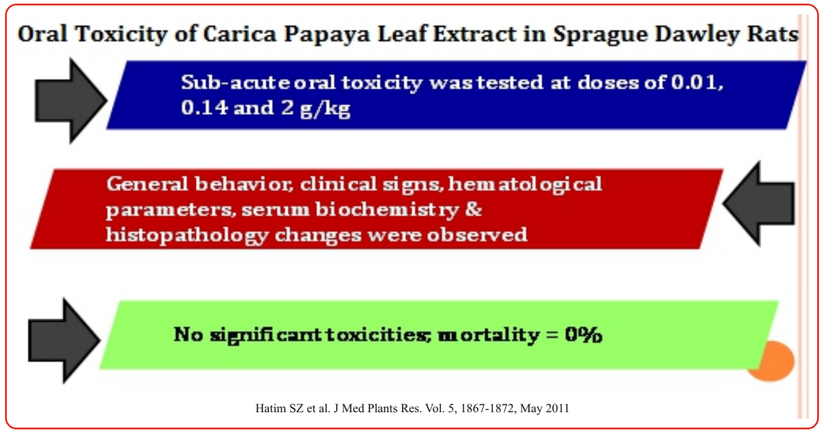
Hatim SZ et al. J Med Plants Res. Vol. 5, 1867-1872, May 2011

Objective & Methods: This study was conducted to characterize the chemical composition of the *C. papaya* leaf extract from 'Sekkai' *C. papaya* by UPLC-TripleTOF-ESI-MS and to investigate the sub-acute oral toxicity in Sprague Dawley rats at doses of 0.01, 0.14 and 2 g/kg by examining the general behavior, clinical signs, hematological parameters, serum biochemistry and histopathology changes.

Results: A total of twelve compounds consisting of one piperidine alkaloid, two organic acids, six malic acid derivatives, and four flavonol glycosides were characterized or tentatively identified in the *C. papaya* leaf extract. In the acute study, the *C. papaya* extract did not cause mortality nor were treatment-related changes in body weight, food intake, water level, and hematological parameters observed between treatment and control groups.

Some biochemical parameters such as the total protein, HDL-cholesterol, AST, ALT and ALP were elevated in a non-dose dependent manner. Histopathological examination of all organs including liver did not reveal morphological alteration. Other parameters showed non-significant differences between treatment and control groups.

The present results suggest that *C. papaya* leaf extract at a dose up to fourteen times the levels employed in practical use in traditional medicine could be considered safe as a medicinal agent.



Conclusion: *C papaya* leaf extract at a dose of up to 2000mg/kg body weight in rats was safe indicating that in humans, a dose of up to 19g of *C papaya* leaf extract would be safe.

Caripill

In Vitro Study

In vitro erythrocyte membrane stabilization properties of *C. papaya* leaf extracts [87]

Background: *C. papaya* fruit juice and leaf extracts are known to have many beneficial medical properties. Recent reports have claimed possible beneficial effects of *C. papaya* leaf juice in treating patients with dengue viral infections. This study aims to evaluate the membrane stabilization potential of *C. papaya* leaf extracts using an in vitro hemolytic assay.

Materials and Methods: The study was conducted in between June and August 2010. Two milliliters of blood from healthy volunteers and patients with serologically confirmed current dengue infection were freshly collected and used in the assays. 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. 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. 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 hypotonicity-induced hemolysis assays.

Results: Extracts of papaya leaves of all three maturity levels showed a significant reduction in heat-induced hemolysis compared to controls ($P < 0.05$). *C. papaya* leaf extracts of all three maturity levels showed more than 25% inhibition at a concentration of 37.5µg/ml. The highest inhibition of heat-induced hemolysis was observed at 37.5 µg/ml. Inhibition activity of different maturity levels was not significantly ($P < 0.05$) different from one another. Heat-induced hemolysis inhibition activity did not demonstrate a linear dose response relationship. At 37.5 µg/ml concentration of the extract, a marked inhibition of hypotonicity-induced hemolysis was observed.

Conclusion: C. papaya 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.

Clinical Data

Caripill

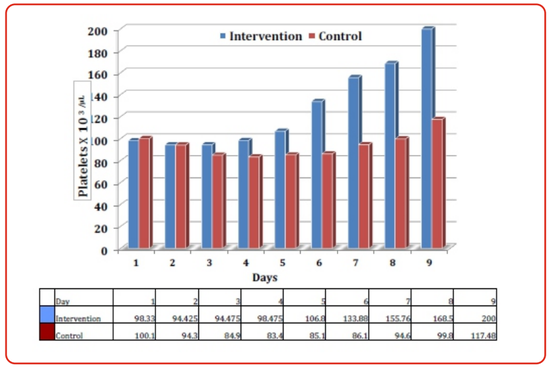
Study #1

The effect of *C. papaya* leaves extract capsules on platelets count and hematocrit level in dengue fever patient[88]

Aim: This study was conducted to determine the effects of C. papaya leaves extract capsules (CPC) to dengue fever patient.

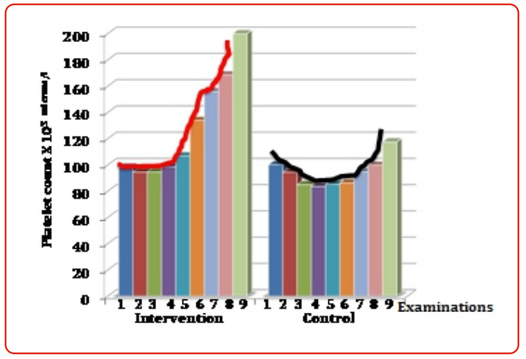
Method: The study was a randomized clinical trial with a sample size of 80 subjects. These subjects were randomized into two groups of 40, including the control and intervention group (received two CPC three times daily).

Results: The results showed that CPC had significant increased the platelet count ($p<0.05$), maintained stability of hematocrit in the normal level, shorten hospitalization ($p<0.05$) in dengue fever patients, and accelerates the increase in the platelets count compared with the control group. Platelets count in intervention group rose faster and higher than in the control group. Hematocrit changes in intervention and control group are not significantly different.



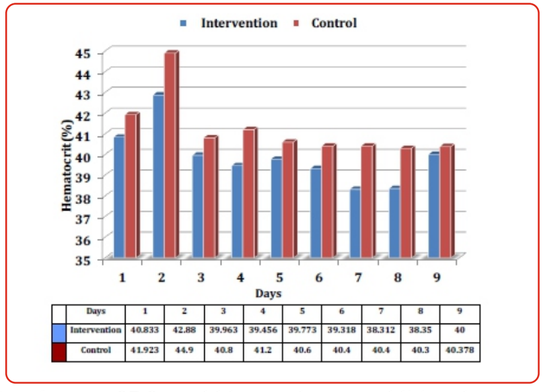
Day	1	2	3	4	5	6	7	8	9
Intervention	98.33	94.425	94.475	98.475	106.8	133.88	155.76	168.5	200
Control	100.3	94.3	84.9	83.4	85.1	86.1	94.6	99.8	117.48

Graph showing the Change in platelet count of all subjects



Graph showing the trend in increasing the platelets in intervention and control groups

- The rise in the intervention group is 'J' shaped & shallow 'u' in the control group respectively, demonstrating faster and significant rise of platelets during the critical phase of defervescence.
- Statistical analysis with dependent t test showed significant differences of platelet count ($p<0.05$).



Days	1	2	3	4	5	6	7	8	9
Intervention	40.833	42.88	39.963	39.456	39.773	39.318	38.312	38.35	40
Control	41.923	44.9	40.8	41.2	40.6	40.4	40.4	40.3	40.378

Graph showing the change in Haematocrit levels (%) of all the subjects

Conclusion: CPC could be used as an additional or as a complementary drug in dengue fever patients; it accelerates the increase in the platelets count and shorten the hospitalization duration thereby reducing the cost of hospitalization significantly.

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Study #2

C. papaya Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever [83]

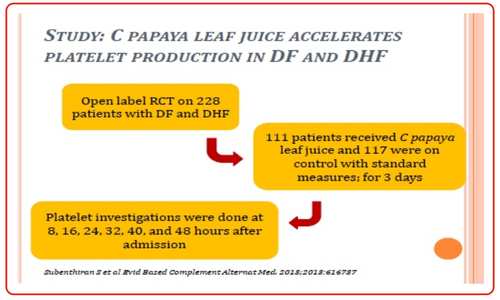
Aim: The study was conducted to investigate the platelet increasing property of *C. papaya* leaves juice (CPLJ) in patients with dengue fever (DF).

Method: An open labeled randomized controlled trial was carried out on 228 patients with DF and dengue haemorrhagic fever (DHF). Approximately half the patients received the juice, for 3 consecutive days while the others remained as controls and received the standard management.

Results: 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.

Multiple comparisons of mean platelet count 8 hours after admission with mean platelet count at 16, 24, 32, 40, and 48 hours after admission for interventional and control group was done. There was a significant increase in mean platelet count over 40 hours in both groups (Wilk's Lambda = 0.939, = 0.015, effect size= 0.06, and power = 84.0%) after adjusting for age.

Further analysis by using multiple paired t-test on each of the groups showed that there was a significant increase in mean platelet count at 40 hours compared to 8 hours after intervention in the intervention group (= −4.256, ≤ 0.001) but not in the control group (= −2.399, = 0.018) after adjustment of Bonferroni correction (= 0.05/5 = 0.01).



Study found that there was a significant increase in the platelet counts in the intervention group at the end of 40 h with no significant rise in the control group.

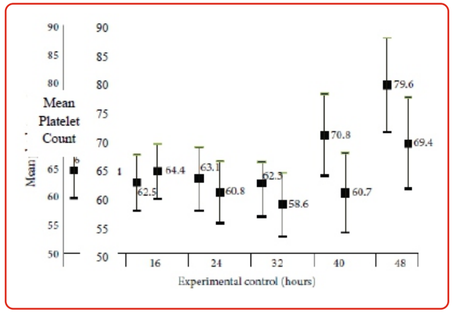


Figure 1.Shows the time treatment of CPLJ. The intervention group had a significantly higher mean platelet count than control group at 40 hours and 48 hours of intervention.

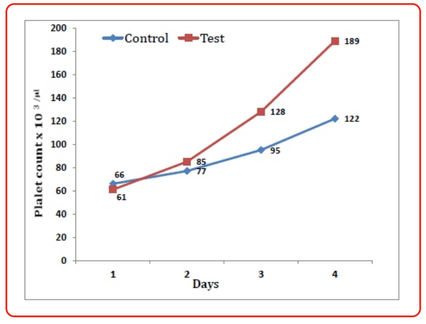
Conclusion: Comparison of mean platelet count between intervention and control group showed that mean platelet count in intervention group was significantly higher than control group after 40 and 48 hours of admission (< 0.01). The ALOX 12 (FC = 15.00) and PTAFR (FC = 13.42) genes were highly expressed among those on the juice. It was concluded that the administration of CPLJ in DF and DHF is safe and does induce the rapid increase in platelets count. It may play a valuable role in the management of DF in the near future.

Study#3

Effect of Carica Papaya leaf extract on febrile thrombocytopenia in patients with Dengue[89]

Aim: The study was conducted to assess the effect of Carica Papaya leaf extract on febrile thrombocytopenia in patients with Dengue.

Methodology: Six subjects were randomly allotted in control and study group. The control group subjects were treated with only medical management and study group were treated with C. papaya leaf extract 5ml twice a day for three days in addition to medical management. In this case series, we observed that compared to the control group, those in the study group recovered earlier clinically with a faster rise in platelet count.



Graph showing the trend of platelets in test and control groups

Results: Compared to the control group, those in the study group recovered faster clinically with a faster rise (Statistically it shows 2:1 ratio) in platelet count.

Conclusion: This observational case series showed that the fresh extract from Carica papaya leaves may help in early improvement of dengue patients both clinically and with respect to platelet counts.
Thus, Patil N J et al; in their study demonstrated significant rising trend of thrombocytes with Carica Papaya leaf extract in febrile thrombocytopenia patients with Dengue.

Study #4

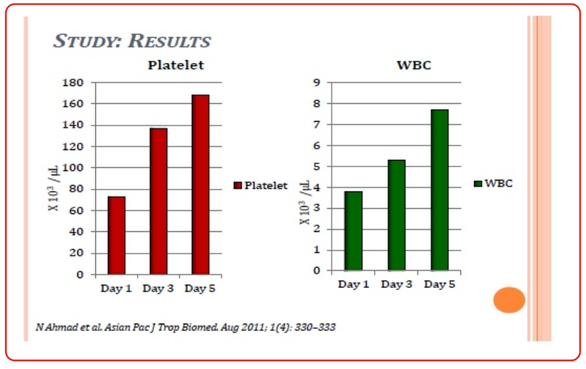
Dengue fever treatment with *C. papaya* leaves extracts [90]

Aim: The main objective of this study was to investigate the potential of *C. papaya* leaves extracts against dengue fever in 45 year old patient bitten by carrier mosquitoes.

Method: 25 ml of aqueous extract of *C. papaya* leaves was administered to patient infected with Dengue fever twice daily (morning and evening) for five consecutive days. The blood samples were analyzed for platelets, WBC count and Neutrophils before and after administration.

Results: It was observed that the PLT count, WBC and Neutrophil increased to 73 x103 /µL , 3.8 x103/µL and 56% respectively. With similar dose of the extract, on the subsequent days the blood report showed an increase in the Platelets and WBCs and Neutrophils to 120 x103 /µL , 4.4 x103/µL and 64.2% on day 2: 137 x103 /µL , 5.3 x103 /µL & 71.1% on day 3: 159 x103 /µL , 5.9 x103 /µL & 73% on day 4 and 168 x103 /µL , 7.7 x103 /µL & 78.3% on day 5 respectively.

Conclusion: The rise of PLT count in the present case from 55 x 103 /µL to 168 x 103 /µL indicates the activity of *C. papaya* leaves extract. Hence, it showed that *C. papaya* leaves aqueous extract exhibited potential activity against dengue fever. Furthermore, the different parts of this valuable specie can be further used as a strong natural candidate against viral diseases.



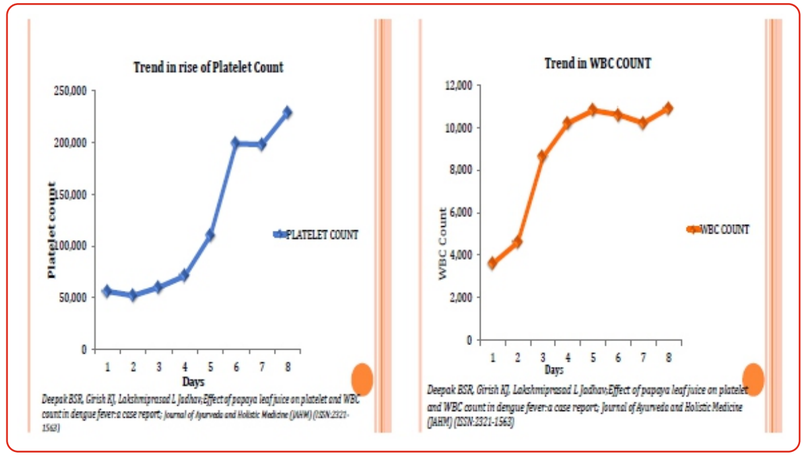
Study #5

Effect of papaya leaf juice on platelet and WBC count in dengue fever: a case report[91]

Aim: A pilot study in a tertiary Ayurvedic hospital in India demonstrated that administration of papaya leaf juice was beneficial in dengue patients in elevating the total white cell counts and platelet counts.

Methodology: The patient was administered papaya leaf juice in the dose of 25 ml twice daily along with conventional line of management for a period of eight days.

Result: There was remarkable improvement in the subjective symptoms and the white blood cell count and platelet count were restored to normalcy.



Conclusion: Administration of papaya leaf juice was beneficial in restoration of white blood cell count and platelet count in the presented case. Further experimental studies and clinical trials on large samples need to be carried out to establish its effectiveness.

Caripill

Clinical Trials in India with
Caripill

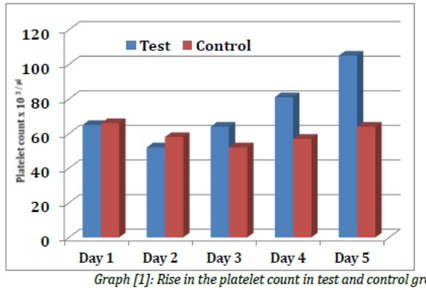
Pilot Study

A pilot study to evaluate the effectiveness of carica papaya leaf extract in increasing the platelet counts in cases of dengue with thrombocytopenia [92]

A pilot study on 30 subjects with confirmed cases of dengue with thrombocytopenia was conducted at two centres at Bangalore, to assess the effect of carica papaya leaf extract.

Dengue cases were confirmed with NS1 test and those with platelets less than 100000 /µL were put on standard treatment with caraca papaya as adjuvant. No steroids were administered to any of the subjects.
Carica Papaya leaf extract was given in a dosage of 1100mg tid for five days and the platelets were monitored.

The monitoring of platelet count clearly indicated that the change in the Platelet count is faster in the intervention group as compared to the control group (graph 1).



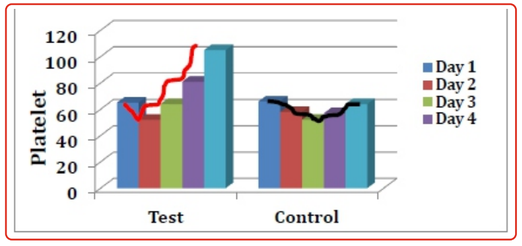
Graph [1]: Rise in the platelet count in test and control groups

	Day 1	Day 2	Day 3	Day 4	Day 5
Test	65	52	64	81	105
Control	66	58	52	57	64

Consolidated values
Platelet count values X 10 3/µL

The graph [2] below clearly indicated a rising trend(steep) in the platelets of the study group, whereas in the control group there was a gradual rise(shallow) on 4th and 5th day.

In the study group there was a significant increase in the platelet count after 2nd day onwards which was very much evident at the end of 5th day.



Graph [2]: Rise in the platelet count in test and control groups

The trend line is 'J' shaped where 2nd day onwards a steep rise was observed in the control group. When compared to the control group rise which showed as shallow rise increasing gradually only on 4th and 5th day.

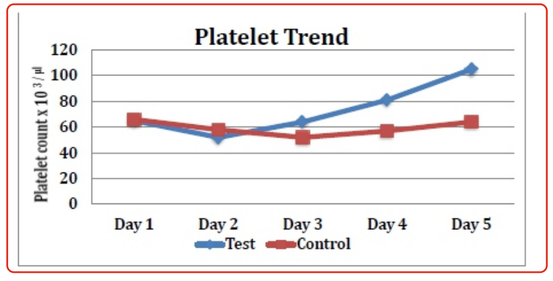


Figure [3]: Day wise trend in the platelet counts in both the groups.
This line graph [3] indicates rise in the platelet count at the point of defervescence which is supposed to be critical. The wide gap implies a significant rise in the study group as compared to the control group.

Conclusion:

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.

Interaction with drugs:

Based on pharmacology, papain should be used with caution in individuals with bleeding disorders or those taking blood thinning medications such as aspirin or warfarin.[95]

Co administration of extracts of Carica papaya with oral hypoglycemic (glimepiride or metformin) 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 hypoglycemia.[98]

The results found in rat study conducted by Rodrigues et al,suggest an herb-drug interaction between C. papaya extract and amiodarone, which clearly increases the drug bioavailability of amiodarone.[99]

In vitro study demonstrated potentiating the action of various antibiotics like penicillin G , ampicillin , amoxyclav , cephalothin,polymyxin B, rifampicin ,amikacin,nalidixic acid, gentamycin, cholarmphenicol, oflxacin when co administered with C.Papaya . The extract of C. papaya with antimicrobial agents possesses synergistic properties which act against the pathogenic organisms. [100]

Side Effects:

C.papaya and the enzyme papain have been safe in recommended doses.

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.[93,94]

Pregnancy:

Use should be avoided as preclinical studied in rats have demonstrated deleterious effects.[96]

Age limitation & adverse reactions:

No documentation [95]

Paediatric Trial

A Pilot study to assess the efficacy of Carica Papaya Leaf Extract in dengue associated with thrombocytopenia, in pediatric age group.

Dr.S M Prasad ;(Professor and HOD, Pediatric Department, Dr.Ambedkar Medical College, Bangalore);

Objective: This study was conducted to evaluate the efficacy of Carica Papaya Leaf Extract (as syrup formulation), in patients with dengue and associated thrombocytopenia.

Materials and Methodology: This study was conducted in the pediatric department of Dr.Ambedkar medical college, Bangalore.

Subjects in the age group of more than one year and less than 18 years were included after considering the inclusion criteria and taking the consents from the parents/guardian.

This study was an open labeled, non randomized study with 35 cases/ subjects (n=35) diagnosed as dengue by NS1 antigen test were recruited and given the syrup formulation of Carica papaya leaf extract in the dosage as mentioned below depending upon the age and weight.

For children more than 1 year and less than 5 years 275 mg (5 ml) three times a day, children > 5years and < 18 years 550 mg (10 ml) three times a day for five days.

For children weighing more than 40 kg 1100 mg tablet three times a day for five days was advised.

All the children were followed up every day for five days and their platelet counts were monitored on 1, 3 and 5 days.

Inclusion Criteria:

a) Is the subject aged > 1 and < 18 years of age?
b) Is the patient's diagnosis confirmed as DF or DHF Grade I ,Grade 2
c) Patients platelet count is below 100,000 and above 30,000 per µL
d) Has the subject's parents/guardians willingly given written informed consent?

Exclusion Criteria:

a) Patient diagnosed with DHF Grade 3 or 4
b) Platelet levels are less than 30,000 per µL
c) Has received blood products or blood transfusion during the current hospital stay Or during last one month
d) Is the patient diagnosed with ITP, Leukaemia or Hemophilia
e) Patient has participated in another trial within past one month
f) The investigator can exclude patient at his/her discretion depending upon the condition of the patient.

Results and Discussions: Distribution of sex of the subjects in the two groups did not show much difference, male were more than female, most subjects infected are in the age of 6-10 years old followed by 1-5 years old (Table 1).

Table 1:Gender and Age comparisons of Dengue patients (n=35)

Variables	Subjects (%) n=35
Sex :	
Male	20 (57)
Female	15 (43)
Age (years):	
1-5	08(22.9)
6-10	18(51.4)
11-15	07(20)
>15 & < 18	02(5.7)

Table 2:Trend in the mean platelet counts

	Day1	Day 3	Day 5
Mean Platelet Count (per µL)	48029	56514	83429
Differences in the platelet count (per µL)	**D1-3**	**D3-5**	**D1-5**
	8485	26915	34500

Above data reveals that at baseline, mean Platelet Count was 48029 among the study group, after the treatment at the end of Day 5, the mean platelet count showed a remarkable increase to 83429.There was a gradual increase of 8485 at the initial days of therapy and then a substantial increase of 26915 from day3 to day 5.Overall ,from baseline to end of treatment (day 5) there was a marked increase of 34500 platelet counts, only indicating that Carica papaya leaf extract was effective in increasing the platelet counts in patients of dengue with associated thrombocytopenia.

None of the subjects complained about any adverse effects and all of them completed the 5 days therapy.

The increasing trend of mean platelet counts in the duration of 5 days therapy of Carica papaya leaf extract is demonstrable in the figure:1 as below:-

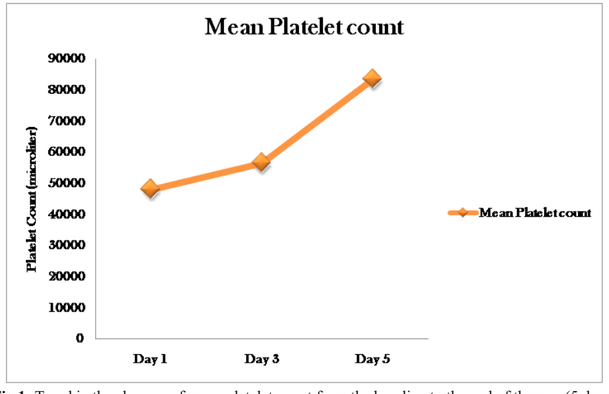


Fig 1: Trend in the changes of mean platelet count from the baseline to the end of therapy (5 days)

From the extensive literature search on carica papaya leaf extract and its property for significantly increasing the platelets in cases of dengue, confirmed several studies preclinical and clinical, been conducted and inferred on possessing the property of increasing the platelets.

One of the studies documented its mechanism of action through stimulation of genes responsible for production of platelets, thereby increasing the platelets remarkably in dengue cases associated with thrombocytopenia.

Our study reiterated similar findings with significant increase in the platelets of cases with dengue in pediatric age group. However, large scale randomized and controlled clinical trials are necessary to further establish its pivotal role in the management of dengue in pediatric age group.

Conclusion:

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. The syrup was well accepted by all the children at large indicative of being palatable as well.

Limitations:

Since this was a pilot study to assess the effectiveness of Carica papaya leaf extract in the syrup formulation on platelets, other parameters were not monitored.

It being a pilot study the sample size may not be representative and larger studies should be conducted for representation purpose.

The associated higher mortality rates with severe DHF (grade 3/4) and DSS did not allow us to include those patients and thereby we could not infer on the beneficial effects in cases with severe DHF or DSS.

300 Patients trial: Published in JAPI, 2016

A Multi-centric, Double blind, Placebo controlled, Randomized, Prospective study to evaluate the Efficacy and Safety of Carica Papaya Leaf Extract, as empirical therapy for thrombocytopenia associated with dengue fever. [101]

ABSTRACT

Dengue is a rapidly expanding global health problem. Approximately 2.5 billion people live in dengue-risk regions with about 100 million new cases each year worldwide. The cumulative dengue diseases burden has attained an unprecedented proportion in recent times with sharp increase in the size of human population at risk. The management of dengue virus infection is essentially supportive and symptomatic and no specific treatment is available for increasing the fallen platelets, which have a significant role in causing the mortality of dengue patient .This study was conducted to evaluate the platelet increasing efficacy of Carica papaya leaf extract (CPLE) in patients with dengue fever (DF).

Aim: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.

Material & Method: A Multi-centric, Double blind, Placebo controlled, Randomized, Observational study was conducted in 300 patients across 5 centre's in the country, 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)

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.
Conclusion: 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.

Introduction:
Dengue has been named one of the most important emerging infections in 2014. The geographic region at risk for dengue has increased fourfold over the past three decades, unprecedented for a vector-borne disease [1]. DENV is an arthropod-borne flavivirus associated with both hemorrhagic fever and hemorrhagic shock [2]. The classical clinical presentation of DENV is characterized by abrupt onset of headache, myalgia and high fever, in addition to arthralgia, retro-orbital pain and hemorrhagic manifestations. The DENV hemorrhagic fever is characterized by fluid leakage into the interstitium. These symptoms are commonly seen in many other infectious diseases, which complicates diagnosis.

Epidemiology:
2.5 billion people live in DENV-endemic regions[2], and roughly 400 million infections occur per year with a case fatality rate exceeding 5-20% in some areas. Over 100 countries are affected, including Europe and the United States.
DENV is endemic in many parts of Asia Pacific regions, and the DENV case frequency and fatalities are increasing, where the total number of DENV cases reported quadrupled between the 1980s and 2000-2007. Furthermore, in recent years, infections in many LMICs are increasingly noted in adults, leading to significant number of work days lost and increasing costs to society[3].

According to the World Health Organisation, primary prevention is the most effective measure in dengue prevention and control since no vaccine is currently available[3].

The preventive measures include use of insecticide sprays and elimination of all mosquito breeding grounds (areas of standing water are cleared, particularly in schools). While attempts at early diagnosis paired with prevention are helpful, the combined lack of effective treatment for dengue and increasing dengue transmission are worrisome.

Pathology:

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[4,5].

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[4,5]. In this mechanism, anti –platelet antibodies clears the virus attached platelets via complement activation and also inhibits ADP-induced platelet aggregation [4 - 9].

Management of dengue fever:
Currently there is no specific treatment for DENV, recent hopeful vaccine candidates have just been deemed ineffective[10], 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 defervescence 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.

Challenges and Obstacles:

Attempts to develop an antiviral agent for dengue have met several hurdles. Dengue is caused by four distinct serotypes which often undergo mutations.[14] Like in other ribonucleic acid (RNA) viruses, these mutations are due to the error-prone nature of RNA polymerase, which results in the formation of quasispecies. It is currently unclear which viral genome results in a higher viral titre.[15] An antiviral would have to be effective against all the serotypes.[17]

A lot of hope rests on the development of effective vaccines, many of which are undergoing clinical trials.[18] Besides vaccines, every other possible treatment including traditional medicines are being investigated to test their usefulness in controlling this problem.[16]

Severeal studies have been conducted to determine the usefulness of herbal medicine in curing dengue. Researchers have indicated that the juice of the leaves of the Carica papaya plant from the family Caricaceae helps to increase the platelet levels and have demonstrated definitive beneficial effects in these patients [18-20].

Aim:

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.

Materials & Methods:

A Multi-centric, Double blind, Placebo controlled, Randomized, Prospective study was conducted in 300 patients across 4 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.

The entire four centre's Ethics committee approved the protocol and the trial was registered under clinical trial registry system of India (CTRI Registration No: CTRI/2015/05/005806).

Inclusion Criteria:

1. Male and female patients above 18 years and below 60 years old,
2. Patients who are confirmed to have DF or DHF grade I and II by NS1 antigen test,
3. Patients having thrombocytopenia with at platelet count between 30,000 /micro litre to 100,000/micro litre,
4. Patients with a baseline alanine transaminase (ALT) level of not more than 3 times of the upper limit of the normal range (not more than 165 U/L),
5. Patient who is willing to give informed consent to participate in study.

Exclusion Criteria:

1. Patients with Dengue hemorrhagic fever grade III and IV,
2. Patients with platelet count less than 30,000/micro litre,
3. Pregnant or lactating women,
4. Patients who have received blood or blood products transfusion during the current illness,
5. Patients with thrombocytopenia Purpura (ITP), Leukemia, Hemophilia,
6. Patients who have a serum ALT level 3 times higher than the upper limit of the normal range (>165 U/L),
7. Impaired renal function with serum creatinine >1.5 mg/dl(males) and >1.4 mg/dl(females)
8. Participation in another trial with an investigational drug within 1 month prior to this trial.
9. Hypersensitivity to any of the components of the formulation,
10. The presence of any other condition that leads the investigator to conclude that the patient is inappropriate for inclusion in this clinical study.

Intervention and Duration:

All the study subjects were managed with the standard protocol/guidelines therapy for Dengue fever. In addition to the standard management protocol, after randomization in two groups, the study/intervention group received Carica Papaya leaf extract (Tablet Caripill) per orally with a strength of 1100 mg tablet, three times a day for 5 days and the control group received Placebo for the same frequency and duration as the intervention group. All the subjects were followed daily for 5 days.

Results:

All the 300 subjects enrolled were diagnosed as dengue cases by NS1 antigen test. After administering the tablet Carica papaya leaf extract (Caripill) to the intervention group (n=150) and placebo to the control group (n=150); every day platelets of both the groups were monitored.

1.1 Demographic Characteristics:

Distribution of sex of the subjects in the two groups did not show any difference (Table 1), men were more than women, most subjects infected are in the age of 26-45 years old and the distribution in both the groups did not show any difference (Table 2).

Table 1: Sex distribution between Caripill and placebo groups

Sex	Caripill	Placebo	Total
	Count (%)	Count (%)	Count (%)
Female	63 (42)	71 (47.3)	134 (44.7)
Male	87 (58)	79 (52.7)	166 (55.3)
Total	150 (100	150 (100)	300 (100)

P not significant

Table 2: Age distribution between Caripill and placebo groups

Age (yrs)	Caripill	Placebo	Total
	Count (%)	Count (%)	Count (%)
18 - 25	16 (10.7)	18 (12)	34 (11.3)
26 - 35	47 (31.3)	49 (32.7)	96 (32)
36 - 45	55 (36.7)	54 (36)	109 (36.3)
46 - 55	32 (21.3)	29 (19.3)	61 (20.4)
Total	150 (100)	150 (100)	300 (100)

Majority of the cases were febrile (99%) in both the groups and many of them had associated headache and muscular pain as predominating symptoms (78.3% & 93.7% respectively). The other symptoms observed in the study subjects were rash (30.3%), joint pain (67%), retro orbital pain (55.3%) and vomiting (19.3%).

1.1 Primary outcome variables

In this study, Platelet Count was considered as the primary outcome whereas WBC, RBC and Hematocrit are considered as secondary end points. Non parametric test – Friedman's test was used to compare difference between different time points in both the groups.

Table 3: Platelet minimum, maximum and median values for both the groups

Platelet count	Caripill				Placebo			
	N	Min	Max	Median	N	Min	Max	Median
Baseline	150	32,500	97,500	52,543	150	35,000	94,500	51,850
Day 1	150	32,000	94,000	48,000	150	32,000	94,000	45,345
Day 2	150	37,000	98,000	59,500	150	31,500	95,000	49,437
Day 3	150	60,500	1,22,000	88,897	148	32,500	95,000	55,633
Day 4	149	80,000	1,48,500	1,02,579	148	35,000	96,500	64,582
Day 5	147	98,500	2,18,500	1,55,886	145	35,000	98,500	70,528

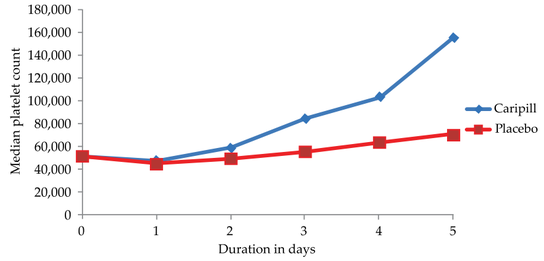


Fig. 1: Comparison of platelet count between two groups during different timepoint

Table 4: WBC minimum, maximum and median values for both the groups

WBC	Caripill				Placebo			
	N	Min	Max	Median	N	Min	Max	Median
Baseline	150	2.90	8.20	4.30	150	2.70	8.10	4.23
Day 1	150	2.90	7.90	3.90	150	2.70	7.20	4.00
Day 2	150	3.30	8.70	3.90	150	2.90	7.70	3.80
Day 3	150	3.90	9.90	4.20	148	3.20	7.90	3.90
Day 4	149	4.10	9.90	5.80	148	3.80	7.90	4.50
Day 5	147	4.50	9.90	7.90	145	3.80	8.10	4.90

The above data indicates no significant difference in the baseline values of WBC in both the groups, however at the end of treatment the WBC in the test group was significantly increased and comparing with the control group this increase was found to be statistically significant ($p<0.05$).

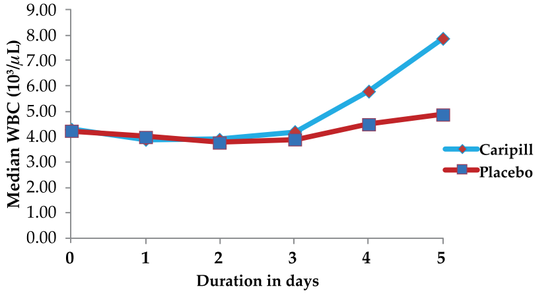


Fig. 2: Comparison of WBC between two groups during different time point

Table 5: RBCs minimum, maximum and median values for both the groups

RBC	Caripill				Placebo			
	N	Min	Max	Median	N	Min	Max	Median
Baseline	150	3.70	5.60	4.15	150	3.58	4.60	4.10
Day 1	150	3.80	5.50	4.40	150	3.60	4.60	4.35
Day 2	150	4.00	5.60	4.60	150	3.80	4.80	4.43
Day 3	150	4.10	5.60	4.64	148	3.80	4.80	4.57
Day 4	149	4.10	5.60	4.70	148	3.90	5.00	4.67
Day 5	147	4.10	5.70	4.72	145	3.90	5.10	4.68

The data in the table above indicates similar baseline values of RBC in both the groups and the values in both the groups had increased marginally which was not statistically significant. The difference in the RBC values of both the groups at the end of the treatment was not significant statistically (p=0.625).

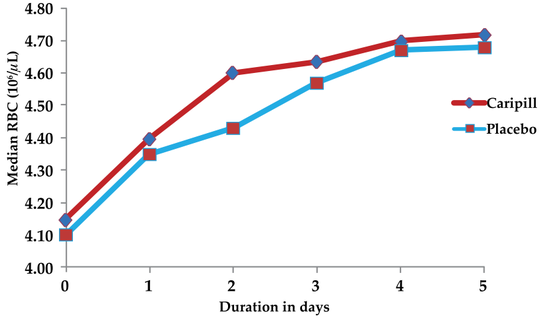


Fig. 3: Comparison of RBC between two groups during different time point

Table 6: Hematocrit (%) minimum, maximum and median values for both the groups

Hematocrit	Caripill				Placebo			
	N	Min	Max	Median	N	Min	Max	Median
Baseline	150	45	65	54	150	42	67	55
Day 1	150	44	67	52	150	42	65	53
Day 2	150	40	55	47	150	41	60	49
Day 3	150	40	58	42	148	41	60	45
Day 4	149	38	45	40	148	40	58	42
Day 5	147	35	42	38	145	40	54	40

There was no significant difference in the hematocrit values in both the groups at the baseline and no significant difference values in them were observed even at the end of the treatment too. The median values of both the group showed a declining trend at the end of day 5 as compared to the baseline however this decrease was not statistically significant(p=0.378).

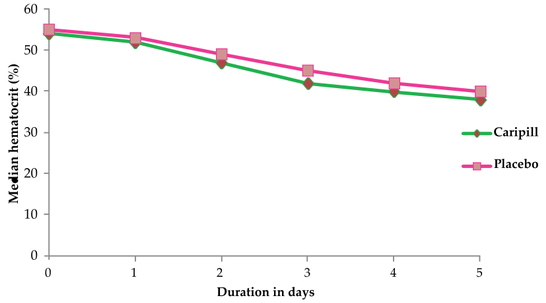


Fig. 4: Comparison of hematocrit between two groups during different time point

Discussions:

Thrombocytopenia is one of the associated conditions in dengue cases and can lead to DHF further aggravating the shock leading to a fatal state.

In this study we observed a significant increase in the platelets in the intervention group which reaffirmed the results of our earlier pilot study. It is demonstrable that the subjects in the intervention group that received CPLE (Caripill) can reach faster and higher increase in platelet count as compared to the control group. Additionally, there was significant increase in the WBC counts in the intervention group as compared to the control group from the baseline values.

The results are corroborative to those reported by Sathasivam et al. (2009) that CP leaves extract can increase platelet count in mice, and also in dengue fever patient as reported by our own pilot study by Gowda et.al[19], Subenthiran[14].

Carica papaya leaf extract is shown to increase the expression of Arachidonate -12 – Lipooxygenase (ALOX 12) and Platelet Activating Factor Receptor (PTAFR) gene responsible for platelet porodcution by FC = 15 and FC = 13.42 respectively [14]

The WBC values in both the groups showed an increasing trend after third day onwards and can be correlated to the declining viraemia at this point of time. The increase in the WBC in the intervention group was significant as compared to the control group indicative of CP leaf extract may have stimulating action at the myeloid stem cells in the bone marrow. Nwangwa E K et.al (2013) in their preclinical study documented an increase in the WBC counts with the administration of Carica Papaya leaf juice in mice, and clinical studies by Siddique et al [20], corroborated the same in humans.

There were few adverse events reported related to GI disturbances like nausea (26), vomiting (17) which were distributed similarly in both the groups and not related to drugs displaying the tolerability and safety of CPLE (Caripill). Nine (9) subjects in the test group reported to have rashes which were mild and self limiting. None of the subjects discontinued the treatment because of any adverse events. However 3 and 5 subjects in test and control group respectively did not turn up for follow up and treatments remained incomplete and therefore were considered as drop outs. Twelve patients (8.3%) from the control group went for platelet transfusion as there was a fall in their platelets to the less than 20,000 /micro liter.

None of the patients in the test group required platelet transfusions and had a remarkable recovery with rapid increase in the platelets.

The above findings reinforce the similar findings of our earlier pilot study and reaffirm the platelet increasing property of Carica Papaya leaf extract.

Conclusion:

This randomized double blind study with a representative sample size reiterated the beneficial effect of Carica Papaya leaf extract in thrombocytopenia associated with dengue.

Drastic fall of the platelets being one of the concerns in dengue cases, this novel option of Carica Papaya leaf extract [Caripill] can be optimum offering which is simple, convenient, cost effective, safe and efficacious adjuvant in the treatment of thrombocytopenia.

Summary

- Dengue fever is an acute viral infection with fatal complications
- Dengue virus has four serotypes, viz., DEN-1, DEN-2, DEN-3 and DEN-4. All four types are reported from India and more than one serotype is involved in outbreak.
- Management of dengue fever is challenging; even with optimal treatment significant number of dengue fever patients end up in Dengue hemorrhagic fever and dengue shock syndrome.
- Currently available treatment modalities include corticosteroids, immunoglobulins and platelet transfusions.
- Caripill is a breakthrough in the management of thrombocytopenia in dengue fever patients.
- Caripill is *Carica papaya Leaf extract* (CPLE) which contain many active ingredients such as glycosides, flavonoids, carpines and alkaloids responsible for its beneficial action.
- CPLE increases ALOX 12 and PTFAR gene expression in megakaryocytes and increase platelet production rapidly.
- Preclinical data suggested that CPLE increase platelet counts significantly.
- In clinical trials CPLE accelerated platelet production in patients with Dengue fever with good safety profile.
- A randomized double blind study done in 300 Indian patients reiterated safety and efficacy of CPLE in thrombocytopenia associated with Dengue fever.

Caripill is cost effective, safe and well tolerated for the management of thrombocytopenia associated with Dengue fever.

Abbreviations:

DV	Dengue Virus
NS1P	Non structural 1 Protein
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
HSC	Haemopoietic Stem Cells
MKs	Megakaryocytes
TPO	Thrombopoietin
CBFA2	Core-binding factor subunit alpha-2
AML1	Acute myeloid leukemia-1
RUNX1	Runt related transcription factor 1
RHD	Runt homology domain
TRALI	Transfusion related acute lung injury
TACO	Transfusion associated circulatory overload
FNHTR	Febrile non hemolytic transfusion reaction
TaGvHD	Transfusion associated graft versus host disease
ALOX 12	Arachidonate 12 Lipoxygenase
PTAFR	Platelet activating factor receptor
HETE	Hydroxyeicosatetraeonic acid

Caripill

Caripill

Caripill: Abbreviated Prescribing Information

Name & Composition: Carica Papaya Leaf Extract; each tablet containing 1100 mg strength.

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

MOA: 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.

Dosage & Administration: In Adults: 1100 mg t.i.d for five to seven days.

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 hypoglycemic 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 hypoglycemia.
It has been found to increase the bioavailablity of amiodarone and therefore the dose should eb adjusted accordingly when coadministered with carica papaya leaf extract.
In vitro study demonstrated potentiating the action of various antibiotics like penicillin G , ampicillin, amoxyclav, cephalothin,polymyxin B, rifampicin, amikacin,nalidixic acid, gentamycin, cholarmphenicol, oflxacin 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.
Further information for the physicians is available upon request in the Medical Department of Micro Labs; 27 Race Course road, Bangalore-560001. Phone: (080) 22370451;
Email:medicalservices@microlabs.in

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