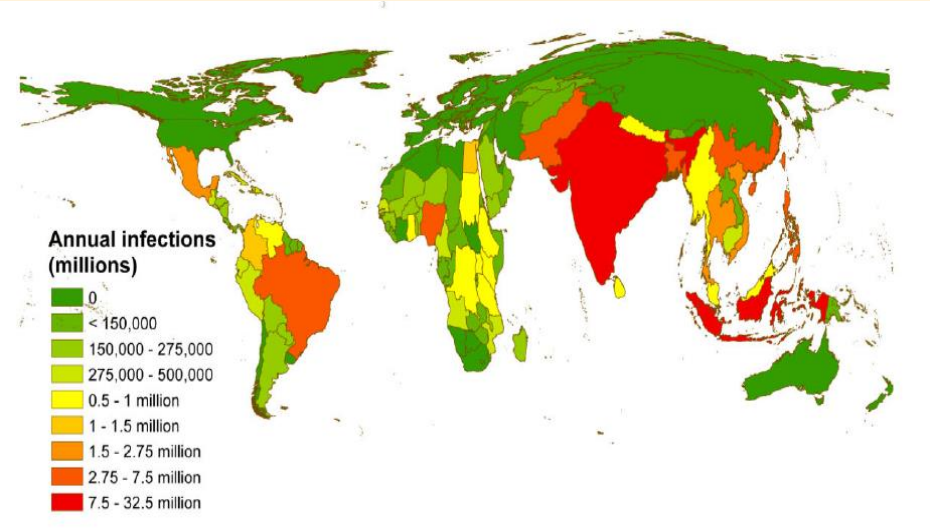
# Overview of Dengue fever
# and
# Role of Carica Papaya Leaf Extract

# INTRODUCTION

- Dengue is most rapidly spreading mosquito-borne viral disease in the world
- Has reached alarming proportions in the past few years
- Endemic in over 100 countries
- Annual 390 million infections and 5,00,000 DHF cases
- Disease causes death in approximately 4% of DHF cases




**40% of the world's population lives in countries where dengue is endemic**


1. *WHO | Dengue and severe dengue. Fact sheet. Updated April 2017*
2. *Pangtey GS et al. J Assoc Physicians India .2016 Jun;64:11-12*
3. *Torres JR. J Trop Med. 2017 : Article ID 8045435*
4. *https://www.cdc.gov/dengue/epidemiology*
5. Moraes GH et al. Am J Trop Med Hyg. 2013 Apr 3; 88(4): 670–676.


DHF - Dengue Haemorrhagic Fever

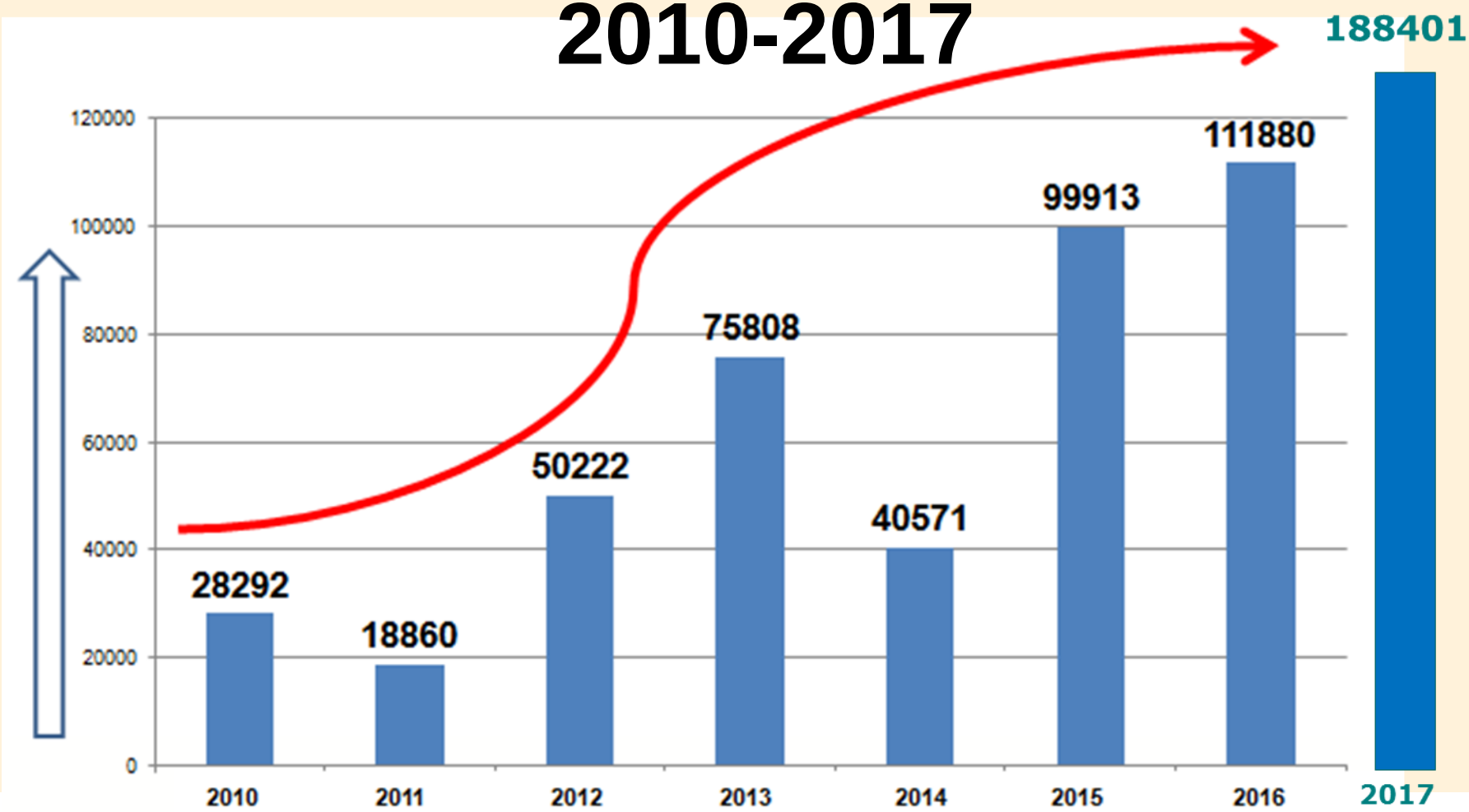
# INDIAN EPIDEMIOLOGY

- First virologically proved epidemic of DF- Calcutta in 1963
- First major wide spread epidemics of DHF/DSS - Delhi and Lucknow in 1996
- Epidemiology in Indian subcontinent has been complex; substantially changed over almost past six decades in terms of
  - prevalent strains
  - affected geographical locations
  - severity of disease


*Directorate of National Vector Borne Diseases Control Programme; 2017*
*Gupta n et al. Indian J Med Res. 2012 Sep; 136(3): 373–390*

DHF - Dengue Haemorrhagic Fever
DSS - Dengue Shock Syndrome

# DENGUE CASES IN INDIA SINCE 2010-2017




*Directorate of National Vector Borne Diseases Control Programme; 2017*

National Vector Borne Disease Control Programme
Directorate General of Health Services
Ministry of Health & Family Welfare, Government of India

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# DENGUE –2019

- **Till 26 th May 2019 - 5504 cases**

***Available at National Vector Borne Diseases Control Programme***
***http://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=431&lid=3715***
***accessed on 12-07-2019***

# National Vector Borne Disease Control Programme

Directorate General of Health Services
Ministry of Health & Family Welfare, Government of India

## Dengue Cases and Deaths in the Country since 2015

| Sl. No. | Affected States/UTs | 2015 | | 2016 | | 2017 | | 2018( Prov.) | | 2019( till 26th May) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C | D | C | D | C | D | C | D | C | D |
| 1 | Andhra Pradesh | 3159 | 2 | 3417 | 2 | 4925 | 0 | 4011 | 0 | 302 | 0 |
| 2 | Arunachal Pradesh | 1933 | 1 | 13 | 0 | 18 | 0 | 1 | 0 | | |
| 3 | Assam | 1076 | 1 | 6157 | 4 | 5024 | 1 | 166 | 0 | 14 | 0 |
| 4 | Bihar | 1771 | 0 | 1912 | 0 | 1854 | 0 | 2142 | 0 | 3 | 0 |
| 5 | Chattisgarh | 384 | 1 | 356 | 0 | 444 | 0 | 2674 | 10 | 60 | 0 |
| 6 | Goa | 293 | 0 | 150 | 0 | 235 | 0 | 335 | 1 | 79 | 0 |
| 7 | Gujarat | 5590 | 9 | 8028 | 14 | 4753 | 6 | 7579 | 5 | 320 | 0 |
| 8 | Haryana | 9921 | 13 | 2493 | 0 | 4550 | 0 | 1898 | 0 | 2 | 0 |
| 9 | Himachal Pradesh | 19 | 1 | 322 | 0 | 452 | 0 | 4672 | 7 | 14 | 0 |
| 10 | J & K | 153 | 0 | 79 | 1 | 488 | 0 | 214 | 0 | 0 | 0 |
| 11 | Jharkhand | 102 | 0 | 414 | 1 | 710 | 5 | 463 | 1 | 26 | 0 |
| 12 | Karnataka | 5077 | 9 | 6083 | 8 | 17844 | 10 | 4427 | 4 | 1076 | 0 |
| 13 | Kerala | 4075 | 25 | 7439 | 13 | 19994 | 37 | 4083 | 32 | 356 | 3 |
| 14 | Madhya Pradesh | 2108 | 8 | 3150 | 12 | 2666 | 6 | 4506 | 5 | 55 | 0 |
| 15 | Meghalaya | 13 | 0 | 172 | 0 | 52 | 0 | 44 | 0 | 0 | 0 |
| 16 | Maharashtra | 4936 | 23 | 6792 | 33 | 7829 | 65 | 11011 | 55 | 715 | 2 |
| 17 | Manipur | 52 | 0 | 51 | 1 | 193 | 1 | 14 | 0 | 3 | 0 |

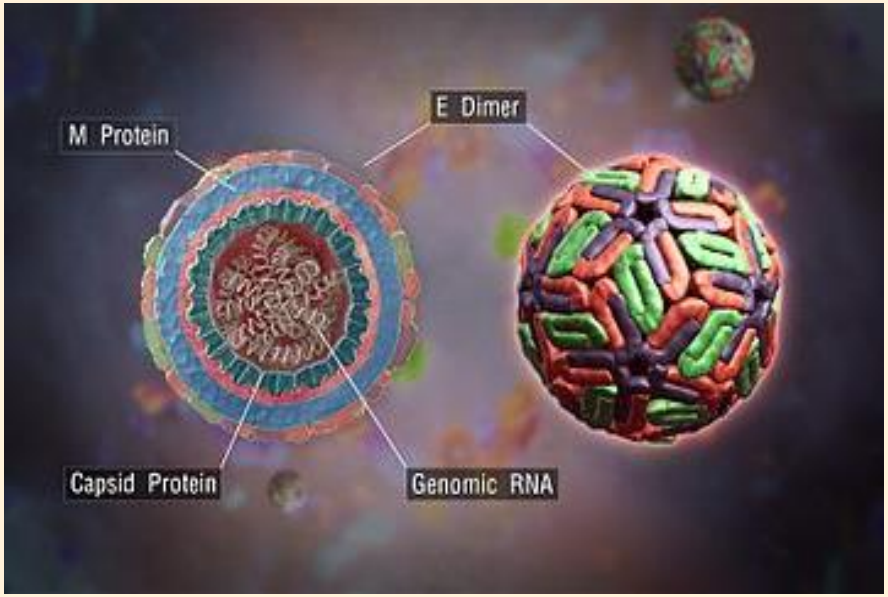
***Available at National Vector Borne Diseases Control Programme***
***http://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=431&lid=3715***
***accessed on 12-07-2019***

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | Mizoram | 43 | 0 | 580 | 0 | 136 | 0 | 68 | 0 | 6 | 0 |
| 19 | Nagaland | 21 | 1 | 142 | 0 | 357 | 0 | 369 | 0 | 0 | 0 |
| 20 | Odisha | 2450 | 2 | 8380 | 11 | 4158 | 6 | 5198 | 5 | 2 | 0 |
| 21 | Punjab | 14128 | 18 | 10439 | 15 | 15398 | 18 | 14980 | 9 | 11 | 0 |
| 22 | Rajasthan | 4043 | 7 | 5292 | 16 | 8427 | 14 | 9587 | 10 | 338 | 0 |
| 23 | Sikkim | 21 | 0 | 82 | 0 | 312 | 0 | 320 | 0 | 7 | 0 |
| 24 | Tamil Nadu | 4535 | 12 | 2531 | 5 | 23294 | 65 | 4486 | 13 | 951 | 0 |
| 25 | Tripura | 40 | 0 | 102 | 0 | 127 | 0 | 100 | 0 | 29 | 0 |
| 26 | Telangana | 1831 | 2 | 4037 | 4 | 5369 | 0 | 4592 | 2 | 756 | 0 |
| 27 | Uttar Pradesh | 2892 | 9 | 15033 | 42 | 3092 | 28 | 3829 | 4 | 44 | 0 |
| 28 | Uttrakhand | 1655 | 1 | 2146 | 4 | 849 | 0 | 689 | 3 | 0 | 0 |
| 29 | West Bengal | 8516 | 14 | 22865 | 45 | 37746 | 46 | | | | |
| 30 | A& N Island | 153 | 0 | 92 | 0 | 18 | 0 | 49 | 0 | | |
| 31 | Chandigarh | 966 | 1 | 1246 | 0 | 1125 | 0 | 301 | 0 | 0 | 0 |
| 32 | Delhi | 15867 | 60 | 4431 | 10 | 9271 | 10 | 7136 | 4 | 53 | 0 |
| 33 | D&N Haveli | 1154 | 0 | 4161 | 2 | 2064 | 0 | 493 | 0 | 15 | 0 |
| 34 | Daman & Diu | 165 | 0 | 89 | 0 | 59 | 0 | 163 | 0 | | |
| 35 | Puduchery | 771 | 0 | 490 | 2 | 4568 | 7 | 592 | 2 | 267 | 0 |
| | **Total** | **99913** | **220** | **129166** | **245** | **188401** | **325** | **101192** | **172** | **5504** | 5 |

***Available at National Vector Borne Diseases Control Programme***
***http://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=431&lid=3715***
***accessed on 12-07-2019***

# DENGUE VIRUS (DENV)

- Arthropod-borne viruses
- Genus *Flavivirus* (family Flaviviridae)
- Single-stranded RNA
- Four genetically related but antigenically distinct DENV serotypes (DENV-1, **DENV-2**, DENV-3, and DENV-4).
- In India all 4 serotypes prevalent




***Subsequent infections by other serotypes in a previously dengue-suffered person increase the risk of developing severe dengue***

*WHO | Dengue and severe dengue. Fact sheet. Updated April 2017*

# VECTOR PROFILE

## Aedes aegypti

- Small, black mosquito with white stripes
- Approximately 5 mm in size
- Day biter

## Aedes albopictus

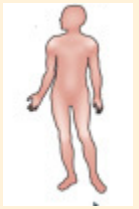
a secondary vector in Asia

- Highly adaptive due to tolerance to temperatures - below freezing, hibernation

**Eggs of *Aedes aegypti* can live without water for more than one year**

# REPLICATION AND TRANSMISSION OF DENGUE VIRUS

1. Virus transmitted to human through bite of mosquito



2. Replicates in target organs

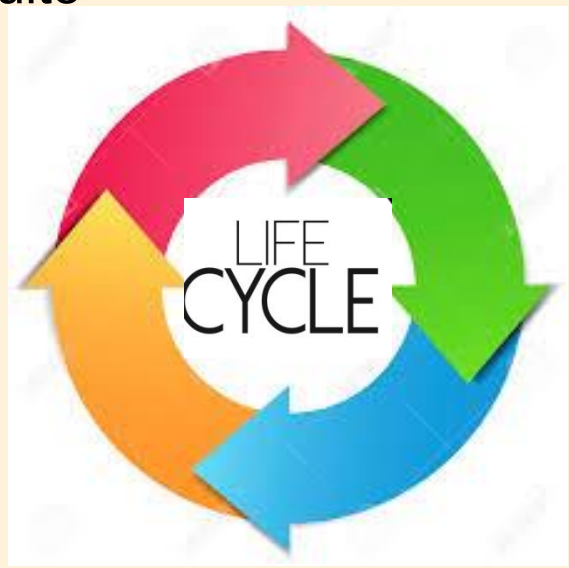
3. Infects WBCs and lymphatic tissues

4. Virus released and circulates in blood

5. Second mosquito ingests virus with blood

6. Virus replicates in mosquito midgut and other organs, infects salivary glands

7. Virus replicates in salivary glands of Mosquito




*Carrington LB . et al. Frontiers Immunol. 2014 Jun; 5: 1-8*

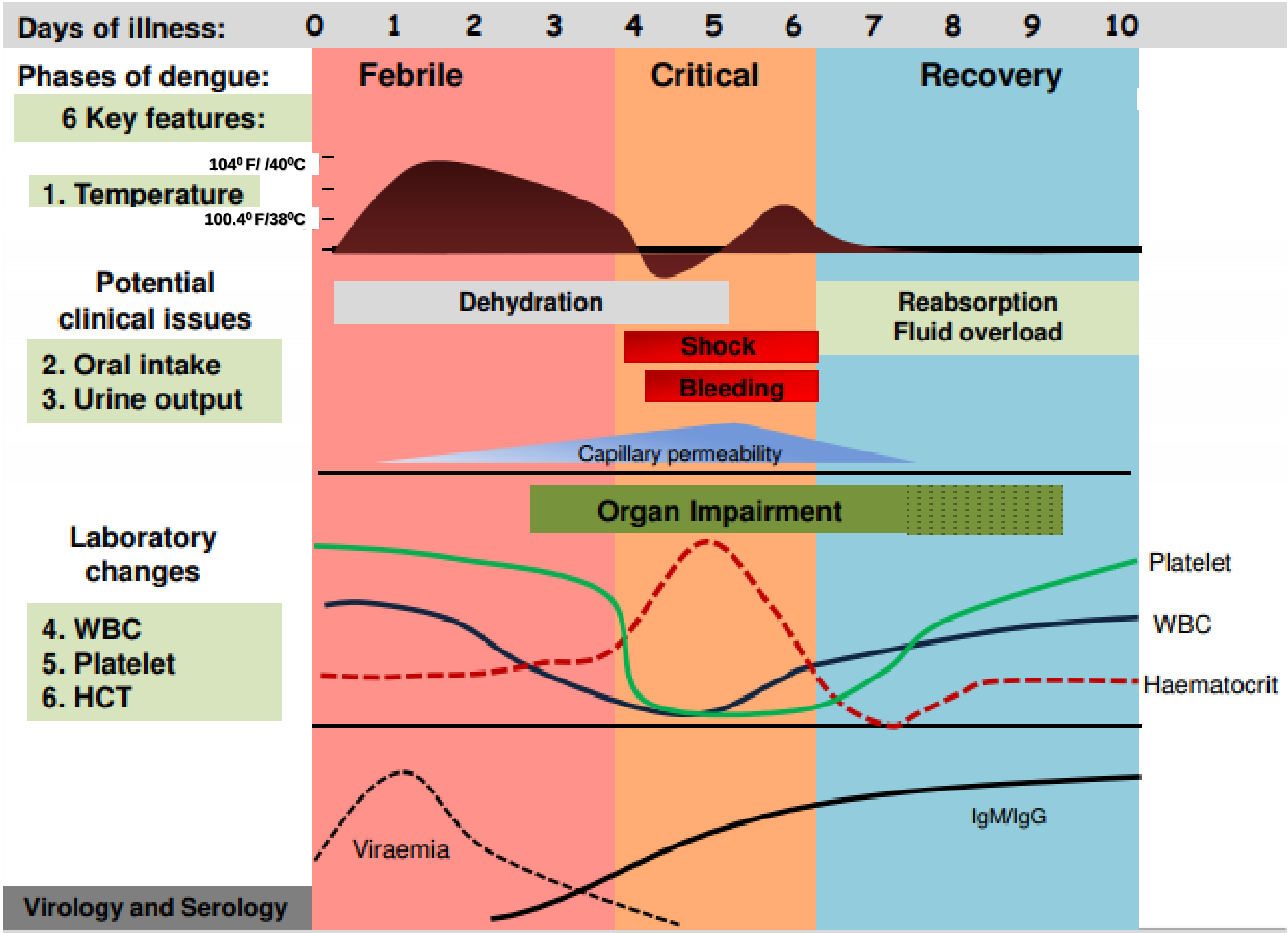
# DENGUE FEVER CHARACTERISTICS

- ❑ Incubation period 4–10 days
- ❑ Flu-like illness
- ❑ Sudden, high fever (40°C/104°F)
- ❑ Accompanied by at least 2 of the following symptoms:

  *Severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands or rash*

- ❑Symptoms usually last for 2–7 days

*WHO | Dengue and severe dengue. Fact sheet. Updated April 2017*




Adapted from WCL Yip, 1980 by Hung NT, Lum LCS, Tan LH

**Hemorrhagic manifestations**: Petechiae, Purpuric lesions, Ecchymoses, Epistaxis, Bleeding gums, GI hemorrhage, Hematuria

Subconjunctival Haemorrhage with Ecchymosis in a patient with DHF

Chemosis and subconunctival haemorrhage in a patient with DSS

***24–48 hours of the critical stage can be lethal; proper medical care is needed to avoid dengue complications (DHF & DSS)***

*Dengue-National-Guidelines-2014*

# GRADING THE SEVERITY OF DENGUE INFECTION

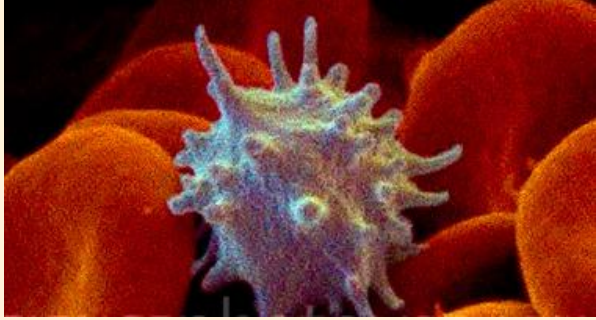
| DF/ DHF | Grade | Symptoms/signs | Laboratory findings |
|---|---|---|---|
| DF | | Fever with two or more of following<br>- Headache<br>- Retro-orbital pain<br>- Myalgia<br>- Arthralgia | Leucopenia, thrombocytopenia |
| DHF | I | Above criteria for DF plus positive tourniquet test, evidence of plasma leakage | Thrombocytopenia : Platelet count less than 100,000/cu.mm.<br>Haematocrit rise 20% or more |
| DHF | II | Above signs and symptoms plus some evidence of spontaneous bleeding in skin or other organs (black tarry stools, epistaxis, bleeding from gums, etc) and abdominal pain | Thrombocytopenia platelet count less than 100,000/cumm<br>Haematocrit rise 20% or more |
| DHF | III | Above signs and symptoms plus circulating failure (weak rapid pulse, pulse pressure ≤20 mm Hg or high diastolic pressure, hypotension with the presence of cold clammy skin and restlessness) | Thrombocytopenia: Platelet count less than 100,000/cumm<br>Haematocrit rise more than 20% |
| DHF | IV | Profound shock with undetectable blood pressure or pulse<br>Haematocrit rise more than20% | Thrombocytopenia : Platelet count less than 100,000/cumm<br>Haemotocrit rise more than 20% |

*Pongpan S. et al. ISRN Pediatrics. 2013;6*

# Expanded Dengue

- WHO terminology – 2012
  - Several atypical findings dengue.
  - Unusual manifestations
  - No plasma leakage
  - Co-infections
  - Under reported / Unrecognised
  - Proper assessment is necessary

# THROMBOCYTOPENIA



Thrombocytopenia is an important criteria used by WHO guidelines as an indicator of clinical severity

**Thrombocytopenia is rapid decline in platelet count or a platelet count less than 150,000 per microliter of blood**

*de Azeredo EL et al. Mediators Inflamm. 2015;2015:313842.*

# MULTIPLE MECHANISMS OF THROMBOCYTOPENIA IN DENGUE

## *Decreased production*

- **Virus induces BM suppression affecting hematopoietic progenitor cells**
- **Decreased/Defective megakaryocytes**
  **Less platelet production**

## *Increased peripheral destruction*

- **Molecular mimicry - Cross reactivity of dengue anti NS1 with platelet and endothelial cells**
- **Destruction of platelets- Macrophages phagocytosis the autoantibody coated platelet**

## *Increased consumption*

- **Disseminated intravascular coagulation (DIC)**

*de Azeredo EL et al. Mediators Inflamm. 2015;2015:313842.*

# PATHOGENESIS OF DHF AND DSS

Haemostatic changes in DHF and DSS

- ❑ Thrombocytopenia
- ❑ Capillary leak syndrome
- ❑ Coagulation disorders (DIC)

**CAPILLARY LEAK SYNDROME**

Dengue virus–infected monocytes and endothelial cells produce multiple cytokines, including TNF-α

↓

Increased vascular permeability due to malfunction of vascular endothelial cells and plasma leakage

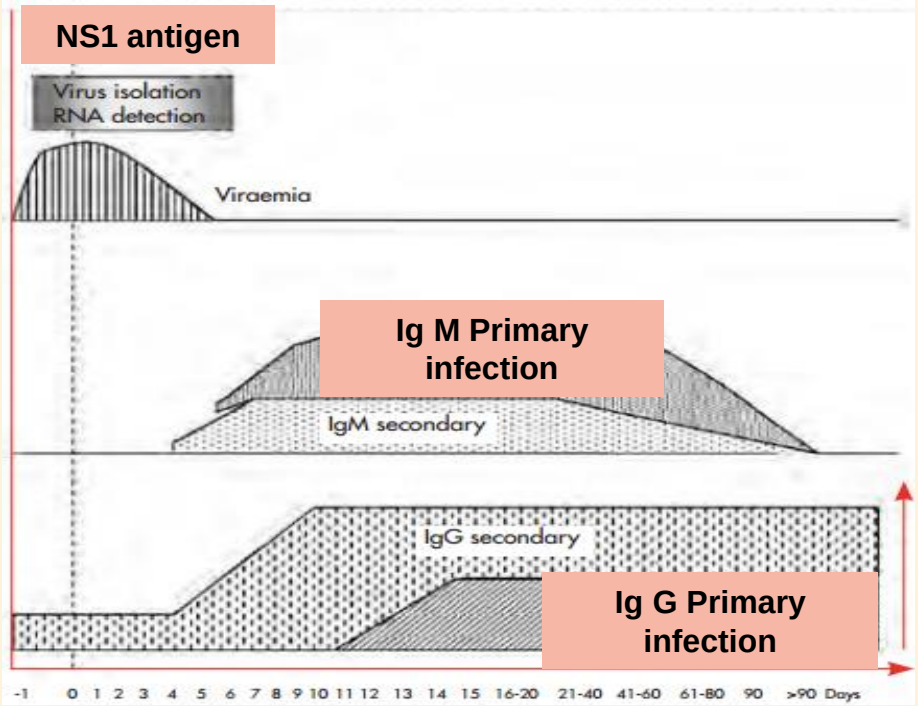
↓

Decreased plasma volume leads to DHF/DSS


1. *Martina BEE et al.clinical microbiology reviews. 2009 Oct; 22(4) : 564–581.*
2. *Gubler DJ. Clin Microbiol Rev. 1998 Jul; 11(3): 480–496.*
3. *Rajapakshe S. J Emerg Trauma Shock. 2011 Jan-Mar; 4(1): 120–127.*
4. *Azeredo EL et al. Mediators of Inflammation . 2015 ; Article ID 313842:16*
5. *Verma SK. Dengue Bulletin . WHO IRIS. 2011; 35: 65-70*

# LABORATORY TESTS

- Leucopoenia, thrombocytopenia and raise in hematocrit (Hct)
- NS1 antigen (non-structural antigen) by ELISA method or PCR (polymerase chain reaction)
- Ig M, Ig G titres
- Liver function tests
- Renal function tests
- USG abdomen
- Chest X-Ray





1. *Muller DA et al. J Infect Dis. 2017 Mar 1;215(2):S89-S95.*
2. *Nisalak A. Southeast Asian J Trop Med Public Health.2015;46 (1):55-76*
3. *Dengue: guidelines for diagnosis, treatment, prevention and control . WHO.2009*
4. *Gubler DJ. Clin Microbiol Rev. 1998 Jul; 11(3): 480–496.*

# MANAGEMENT

- No specific treatment
- Symptomatic and supportive care
- Platelet transfusion (platelet count <10,000 cu mm)
- Thrombopoietin receptor agonists (Eltrombopag 50 mg OD, Romiplastim 1 mcg/kg SC Weekly)
- Vaccines-???

***WHO | Dengue and severe dengue. Fact sheet. Updated April 2017***
***Visentin GP et al. Hematol Oncol Clin North Am. 2007 Aug ; 21(4): 685–vi***
***Guidelines for clinical management of dengue fever, dengue hemorrhagic fever and dengue shock syndrome. Directorate of national vector borne diseases control programme. 2008***

# MANAGEMENT CONT...

- **Reduction of high fever:** paracetamol only (avoid aspirin, NSAIDs)
- Soft diet, milk, fruit juice, oral rehydration solution (ORS)
- Follow up CBC everyday
- Detection of pleural effusion and ascites early
- Proper IV fluid management :Isotonic salt solution in the critical period (6ml/kg/h for 1-2 hrs → 10ml/kg/h)
  - 5% dextrose in normal saline solution (Preferable)
  - 5% Ringer Acetate, 5% Ringer-Lactate

*WHO | Dengue and severe dengue. Fact sheet. Updated April 2017*

# CURRENT THERAPIES AND CHALLENGES

- Limited treatment options
- Platelet transfusion → immunologic reaction, risk of infections (Hep C, Hep B, HIV ), Cost of Hospitalization
- Prompt and timely treatment is required to prevent complications
  - Dengue hemorrhagic fever and dengue shock syndrome are often lethal

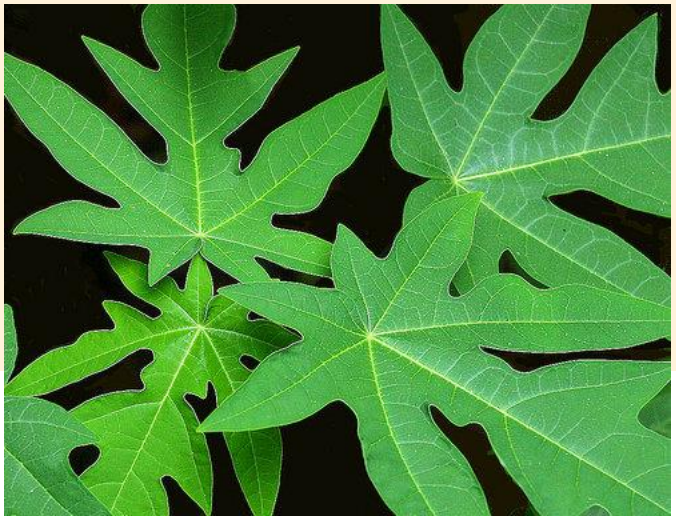

1. *Kumawat V et al.* Asian J Transfus Sci. 2015 Jan-Jun; 9(1): 61–64.
2. Prati D. J Hepatol.2006 Oct; 45(4): 607–616
3. *Chen X et al. Iran J Pediatr.Sep 2012; 22 (3):417-420*
4. *Seo DH et al. World J Hepatol 2015 March 27; 7(3): 600-606*
5. *Rajapakshe S. J Emerg Trauma Shock. 2011 Jan-Mar; 4(1): 120–127*

# Novel therapy in Dengue management

## *Carica papaya* Leaf Extract (CPLE)

# CARICA PAPAYA

- Commonly called the papaya plant
- *Carica papaya* has been long known to possess a number of medicinal properties
- The plant contains many active components with varying concentrations in its different parts



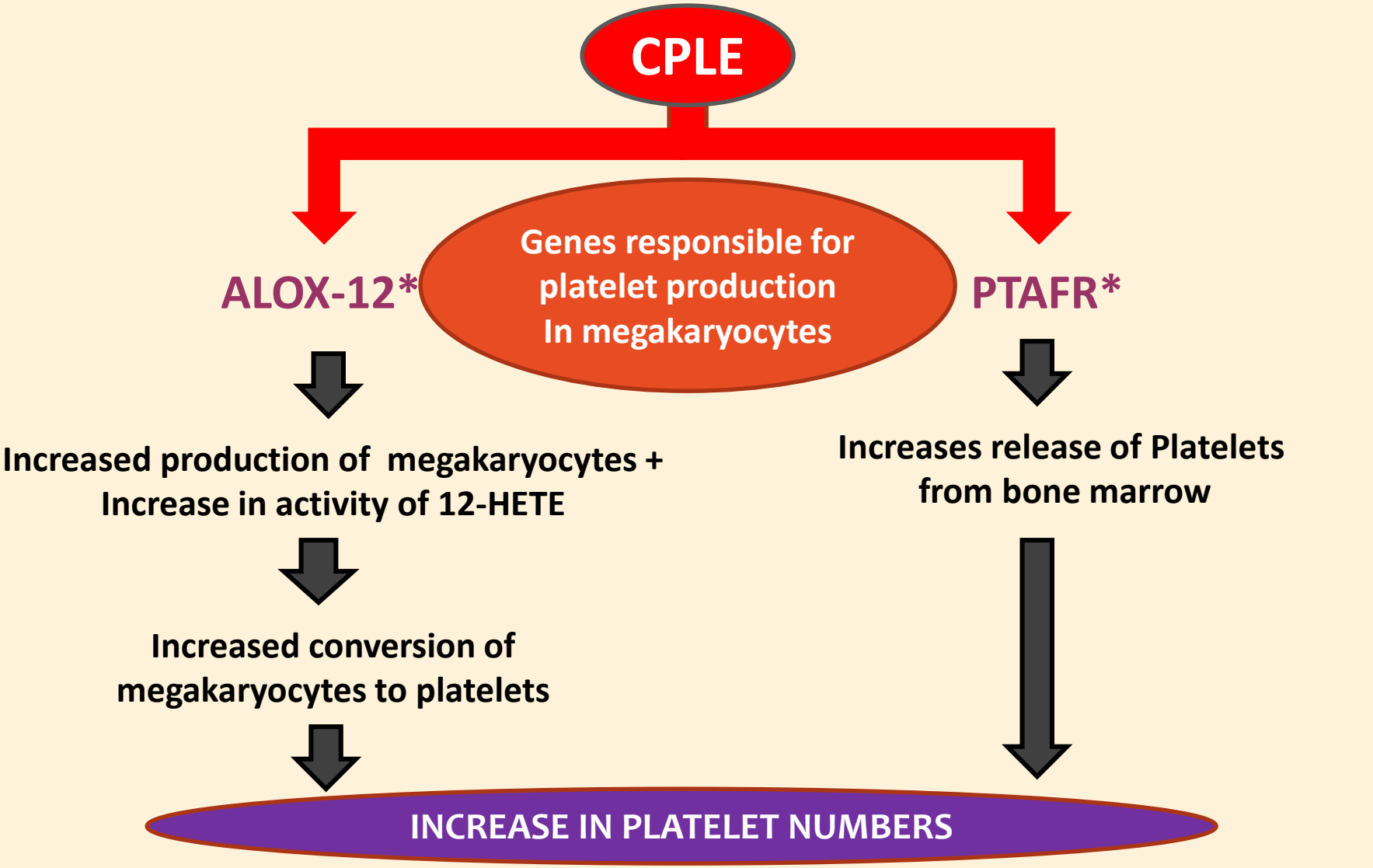

1. *Srivastava AK et al. International J Res Studies Bioscie . 2016 Nov.;4(11):19-25*
2. *Maisarah AM et al. J Tissue Sci Eng. 2014: 5:1*
3. *Sarala N et al. Ann Med Health Sci Res. 2014 MayJun; 4(3): 320–324.*

# ACTIVE INGREDIENTS IN CPLE

- Glucosides
- Papain, chymopapain
- Cystatin
- Glycyl endopeptidase
- Flavonoids
- Cyanogenic-glucosides


1. *Zunjar V et al. Pharmacognosy Journal. 2011; 3: 5-8*
2. *Otsuki N et al. J Ethnopharmacology. 2010; 127: 760-767*

# Mechanism of increased platelet production




*Subenthiran S et al Evid Based Complement Alternat Med. 2013:616-737*

*ALOX-12 : Arachidonate-12-lipoxygenase
PTAFR: platelet activating factor receptor gene
12-HETE: 12-Hydroxytetraenoic acid

# CPLE UPREGULATES THROMBOPOETIC CYTOKINES

- **IL–6**
  - Increases the proliferation & maturation of Megakaryocytes which increases thrombocyte production
  - Enhances  thrombopoietin (TPO) production in liver which increases thrombocyte production

- **Stem cell factor (SCF)**
  - A cytokine essential for haematopoiesis

*Rose B. et al. Clin Exp Immunol. 2006;143:85–92*
*Kaser A. Et al. Blood. 2001;98:2720–5..*

# CPLE- ANTI VIRAL ACTIVITY

- The viral non structural 2B and 3 (NS2B-NS3) protease complex is crucial for virus replication

- Analysis of anti-dengue activities of the extracts from Carica papaya by using bioinformatics tools shows

**Flavonoid quercetin exerts highest binding energy against NS2B-NS3 protease**

**Flavonoid quercetin from Carica papaya have significant anti-dengue activities**

*Senthilvel P. et al. Bioinformation. 2013; 9(18): 889-895*

# EVIDENCES

- Preclinical Studies
- Toxicity Studies
- Clinical Studies

# STUDY #1: C PAPAYA & PLATELETS IN MURINE MODEL

36 mice; 18 in test group given fresh *C. papaya* leaf extract [0.2 mL (2 g)/ mouse]

General behavior, clinical signs and feeding patterns observed, hematological parameters (CBC, LFT, RFT) tested

Results

No alteration of behavior

**Platelet count:**
$3.36 \times 10^5$ cells/cmm$^3$ (Day 1 )
$9 \times 10^5$ cells/cmm$^3$ (Day 7)
$10.86 \times 10^5$ cells/cmm$^3$ (Day 14)

No significant changes in SGOT, SGPT or serum creatinine

*Dharmarathna ACLS et al. Asian Pac J Trop Biomed. 2013 Sep; 3(9): 720–724*

# STUDY #2: ORAL TOXICITY OF C PAPAYA LEAF EXTRACT IN SPRAGUE DAWLEY RATS

Sub-acute oral toxicity was tested at doses of 0.01, 0.14 and 2 g/kg

General behavior, clinical signs, hematological parameters, serum biochemistry & histopathology changes were observed

No significant toxicities; mortality = 0%

**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**

*Halim SZ et al. J Med Plants Res. 2011 May; 5: 1867-1872*

# INTERNATIONAL CLINICAL TRIALS

# INTERNATIONAL CLINICAL STUDY#1

**Internal medicine ward hospital, Bekasi, West Java, Indonesia**

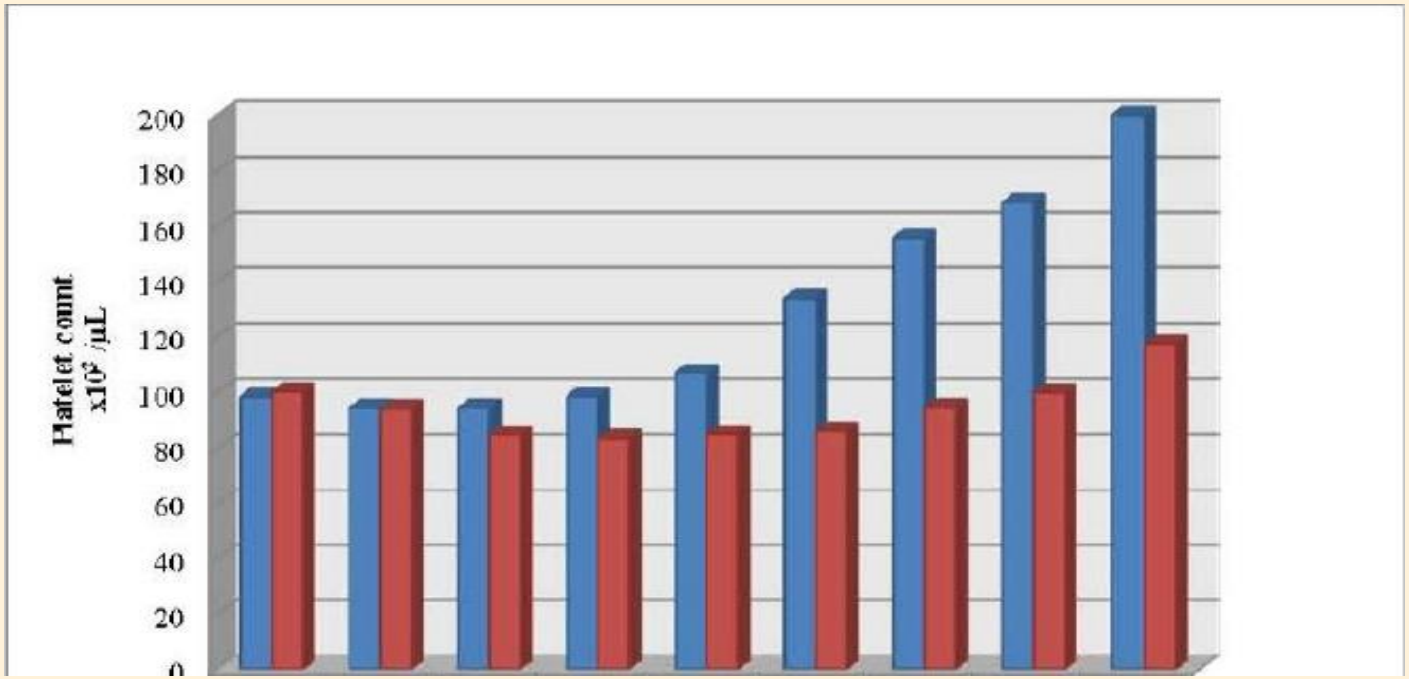
Open label, Randomized, controlled clinical trial; 80 patients with confirmed dengue

Control group: 40 patients. Intervention group: 40 patients. Test group received 2 capsules TID for 4 days

Each capsule used in test group contained 550 mg of C papaya leaf extract (70% of ethanolic extract of CP leaves)

*Yunita F. et al. Int J Med Arom Plants. 2012 Dec; 2(4): 573-578*

# INTERNATIONAL CLINICAL STUDY#1: RESULTS




| | 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 | 100.1 | 94.3 | 84.9 | 83.4 | 85.1 | 86.1 | 94.6 | 99.8 | 117.48 |

*Yunita F. et al. Int J Med Arom Plants. 2012 Dec; 2(4): 573-578*

# INTERNATIONAL CLINICAL STUDY#2

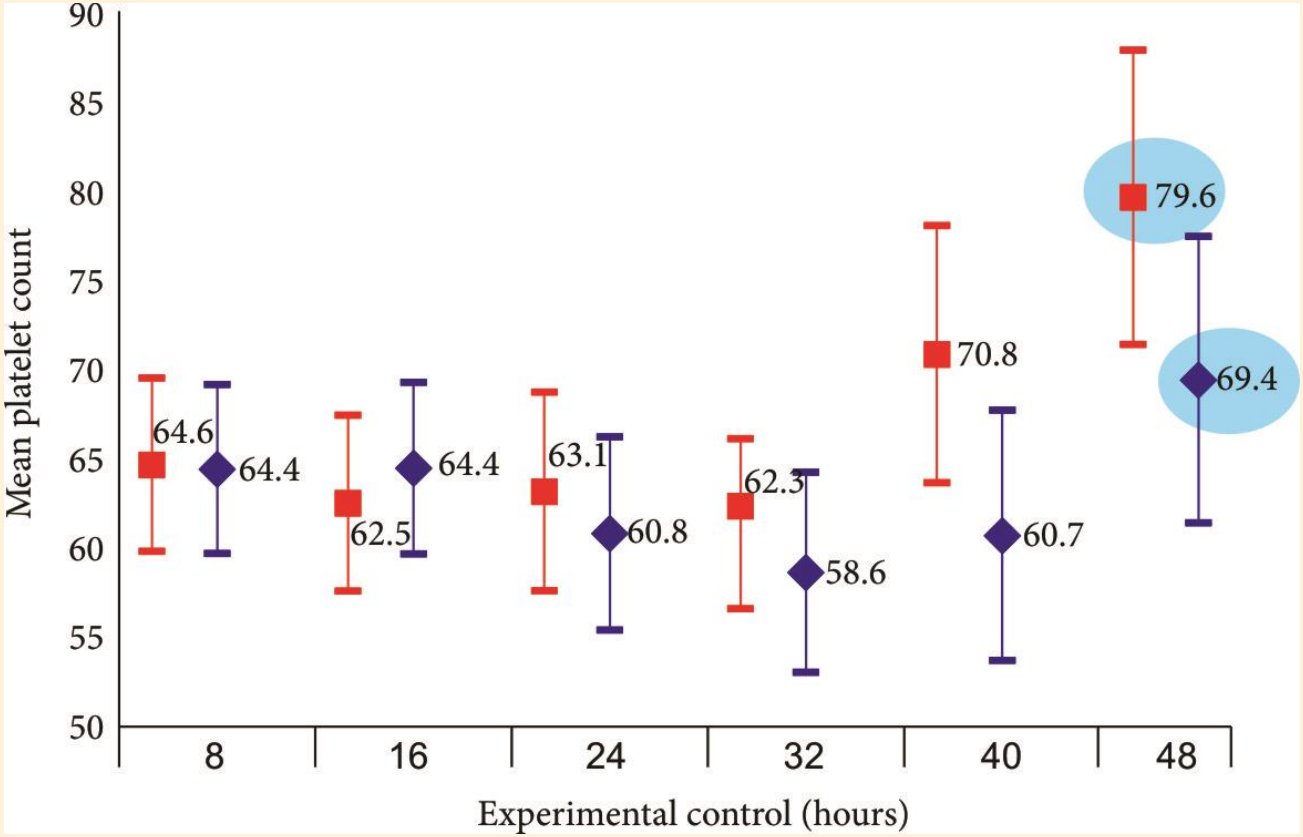
**Dengue Ward of Hospital Tengku Ampuan Rahimah, Klang, Selangor Malaysia**
Open label RCT on 290 patients with DF and DHF

145 patients received C *papaya* leaf extract and 145were on control with standard measures; for 3 days

Platelet investigations were done at 8, 16, 24, 32, 40, and 48 hours after admission

*Juneja V et al. Int J Med Res Health Sci. 2016; 5(1)254-257*

# INTERNATIONAL CLINICAL STUDY#2: RESULTS




**Comparison of mean platelet count between intervention and control group based on time (time-treatment effect).** ■ ***Experimental arm*** ◆ ***Control arm***

*Juneja V et al. Int J Med Res Health Sci. 2016; 5(1)254-257*

# INTERNATIONAL CLINICAL STUDY#2: RESULTS

The **ALOX 12 (FC = 15.00) and PTAFR (FC = 13.42) genes were highly expressed** among those on Carica papaya leaf extract

ALOX and PTAFR are important genes involved in production of platelets

*Arachidonate lipoxygenases (ALOX) Gene
PTAFR platelet activating factor receptor gene
FC- Fold change

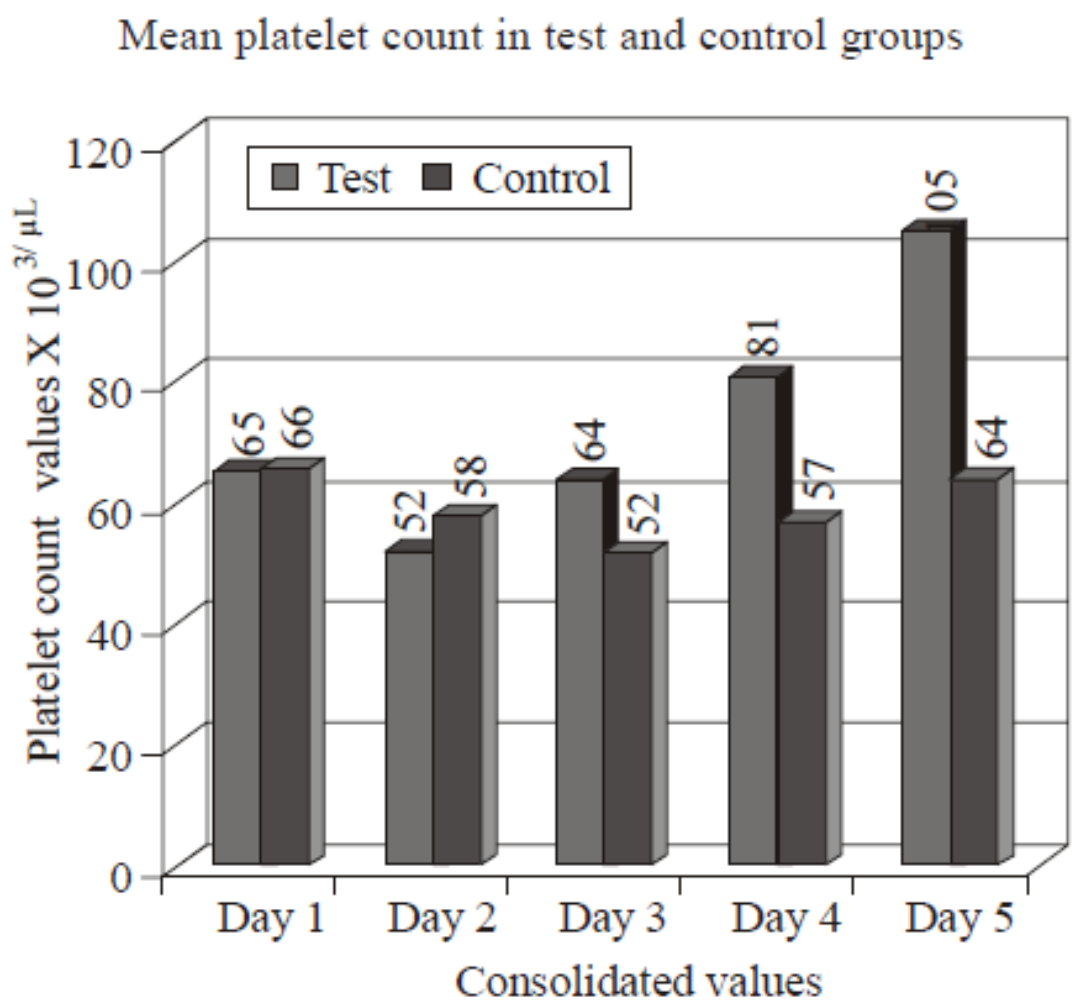
# CLINICAL TRIALS IN INDIAN PATIENTS

# INDIAN CLINICAL STUDY #1

- Conducted at 2 sites in Bangalore
  **Poornima Hospital and S V Hospital, Bangalore**
- Included 30 patients with dengue fever (confirmed by NS1 antigen test)
- Subjects were given *C papaya* leaf extract tablets at a dose of 1100mg TID for 5 days
- Platelet levels were monitored on a daily basis

*Gowda AC et al Indian medical Gazette 2015 Mar.*

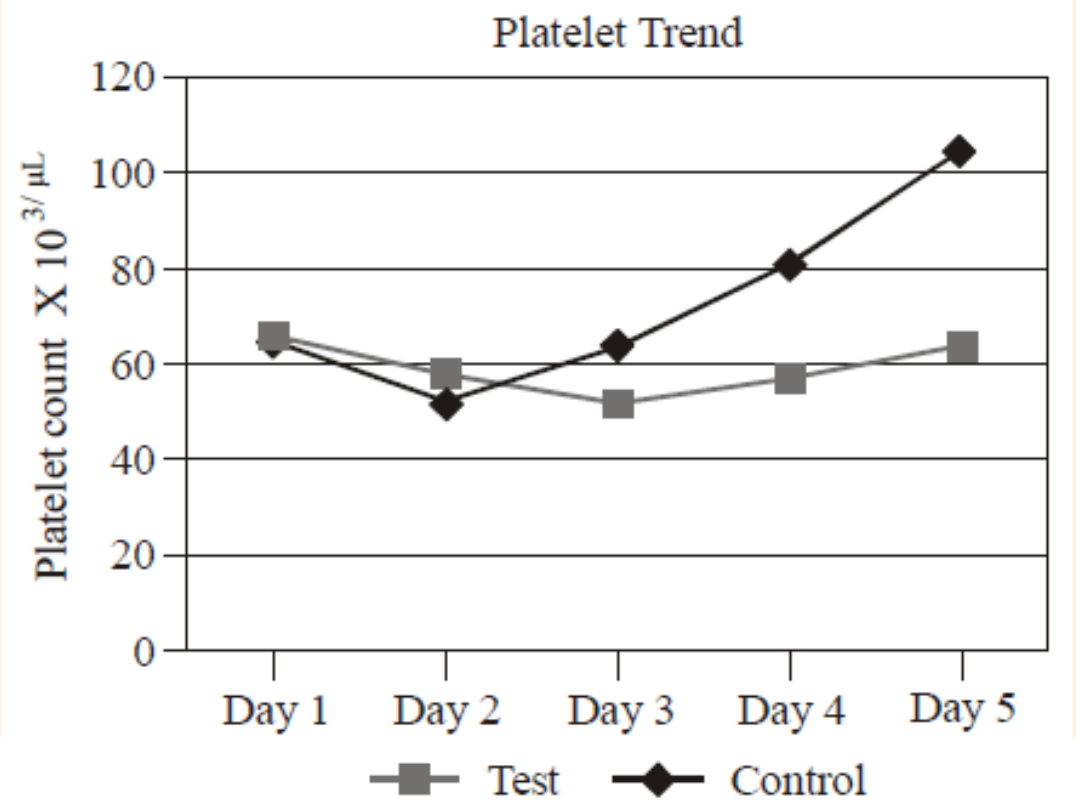
# RESULTS




*Gowda AC et al Indian medical Gazette 2015 Mar.*

# PLATELET TREND

Day wise trend in the platelet counts in both the groups.




*Gowda AC et al Indian medical Gazette 2015 Mar.*

# INDIAN CLINICAL STUDY #2

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2016, 5, 1:254-257

## The effect of Carica papaya leaves extract capsules on platelets count and hematocrit levels in acute febrile illness with thrombocytopenia patient

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*Department of Medicine, Sri Aurobindo Medical College & PGI, Indore, India*

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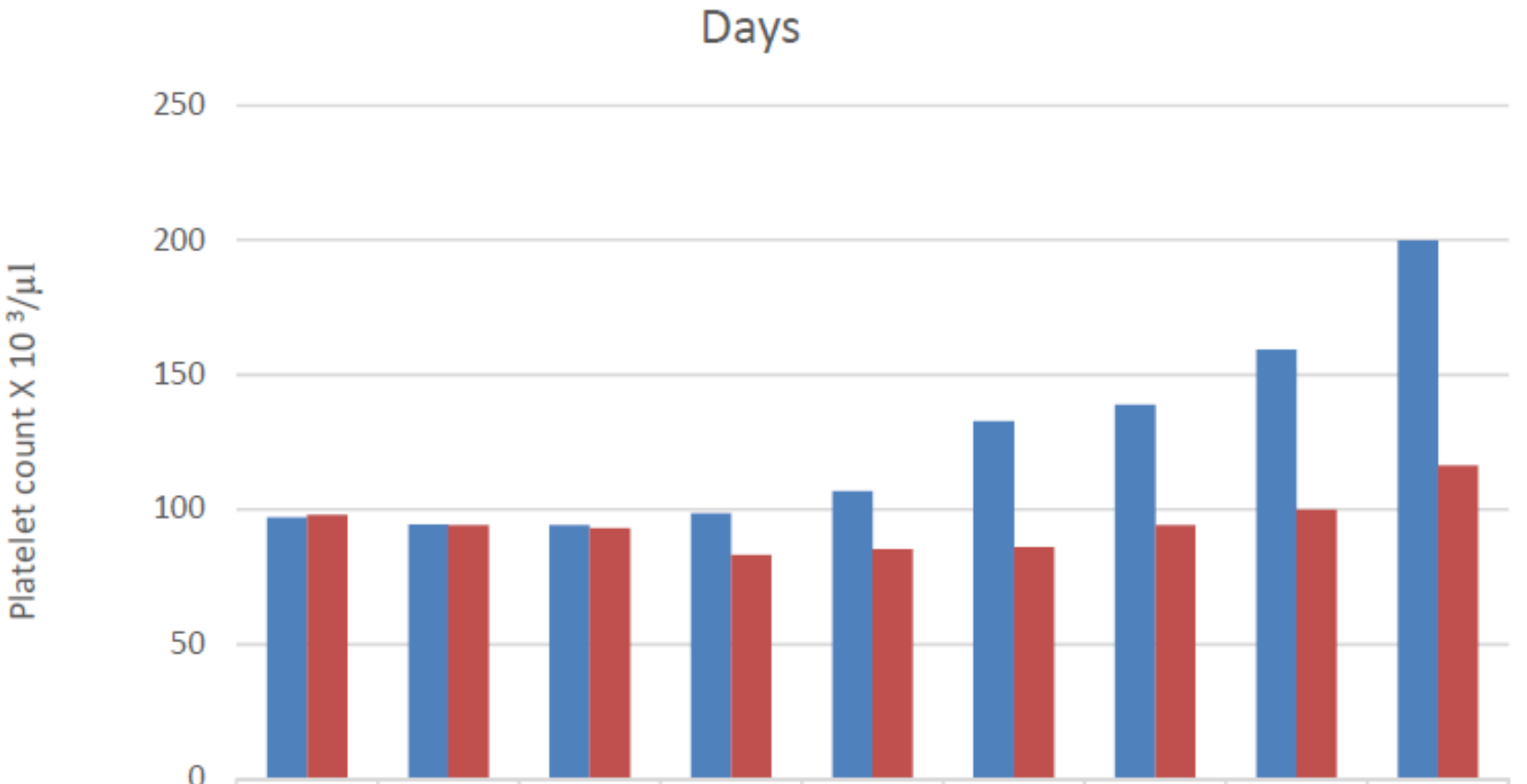
# STUDY DESIGN AND METHODOLOGY

- An observational, prospective, uncontrolled, open label, study
- **Study centre:** Department of Medicine, Sri Aurobindo Medical College & PGI, Indore, India
- Total 80 patients were enrolled
- Randomized into two groups
  - Control (Supportive care)
  - Intervention groups (Supportive care + Carica papaya leaf extract three times daily)

# RESULTS




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| Intervention | 97.23 | 94.46 | 94.37 | 98.46 | 106.78 | 132.8 | 138.78 | 159.3 | 199.9 |
| Control | 97.98 | 94.34 | 93.14 | 83.14 | 85.26 | 86.1 | 94.16 | 100 | 116.4 |

Days

*Juneja V et al. Int J Med Res Health Sci. 2016; 5(1)254-257*

# INDIAN CLINICAL STUDY #3



ORIGINAL ARTICLE

## 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

*Kasture PN et al. J Assoc Physicians India. 2016 Jun. 64: 15-20*

# STUDY DESIGN

- Double blind, randomized, placebo controlled
- 300 patients across 5 centres in India
  - Control : standard therapy
  - Intervention group: standard therapy + Carica papaya leaf extract (Caripill 3 times daily for 5 days)
- **Primary end point**: Platelet count
- **Secondary end points**: WBC count, Hematocrit, Safety

**Study centres:** Dr. B R Ambedkar College, **Bangalore**; King George Hospital, **Visakhapatnam**, Andhra Pradesh; Prashanth Hospital **Bangalore**; Rajiv Gandhi Institute of Medical sciences, **Srikakulum**, Andhra Pradesh; Sri Venkateshwara Hospital, **Bangalore**

# RESULTS-PLATELET COUNT

**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 |

*Kasture PN et al. J Assoc Physicians India. 2016 Jun. 64: 15-20*

# RESULTS-PLATELET COUNT

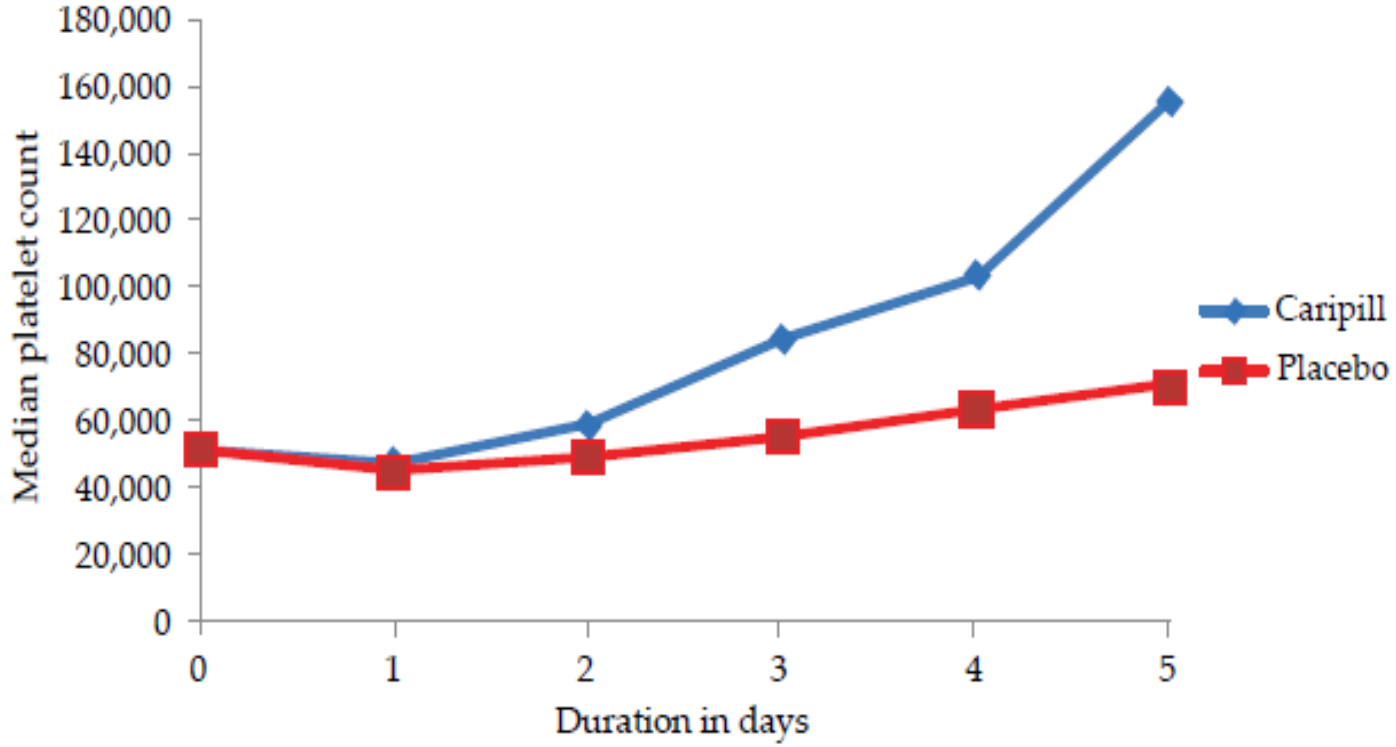



**Fig. 1: Comparison of platelet count between two groups during different timepoint**

# RESULTS-WBC COUNT

**WBC minimum, maximum and median values for both the groups ($10^3/\mu L$)**

| 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 |

*Kasture PN et al. J Assoc Physicians India. 2016 Jun. 64: 15-20*

# RESULTS-WBC COUNT

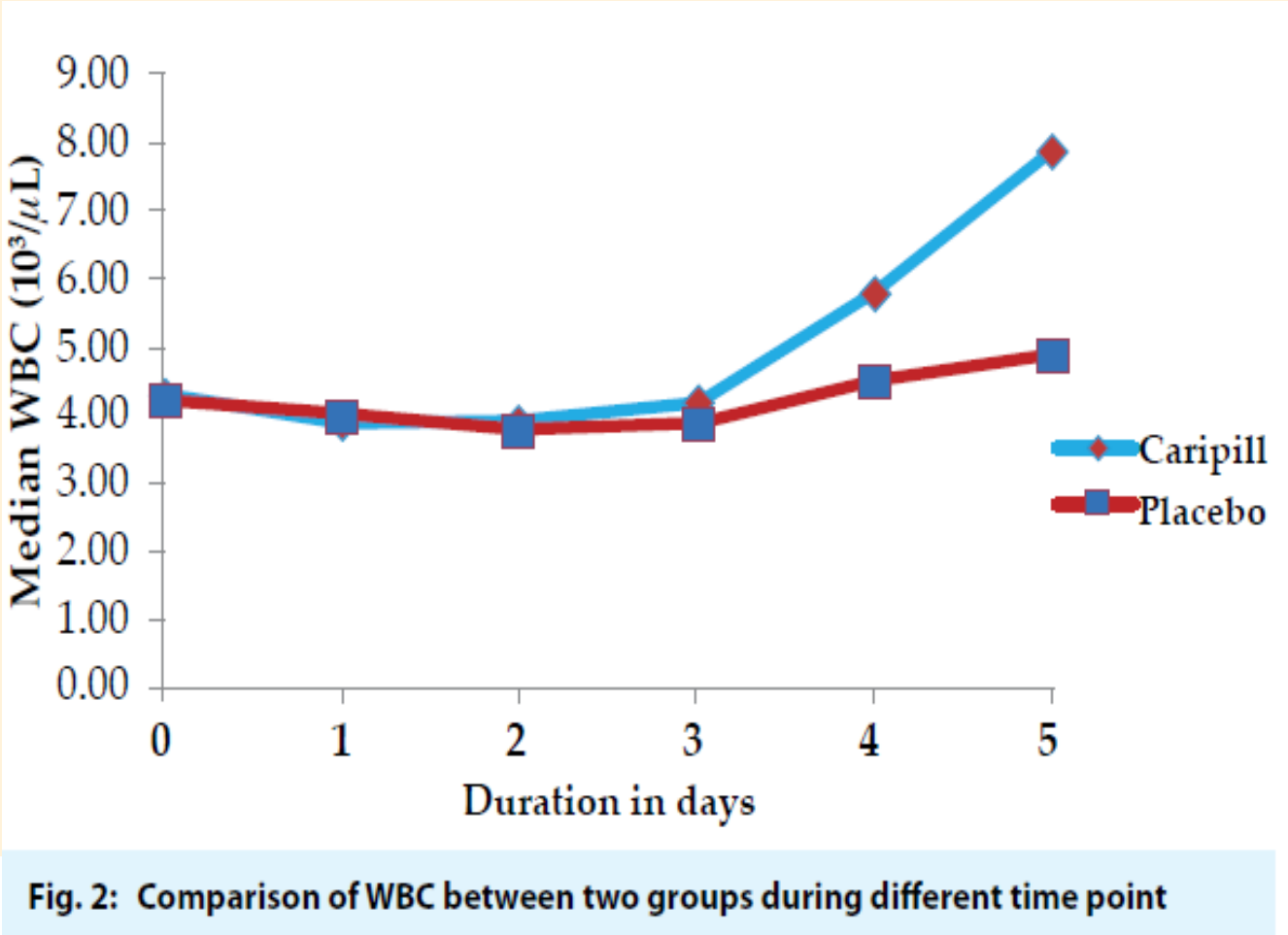



**Fig. 2: Comparison of WBC between two groups during different time point**

ORIGINAL ARTICLE

# Effect of *Carica papaya* Leaf Extract Capsule on Platelet Count in Patients of Dengue Fever with Thrombocytopenia

# STUDY DESIGN

- Total 400 cases, (275 male and 125 female) of dengue fever with thrombocytopenia

- Randomized into two groups

  – Study group **-** Papaya leaf extract capsule (500 mg) once daily and routine supportive treatment for consecutive five days

  – Control group-The control group was given only routine supportive treatment and no placebo drug was given.

*Gadhwal AK et al. J Assoc Physicians India. 2016 Jun. 64: 22-26*

# AVERAGE HOSPITALIZATION PERIOD (DAYS) OF BOTH GROUPS

| Admission day | Study group (n) | Control group (n) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 18 | 2 |
| 3 | 71 | 3 |
| 4 | 82 | 23 |
| 5 | 70 | 53 |
| 6 | 8 | 80 |
| 7 | 2 | 21 |
| After 7 days | 2 | 18 |

Mean hospitalization days in both groups

| Study group | Control group | P value |
|---|---|---|
| 3.65±0.97 | 5.42±0.98 | <0.01 |

*Gadhwal AK et al. J Assoc Physicians India. 2016 Jun. 64: 22-26*

# PLATELET TRANSFUSION IN BOTH GROUPS

| Units of platelets | Study group | Control group |
|---|---|---|
| 0 | 145 | 107 |
| 1 | 11 | 15 |
| 2 | 21 | 38 |
| 3 | 13 | 26 |
| 4 | 6 | 7 |
| 5 | 3 | 3 |
| 6 | 1 | 4 |

Average platelet transfusion (units/patient) in both groups

| Study group | Control group | P value |
|---|---|---|
| 0.685 | 1.19 | <0.01 |

*Gadhwal AK et al. J Assoc Physicians India. 2016 Jun. 64: 22-26*

# CARICA PAPAYA LEAF EXTRACT(CPLE)

- Increases platelet count
- Decreases requirement for hospitalizations
- Decreases need for platelet transfusion

*Gadhwal AK et al. J Assoc Physicians India. 2016 Jun. 64: 22-26*

# CLINICAL TRIALS IN IN PEDIATRIC AGE GROUP

# A PILOT STUDY TO ASSESS THE EFFICACY OF CARICA PAPAYA LEAF EXTRACT IN DENGUE ASSOCIATED WITH THROMBOCYTOPENIA, IN PEDIATRIC AGE GROUP

- Study centre: Dr. Ambedkar Medical College, Bangalore
- Principal investigator: Dr. S M Prasad ,Professor and HOD, Pediatric Department

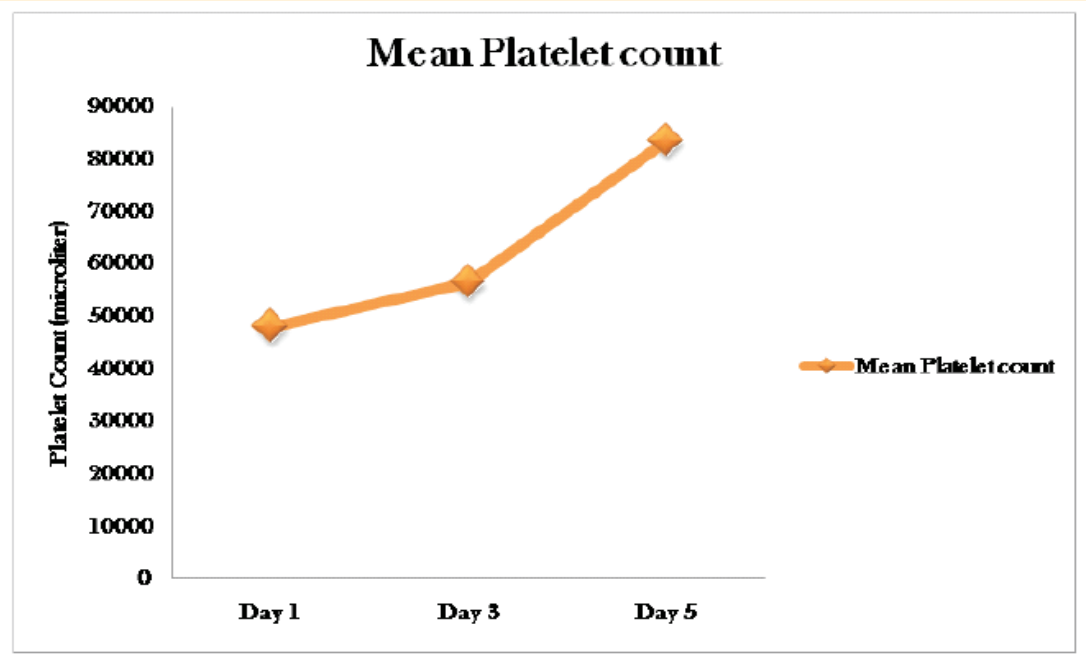
***Inclusion Criteria:***

- Is the subject aged > 1 and < 18 years of age
- Is the patient's diagnosis confirmed as DF or DHF Grade I ,Grade 2
- Patients platelet count is below 100,000 and above 30,000 per µL

***Exclusion Criteria:***

- Has received blood products or blood transfusion during the current hospital stay Or during last one month
- ITP, Leukaemia or Hemophilia

# RESULTS




| | Day1 | Day 3 | Day 5 |
|---|---|---|---|
| Mean Platelet Count (per µL) | 48029 | 56514 | 83429 |

**Paper published on 18th Jan 2019**

Pediatric Health, Medicine and Therapeutics

Dovepress

ORIGINAL RESEARCH

# An open-label, randomized prospective study to evaluate the efficacy and safety of *Carica papaya* leaf extract for thrombocytopenia associated with dengue fever in pediatric subjects

BK Srikanth[1] Lakshminarayana Reddy[1] Sunita Biradar[1] Manjula Shamanna[2] Deepak D Mariguddi[2] M Krishnakumar[2]

1 Department of Paediatrics, Vijayanagara Institute of Medical Sciences, Bellary, Karnataka, India; 2 Department of Medical Services, Micro Labs Ltd, Bengaluru, Karnataka, India

Pediatric Health, Medicine and Therapeutics 2019:10 5–11

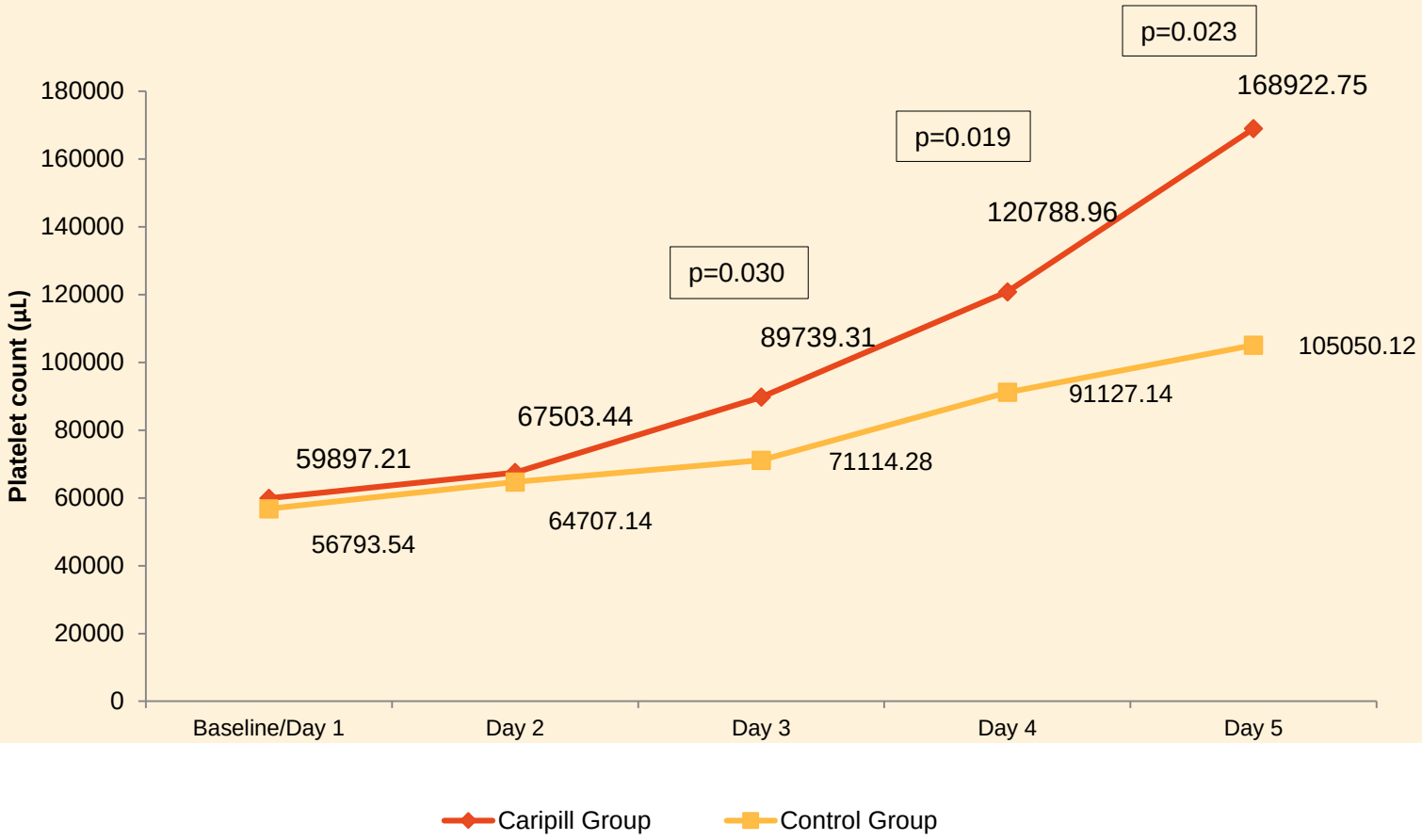
# DETAILS

- Prospective, Open label, Randomized controlled study
- Study Centre: VIMS,Bellary,Karnataka
- N=294
- Subjects were randomized into intervention group(n=147, CPLE syrup + standard Therapy) and the control group(n=147, received only standard therapy).

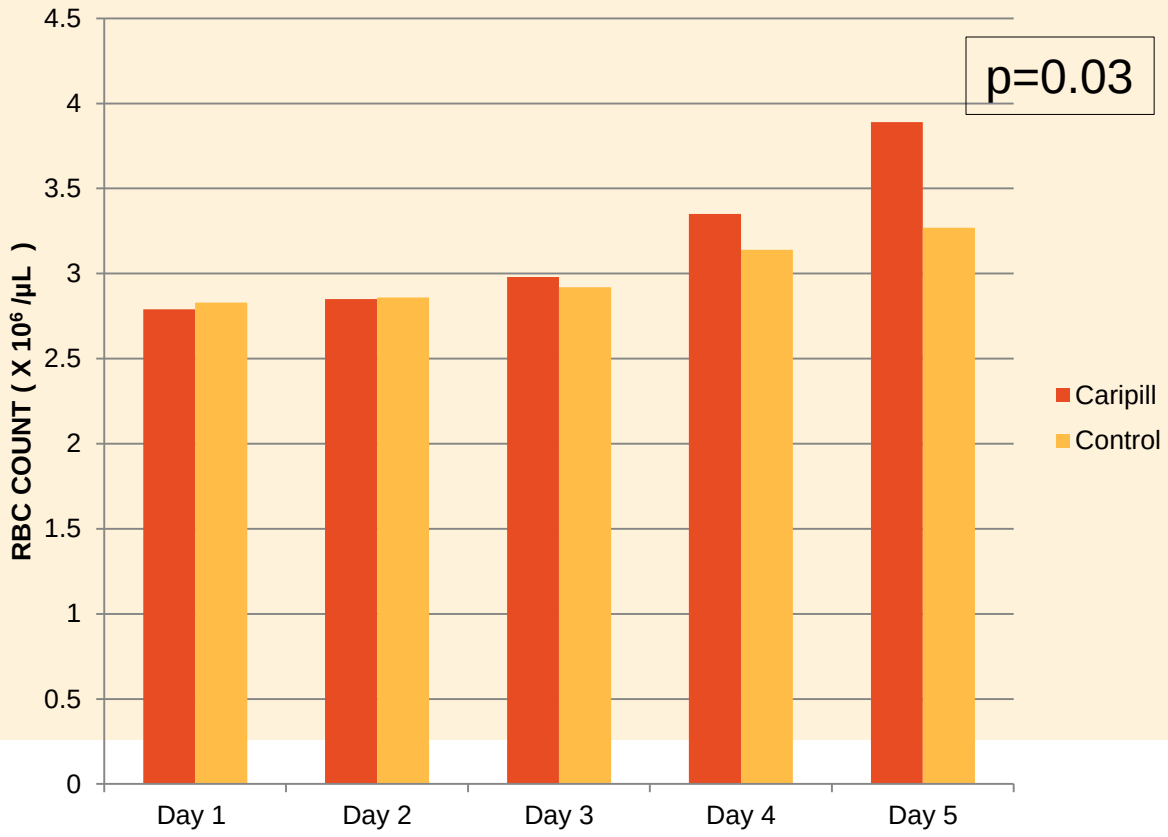
# DOSAGE

- Carica Papaya leaf extract Syrup formulation according to the age groups:
  - Children aged between 1 to 5 years received 275mg three times daily for 5 days
  - Children above 5 years received 550 mg three times for 5 days

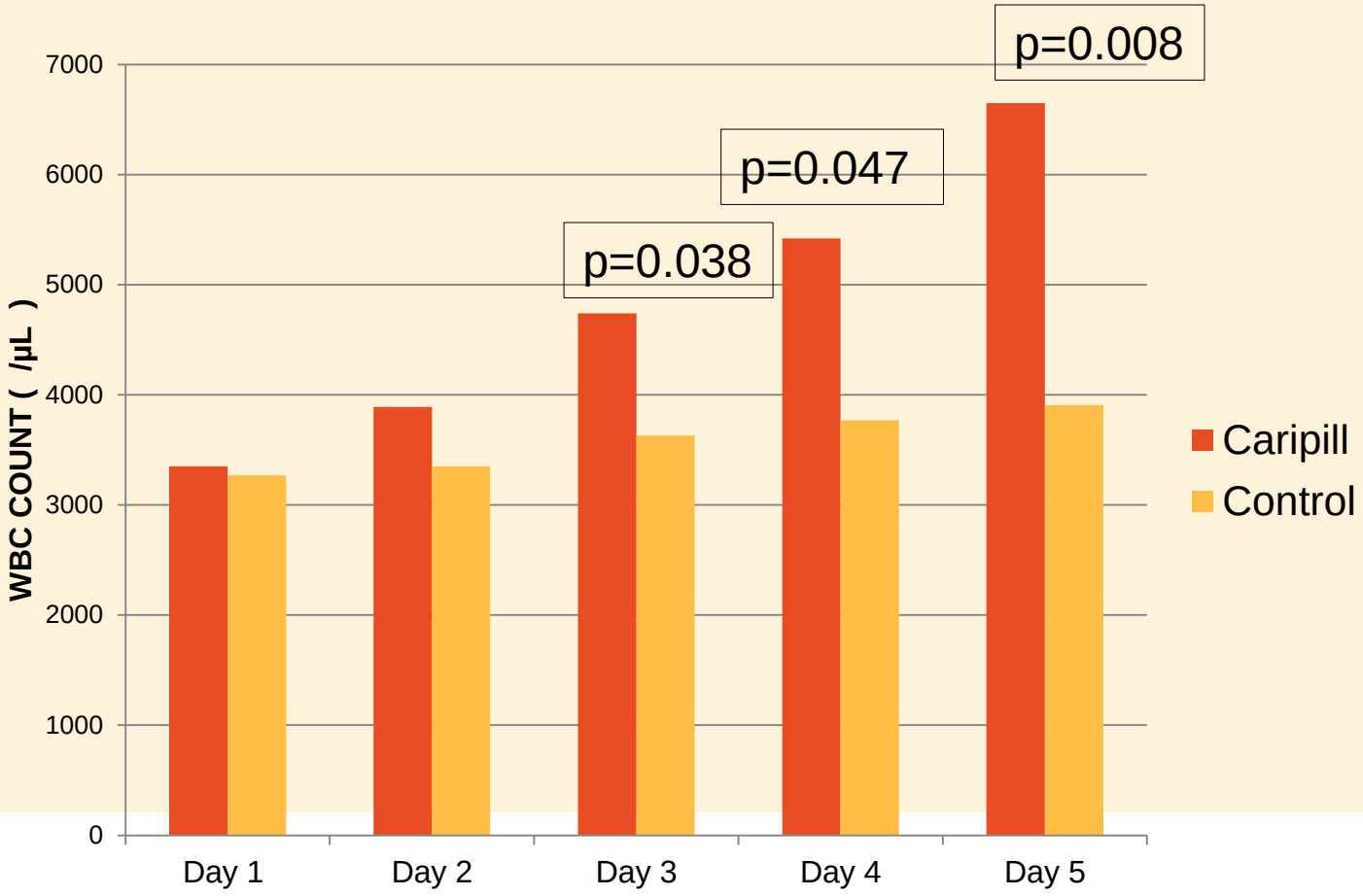
# CHANGES IN THE PLATELET COUNT IN THE STUDY SUBJECTS



# MEAN CHANGE IN RBC COUNT



# MEAN CHANGE IN WBC COUNT



# ONGOING CLINICAL TRIAL…

- Caripill in Severe dengue **(DHF grade 3 and 4)**
- With severe thrombocytopenia (platelets < 30,000/ul).

- **Amrita Institute of Medical sciences and Research Center, Cochin**

**STUDY CENTRE:**

Dept. of General Medicine, Dept. of Emergency Medicine and Dept.of Virology, Amrita Institute of Medical Sciences and Research Center, Ponekkara, AIMS, Kochi.

# OBJECTIVES:

- Primary: To determine the impact of Caripill administration (1100mg t.i.d for 5 days on the following:
  - Platelet count and hematocrit values in dengue patients with severe thrombocytopenia.
  - Reducing the number of blood product transfusions esp. platelet transfusion and
  - All-cause mortality rates.

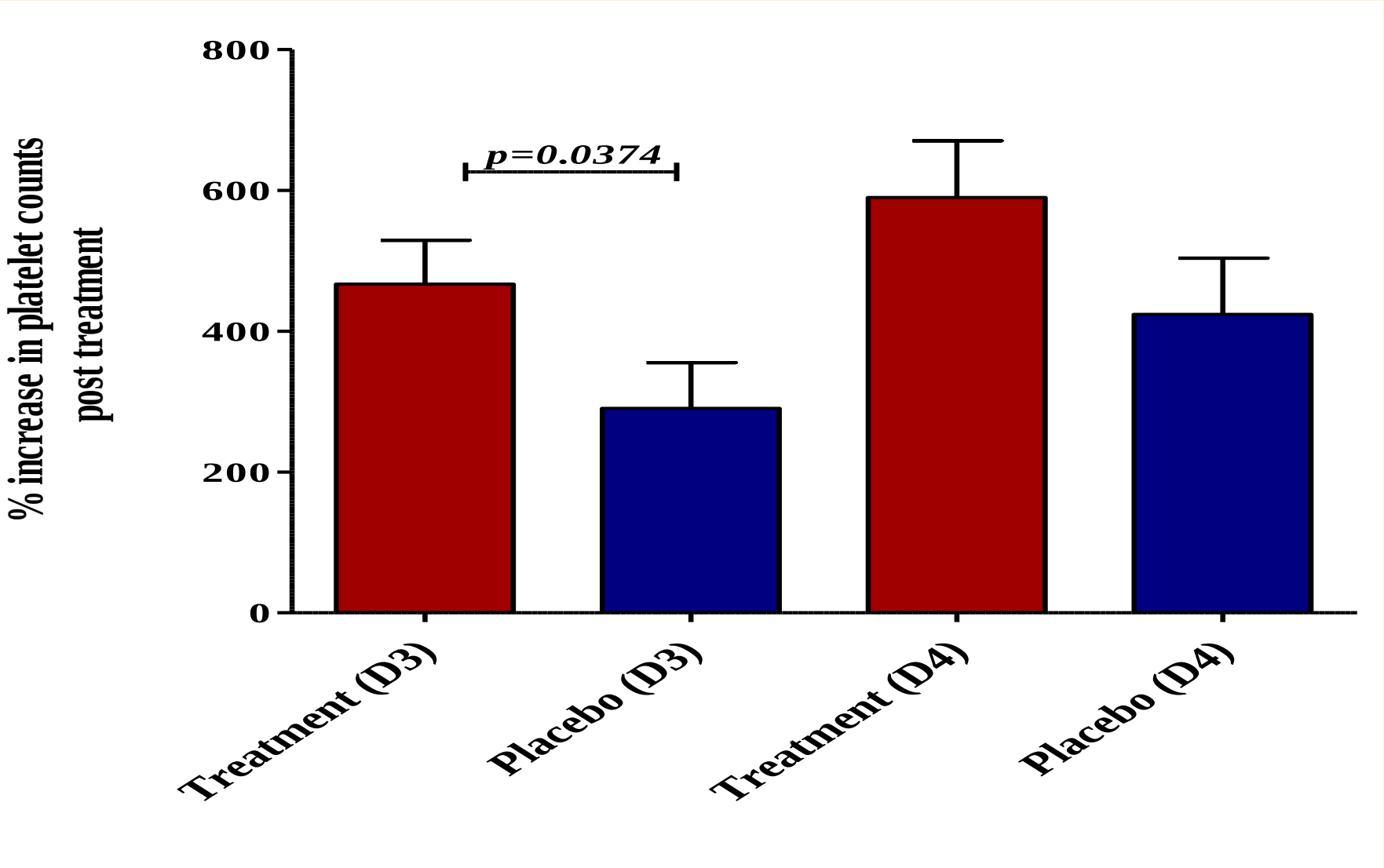
# OBJECTIVES:

- Secondary: To evaluate the effect of Caripill administration (1100mg t.i.d for 5 days) on the following:
  - Magnitude and kinetics of serum viremia
  - Magnitude and kinetics of cytokines IL12p70, IFN$\gamma$,, IL6, TNF$\alpha$ and IL8.
  - The total length of hospital (ICU & ward) stay,
  - Total cost of care

# INTERIM RESULTS (40 SUBJECTS)

# CARIPILL EFFECT ON PLATELET COUNTS

**Percentage increase of platelet count on day 3 and day 4.**



# THE SAFETY AND TOLERABILITY PROFILE OF ORAL CARIPILL TABLETS.

1. No significant adverse event or side effect profiles were observed

2. No serious dose related adverse events were reported in the treatment group

# CPLE - SUMMARY FROM CLINICAL TRIALS

**Increases platelet count**

**Marginal increase in WBC count**

**Decreases requirement for hospitalizations**

**Decreases need for platelet transfusion**

*Carica papaya leaf extract* offer simple, convenient, cost effective, safe and efficacious adjuvant in the treatment of thrombocytopenia

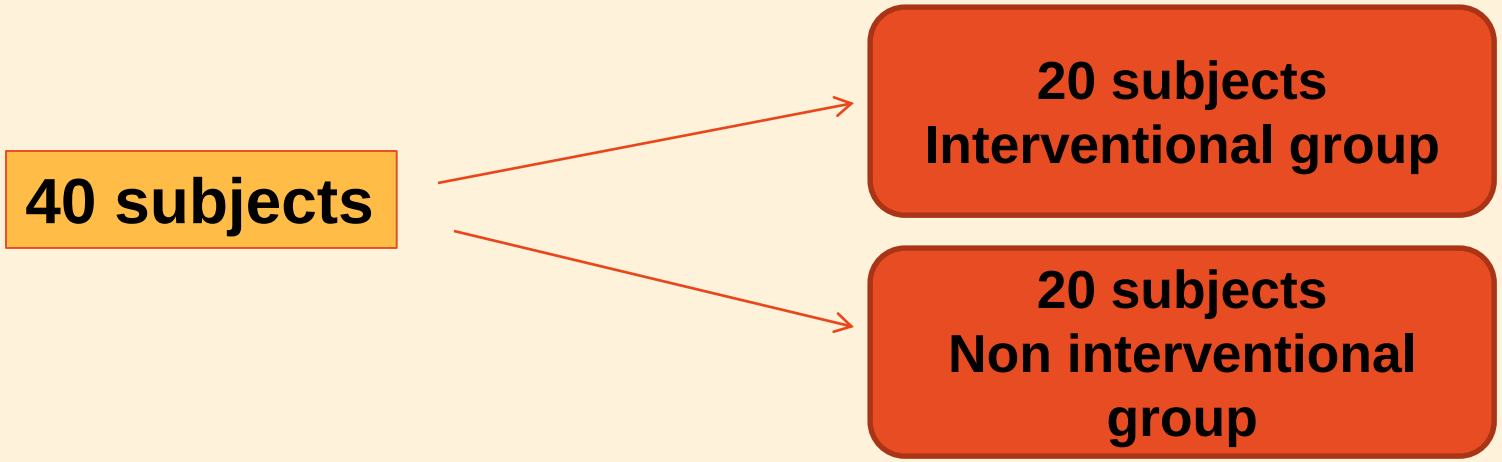

1. *Kasture PN et al. J Assoc Physicians India. 2016 Jun. 64: 15-20.*
2. *Gadhwal AK et al. J Assoc Physicians India. 2016 Jun. 64: 22-26.*
3. *Juneja V et al. Int J Med Res Health Sci. 2016; 5(1)254-257.*
4. *Gowda AC et al Indian medical Gazette 2015 Mar.*

# INTEGRATIVE APPROACH OF CHEMOTHERAPY INDUCED THROMBOCTOPENIA

# CARICA PAPAYA LEAF EXTRACT IN CHEMOTHERAPY INDUCED THROMBOCYTOPENIA

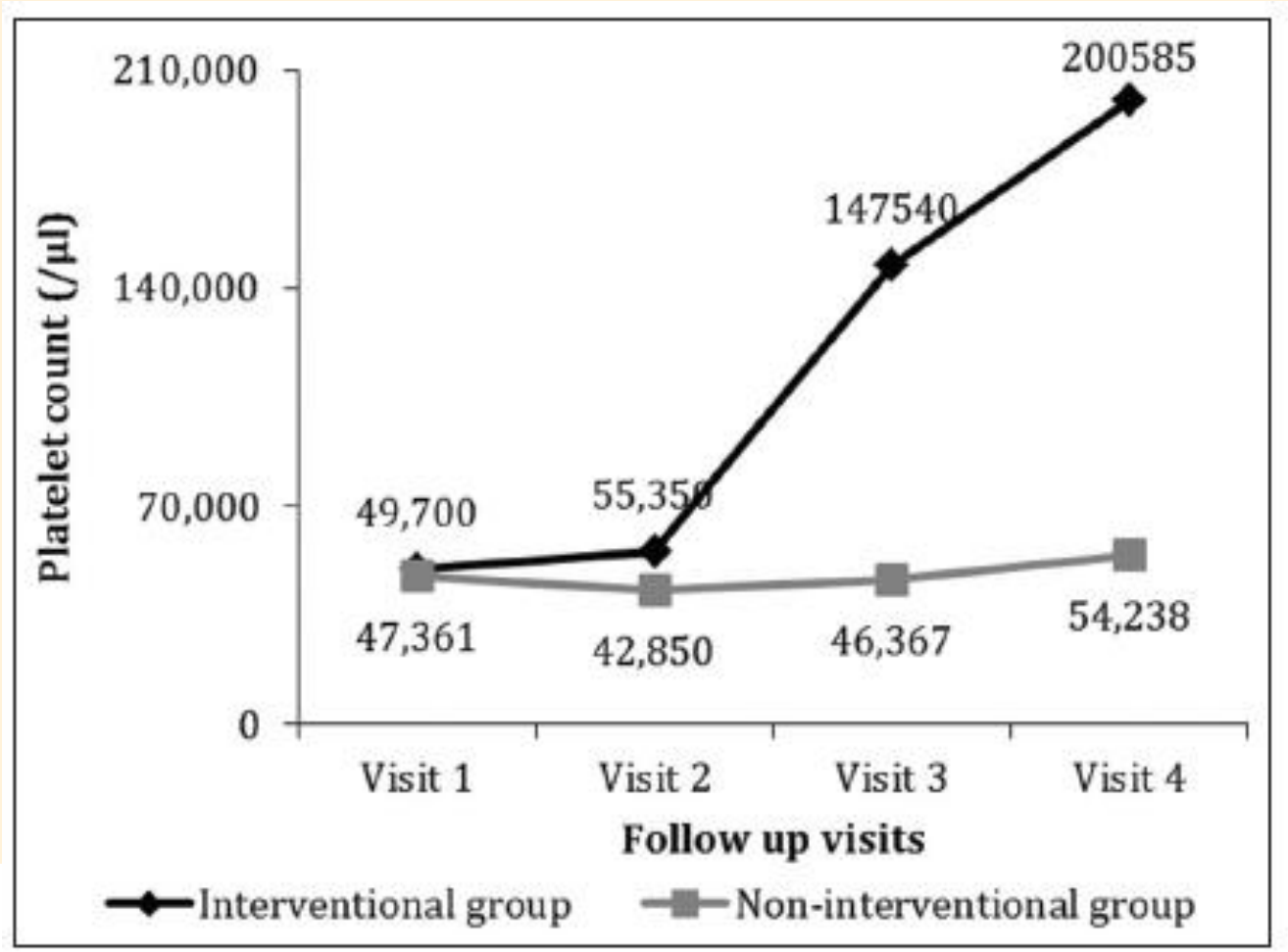
# EFFECT OF CARICA PAPAYA LEAF EXTRACT ON PLATELET COUNT IN CHEMOTHERAPY-INDUCED THROMBOCYTOPENIC PATIENTS: A PRELIMINARY STUDY

- **Study centre:** Kidwai Memorial Institute of Oncology, Bangalore
- **Investigator:** Dr K C Lakshmaiah, Department of medical oncology, Kidwai Memorial Institute of Oncology, Bangalore

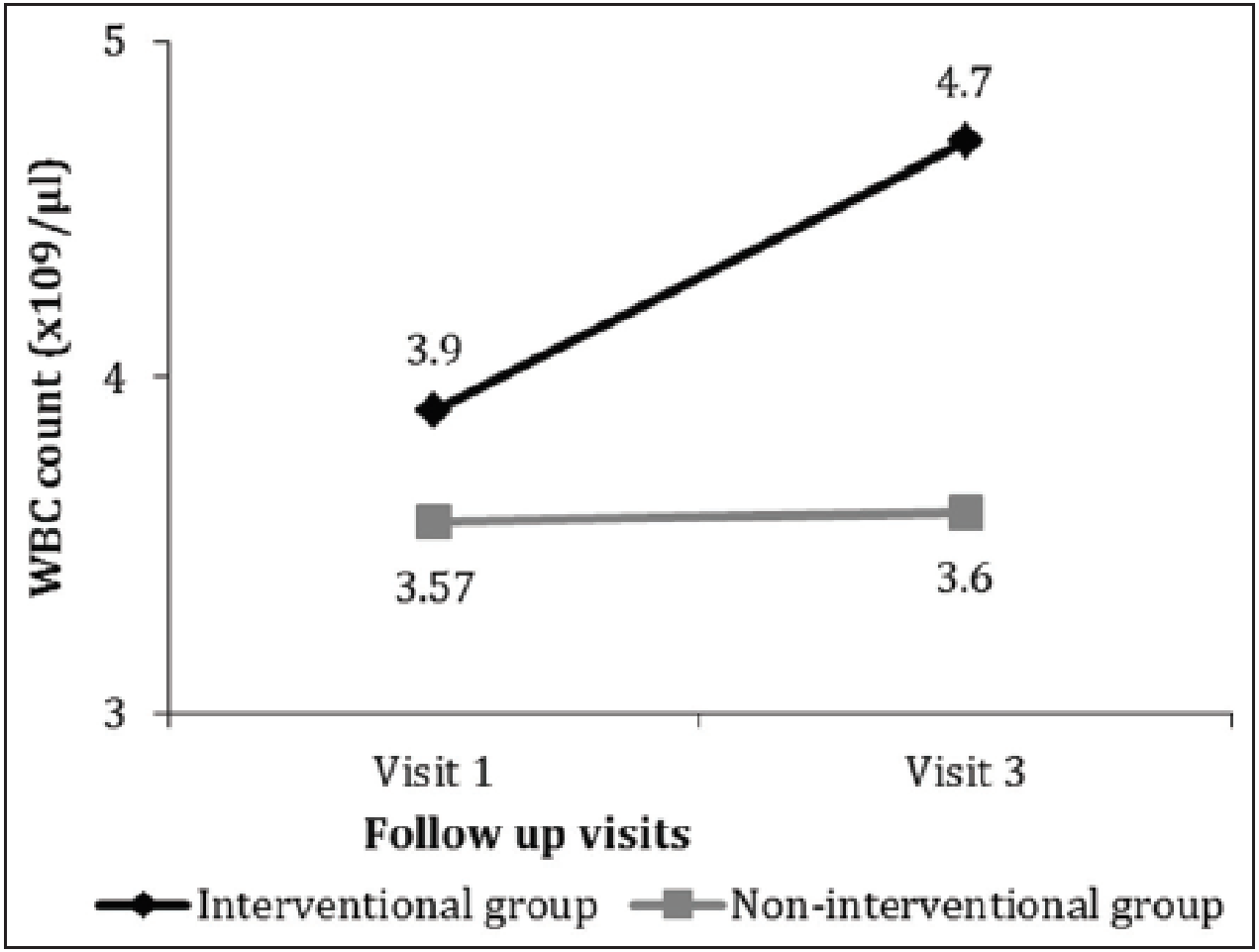



- Interventional group received CPLE 1100 mg TID for 7 days post chemotherapy day and non-interventional group did not receive any active treatment
- Complete hemogram was done at post chemotherapy day 7, 10, 13, and 16

# MEAN PLATELET COUNT



# MEAN WHITE BLOOD CELL COUNT




(unpaired *t-test: P < 0.001)*

## Adverse Effects

| Adverse effects | *n* (%) | |
|---|---|---|
| | Interventional group | Non-interventional group |
| Nausea | 0 | 1 (5) |
| Diarrhea | 3 (15) | 4 (20) |
| Dizziness | 2 (10) | 1 (5) |
| Vomiting | 3 (15) | 5 (25) |
| Headache | 2 (10) | 2 (10) |
| Dysgeusia | 4 (20) | 2 (10) |

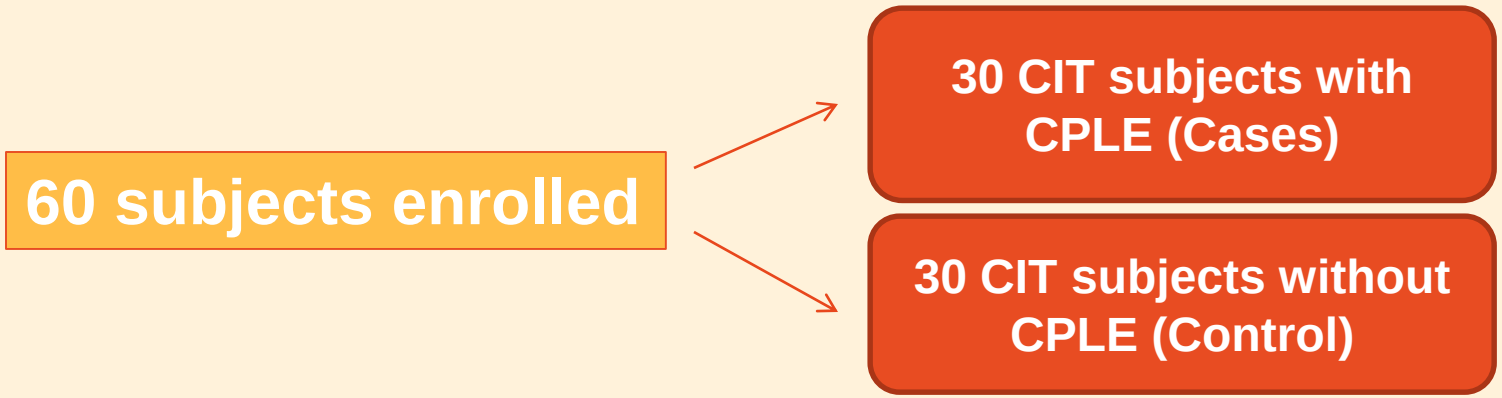
## CONCLUSION:

**CPLE increased platelet count by day 13 of post chemotherapy along with other hematological parameters. Hence, CPLE could be a viable option for treatment of CIT.**

Sundarmurthy D, Jayanthi CR, Lakshmaiah KC. Effect of Carica papaya leaf extract on platelet count in chemotherapy-induced thrombocytopenic patients: A preliminary study. Natl J Physiol Pharm Pharmacol 2017;7(7):685-692.

# CLINICAL USE OF CARICA PAPAYA LEAF EXTRACT (CPLE) IN CHEMOTHERAPY INDUCED THROMBOCYTOPENIA

- **Study centre:** Department of Oncology, North East Medical College Cancer Hospital, Sylhet, Bangladesh
- **Investigator:** Dr. Syed MdAkram Hussain, Bangladesh.




- CPLE given twice daily in 'cases' for 5 consecutive days or till to normal platelet count
- Platelet count was observed at 5 days intervals or more frequently
- Pre and post-treatment platelet counts were compared individually in both arms by statistical tests

*Hussain S M et al. Int J Clin Exp Med 2017;10(2):3752-3756*

# OVERALL EFFICACY

| 'Cases' number (N)=28 | Baseline platelet count ($\times 10^3$/uL) | Platelet count ($\times 10^3$/uL) after treatment with CP capsules (within day-1 to day-12) |
|---|---|---|
| Mean ± standard deviation | 101.93 ± 26.15 | 173.75 ± 29.98 |
| *P* value (one tailed, dependent t test) | 1.37225E-09 (<0.05) (Statistically significant) | |
| Minimum baseline | 60 | 170 (on day-5) |
| Maximum baseline | 140 | 160 (on day-5) |

| 'Control' number (N)=28 | Baseline platelet count ($\times 10^3$/uL) | Platelet count ($\times 10^3$/uL) without intervention (within day-1 to day-12) |
|---|---|---|
| Mean ± standard deviation | 99.36 ± 16.62 | 101.75 ± 16.03 |
| *P* value (one tailed, dependent t test) | 0.10532466 (>0.05) (Not significant) | |
| Minimum baseline | 64 | 80 (on day-5) |
| Maximum baseline | 138 | 140 (on day-5) |

***Conclusion: CP leaf extracts significantly increased thrombocytes in post-chemotherapy cancer patients. Treatment related adverse events were not found***

*Hussain S M et al. Int J Clin Exp Med 2017;10(2):3752-3756*

# A PROSPECTIVE, RANDOMISED CONTROLLED STUDY ON CARIPILL IN MANAGEMENT OF CHEMOTHERAPY INDUCED THROMBOCYTOPENIA IN SOLID TUMORS

- **Study centre:**
  - Department of Medical Oncology, HCG Hospital, Bangalore

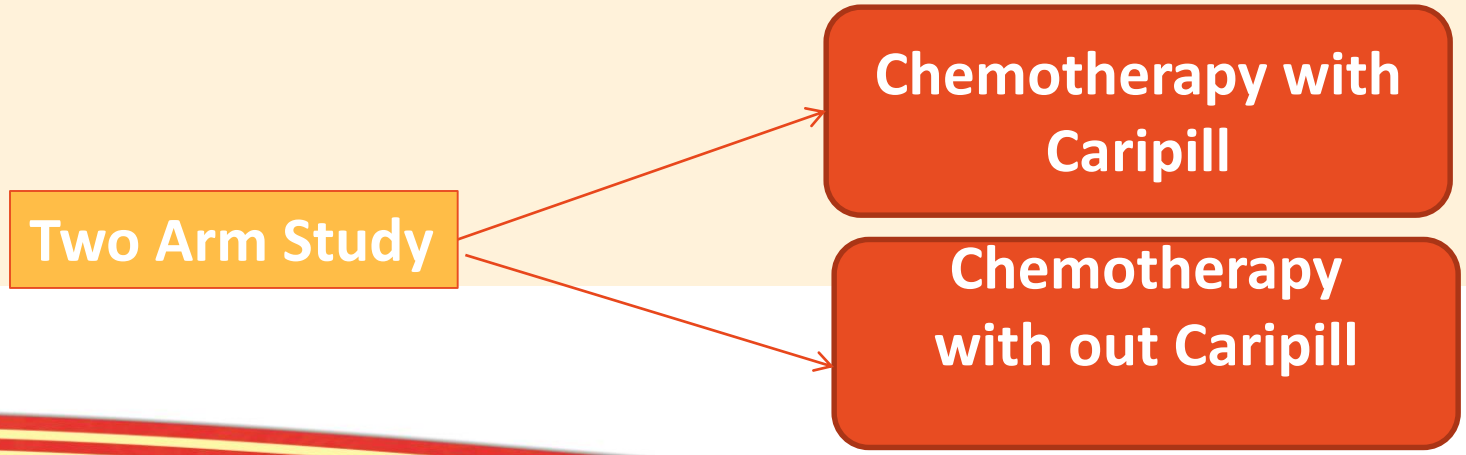
- **Principal Investigator:**
  - Dr. Radheshyam Naik, Senior medical oncologist

- **Co-Investigator**:
  - Dr. Srinivasa, Medical oncologist

Manuscript under publication

# STUDY DETAILS

- **Study Type:** Prospective
- **Randomization:** allocation ratio of 1:1
- **Number of subjects:** N=160
- **Study Medications:** Caripill tablet 1100mg of CPLE
- **Dose:** Caripill three times daily throughout the chemotherapy cycle

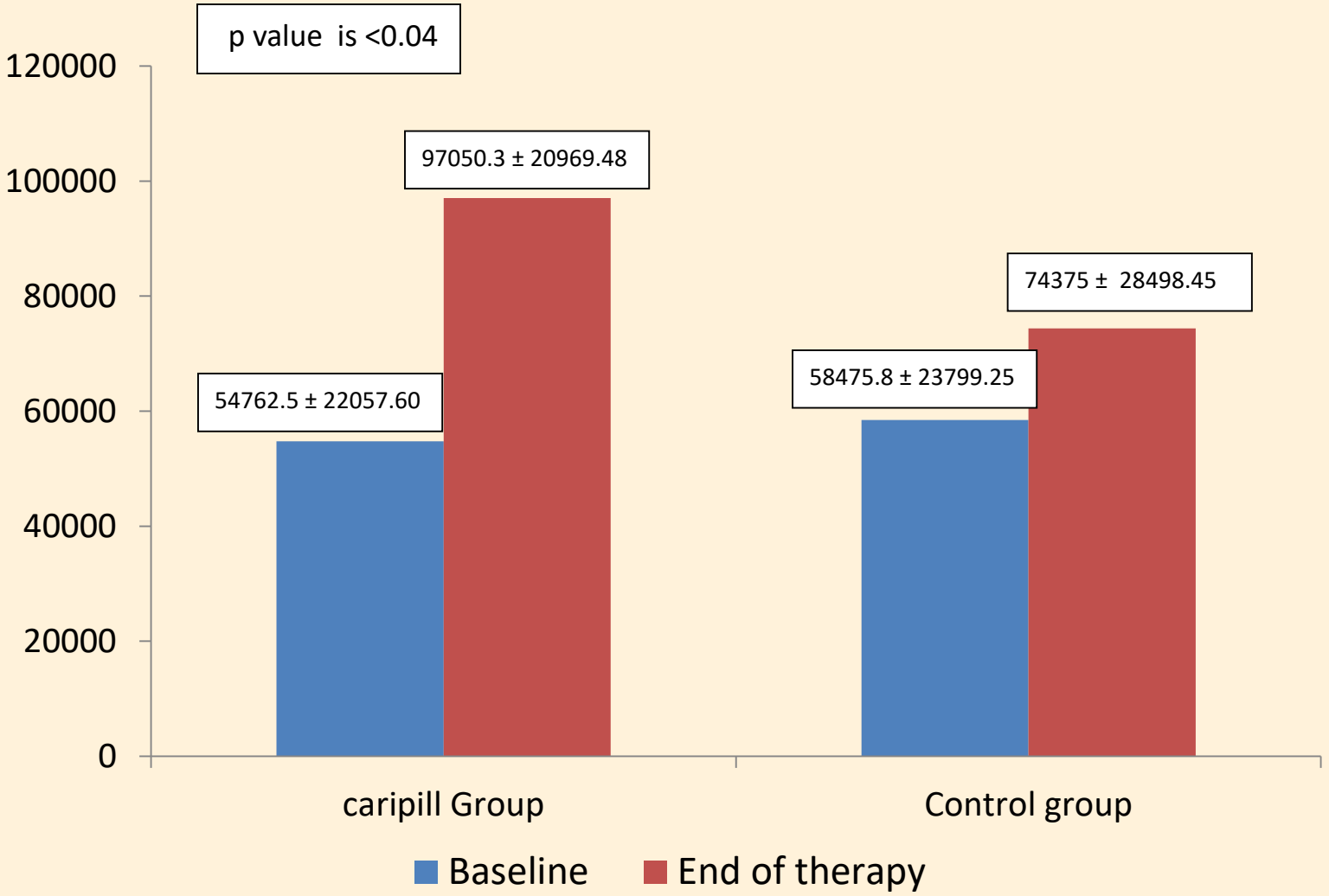


# CHEMOTHERAPY REGIMEN

| Cancer type | Agent | Caripill | Control |
|---|---|---|---|
| Ca Breast | Carboplatin+Gemcitabine | 9 | 7 |
| | Carboplatin+Taxol | 8 | 11 |
| | Fluorouracil + Adriamycin + Cyclophosphomide | 4 | 6 |
| | Adriamycin + Cyclophosphomide | 11 | 9 |
| | Docetaxel | 4 | 8 |
| | Fluorouracil + Adriamycin + Cyclophosphomide | 8 | 10 |
| Ca Ovary | Carboplatin+Taxol | 13 | 8 |
| Ca Lung | Carboplatin+Etoposide | 6 | 4 |
| | Carboplatin+Radiation | 4 | 7 |
| | Carboplatin+ Pemetrexed | 8 | 6 |
| Sarcoma | Docetaxel+ Gemciatbine | 5 | 4 |

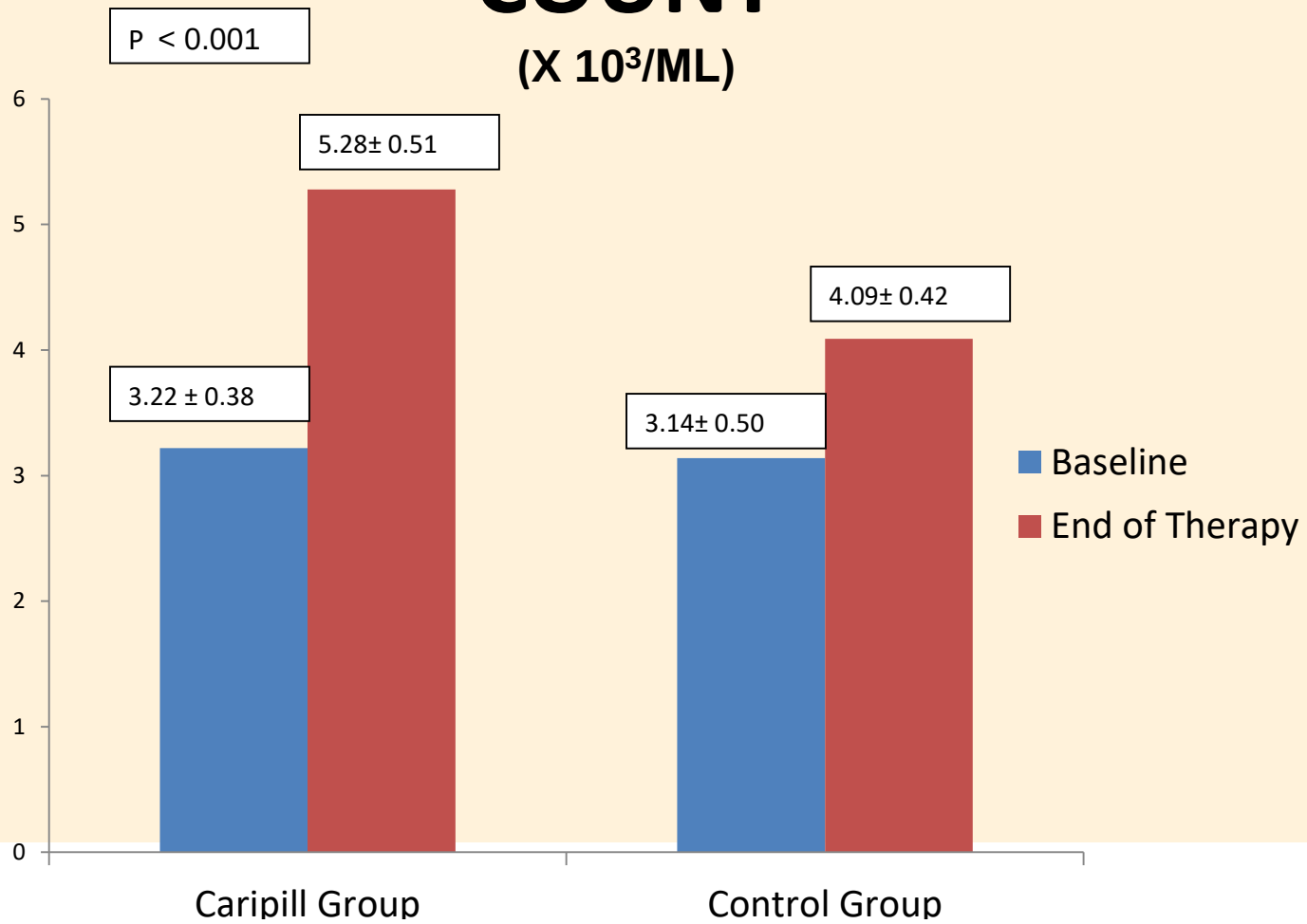
Manuscript under publication

# Mean increase in Platelet count




Manuscript under publication

# MEAN INCREASE IN WBC COUNT



# UPCOMING CLINICAL TRIAL

| | |
|---|---|
| Study | Two arm, randomized open label prospective, study to evaluate the role of Carica papaya leaf extract (CPLE) in reducing the duration of chemotherapy induced thrombocytopenia and adverse events related to thrombocytopenia (PACT study). |
| **Centre** | **Tata Memorial Cancer Hospital, Mumbai** |
| Study Subjects | 680 subjects (Duration – 36 months) |
| Treatment arm | Caripill 1100 mg TID will be throughout the chemotherapy cycle |

# CARICA PAPAYA LEAF EXTRACT TABLET - DOSAGE

Each tablet contains 1100 mg of Carica papaya leaf extract
Syrup-5 ml contains 275 mg of Carica papaya leaf extract

**Dosage and administration:**
**In adults**
1 tablet three times daily for 5-7 days

**In children**
1-5years 5 ml 3 times daily
>5-18 years 10 ml 3 times daily for 5-7 days

**Contraindications**:

- Hypersensitivity
- pregnancy and lactation (No data available)

**Precautions and interactions:** Should be used with caution in individuals with

- Bleeding disorders or those taking blood thinning medications such as aspirin or warfarin.
- Oral hypoglycaemic agent may lead to very low sugar level as observed in one of experimental animal study

**Adverse effects:** Nausea, vomiting, abdominal pain, heart burn, dyspepsia

# SUMMARY

- **Thrombocytopenia is the important point of concern in Dengue due to looming threat of DHF and DSS**
- **CIT result in an increased risk of bleeding and also lead to reduction in chemotherapy dose and frequency**
- **CPLE acts by stimulation of ALOX-12 and PTAFR genes**
- **Several Clinical studies show Caripill increases platelet count significantly in patients with dengue induced thrombocytopenia and CIT**
- **Caripill is effective and well tolerated as an integrative approach**


Thank you…