

# Effect of doxycycline and doxycycline with carica papaya on thrombocytopenia and leucopenia in acute dengue fever patients

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## ABSTRACT

**Background:** Dengue fever is a mosquito borne disease commonly manifest leucopenia and thrombocytopenia. Dengue fever and its complications like bleeding manifestation can be life threatening. This study was conducted to study the effect of doxycycline and doxycycline with carica papaya on thrombocytopenia and leucopenia in acute dengue fever patients. **Methods:** This case control study was conducted amongst the patients suffering from dengue fever with thrombocytopenia. Cases were dengue patients with thrombocytopenia and leucopenia both. Controls were dengue patients with thrombocytopenia with normal leukocyte count. An effect of doxycycline and doxycycline with carica papaya was observed on platelet and leukocyte counts at baseline and first, second, fourth, and seventh day in cases and comparison was done. **Results:** The maximum improvement in mean platelet count and leukocyte count was observed in doxycycline with carica papaya group followed by doxycycline alone group followed by controls (conservative treatment) in decreasing order on day 4<sup>th</sup> and 7<sup>th</sup> day of admission. Reduced hospital stay was also in the same order. **Conclusion:** The study results indicate that doxycycline and carica papaya are useful modality to improve leucopenia and thrombocytopenia in dengue patients and to minimize hospital stay.

**Keywords:** Carica papaya, dengue, doxycycline, leucopenia, thrombocytopenia

## Introduction

Dengue is an acute viral infection caused by flavivirus and transmitted mainly by *Aedes aegypti* mosquitoes associated with thrombocytopenia and leucopenia. Characteristic features of dengue fever are continuous high fever, headache, retroorbital pain, myalgia, arthralgia, hemorrhagic tendency, thrombocytopenia, and increase in hematocrit values.

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Dengue is one of the rapidly spreading mosquito-borne viral diseases having major public health concern throughout the world. WHO estimates that there may be 50–100 million dengue infections and half a million dengue hemorrhagic fever (DHF) worldwide every year, with an average case fatality rate of around 5%.<sup>[1]</sup>

A total of 3.6 billion people are at the risk of infection across 120 dengue-endemic countries. More than 70% of those at risk live in the Asia Pacific region, making this region an epicenter of dengue activity. Increasing burden of dengue has been a matter of serious concern worldwide. Dengue is widespread in India, and outbreaks occur every year. Most of the cases are being reported

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in the monsoon and postmonsoon seasons. There is no specific treatment for dengue; early detection and intensive supportive care are the most essential aspects of management.<sup>[1-6]</sup>

Approach for the prevention of dengue virus infection and disease in endemic areas includes mosquito control, personal protective measures, and vaccination. A number of dengue vaccine candidates are currently under development, while one vaccine, CYD-TDV (dengvaxia), has been licensed for use in a few endemic countries in Latin America and Southeast Asia. There is no direct antiviral therapy available against dengue. Management is supportive primarily consisting of maintaining adequate intravascular volume. Most of the current strategies for antidengue drug discovery are targeted toward finding potent inhibitors against virus entry and its serine protease activity, which is crucial for viral replication.<sup>[6-8]</sup>

The isolation of viral RNA from bone marrow of dengue-infected individuals as well as hypocellularity in bone marrow and inhibition of maturation of megakaryocyte during the primary stage of the disease suggest the suppressive effect of the dengue virus on bone marrow to cause thrombocytopenia.<sup>[6,8]</sup>

*Carica papaya* is a member of the Caricaceae and is a dicotyledonous, polygamous, and diploid species. The latex, ripe fruits, unripe fruits, seeds, seeds juice, root, leaves, flower, and stem bark of *C. papaya* are used as antimicrobial, anthelmintic, antimalarial, antifungal, antiamebic, hepatoprotective, male and female antifertility, immunomodulatory, and against histaminergic. *Carica papaya*, which is commonly known as papaya or pawpaw, has been used for centuries as an ethnomedicine to treat many diseases, which includes dengue fever. The leaves were found to be rich in phenolic compounds such as alkaloids, quercetin and kaempferol. On top of that, the leaf extract contains antioxidant compounds such as  $\alpha$ -tocopherol, ascorbic acid, and flavonoids. Some case studies reported that the papaya leaves aid for better recovery of dengue in terms of clinical symptoms and platelet counts.<sup>[9,10]</sup> A toxicity study (acute, subacute, and chronic toxicity) conducted on Sprague Dawley rats administered with *Carica papaya* leaves juice of the sekaki variant revealed that it was safe for oral consumption.<sup>[11]</sup>

Doxycycline is a derivative of tetracycline that possesses broad antimicrobial and antiinflammatory activities. Further, antiviral activity of doxycycline has been reported against retroviruses, and a significant reduction in retrovirus titre was observed after incubation of infected cells with doxycycline. Previous studies have shown that doxycycline inhibits dengue virus plaque formation by disrupting the conformational changes in the viral envelope that are necessary for virus entry.<sup>[12-15]</sup> Previous studies also found the antidengue properties of doxycycline against all four dengue virus serotypes *in vitro*.<sup>[12-15]</sup> The results showed that doxycycline interfered with dengue virus protease and impaired virus binding to the host cells, leading to reduced viral replication in infected cells.

Taken together, there was strong basis to warrant further experimental and clinical investigations toward reducing dengue morbidity by utilizing doxycycline and carica papaya. Hence, under the light of above-mentioned data, the present study was undertaken for comparing the efficacy of doxycycline and doxycycline with carica papaya on thrombocytopenia and leukopenia in acute dengue fever patients. Hospital stay and clinical outcome was also observed.

## Materials and Methods

The current study was a case control study conducted for a period of 2 years (September 1, 2019 to August 31, 2021) at a tertiary health care institute of Rajasthan, India after ethical approval from institutional ethical committee. This study included the indoor patients (age 14 years or above) suffering from dengue fever (NS1 antigen and/or IgM positivity by ELISA method) with thrombocytopenia (platelet count <1.5 lakh/cu mm) after informed consent. The patients suffering from other primary/secondary hematological disorders or using drugs which may impact platelet count and leukocyte count were excluded from the study. Dengue patients needed platelet transfusion or blood transfusion were also excluded from the study.

Study subjects were divided into controls and cases. The controls were dengue fever patients with thrombocytopenia with normal leukocyte count (4000–11000/cu mm). The cases were dengue fever patients with thrombocytopenia with low leukocyte count (<4000/cu mm). The cases were further divided into four parts according to thrombocytopenia as grade I (100001 to 1.5 lakh/cu mm), grade II (50001 to 1 lakh/cu mm), grade III (20000 to 50000/cu mm), and grade IV (<20000/cu mm).

The controls were treated conservatively by intravenous fluids in the form of 0.9% normal saline in a dose of 500 mL thrice a day with symptomatic treatment. The cases with grades I and II thrombocytopenia (doxycycline group) were treated with the same treatment as controls with additional oral tablet of doxycycline 100 mg twice a day for 5 days. The cases with grades III and IV thrombocytopenia (doxycycline with carica papaya group) were treated with the same treatment as controls with an additional oral tablet of doxycycline 100 mg twice a day for 5 days and oral tablet carica papaya 1100 mg thrice a day.

All patients of cases and controls were observed for platelet counts and total leukocyte counts at baseline (day 0) and days 1, 2, 4, and 7 of admission. Improvement of platelet and leukocyte count, duration of hospital stay, and clinical outcome were observed and compared by statistical analysis between the controls and cases groups to see the effect of doxycycline and carica papaya on thrombocytopenia and leucopenia.

The comparison between controls and case groups was done by ANOVA test, and  $P < 0.05$  was considered as significant difference.

## Results

The present study included 120 indoor dengue fever patients having thrombocytopenia. The mean age of dengue patient was 39. 6 ± 13.4 years and male female ratio was 3:2.

Out of 120 thrombocytopenic dengue patients, 55 patients had normal leukocyte were considered as controls and 65 patients had leucopenia were considered as cases.

The controls were treated with conservative management of intravenous fluid and symptomatic treatment. The cases were further divided according to grade of thrombocytopenia and treated accordingly as per methodology. The cases having grades I and II thrombocytopenia (*n* = 35) were treated with doxycycline (doxycycline group), and the cases having grades III and IV thrombocytopenia (*n* = 30) were treated with doxycycline and carica papaya both (doxycycline with carica papaya group). [Table 1]

Mean platelet count in controls, doxycycline group, and doxycycline with carica papaya group was observed at baseline and first, second, fourth, and seventh day of admission [Table 2] and compared with each other. [Table 3]

No significant difference was there on comparison of the mean platelet count on first day and second day in between controls and case groups. However, there was significant improvement of mean platelet count at fourth and seventh day in increasing order of controls < doxycycline group < doxycycline with carica papaya group. [Table 3]

Mean leukocyte count in controls, doxycycline group, and doxycycline with carica papaya group was also observed at baseline and first, second, fourth, and seventh day of admission [Table 4] and compared with each other [Table 5].

**Table 1: Distribution of patients among cases groups according to treatment**

Cases group	Grading according to platelet count (cells/cu mm)	Number of patients	Percentage
Doxycycline group	Grade I	35	53.85
	Grade II		
Doxycycline with Carica papaya group	Grade III	30	46.15
	Grade IV		
Total		65	100

**Table 2: Day wise distribution of mean platelet count among different study groups**

Group	Baseline		1 <sup>st</sup> Day		2 <sup>nd</sup> Day		4 <sup>th</sup> Day		7 <sup>th</sup> Day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	68,700	1350	74,000	1860	88,000	1970	96,000	2010	134,700	2530
Cases (Doxycycline group)	59,100	1180	76,200	1420	91,200	1580	113,100	1760	163,800	2410
Cases (Doxycycline with Carica papaya)	34,200	1080	72,300	1380	93,500	1660	124,600	1870	179,300	2680

No significant difference was there on comparison of the mean total leukocyte count on first day and second day in between controls and case groups. However, there was significant improvement of mean total leukocyte count at fourth and seventh day in increasing order of controls < doxycycline group < doxycycline with carica papaya group. [Table 5]

Mean duration of hospital stay was the highest in the control group (9.1 days) followed by doxycycline group (8.2 days) and doxycycline with carica papaya group (7.3 days). There was significant difference in mean duration of hospital stay in decreasing order of controls > doxycycline group > doxycycline with carica papaya group. [Table 6]

No mortality was observed among cases and controls, all patients discharged were in stable condition and in the symptom free state.

## Discussion

The present study was undertaken for comparing the efficacy of doxycycline and doxycycline with carica papaya on thrombocytopenia and leukopenia in acute dengue fever patients.

In current study, the mean age of dengue patient was 39. 6 ± 13.4 years, and the male to female ratio was 3:2. AL-Samadi MM *et al.*<sup>[16]</sup> reported that the mean age of the dengue patients was 25.32 years and 54% of the patients were male. In an another study conducted by Sathyapalan DT *et al.*<sup>[17]</sup> the mean age of the patients was 51 years and 73% of the patients were males. Patel K *et al.*<sup>[18]</sup> reported that 67% of the patients were males. A comparison of the studies shows that young patients are more involved with male predominance. The lower occurrence of dengue in old age and females should be evaluated on genetic, pathological, and social basis in further studies. Social negligence of old age and female patients to avail health facility may be one of the factors responsible for lower occurrences among them.

In the current study, significant improvement was seen in respect to the mean platelet count and mean leukocyte count on fourth and seventh day of hospital admission in patients treated with doxycycline (cases) in comparison of the control group. Non significant results were obtained while comparing the mean platelet count at first day and at second day in between the control group and doxycycline group.

Our results were in concordance with the results obtained by Mangulabnan JL *et al.*<sup>[19]</sup> who also reported similar findings. Their study assessed the effect of doxycycline on lowering interleukin

6 (IL-6) and tumor necrosis factor (TNF) among patients with DHF. In the pooled analysis using standardized paired difference in mean, doxycycline was favored in lowering the serum IL-6 and serum TNF, both in third and seventh day posttreatment with a *P* value of <0.00001. Their study showed that doxycycline lowered the levels of serum IL-6 and TNF, and cytokines were directly implicated in the severe type of dengue.

Rothan HA *et al.*<sup>[20]</sup> determined the potential activity of doxycycline against dengue virus replication *in vitro*. They concluded that the doxycycline significantly inhibited viral entry and postinfection replication of dengue, with serotype-specific inhibition.

Another study conducted by Fredeking TM determined the effect of doxycycline treatment on cytokine levels, including TNF and interleukin 6 (IL-6) along with mortality in dengue patients at high risk of complication. In their study group of DHF patients, *n* = 231 were randomized to receive either standard supportive care or supportive care in addition to oral doxycycline twice daily for 7 days. Their findings suggested that doxycycline can provide a clinical benefit to dengue patients at high risk of complications.<sup>[21]</sup>

An additional potential benefit to using doxycycline in the treatment of dengue fever or DHF is its recently discovered ability to inhibit dengue virus multiplication in tissue culture. Doxycycline, but not tetracycline, was able to interact with the dengue virus E protein to inhibit a conformational change, which is an essential step in the process by which the virus enters susceptible cells. The study indicates that doxycycline may provide a clinical benefit in the treatment of dengue virus infection by modulating the cytokine cascade.<sup>[22]</sup>

In the current study, significant improvement was seen in respect to the mean platelet count and mean leukocyte count at fourth

and seventh day of hospital admission in doxycycline with carica papaya group in comparison of the control and doxycycline groups. Not many studies are there targeted to look the effect of both doxycycline and carica papaya simultaneously in dengue patients like in the current study.

Based on the current understanding on the ability of carica papaya extract to increase the platelet count, there is possible explanation that it may stimulate the thrombopoietic mechanism. In an *in vivo* study carried by Anjum *et al.*,<sup>[23]</sup> there was an increase in the platelet count observed in the Wistar rat within 72 h after the oral administration of 150 mg/kg of aqueous extract of papaya leaf. The study has postulated that the papaya leaf aqueous extract can stimulate and induce the megakaryopoietic/thrombopoietic stimulatory activity or cause splenic contraction to produce thrombocytes. On top of that, it was suggested that the increase in platelet activity might due to the presence of high flavonoids and phenolic compounds such as kaempferol, trans-ferulic acid, caffeic acid, and myricetin in the papaya leaf extract.

Another study carried out by Sathasivam *et al.*<sup>[24]</sup> claimed that the oral administration of 15 mg/kg of powdered papaya leaves in palm oil has significantly increased the thrombocyte counts temporarily up to 12 h in Swiss albino mice, indicating that papaya extract that was dissolved in oil with a lower dose (15 mg/kg) could also exert the antithrombocytopenic effect.

Several case studies have been carried out in dengue patients to investigate the effect of papaya leaf extract. Siddique O *et al.*<sup>[25]</sup> proved that the oral consumption of papaya leaves juice has significantly increase the thrombocyte counts as compared to control groups within five consecutive days in dengue patients. Apart from increase in the thrombocyte, the study also suggested the improvement of the symptoms in dengue might due to the antihemolytic activity of papaya too.

In another study by Sathyapalan DT *et al.*,<sup>[17]</sup> the patients with severe thrombocytopenia who have taken 1100 mg of papaya leaf extract in tablet three times a day for 5 days showed an increase in the platelet count in the first 4 days and then the platelet count is maintained on day 5 compared to the placebo group in which the platelet count increases slowly and the platelet count drops on day 5. This indicates that the Carica papaya leaf extract (CPL) has the capability to maintain the platelet count and could be used in severe condition, thus proving the reliability as an alternative treatment for dengue patients.

**Table 3: Comparison of day wise mean platelet count between controls and cases groups**

Group Versus Group	Follow-up				
	Baseline	1 <sup>st</sup> Day	2 <sup>nd</sup> Day	4 <sup>th</sup> Day	7 <sup>th</sup> Day
Controls versus Cases (Doxycycline group)	0.01*	0.82	0.43	0.01*	0.01*
Controls versus Cases (Doxycycline with Carica papaya)	0.00*	0.37	0.82	0.00*	0.01*
Cases (Doxycycline group) Versus Cases (Doxycycline with Carica papaya)	0.04*	0.93	0.75	0.03*	0.02*

\*Significant P value

**Table 4: Day wise distribution of mean total leukocyte count among different study groups**

Group	Baseline		1 <sup>st</sup> Day		2 <sup>nd</sup> Day		4 <sup>th</sup> Day		7 <sup>th</sup> Day	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	5100	121	5900	131	6700	183	7400	208	7670	210
Cases (Doxycycline group)	3000	143	5850	135	6820	180	8500	192	8750	209
Cases (Doxycycline with Carica papaya)	3200	112	5960	143	6980	189	9230	197	9450	218

**Table 5: Comparison of day wise mean total leukocyte count between controls and cases groups**

Group Versus Group	Follow-up				
	Baseline	1 <sup>st</sup> Day	2 <sup>nd</sup> Day	4 <sup>th</sup> Day	7 <sup>th</sup> Day
Controls versus Cases (Doxycycline group)	0.00*	0.43	0.64	0.01*	0.03*
Controls versus Cases (Doxycycline with Carica papaya)	0.01*	0.84	0.29	0.00*	0.04*
Cases (Doxycycline group) Versus Cases (Doxycycline and Carica papaya)	0.45	0.64	0.71	0.00*	0.01*

\*Significant P value

**Table 6: Comparison of day wise mean duration of hospital stay between controls and cases groups**

Comparison of mean hospital stay in days	P
Controls versus Doxycycline group (9.1 vs 8.2 days)	0.00*
Controls versus Doxycycline with Carica papaya group (9.1 vs 7.3 days)	0.01*
Doxycycline group versus Doxycycline with Carica papaya group (8.2 vs 7.3 days)	0.00*

\*: Significant

This antithrombocytopenic effect is also supported by Subenthiran S *et al.*<sup>[9]</sup> in which they discovered that the gene in the red blood cells known as ALOX 12 has increased by 15-fold among dengue patients who took carica papaya leaf juice (50 grams) for 3 days. This ALOX 12 gene is known to increase the megakaryocyte production and further conversion to platelets, thus increasing the platelet production. The platelet increase was significant at 40 and 48 h, suggesting that the papaya leaf extract could rapidly induce the production of platelets in human.

In a systematic review conducted by Charan J *et al.*,<sup>[26]</sup> four different formulations of Carica papaya extract which are leaf juice, capsule form, syrup form, and tablet form were given to dengue patients. Interestingly, the results showed that the platelet count has significantly increase ( $P = 0.005$ ) in all formulations as compared to the control group. Henceforth, regardless of different formulation, this suggests that Carica papaya extract has a good bioavailability, where it can accommodate high compliance in different populations that are having other health issues such as those with difficulty in swallowing or children.

Another systematic review by Rajapakse S *et al.*<sup>[27]</sup> critically analyzed that even the dose of papaya leaf extract varies; the platelet count of patients is increasing at day 3–5 following papaya juice, substantially shortening the hospital stay of the patients.

In a study cohort of 400 dengue patients with mild to moderate thrombocytopenia, Gadhwal AK *et al.*<sup>[28]</sup> showed that CPLE-treated patients reported a rapid increase in platelet counts and reduced hospitalization days. Similarly, Kasture PN *et al.*<sup>[29]</sup> also reported an increase in platelet counts to more

than 150,000/ $\mu\text{L}$  by day 5 in patients administered CPLE compared to only 95,000/ $\mu\text{L}$  in the placebo group. A study conducted by Sathyapalan DT *et al.*<sup>[17]</sup> demonstrated similar outcomes, where significant increase of almost 500% was noted in the platelet counts by day 3.

The current study also found favorable effect of carica papaya on leucocyte count beside improvement of platelet count. Not many studies are there to compare results of improvement in leucocytes by carica papaya, although in a case series conducted by Ahmad N *et al.*<sup>[30]</sup> found that mean WBC count and platelet count at baseline was  $3.8 \times 10^3/\mu\text{L}$  and  $73 \times 10^3/\mu\text{L}$  respectively. After administration of carica papaya, they observed a significant rise in WBC count and platelet count to value of  $5.3 \times 10^3/\mu\text{L}$  and  $137 \times 10^3/\mu\text{L}$  at the third postoperative day.

In the current study, mean length of hospital stay was the highest in the control group (9.1 days) followed by the doxycycline group (8.2 days) and minimum in doxycycline with carica papaya group (7.3 days), and statistically significant results were there on comparison. Mortality was absent in all dengue patients. Our results were in concordance with the results obtained by Sathyapalan DT *et al.*<sup>[17]</sup> who reported the absence of mortality among acute dengue fever patients.

## Conclusions

Under the light of above-obtained data, conclusion can be withdrawn that the treatment with doxycycline with carica papaya significantly shows better and faster positive outcome in dengue patients in form of improving platelet and leukocyte count. Their use may also reduce related complications, morbidity, hospital stay, and financial burden. The study recommends their inclusion in treatment guidelines of dengue. Further studies are needed to understand their synergetic or additive effect.

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## Ethics approval and consent to participate

Taken Institutional ethics approval No. GU/HREC/EC/2019/1718)

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## Conflicts of interest

There are no conflicts of interest.

## References

1. WHO. Dengue and Dengue Haemorrhagic Fever. Factsheet No 117, Revised May 2008. Available from: <http://www.who.int/mediacentre/factsheets/fs117/>

- who.int/mediacentre/factsheets/fs117/en/. [Last accessed on 2021 Nov 30].
2. Ng LC. Challenges in dengue surveillance and control. *West Pac Surveill Response J* 2011;2:1-3.
  3. Sarkar JK, Chatterjee SN, Chakravarty SK. Haemorrhagic fever in Calcutta: Some epidemiological observations. *Indian J Med Res* 1964;52:651-9.
  4. Chatterjee SN, Chakravarti SK, Mitra AC, Sarkar JK. Virological investigation of cases with neurological complications during the outbreak of haemorrhagic fever in Calcutta. *J Indian Med Assoc* 1965;45:314-6.
  5. Carey DE, Myers RM, Reuben R, Rodrigues FM. Studies on dengue in Vellore, South India. *Am J Trop Med Hyg* 1966;15:580-7.
  6. Singh M, Chakraborty A, Kumar S, Kumar A. The epidemiology of dengue viral infection in developing countries: A systematic review. *J Health Res Rev* 2017;4:104-7.
  7. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, *et al.* The global distribution and burden of dengue. *Nature* 2013;496:504-7.
  8. Henchal EA, Putnak JR. The dengue viruses. *Clin Microbiol Rev* 1990;3:376-96.
  9. Subenthiran, S, Choon, TC, Cheong KC, Thayan R, Teck MB, Muniandy PK, *et al.* Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue haemorrhagic fever. *Evid Based Complement Alternat Med* 2013;2013:616737.
  10. Huet J, Looze Y, Bartik K, Raussens V, Wintjens R, Boussard P. Structural characterization of the papaya cysteine proteinases at low pH. *Biochem Biophys Res Commun* 2006;341:620-6.
  11. Adebowale A, Garnesan AP, Prasad RNV. Papaya (*Carica papaya*) consumption is unsafe in pregnancy: Fact or fable? Scientific evaluation of a common belief in some parts of Asia using a rat model. *British J Nutr* 2002;88:199-203.
  12. Orellana MA, Gomez-Lus ML. Which is the best empirical treatment in patients with urethritis? *Rev Esp Quimioter* 2011;24:136-42.
  13. Polat KY, Tosun MS, Ertekin V, Aydinli B, Emre S. Brucella infection with pancytopenia after pediatric liver transplantation. *Transpl Infect Dis* 2012;14:326-9.
  14. Skulason S, Holbrook WP, Thormar H, Gunnarsson GB, Kristmundsdottir T. A study of the clinical activity of a gel combining monocaprin and doxycycline: A novel treatment for herpes labialis. *J Oral Pathol Med* 2012;41:61-7.
  15. Wilcox JR, Covington DS, Paez N. Doxycycline as a modulator of inflammation in chronic wounds. *Wounds* 2012;24:339-49.
  16. AL-Samadi MM, Ali KS. Evaluation of some hematological and serological changes in dengue patients of Lahj-Yemen. *Electronic J University Aden Basic Appl Sci* 2020;1:25-9.
  17. Sathyapalan DT, Padmanabhan A, Moni M, P-Prabhu B, Prasanna P, Balachandran S, *et al.* Efficacy & safety of *Carica papaya* leaf extract (CPLE) in severe thrombocytopenia ( $\leq 30,000/\mu\text{l}$ ) in adult dengue - Results of a pilot study. *PLoS one* 2020;15:86-99.
  18. Patel K, Patel D, Das VK. Hematological parameters and its utility in dengue fever: A prospective study. *Int J Sci Res* 2016;1077-9.
  19. Mangulabnan JL, Ogbac F. Effects of doxycycline on lowering IL-6 and TNF among patients with dengue haemorrhagic fever: A meta-analysis. *J Infect Dis Ther* 2017;5:71.
  20. Rothan HA, Buckle MJ, Ammar YA, Mohammadjavad P, Shatrah O, Noorsaadah AR, *et al.* Study the antiviral activity of some derivatives of tetracycline and non-steroid anti-inflammatory drugs towards dengue virus. *Trop Biomed* 2013;30:681-90.
  21. Fredeking TM, Zavala-Castro JE, González-Martínez P, Moguel-Rodríguez W, Sanchez EC, Foster MJ, *et al.* Dengue patients treated with doxycycline showed lower mortality associated to a reduction in IL-6 and TNF levels. *Recent Pat Antiinfect Drug Discov* 2015;10:51-8.
  22. Yang JM, Chen YF, Tu YY, Yen KR, Yang YL. Combinatorial computational approaches to identify tetracycline derivatives as flavivirus inhibitors. *PLoS One* 2007;2:e428.
  23. Anjum V, Arora P, Ansari SH, Najmi AK, Ahmad Sayeed. Antithrombocytopenic and immunomodulatory potential of metabolically characterized aqueous extract of *Carica papaya* leaves. *Pharm Biol* 2017;55:2043-56.
  24. Sathasivam K, Ramanathan S, Mansor SM, Haris MR, Wernsdorfer WH. Thrombocyte counts in mice after the administration of papaya leaf suspension. *Wien Klin Wochenschr* 2009;121:19-22.
  25. Siddique O, Sundus A, Ibrahim MF. Effects of papaya leaves on thrombocyte counts in dengue--A case report. *J Pak Med Assoc* 2014;64:364-6.
  26. Charan J, Saxena D, Goyal J, Yasobant S. Efficacy and safety of *Carica papaya* leaf extract in the dengue: A systematic review and meta-analysis. *Int J App Basic Med Res* 2016;6:249-54.
  27. Rajapakse S, De Silva NL, Weeratunga P, Rodrigo C, Sigera C, Fernando SD. *Carica papaya* extract in dengue: A systematic review and meta-analysis. *BMC Complement Altern Med* 2019;1:265.
  28. Gadhwal AK, Ankit BS, Chahar C, Tantia P, Sirohi P, Agrawal RP. Effect of *Carica papaya* leaf extract capsule on platelet count in patients of dengue fever with thrombocytopenia. *J Assoc Physicians India* 2016;64:22-6.
  29. Kasture PN, Nagabhushan KH, Kumar A. 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. *J Assoc Physicians India* 2016;64:15-20.
  30. Ahmad N, Fazal H, Ayaz M, Abbasi BH, Mohammad I, Fazal L. Dengue fever treatment with *Carica papaya* leaves extracts. *Asian Pac J Trop Biomed* 2011;1:330-3.