Potential Antiplatelet Effects of Carica Papaya Leaf Extract: Inhibition of Aggregation and Count Proliferation

Santiago R. Alvarez*1, Keiko N. Tanaka2, Giovanni L. Romano3 & Maria F. Gonzalez4
1A Biomedical Scientist, University of Buenos Aires, Argentina
2A Scientific Writer, Kyoto University, Japan
3A Researcher, University of Milan, Italy
4A Scientific Writer, Springer Nature, UK

Abstract

Dengue is a global health concern that is growing rapidly. Among dengue threat areas, around 2.5 billion people live with about 100 million new cases worldwide each year. The WHO study indicates that deaths in untreated cases of dengue fever were as high as 20%, while inpatients had a death rate of less than 1%. In particular, the female Aedes-genus mosquito transmits the dengue virus. The patient experiences symptoms such as heavy fever, nausea, vomiting, muscle, and vocal pains and bodily fluid falls. The findings of previous research studies have shown that both dengue fever and dengue hemorrhagic fever can cause severe thrombocytopenia. This is one of the dengue hemorrhagic fever diagnostic criteria. The primary outcome of dengue, therefore, lies in avoiding thrombocytopenia, correcting the excess in body fluid and delivering symptomatic care. There are many different treatments available to increase the number of platelets, which have their own advantages and disadvantages addressed. In this research, we focused primarily on how the number of platelets in dengue patients decreases? And how can the leaf extract treat the patient with dengue for thrombocytopenia? When patients are relying on papaya leaves and experiencing good results, some extensive research should be conducted in humans to make this drug available to all patients.

Keywords:
Dengue
Carica Papaya,
Thrombocytopenia,
Thrombopoiesis, Steroids.

Introduction

Dengue fever caused as a tropical vector-borne disease by a mosquito-borne flavivirus. An infectious disease occurs from female germ mosquitoes Aedes. After a dipterous infectious virus is infected, the virus comes into the skin through the mosquito secretion (1). They bind and enter white blood cells and replicate throughout the body cells. White blood cells are responsible for a number of complications, such as fever, flu-like symptoms, and severe pain, by releasing multiple signal protectors, such as cytokines and interferons (2).

Epidemiology reports, with about 50–100 million infections and 2,00,000–5.000,000 cases of hemorrhagic fever in the world, that it is most prevalent in tropical regions. It is estimated that the congenital fever was as high as 20% while the mortality rate was lower than 1% in hospitalized patients. Millions of people are vulnerable to dengue (50-100 million / year) (3).

Sudden start fever, migraine (normally placed behind the eye), muscle and joint pains and rashes are the medical signs of dengue. Fluid from the bloodstream flows into the body cavities through the wall of small blood vessels and therefore, reduces the flow of blood into the blood vessels and increases the blood pressure, leading to bone marrow dysfunction due to infections of the stromal cell leads to a reduced number of platelets required for active blood coagulation. There are no particular antiviral medicines for dengue, as a viral disease; however, it is important to maintain the proper fluid balance (4).

Gravity bleeding is commonly seen in extreme dengue disease, dengue hemorrhagic fever. Blood leakage from blood vessel is the pathogenesis of bleeding. This tends to be caused by platelets being destroyed by a supplementary process or bone marrow failure due to dengue viral infection or both. Platelets fleeing destruction are also found to be non-functional or less functional. Several studies have reported a direct correlation between platelet count and dengue prognostics (5).

Dengue fever is usually an independent illness with less than 1% mortality if early diagnosed and with access to appropriate medical attention. When treated, serious dengue has a2%-5% mortality rate, but when left untreated, the death rate is as high as 20%. Dengue fever, known as Dengue hemorrhagic fever, can cause severe bleeding and rapid blood pressure drop (shock) as well as death. These include dengue hemorrhagic fever, an unusual fever-related appearance, damage to lymph and blood vessels, nose and gum bleeding, liver hypertrophy and circulatory failure. Mass bleeding, shock, and death can result in symptoms. Dengue shock syndrome (DSS) is a commonly cited condition (6).

In the treatment of thrombocytopenia, the main concept is to eliminate the underlying problem, whether it includes discontinuing suspect drugs that cause or treat underlying thrombocytopenia. Newer treatments including rituximab and thrombopoietin receptor agonists, however, reshape conventional treatment strategies. Corticosteroids, intravenous immunoglobulin, and splenectomy remain the cornerstone of care. Transfusion of platelets may be recommended in severe cases of bleeding. All of these therapy options have their own advantages and disadvantages. Therefore, consideration should be given to alternative therapies for battling low platelet counts, relatively free of the drug's harmful adverse effects (7).

As mentioned above, it is not necessary to rely on additional treatments that maintain the platelet count on specific treatments for viruses. Dengue patients are currently undergoing therapy with platelet suspension, all blood to maintain a regular count of platelets. This, however, is risk-based since platelet injections are expensive and other microorganisms may be transmitted. Therefore, it is important to see alternative treatments to increase the count of platelets. We based on this review on conventional platelet inhibition therapies and on how to use dengue therapy.

Carica papaya **is a tropical fruit, which has been consistently associated with numerous medicinal properties.** It is also called pawpaw. Papaya is a member of the Caricaceae family. Since ancient times papaya has been used in treating a few cases of illness. Different benefits of c. papaya extracts from the leaves, fruits, and seeds are suggested for different treatments according to the information obtained. The leaves are useful for the treatment of digestive disorders through chymopapain and Papain extracts. Extracts from seeds and fruit have bactericidal properties, such as anti-cancer, antioxidant, anti-inflammatory, antibacterial, nephroprotective, hepatoprotective, hypoglycemic and hypolipidemic effects and anti-sickling effects in sickle cell disease, have been demonstrated for the fruit juice and leaf extract. Ripe fruit was used against ringworm and green fruit was used as an aphrodisiac to alleviate blood pressure and cause abortion. It is also known that leaf extract has larvicidal characteristics against the DENV vector, the Aedes aegypti mosquito (8).

Mechanism of action of C. papaya for platelet proliferation: The Arachidonate 12-Lipoxygenase and Lipoxygenase-type platelet (ALOX-12) genes are highly expressed in megakaryocytes, and Platelet-Activating Factor Receiver genes (PTAFR). 12-Hydroxyeicosatetraenoic acid (12-HETE) platelet production is believed to be responsible for ALOX-12. C. The PTFAR activity, which increases the development of the platelet by acting on the bone marrow, was shown to increase ALOX 12 activity by 15 and 13,42 times (9).According to previous studies the membrane-stabilizing properties of C. papaya leaf extracts *in-vitro* studies have found that leaf extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and dengue patient are. In in vitro studies, papaya leaf extracts found to be an inhibitor of heat and hypotonicity mediated erythrocyte hemolysis in both stable and dengue-patient individuals. At the lower levels of the extracts the effect was detected. The extracts are therefore likely to have membrane-stable properties and avoid stress-induced degradation of the blood cells. It can, therefore, be beneficial in dengue-infected patients where the leaf extracts can stop platelet lysis. This influence was postulated by the researchers because of the presence of the papaya leaves of flavonoids and other phenolic compounds (10).

Table 1 dengue during the recovery phase:

DESCRIPTION	EARLY RECOVERY PHASE	INTERMEDIATE RECOVERY PHASE	LATE RECOVERY PHASE
Clinical presentation. (11)**.**	Erythematic, pruritus and bradycardia causes. In the vital and/or recovery processes, if unnecessary intravenous fluids have been administered, respiratory distress can occur from large pleural effusion and ascites, pulmonary edema or congestive heart failure.	Depression, Convulsions, intracranial Thrombosis, Myelitis, Mononeuropathies, Polyneuropathies, Encephalopathy, Encephalitis.	Fever, Headache, Retro-ocular pain, Insomnia, Alopecia, Myalgia, Arthralgia, Asthenia, Anorexia, Dizziness or Poor appetite.
Existing Treatment (11).	Treat accordingly and avoid fluid overload.	Standards treatment of steroids for neurological diseases. Intravenous immunoglobulin (IVIg) appears plasma exchange for GBS.	Symptomatic
Propose additional or new treatment (11).	32 mg oral methyl prednisolone for three days. If patients test positive for higher titers of anti-dengue Immunoglobulin G antibodies or other immune markers.	32 mg per day of oral methyl prednisolone for seven days and tailed off gradually within 2 months.	32 mg per day of oral methyl prednisolone for seven days and tailed off gradually within 2 months. If symptoms are severe or show high morbidity, IV of methyl prednisolone 125 mg is recommended for use as a loading dose.

The results obtained from several peer-reviewed publications were discussed in this paper. This article concentrates on the proliferation of platelet counts with papaya leaflet extract. It shows how important it is to use as an medicine in human and livestock or papaya leaves, which enhances platelet when affected by fever, to increase thrombopoiesis and erythropoiesis.

Results

Case study: The author lived and studied numerous cases in the dominant country of Dengue. Most dengue patients had high fever and joint pain and no medication was available. Patients displayed a reduced count of platelets throughout the blood image. Patients administered opioid pain and acetaminophen for fever to relieve their joints. Most physicians used to provide antibiotics, but the case was not resolved. Patients used to drink Papaya leaves extraction and saw good results in symptoms improvement. There was no medical history of the patient or knowledge of co-suspects.

Through social media, there was also widespread recognition of papaya leaves & dengue-related thrombocytopenia diagnosis. Following review of many journals, the papaya leaf could be an antidote to dengue and malaria fever rather than medication prescription.

Table 2 Presents associated events in patients suffering from dengue fever.

Associated Event	Study/publication	Findings	Reference
The disease often presents with high fever, severe headache, and joint/muscle pain that usually goes away on its own, but it can also present as a sometimes deadly hemorrhagic (bleeding) disease. (12).	Safety and Immunogenicity Study of a Dengue Virus DNA Vaccine.	As per study, there are no adverse events and serious adverse events but other (Not Including Serious) Adverse Events.(1.0 ,5mg) ofdengue-1 pre-membrane/envelope DNA vaccine)D1ME100 Vaccine-associated with minor Adverse Events e.g.:nausea vomiting, Tenderness, and malaise.	Danko JR et.al (12) (2017).

The study was associated with events Eye disorders, Gastrointestinal disorders, Muscle aches, and rashes. (13).	A Phase I/II Trial of a Tetravalent Live Attenuated DEN Vaccine in Flavivirus Antibody Naive Children.	The study has not found any adverse events and serious adverse events but there are other adverse events as per study Affected / at Risk 7/7(100.00%).	U.S. Army Medical Research and Development Command. (13) (2018).

Table 3 Available treatments for dengue and platelet proliferation

Treatment	**Outcome**	**Reference**
Safety and Immunogenicity with Two Different Serotype 2 Potencies of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in Adults in Singapore **(14)**.	Total affected by High dose Tetravalent Dengue Vaccine (HD-TDV) Affected/ at Risk% 0/176. Tetravalent Dengue Vaccine (TDV) Affected / at Risk 0/175 Serious Adverse Events of HD-TDV affected/at risk 3/176. TDV Affected / at Risk 3/175 (1.71%) Other (Not Including Serious) Adverse Events HD-TDV Affected / at Risk (%) 45/176 (25.57%). TDV Affected / at Risk 49/175 (28.00) %.	Sponsor and Information provided by Takeda (14).
Safety and immunogenicity of tetravalent live- dengue vaccine in flavivirus-Naïve infants (15).	The Dengue virus vaccine was well-tolerated without any related Serious adverse events. After the second dose, 85.7% of full-dose vaccines developed at least trivalent and 53.6% developed tetravalent neutralizing antibodies ≥ 1:10 to vaccine.	V Watanaveeradej, et al.(15) (2011).
Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomized, placebo-controlled study (16).	Tetravalent dengue vaccine is safe and immunogenic in individuals aged 2-17 years, irrespective of previous dengue exposure. A second dose of vaccine-induced enhanced immunogenicity against dengue virus serotypes 3 & 4 in children who were seronegative before vaccination.	X Sáez-Llorens, et al. (16)(2017).

Table 4 Pesents the outcomes of papaya leaf extract on proliferation of platelet count.

Study	**Outcome**	**Reference**
Does C. papaya leaf-extract increase the platelet count? An experimental study in a murine model. (17)	Papaya leaves cause critical growth counts without acute/subacute toxicity in the murine model. Therefore, we recommend that papaya leaf extract may be used in a disease-suppressed form as a medicine to support hemopoiesis and thrombopoiesis.	DharmarathnaSL, et al. (17) 2013.
Effect of C. papaya Leaf Extract Capsule on Platelet Count in Patients of Dengue Fever with Thrombocytopenia. **(18)**	According to this report, leaf extract increases the number of platelets in dengue fever without any side effects and prevents thrombocytopenia from becoming complicated.	Gadhwal AK, et al. (18) 2016.

The effect of freeze-dried leaf juice treatment on NS1 and viremia levels in dengue fever mice model. (19)	Including the introduction of traditional dengue management systems such as the hydration and paracetamol treatments the patients who were enrolled in the papaya juice clinical study. Nevertheless, it cannot be emphasized the possible effect of freeze-dried CPLJ treatment on the viability of dengue viruses in species such as liver, spleen, kidney, and brain.	Mohd Abd Razak,et al. (19) 2018.

Discussion

The Dengue virus is an RNA virus that can penetrate other white blood cells, such as monocytes and macrophages, in the family of Flaviviridae. In very few studies conducted in Asia, papaya leaf extract has been recorded in humans. In Sri Lanka, a pilot study of 12 suspected patients with dengue was performed. The patients had < 130.000/cu mm platelet counts, but only six patients have been reported to have dengue serologically. Two doses of papaya leaf extract were given to patients with 8 h intervals. Normal symptomatic treatment was also given for dengue. The study found that platelet counts and total white blood cell counts were increased in patients with papaya leaf extract within 24 hours of extract therapy (20).

In a report from Pakistan, the efficient treatment of dengue in a leading truck was addressed with papaya leaf extract. The patient was trapped in 25 ml of papaya leaf extract twice a day for five days. After 2 days of treatment, platelet and white blood cell levels have been steadily increased. Nevertheless, the findings should be interpreted with caution, given the ambiguous and incorrect information mentioned in the report. The report states, for instance, that a "Dengue virus mosquito" that started to develop symptoms after biting the driver 24 hours later. These and other similar statements contradict the validity of this report (21).

In Indonesia, papaya leaves have been used and evaluated. Leaves extract capsules (CPC) of 70 percent C ethanol extract. In addition to 80,000/µL of thrombocyte and 20% or more of hematocrit, this study included 80 patients with 2-7 days of high recurrent fever. In addition to standard care, CPC was obtained by one party and conventional dengue treatment was given for the other. The study revealed that dengue patients treated with dengue were growing faster in the CPC. Therefore, the researchers conclude that the extract produces phenols to produce positive results. In one analysis, papaya plant leaves are rich in a variety of minerals. Studies have proposed that these minerals can balance and improve immune cells against the virus ' mineral deficiency (22).

Alternative treatment to increase platelet count advantages and disadvantages:

Corticosteroids: Dexamethasone or prednisone is typically prescribed to raise your platelet count, once a day in the form of a pill or tablet. However, short-term & long-term treatment may cause irritability, stomach upsets, sleep problems, weight gain, lower bone density, acne, etc. The major disadvantage includes recurrence of thrombocytopenia after withdrawal of the drug(23).The advantage of intravenous immunoglobulin (IVIG) over prednisone is that it can raise your platelet count quickly but for the short term. The side effects include nausea, headache, fever, and chills.(23).

Blood transfusion. Whole blood or platelet extractions are administered to the patient in severe conditions. However, it is expensive and may be associated with transmission of allergies along with hepatitis & HIV.

Surgery: In severe conditions, the spleen can be removed to stop destruction of platelets however, spleen removal can make it harder for you to fight infections. infection risk is greatest in the first 3 months after the surgery(23).

Thrombopoietin (TPO) receptor agonists: The TPO drug may also be used in someone who needs a boost in platelet count for a period, such as during an acute bleeding episode, in preparation for elective surgery, or while deciding about, planning, or awaiting a splenectomy. Side effects include nausea, vomiting, headache, and a higher chance of getting blood clots (23).

Immunosuppressants can work by keeping their immune systems in check(23).

Androgens also may be suggested if patients are having severe bleeding and their platelet count isn't getting a boost from other treatments(23).

Papaya (papaya Linn.) Papaya leaf extract could be used either as a supplemental or complementary medicinal drug in the patients with the acute febrile disease with thrombocytopenia; it speeds up the rise in platelets count and thus shortens

hospitalization costs significantly (24). A fall in platelet counts is one of the main concerns in dengue cases. The use of Papaya Leaf Extract increases the number of platelets dramatically in such situations and serves as adjuvant therapy to avoid thrombocytopenia complications (25).

Papaya phytochemicals are being increasingly researched and have demonstrated their antioxidant, anti-inflammatory, immunomodulatory and antifungal properties to a wide pharmacological promise (26)

One study showed that the extract of papaya leaves can neutralize dengue virus plasma, significantly reducing platelet agglomeration. Papaya leaf extract has been shown to 15 times lower in ALOX12. This enzyme encourages the development of platelets by increasing megakaryocyte numbers and differentiation. The PTAFR gene is platelet-specific and is increased 13.5 times in comparison with controls following extract management (27).Serin NS2B and NS3 are essential for replicating the dengue virus but are inhibited by the quercetin, one of the papaya flavonoids. This extract prevents the assembly of viruses. One study showed the early growth of the platelet number even as soon as 24 hours in the oral administration of papaya leaf extract. The maximum number of white blood cells increased considerably (28).

The papaya plant may have an impact on dengue by treating the related thrombocytopenia. A study reported the properties of C .papayato stabilize the membrane. Extracts of papaya leaf in in-vitro testing and also C.papaya effect was observed at lower levels of extracts of papaya leaf extracts of heat-and hypotonic-induced hemolysis of erythrocytes from individuals who are both stable and persons with dengue infection. The extracts are therefore immune to membrane-stabilizing properties and avoid stressful death of blood cells. This function can be beneficial if the leaf extracts can stop platelet lysis in patients with Dengue infection. This effect can be triggered by flavinoids and other phenolic compounds in the papaya leave according to the researchers (29).

In the mice, 15 mg of powdered papaya leaves/kg body weight was shown to increase in thrombocytic counts among the mice after dosing between 1 and 12 hours. In a cyclophosphamide-induced thrombocytopenic rat modeler, the platelet counts increased considerably in further analysis, with a watery extract of 400 mg/kg and 800 mg/kg in concentrations of papaya leaf. The time spent in the treated rats was also reduced (30).

After reading various articles and various studies, we have checked various papers and gathered some important data on Papaya. Papaya is one of the best and most economical Dengue therapies that lead to reduced platelet count.

Conclusion

There is no doubt about the potential therapeutic effect of fresh C. Papaya leaf extract provides potential therapeutic effectiveness that is cost-effective, more affordable and easily available to patients with dengue. The data is limited, and it is recommended to conduct further research so that cheap & effective medicine is available to all dengue patients.

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References

1. Role of carica Papaya Leaf Product in Improving the Platelet. Adarsh V B, Kotresh Doddamane ,V Deepak Kumar. 2017, Vol. 2, pp. 63-68. 2320-2742.
2. Epidemiology of dengue fever in India, based on laboratory surveillance data, 2014-2017. Murhekar M, Joshua V, Kanagasabai K et al. 2019 .
3. Role of Carica papaya leaf extract tablets/capsules on platelet counts in. Venugopal K, Suresh R. M., Halesha B. R. 5, s.l. : International Journal of Advances in Medicine, April 15, 2018, Vol. 4, pp. 845-48.
4. Papaya Leaf Extract To Treat Dengue: A Review. Ram Pentewar, Dr. Shailesh Sharma,Priyanka Kore,Dattatraya Kawdewar, Srushti Somwanshi. 6, Jaipur : Scholars Academic Journal of Pharmacy, 2017, Vol. 4, pp. 113-19. 2320-4206.
5. Efficacy and safety of Carica papaya leaf extract in the dengue: A systematic review and meta-analysis. Jaykaran Charan, Deepak Saxena, et.al. 4, 2016, Vol. 6, pp. 249–254.
6. Role of Carica papaya leaf extract tablets/capsules on platelet counts in cases of dengue thrombocytopenia. Venugopal K, Suresh R. M., Halesha B. R. et.al. 4, 2018, International Journal of Advances in Medicine, Vol. 5, pp. 845-848.

7. Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammatory Mediators. Elzinandes Leal de Azeredo, Robson Q. Monteiro, Luzia Maria de-Oliveira Pinto et.al. 2015, Hindawi, Vol. 2015, p. 16 .
8. Carica papaya Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients. Soobitha Subenthiran, Tan Chwee Choon,Kee Chee Cheong et.al. s.l. : Hindawi , 2013, Vol. 2013.
9. Papaya Extract to Treat Dengue: A Novel Therapeutic Option? N Sarala, SS Paknikar et.al. 2014, Vol. 3, pp. 320-24.
10. Papaya Extract to Treat Dengue: A Novel Therapeutic. Sarala N, Paknikar SS et.al. 3, s.l. : Annals of Medical and Health Sciences Research |, 2014 , Vol. 4.
11. Management of Dengue and Post Dengue Complication Syndrome: A Review. S M Rathnasiri Bandara1, H M M T B Herath. 4, s.l. : ACTA SCIENTIFIC MICROBIOLOGY, 2019, Vol. 2. 2581-3226.
12. Safety and Immunogenicity of a Tetravalent Dengue DNA Vaccine Administered with a Cationic Lipid-Based Adjuvant in a Phase 1 Clinical Trial. Danko JR, Kochel T, Teneza-Mora N, et.al. 3, 2018, The American Journal of Tropical Medicine and Hygiene., Vol. 98.
13. Online] https://clinicaltrials.gov/ct2/show/NCT00384670.
14. [Online] https://clinicaltrials.gov/ct2/show/NCT02425098.
15. Safety and immunogenicity of a tetravalent live-attenuated dengue vaccine in flavivirus naive children. Simasathien S, Thomas SJ, Watanaveeradej V et.al. 3, 2008, The American Journal of Tropical Medicine and Hygiene., Vol. 78. 426-33.
16. Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study. Sáez-Llorens X, Tricou V, Yu D et.al. 6, 2017, Lancet Infection disease, Vol. 17, pp. 615-625.
17. Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model. Dharmarathna SL, Wickramasinghe S, Waduge RN et.al. 13, 2013, Asian pacific journal., Vol. 1691, pp. 720-4.
18. Effect of Carica papaya Leaf Extract Capsule on Platelet Count in Patients of Dengue Fever with Thrombocytopenia. Gadhwal AK, Ankit BS, Chahar C et.al. 6, 2016, The Journal of the Association of Physicians of India., Vol. 64, pp. 22-26.
19. The effect of freeze-dried Carica papaya leaf juice treatment on NS1 and viremia levels in dengue fever mice model. Mohd Abd Razak MR, Mohmad Misnan N, Md Jelas NH et.al. 1, 2018, BMC Complementary and Alternative Medicine., Vol. 18, pp. 2390-7.
20. Dengue fever treatment with Carica papaya leaves extracts. Nisar Ahmad, Hina Fazal et.al. 4, s.l. : Asian Pacific Journal of Tropical Biomedicine, 2011, Vol. 1, pp. 330–333.
21. effects of Carica papaya leaf extract in dengue fever patients a pilot study. S, Hettige. 3, 2008, Annals of Medical and Health Sciences Research, Vol. 4, pp. 17-9.
22. Dengue fever treatment with Carica papaya leaves extracts. Ahmad N, Fazal H, Ayaz M, Abbasi BH, Mohammad I, et.al. s.l. : Asian Pacific Journal of Tropical Biomedicine, 2011, pp. 330-3.
23. [Online] https://www.webmd.com/a-to-z-guides/thrombocytopenia-symptoms-causes-treatments#1.
24. A review on pharmacognosy, phytochemistry and pharmacological activity of carica papaya (linn.) Leaf. Ram, apurva priyadarshi and bhuwal. S.l. : international journal of pharmaceutical sciences and research, 2018, pp. 4071-78.
25. Dengue. Cameron P. Simmons, Ph.D., Jeremy J. Farrar, M.D., Ph.D.,. s.l. : The New England Journal of Medicine, 2012, pp. 1423-32.
26. Papaya Extract to Treat Dengue: A Novel Therapeutic Option? N Sarala, SS Paknikar. 4, s.l. : Annals of medical and Health Sciences Research, 2014, Vol. 3, pp. 320-24.
27. Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model. Sinhalagoda Lekamlage Chandi Asoka Dharmarathna, Susiji Wickramasinghe, Roshitha Nilmini Waduge, Rajapakse Peramune Veddikkarage Jayanthe Rajapakse, and Senanayake Abeysinghe Mudiyanselage Kularatne. 3, s.l. : Asian Pacific Journal of Tropical Biomedicine, 2013, Asian Pacific Journal of Tropical Biomedicine, Vol. 9, pp. 720-24.
28. Flavonoid from Carica papaya inhibits NS2B-NS3 protease and prevents Dengue 2 viral assembly. Padmanaban Senthilvel, Pandian Lavanya, Kalavathi Murugan Kumar, Rayapadi Swetha, Parimelzaghan Anitha, Susmita Bag, Sundaramoorthy Sarveswari, Vijayaparthasarathi Vijayakumar, Sudha Ramaiah,and Anand Anbarasu. 9, s.l. : Bioinformation discovery at the interface of Physical and bioligical sciences, 2013, Vol. 18, pp. 889-95.

29. A post marketing randomized placebo controlled study to evaluate the efficacy of study product UPLAT® (Carica papaya leaf extract +Tinospora cordifolia extract) in the cancer patients with thrombocytopenia induced by chemotherapy. Rajeev Tiwari, Deepak Kumar Mandal and Jigar Patel. et.al. s.l. : International Journal of Clinical Trials, 2018, International Journal of Clinical Trials, Vol. 4, pp. 170-74.
30. Management of Dengue and Post Dengue Complication Syndrome: A Review . S M Rathnasiri Bandara, H M M T B Herath, DMPUK Ralapanawa et.al. 4 , s.l. : ACTA SCIENTIFIC MICROBIOLOGY, 2019, Vol. 2. 2581-3226.
31. From research to phase III: Preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine. panelBrunoGuya, BeatriceBarrere ET.AL. 42, 2011, Vol. 29, pp. 7229-7241.
32. The effect of Carica papaya leaves extract capsules on platelets count and hematocrit levels in acute febrile illness with thrombocytopenia patient. Abhishek Singhai, Vikas Juneja et al. 1, s.l. : International journal of medical research & Health Sciences,, 2016, Vol. 5, pp. 254-257. 2319-5886.
33. Safety and immunogenicity of a tetravalent live-attenuated dengue vaccine in flavivirus-naive infants. Watanaveeradej V1, Simasathien S et al. 2, 2011, American Journal of tropical medicine and hygiene, Vol. 85, pp. 341-51. .
34. Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study. Sáez-Llorens X1, Tricou V et al. 6, 2017, American Journal of tropical medicine and hygiene, Vol. 17, pp. 615-625.
35. Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model. Dharmarathna SL1, Wickramasinghe S et al. 9, 2019, Asian Pacific Journal of Tropical Biomedicine, Vol. 3, pp. 720-4.
36. The effect of freeze-dried Carica papaya leaf juice treatment on NS1 and viremia levels in dengue fever mice model. Mohd Abd Razak MR1, Mohmad Misnan N et al. 1, 2018, BMC Complement Altern Med, Vol. 5;18.