

REVIEW ON PREPARATION AND EVALUATION OF "CARICA PAPAYA" LEAF EXTRACT SYRUP

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ABSTRACT

Carica Papaya is a herbaceous plant belonging to the family Caricaceae and is well known for its therapeutic and nutritional properties all over the world. The different parts of the papaya plant have been used since ancient times for its therapeutic application. Leaves, seeds, latex, root, bark and fruits possess excellent medicinal properties for treatment of different ailments. Medicinal plants have been used for various diseases traditionally in many countries, because of its advantages like easy availability, effective and economical in therapeutics. *Carica Papaya* contains Enzyme, Papain, Chymopapain, Carotenoids, B carotene, Cryptoxanthin, Glucosinolates, Benzyl isothiocyanate, Minerals, Monoterpenoids, Linalool, 4-terpinol, Flavonoids, Myricetin, Kaempferol, Alkaloids, Carpinine, Carpaine, Vitamins which increase the immune system. The bioactive components are responsible for the pharmacological properties of this plant and demonstrate its importance in daily intake of food. The *Carica Papaya* majorly acts as Anti-inflammatory, Anti-viral, Anti-dengue fever etc. Dengue viruses are the causative agents of dengue fever (DF) and dengue hemorrhagic fever. Dengue virus belongs to the family Flaviviridae, having four serotypes that spread by the bite of infected *Aedes* mosquitoes. It causes a wide spectrum of illness from mild asymptomatic illness to severe fatal dengue hemorrhagic fever/dengue shock syndrome. *Carica papaya* leaves along with proper care with hospitalization to fasten the cure of the disease. Papaya leaves, their juice or extract, as well as their different forms of preparation have long been used traditionally for treating dengue fever and its complications to save patients' lives.

KEYWORDS: *Carica papaya*, dengue, viral infection, *Aedes aegypti* virus, immunity, dengue treatment.

INTRODUCTION

Herbal Syrup: Herbal syrup is defined as a prepared and combination and concentration decoction with Honey sugar or either some time use alcohol. The base of such syrup is a strong herbal decoction and mixing a decoction with sugar honey help to thicken preserves the decoction.^[1] The anti-dengue syrup medication is a liquid dosage form use of oral liquid pharmaceutical has been confirmed on basic ease of administration to those people who have the problem in the swallowing of solid dosage from medication. Syrup is a concentrated solution contains sugar and purified water. Therefore *carica papaya* leaf extract syrup use for treatment of high fever of dengue.

ADVANTAGE OF SYRUPS^[1]

- ❖ The active agent is homogeneously dispersed through the product.
- ❖ The active agent is in solution and does not need to undergo dissolution; therefore the therapeutic response is generally faster than if a tablet or capsule dosage form is used for treatment.

- ❖ The dose of the active agent is easily and conveniently adjusted by measuring a different volume.^[1] Syrups may be swallowed by patients who have difficulty taking tablets or capsules, as might be these with pediatric patients.
- ❖ Drugs such as potassium chloride that may cause ulceration to the mucosa in a tablet formulation avoid this side effect when present in solution.

DISADVANTAGE OF SYRUPS^[1]

- ❖ The active ingredients, when present in solution, are usually more susceptible to chemical degradation, particularly hydrolysis, than when they are in solid dosage form.
- ❖ As a consequence of this, the solution product has a shorter shelf life than the solid formulation. Some pharmacologic agents taste or smell bad enough in solution that the patient has difficulty taking the medication.^[1]
- ❖ Liquid dosage forms are heavier and take up more shelf space than corresponding solid dosage forms. If the container breaks, the product is irretrievably

lost.

DENGUE

Dengue fever is a mosquito-borne tropical disease caused by the dengue virus. Symptoms typically begin three to fourteen days after infection. These may include a high fever, headache, vomiting, muscle and joint pains, and a characteristic skin itching and skin rash. Recovery generally takes two to seven days. In a small proportion of cases, the disease develops into a more severe dengue hemorrhagic fever, resulting in bleeding, low levels of

blood platelets and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs. Dengue is spread by several species of female mosquitoes of the *Aedes* genus, principally *Aedes aegypti*. The virus has five serotypes, infection with one type usually gives lifelong immunity to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications. A number of tests are available to confirm the diagnosis including detecting antibodies to the virus or its RNA.^[6]

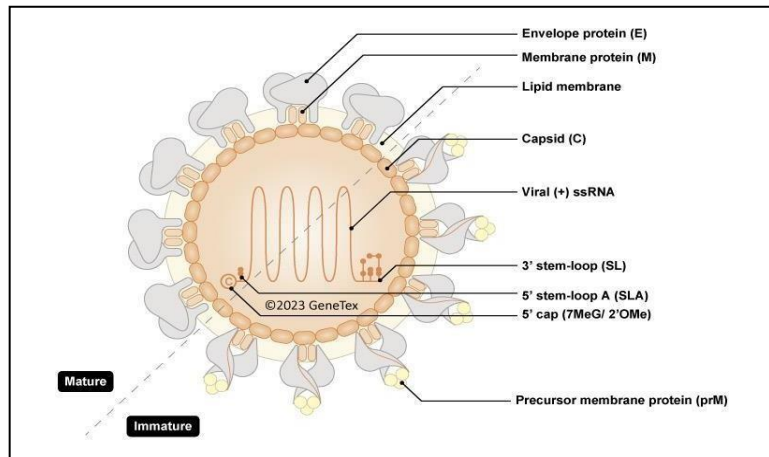


Figure No 1:^[6]

MECHANISM OF DENGUE

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells, and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing several signaling proteins, such as cytokines and interferons, which are responsible for many of the symptoms, such as the fever, the flu-like symptoms, and the severe pains. In severe infection, the virus production inside the body is greatly increased, and

many more organs (such as the liver and the bone marrow) can be affected.^[5] Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue.^[5]

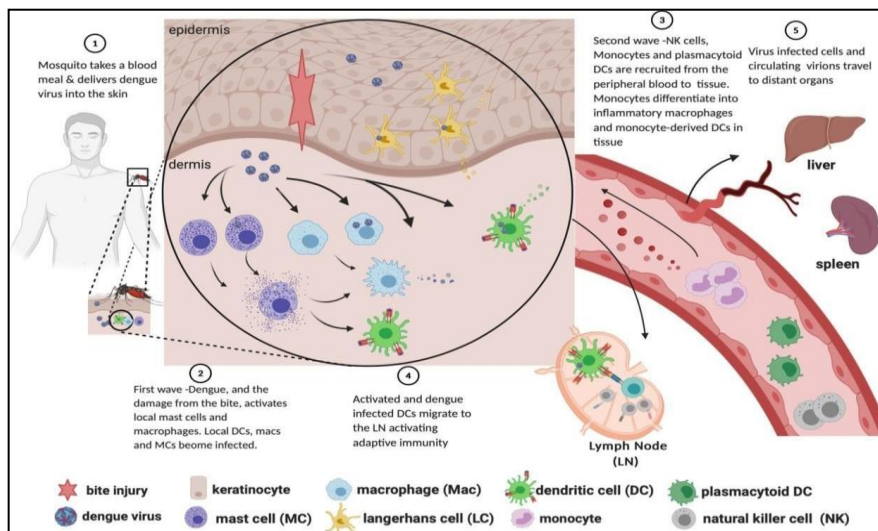


Figure No. 2:^[6]

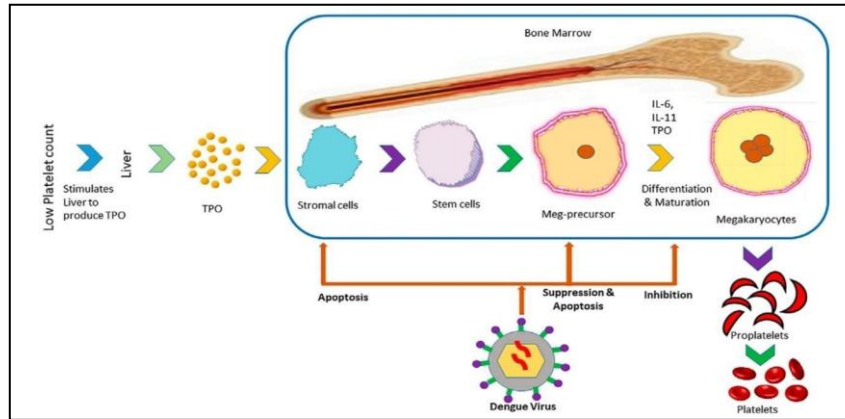


Figure No. 3:^[5]

Mechanism of inhibition of the formation of platelets in bone marrow by dengue virus. The panel illustrates the steps in the formation of platelets from the liver that is stimulated by low platelet count in the blood. After the

infection of the host with dengue virus, it prevents the formation of platelets from stromal cells and maturation in different stages.^[5]

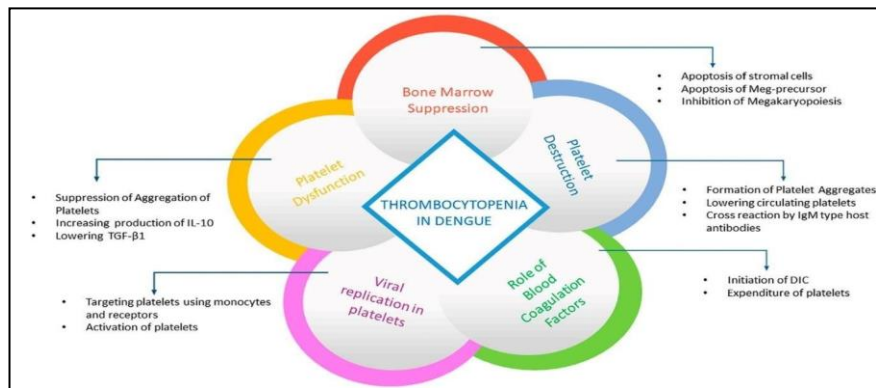


Figure No. 4:^[5]

Summary of processes behind thrombocytopenia in dengue. The panel summarizes how platelets are destroyed after dengue infection. After viral replication in platelets, it activates platelets using receptors and

monocytes as well as aggregates the platelets, reducing its availability. It also suppresses bone marrow and prevents platelet formation by destroying premature cells.^[5]

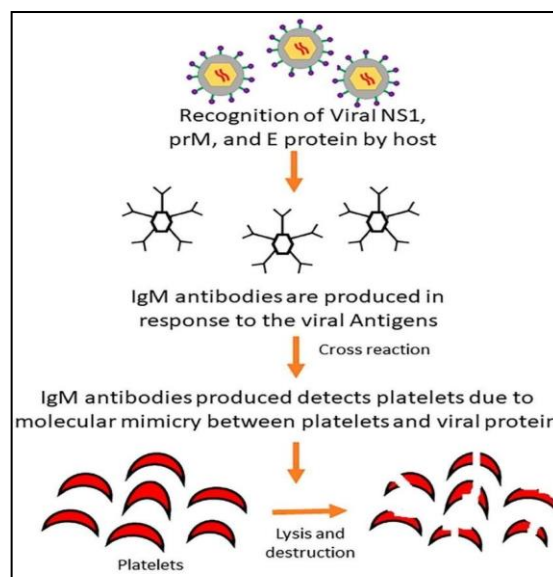


Figure No. 5:^[5]

Mechanism of platelet destruction by antibody crossreaction induced by dengue virus. Invading viral proteins mimics the platelets of the body and are destroyed by IgM antibodies produced upon recognition of viral proteins by the host defense system.

SIGN AND SYMPTOMS

Typically, people infected with dengue virus are asymptomatic (80%) or have only mild symptoms such as an uncomplicated fever. Others have more severe illness (5%), and in a small proportion it is life-

threatening. The incubation period (time between exposure and onset of symptoms) ranges from 3 to 14 days, but most often it is 4 to 7 days. Therefore, travelers returning from endemic areas are unlikely to have dengue fever if symptoms start more than 14 days after arriving home. Children often experience symptoms similar to those of the common cold and gastroenteritis (vomiting and diarrhea) and have a greater risk of severe complications, though initial symptoms are generally mild but include high fever.^[6]

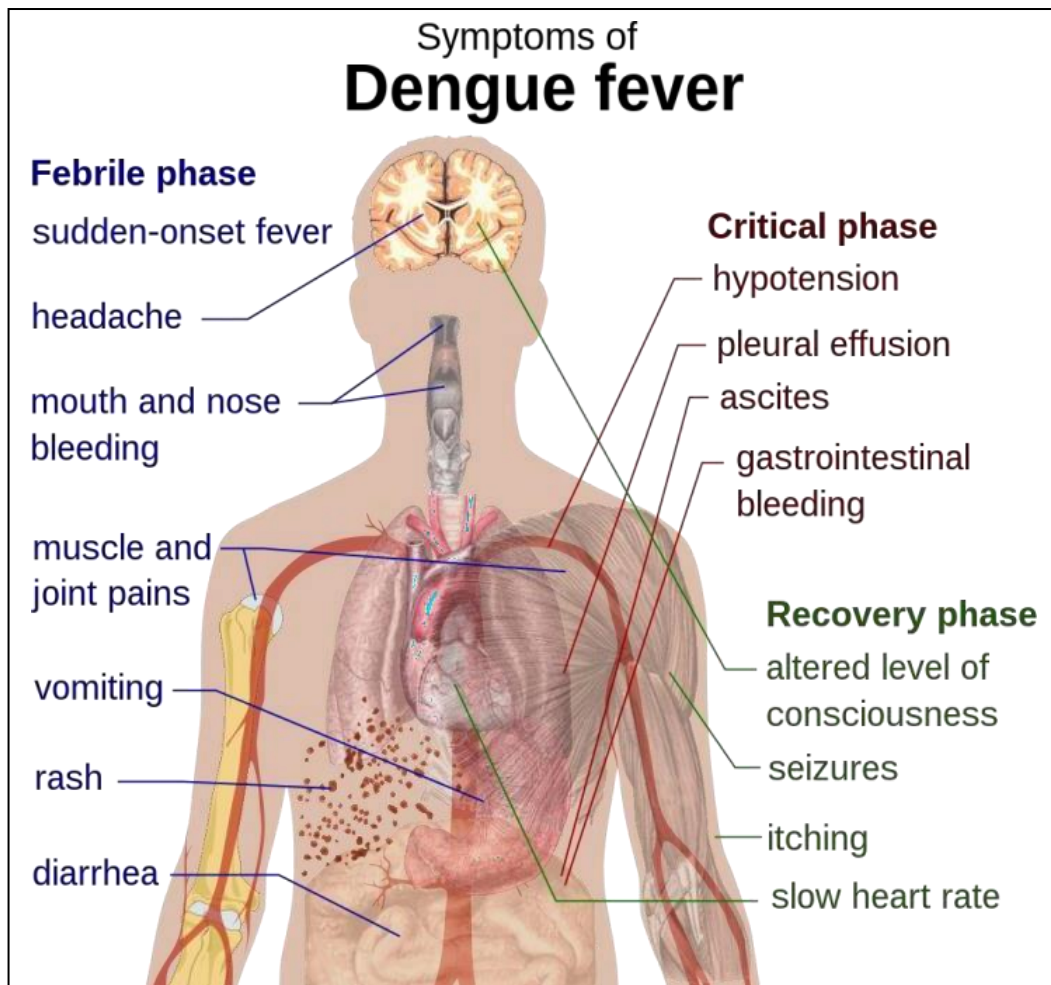


Figure No. 6:^[6]

TRANSMISSION

Spread Just like in malaria, dengue fever is also spread by bites of mosquitoes. In this case, the mosquitoes are "Aedes" mosquitoes which are very tough and bold mosquitoes and bite even during day time. This disease occurs more frequently in the rainy season and immediately afterwards (July to October) in India. The Dengue virus is present in the blood of the patient suffering from Dengue fever.^[7] Whenever an aedes mosquito bites a patient of dengue fever, it sucks blood and along with it, the dengue virus enters into its body. The virus undergoes further development in the body of the mosquito for a few days. When the virus containing mosquito bites a normal human being, the virus is

injected into the person's body and he/she becomes infected and can develop symptoms of dengue fever.^[7]

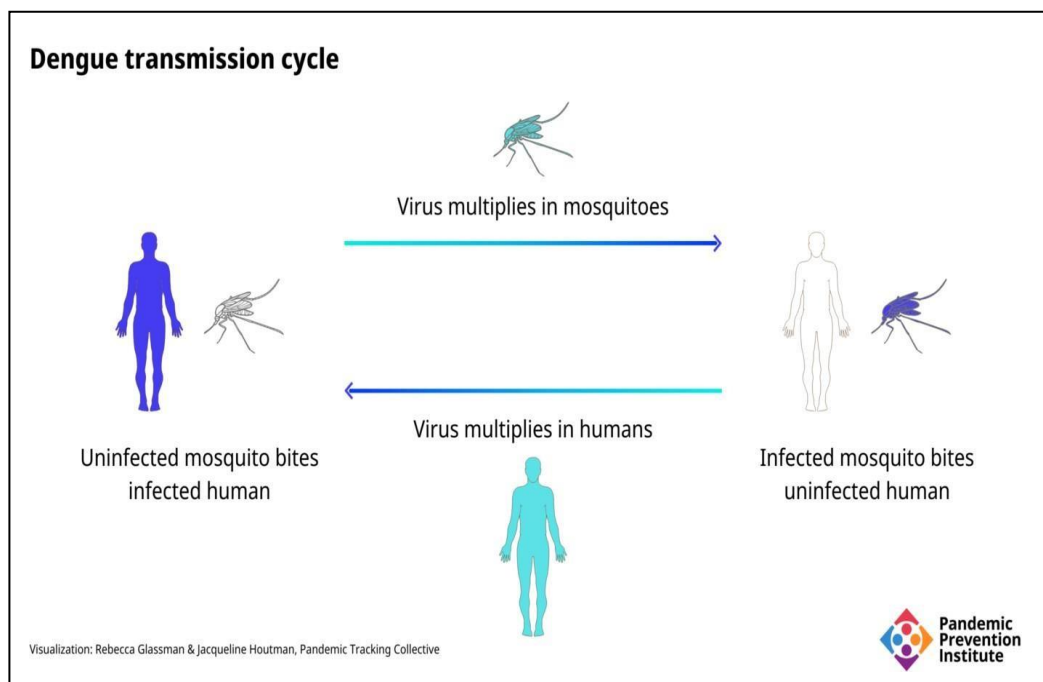
Figure No. 7:^[7]**PLANT DESCRIPTION**

Table No. 1.

Domain	Flowering plant
Kingdom	Plantae
Sub Kingdom	Tracheobionta
Class	Magnoliopsida
Subclass	Dilleniidae
Super division	Spermatophyta
Phylum	Steptophyta
Order	Brassicales
Family	Caricaceae
Genus	Carica
Botanical Name	<i>Carica Papaya</i>

Carica Papaya is sometimes known as paw paw which is a fast growing herbaceous plant. *Carica papaya* is an evergreen, tree-like herb, 2-10 m tall, usually unbranched, although sometimes branched due to injury, containing white latex in all parts. Stem cylindrical, 10-30 cm in diameter, hollow with prominent leaf scars and spongy-fibrous tissue. Has an extensive rooting system. Leaves spirally arranged, clustered near apex of trunk; petiole up to 1 m long, hollow, greenish or purplish-green; lamina orbicular, 25-75 cm in diameter, palmate, deeply 7-lobed, glabrous, prominently veined; lobes deeply and broadly toothed.^[8] The leaves are deeply incised and lobed. Mature leaves are palmate with deep lobes and are supported by smooth and hollow petiole. The leaf scars given by petiole enlarge as the plant grows in circumference.

The leaves are used for colic, fever, beriberi, abortion, asthma in India and cancer in Australia papaya leaves are used traditionally in treatments like jaundice, malaria, dengue immunomodulatory and antiviral activity.^[10]

Young leaves are used in cooking and eaten like spinach in East Indies. Papaya leaves are used as a tonic for heart disease, treatment for stomach ache and have antioxidant, anticancer, antiseptic and analgesic property, immunomodulatory, anti tumour, antiplasmodial, antibacterial, anti dengue also used in treating wounds, burns and malignant tumors.^[10]

Dried leaves are known as blood purifiers and taken as tonic. Papaya leaf tea is used to treat obesity and helps in losing weight and it acts against chronic indigestion, high blood pressure and arteriosclerosis weakening of heart. Fresh leaves are used to cure gastrointestinal problems and hepatic disease and it also acts as anti-inflammatory and natural abortion agent. In India traditional, siddha medicinal systems prescribe *Carica Papaya* leaf extract to patients with dengue fever symptoms.^[10]

Daily consumption of leaves helps to prevent malaria, aqueous extract of papaya leaves consumption also increases platelets WBC and neutrophils counts (especially in dengue patients). Dried leaves have been indicated in sickle cell anemia management.^[10]

LEAF MORPHOLOGY

Table No. 2.

Leaf arrangement	Alternate
Leaf type	Simple
Leaf margin	Parted
Leaf shape	Star-shaped
Leaf venation	Palmate
Leaf type and persistence	Evergreen
Leaf blade length	18 to 23 inches
Leaf color	Green to olive green on top, paler green to whitish underneath
Fall color	No fall color change
Fall characteristic	Not showy ^[8]

MECHANISM OF *CARICA PAPAYA* LEAF EXTRACT AGAINST DENGUE

The juice from the leaves of *Carica Papaya* helps to increase the count of white blood cells and platelets count. It also helps to normalize clotting and repairs the liver. The extract of papaya juice was given to patient with dengue fever within 24 hours the platelets count and white blood cell count raise to normal level. The secondary metabolite of this plant makes up a vast repository compound. The aqueous extract exhibits potential activity against dengue fever.^[11] Currently no vaccine or antiviral drugs are existed for the control of

dengue disease. Only patients receive supportive treatment with blood, blood components and fluids for the prevention of the disease or maintenance therapy.^[12] Possible mechanisms behind the role of papaya leaves in improving platelet count. This figure summarizes the mechanism of papaya leaves in reducing thrombocytopenia by the dengue virus. It stabilizes the membrane of platelets and reduces platelet destruction. It also prevents viral assembly in cells and hemolysis. Furthermore, it increases the expression of genes that elevate the production of platelets.^[5]

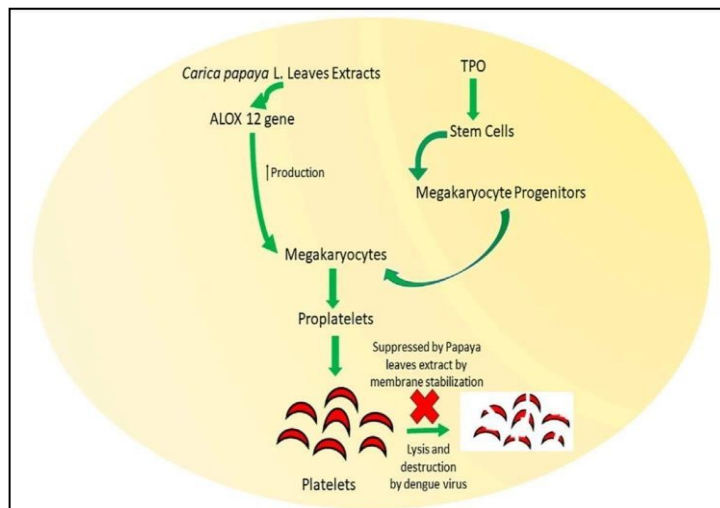
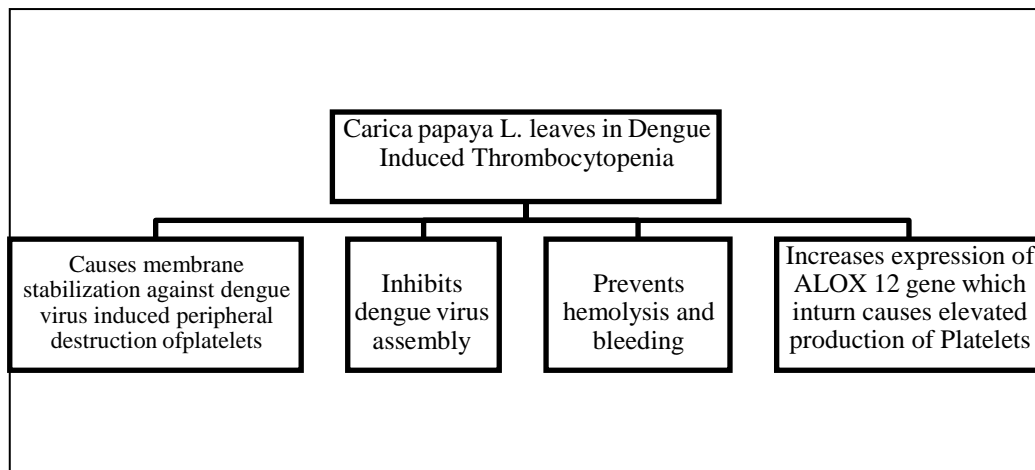


Figure No. 8.

Mechanisms behind the role of papaya leaves in improving platelet count by membrane stabilization and production of ALOX 12 gene. *Carica papaya* L. leaf extract promotes the formation of megakaryocytes and megakaryocyte progenitors that induce the formation of proplatelets. Lysis and destruction of these proplatelets are also inhibited by *Carica papaya* L. leave extract.^[5]

AIM AND OBJECTIVE

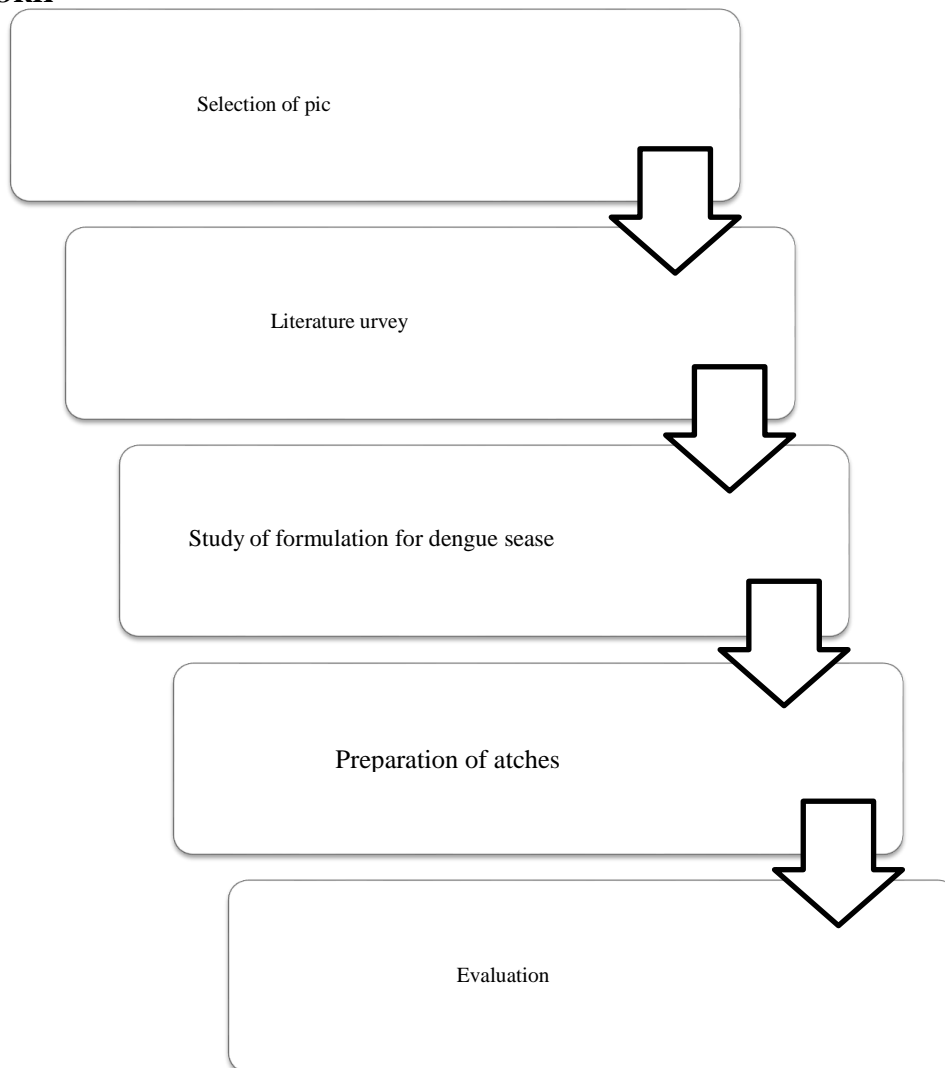
Aim

The aim of this research was to study the preparation and evaluation of “*CaricaPapaya*” leaf extract syrup.

Objective

- To increase the platelet count in the treatment of dengue disease.
- To improve the immune system.
- Treat symptoms related to dengue fever.
- Promots platelet production via the increased number and differentiation of megakaryocytes.

PLAN OF WORK



LITERATURE REVIEW

Dr.C.V.M. Naresh Kumar et.al (June 2015)

The present study suggests the therapeutic role of papaya leaf extract (PLE) as a cheap and potential herbal therapy for treating the dengue infected patients. Further studies should be carried out for identification of the compounds present in *Carica papaya* leaf extract and exploring their therapeutic role in curing dengue infection. *Carica papaya* leaf extracts are known to have many beneficial medicinal properties. Recent studies have claimed

possible beneficial effects of *Carica papaya* leaf extracts in treating patients with dengue infection. The present study aims to evaluate the therapeutic potential of *Carica papaya* leaf extracts in treating dengue patients. *Carica papaya* leaf extracts were given to dengue infected patients and their blood samples were daily monitored. Polyserositis condition of the patients was analysed by ultrasonography before and after the completion of *Carica papaya* leaf extract treatment. Blood analysis reports, ultrasonographic findings, statistical results and

patients recovery from dengue infection clearly shows the therapeutic role of *Carica papaya* leaf extracts in treating dengue infected patients. Further studies are necessary for identification of the compounds present in *Carica papaya* leaf extract and exploring their therapeutic role in curing dengue infection.

Jaykaran Charan et.al (Oct-Dec 2016)

This study suggest that *C. papaya* leaf extract has a definitive role in improving the platelet count in patients of dengue. Looking at the wider CI, the rise in platelet count may be very less and may not clinically significant. There is a statistically significant positive effect on the rise of platelet count, but whether this rise is clinically significant or not? That can be explored further by designing high-quality clinical trials based on large sample size with all measures to prevent incorporation of bias. Dengue is an infectious disease associated with high mortality and morbidity. Being a viral disease, there is no specific drug available for treatment. There are some reports that *Carica papaya* leaf extract may improve the clinical condition of dengue patients.

Vijeth S. B. et. al. (July 2018)

Studies that dengue is a threat to almost 40% of the world's population. There is still no specific treatment for dengue. *Carica papaya* leaf extract can be used as supplementary drug in acute febrile illness patients with thrombocytopenia. It accelerates the increase in platelet count and reduces the hospital stay thereby reducing the dengue as a global public health problem and thrombocytopenia associated with it is a serious complication for which there is no specific treatment available. This study was done to assess the effect of *Carica papaya* Leaf Extract (CPL) on thrombocytopenia associated with Dengue and to study other clinical parameters of dengue. Most of hospitalization. *Carica papaya* leaf extract accelerates the increase in platelet count and reduces the hospital stay. So, it can be used as supplementary drug to reduce complications.

Adhuri Prakash Reddy et.al (March 2019)

The work suggest that the compound extracted from leaves are used for the treatment of dengue activity and this effect is increased by increasing the quantity of this compound. The crude leaves were collected from local forest which are then subjected for drying, extraction using maceration process. Therefore, pharmacological test is necessary to isolate and characterize their active compounds. This extract used to prepare syrup, and evaluate purpose we are using various evaluation parameters of stability, viscosity, pH. To formulate and evaluate papaya leaves and *Euphorbia hitra* by using different sweetening agents like sucrose, maltose, sucralose and saccharin etc. Medicinal plants such as *Carica papaya*, and *Euphorbia hitra*, is an ever green medicinally useful tree that tolerates various stress of the desert. Medicinal plants have been a variable source of

natural activity phytochemical constituents that play an important role in the treatment of many human diseases. In the present study, leaves of *Carica papaya*, *Euphorbia hitra* was by its Anti-bacterial activity the qualitative phyto-chemical analysis and bacterial potential.

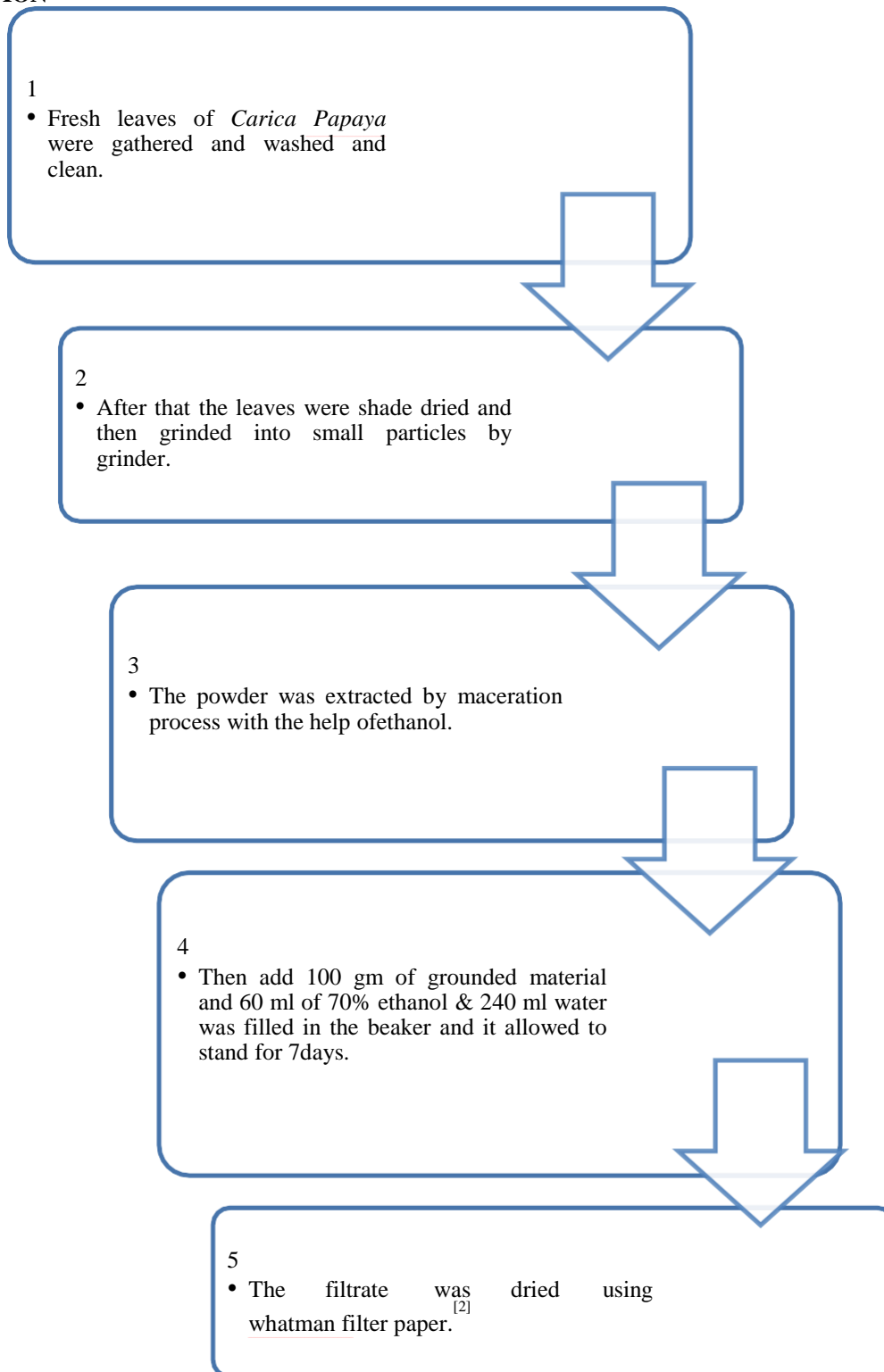
Javesh Kashinat Patil et.al (June 2019)

The formulation having antioxidant property hence it will be very helpful for researchers as well as industries to make the similar formulations on large scale. Most of herbal syrup was originally derived from plant herbal medicine refers to use extract of leaves for medicinal purpose. Along with other dosage from herbal drugs also formulated in form of syrups. Today syrup is used for treatment of many ailments and to overcome symptoms of diseases. The antidengue syrup is used to treat the dengue because of many stress condition and other oxidative reaction in body the free radical are generated, by using these syrup the condition is overcome.

Moklesur Rahman Sarker et. al. (April 2012)

Therapeutic application of *Carica papaya* leaf and how papaya leaf help in dengue to increase platelet count several reports have suggested that papaya leaves have the ability to inhibit destructive effects on platelets by the dengue virus and increase the expression of ALOX 12 gene responsible for elevating platelet count. Moreover, papaya leaves have been found to have a wide therapeutic range with very few toxic effects. However, very few investigations were done to explore the mechanism(s) behind the role of papaya leaves to improve the platelet count. If the exact mechanisms are known, papaya leaves extract could be optimized for better effectiveness as well as therapeutic preparations that could be formulated targeting the same pathway as papaya leaves. Also, the anti-thrombocytopenic potential of papaya leaves is not very widely known.

EXTRACTION PROCEDURE MACERATION



FORMULATION DEVELOPMENT FORMULATION DEVELOPED IN THREE STEPS

- Preparation of Extracts The collected papaya leaves (100gm) were dried and size reduced into coarse powder and macerated separately with 60 ml of 70% ethanol & 240 ml water. After 7days of maceration both the extract was filtered out with the help of whatman filter paper. The residue was obtained and kept in a dessicator for the present study.^[2]
- Preparation of Simple Syrup Take 66.7gm of sucrose was weighed and added in to purified water heated until It dissolved with occasional stirring. Sufficing boiling water will be added to produce 100ml of simple syrup.

- Other excipients add for enhance activity.^[2]

INGREDIENTS AND THEIR ROLE

Table No. 3.

Ingredients	Role
Papaya leaf extract	Active ingredient
Simple syrup	Sweetener
Honey	Sweetning agent
Glycerine	Thickening agent
Sodium benzoate	Preservatives
Orange oil	Flavouring agent
Xanthum gum	Viscosity enhancer
Water	Make up volume

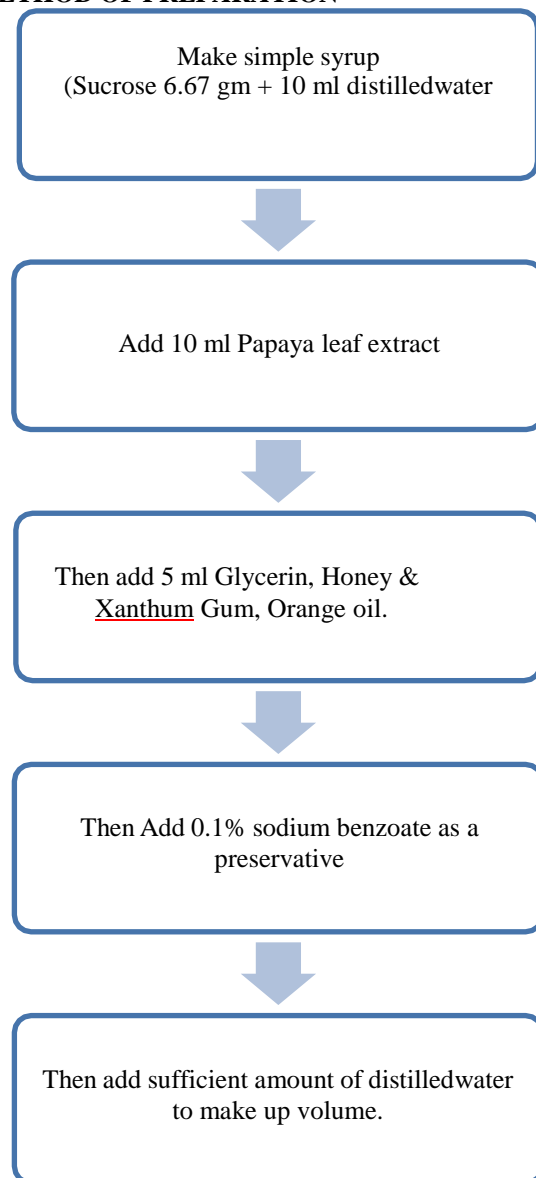
Table No. 4.

Ingredients	Official quantity	Required quantity
Sucrose	667 gm	6.67 gm
Distilled Water	1000 ml	10 ml

- **Honey** - Honey is thought to be helpful in various antimicrobial and anti-inflammatory properties. It has also been suggested that due to its viscous nature it coats the throat causing a soothing effect.
- **Glycerine** - It is often thought of only as a solvent or thickening agent its special properties of lubrication, demulcency, sweetness, and acting as a humectant.
- **Sodium Benzoate** - Sodium benzoate is used as a preservative in some over-the-counter and prescription medications.
- **Orange oil** - Flavors are used for orally consumed products such as syrups, Flavors are used for orally consumed products such as syrup. Provide aromatic properties to syrup.
- **Xanthum gum** - used in refrigerated dough formulations to control syrup formation and stabilize the dough during storage.
- **Water** - The use of boiled purified water in the preparation of syrup can enhance its permanency, and the addition of preservative agents, when permitted, can protect it during its shelf life. Storage in a tight container is a requirement for all syrups.

- **Papaya leaf extract** – Main therapeutic agent those show anti-dengue, anti-inflammatory and anti-malaria action, Papaya leaf extract increases the platelet, WBC count in the blood.
- **Simple syrup** - sweetening which doubles the sweetness of glucose and make sucrose distinctively sweet in comparison to other carbohydrate foods. It can also act as a food preservative when used in sufficient concentrations. It is a common ingredient in many processed foods.^[2]

METHOD OF PREPARATION



BATCH PREPARATION

Table No. 4.

Sr. No.	Ingredients	BatchA	BatchB	BatchC
1	Papaya leafextract	10 ml	10 ml	10 ml
2	Simple syrup	10 ml	15 ml	—
3	Glycerin	2 ml	2 ml	2 ml
4	Honey	5 ml	—	15 ml
5	Sodium Benzoate	0.1%	0.1%	0.1%
6	Xanthum Gum	0.5 gm	0.5 gm	0.5 gm
7	Orange Oil	3-4 drops	3-4 drops	3-4 drops
8	Distilled Water	q.s	q.s	q.s



Figure No. 9.



Figure No. 10.



Figure No. 11.



Figure No. 12.

EVALUATION PARAMETER**Colour**

- 5 ml of prepared syrup was taken on a watch glass.
- Watch glass placed against white background in white tube light.
- Colour was observed by naked eyes.

Odour

- 2ml prepared syrup was taken and smell by individually.
- The time interval between 2 smelling was 2 min to nullify effect of previous smelling.

Taste - Taste has been checked.

Density

- Take the weight of empty dry bottle with capillary tube stopper.
- Fill the bottle with syrup and place the stopper, wipe out excess liquid from outside the tube using tissue paper.
- Weight bottle with syrup on analytical balance.
- Calculate weight in grams of syrup.

Weight = Weight of bottle with syrup – Weight of empty bottle

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}}$$

Viscosity

1. Thoroughly clean the Ostwald viscometer with warm chromic acid and if necessary used an organic solvent such as acetone.
2. Mount viscometer in vertical position on a suitable stand.
3. Fill water in dry viscometer up to mark G.
4. Count time required, in second for water to flow from mark A to mark B.
5. Repeat step 3 at least 3 times to obtained accurate reading.
6. Rinse viscometer with test liquid and then fill it up to mark A, find out the timerequired for liquid to flow to mark B.
7. Determination of densities of liquid as mentioned in density determinationexperiment.

$$\text{Viscosity} = \frac{\text{Density of test liquid} \times \text{Time required to flow test liquid}}{\text{Density of water} \times \text{Time required to flow water}} \text{Viscosity of water}$$

pH Determination

The pH determination of syrup by using two techniques.

- a) Glass electrode
- b) pH paper

Procedure for glass electrode

1. Prepare 30ml buffer of each pH. The volume of the stock solution to be taken.
2. Prepare the buffer by mixing appropriate volume.
3. Allow the solution for 15minutes to establish equilibrium.
4. Measure the pH of solution using a pH meter.

Stability testing

1. Stability testing of the prepared herbal syrup was performed on keeping the samples at accelerated temperature conditions.

2. The final syrup was taken in culture tubes and were kept at accelerated temperature at 4°C, Room temperature and 47°C respectively.
3. The samples were tested for all the physicochemical parameters, turbidity and homogeneity at the interval of 24 hr, 36hr and 72 hr to observe any change.^[35]

RESULT AND DISCUSSION

The results obtained in this study suggest that the herbal formulations prepared possesses Anti-dengue activity. The component of the herbal syrup formulation was selected due to their reported action that plays a preventative and curative role in treatment of dengue. Syrup prepared passes all the physical parameters and shows the significant Antitussive activity.

Table No. 5.

	Parameter	Batch A	Batch B	Batch C
Physicochemical Parameter	Colour	Brownish	Brownish	Dark Brown
	Odour	Sweet orange	Sweet orange	Sweet orange
	Taste	Sweet	Sweet	Sweet
	Apperance	Clear	Clear	Clear
Quantitative Parameter	Density	1.66	1.70	1.75
	Viscosity	3.70 cp	3.60 cp	3.66 cp
	PH	6.0	5.8	5.6

CONCLUSION

Study suggests the therapeutic role of papaya leaf extract (PLE) as a cheap and potential herbal therapy for treating the dengue infected patients. dengue is a threat to almost 40% of the world's population. There is still no specific treatment for dengue. Carica papaya leaf extract can be used as supplementary drug in acute febrile illness patients with thrombocytopenia. It accelerates the increase in platelet count and reduces the hospital stay thereby reducing the cost of hospitalization. The result of this work suggest that the compound extracted from leaves are used for the treatment for dengue activity and this effect is increased by increasing the quantity of compound. This extract used to prepare syrup, and evaluate purpose by using various evaluation parameters of viscosity, pH, Density.

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