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PAPAYA LEAF EXTRACT IN DENGUE THERAPY OTHER HEALTH BENEFITS AND FORMULATION ADVANCES

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ABSTRACT

Dengue is a viral mosquito-borne disease and is known to possess threat to public health on large scale. Carica Papaya leaf extract (CPLE) is a natural remedy that has demonstrated promising way to comb-act dengue symptoms by increasing platelet levels in dengue patient. This review also highlights PLE's efficacy in treating dengue, alongside its various health benefits, including Immunomodulation, Antioxidant activity, Anti-cancer and Anti-viral properties. Hepatoprotective and Gastroprotective effects, Cardiovascular health and Anti-diabetic potential. Various novel formulation strategies to enhance PLE's treatment efficiency and to overcome stability issues are under study which are discussed in short. Also highlights the existing challenges for use of papaya in health condition and required future research directions that will uncover potential of papaya leaf extract in medical science.

KEYWORDS: *Dengue, Papaya Leaf Extract (PLE), Dengue Fever, Antiviral Therapy, Thrombocytopenia, Natural Remedies, Cancer Prevention, Wound Healing, Nanotechnology*.

1.INTRODUCTION

Dengue is an arthro-pod infectious disease caused by bite of female aedes aegypti-flavirida virus. When a person is infected with one serotype of dengue then he develops life-long immunity for that particular serotype.

But if patient is affected with other serotype during the life-time then he is at the risk of developing dengue hemorrhagic fever, low blood pressure, vessel leakage, decreased platelets. A study revealed 390 million people were infected with Dengue. Four serotypes of dengue are DEN1, DEN2, DEN3, & DEN4.

Even though dengue effect such a big number of populations there is no determined or specified treatment or vaccine developed to treat and prevent dengue. The treatment for dengue is done on the basis of symptoms of particular infected person. As there is lack of proper treatment dengue is greatly affecting the human mortality rate.

Different studies have observed lower platelet count in Dengue infection the platelet count is lowered mainly due to DEN 2 serotype this is the one which causes thrombocytopenia. Not only for dengue there are several diseases which lack defined medication for their treatment. So Researchers and Developers exhibited effective use of natural plants in treatment of various diseases.

A study reveals effectiveness of Papaya leaf extract in treatment of dengue infected patient. There are certain evidences that can show treatment of thrombocytopenia occurred due to Dengue infection.

Some investigation demonstrated that lower platelet count of a dengue patient can be increased by giving the patient papaya leaf extract as a part of treatment.

Carica papaya leaf is a rich source of bioactive compounds it includes alkaloids, saponins, tannins, flavonoids, and glycosides. These phytochemicals confer numerous therapeutic properties, making papaya leaf a valuable natural remedy.

The leaf has been found to possess various active compounds which can help prevent and manage various diseases:

- Dengue
- Antibacterial
- Anti-inflammatory
- Antiviral
- Hypoglycemic
- Antitumor activities.

Overall, the therapeutic properties of Carica papaya leaf make it a promising natural solution for promoting overall health and well-being.

Taking into regard the widespread use of Carica papaya leaf some formulation approaches are being made by the researchers such as nano-emulsion, popping balls, green tea, Transdermal patches, edible oral emulsions. So as to increase its use in various health conditions and with improved patient compliance.

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2.OBJECTIVE

- A. Effective treatment for Dengue fever
- B. Enhanced platelet count and reduced bleeding risk
- C. Improved immune response and reduced inflammation
- D. Expanded understanding of PLE's health benefits
- E. Patient-friendly, efficient, and safe formulations of PLE.

3. DENGUE VIRUS

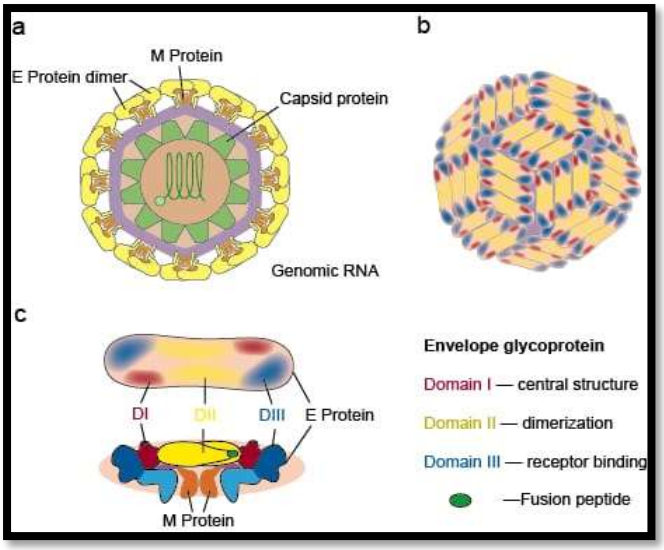


Fig (1) Structure of Dengue Virus

- Structure and Proteins of Dengue Virus
  - Family: Flaviviridae.
  - It is icosahedral virus
  - It is a small, rounded shaped virus with an outer protective layer.
  - The outer layer is enveloped by a fatty membrane.
  - Its size is approximately 500 Angstrom (50nm).
  - It has 4 serotypes: DEN1, DEN2, DEN3, & DEN4
  - It consists of 11 KB positive single standard RNA.

RNA contains instruction for development of two proteins of virus which are called structural and non-structural proteins. See figure 1.

- Structural proteins

E and M present on viral surface this are mainly required for developing of virus particles so that virus get ready for to be transferred in host cell. These are called binding blocks of virus.

- Non-structural proteins

It takes the responsibility of replication of virus genome it's translation and encapsulation and folding of viral proteins. These are called managers which oversee function of virus.

4.LIFE CYCLE OF DENGUE VIRUS

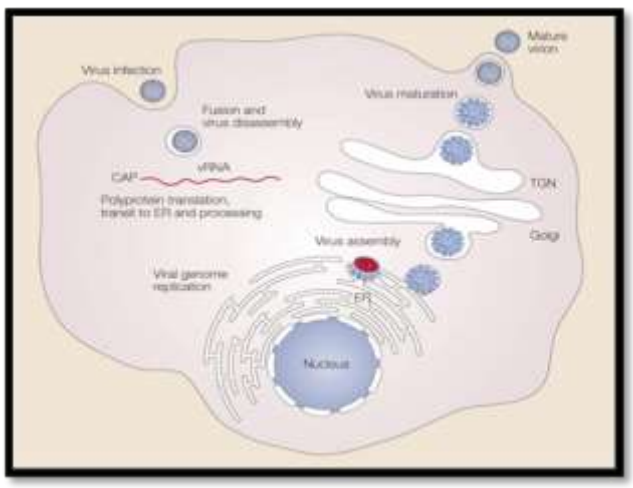


Fig (2) Life Cycle of Dengue Virus

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Dengue virus enters the host body after bite of an infected Aedes mosquito. Life cycle of virus include following stages like viral entry, replication, assembly, release.

- Life cycle begins as follows
- Attachment of host receptor protein and DEN virus on surface proteins of dendritic cells.
- Host receptor cell recognize it and bind with it. Protein E is essential for recognition of receptor.
- Entry of DEN virus in host cell take place
- At low PH endosomes and membrane fusion take place.
- Pores are formed on membrane
- DEN virus is released in cytoplasm of host.
- Protein synthesis take place.
- RNA replication, DEN virus replication mainly takes place in cells and organs including kidney, lymph nodes.
- Then it is followed by nucleic and capsid formation.
- Virus maturation take place.
- Release mature DEN virus particles.
- After 4 to 7 days of incubation of virus in host body symptoms of disease appear which are vomiting, rash, headache, high fever, muscle soreness. See figure 2.

5.THROMBOCYTOPENIA DUE TO DENGUE VIRUS INFECTION

During the dengue fever the platelet count of the patient falls rapidly and there is also a decrease in platelet production.
Dengue virus 2 causes thrombocytopenia, it affects the platelet production in infected person. It targets the young platelet making cells called the Megakaryocytic progenitors.
According to some studies thrombocytopenia may be due to following reasons.

- Virus induced damaged to bone marrow
- Damage to cytokinin
- Platelet lysis

6.PAPAYA PLANT

It is a shrub, grown in most of the tropical and subtropical countries like Southern and Central Mexico, Brazil, Indian. See figure 3.



Fig (3) Papaya plant

Synonym: Papaya, Pawpaw, Kate.
Family: Caricaceae.

- ACTIVE CHEMICAL COMPOUNDS PRESENT IN PAPAYA LEAF EXTRACT

- Major phytochemicals

Carpaine, kaempferol-3, Papain, Cystain, Chymopapain, Tocopherol, Phenolic acids, Cyanogenic glucosides, Vitamin C. Carpaine, Dehydrocarpaine-1, Dehydrocarpaine-2, are majorly responsible to treat dengue.
Carpaine also gives anticancer and anthelmintic properties.

- Phenolic compounds

Caffeic acid, Quercetin.

- 7 flavonoids present are Quercetin, kaempferol-3 rutinoside, Quercetin-3, Quercetin 3-rutinoside, Kaempferol 3, Myricetin 3-rhamnoside.
- Vitamins and Minerals
  It contains vitamin C and minerals like iron, zinc, manganese, ascorbic acid, calcium, magnesium.
  Vitamins and minerals help to improve protein and immunity of individual person.
- Enzymes
  Enzymes like papain help to treat digestive ailments.
  Papain helps to treat digestive ailments.

7.METHOD TO PREPARE PAPAYA LEAF EXTRACT JUICE



Fig (4) Papaya Leaf Juice

- Collect and wash fresh papaya leaves.
- Chop leaves into small pieces.
- Combine 50g leaf powder, 50ml water, and 25g sugar
- Blend mixture and squeeze out liquid.
- Refrigerate extract for 24 hours.

8.MECHANISM OF PAPAYA LEAF EXTRACT

A study claims that papaya leaf juice can neutralize the dengue virus in blood and significantly reduce platelet clumping.
Alox-12 gene is essential for platelet type 12 lipo-oxygenase which mediate various functions of platelet cell.
Papaya leaf extract has been found to increase the production of an enzyme called ALOX 12 by 15 times.
Papaya leaf juice stimulates growth and maturation of cells that produce platelets called the megakaryocytes thus boosts platelet production and synthesis. It increases platelet production by increasing the PTAFR gene by 13.5 times
It's constituents like flavonoid and quercetin prevent replication of dengue virus by inhibiting NS2B and NS3 essential for DNA virus replication. It increases platelet and WBC count within 24 hours of administration.

9.CLINICAL EVIDENCES ON THE USE OF PAPAYA LEAF EXTRACT FOR DENGUE

- In Sri lank

The study included 12 patients with a low platelet count, less than 130,000/cu mm.

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But only 6 of them were diagnosed with Dengue. Patient were given two doses of Papaya leaf extract at 8-hour time gap.
And it was found that the patient platelet count and WBC was increased in 24 hours of administration with papaya leaf extract.

- In Pakistan

A truck driver was given 25 ml papaya leaf extract for 5 days and increase in platelet and WBC was observed in 2 days.

- In Indonesia

80 dengue patients were given C. papaya leaf extract capsule. They were divided in two groups one group was give C. papaya leaf extract and another group was given advanced medical treatment.
The patient who administered with C. papaya leaf extract tablet, showed a rapid increase in platelet count.

- In Malaysia

A study in Malaysia was conducted to analyze the mean platelet count difference in person suffering from dengue without administration of papaya leaf extract.
Two groups of patients were selected, one group was provided with papaya leaf extract and other group was the control group. There were no differences in mean platelet count of the two groups from 8 hours to 40 hours.
But after 40 hours the patient who were given papaya leaf extract showed marked increment in platelet count.

10.OTHER HEALTH BENEFITS OF CARICA PAPAYA LEAF EXTRACT

- IN TREATMENT OF CANCER

Scientists are trying to develop herbal based therapies to treat cancer. A patent claims that cancer cell growth can be reduced by administrating papaya leaf extract to cancer patient and improve patient health. And papaya leaf extract can be helpful in various cancer treatment such as lung, cancer, stomach, pancreatic, liver, ovarian, breast, blood cancer.
Some studies claim that papaya leave give anti-cancer property due to activation of caspase 3/ 7 which can induced cell death. Activating P53 a protein which is known to destroy damaged cells. Study revealed that papaya can treat prostate cancer cells by preventing them from dividing in S phase leading to cell death and prevent cancer growth.

- DIABETES

Some studies claim that Papaya leave extract can be an alternative to control diabetes the large-number of phytochemicals present in PLE and help to decrease secondary diabetes complications. PLE can show its antidiabetic activity by inducing pancreas to release more insulin and allows glucose to enter cell more efficiently it also slows down fatty acid production and decrease cholesterol production.

- AS AN ANTIOXIDANT

Study explained the water papaya leaf extract antioxidant activity found highest antioxidant activity.

- IN IMMUNOMODULATION

PLE gives notable immunomodulatory effects by regulating and balancing immune system in following manner it reduces TH2 response that reduces allergic reaction and increases TH1 response which is known to boost anti-cancer immunity. It can also increase production of useful cytokinin like IL 12 TNF and IFN-Y and decreases harmful cytokines like IL4 and IL2.

- AS A NEUROPROTECTIVE

During a study it was found that PLE can give neuro protective effect for Alumminium induced cognitive impairment in a animal model.

- TO TREAT DIGESTIVE DISORDERS

Some studies reveal that PLE tea and extracts can help to relieve blotting, gas, heartburn as it is rich in fiber and contains Papain a compound that breaks proteins and reduces inflammation and support gut health.

- AS AN ANTI-INFLAMMATORY

Papaya leaf has also given remarkably results as an anti-inflammatory agent it has shown reduction in internal and external inflammation, relieve pain. anti-inflammatory compound present are papain, flavonoids and Vitamin E that prevents damage to cells.

- TO PROMOTE HAIR GROWTH

Papaya may show hair growth and scalp health properties due to antioxidants present in it like flavonoids, Vitamin E, it has potential to reduce oxidative stress. It can even show antifungal properties by reducing dandruff causing fungus. But there are Limited evidence for use of Papaya leaf extract in hair growth.

- TO IMPROVE SKIN HEALTH

The key compound present in PLE helps to promote healthy glowing skin taken orally or applied topically. Papain can remove dead skin cells, unclogs, pores, reduces in grown hairs acne.

- TO TREAT MENSTRUATION PROBLEM

PLE can be used to treat irregular menstruation.

- IN ULCER TREATMENT

It helps to treat ulcer when consumed orally.

- ROLE IN INCREASING SHELF LIFE OF PLATELETS.

Researches have been discovering to use papaya leaf extract to improve the quality of platelet during its storage. PLE contains active compounds like Tannins, Alkaloids, flavonoids, oleic acid. It reduces platelet damaging during storage. Patelet lessions are controlled with beerly Hexane extract of PLE. Hexane extract of PLE shows maximum antimicrobial activity and prevent bacterial contamination. No microbial growth was observed in storage platelets with hexane extract it helps to extent platelets shelf life up to 7 days and maintain platelet quality and blood safety and Tannins present in PLE is responsible activity.

11.NEW FORMULATION ADVANCES OF PAPAYA LEAF EXTRACT TO TREAT DENGUE

The bitter test limits its use and becomes unpleasant for patient to consume.
So researches are trying to developed new formulations to use papaya leaf extract to treat dengue
Some of this are:

- Papaya leaf extract edible o/w emulsion.
  - Fresh papaya leaf edible o/w emulsion. (FPL)

In a study fresh papaya leaves extract were mixed with virgin coconut oil and whey protein as surfactant stable fresh papaya leaf emulsion was obtained by Tarnary Phase diagram (TPD).

- Saponins modified papaya leaf extract emulsion.

The bitter taste of papaya leaf extract is due to the presence of saponin in it. Saponin reduction method helps to reduce the bitter taste of papaya leaf extract and helps to develop a suitable formulation.

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So papaya leaf extract with reduced saponin content were mixed with virgin coconut oil and whey protein as surfactant to develop a suitable papaya leaf extract edible emulsion of reduced bitter taste.

Both emulsions were formulated by using Tarnary phase diagram method. Effective dosage of both emulsions were two tablespoons twice a day for three consecutive days.

After exposure of BEAS-2 B cells to both emulsion an increase in cell viability was observed and it increased with time from 24 hour to 48 hours and 100% at 72 hours.

- Silver Nano Particles based on Papaya leaf extract.

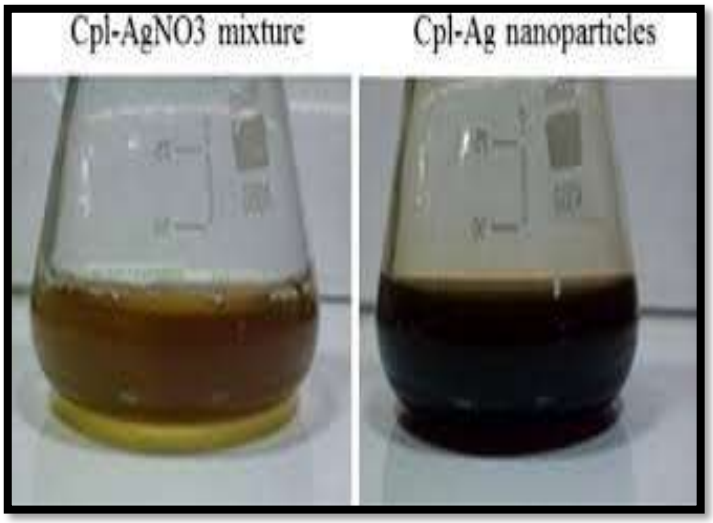


Fig (5) Papaya Silver Nanoparticles

- A study formulated papaya-based silver nanoparticles and other three formulations of papaya. PNP demonstrate antiviral activity against DEN 2 serotype of dengue virus under various conditions such as pretreatment co-treatment and post treatment.
- But the more appreciable effect was found in post infection treatment it was observed that PNP showed 100% reduction activity DEN 2 virus levels this describe the PNP has potential to completely eliminate DEN 2 virus.
- In another study Papaya leaf extract silver nanoparticles were made from Papaya Leaves using a special liquid methanol showed 90% inhibitory activity on DEN 2 during the in- vitro study. Figure 5 papaya leaf silver nanoparticles.

- Carbonation of Papaya leaf juice.

  A new way to consume papaya leaf extract for treating dengue was introduced such as carbonation of Papaya leaf juice as papaya leaves are unstable and unpleasant to consume. This innovative way improves stability and makes it more viable.

- Popping balls of papaya extract for pediatric dengue cases.



Fig (6) Papaya Leaf Popping Balls

During a study scientist developed popping balls of Papaya leaf extract by Spherification method to treat pediatric patient of dengue associated thrombocytopenia.

This were found easy to take, easy to swallowed, showed high drug release up to 91% and stability for 3 months.

They were determined to be a kid friendly approach to boost platelet count in thrombocytopenic pediatric patient and as an alternative to solid dosage forms. See figure 6.

12.CHALLENGES AND LIMITATIONS

Papaya leaf extract has given a positive impact in Dengue treatment by increasing the platelets level or platelets count as per the result of clinical trials conducted till date.

The result might be influenced by factors of which we are unaware and accurate results are necessary to make correct decisions. Biased result can lead to wrong decision. So more information is required to trust the result.

The increase in platelet count may be not as much required or less which is not clinically significant. Larger research trials are not conducted for use of PLE in Dengue treatment.

Papaya leaf extract even today is not approved by clinical official and US FDA to manage dengue fever. The papaya leaf extract remains unapproved due to lack of quality study.

The research carried out by Asian countries and the outcoming of this research may not work for other countries and people with different genetic profile, as environment and genetics influence the treatment.

- To get proper benefits from papaya leaf extract:
  - Larger clinical test must be conducted.
  - Ensure bias-free research program.
  - Also investigate long term advantages.

13. FUTURE DIRECTION AND RESEARCH

National agency and food control must provide complete support to increase products of papaya leaf extract and create an easy way for formulation registration.

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Traditional medicines are not regarded as main treatment option due to lack of sufficient scientific proofs. However traditional medicines were and are used for treatment by various communities who cannot approach modern medicines.

There is a vast necessity to conduct various research trials to established 12th standard proof to incorporate traditional medicine role in disease treatment. One such traditional medicine is Papaya leaf extract.

14.CONCLUSION

Papaya leaf extract has emerged as a promising natural, safe, effective remedy for treating dengue fever. Studies have consistently shown that the extract increases platelet count, reduces symptoms, and accelerates recovery. Clinical trials and case studies have demonstrated the efficacy and safety of papaya leaf extract in treating dengue patients. The bioactive compounds present in papaya leaves, such as papain, alkaloids, and flavonoids, exhibit immunomodulatory, anti-inflammatory, and antioxidant properties. Further research and development of novel formulations will pave the way for its widespread adoption as a complementary therapy for dengue fever. Further research and development are necessary to fully unlock its therapeutic potential.

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