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Review

Exploring Carica Papaya Leaf-Based Preparations for Dengue Treatment: A Comprehensive Review

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Abstract

The Dengue illness is a prominent worldwide health issue, especially in tropical and subtropical areas where the Aedes mosquito species reside. Despite substantial research efforts, there are currently no proven antiviral treatments available for dengue. In recent times, there has been a growing focus on the examination of alternative medicine, which encompasses the study of natural treatments produced from medicinal plants. The popularity of papaya, scientifically known as carica papaya, has risen because of its alleged therapeutic benefits, namely in the treatment of dengue fever. The purpose of this thorough review is to gather the current body of research on the possible effectiveness of formulations made from Carica papaya leaves in the treatment of dengue fever. The antiviral, immunomodulatory, and anti-inflammatory activities of Carica papaya leaf extracts are explained by thoroughly analysing in vitro research, animal models, and clinical trials to understand the pharmacological pathways involved. Additionally, we provide a summary of the different compositions and timing of administration used in scientific studies investigating the effectiveness of papaya leaf extracts in alleviating symptoms and decreasing the severity of dengue. In order to fully exploit the therapeutic benefits of Carica papaya in treating dengue fever, this study provides suggestions for future research and also evaluates the problems and constraints experienced during the present work. In order to eliminate dengue fever and improve worldwide public health results, it is crucial to create treatments that are easily accessible, reasonably priced, and secure. This study emphasises the need of combining traditional knowledge with scientific investigation.

Keywords: *Dengue, anti-inflammatory activities, carica papaya, Aedes mosquito.*

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Introduction of dengue:

Dengue fever, mostly spread by Aedes mosquitoes and caused by the dengue virus, is a major public health issue, particularly in tropical and subtropical areas worldwide. Despite significant efforts in vector control and disease prevention, the World Health Organization (WHO) reports that the incidence of dengue remains high, with an estimated 390 million illnesses each year. The increasing occurrence of dengue, intensified by urbanization, globalization, and climate change, persists in burdening healthcare systems and communities. This emphasises the crucial need of creating effective therapeutic treatments (Abd Kadir et al., 2013).

Traditionally, the management of dengue fever has focused on providing supportive care to alleviate symptoms and prevent complications, since there is no specific antiviral treatment available ("The Papaya-Based Poly-Herbal

Extract Eases Thrombocytopenia and Pyrexia in Rats," 2023). The limitations of conventional approaches have sparked interest in exploring complementary and alternative medicines, particularly those derived from natural sources that are believed to have therapeutic properties. Particulate formulations obtained from Carica papaya leaves have attracted considerable interest and investigation because to their possible usefulness in the treatment of dengue (Razak et al., 2018).

Carica papaya, a tropical plant native to Central America, is widely grown in tropical places across the globe. It is often known as papaya or pawpaw. The many parts of the papaya plant, including the fruit, seeds, and leaves, have been used in traditional medicine for many years due to their diverse pharmacological properties, as well as its gastronomic uses. Carica papaya leaves have attracted considerable attention in recent years due to their possible therapeutic effects in treating dengue infection. The interest in the leaves' therapeutic effects has been stimulated by clinical observations, experimental investigations, and anecdotal accounts that confirm their potential to relieve symptoms and enhance clinical results (Mohd Abd Razak et al., 2019).

The aim of this comprehensive study is to do a thorough examination of the existing literature on Carica papaya leaf preparations used for treating dengue. This study aims to provide a thorough comprehension of the pharmacological mechanisms, therapeutic effectiveness, safety profile, and possible obstacles associated with the use of Carica papaya leaf extracts for treating dengue fever (Shrivastava et al., 2022). In order to do this, data will be consolidated from preclinical investigations, clinical trials, and observational reports. In addition, this review aims to thoroughly evaluate the strengths and weaknesses of the current evidence in order to give healthcare practitioners, researchers, and policymakers a clear understanding of the current state of knowledge and the possible future directions of clinical practice and research in this rapidly changing field. This study intends to provide scientific data to the growing collection of information on natural therapies for infectious illnesses by performing a thorough research of concoctions made from Carica papaya leaves, which are used to treat dengue (Munir et al., 2022). By doing this, it encourages informed decision-making and allows the development of novel treatment methods to tackle dengue fever and reduce its global health impact (Bok et al., 2020).

Dengue virus types and transmission:

The transmission of dengue illness occurs by the Aedes egypti mosquito, which is a virus belonging to the flaviviridae family (Singh et al., 2020). Dengue often manifests after a period of 5 to 7 days following the bite of a mosquito carrying the virus, when it infects an individual who is not yet affected. The typical symptoms of the infection often consist of elevated body temperature, skin rash, and headaches, along with discomfort in the muscles and joints, pain in the eyes, and episodes of vomiting and naus (Sarker et al., 2021). The Dengue virus consists of four distinct serotypes, namely Dengue virus-1 to Dengue virus-4. An person might have several infections as a result of exposure to various serotypes of the virus. Multiple dengue virus infections may result in dengue hemorrhagic fever (DHF), a dangerous illness (Morens and Brody, 2008). Dengue is a very prevalent global disease, with an estimated annual occurrence of around 50-100 million cases of dengue fever (DF) and 500,000 cases of dengue hemorrhagic fever (DHF) (Akhter et al., 2015). Electron micrographs revealed that the dengue virus exhibits visions that are quite smooth and have a diameter of about 500 Å. The virus has a plus-sense RNA genome and encodes three structural proteins, including core, membrane, and envelope proteins (Suryani, 2020). As previously mentioned, dengue is associated with thrombocytopenia, a medical condition. The exact cause of thrombocytopenia in dengue fever cases is yet unknown. Dengue thrombocytopenia is thought to have many causes, including bone marrow platelet destruction, decreased platelet production, antibody generation, and antibody-mediated platelet elimination (Pal & Lal, 2024). Currently, there are no existing therapies or vaccines for the dengue virus. Despite several hypotheses, the precise mechanism by which the dengue virus causes dengue fever remains unknown. Natural plants have played a vital role throughout history in the discovery and advancement of several developing medications across various therapeutic categories (Pal & Lal, 2023). Carica papaya L. is a significant botanical specimen that has lately undergone examination to uncover its therapeutic attributes, identify its bioactive components, and understand their mechanisms of action. Papaya leaves have long been used in traditional medicine for treating dengue fever and have been shown to be useful in alleviating thrombocytopenia in laboratory and animal models. However, the exact mechanism underlying this potential benefit is not stated (S. Y. M. Lim et al., 2021).

Epidemiology of Dengue

The first individual to identify and name the DF was Benjamin Rush in 1789. Myalgia and arthralgia were among the symptoms he described with the term "break-bone fever" The 1780s saw the documented and investigated occurrence of DF epidemics in North America, Africa, and Asia all happening at the same time. Many nations in the Western Pacific, Asia, Africa, the Americas, and the Eastern Mediterranean are seeing high rates of the disease (Saleh & Kamisah, 2021). Diseases caused by DF are most common in the Americas, Southeast Asia, and the Western Pacific. Approximately 70% of the world's DF cases occur in Asia. Variations in burden reporting across regions are caused by the absence of a unified and coordinated effort at the regional level to establish population-based epidemiological surveillance with well-defined operational objectives. More than threefold increase in the risk of DENV infection have occurred since 1940, and a marked rise in frequency has occurred since the global movement of people during WWII . Nearly 40 million instances of DF and hundreds of thousands of cases of DHF were reported each year in the late 1990s, making it the second most common mosquito-borne illness after malaria (Canini et al., 2007). At this time, DF disease poses a threat to half of the global population. Nearly 390 million people have DF infections year; of them, over 100 million develop symptoms, and nearly a thousand die from DHF or DSS. Asia, Africa, and the Americas are among the tropical and subtropical regions that are most affected by these illnesses. Globalization, population expansion, urbanization, climate change, inadequate sanitation services, ineffective mosquito control, and an increase in the reporting of DENV cases are some of the variables that contribute to the distribution and spread of DF infections. An increase in mosquito populations and susceptibility to circulating serotypes may be caused by factors that improve the ideal circumstances for mosquito reproduction, feeding habits, and the incubation period of the Dengue virus (DENV) (Renstra kemenkes, 2020). There has been a recent and substantial epidemic of DENV in tropical urban districts. This is at least in part due to changes that allow replication at increased carrier temperatures and a reduction in the requirement for amplification in animal hosts [29]. Dengue fever (DF) transmission cycles cause substantial economic losses, illness, and mortality, especially in developing nations (Vuong et al., 2013).

A large number of countries have reported an increase in the number of cases of DF since the year 2000. The possibility of transmission from urban areas to rural areas affects about half of the global population. A total of 129 countries have reached dengue fever's infectivity limit; among them are 36 that were formerly deemed dengue-free by the WHO and/or the US CDC. The large number of dengue cases and outbreaks corroborate this. The annual estimated number of DENV infections is about 390 million. Of these, 67–136 million instances have the potential to manifest clinically, with a sizeable portion progressing to more severe or fatal manifestations. The prevalence of DENV infections is highest in countries situated in tropical and subtropical areas. A number of variables have been identified as contributing to this upward trend, including but not limited to: increased monitoring and reporting of DENV cases, inadequate sanitation services, ineffective mosquito control, climate change, population growth, and urbanisation (Syamsuddin, 2020).

More than eight times as many DF cases have been reported to WHO in the last 20 years, with a corresponding fourfold rise in fatalities. Starting at 505,430 in 2000, the number of recorded cases skyrocketed to almost 2.4 million in 2010, and then surpassed 5.2 million in 2019. From 960 in 2000 to 4032 in 2015, there was a corresponding rise in the number of recorded fatalities [5]. In addition, DF has spread from mostly affecting children to affecting people of all ages in the last forty to fifty years. On the flip side, the total number of reported cases and fatalities decreased considerably during 2020–2021. But there is still a lack of information on the COVID-19 epidemic and how it affected case reporting in different nations. There has been an uptick in DF cases and fatalities across age groups and geographies, although the precise global dissemination of the virus is now very unclear (Farhood et al., 2019).

Even though all serotypes of DENV are common in 19 African nations and vector mosquitoes may be found in Sub-Saharan Africa and the neighboring Middle East, our knowledge of the epidemiology of DF in Africa is still limited. With estimated rates of 25% (21-29%) based on IgG testing, 10% (9-11%) based on IgM testing, and 14% (12-16%) based on viral RNA tests, the frequency of DENV infection in Sub-Saharan Africa is a major public health concern [30]. Moreover, additional African nations have reported DF occurrences to the Africa CDC [31]. In 2016, and 2017, Burkina Faso, Côte d'Ivoire, Cape Verde, and Egypt were all included. In 2009, the same was true.

Pathogenesis of dengue fever:

DENV is a common pest in urban and semiurban areas of the world's tropical and subtropical regions. Any person, regardless of age, may get DENV from an infected mosquito. Break bone fever, dengue hemorrhagic fever, charming fever, and, in severe instances, dengue shock syndrome are symptoms that have been associated with DENV infection. During the monsoon season, tropical regions of South America and Asia are more likely to have dengue virus (DENV) infection epidemics. Typically, DENV is transmitted to humans by infected female Aedes mosquitoes. Although DENV cannot be spread via direct bodily contact, it may be passed from an infected individual to a healthy one through blood transfusions (Teh et al., 2022).

Diagnosis:

The presence of the virus, viral nucleic acid, antibodies, antigens, or a mix of these, by means of one or more of the following procedures, is one of the laboratory criteria for dengue diagnosis:

- IgG or IgM antibody levels against one or more dengue viral antigens must increase by a factor of four or more in matched serum samples to indicate a reciprocal response.
  It is possible to establish the presence of the dengue viral antigen in postmortem tissue using immunohistochemistry, immunofluorescence, or enzyme assays in serum samples (MAC-ELISA, IgG ELISA, nonstructural protein 1 [NS1] ELISA, EIA).
- The reverse-transcriptase polymerase chain reaction (RT-PCR) test may detect viral genomic sequences in CSF, serum, or tissue samples taken during an autopsy. RT-PCR allows for a quicker and more precise diagnosis
- It is very unusual to be able to isolate dengue virus from blood, plasma, white blood cells, or samples taken after death.

Tissues, plasma, CBCs, and serum may all reveal the presence of the virus in the first four or five days of illness. The most effective methods for diagnosing infections include the detection of antigens, the isolation of viruses, and the detection of nucleic acids. Once the acute phase of an illness has passed, serology is the method of choice.

If someone is thought to have dengue, further laboratory testing should be carried out on them.

- A hepatic function panel
- A full blood count
- Panel for coagulation, which may or may not include a DIC panel
- Dengue fever is characterised by elevated levels of serum protein and albumin.
- A drop in white blood cell count, or leukopenia, is a medical condition.
- When the platelet count is below 100 x 109/L, it is known as thrombocytopenia.
- Increases in alanine and aspartate aminotransferase levels that are mild to moderate. The following symptoms may be seen by patients with acute dengue:

Blood protein levels are low, the activation partial thromboplastic time is prolonged, fibrinogen levels are reduced, and fibrin split products are high. The hematocrit is increased as a result of fluid loss in body compartments and/or plasma leakage into tissues.

The guaiac test, which may detect undetectable blood in stool, should be administered to all patients who are thought to be infected with the dengue virus. Blood in urine is a sign of hemorrhage.

The following are included in imaging studies:

- Brain edoema or abnormalities on chest x-rays that point to severe dengue Ultrasound may detect pericardial effusion, a thicker gallbladder wall, fluid in the abdominal and thoracic cavities, and severe dengue fever in patients.

Carica Papaya

Papaya, scientifically known as Carica papaya L., is a highly adaptable and globally recognised tropical fruit tree with many regional names. From "papaw" in Australia to "Mamao" in Brazil, "Pepe" in Bangladesh, and "Papeeta"

in Hindi, the many names it is called demonstrate its worldwide existence and cultural importance (X. Y. Lim et al., 2021).

The papaya tree is known for its rapid growth, somewhat woody structure, and ability to produce latex. Typically, it has a rather short lifetime. Different varieties of Carica papaya are distinguished by numerous botanical characteristics, such as the number of primary leaf veins, kinds of stomata, colour of the petiole, lobes on leaf edges, leaf shape, and wax structure on the leaf surface.

Papaya, scientifically known as Carica papaya, has a long history of spreading that may be traced back to the time of exploration. The prevailing belief is that it evolved in tropical America, particularly in southern Mexico and the adjacent area of Central America. The dispersion of the drug to various parts of the world was expedited by explorers and traders.

Carica papaya, a member of the Caricaceae family, has a lifetime of about five to ten years and grows as a single, non-branching trunk. Being a herbaceous perennial, this plant produces a milky latex and may grow as tall as 12 meters. The fruits of this plant, which weigh between 1,000 and 3,000 grammes, may be gathered throughout the year. They have a smooth, green exterior that changes to yellow or orange when they are mature. Inside, the fruit resembles a melon and contains over 1,000 seeds.

The leaves of Carica papaya are palmately lobed, with hollow petioles and blades split into five to nine segments, reaching a width of up to 75 centimeters. The blooms appear on inflorescences, located inside the axils of the leaves, enhancing the plant's aesthetic appeal and reproductive process.

Papaya, a very adaptable fruit, is highly respected worldwide for its culinary and medical properties. The platypus is highly regarded in global cuisine, whether it is eaten fresh as a fruit, used in various processed items like jams and preserves, or consumed as a vegetable.

Furthermore, several constituents of the papaya plant have traditionally been used in alternative medicine to cure a broad spectrum of ailments, in addition to its gastronomic significance. The enzyme "papain," found in the white latex, has several uses in the culinary and medical domains. Papain, widely used as a meat tenderizer, has antibacterial properties that make it a desirable component in wound dressings. Moreover, latex has been historically used for its purported abortifacient characteristics and to address other ailments such as dyspepsia, ringworm, psoriasis, and even malignant tumors. This exemplifies the many medicinal applications of papaya-derived compounds. Supplementary sections of the papaya plant have been used in traditional medicine because to their medicinal properties. An illustration of the many therapeutic uses of root infusions is shown in their use for treating hemorrhoids, venereal illnesses, and yaws, showcasing the extensive spectrum of healing properties inherent in this botanical phenomena. Essentially, papaya goes beyond its role in cooking and becomes a multipurpose plant with a significant therapeutic history. The extensive array of applications for this substance underscores its significance not only in supplying sustenance for the body, but also in fostering health and wellness via traditional therapeutic approaches. Modern study continues to uncover the pharmacological effects of the elements found in papaya, which helps to preserve its lasting significance as a tropical gem. This research serves as a connection between traditional knowledge and new advancements in the quest for overall well-being (Ong & Norzalina, 1999).

Therapeutic application of Carica papaya:

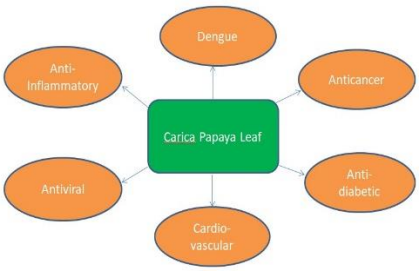

Figure 1: Therapeutic application of Carica papaya

Anti-dengue activity Carica papaya L. Leaves:

Like papaya leaves, guava leaves contain quercetin, a chemical that may increase platelet synthesis and has anti-dengue properties. It has been shown that the virus is unable to synthesize enzyme MRN. We used Vero E6 cells to test Andrographis paniculata antiviral efficacy against dengue virus. The presence of terpenoids, flavonoids, and polyphenols in the plant was thought to be responsible for this action. It has been acknowledged that cladogynos orientalis, together with flavonoids, quercetin, and determines, have anti-dengue properties. At a concentration of 12.5 µg ml−1, the dichloromethane ethanol extract inhibited DENV-2 by 34.85%, as shown in an MTT assay. In addition, the quercitin found in Azadirachta indica L. possesses properties that prevent the dengue virus from replicating. discovered that a water-based extract of neem leaves effectively inhibited the virus's growth at a TCID50 range of 100-10,000 (Anju Krishnan et al., 2018).

Anti-inflammatory activity Carica papaya L. Leaves

Numerous studies in both animals and humans have shown that papaya leaf extracts, whether in an ethanolic aqueous or basic form, may increase platelet counts and have anti-inflammatory effects. Dengue fever is characterised by low levels of platelets, red blood cells, and white blood cells; using papaya extract may help with a quick recovery. There has been strong evidence from a small number of recent case studies that it reduces the overall number of plates. Dengue patients were given a 25 mL oral extract of papaya leaves twice daily, in the morning and evening, for five days in a row. There was a significant increase in the platelet, white blood cell, and neutrophil (NEUT) counts in the days after the second day of oral dosing. These levels, however, had returned to normal by the time the therapy was over. A newborn baby with congenital thrombocytopenia was the subject of an investigation on the effects of many platelet transfusions. Phototherapy, intravenous immunoglobulin, two exchange transfusions, antibiotics, and antifungal treatment failed to improve the patient's condition. However, the child's platelet count increased noticeably when oral papaya leaf extract was administered at a dosage of 20 mg/kg three times daily. Even during the later examination, no detrimental outcomes were seen, which is rather significant (Keramagi & Skariyachan, 2018).

Anticancer activity of Carica papaya L. Leaves

Plants medicinal properties are determined by their chemical constituents, which are known to have beneficial pharmacological and physiological effects on humans. Extensive research on papaya has shown that the whole plant is rich in secondary metabolites, some of which have been associated to potent anticancer effects in humans. Male and female cancer patients of varying ages, weights, and ethnicities were the subjects of a recent research that looked at the efficacy of papaya capsules. The participants ranged from 18 to 72 years old. Compared to the control group, patients given papaya leaf extract at a dosage of 0.16 g/kg body weight exhibited a significant reduction in the proliferation of malignant cells. According to the results, papaya leaf extract has great potential as a powerful anticancer medication for the treatment and prevention of prostate cancer. This is due to the presence of several phytochemicals, such as amino acids, flavonoids, alkaloids, and phenolic. The authors recommend familiarizing oneself with the anticancer mechanism of papaya leaf extract before using it as an adjuvant treatment for cancer. This herbal extract has a markedly beneficial impact on several cancer cell lines, according to numerous in vitro experiments. To confirm papaya leaf extract's potential as an anti-cancer agent and understand its mechanism of action, more research is required (Ul Qamar et al., 2017).

Anti-diabetic activity of Carica papaya L. Leaves

Preclinical studies conducted on diabetic mice have shown that extracts from papaya leaves have anti-diabetic properties, according to the existing literature. However, these herbal leaf extracts may have anti-diabetic effects, although no human clinical studies have looked at this yet. Scientists have discovered that papaya leaves have no harmful side effects, making them a potential alternative treatment for diabetes. Phytochemicals, found in abundance in the leaf extract, have a crucial role in lowering the risk of complications associated with diabetes [87]. In 2007, the first preclinical investigation of papaya's potential medicinal effects on diabetic Wistar rats began. The male Wistar rats were given 5.0 mg/kg BW of papaya ethanolic leaf extract for twenty-four hours as part of the trials. Researchers found that diabetic rats' blood glucose levels dropped significantly after 24 hours of oral administration, dropping from 12.75 to 1.23 mmol/L (a decrease of 88 percent).

Table1: Therapeutic uses of Carcia Papaya plant:

S. No.	Name of plant parts	Uses	References
1	Green Fruit	Jaundice, malaria, hypertension, diabetes mellitus, and hypercholesterolemia are medical conditions. Nigerian intestinal helminthiasis refers to the presence of parasitic worms in the intestines of individuals in Nigeria.	(T. T. Nguyen et al., 2016)
2	Ripe Fruit	Chronic skin ulcers appear as sinuses in Caribe, Philippines, and even in Jamaica. Gastrointestinal bleeding, diuretic, expectorant, sedative, or tonic bleeding Gastrointestinal discomfort and haemorrhoids in India	(Kirchmaier & Pillitteri, 2010)
3	Leaves	Heart tonic, antipyretic, anthelmintic, colic, dengue fever, beriberi, abortion, asthma in India, gastrointestinal disorders, cancer in Australia	(Al-Huniti & Kahr, 2020)
4	Latex	Psoriasis and dermatitis are widespread throughout Asia, Africa, and Europe.	(Cox et al., 2011)
5	Root	In Australia, this substance has digestive, tonic, and abortifacient properties.	(Greinacher & Eekels, 2019)
6	Bark	India has dental pain, while Africa faces the challenge of syphilis.	(Yogarajalakshmi et al., 2020)
7	Flower	Asia experiences cases of jaundice, cough, hoarseness, bronchitis, laryngitis, and tracheitis.	(Ibrahim & Ghareeb, 2020)
8	Seed	Contraceptive. Antimicrobial, fungicidal, carminative, and anti-irritating properties.	(Ibrahim & Ghareeb, 2020)

Phytochemical composition of Carica papaya:

The term "phytochemical" refers to a class of chemical substances that exist naturally in plants. Many species benefit from their therapeutic properties. Several studies have demonstrated that papaya leaves contain phytochemicals that are beneficial to health. Research consistently found high concentrations of enzymes, phenolic compounds, alkaloids, saponins, glycosides, flavonoids, carbs, vitamins, and mineralsIricetin 3-rhamnoside, quercetin, kaempferol 3-rutinoside, quercetin 3-(2G-rhamnosylrutinoside), and quercetin 3-rutinoside are the seven separate flavonoids found in papaya leaves. Protocatechuic acid, 5,7-dimethy coumarin, quercetin, caffeine, and p-coumaric acid are some of the phosphorous compounds found in the leaves. Among the several phytochemicals found in the leaves are carpaine, 1-rhamnoside, kaempferol 3-(2-rhamnosylgalactoside), kaempferol 3-(2G-glucosylrutinoside), and kaempferol 3-rhamnosyl-(1->2).Take a look at these examples: This chemical mixture contains luteolin, orientin, palmiticamide, 2-hexaprenyl-6-methoxyphenol, 11-hydroperoxy-12,13-epoxy-9-octadecenoic acid, and 7-galactosyl-(1->6)-galactoside. Because of the high concentrations of bioactive chemicals in the aforementioned leaves, their extracts are perfect building blocks for new kinds of nutraceuticals and herbal remedies. C. papaya leaf chemical composition and structure. Rumour has it that some illnesses may be curable by combining C. papaya leaves with other plants. It is used by traditional healers in Nigeria to control diabetes. It treats malaria and fungal diseases when used with other botanicals in Cameroon. Traditional healers among Australia's Indigenous population have long relied on leaf decoctions to combat cancer. The bioactive chemicals found in papaya leaves have the potential to boost the body's antioxidant defences. Phenolic acids, cystatin, chymopapain, tocopherol, cyanogenic glucosides, glucosinolates, and vitamin C are the primary phytochemicals found in papaya leaves. Alkaloids, saponins, glycosides, phenolic compounds, and flavonoids are the main components of papaya leaves that possess anti-inflammatory and anticancer properties. Papaya leaves are rich in protein, minerals, and vitamins, which all work together to boost the immune system, total haemoglobin levels, and overall protein content in humans. Papaya leaves include four primary bioactive compounds: carpaine, dehydrocarpaine I, dehydrocarpaine II, and a third component that is unknown. These botanical leaves are used in Ayurvedic medicine to cure a range of physical ailments and viral illnesses, including dengue and chikungunya, since they contain carpaine. The aforementioned alkaloid moves segments of the intestines, relaxes the uterus, and widens the bronchioles; it also

possesses antiplasmodial properties. Lowering hypertension and slowing the heart rate are two other potential benefits. Carpaine also possesses significant anticancer and antihelminthic effects. The highest quantity was found in completely mature papaya leaves (9.30 mg/g), according to the study. Then, 4.90 mg/100 g of fruit, 1.99 mg/100 g of fruit rind, and 0.65 g/g of fruit seeds were determined. Variations in numerous elements may be seen in the leaf composition. For example, there are 8.3% carbohydrates, 36.6% vitamin C, 5.6% protons, and 0.23 percent phosphoric acid. The tannin content of papaya leaf extract has been shown to be low, at 0.824 percent, according to many investigations. According to research, the total phenolic compounds were most concentrated in the papaya leaves, then in the mature fruit, in the immature fruit, and finally in the seeds. The plant's leaves have already been improved by the bioactive chemicals mentioned previously, leading to a remarkable 90% antioxidant capacity. Concentrations of 3480 mg/kg of calcium and 5928 mg/kg of magnesium were determined by the researchers. Significant quantities of iron (558 mg/kg), zinc (33.4 mg/kg), manganese (22.88 mg/kg), chromium (7.50 mg/kg), and copper (2.16 mg/kg) were detected [16]. At 85.6 mg/100 g, ascorbic acid was highest in papaya leaves, then in mature papaya at 45.8 mg/100 g, in unripe papaya at 37.8 mg/100 g, and finally in papaya seeds at 14.4 mg/100 g. The papaya leaves are rich in papain and chymopapain, two types of biological enzymes. Papain, which is present in papaya leaf extract at concentrations between 0.054 and 0.002 mg/mL , is more effective in digesting food than pepsin. A vital phytochemical component present in leaves, papain also has structural and functional characteristics (Shen et al., 2018).

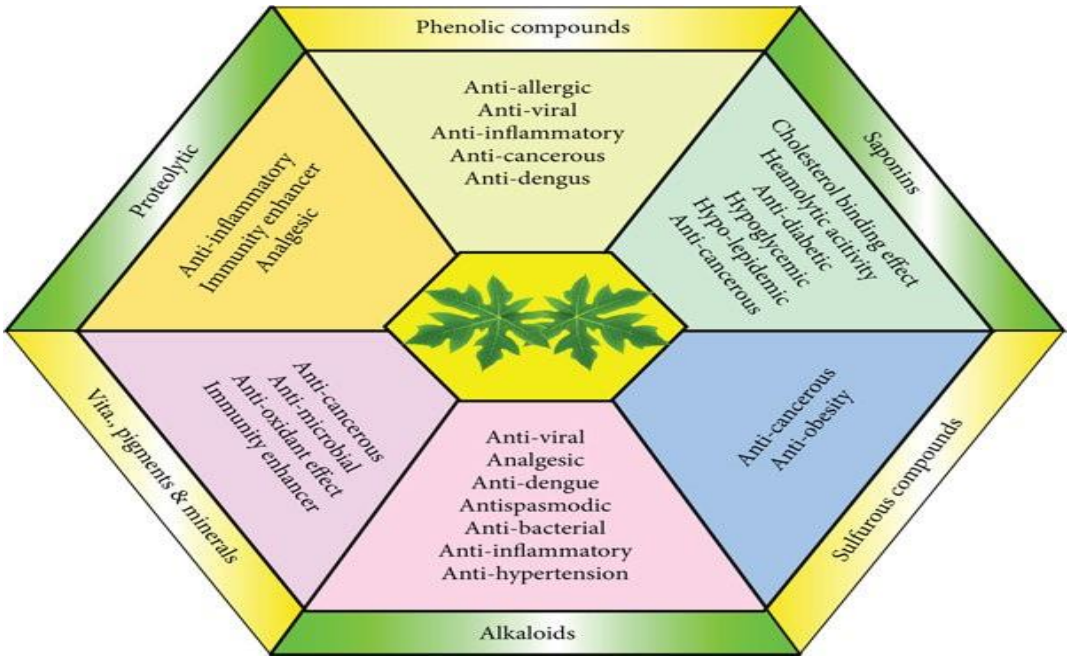

Figure 2: Phytochemical composition of Carica papaya

Mechanism of action of Carica papaya L. Leaves

Dengue virus assembly requires the NS2B-NS3 serine protease, which quercetin, a component of Carica papaya L. leaves, has been shown to inhibit. In addition, quercitin may inhibit ADP-induced platelet aggregation, as shown in a 1991 research by Tzeng et al. Myristic acid inhibits thrombin-induced platelet aggregation in rabbits, according to an in vitro study. According to research coumarin inhibits the dengue virus's DEN2 NS2B/NS3 protease. Shown that kaempferol, a papaya leaf component, successfully prevents thrombosis and platelet aggregation in Sprague Dawley rats and Imprinting Control Region (ICR) mice. To do this, we inhibit thrombin and FXa enzyme activity. In Wistar rats that had thrombocytopenia caused discovered that carpaine and alkaloid extract had an antithrombocytopenic effect. Additionally, research has shown that papain, which is extracted from papaya leaves, might hinder the immune system's capacity to destroy platelets (Saba, 2022).

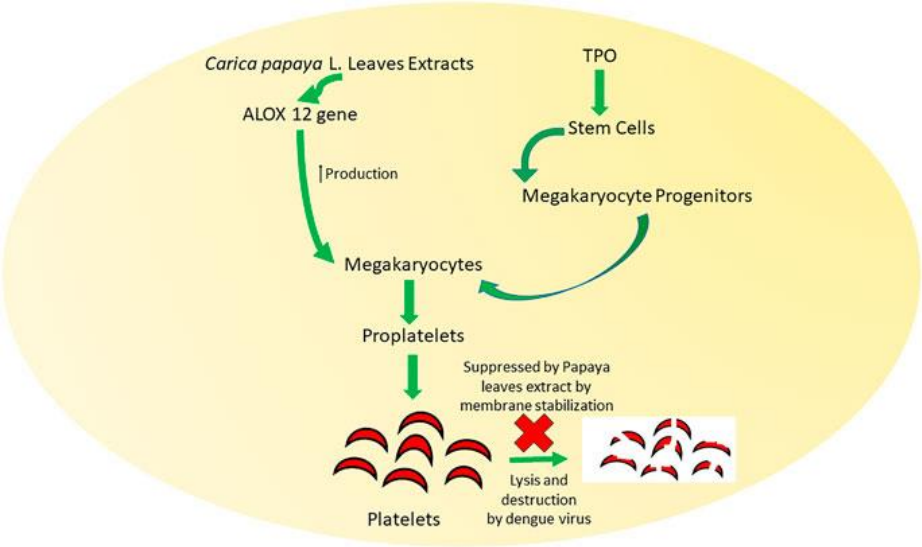

Figure 3: Mechanism of action of Carica papaya L. Leaves

Papaya Leaves to Improve Thrombocytopenia in Dengue

Giving dengue patients papaya leaves increased their platelet counts, according to many studies. The platelet count of the group that received 1,100 mg of papaya leaf extract three times daily after five days of therapy was considerably higher ($p < 0.01$) compared to the other 300 dengue patients from five different healthcare institutions. However, it has been some time since anybody has found out if the 1,100 mg tablet is effective when taken three times daily. Four hundred people with a history of dengue fever and thrombocytopenia were researched by scientists from the Associated Group of P.B.M. Hospitals in Bikaner and the Department of Medicine at S.P. Medical College. Of the total number of patients, 125 were female and 275 were male. For five consecutive days, the study participants received the standard supportive treatment regimen, which included antiemetic medication, paracetamol (an antipyretic), intravenous 0.9% normal saline, and a 500 mg capsule of papaya leaf extract daily. began treatment on day three; blood platelet count increased significantly (p 0.01), according to the study. Taken together, Carica papaya L. leaf extract (CPLE) and dengue fever-associated thrombocytopenia resulted in noticeably elevated platelet counts in 30 patients in 2015 ($p < 0.01$). Papaya leaf extract patients outperformed the control group in terms of both length of hospital stay and time to platelet count increase. A significantly shorter hospital stay of 5.42 days was seen in the extract group compared to the control group's 7.2 days. Not only that, but the treated group required fewer platelets transfusions than the control group. Out of the total 500 participants, 120 were female and 380 were male. Along with symptomatic and supportive therapy, the experimental group received 1,100 mg of papaya leaf extract (CPLE) three times daily for five days. the control group only got symptom-and support-focused treatment. The treatment group consisted of fifty percent of the 228 patients who were randomly assigned to have dengue hemorrhagic fever. For three days, this set of participants took a beverage made from papaya leaves orally. At 8-hour intervals, the individuals' blood parameters were assessed. the platelet count of the group that received the juice treatment dramatically increased ($p < 0.001$) (Sharma et al., 2020).

Patients with dengue-associated thrombocytopenia, including a 23-year-old male patient, saw an increase in platelet count after each injection of the extract. The platelet count increased dramatically from 28,000/microliter to 138,000/microliter throughout the five-day treatment period (Siddique et al., 2014). Another instance was a 45-year-old dengue patient who, for five consecutive days, was given 25 ml of an aqueous extract of papaya leaves. Reported that the platelet count rose from $55 \times 10^1/\mu L$ to $168 \times 10^2/\mu L$, the white blood cell count climbed from $3.7 \times 10^2/\mu L$ to $7.7 \times 10^2/\mu L$, and the neutrophil count rose from 46.0 to 78.3% (Ahmad Parray et al., 2018).

A systematic review and meta-analysis of clinical evidence about papaya leaf therapy for dengue fever was conducted Only nine studies out of eighty- six met the inclusion criteria. Papaya leaf extract demonstrated anti-thrombocytopenic effects, according to the analysis of seven selected studies. Based on three trials with 580 individuals, with evidence of poor quality, indicated that the extract was associated with a decrease in the length of

time patients spent in the hospital (mean difference of -1.98 days, 95% confidence range of -1.83 to -2.12). According to three trials with 129 participants and evidence of poor quality, the extract was also linked to a rise in average platelet count from the beginning to the fifth day of therapy (mean difference of 35.45, 95% confidence range of 23.74 to 47.15). In a separate meta-analysis and extensive interview with 377 participants, researchers found that papaya leaf extract was associated with higher platelet counts in all studies (MD = 20.27; 95% CI 6.21-34.73; p = 0.005). The researchers found that these extracts reduced the amount of time patients spent in the hospital (mean difference = 1.90; 95% confidence range 1.62-2.18; p < 0.00001) (T. T. T. Nguyen et al., 2013).

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192

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