Review Article

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NATURAL THERAPEUTICS: CARICA PAPAYA LEAVES AND THEIR IMPACT ON DENGUE FEVER – A REVIEW

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ABSTRACT

Every year during the monsoon, there is a high prevalence of dengue, an infectious disease spread by mosquitoes carrying the Aedes aegypti virus. The occurrence and rate of dengue fever (DF) have risen markedly as well as deaths from its complications in Bangladesh, Philippines, Thailand, Brazil, and India in recent years. Lately, dengue had spread like an epidemic throughout the South Asia. Even so, the Many individuals worldwide were impacted by this infection; there is no known treatment with synthetic medications that is targeted and efficient. Within this subcontinent, Malaysia could successfully prevent its occurrences and patient deaths by employing substitute medications therapy are made chiefly from Carica papaya Leaf, combined by appropriate maintenance with proper hospital stay. Papaya leaf juice extract's preparation have long been used in various traditional medicine for the treatment of DF and its complications, often saving the lives of patients. Despite the fact that traditional Papaya leaf juice and other preparations are used by healers and the general population for treating DF, this course of treatment is categorically rejected by the medical professionals providing care in hospitals in Bangladesh since they don't think papaya leaves are beneficial. Thus, the purpose of this work is to evaluate critically the scientific foundation. Preclinical and clinical evidence recommends the efficacy of leaf in curing of DF. The most common symptom for dengue is DF, which is frequently seen in affected patients. Additionally, infection and immunity impairment are related to patients with dengue. Various studies on Carica papaya Leaf are compiled in this review. Its capacity to address few dengue aspects.

KEYWORDS: Carica Papaya, Dengue, Viral Infection, Aedes Aegypti Virus, Thrombocytopenia, Dengue Treatment.

INTRODUCTION

Medicinal plants have been used for centuries to heal and prevent disease, and some of these uses have even been validated by science. Researchers from all around the world are interested in creating novel medications to treat infectious diseases because of potential of variety of medicinal plants, particularly those with antiviral properties (1).

As an example, the Carica papaya (C. papaya) is referred to as papaya in Hindi and is also known as "Papita". The papaya plant is indigenous to Central America, and its history in India is thought to date back to the 17th century. These days, it is grown all over the world (2). Malaysia ranks among the world's leading five exporters of papaya (3). C. papaya is a dicotyledonous, polygamous, and diploid plant belongs to the Caricaceae family (2).

Lactiferous plants, including Carica papaya, contain laticifers that produce latex. Papaya latex is rich in 4 cysteine proteinases: papain, chymopapain, glycyl endopeptidase, and caricain, with varying levels present in the fruit, leaves, and roots. Research has demonstrated that active compond of leaf enhances overall blood antioxidant activity and decrease lipid peroxidation. Antibacterial, antitumor, and immunomodulator properties have also been discovered (4).

The papaya leaves contain papain, chymopapain, cystatin, L-tocopherol, flavonoids, ascorbic acid, cyanogenic glucosides, and glucosinolates. This has led to their growing popularity as a potential treatment for dengue-induced thrombocytopenia and other viral infections. However, assessing the safety of these plant goods for human usage is challenging due to different preparations, complex phytochemical compositions, and the presence of extrinsic toxicants. Thus, safety attentions are crucial as effectiveness in this context (5).

In India Every year, over 100,000 new cases of DF are reported, and approximately 50% of the nation's population has antibodies specific to the dengue virus.

Dengue spreads and adjusts to a variety of factors that exert selection pressure, potentially resulting in the emergence of novel variants (6).

The National Center for Vector-Borne Disease Control claims that there were 233251 people affected in India in 2022 and 94198 cases till September 2023 with death troll 303 and 91 respectively (7).

climate, and viral characteristics are all predicted to contribute to an increase in the incidence and prevalence of dengue infection (13).

Thrombocytopenia development is explained as a clinical condition developed with dengue. It is caused by the inhibition of platelet production, the elimination of pre-existing platelets and the development of anti-

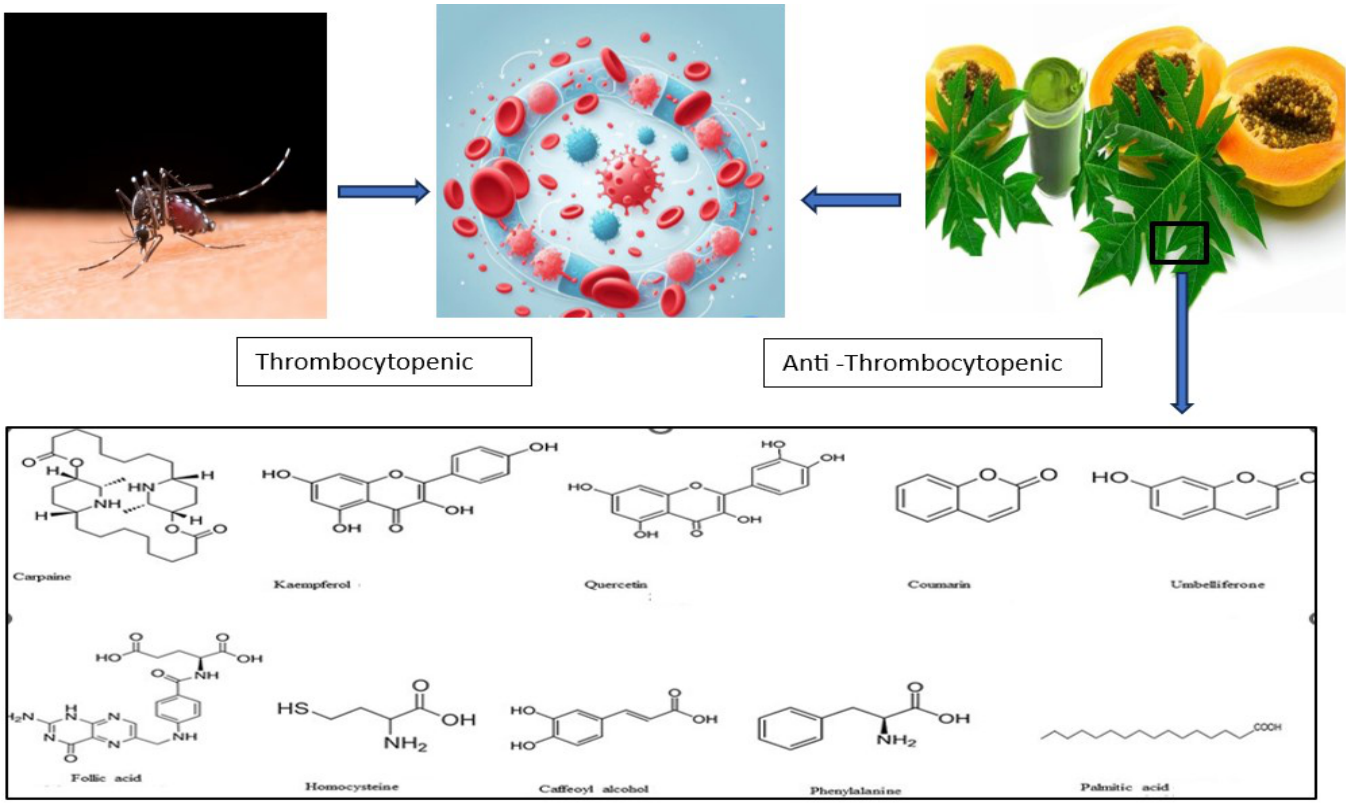

Fig. 1: Overview of C. papaya leaves

The viral disease dengue, which is spread by Aedes mosquitoes, Dengue virus belongs to Flaviviridae family. Dengue hemorrhagic fever (DHF), a severe manifestation of dengue, result from multiple infections by different dengue virus strains. The virus comprises three structural proteins: the core, envelope and membrane. Its virions are relatively smooth, measuring about 500 Å in diameter. Its genome is composed of plus-sense RNA. It has four serotypes, which are designated as Dengue Virus-1, 2, 3, 4 and each one stimulates the production of a distinct antigen (8). The virus consists of a single-stranded RNA (9).

Similar to DF and its variants are: Dengue haemorrhagic fever (DHF) and the Dengue shock syndrome (DSS) have appeared as global community health concerns (10-12).

Future increases in trade, socioeconomic status, travel,

platelet antibodies (14). Ojha et al. recently reported that the level of thrombocytopenia associated with dengue is determined by platelet activation (15).

Symptoms of DF include illness like headache, vomiting, and joints pain, muscles, and bones. On the other hand, internal bleeding, a sign of serious illness could be fatal, so the patient needs to get medical help right away. Variable-severity bleeding is primarily observed in cases of DHF, the more severe form of the disease. The pathophysiology of bleeding entails blood vessel plasma leakage. It appears to be caused by platelets being destroyed by complement system or bone marrow depression brought on by viral dengue infection, or both. Additionally, it's noted that platelets that manage to escape the damage end up nonfunctional or less efficient (16-18). Several studies have documented the treatment of dengue patients with papaya leaf extract (PLE) (19).

Carica papaya leaf on preventing thrombocytopenia

Degradation of Platelets

A major factor in the direct degradation of platelets occurs due to molecular similarities between host platelets, endothelial cells, blood clotting molecules, and viral proteins. Either directly through antibody cross-reactivity or indirectly by generating assembles with endothelial or leukemic cells (20). Platelet and macrophage activation may result from antibodies produced against these viral proteins and their cross-reactivity.

Additionally, IgM antibodies generated in response to NS1 viral proteins has the ability to cause cell lysis or peripheral platelet destruction. stopping the aggregation of platelets. These antibodies against IgM have been detected in large quantities in Dengue patients compared to people who have DF, DHF in addition to higher platelet lysis in DHF individuals (21).

Furthermore, dengue infection results in endothelial cells activation, resulting in the adhesion and activation of platelets also cause P-selectin to be expressed on their surfaces (22).

Leukocytes and activated platelets interact as a result of P-selectin expression. Additionally, aggregates of platelets and neutrophils and monocytes are formed from the P-selectin expression (23). The interaction between endothelial cells and platelets has demonstrated to cause thrombocytopenia (24). Development of this Cell aggregation causes thrombocytopenia. loss of life or a decrease in the quantity of platelets in circulation (25).

Function of Blood Coagulation Factors

During Dengue virus infection causes the activation of coagulation, fibrinolysis, and alterations in coagulation and fibrinolytic parameters, which in turn triggers disseminated intravascular coagulation (DIC) (26). Reduced platelet counts have been associated with the activities of prothrombin, factor VIII, fibrinogen, plasminogen, and antithrombin. In DHF patients with DIC, these relationships have also been shown to prolong prothrombin time (PT) and partial thromboplastin time (PTT) (27). The development of DIC can cause increased platelet activation, fibrin formation, and thrombus accumulation in bloodstream, which can result in organ failure. Additionally, DIC can cause hemorrhagic disturbances by depleting platelets and coagulation factors (28).

According to a study on C. papaya leaf extracts have demonstrated membrane-stabilizing abilities in invitro experiments. In the investigation, it was discovered that lower concentrations of C. papaya leaf extracts stopped hypotonicity and heat which prompt hemolysis of blood cells taken from both healthy as well as infected subjects. It's likely that the extracts can stabilize membranes and shield blood cells from damage brought on by stress. This characteristic could be helpful for dengue infection patients, because platelet lysis might be prevented by the leaf extracts (29).

Nevertheless, the dengue virus prevents megakaryocytopoiesis and also the differentiation of stem cells into megakaryocytes, which results in decrease in platelet production (26). It has been discovered that papaya's leaf extract induce expression of ALOX 12 gene by a factor of 15 or by 15 folds, this further enhances production of megakaryocytes and their transformation into platelets as the platelet production facilitated by the 12-HETE pathway (30-31). It has been discovered that quercetin extracted from Carica papaya L. work as NS2B-NS3 serine protease inhibitor that stands necessary formation for dengue virus (32-33).

Author's (year)	Nation	Subject	Intervention	Result	References
Pambhar V et al. (2022)	India	120 indoor DF patients having thrombocytopenia.	C. papaya leaf extract is given daily	Platelets increases gradually	(34)
Hettige S et al. (2020)	Sri Lanka	Affected person with dengue fever (16–60 years), including 76 subjects in the control group and 43 subjects in the intervention group, with fever lasting at least seven days but not DHF	Twice daily at 12-hour intervals Water is added to 20 milliliters of blended leaf juice until the day of discharge.	The length of fever, sickness, length of hospital stay, and likelihood of developing dengue hemorrhagic fever have all been considerably decreased by papaya leaf extracts.	(35)

Table 1: Papaya Leaf Treatment for Thrombocytopenia in Dengue Patients

Solanki SG et al.(2020)	India	100 dengue cases and 100 controls	Consumed for three days, three servings per day of blended leaf juice added to water (10 mL for adults, 5 mL for children).	Increase white blood cell Increase platelet count	(36)
Ismail IS et al.(2019)	Malaysia	Patients with dengue (≥18 yearsold, 214 responders) admitted between January 2014 and December 2015 were given standard care.	Consumed leaf juice for three days, at least once a day.	131 out of 214 respondents	(37)
Kasture et al. (2016)	India	Patients with DF or DHF I, II, aged 18 to 60, and a platelet count of 30-100 × 109 (150 per group)	Administer 100 mg of leaf extract orally, three times a day for five days.	Platelet increases Moderately	(38)
Srikanth et al. (2019)	India	145 interventions, 140 control Paediatric patients (1–12) years	Administer of leaf extract syrup three times daily: 275 mg for children under five years old, and 550 mg for those over five years old.	Rise in platelet numbers, Increase in red cell count, white cell count	(39)
Adarsh et al. (2017)	India	Patients with DF (50 each)	500 mg capsules of Carica papaya leaf juice three times a day for five days	On days three, four, and five, the intervention group's average platelet count was higher.	(40)
Naresh Kumar CVM et al. (2015)	India	Six female and three male denguepatients were treated with saline, antiemetics, and paracetamol as needed (only after receiving intervention treatment).	Three times per day at six-hour intervals 5 mL of freshly extracted, partially mature leaf extract was combined with sucrose and left it for six days.	Increase platelet count	(41)
Siddique O et al. (2014)	Pakistan	A 23-year-old male dengue patient received treatment with 250 mg of azithromycin once daily, acetaminophen every 8 hours, and unrestricted oral dehydration for the first five days.	Took 150 ml leaf juice mixed with water once a day for the next five days, alternating between sips of the intervention and commercial fruit juice.	Boost the number of platelets. increase in white blood cell counts. Elevate the hemoglobin content.	(42)

Cont. Table 1: Papaya Leaf Treatment for Thrombocytopenia in Dengue Patients

CONCLUSION

An individual can experience multiple DF infections due to the four different virus strains that cause the illness, but only one infection of a specific serotype results in lifelong resistance to that strain. The dengue infections possess variety of symptoms, such as rash, fever, and excruciating muscle pain, and headache in addition to clinical signs like numerous thrombocytopenia, organ failures, and an unusual decline in platelet count. Thrombocytopenia is linked to serious instances of dengue and the majority of deaths happen because of this infectious fever. The dengue virus either directly lowers the host's platelet count or indirectly through altering the bone marrow's environment, impacting various elements related to the production of platelets, reducing the amount, reducing the amount of circulating platelets and destroying and replicating into platelets, as various studies have indicated such phenomena. Although dengue has been known to spread like wildfire every year to many countries, killing many people, As of right now, there is no recognized treatment or preventative measure for the disease. However, it has been observed that papaya leaves enhance platelet include in vivo animal models studies and dengue patient investigations, apart from their potential larvicidal effects. Additionally, a number of cases have been reported that papaya leaves can impede the dengue virus's harmful effects on platelets and enhance the ALOX 12 gene's expression, which is in charge of raising platelet count. Furthermore, it has been discovered that papaya leaves are very rarely toxic and have a wide therapeutic range. Still, quite limited studies were conducted to examine the mechanisms underlying the beneficial effects of papaya leaves on platelet count health. When the precise processes are understood, papaya leaf extract could be improved for increased potency and medicinal formulations that may be developed with the same pathway as leaves of papaya plant. Furthermore, papaya leaves' anti-thrombocytopenic potential is not extremely well-understood because no randomization is present, clinical trial with substantial affected people accessible, the application and usage are ignored isn't given the go-ahead by the US FDA and other authorities. Therefore, more large-scale clinical trials involving patients are needed to investigate the potential medicinal , beneficial benefits of papaya leaves as a treatment for dengue to validate as well as verify its application for affected people with dengue. Moreover, authorized commercial papaya preparation leaves in a variety of dosage forms, including tablets, syrups, and extracts should be provided to dengue patients as an additional treatment, particularly in nations where dengue cases are common, in order to manage the intensity of this viral fever that has numerous clinical problems and is incurable. Medicine made of papaya leaves that are currently available for purchase are deficient in long-term/extensive toxicity study reports, therapeutic regimens, dose optimization, standardization, and appropriate regulatory authority approval for products. However, more investigation and oversight of papaya leaf-based products are necessary constraints. We carried out this analysis to clarify the scientific community regarding papaya's potential for therapeutic leaves so that additional research and analysis can be conducted to cite the preparation of papaya leaves as a potential therapeutic substance in the secure, efficient management of DF Consequently, in order to stop DF from taking many lives, particularly in developing nations. Thus, comprehensive clinical trials and additional research for the creation of a suitable papaya leaf action mechanism preparations in addition to verifying its reported and Certain bioactive compound(s) must be found in order for creation of various C. papaya leaves preparations so that leaves can be used for a secure and efficient cure for DF and to rescue thousands of lives globally.

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