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Unlocking the Potential of *Carica papaya* L.: A Comprehensive Review on Its Antiviral Activity and Therapeutic Role in Dengue Management

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Abstract

Dengue is a rapidly expanding global health problem for which no specific antiviral therapy is currently available, leaving disease management largely supportive and symptomatic. Severe thrombocytopenia is a major clinical concern in dengue infection, while prophylactic platelet transfusion can be costly and may not always be readily accessible. *Carica papaya* leaf juice (CPLJ) has been used off-label in the management of dengue fever and dengue haemorrhagic fever and has been reported to increase platelet counts in thrombocytopenic children and adults with minimal adverse effects. This review synthesizes evidence on the antiviral activity and therapeutic potential of CPLJ and *C. papaya* leaf extracts in the treatment and recovery of dengue-infected patients. It examines recent findings from *in vitro* and *in vivo* studies, documented clinical trials, traditional applications, and research on the phytochemicals, amino acids, and other bioactive constituents of *C. papaya* leaves. The reviewed evidence indicates that CPLJ and its extracts may inhibit dengue virus activity, increase platelet counts, and support recovery among patients with dengue fever and dengue haemorrhagic fever. These findings suggest that *C. papaya* leaves represent a promising natural source of bioactive

compounds for developing supportive or antiviral interventions against dengue virus infection. Nevertheless, further rigorous pharmacological and clinical investigations are required to establish standardized formulations, therapeutic dosages, mechanisms of action, safety profiles, and clinical efficacy.

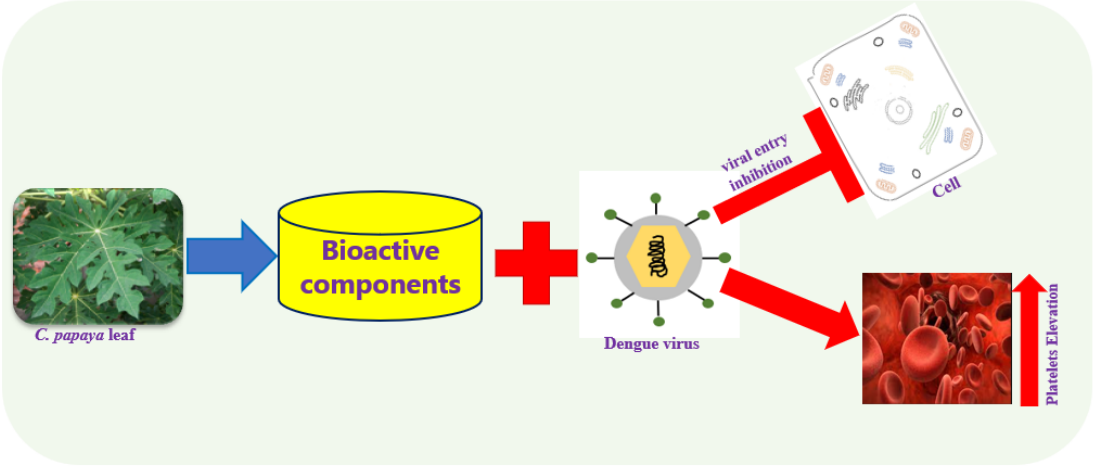
Keywords: Antiviral Activity; *Carica papaya*; Dengue Fever; Dengue Haemorrhagic Fever; Thrombocytopenia

Introduction

Dengue virus

DENV belongs to the Flaviviridae family and is a member of the genus Flavivirus (Kuno et al., 1998). DENV is a positive-stranded encapsulated RNA virus, which consists of three structural proteins: the nucleocapsid (C), membrane-associated (M), and enveloped (E) glycoproteins, as well as seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (Gupta et al., 2012). The structural proteins are essential for the formation of virus particles. Even though NS proteins cannot be detected in mature virions, they are required for DENV RNA replication through their interaction with intracellular membranes (Chambers et al., 1990). Dengue is a serious public health problem around the world (Bhatt et al., 2013). Dengue is responsible for a wide spectrum of clinical illnesses, ranging from mild, self-limiting forms of the disease associated with fever, condition, and other non-specific symptoms to more serious, potentially fatal cases, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Shresta et al., 2006). Dengue is transmitted by mosquitoes *Aedes aegypti* (L.) and *Aedes albopictus* (Skuse) (Rosen et al., 1983). There are four antigenically distinct, but closely related serotypes of the dengue virus (DENV-1, DENV-2, DENV-3 and DENV-4), that exhibits a 65 – 70 % sequence homology (Rico-Hesse, 1990). Among the four serotypes of DENV, DENV-2 is the most widespread (Takahashi et al., 2012). As compared with other serotypes, DENV serotypes one and three are closely correlated (Gaunt et al., 2001; Rico-Hesse, 1990) Dengue has been reported to be endemic in more than one hundred countries, with the Western Pacific, Southeast Asia, and America being the most largely affected regions. These regions continued to record higher cases of dengue disease (World Health Organization, 2009). America recorded about 1.2 million dengue cases in 2014, while Brazil

recorded around 600,000. According to analysis, there will be a two- to three-fold increase in America and Brazil in 2016 and 2017, respectively (Pan American Health Organization, 2018).



Significance of the study

Dengue fever is caused by four different serotypes (DEN 1–4). It has a wide range of symptoms, from a simple febrile illness to a catastrophic disease with organ dysfunction. Plasma leakage can cause shock and organ failure in more severe cases, as well as life-threatening bleeding. Dengue's unusual organ symptoms are becoming more common, forming the enlarged dengue syndrome (Rajapakse et al., 2018). Shock, intractable multi-organ failure, and uncontrollable bleeding are the most common causes of death in dengue fever. Excessive fluid therapy has also been linked to death in individuals with plasma leakage who develop pulmonary oedema during the recovery period. Despite years of research, specific treatment methods for dengue fever are still in their infancy. The use of corticosteroids (Rajapakse et al., 2014) or immunoglobulins (Rajapakse, 2009) as immunosuppressants has not been demonstrated to be beneficial. Several antiviral medications and other host immune modulators are still in clinical testing and will not be available anytime soon (Lee et al., 2017). There are various dengue vaccines in development, and a few have already been approved for use, but there is no clear evidence of efficacy across all age groups, and they do not confer immunity to all serotypes (Hadinegoro et al., 2015). Dengue fever is managed with a combination of fluid restriction, frequent monitoring, and supportive care. Due to a dearth of effective pharmacological interventions for dengue fever, alternative therapies such as natural and herbal remedies have grown in popularity. From the earliest times, plants have remarkably contributed to

the discovery and development of numerous emergent medicines in almost every therapeutic category (Atanasov et al., 2021). Recently, several nutraceuticals, phytomedicines, and herbal medicines have attracted researchers attention for wider investigations with the goal of discovery and development of drugs for treating infectious diseases and inflammatory disorders (Moklesur Rahman Sarker et al., 2015; Nesa et al., 2018; Taheri Rouhi et al., 2017), diabetes (Chen et al., 2018; Munira et al., 2020), neurological and adaptogenic complications (Das et al., 2017; Ibrahim et al., 2020), cancer (Shajib et al., 2018; Sheikh et al., 2017), and autoimmune disorders (Chen et al., 2018; Goto et al., 2010; Moklesur et al., 2014; Sarker, 2012; Sarker, 2021; Sarker & Gohda, 2013; Sarker et al., 2016), due to drug resistance problem, drug adverse effects and chronic toxicities in case of longer treatment. *C. papaya* is a medicinal plant of importance that has been investigated for its numerous traditional medicinal properties, pharmacological properties, and bioactive compounds. The leaves have been proven to effective in treating DENV fever and platelet elevation *in vitro* and *in vivo*, although the specific mechanism of action is still unclear. Few years back, *C. papaya* leaf extract (CPLE) has sparked interest in the treatment of dengue fever, especially on social media, and has been used off-label to treat the disease. While simple papaya leaf extract is routinely utilized, commercial formulations including papaya leaf extract are now available in a country like India. Hence this review provides an insightful and extensive discussion on CP utilisation, safety in research and clinical trials in the treatment of DENV. As per several reports CP has shown promising effect in elevating patients platelet counts and recovery from DENV fever.

***Carica papaya* L. Description**

Carica papaya L., identified as papaya is a member of the plant family Caricaceae. It is a tree-like herbaceous plant. It is often called 'pawpaw' in Australia, Nigeria and India and 'tree melon' in some other countries. The papaya is a herbaceous perennial 2–10 m in height. It usually has a single, semi-woody, hollow, erect stem, which terminates with a cluster of large, palmately lobed leaves with 25–100 cm long petioles and latex vessels in all tissues Fig. 1. Five-petalled, fleshy and slightly fragrant flowers borne in modified cymose inflorescences in the axils of leaves are primarily of three types: staminate (male), pistillate (female) and hermaphrodite or perfect (having both female and male organs) (Vijay et al., 2019). CPLE is prescribed as a tonic for the treatment of pyrexia, fever, diabetes, inflammation, gonorrhoea, syphilis, and for wound dressing (Mehdipour et al., 2006; Sadek, 2012). CP is cultivated in the tropical and subtropical lowland regions

including Australia, Hawaii, and South-East Asia. Indonesia, India, Nigeria, Mexico and Thailand, are among the largest producers of CP in the list of developing countries (Grumezescu & Holban, 2019; Reddy et al., 2009). CPL contains several biologically active compounds including caricain, chymopapain, glycine endopeptidase and papain. These bioactive compounds have been reported to improve acid pH and cause pepsin degradation (Huet et al., 2006). It also contains lipase that is bound to the insoluble aqueous components of papain. Additionally, CPLE have been reported for antiviral activity and haematological effects particularly for the treatment of dengue fever. It is also reported for antioxidant activity (Okoko & Ere, 2012), and improved red cell membrane stabilization (Ranasinghe et al., 2012).

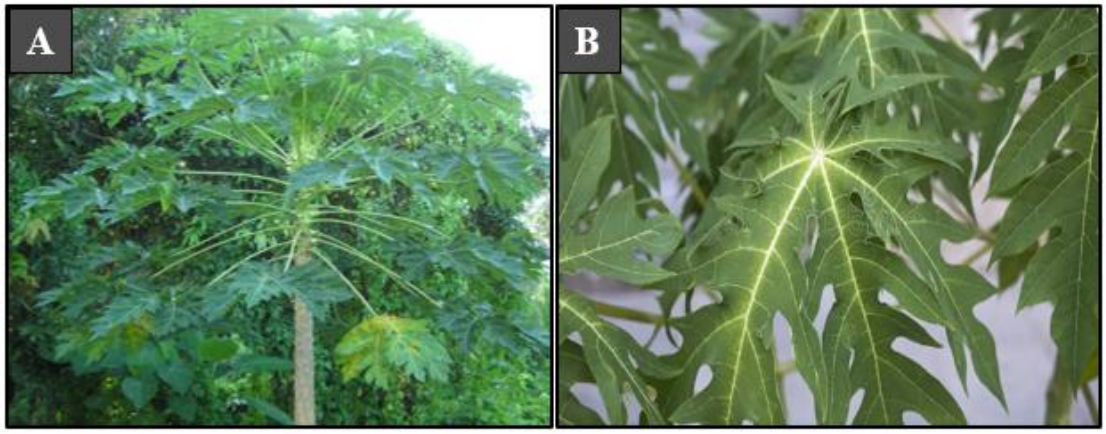


Fig. 1. *Carica papaya* L. Plant. (A) *Carica papaya* L. whole Plant (B) *Carica papaya* L. leaves

Bioactive components of *Carica papaya* Linn.

Different parts CP including the seeds, leaves, latex, bark, root, and fruits contain several bioactive compounds. The leaves contain alkaloid such as carpain that is reported to have cardiovascular effects, enzymes including cystatin, chymopapain and papain that are used to treat digestive disorders, use to improve acidic pH conditions and pepsin degradation (Huet et al., 2006). It contains lipase, a hydrolase that is tightly bound to the water-insoluble fraction of crude papain and is thus considered as a "naturally immobilized" biocatalyst. Additionally, CP parts expresses the white latex known to contain high amount of papain, a proteolytic enzyme reported for its significant role in the pathophysiology of several diseases, drug design, pharmaceutical preparations and industrially for meat tenderizer (Amri & Mamboya, 2012). CPL has ascorbic acid which ranged between 25.2–38.1 mg/100 g (Ojimelukwe et al., 2012). CPL ascorbic acid was reported to be three times higher than other locally consumed leaves such as pumpkin and

sweet potato leaves (United States Department of Agriculture, 2014). Other vitamins contain in CPL are riboflavin (0.1–0.2 mg/100 g), thiamine (0.4–0.5 mg/100 g), niacin (0.3–0.4 mg/100 g), β-carotene (0.3–0.4 IU/100g) and α-tocopherol (Ojimelukwe et al., 2012; Seigler et al., 2002). A report revealed an increased level of total flavonoids (myricetin, kaempferol and quercetin) to 126 mg/100g was found in young CPL (Miean & Mohamed, 2001). CPLE also contains saponins, tannins, nicotinic acid (Duke, 2022; Ikram et al., 2015; Seigler et al., 2002) and phenolic acids including caffeic acid (370.18 ± 6.27 µg/g), trans-ferulic acid (1110.86 ± 2.97 µg/g), para-coumaric acid and vanillic acid (Anjum et al., 2017; Seigler et al., 2002). Proposed chemical structures of some identified molecules from CPLE aqueous extract including ferulic acid, coumaric acid, myricetin, carpaine, vanillic acid, kaempferol, quercetin Fig. 2. CP seeds were reported to contain ascorbic acid (8.2–12.9 mg/100 g), β-carotene (0.03–0.07 IU/100g), thiamine (0.05–0.07 mg/100 g), riboflavin (0.03–0.07 mg/100 g), and niacin (0.2–0.3 mg/100 g)(Ojimelukwe et al., 2012). Niacin (17–21 mg/100 FW) and ascorbic acid (2.1–4.6 mg/100 FW) from celery, and coriander were higher compared to CP seed (Ojimelukwe et al., 2012; United States Department of Agriculture, 2014). CP seed contain about 6.35 g/100 g DW tannin (Marfo et al., 1986). The fruit has been reported to be good source of ascorbic acid and provitamin A with an average ranged between 60 and 40 mg/100 g and about 154 mg/100 g fresh weight(Gebhardt et al., 2002). The fruits contain high amount of β-carotene, β-cryptoxanthin, and lycopene (Gayosso-Garcia Sancho et al., 2011; Ikram et al., 2015; Wall, 2006). Higher concentration of lycopene was reported in red-fleshed cultivars than yellow-fleshed cultivars(De Souza et al., 2008; Schweiggert et al., 2012). CP peels, stem bark and roots extract were reported to contain an appreciable amount of some phytochemicals. Acetone, ethanol and aqueous extracts of CP peels contains tannins (41.29, 87.07, 21.28 mg/meq of tannic acid), flavonoids (247.70, 0.83, 15.48 meq/quercetin) and phenolic (4.22, 3.92, 4.84 GAE/g) (Lydia et al., 2016). CP peels was reported to contain caffeic (4.6–6.8 g/100 g DW) and ferulic acid (13.3–16.2 g/100 g DW) (Rivera-Pastrana et al., 2010). Qualitative phytochemical screening of CP stem bark extract showed the presence of quinones, saponins, phenolic compounds, coumarins, anthocyanins, and alkaloid (Mwelasi, 2015). CP roots extract were reported to contain some phytochemical constituents including terpenes, alkaloids, steroids, saponins, and tannins (Science et al., 2017).

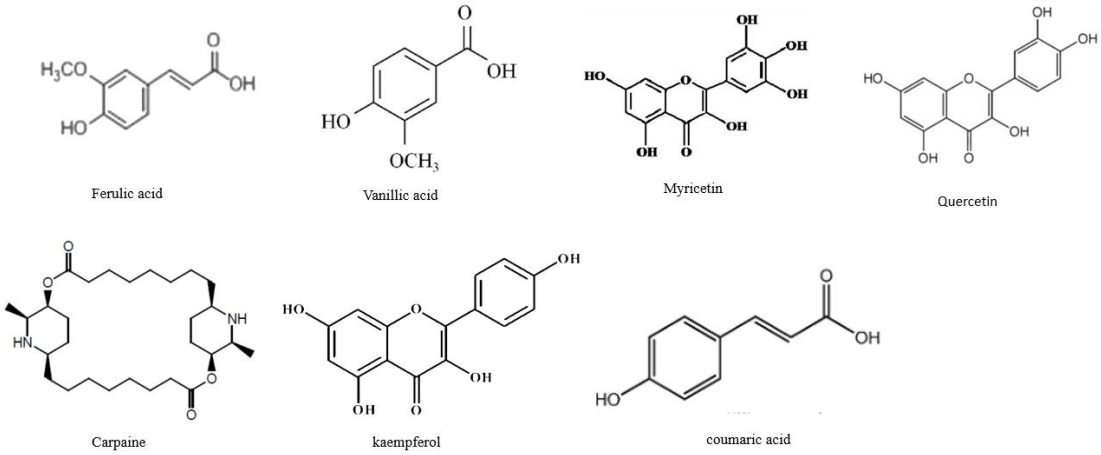


Fig. 2. Structures of ferulic acid, vanillic acid, myricetin, quercetin, carpaine, kaempferol and coumaric acid isolated compounds from CPLE

Traditional Medicinal Uses of *C. papaya* L.

CPL has been used in folk medicine for centuries for wound healing and in the treatment of blood disorders, jaundice, and malaria (Bhatt et al., 2013). It is used as a tonic for the treatment of fever, diabetes, pyrexia, syphilis, gonorrhoea, inflammation, and dressing of infected wounds (Henchal & Putnak, 1990; Mehdipour et al., 2006; Sadek, 2012). The juice or extract of CPL is widely used to treat fever caused by dengue, pyrexia, diabetes, gonorrhoea, syphilis, inflammation, and infected wounds (Bhowmik, 2013; Sharma et al., 2019). Additionally, CP leaves, fruit, flowers, seeds, stem bark, roots, and latex have a wide range of reputed medicinal uses traditionally. In Jamaica, the ripe fruits are used traditionally for topical ulcer dressing to promote desloughing, granulation, healing, and reducing odour in chronic skin ulcers (Dawkins et al., 2003). The green fruit is used for contraceptive purposes by traditional healers in India, Pakistan, and Sri Lanka. It is used for the treatment of malaria, jaundice, hypertension, diabetes mellitus, and gastrointestinal problems in Nigeria (Dhanamani et al., 2011). In Sri Lanka, Pakistan, Malaysia, and India the leaves are used to treat asthma, colic, fever, beriberi, malaria, and dengue fever (Doughari & Manzara, 2007; Edeoga & Eriata, 2001; Erasto et al., 2007). It is documented for the treatment of cancer in Vietnam and Australia (Kanatiwela de Silva et al., 2011). The latex is useful as styptic and debridement and applied for burns and scalds externally (Giordani et al., 1997). Eczema and psoriasis are treated with the latex in Laos, Cambodia, and Vietnam (Gomes et al., 2005).The seeds are known to reduce vermin, alleviate thirst, and ease pain (Gupta et al., 2011).

Methodology

The present review provides an in-depth literature search on the utilisation of CPLJ and CPLE for the management of DENV diseases to date. The review discussed the traditional medicinal uses, pharmacological properties, bioactive components, safety, mechanism of action, and antiviral activity *in vitro*, *in vivo,* and clinical trial. Methodologically, an extensive database retrieval from PubMed, BioMed Central, Scopus, ScienceDirect, and Google scholar was performed using keywords such as "*Carica papaya* leaf juice," "*Carica papaya* leaf extract," "antiviral activity" and "Dengue virus". Book chapters, reviews, scientific journals, and other digital documents were used to collect all scientific literature that provide complete science-based survey of the topic. Scrupulous insight into the antiviral property and platelet elevation of CPLJ and CPLE is salient. CPLJ and CPLE could be an alternative antiviral against DENV.

Results and Discussion

Several findings (*in vitro, in vivo,* and clinical trials) support claims that CPLJ and CPLE has been reported to increase platelet count in DENV patients. This review explicitly discussed outcomes of these investigations as categorised into different sub-headings below.

In vitro antiviral activity of *C. papaya* leaf juice and extract

A study conducted on erythrocyte membrane stabilization properties of CPLE (immature, partly matured, and matured leaves) revealed no significance ($p > 0.05$) difference on hemolysis inhibition level between heat induced hemolysis erythrocytes (healthy: 31.8–38.5%, dengue: 25.7–32.5%) compared to aspirin treated group (healthy: 45.9%, dengue: 43.6%). Hypotonicity-induced hemolysis erythrocytes assessment revealed no significant differences in inhibition level ($p > 0.05$) in the treated group (partly mature leaves) on both types of erythrocytes (healthy: 31.57%, dengue: 57.03%) in contrast to the indomethacin treated group (healthy: 47.67%, dengue: 65.35%). In this study, CPLE at all the maturity levels exhibited significant ($p>0.05$) reduction in heat induced hemolysis in contrast to the control. Additionally, the extracts showed more than 25% inhibition at concentration of 37.5 µg/ml (Ranasinghe et al., 2012). A study conducted to evaluate the inhibitory effects and efficacy of CPLJ on adenosine diphosphate-induced platelet aggregation on plasma rich platelets and plasma poor platelets from healthy volunteers and

dengue patients (Chinnappan et al., 2016). The study showed a significantly lower ($p < 0.05$) platelet aggregation in the intervention-treated healthy and dengue plasma rich platelets compared to the untreated group. A similar observation transpired for the intervention-treated healthy plasma rich platelets (pre-infected with intervention pre-treated dengue plasma poor platelets) compared to the untreated group. The findings showed that CPLE has the capability of DENV-specific neutralization effect on DENV-infected plasma that could have a protective role on platelets (Chinnappan et al., 2016). A study published in 2017 showed that phagocytic activity in intervention-treated peritoneal macrophages (62.5–1000 μg/mL) increased significantly ($p < 0.05$) by 72.91–189.58% (non-dose dependent manner) in contrast to the media control group. Interferon (IFN)-γ and interleukin (IL)-10 levels was significantly ($p < 0.05$) increased in a dose dependent manner against the media control group. The findings showed that phagocytic activity of rat peritoneal macrophages was heightened by the mature leaf concentrate (MLCC) of CP from Sri Lankan then triggered by a Th1 biased cytokine response (Jayasinghe et al., 2017). Conclusively, the use of CPLE *in vitro* has shown potential for DENV neutralization, erythrocyte membrane stabilization, efficient platelet elevation and protection.

In vivo antiviral activity of *C. papaya* leaf juice and extract

The use of animal model for establishing dengue infection *in vivo* that have similar infection pattern with human has been challenging in vaccine preclinical studies and in drug discovery studies (Sarathy et al., 2015). However, reliability of AG129 mouse which is deficient in interferon signalling has proven reliable as a model for preclinical dengue study (Johnson & Roehrig, 1999; Sarathy et al., 2015). Inoculated AG129 mouse with different strains of DENV produced preclinical signs like thrombocytopenia, viremia, splenomegaly, systemic cytokine responses and plasma leakage, similar to human infected with DENV (Milligan et al., 2017; Sarathy et al., 2015; Sarathy et al., 2018). The studies conducted in animal models are discussed below. Sharma et al. evaluated *C. papaya* aqueous leaf extract (CPALE) for its anti-dengue activity and its role in platelet augmentation. Their findings revealed that CPALE significantly decreased the expression of DENV envelope and NS1 proteins in THP-1 infected cells. This was characterised by significant decrease in intracellular viral load upon CPALE treatment indicating antiviral activity and a significant decline in erythrocyte impairment and hydrogen-peroxide-induced lipid peroxidation while thrombocytopenic experimental animals treated with the CPALE showed markable

increase in platelets numbers as well as increased IL-6 and thrombopoietin (TPO) levels. LC-MS analysis followed by integrated library research revealed fourteen abundant constituents in CPALE. Conclusively, the extract help in platelet augmentation and showed antiviral effect against DENV (Sharma et al., 2019). Anti-DENV activity of the extract in DENV-infected THP-1 cells was examined by immunoblotting and flow cytometry. Effect of the extract on erythrocyte damage was assayed using hemolytic and anti-hemolytic assays. Virus infected cells were investigated for IFN-α secretion. Plasma of thrombocytopenic experimental animals was for thrombopoietin (TPO) and IL-6 secretion.

Anjum et al. studied antithrombocytopenic and immunomodulatory effects of standardized *C. papaya* aqueous leaves extract (SCPLE) in cyclophosphamide (CP)-induced animal model. Oral administration of SCPLE (150 mg/kg) in induced-thrombocytopenic rats significant ($p< 0.01$) increased in thrombocytes (1014.83×10^3 cells/mm^3) compared to control group (CP-induced thrombocytopenia). DTH response (0.16 ± 0.004), and phagocytic index (63.15%) were increased against the control group. Minimal fibrosis was observed in spleen histology study. Twenty-four metabolites were identified using Ultra-Performance Liquid Chromatography–Mass Spectrometry (UPLC-qTOF/MS). These includes Hydroxyl-ferulic acid-hexoside, *β*-Sitosterol, Isochlorogenic acid, Quercetin-3-*O*-(20 hexosyl)-hexoside (Q-3-*O*-sophoroside), Quercetin-3-*O*-rutinoside (rutin), Sinapic acid-hexoside, Malic acid, Carpaine, 2-Keto-hexanoic acid, Vanillic acid, 3-Keto-n-caproic acid, Hydroxyl-ferulic acid-hexoside, Coumarylglucaric acid, p-Coumaric acid, Ferulic acid, Carpamic acid, Ferulic acid ethyl ester, trans-cinnamic acid, Kaempferol, Linoleic acid, Trans-2-Oleic acid, 3-Octadecylenic acid, Quercetin, 4-Octadecylenic acid. Six of the metabolites were identified as phenolics, two alkaloids and sixteen hydroxycinnamic acid derivatives. Quantitative High-performance thin-layer chromatography (HPTLC) of SCPLE revealed the presence of myricetin (280.16 ± 5.99 μg/g), caffeic acid (370.18 ± 6.27 μg/g), trans-ferulic acid (1110.86 ± 2.97 μg/g), and kaempferol (160.53 ± 2.48 μg/g) (Anjum et al., 2017). The presence of metabolites in this study is in accordance with previous reports for the presence bioactive compounds in the CP leaf, seed, stem bark and roots extracts (Duke, 2022; Ikram et al., 2015; Yogiraj et al., 2014). Mohd Abd Razak et al., recently evaluated freeze-dried *C. papaya* Leaf Juice (FCPLJ) for immunomodulatory activities on AG129 mice infected with clinical DENV-2 isolate (DMOF015). Infected AG129 mice were orally administered FCPLJ at 500 and 1000 mg/kg/day for three days. Their data revealed FCPLJ increased total white blood cell and neutrophil counts in

DENV-2 infected mice. Furthermore, FCPLJ treatment decreased the level of GM-CSF, GRO-alpha, IL-1 beta, IL-6, MCP-1 and MIP-1 beta in the plasma of DENV-2 infected mice. FCPLJ treatment also decreased intracellular IL-6 and viral RNA levels in the liver of infected mice (Ridzuan Mohd Abd Razak et al., 2021). Overall, these findings indicates that abundant metabolites evaluated in *C. papaya* could be the reason for the remarkable reduction in impaired erythrocytes, platelet enhancement and the observed antiviral activity.

C. papaya leaf juice (CPLJ) clinical trials

CPLJ has been reported to increase platelet count in thrombocytopenic patients. Some of the clinical trials conducted are discussed below. Thrombocytopenia is a known complication in dengue fever (DF) (Deen, 2009). Bone marrow suppression, distributed intravascular coagulation, platelets destruction and circulated intravascular coagulation in DF lead to thrombocytopenia. Acute thrombocytopenia is associated with complications such as DHF and DSS. Acute thrombocytopenia when untreated results in morbidity and mortality(Deen, 2009; Halstead, 1974). Earlier pilot study conducted by Hettige on 12 patients suspected to be dengue patients found an increase in the platelet counts and total white blood cell count within 24 hours of CPLJ administration. The patients received twice doses (5ml and 2.5 ml for adult and children respectively) of the juice at an interval of 8 hours while receiving standard symptomatic care (Hettige, 2008). The patients recovered without hospitalisation. CPLJ had effects on DF patients. Kumar in a case report involving two dengue patients observed dramatic rise in platelet count of the patients (4 hourly) administered with *C. papaya* leaf paste (CPLP). Platelet counts rose from 30,000 to 1,00,000 within 12 hours of treatment in the case of a 10-year-old male patient while a rise in platelet from 29,000 to 2,50,000 within two days of treatment was observed in a 14-year-old male patient (Kumar & Gupta, 2012). A case report of a 23-year-old man administered with CPLJ for five days revealed a significant increase in the thrombocyte count from 28000/microliter to 138000/microliter (Siddique et al., 2014). Their investigation is positive for CPLJ administration improving platelet counts in dengue patient. This finding is in support of an earlier case report by Ahmad et al. for a dramatic rise in the thrombocyte count from 55000/microliter to 168000/microliter of a 45-year-old man with DF administered with 25 mL CPLJ for five days twice daily (Ahmad et al., 2011). Yunita and Hanani conducted a randomized clinical trial of 80 DF patients. The Intervention group received *C. papaya* leaves extract capsules (CPLEC) while control group received standard

treatment. They observed a significant platelet count (p<0.05) increase, stability in the hematocrit within the normal range and reduced hospitalization (p<0.05) in DF patients compared to control. CPLEC reportedly increased the platelet count indicating its effectiveness in treating DF (Yunita et al., 2012). Similarly, a study conducted among five DF patients reported a rise in the platelet counts within 24 hours of drinking CPLJ. The platelet rise was between 8000 to 11000 since the increase varied among patients. The patients restated a significant improvement in their health within 24 hours of drinking CPLJ (Prakash Kala, 2012). Subenthiran et al. conducted an open labelled randomized controlled trial on 228 patients diagnosed with dengue fever (DF) and dengue haemorrhagic fever (DHF). About half the patients received CPLJ for 3 consecutive days whereas other patients received standard management representing the control group. Full blood count of patients was monitored 8 hours for 48 hours. There was significant (P < 0.001) increase in the mean platelet count in the group that received CPLJ compared to control group after 40 and 48 hours. ALOX 12 (FC = 15.00) and PTAFR (FC = 13.42) genes were highly expressed in intervention group with CPLJ against control (Subenthiran et al., 2013). CPLJ significantly increased platelet counts in DF and DHF patients. Conclusively, the findings support claims that CPLJ induced rapid platelets production and arrest bleeding tendencies. CPLJ have therapeutic potential and membrane stabilizing capability (Ranasinghe et al., 2012). Kasture et al. conducted a multi-centric, double blind, placebo controlled randomized prospective study on 300 patients for the evaluation of CPLE efficacy and safety as experiential therapy for thrombocytopenia associated DF. The intervention group was given CPLE tablet three time for five days followed by monitoring platelet counts. CPLE significantly increase ($p< 0.01$) platelet count of dengue fever patients in the intervention group compared to control group. Limited adverse effects such as nausea and vomiting were observed in both groups. The findings confirmed CPLE rises platelet counts and is safe for treatment with very few side effects (Kasture et al., 2016). A clinical trial by Gadhwal et al. was conducted to determine the effect of *C. papaya* leaf extract capsule (CPLEC) on platelet count in dengue patients with thrombocytopenia. The intervention group were given 500 mg of CPLEC once daily and supportive treatment for seven days. There was significant ($p < 0.01$) increases in intervention group at day 3, 4 and 5 compared to control group that received only supportive treatment. Conclusively, CPLEC increased the platelet count in dengue fever, without side effect and thwarted thrombocytopenia complication supporting the fact that it can be used in treating in

dengue fever with thrombocytopenia patients (Gadhwal et al., 2016). Sathyapalan et al. recently evaluated *C. papaya* leaf extract (CPLE) for its efficacy and safety in the management of severe thrombocytopenia (≤ 30,000/μL) in dengue patients. A significant increase in platelet counts of the treatment group (those who received CPLE) was observed compared to the control (those who received placebo) day 3 after administration of CPLE. Additionally fewer patients received platelet transfusion in the treatment group compared to the control group. CPLE was safer and tolerated with no significant decrease in mean hospitalization days. Further, the study revealed CPLE efficacy in increasing platelet counts in severe thrombocytopenia in dengue infections. Plasma cytokine profile revealed less increase in TNFα and IFNγ levels in treatment group compared to the control. IL-6 levels were higher in treatment group at day 3 compared to placebo. Faster clearance kinetics of viral NS1 antigenemia was recorded in the treatment group compared to the control group (Sathyapalan et al., 2020). The findings revealed a possible immunomodulatory and antiviral activity been attributed to CPLE treatment. While there are several studies on *C. papaya* leaf extract (CPLE) effect on adult with dengue fever, dengue haemorrhagic fever, Srikanth et al. studied CPLE effect in the paediatric category between ages 1- and 12-years having thrombocytopenia associated with DF and dengue haemorrhagic fever (DHF). A total of 285 patients were involved in the study to evaluate the effectiveness of CPLE. A significant increase ($p < 0.05$) was observed in CPLE treated group compared to control group. This was observed from day 3-5 of CPLE treatment. CPLE was found well tolerated however two children complained of nausea in the treated group (Srikanth et al., 2019). Overall, their findings revealed significant effect in increasing platelet count and safe for use in children. Until now only one study has reported CPLJ use in neonatal thrombocytopenia. Although, the authors reported that CPLEJ was effective in improving platelet count in neonatal patient with persistent thrombocytopenia, there is no past evidence to support the findings. Its usage is still in the experimental phase. It should be considered in refractory cases only after exhaustive team meeting and extensive discussion with the new-born family (Pandita et al., 2019). It is no doubt from the clinical trial studies that CPLEC or CPLEJ could have the key for unlocking the need antiviral for combating DF and DHF since it has shown to effectively increase platelet count, total white blood cell count, stabilizes hematocrit and treatment of DF and DHF.

Probable mechanism of CPLJ/CPLE in improve thrombocytopenia

Various mechanisms Fig. 3. have been proposed to explicate the potential of CPLJ/CPLE to elevating platelet count. Quercetin, a flavonoid isolated from CPL has been reported to exert antiviral activity against DENV2 by blocking the viral assembly as a mechanism. This was demonstrated in a study where CPL was reportedly inhibits NS2B-NS3 protease and prevent viral assembly (Senthilvel et al., 2013). Additionally, quercetin has also been reported to target TNF, NF-ϰB, IL1β, IL6, CCL-2 and CXCL8 as likely mechanisms for the treatment of SARS-CoV-2 and DENV co-infection (Zheng et al., 2021). Quercetin could scavenge free radicals, stimulate the immune system, and reduce proinflammatory cytokines. It acts as an antiviral, anti-allergy, and inhibiting histamine release (Mlcek et al., 2016). Quercetin inhibits the secretion of TNFα which avoids triggering other pathways like NF-ϰB (Li et al., 2016), afterward the disruption affects IL1β, TNFα and IL6 production (Gardi et al., 2015). Quercetin further significantly decreases CCL-2 expression, a critical chemokine regulating monocytes and macrophages migration and infiltration during inflammation process (Haleagrahara et al., 2018; Iwamoto et al., 2008). Quercetin impedes CXCL8 inducing the neutrophils chemoattraction in a concentration-dependent manner and decreases the activity and recruitment of RELA (Cheng et al., 2019; Ruiz et al., 2007). Furthermore, flavonoids isolated from CPL have been reported to inhibit protease involved in viral assembly (Charan et al., 2016). A report showed that DENV-2 can directly bind to platelets in order to destroy them or cause their indirect peripheral destruction via promoting anti-platelet production (Barros & de-Oliveira-Pinto, 2018). CPLE has also been reported to cause membrane stabilization thereby facilitating the reversal of peripheral platelet destruction by DENV. A study documented on the membrane stabilizing properties of CPLE *in vitro*. CPLE inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from healthy individuals and individuals infected with DENV. CPLE has membrane-stabilizing activity and could protect blood cells against stress-induced destruction. The effect was observed at lower concentrations of CPLE. The effect could be beneficial in DENV infected patients where CPLE could possibly thwart platelet lysis. The property could be attributed to the presence of flavonoids and phenolic compounds in the leaves (Ranasinghe et al., 2012). DENV also induces decrease in proliferation of platelets through obstructing megakaryocytopoiesis or preventing differentiation of stem cells into megakaryocyte precursor cells (Barros & de-Oliveira-Pinto, 2018). CPLE has also been reported to

increase ALOX 12 gene expression Fig. 4 by 15-fold, which additionally increases production of megakaryocyte, its conversion into platelets and the production of platelets by the 12-HETE mediated pathway (McRedmond et al., 2004; Sundarmurthy et al., 2017).

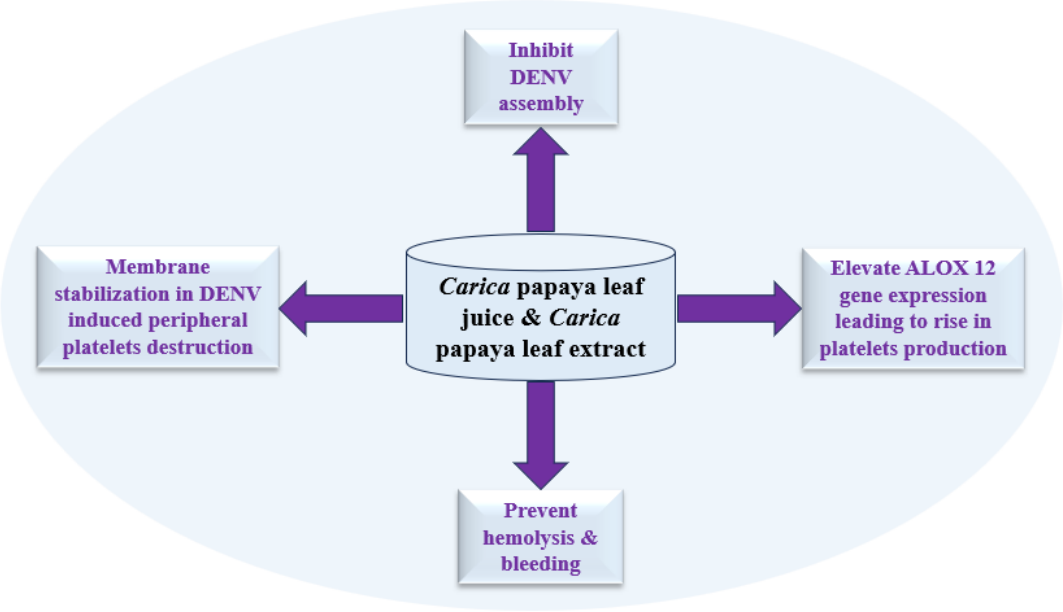


Fig. 3 Probable target of CPLJ/CPLE in inhibiting DENV and elevating platelet count in thrombocytopenia

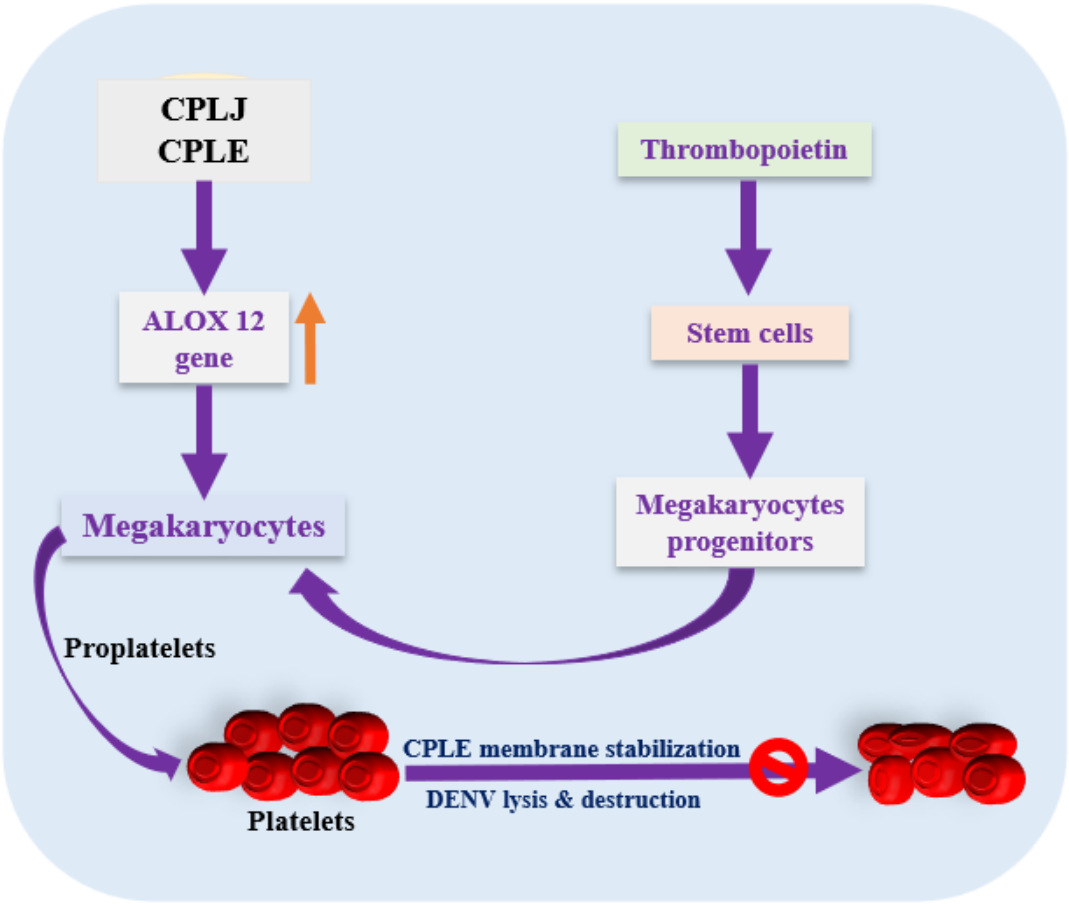


Fig. 4. Mechanisms of CPLJ/CPLE enhancing platelet count by ALOX 12 gene production and membrane stabilization. CPLJ/CPLE stimulates megakaryocytes and megakaryocyte progenitors' formation which in turn induces the formation of proplatelets. CPLJ/CPLE inhibits lysis and destruction proplatelets

C. papaya leaf juice safety studies and evaluation report

Several studies have shown that CPLE is safe and has no toxic effect. CPLE has been employ for the treatment of DF and DHF. Acute toxicity study by Halim et al. on Sprague Dawley rats administered with CPLE at fixed doses of 5, 50, 300 and 2000 mg/kg BW for sighting study showed no sign of toxicity or deaths. Based on this observation, a higher dose of 2000 mg/kg BW was further administered for 14 days. No significant changes were observed in the body weight, food and water consumption of the rats, there was no mortality. The relative weights of the internal organs were normal; there was no significant difference between the haematological and biochemical parameters in the treatment group compared to the control group. The findings revealed that CPLE

administered in this study shows no toxicity (Zaleha Halim et al., 2011). A study evaluated the acute toxicity of *C. papaya* methanol leaf extract (CPMLE) in male Wistar rats. The rats were administered with 1500 mg/kg of CPMLE for 28 days. The results showed no mortalities at the dose of 1500 mg/kg. The rats exhibited reduced aspartate aminotransferase activity, enhanced blood urea, nitrogen levels, slight hyperaemia in heart and moderate hepatic degeneration during histological examination (Chinaka & Nwosu, 2013). A study was conducted to determine the possible acute and chronic toxicity CPLE in Wister strain white mice. Acute toxicity test was evaluated after 24 hours of mice administered with CPLE while sub-chronic toxicity test was determined by computation for the lethal dose value (LD_{50}). The mice were administered CPLE doses of 200 mg, 400 mg, 800 mg, 1600 mg, and 3200 mg/kg. The animals did not die and no behavioural changes was observed during acute toxicity test. The treatment was continued for another 60 days for sub-chronic toxicity test and SGOT and SGPT levels in blood sample was assessed. None of the mice died after 60 days, treatment. The average SGOT and SGPT level in all doses were in ranges of 111-327 U/L and 51-267 U/L respectively compared to the control group with average SGOT level of 45 U/L and SGPT level of 35 U/L. Kruskal–Wallis statistical test revealed that SGOT level was significant while SGPT level was insignificant. The result revealed no toxicity 'in mice was observed upon CPLE administration (Peristiowati & Puspitasari, 2017). Aqueous CPLE was evaluated in pregnant Wistar rats on gestation at dose of 60 or 120 mg/kg for 12–18 days. There were deformities in the morphometry of foetuses and a 100% resorption was observed in rats treated with 120 mg/kg of the extract (Ekong et al., 2011). Another study conducted showed that male Wistar rats administered with 500 mg/kg bw CPLE orally for 21 days showed in significant decreases in the mean sperm count, motility, viability, and serum testosterone concentration in the treatment group compared to control group (Olanrewaju et al., 2010). Recently, CPLE was evaluated for its cytotoxicity activity against T47D, a breast cancer cell line, using an MTT assay. The result revealed that CPLE hexane and aqueous fraction at 800 mg/ml concentration did not inhibit T47D cells growth, although there was decrease in T47D cells viability with IC_{50} values of 2231.30, 557.33, and 2112.81 µg/mL for CPLE hexane, ethyl acetate, and aqueous fractions. Earlier, CPLE was mixed with 96% ethanol followed by partitioning into hexane, ethyl acetate, and aqueous fractions. The high IC_{50} values of CPLE fractions revealed no possible cytotoxicity in T47D cells (Yuliani & Syahdeni, 2020). Lately, a systematic scoping review on CPLE

biological safety revealed that CPL ingestion (as juice and standardised aqueous extract) was well tolerated by adult human beings for duration of about less than five days. A randomised controlled clinical trial reported safe consumption of CPL standardised aqueous extract in children aged 1-12 years. Common side effects of CPL juice and standardised aqueous extract was minor gastrointestinal disturbance. Studies on animals have raised concerns about hepatotoxicity and reproductive toxicity with long-term use. There were adverse herb-drug interactions with metformin, glimepiride, digoxin, ciprofloxacin, and artemisinin. Lastly, consuming papaya leaves is generally safe for adults for short periods, though pregnant women and those with liver impairment should be cautious. Additionally, herb-drug interactions may occur with oral hypoglycaemic agents, p-glycoprotein substrates, and antibiotics with chelating properties (Dharmarathna et al., 2013).

Conclusion

CPLJ and CPLE is rich in several bioactive compounds that have been reported in this article demonstrating several medicinal properties. The juice and extract have been reported to significantly elevate lowered platelet count in DENV patients. Numerous clinical trials conducted so far supported the facts the juice significantly increased platelet counts in DF and DHF patients. As per several documentation the juice is reportedly safe for consumption with minimal side effect. There is need for more clinical trials with clear methodology on the use of CPLJ for it to gain acceptance in general medicine. Apart from the above presumed mechanisms, further studies should be conducted to evaluate the lessening property of the juice in DF and DHF.

Abbreviations

DENV: Dengue virus, **DF**: Dengue fever, **DHF:** Dengue haemorrhagic fever, **DSS**: Dengue shock syndrome, **CP**: *Carica papaya*, **CPLE**: *Carica papaya* leaves extract, **CPLJ**: *Carica papaya* leaf juice, **SCPLE**: Standardized *C. papaya* aqueous leaves extract, **LC_{50}**: Lethal concentration, **LD_{50}**: Lethal dose**, SGOT**: serum glutamic-oxaloacetic transaminase, **SGPT**: **Serum Glutamic Pyruvic Transaminase, AMPs**: Aromatic and medicinal plants, **CP**: Cyclophosphamide, **TPO**: Thrombopoietin, **HPTLC**: High-performance thin-layer chromatography, **LPS**: Lipopolysaccharide, **NO**: Nitric oxide, **IPP**: isopentenyl pyrophosphate, **SCD**: Sickle cell disease, **RBCs**: Red blood cells, **HBB**:

Hemoglobin beta gene, **HbS**: hemoglobin S., **UPLC-qTOF/MS:** Ultra-Performance Liquid Chromatography–Mass Spectrometry, **IFN:** Interferon, **IL:** interleukin, **GM-CSF:** granulocyte-macrophage colony-stimulating factor, **GRO-alpha:** growth-regulated protein (GRO)-alpha, **IL-1 beta:** interleukin-1 beta, **IL-6:** interleukin-6, **MCP-1:** monocyte chemoattractant protein-1, **MIP-1 beta:** macrophage inflammatory protein-1 beta.

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Conflict of Interest

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