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# Pharmacological updates of *Carica papaya* L. in the management of dengue

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Dengue is an acute febrile viral infection affecting several tropical inhabitants. *Carica papaya* L. is a plant of choice for symptomatic treatment of dengue in several countries. In India, the plant, particularly the leaf extract is very popular in the management of Post Graduate dengue. Presently, several studies have been carried out on this plant to investigate its role in the management of dengue. This pharmacological review discusses the diversified role of *C. papaya*, from the prevention to the management of dengue.

**Keywords:** *Carica papaya* L., Dengue, Dengue hemorrhagic fever, DENV, Platelet count.
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## Introduction

Dengue is an acute febrile viral infection caused by RNA virus of family Flaviviridae and transmitted by the female *Aedes ageypti* L. mosquito. A severe form of dengue fever, also called dengue hemorrhagic fever, can cause severe bleeding, a sudden drop in blood pressure (shock) and death. According to Mayo Clinic, the major symptoms of dengue are fever as high as 106 $^{o}$F (41 $^{o}$C), headache, and pain in the muscles, bones, joints and behind the eyes. Sometimes widespread rash associated with nausea and vomiting may arise as secondary symptoms of dengue. Thrombocytopenia, coagulopathy, vasculopathy are hematological abnormalities related to platelet and endothelial dysfunction generally observed in severe dengue. Thrombocytopenia is one of the criteria in the WHO guidelines, as a potential indicator of clinical severity[1,2]. Dengue cases have been reported to undergo platelet activation and thrombocytopenia by an unknown or poorly understood mechanism. Several hypotheses have been suggested to elucidate the mechanism involved. An *in vitro* study conducted by Funahara *et al.* suggests change in platelet count by dengue virus-platelet interaction and the participation of anti-dengue virus antibody to such changes[3]. The study revealed that the antigen of dengue virus gets attached to human platelets without immune-mediated reaction. A decrease in platelet count was more markedly demonstrated by the binding of anti-dengue virus antibody on the dengue virus antigen associated with platelets than by the binding of the antigen-antibody complex on platelets. Thrombocytopenia may be due to modulation of endothelial cell by the infection of dengue virus to the cell[3]. Another study showed that dengue virus could directly or indirectly affect bone marrow progenitor cells by inhibiting their function[4].

In adults, a platelet count of $5\times10^{9}$/L and packed cell volume >50 are significantly associated with bleeding manifestations. However, a study on dengue patients revealed that there is no correlation between clinical bleeding and platelet count[5]. The study found that 81 non bleeding patients had counts of less than $20\times10^{9}$/L. In contrast, another study[6] suggested that bleeding occurred more often in patients with platelet counts below $20\times10^{9}$/L.

Platelet transfusions to patients are a standard clinical guideline for the patients who develop a serious hemorrhagic condition or have very low platelet counts. The efficacy of platelet transfusions is controversial. In a study carried out on paediatric patients with dengue fever associated with thrombocytopenia, there was no significant difference in hemorrhage between patients who received preventive transfusions as compared to those who did not receive transfusion[7]. Patients receiving transfusion had a higher rate of pulmonary oedema and greater

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length of hospitalization. Platelet transfusion did not prevent the development of severe bleeding or shorten the time of bleeding and obviously associated with significant side effects[8]. Thus, there is need to deal with the low platelet count in severe dengue and to choose measures or approach to control thrombocytopenia to curb the morbidity associated with dengue[9].

*Carica papaya* L. has recently been in the news for the last few years due to its potential in controlling dengue and dengue related complexities. This review will focus on the recent pharmacological developments of *C. papaya* and discuss methodically an all-round activity of *C. papaya* from prevention of dengue virus and vector to controlling symptoms and complexities of dengue as a disease. The review will be of use to researchers in the field of tropical diseases and vector borne diseases, to develop more comprehensive strategy in the management of dengue by plant and plant derived medicines.

## *C. papaya* L. and dengue associated thrombocytopenia

*C. papaya* L. is a plant, which has a hidden potential to combat the complications of dengue. It is a species within the genus *Carica*, having palm-like segmented leaves, yellow flowers, and large black seeded yellow to orange fruits. *C. papaya* fruit juice and leaves extracts have demonstrated anti-cancer[10], anti-oxidative[11], anti-inflammatory[12], and anti-bacterial[13] properties. In addition, nephro-protective[14], hepato-protective activity against toxins[15], hypoglycemic and hypolipidemic effects[16], and anti-sickling properties in sickle cell disease[17] have also been reported.

The promising effect of *C. papya* is highlighted frequently in the treatment regimen of dengue in leading dailies. But the treatment of dengue with *C. papaya* has not been officially announced as a standard treatment in the AYUSH treatment guidelines for dengue in India. This may be due to scattered clinical report and absence of proper validation of the dosage specimen of *C. papaya* used in the treatment of dengue haemorrhagic fever.

In ayurvedic literature, there is not a single reference of *C. papaya* to be used in the treatment of dengue. But it has been used by ayurvedic practitioners in several sections in India[18]. In general, for a drug to be formally accepted as an established medicine, adequate preclinical and clinical research is required. The active principles are expected to be screened, which may be responsible for increment in platelet count (if any). There are several studies including pre-clinical and clinical research on the therapeutic effects of papaya leaves in the management of dengue, which are described subsequently in this article.

## Therapeutic effect of *C. papaya*

The literature search was carried out by the authors using PubMed, Google scholar, and the Scopus database. The keywords used for the search included dengue treatment, dengue ayurvedic treatment, dengue papaya leaf, dengue *C. papaya,* etc. A search in PubMed was conducted from 2002 to 2016. The pharmacological review in this paper is broadly classified into two sections. First section, 'Indirect action' of the plant, highlighting the researches on *C. papaya* in controlling the complications of dengue like hemorrhagic fever and decreased platelet count. The section is further divided into clinical study, preclinical *in vivo* and *in vitro* study. The second section is 'Direct action' of the plant, which discusses the role of *C. papaya* in controlling the vector and the virus. The section is further divided into larvicidal activity and antiviral activity.

### Indirect therapeutic action

#### *Clinical/case study*

A recent multi-centric, double blind, placebo controlled, randomized, prospective study conducted in 300 patients to evaluate the efficacy and safety of *C. papaya* leaf extract for thrombocytopenia associated with dengue fever indicated that leaf extracts of the plant had significant increase in the platelet count in dengue patients ($p<0.01$) as compared to the controlled group[19].

In another recent study, *C. papaya* leaf extract in capsule form exhibited positive effect in the treatment of dengue mediated thrombocytopenia. The study group was given *C. papaya* leaf extract capsule of 500 mg once daily with routine supportive treatment for five consecutive days, whereas the controls were given only the routine supportive treatment. On third day, platelet count of study group was observed to be significantly higher than the control group (82.96±16.72, 66.45±17.36 thousands, respectively, $p<0.01$). On fourth and fifth day also, platelet count of study group (122.43±19.36 and 112.47±17.49 thousands, respectively) was significantly higher than the control group (88.75±21.65 and 102.59±19.35 thousands) ($p<0.01$). Average platelet transfusion requirement (0.685 units per patient) in the study group was significantly less than control group (1.19 units per patient) ($p<0.01$)[20].

In a recent study on 80 patients in a tertiary healthcare centre in central India, the intervention group received two capsules of *C. papaya* leaves extract thrice daily. The results indicated that the *C. papaya* leaf juice was beneficial in elevating the platelet count ($p<0.05$) in dengue patients and maintaining stability of hematocrit in the normal value, in patients receiving *C. papaya* leaves extract capsules[21].

In another study, a 45 year old patient suffering from dengue fever was administered about 25 mL of aqueous extract of *C. papaya* leaves twice daily for five consecutive days[22]. It was observed that the platelet count increased from $55\times10^3$ to $168\times10^3$ /µL, WBC increased from $3.7\times10^3$ to $7.7\times10^3$ /µL and neutrophiles increased from 46.0 to 78.3 %.

In another study, juice of *C. papaya* leaves was administered to 228 patients with dengue and dengue hemorrhagic fever for three consecutive days. Gene expression studies were conducted on the arachidonate 12-lipoxygenase gene and platelet activating factor receptor genes. The results revealed that there was a significant increase in mean platelet count observed in the intervention group but not in the control group and it was significantly higher in the intervention group than the control group after 40 and 48 h of admission[23].

A case study, described the rapid recovery of platelet counts in two children suffering from dengue[24]. These cases were proved to be positive for dengue by the demonstration of the dengue antigen in the serum. Patients, aged 10 and 14 years, were administered papaya leaves paste every 4 h. A dramatic increase in platelet counts was observed. In one case, within 12 h of initiating treatment, the count increased to 1,00,000. In the second case, within 2 days, it increased to 2,50,000.

A study conducted in Indonesia, used capsules containing 70 % ethanol extract of *C. papaya* leaves. Patients included in the study had high continuous fever for 2-7 days, thrombocyte count of <150,000 /µL, and hematocrit of 20 % or more. The patients were divided into two groups: one group received capsules in addition to standard treatment, whereas the other group received only the standard treatment. The study found that platelets in patients with dengue increased faster in those who took capsule of the leaf extract along with standard treatment[25].

***Preclinical in vivo animal study***

Sathasivam *et al*. studied the effect of powdered *C. papaya* leaves suspension in palm oil on thrombocyte counts in mice at the dose of 15 mg of powdered leaves per kg body weight[26]. Thrombocyte counts before and after dosing at specific hour schedule revealed significantly higher mean count at 1, 2, 4, 8, 10, and 12 h after dosing as compared to the mean count at 0 h. The results support that the *C. Papaya* may be responsible for the production of thrombocytes.

***Preclinical in vitro biological membrane stability study***

A recent *in vitro* study revealed that the leaf extracts of *C. papaya* possess a dengue-specific neutralizing effect on dengue viral-infected plasma and causes inhibition of platelet aggregation in dengue fever. Sixty dengue patients and 60 healthy subjects were studied. Platelet-rich plasma and platelet-poor plasma were prepared from the blood samples of both the groups. The study noted that the platelet aggregation was significantly reduced when leaf extract pre-incubated with dengue plasma was added into control platelet-rich-plasma, whereas no change in aggregation was observed when leaf extract incubated-control plasma was added into control platelet-rich-plasma. Upon direct administration of *C. papaya* leaf extract, both, the dengue and the control platelet-rich-plasma showed a significant reduction in platelet aggregation[27].

Another *in vitro* study was conducted on blood samples collected from healthy volunteers and patients with confirmed dengue infection. Within the study, fresh papaya leaves at three different maturity stages were taken and their juice was extracted with distilled water. Each mL of the extract containing 30 µL of papaya leaf extracts, 20 µL from 40 % erythrocytes suspension, and 950 µL of phosphate buffered saline were used in the heat-induced and hypotonic-induced hemolytic assay study. The study revealed that *C. papaya* leaf has biological membrane stabilization properties preventing stress-induced destruction of the plasma membrane. Extract of *C. papaya* leaf inhibit heat-induced and hypotonicity-induced hemolysis of R.B.S.s from both healthy individuals and patients with dengue viral infections[28].

**Direct action of *C. papaya***

***Larvicidal activity***

Vector control is considered as one of the most essential steps to minimise the incidences of dengue. A study revealed that the components of *C. papaya* seed are toxic to *A. aegypti*. Aqueous extracts of the

seed tegument and cotyledon are not larvicidal in isolate condition. However, the research revealed that a mixture of 17 µg/mL tegument extract and 27 µg/mL cotyledon extract caused 100 % larval mortality in the bioassay[29].

***Antiviral activity***

A recent molecular docking study of the phytocompounds from the methanol leaf extract of *C. papaya* exhibited high inhibitory activity against envelope protein of the dengue virus. The study included molecular docking using Autodock 4.2 and the results revealed that six compounds showed high inhibitory activity against the envelope protein. Six compounds; Stigmast-5-en-3-ol, (3á,24S); D:A-Friedooleanan-7-one, 3-hydroxy; 2-(4'-Chlorophenyl) naphtho[2,3-b]furan-4,9-dione; Neurosporaxanthin methyl ester; 3,6-bis(t-Butyl)fluorenone; and 5,11,17,23-Tetrakis(1,1-dimethylethyl) pentacyclo [19.3.1.1(3,7).1 (9,132).1 (15,19)] octacosal (25),3,5,7(28),9,11,13(27), 15, 17,19(26),20,22-dodecaene-4,12,16-triol-24-one) showed high inhibitory activity against the hydrophobic pocket between the domain I and II of envelope protein[30].

Another study showed that the *C. papaya* leaf extract had inhibitory activity against dengue virus type 2 by studying the cytotoxic effect and antiDENV2 activity on the LLC-MK2 cell line. Methanolic extracts, containing triterpenoids and flavonoids, showed cytotoxic effects, whereas a chloroform extract rich in alkaloids, tannin, and saponin was non-cytotoxic to LLC-MK2 cells and it showed inhibitory activity ($EC_{50}$= >1 mg/mL) against DENV2 with a selectivity index value of ± >1. This exhibit positive activity of *C. papaya* extract on dengue pathogens with high efficacy[31].

Another study revealed the antiviral activity of *C. Papaya*, which is active against DENV2. The viral non structural 2B and 3 (NS2B-NS3) protease complex is crucial for virus replication and hence, it is considered to be a good anti-viral target. Analysis was carried out using bioinformatics tools. The flavonoid quercetin was found to be highly efficient with highest binding energy against NS2B-NS3 protease, which is evident by the formation of six hydrogen bonds with the amino acid residues at the binding site of the receptor[32].

## Discussion and Conclusion

The year 2015 witnessed large dengue cases worldwide. Philippines reported more than 1,69,000 cases and Malaysia exceeded 1,11,000 suspected cases of dengue, represented a 59.5 and 16 % increase in case numbers, when compared with previous year, respectively. Brazil reported over 1.5 million cases in 2015, which is three times higher than 2014 report. The Island of Hawaii, USA, was affected by an outbreak with 181 cases reported in 2015 and ongoing transmission in 2016. India, recorded its worst outbreak in Delhi with over 15,000 cases in 2015. Around 5,00,000 people with dengue require hospitalization every year, a large proportion of whom are children. About 2.5 % of them die[33]. Dengue is overtaking malaria in terms of morbidity[34]. Thus, to prevent dengue, a proper dengue management programme is the need of the time.

According to various reports published in scientific literature, *C. papaya* has antiviral activity against dengue virus. For the prevention purpose also, we can use *C. papaya* as it has larvicidal activity against the vector of dengue. And as prevention is more beneficial than curing dengue, more research is necessary to explore *C. papaya* as a potent natural control of vector.

Further, the rapid increase in platelet count, the possible cause may be attributed to its membrane-stabilizing property. An earlier study concluded that *C. papaya* is rich in several minerals and that those minerals may combat the mineral and nutrients deficiency caused by the virus and strengthen the immunity of the body[35].

The empirical research that has been conducted in case of *C. papaya* is scattered. There is not a single chemical entity, but a mixture of several phytoconstituents, hence proper standardization of the phytoconstituents is necessary for effective validation of the plant and also to investigate the chief phytomolecules that may be responsible for its therapeutic activities. Proper dose optimization and multicentre clinical trial is very much necessary to establish *C. papaya* as a first line of treatment of choice for the dengue disease as all the above mentioned case reports have taken different drug concentrations for their studies.

Several nutraceutical companies came forward to develop herbal papaya supplement, which implement several pharmaceutical preparations like micronization and fermentation of liquid extraction of *C.papaya*. Nusrat *et al*. in their research paper suggested that extraction methods such as milling and supercritical fluids used in micronization can cause mechanical stress and affect the active compounds of the plant extract. Milling and grinding during

micronization can also cause physical stress and degradation of the product[36]. Hence, proper dosage form development is also crucial for *C. papaya* supplement for good bioavailability. This review thus made an attempt to study the pharmacological developments of *C. papaya* in the management of dengue in recent years.

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