

## Short Review

# Papaya Extract to Treat Dengue: A Novel Therapeutic Option?

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## Abstract

Dengue is a viral disease that today affects a vast number of people in over 125 countries and is responsible for a sizable number of deaths. In the absence of an effective antiviral drug to treat the disease, various treatments are being investigated. Studies have indicated that the juice of the leaves of the *Carica papaya* plant from the family Caricaceae could help to increase the platelet levels in these patients. This review describes some of the published studies on this topic. The search was done independently by the two authors using PubMed, Google and the library database and included relevant articles of the last 10 years. A total of 7 studies were included in this review, which were one animal study, one case report, three case series and two randomized controlled trials. Although many of the studies and case reports published in literature lack adequate information, some of the studies do raise the possibility that this treatment could be an important option in the future. Further large-scale studies could establish the usefulness or ineffectiveness of this natural product in the treatment of dengue.

**Keywords:** *Carica papaya* leaves, Dengue, Dengue treatment

## Introduction

Dengue, a viral disease transmitted by the bite of the *Aedes* mosquito, has reached alarming proportions in the past few years. Today endemic in over 125 countries, it infects nearly 50-270 million people every year, resulting in a sizable number of deaths.<sup>[1]</sup> In fact, dengue appears to be overtaking malaria in terms of morbidity and economic impact of the disease.<sup>[2]</sup> Unfortunately, due to lack of adequate surveillance systems in the underdeveloped and developing countries, the exact extent of the problem is not known.<sup>[1]</sup> Travellers from non-endemic areas to the dengue-affected areas are also exposed to the possibility of infection.<sup>[3]</sup> This makes it an international public health concern, affecting individuals from countries even where the disease is not prevalent.

A herbal medicine being investigated to control the mammoth problem of dengue is the extract of the leaves of the papaya plant, *Carica papaya*. There have been conflicting reports on


the effectiveness of this extract in the treatment of dengue. In this article, we present a brief overview of dengue and a review of available literature regarding the use of the papaya leaf extract for the treatment of this condition.

## Materials and Methods

The literature search was carried out independently by the two authors using PubMed, Google and the library database. The keywords used for the search included dengue treatment, dengue herbal treatment, dengue papaya leaf extract, dengue *C. papaya*. A search in PubMed was conducted for relevant articles over the last 10 years, from 2002 to 2013. A Google search was done using the same keywords to identify articles that were not indexed in PubMed. In addition, the authors also did a detailed search in the library database for relevant articles in journals not indexed in PubMed. A total of 7 studies were selected for this review, which included one animal study, one case report, three case series and two randomized controlled trials. The studies were published in the years 2008 or later. A brief summary of the included *in vivo* studies is listed in Table 1.

## Dengue – Brief Overview

Dengue is a viral infection caused by four closely related, but antigenically distinct serotypes of the Flaviviridae family,

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**Table 1: Details of the studies included in the review**

Authors	Subjects/animals	Article type	Article title	Key message
Patil, Shetty, Bhide, Narayanan	n=24 (4 groups with 6 animals in each)	Placebo controlled	Evaluation of platelet augmentation activity of Carica papaya leaf aqueous extract in rats	Increased platelet counts and reduced clotting time by Carica papaya leaf aqueous extract in cyclophosphamide-induced thrombocytopenic rat model
Hettige	n=12	Case series	Salutary effects of Carica papaya leaf extract in dengue fever patients-a pilot study	Papaya leaf juice elevated total white cells and platelets in dengue patients
Ahmad, Fazal, Ayaz, Abbasi, Mohammad, Fazal	n=1	Case report	Dengue fever treatment with Carica papaya leaves extracts	Carica papaya leaves extracts increased platelets over 5 days
Yunita, Hanani	n=80	Randomized clinical trial (dengue not confirmed)	The effect of Carica papaya L. leaves extract capsule on platelet count and hematocrit level in dengue fever patient	Carica papaya L. leaves extract increased platelets and hastened recovery
Kumar	n=2	Case series (rapid response)	Dengue: An escalating problem	Increase in platelets within 12 h and 2 days respectively
Kala	n=5	Case series	Leaf juice of Carica papaya L.: A remedy of dengue fever	Increase in platelets by 24 h
Subenthiran, Choon, Cheong, Thayan, Teck, Muniandy <i>et al.</i>	n=228	Open labeled randomized control trial	Carica papaya leaves juice significantly accelerates the rate of increase in platelet count among patients with dengue fever and dengue hemorrhagic fever	Increase in platelets after 40 h of the first dose

which are designated as dengue virus (DENV) DENV-1, DENV-2, DENV-3 and DENV-4. Many cases of dengue are asymptomatic, especially in children and in adults with a first infection. In other cases, it may appear as self-limited, undifferentiated fever or classic dengue fever.<sup>[3]</sup> An incubation period varying from 3 to 14 days is followed by a febrile illness consisting of sudden-onset fever, headache, myalgia, arthralgia and rash. Thrombocytopenia is a common feature of the illness.<sup>[4]</sup> The patient develops hemorrhagic manifestations such as petechiae and bleeding through the nose, gastrointestinal tract and gums. A number of atypical manifestations have also been reported in the literature, which include encephalitis, encephalopathy, myocarditis, hepatitis and cholecystitis.<sup>[5]</sup>

Deaths due to dengue are usually a consequence of patients developing complications like dengue hemorrhagic fever and dengue shock syndrome.<sup>[6]</sup> Dengue hemorrhagic fever, if untreated, has a mortality rate of 10-20%. It occurs due to progression of thrombocytopenia and development of increased vascular permeability and plasma leakage. It progresses to dengue shock syndrome, which is again associated with high mortality.<sup>[4]</sup>

Treatment for dengue is usually symptomatic. Some cases require platelet transfusions and fluid management.<sup>[3]</sup> One of the most disturbing aspects of the problem of dengue is that there are no effective antiviral agents available to treat dengue complications. Though symptomatic treatment works in most

mild cases, some cases progress to complications very fast and this often make it difficult to save the life of the patient.

Attempts to develop an antiviral agent for dengue have met several hurdles. Dengue is caused by four distinct serotypes which often undergo mutations.<sup>[7]</sup> Like in other ribonucleic acid (RNA) viruses, these mutations are due to the error-prone nature of RNA polymerase, which results in the formation of quasispecies. It is currently unclear which viral genome results in a higher viral titre.<sup>[8]</sup> An antiviral would have to be effective against all the serotypes. The current mouse model for dengue (AG129) is inefficient due to low viral load and short period of viremia.<sup>[7]</sup>

A lot of hope rests on the development of effective vaccines, many of which are undergoing clinical trials.<sup>[2]</sup> Besides vaccines, every other possible treatment including traditional medicines are being investigated to test their usefulness in controlling this problem. A recent *in vitro* study demonstrated the possible effectiveness of cocktail extracts prepared from four species of phyllanthus against the DENV.<sup>[9]</sup>

### Mechanism of Thrombocytopenia in Dengue

Dengue hemorrhagic fever is characterized by a thrombocyte count of <100,000 cells/mm<sup>3</sup>.<sup>[3]</sup> Two mechanisms have been

that treatment with CPC can hasten recovery of patients and therefore reduce hospitalization. However, there is no clear mention if any of the patients including those in the control group died due to dengue. The study also does not confirm the diagnosis of dengue in these patients.<sup>[17]</sup>

A report in the British Medical Journal website described the rapid recovery of platelet counts in two children suffering from dengue. These cases were proved to be positive for dengue by the demonstration of the dengue antigen in the serum. The boys, aged 10 years and 14 years, were administered a spoonful of ground papaya leaves paste every 4 hourly. A dramatic increase in platelet counts was observed; in one case within 12 h of initiating treatment, the count increased to 100,000. In the second case, it increased within 2 days to 250,000. The duration of treatment was not mentioned in the report.<sup>[18]</sup>

A study in the journal of Medicinal and Aromatic Plants reported an increase in platelet counts in five patients within 24 h who had taken papaya leaf extract for dengue. However, no other details have been provided – whether the dengue was confirmed in these patients, what other treatment was given and whether the increase in platelet count is significant. Furthermore, the response in platelet count beyond 24 h has not been described.<sup>[19]</sup>

A study conducted in Malaysia had a more systematic approach in evaluating the use of papaya leaf juice in the treatment of dengue. The juice was obtained from the papaya leaves under hygienic conditions from trees that were grown without insecticides or pesticides. An open-labeled randomized controlled trial was conducted on 290 patients between the ages of 18 and 60 years with platelet counts  $\leq 100,000/\mu\text{L}$ . The patients were confirmed to be suffering from dengue using a rapid dengue bedside test. Patients in the intervention group were administered fresh juice from 50 g of *C. papaya* leaves once a day 15 min after breakfast for 3 consecutive days. In addition, they received the standard treatment for dengue. The controls only received the standard treatment. The final analysis was conducted on 111 patients from the intervention group and 117 controls. The study found that there was a significant increase in the platelet counts in the intervention group at the end of 40 h when compared to the counts 8 h after the intervention began. This significant increase was not observed in the control group. An increase in arachidonate 12-lipoxygenase and the platelet-activating factor receptor gene expression was also observed in the intervention group. These genes are associated with increased platelet production.<sup>[7]</sup>

## Discussion

From the various reports published in scientific literature, it appears that *C. papaya* L. leaf extract does have beneficial properties in dengue. It has been shown to bring about a rapid increase in platelet count. This could be possibly attributed to its membrane-stabilizing property. The flavonoids and other

phenols present in the extract have been suggested to provide the beneficial effects. One study found that the leaves of papaya plant are rich in several minerals. The researchers suggested that these minerals may balance the mineral deficiency caused by the virus and strengthen the immune cells against it.<sup>[20]</sup>

However, the picture is not entirely clear. First of all, there are very few cases reported in literature. Many of the reports have presumed that the patients suffer from dengue due to the presence of thrombocytopenia and have not confirmed the diagnosis. This may have been due to the high cost of the test, which is often unaffordable to people in the underdeveloped and developing countries, where most of these studies were conducted. Therefore, it cannot be proved based on these case reports that the extract is conclusively effective in dengue. It is possible that the extract may be beneficial in other cases of thrombocytopenia as well. Thus, it is first important to diagnose the cases correctly and prove beyond doubt that the patient indeed suffers from dengue infection.

Most of the cases were given a crude leaf extract prepared by grinding the papaya leaves. The amount of extract given also differed among the studies. Thus, the active principle needs to be identified and the dosage standardized to conduct clinical studies on it to prove its efficacy in dengue beyond doubt. It is also necessary to conduct pharmacokinetic studies to ensure that the active principle is absorbed from the digestive tract.

In addition to its effect against the virus, the papaya plant also appears to be effective against the *Aedes* mosquito. Thus, if proved to be effective, this plant could control dengue at two levels, at the level of transmission as well at the host level.

Papaya extract no doubt offers a cheap and possibly effective treatment for dengue. However, currently, it is also necessary not to rely entirely on the leaf extract and ignore standard treatment for dengue until the benefits are established. Large scale randomized clinical trials in dengue-confirmed patients is necessary to establish their usefulness.

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suggested that could be responsible for dengue-induced thrombocytopenia-impaired thrombopoiesis and peripheral platelet destruction. In support of the theory of impaired thrombopoiesis, studies have suggested reduced megakaryopoiesis at the onset of infection, which is normal at the time of clinical recovery. This effect could be due to a direct effect of the virus on the megakaryocytes, or an effect on the stromal cells which are responsible for the release of cytokines and control of megakaryopoiesis. Studies have also indicated altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis as possible mechanisms of thrombocytopenia.

The other main mechanism proposed for thrombocytopenia is the increased peripheral platelet destruction by the DENV. This could be due to an autoimmune reaction, where antibodies produced by the host against the DENV bring about activation and destruction of platelets. Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction. Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the destruction. Recent studies indicate a direct infection of the platelets by the DENV. Increased levels of mediators like tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  were associated with the thrombocytopenia.<sup>[10]</sup>

### Use of Papaya Plant in Medicine

The papaya plant or *C. papaya* has been used since ancient times for the treatment of a number of disease conditions. Various beneficial effects of extracts from the leaves, fruit and seeds have been suggested through scientific studies. The chymopapain and papain extracts of the leaves are useful in the treatment of digestive disorders. The extracts from fruits and seeds have bactericidal properties.<sup>[11]</sup> The fruit juice and leaf extract have been demonstrated to have a wide variety of properties including anticancer, antioxidative, anti-inflammatory, anti-bacterial, nephroprotective, hepatoprotective, hypoglycemic and hypolipidemic effects, and anti-sickling effect in sickle cell disease. The ripe fruit has been used against ringworm, whereas the green fruit has been used to lower blood pressure, as an aphrodisiac and to induce abortion.<sup>[12]</sup> The leaf extract has also been shown to have larvicidal properties against the *Aedes aegypti* mosquito, the vector of the DENV.<sup>[11]</sup>

### Possible Mechanism of Action of Papaya Extract in Dengue

The papaya plant possibly brings about its effect in dengue by treating the thrombocytopenia associated with the condition. A study has reported membrane stabilizing properties of *C. papaya* L. leaf extracts in *in vitro* studies. The study found that *C. papaya* L. leaf extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue

infection; the effect was observed at the lower concentrations of the extracts. Thus, the extracts are likely to possess membrane-stabilizing properties and protect blood cells against stress-induced destruction. This property may be useful in patients with dengue infection where the leaf extracts could possibly prevent platelet lysis. The authors postulate that this effect could be due to the presence of flavonoids and other phenolic compounds in the papaya leaves.<sup>[12]</sup>

### Studies in Animals

A study in mice found an increase in thrombocyte counts in mice administered 15 mg of powdered papaya leaves/kg body weight between 1 and 12 h following dosing.<sup>[13]</sup> Another study found that the *C. papaya* leaf aqueous extract at concentrations of 400 mg/kg and 800 mg/kg significantly increased the platelet counts in cyclophosphamide-induced thrombocytopenic rat model. It also reduced the clotting time in the treated rats.<sup>[14]</sup>

### Studies in Humans

Treatment of dengue using *C. papaya* leaf extract in humans has been reported in very few studies conducted in Asia. A pilot study was conducted in Sri Lanka on 12 patients suspected of suffering from dengue. The patients had a platelet count of <130,000/cu mm, but only six patients were serologically confirmed to be suffering from dengue. The patients received 2 doses of papaya leaf extract at intervals of 8 h. They also received standard symptomatic care for dengue. The study found an increase in platelet count and total white blood cell count in patients administered papaya leaf extract within 24 h of treatment with the extract.<sup>[15]</sup>

A case report from Pakistan described the effective treatment of dengue in a truck driver with papaya leaf extract. The patient received 25 mL of papaya leaf extract twice a day for 5 days. A steady increase in the platelet and white blood cell count was observed after 2 days of treatment. However, the results of the study have to be interpreted with caution, taking into consideration the vague and incorrect details mentioned in the report. For example, the report states that the driver was bitten by a "mosquito carrying Dengue virus", 24 h after which he started developing symptoms. These and similar other statements raise questions regarding the credibility of this report.<sup>[16]</sup>

A study conducted in Indonesia used *C. papaya* L. leaves extract capsules (CPC), which contained 70% ethanol extract of *C. papaya* leaves. The 80 patients included in the study had high continuous fever for 2-7 days, thrombocyte count of <150,000/ $\mu$ L and hematocrit of 20% or more. They were randomized into two groups; one group received CPC in addition to standard treatment, whereas the other group received only standard treatment for dengue. The study found that platelets in patients with dengue increased faster in those who were administered the CPC. The authors thus conclude

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## Abstract

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A report in the British Medical Journal website described the rapid recovery of platelet counts in two children suffering from dengue. These cases were proved to be positive for dengue by the demonstration of the dengue antigen in the serum. The boys, aged 10 years and 14 years, were administered a spoonful of ground papaya leaves paste every 4 hourly. A dramatic increase in platelet counts was observed; in one case within 12 h of initiating treatment, the count increased to 100,000. In the second case, it increased within 2 days to 250,000. The duration of treatment was not mentioned in the report.<sup>[18]</sup>

A study in the journal of Medicinal and Aromatic Plants reported an increase in platelet counts in five patients within 24 h who had taken papaya leaf extract for dengue. However, no other details have been provided – whether the dengue was confirmed in these patients, what other treatment was given and whether the increase in platelet count is significant. Furthermore, the response in platelet count beyond 24 h has not been described.<sup>[19]</sup>

A study conducted in Malaysia had a more systematic approach in evaluating the use of papaya leaf juice in the treatment of dengue. The juice was obtained from the papaya leaves under hygienic conditions from trees that were grown without insecticides or pesticides. An open-labeled randomized controlled trial was conducted on 290 patients between the ages of 18 and 60 years with platelet counts  $\leq 100,000/\mu\text{L}$ . The patients were confirmed to be suffering from dengue using a rapid dengue bedside test. Patients in the intervention group were administered fresh juice from 50 g of *C. papaya* leaves once a day 15 min after breakfast for 3 consecutive days. In addition, they received the standard treatment for dengue. The controls only received the standard treatment. The final analysis was conducted on 111 patients from the intervention group and 117 controls. The study found that there was a significant increase in the platelet counts in the intervention group at the end of 40 h when compared to the counts 8 h after the intervention began. This significant increase was not observed in the control group. An increase in arachidonate 12-lipoxygenase and the platelet-activating factor receptor gene expression was also observed in the intervention group. These genes are associated with increased platelet production.<sup>[7]</sup>

## Discussion

From the various reports published in scientific literature, it appears that *C. papaya* L. leaf extract does have beneficial properties in dengue. It has been shown to bring about a rapid increase in platelet count. This could be possibly attributed to its membrane-stabilizing property. The flavonoids and other

phenols present in the extract have been suggested to provide the beneficial effects. One study found that the leaves of papaya plant are rich in several minerals. The researchers suggested that these minerals may balance the mineral deficiency caused by the virus and strengthen the immune cells against it.<sup>[20]</sup>

However, the picture is not entirely clear. First of all, there are very few cases reported in literature. Many of the reports have presumed that the patients suffer from dengue due to the presence of thrombocytopenia and have not confirmed the diagnosis. This may have been due to the high cost of the test, which is often unaffordable to people in the underdeveloped and developing countries, where most of these studies were conducted. Therefore, it cannot be proved based on these case reports that the extract is conclusively effective in dengue. It is possible that the extract may be beneficial in other cases of thrombocytopenia as well. Thus, it is first important to diagnose the cases correctly and prove beyond doubt that the patient indeed suffers from dengue infection.

Most of the cases were given a crude leaf extract prepared by grinding the papaya leaves. The amount of extract given also differed among the studies. Thus, the active principle needs to be identified and the dosage standardized to conduct clinical studies on it to prove its efficacy in dengue beyond doubt. It is also necessary to conduct pharmacokinetic studies to ensure that the active principle is absorbed from the digestive tract.

In addition to its effect against the virus, the papaya plant also appears to be effective against the *Aedes* mosquito. Thus, if proved to be effective, this plant could control dengue at two levels, at the level of transmission as well as at the host level.

Papaya extract no doubt offers a cheap and possibly effective treatment for dengue. However, currently, it is also necessary not to rely entirely on the leaf extract and ignore standard treatment for dengue until the benefits are established. Large scale randomized clinical trials in dengue-confirmed patients is necessary to establish their usefulness.

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suggested that could be responsible for dengue-induced thrombocytopenia-impaired thrombopoiesis and peripheral platelet destruction. In support of the theory of impaired thrombopoiesis, studies have suggested reduced megakaryopoiesis at the onset of infection, which is normal at the time of clinical recovery. This effect could be due to a direct effect of the virus on the megakaryocytes, or an effect on the stromal cells which are responsible for the release of cytokines and control of megakaryopoiesis. Studies have also indicated altered proliferative capacity, inhibition of differentiation and megakaryocytic progenitor apoptosis as possible mechanisms of thrombocytopenia.

The other main mechanism proposed for thrombocytopenia is the increased peripheral platelet destruction by the DENV. This could be due to an autoimmune reaction, where antibodies produced by the host against the DENV bring about activation and destruction of platelets. Platelets may also show an increased reaction with leucocytes and endothelial cells, leading to their destruction. Platelet dysfunction due to abnormal activation and inhibition of platelet aggregation in dengue patients may also be responsible for the destruction. Recent studies indicate a direct infection of the platelets by the DENV. Increased levels of mediators like tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  were associated with the thrombocytopenia.<sup>[10]</sup>

### Use of Papaya Plant in Medicine

The papaya plant or *C. papaya* has been used since ancient times for the treatment of a number of disease conditions. Various beneficial effects of extracts from the leaves, fruit and seeds have been suggested through scientific studies. The chymopapain and papain extracts of the leaves are useful in the treatment of digestive disorders. The extracts from fruits and seeds have bactericidal properties.<sup>[11]</sup> The fruit juice and leaf extract have been demonstrated to have a wide variety of properties including anticancer, antioxidative, anti-inflammatory, anti-bacterial, nephroprotective, hepatoprotective, hypoglycemic and hypolipidemic effects, and anti-sickling effect in sickle cell disease. The ripe fruit has been used against ringworm, whereas the green fruit has been used to lower blood pressure, as an aphrodisiac and to induce abortion.<sup>[12]</sup> The leaf extract has also been shown to have larvicidal properties against the *Aedes aegypti* mosquito, the vector of the DENV.<sup>[11]</sup>

### Possible Mechanism of Action of Papaya Extract in Dengue

The papaya plant possibly brings about its effect in dengue by treating the thrombocytopenia associated with the condition. A study has reported membrane stabilizing properties of *C. papaya* L. leaf extracts in *in vitro* studies. The study found that *C. papaya* L. leaf extracts inhibited heat-induced and hypotonicity-induced hemolysis of erythrocytes obtained from both healthy individuals and individuals with dengue

infection; the effect was observed at the lower concentrations of the extracts. Thus, the extracts are likely to possess membrane-stabilizing properties and protect blood cells against stress-induced destruction. This property may be useful in patients with dengue infection where the leaf extracts could possibly prevent platelet lysis. The authors postulate that this effect could be due to the presence of flavonoids and other phenolic compounds in the papaya leaves.<sup>[12]</sup>

### Studies in Animals

A study in mice found an increase in thrombocyte counts in mice administered 15 mg of powdered papaya leaves/kg body weight between 1 and 12 h following dosing.<sup>[13]</sup> Another study found that the *C. papaya* leaf aqueous extract at concentrations of 400 mg/kg and 800 mg/kg significantly increased the platelet counts in cyclophosphamide-induced thrombocytopenic rat model. It also reduced the clotting time in the treated rats.<sup>[14]</sup>

### Studies in Humans

Treatment of dengue using *C. papaya* leaf extract in humans has been reported in very few studies conducted in Asia. A pilot study was conducted in Sri Lanka on 12 patients suspected of suffering from dengue. The patients had a platelet count of <130,000/cu mm, but only six patients were serologically confirmed to be suffering from dengue. The patients received 2 doses of papaya leaf extract at intervals of 8 h. They also received standard symptomatic care for dengue. The study found an increase in platelet count and total white blood cell count in patients administered papaya leaf extract within 24 h of treatment with the extract.<sup>[15]</sup>

A case report from Pakistan described the effective treatment of dengue in a truck driver with papaya leaf extract. The patient received 25 mL of papaya leaf extract twice a day for 5 days. A steady increase in the platelet and white blood cell count was observed after 2 days of treatment. However, the results of the study have to be interpreted with caution, taking into consideration the vague and incorrect details mentioned in the report. For example, the report states that the driver was bitten by a "mosquito carrying Dengue virus", 24 h after which he started developing symptoms. These and similar other statements raise questions regarding the credibility of this report.<sup>[16]</sup>

A study conducted in Indonesia used *C. papaya* L. leaves extract capsules (CPC), which contained 70% ethanol extract of *C. papaya* leaves. The 80 patients included in the study had high continuous fever for 2-7 days, thrombocyte count of <150,000/ $\mu$ L and hematocrit of 20% or more. They were randomized into two groups; one group received CPC in addition to standard treatment, whereas the other group received only standard treatment for dengue. The study found that platelets in patients with dengue increased faster in those who were administered the CPC. The authors thus conclude

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