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Literature Review

Potency of *Carica papaya* Leaf Extract as Thrombocytopenia Therapy for Dengue Hemorrhagic Fever: A Systematic Review of Randomized Control Trials

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ABSTRACT

Background: Dengue fever is a common disease in tropical countries. According to the data from the Indonesia Ministry of Health, there were 71.633 Dengue Haemorrhagic Fever (DHF) cases reported in Indonesia, with approximately 459 people dying from the disease. Thrombocytopenia is the most common clinical feature of DHF and often causes serious complications if not treated properly. Several studies have analyzed the potency of *Carica papaya* leaf which has been proven as an effective therapy for thrombocytopenia. **Objectives:** This systematic review aims to discover the potency of *Carica papaya* leaf extract as a therapy for thrombocytopenia. **Method:** Literature was searched by using keywords in accordance with the topic, then filtered according to the inclusion criteria that had been determined according to the PRISMA rules. Publication bias in this review was conducted subjectively using the Revman 5.4 software. **Results:** From 138 studies, it was found that screening was carried out based on inclusion criteria, including a randomized controlled trial study in humans with a population of dengue fever patients and received the intervention of papaya leaf extract so that 6 studies were included in the inclusion study, which was then carried out by qualitative synthesis from the study. Based on the results of the qualitative analysis, it was found that there was a faster and more significant improvement in the platelet count between the intervention group compared to the control group in the 6 studies. **Conclusion:** *Carica papaya* leaf extract has potential as a thrombocytopenia therapy in dengue fever patients

Keywords: Dengue Fever, Thrombocytopenia, Carica papaya

ABSTRAK

Latar Belakang: *Demam dengue merupakan penyakit yang banyak terjadi pada negara yang beriklim tropis. Berdasarkan data dari Kementerian Kesehatan Indonesia jumlah kasus Demam Berdarah Dengue (DBD) dilaporkan sebanyak 71.633 kasus dengan jumlah kasus yang meninggal sebanyak 459 orang. Trombositopenia merupakan manifestasi yang paling sering ditemukan dan menyebabkan komplikasi serius jika tidak ditangani dengan baik. Beberapa studi telah menganalisis potensi dari daun Carica papaya yang terbukti efektif sebagai terapi trombostiopenia.* ***Tujuan:*** *Studi kajian sistematis ini dibuat dengan tujuan menggali lebih dalam potensi dari ekstrak daun carica papaya sebagai terapi trombositopenia.* ***Metode:*** *Pada literatur ini dilakukan pencarian literatur menggunakan kata kunci yang sesuai dengan topik, kemudian dilakukan penyaringan sesuai dengan kriteria inklusi yang telah ditetapkan sesuai dengan kaidah PRISMA. Publication bias pada kajian ini dilakukan secara subjektif dengan menggunakan software Revman 5.4.* ***Hasil:*** *Dari 138 studi yang ditemukan dilakukan penyaringan berdasarkan kriteria inklusi, yakni studi randomized controlled trial pada manusia dengan populasi yaitu pasien demam dengue serta yang mendapatkan intervensi berupa ekstrak daun papaya sehingga diperoleh 6 studi yang masuk ke dalam studi inklusi yang selanjutnya dilakukan qualitative synthesis dari studi tersebut. Berdasarkan hasil dari qualitative analysis ditemukan*

terjadinya perbaikan yang lebih cepat dan signifikan dari jumlah platelet antara kelompok intervensi dibandingkan kelompok kontrol pada 6 studi tersebut. ***Kesimpulan:*** *Ekstrak daun Carica papaya memiliki potensi sebagai terapi trombositopenia pada pasien demam dengue.*

Kata Kunci: Demam Dengue, Trombositopenia, Carica papaya

INTRODUCTION

Indonesia is a tropical archipelagic country located at the equator, with two seasons: summer and rainy season. Various tropical diseases including Dengue Hemorrhagic Fever (DHF) is one of the health impacts of the climate in tropical countries. DHF is an infection caused by the dengue virus which is transmitted by the *Aedes spp*. mosquito, which is the fastest growing mosquito in the world, especially in tropical countries such as Indonesia. There were at least 390 million people infected by this mosquito every year.[1]

Until July 2020, there are 71,633 people suffering from DHF, with approximately 459 people dying due to DHF, with the Incident Rate (IR) of 49 per 100,000 population. In 2019, there were 3 provinces with the highest CFR of DHF in Indonesia, including Gorontalo Province (CFR=1.88%), Maluku Province (CFR=2.12%), and Central Kalimantan Province with CFR of 1.49 (High CFR defined as >1%).[2] Data from the Health Office from several districts and cities in South Sulawesi Province was reported DHF incidence rate (IR) of 36.89 per 100,000 population in 2017, with CFR value of 0.58%. The highest number of DHF cases was found in Maros Regency (253 people), Bulukumba Regency (197 people), and Makassar city (135 people). Makassar City reported 8.11 IR per 100,000 population, while Pangkep Regency reported 34.01 IR per 100,000 population. Meanwhile, Selayar Regency reported the lowest IR in South Sulawesi, with 0 incidences per 100,000 population.[3] According to high IR and CFR of DHF which reported from several districts and cities, good prevention and treatment strategy are still needed to reduce mortality due to DHF, especially in districts and cities with large IRs and CFRs.

Dengue Hemorrhagic Fever usually comes with several clinical manifestations, such as continuous high fever for 2-7 days; plasma leakage due to impaired vascular permeability, and thrombocytopenia (defined as drop of platelets < 150,000/µL).[4] Drop of platelets in patients with dengue hemorrhagic fever commonly occurs in the 3rd to 7th day of the disease and will returned to normal on the 8th or 9th day.[5] Thrombocytopenia is closely related to the plasma leakage in dengue patients and responsible for disease severity and higher mortality in dengue.[6] The exact cause of thrombocytopenia in dengue hemorrhagic fever is still controversial, but some literature states that bone marrow suppression, also destruction and shortening of the life span of platelets were the pathogenesis of thrombocytopenia in DHF.[7] It is hypothesized that thrombocytopenia in DHF is caused by platelets destruction due to attachment of antigen-antibody complexes to the platelet membrane which resulting in the release of adenosine diphosphate. Secretion of adenosine diphosphate from antigen-antibody complexes attachment will trigger reticuloendothelial system to destroy the platelets.[8] Untreated thrombocytopenia in DHF can lead to massive bleeding which can worsen the prognosis of the patients and potentially life-threatening, thus treating the thrombocytopenia condition in dengue is very important to achieve better

clinical outcome and decrease the mortality rate.[6]

Dengue hemorrhagic fever without shock is commonly treated with symptomatic and supportive therapy. Adequate fluid administration including oral rehydration solution (ORS) should be given as fast as possible to reduce thirst and dehydration due to high fever, anorexia, and vomiting. In some patients ORS usually combined with several symptomatic therapies, including antipyretics, and surface cooler. Anticonvulsants such as diazepam (Valium) and phenobarbital (Luminal) can also administered in case of seizures.[9] Fluid resuscitation should be performed immediately for shock patients, even in unclear etiology, to avoid worsens of the disease and life-threatening conditions, followed by laboratory examination to identify the causes of shock. Together with fluid therapy, the oxygen therapy at a dose of 2-4 liters per minute should be started. If possible, Central Venous Pressure (CVP) should be installed immediately in order to optimizing and monitoring the fluid management. There are various fluids used for the management of shock, including crystalloid, colloid, dextrose solution, crystalloids and dextrose combination, and also blood or blood components. The fluids type and its administration method can be selected based on the patient's condition and the purpose of fluid administration.[9] In case of unresolved shock even with crystalloid fluids, the colloid fluids can be administered immediately with dosage of 10-20 ml/kg/hour, especially if the hematocrit value is above 30%. The colloid fluid which used for shock resuscitation must be the fluid that doesn't interfere with the clotting mechanism of blood or blood cells, such as iso-oncotic and isotonic colloid. [9]

Shock treatment including in DHF cases is still limited to fluid resuscitation only. Unfortunately, the fluid resuscitation sometimes does not result in a good result, indicating the emergence to intensify the therapy to get a better clinical outcome.[9] Recently, several studies on rats have shown effect of *Carica papaya* leaf extract in increasing the levels of platelet that can potentially bring better clinical outcome for patients with DHF.[10] *Carica papaya* is a plant that is often found in Indonesia. The leaf of the papaya tree contain the proteinolytic enzymes papain and chymopapain. Papain is a protease that can induce thrombopoietic cytokines such as IL-6, SCF and IL-3 that will stimulate platelet production by increasing liver thrombopoietin (TPO) secretion.[11] However, there are only few studies discussing this potency. Therefore, this literature was performed using a systematic review to explore the potency of *Carica papaya* as a therapy for thrombocytopenia in patients with dengue hemorrhagic fever.

Figure 1. Carica papaya leaf

METHOD

Literature Searching

Literature searching was conducted on October 29 2020 in various valid databases, such as: PUBMED, ScienceDirect, DOAJ, and COCHRANE using the keywords: "Dengue Fever" AND "Carica Papaya". In addition, valid studies outside the database will also be included if the studies meet the inclusion criteria.

Eligibility Criteria and Study Screening

The studies involved in this review should meet the following criteria: 1) Scientific publications in the last 10 years; 2) The research design was a randomized controlled trial conducted on humans; 3) The language used is Indonesian or English; 4) The subject population is patients who have been diagnosed with dengue fever; 5) Intervention using leaf extract *Carica papaya* 6) Control in the form of giving placebo or standard treatment 7) Outcome total of platelet count 8) Abstract available access.

After the literatures were searched, the duplicate journals from various databases will be excluded, then the journals will enter the screened based on title and abstract. Studies that pass the screening stage will be included according to the eligibility criteria that have been determined.

Data Collection

The data collection will be carried out on all included studies. The collected data are as follows: 1) Main author; 2) Year of publication; 3) The place where the research is conducted; 4) Sample characteristics (race, age, gender); 5) Number of samples; 6) Type of Exposure; 7) Outcome; 8) Data on the incidence of Exposure and Outcome.

Data collection was carried out by 2 reviewers. If the included literature study contains incomplete data, the reviewer will contact the author of the study, if the author does not respond, the study is then excluded with the agreement of the reviewer.

DISCUSSION

Results of Literature Searching and Screening

There are 138 studies which obtained from literature searching from various databases such as: PUBMED, ScienceDirect, DAOJ, COCHRANE, and other valid literature sources, using the keywords "Dengue fever" AND "Carica papaya". The obtained literatures then be filtered according to predetermined criteria. Subsequently, 21 duplicate studies were excluded. Furthermore, 117 study titles and abstracts were screened independently by *reviewers.* A total of 110 studies were excluded because they did not meet the predetermined criteria. The next 7 studies were screened by reading the full text. As a result, 1 study was excluded because the *outcome* was incomplete, so the remaining 6 studies met the criteria and were included for qualitative and quantitative analysis. Full details of search and filtering results are presented in Figure 2.

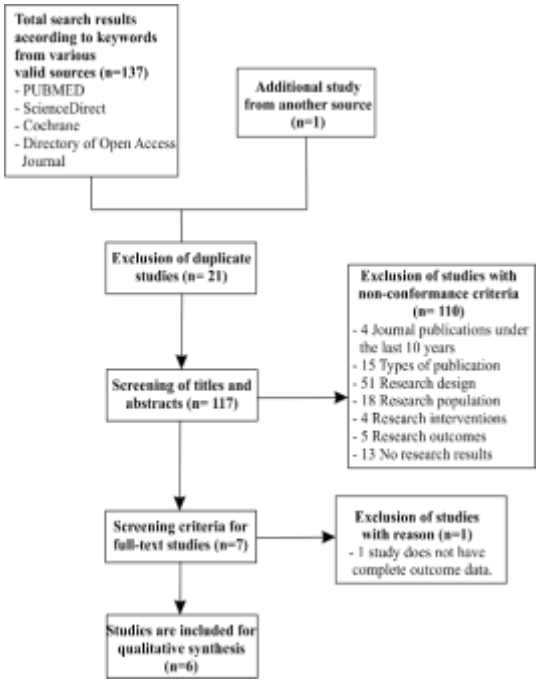

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta- analyses (PRISMA)

Risk Assessment of Bias in Inclusion

The included studies had varying risks of bias, 3 of the 6 studies had a low risk of

bias in the method for randomization of the sample while the other 2 studies[12,13] were unclear in conveying the technique used. There are 2 out of 6 studies that have other bias where the study reported by (Yunita, Hanani & Kristianto 2012)[13] had *outcomes* between the control group and the intervention group and the study reported by (Subenthiran et al. 2013)[14] did not have a *baseline* for the control group. and intervention at the 8th-hour examination so *outcomes* may lead to bias. In general, a summary of the risk of bias in inclusion studies can be seen in Figure 3.

Characteristics of Inclusive Studies

Six included studies were primary studies with a Randomized Controlled Trial conducted in 3 different countries with a total sample of 1126 people. All studies have intervention in the form of C*arica papaya* leaf extract and outcome in the form of platelet count. Full details of the characteristics of the inclusion studies are presented in Table 1.

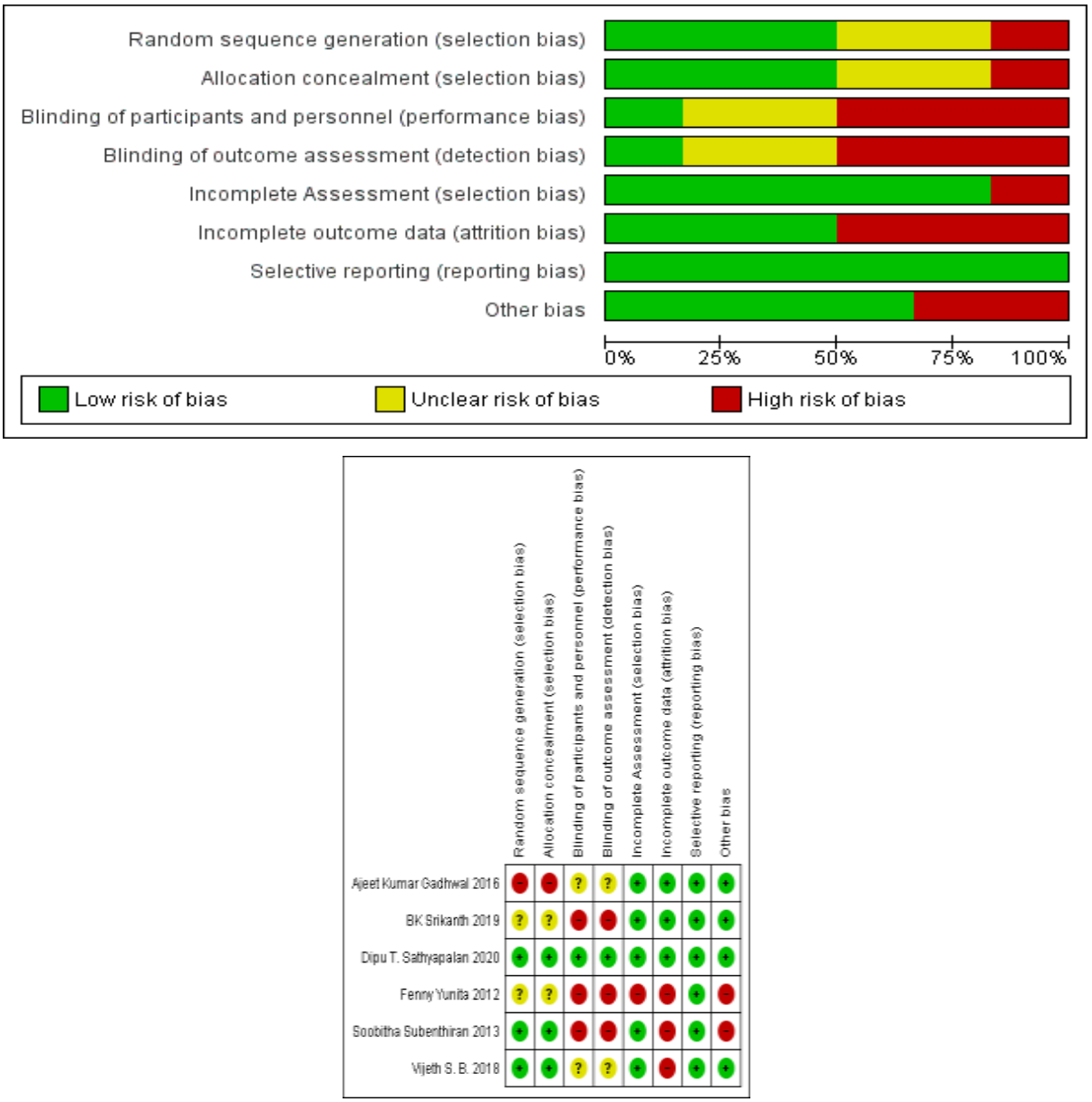

Figure 3. Result of the Inclusion Study Bias Risk Assessment

Table 1. Characteristics of Inclusion Studies. RCT: Randomized Controlled Trial; CPLE: Carica Papaya Leaf Extract; CPC: Carica Papaya Capsule; DF: Dengue Fever; DHF: Dengue Hemorrhage Fever

No	Author (Year)	Study Design	Country	Type of parti-cipant	Number of sample (Interven-tion / Control)	Mean Age/ Range	Inter-vention Day	Exposure	Control	Outcome	Baseline platelet (Control Group/Interve ntion Group)	Post Intervention Platelet (Control Group/Interventi on Group)
1	Ajeet (2016)	RCT	India	Dengue patient	400 (200/200)	>16 years	5 days of inter-vention	CPLE + Supportive Therapy	Support-ive treatment	Total of platelet count and length of hospitalization	61.06±20.03, 95% CI ± 2.78 / 59.82±18.63, 95% CI ± 2.58	102.59±19.35, 95% CI 2.68 / 112.47±17.49, 95% CI ± 2.42
2	BK Srikanth (2019)	RCT	India	Patient Dengue fever or Dengue hemor-rhage stage I or II	285 (145/140)	Inter-vention Group: 7.43±3. 61 Controll ed Group: 8.07±2. 92	5 days of inter-vention	CPLE(Caripi ll) + Standard therapy	Standard treatment	Total of platelet, red blood cells and white blood cells	56793.54 / 59897.21/µL (mean)	105050.12 / 168922.75/µL (mean)
3	Dipu T Sathyapal an (2020)	RCT	India	Dengue patient	50 (26/24)	≥ 18 years old	5 days of inter-vention	CPLE	Placebo	Increase of platelet count and length of hospitalization	22,000/µL±800 0/µL / 19,000/µL±600 0/µL (p = 0.37)	482%±284 / 331%±370 (p = 0.007) third day
4	Fenny Yunita (2012)	RCT	Indonesi a	Dengue patient	80 (40/40)	15 - 55 years old	5 days of inter-vention	CPC + Standard Therapy	Standard Therapy	Total of platelet count, hematocrit level and length of hospitalization	100.10 ± 28.981 / 98.33 ± 38.721 x 1000 µ/L	9th on fifth day (117.48 ± 24.550) / 6th on third day (133.88 ± 33.956) x 10^3 µ/L
5	Soobitha Subenthir an (2013)	RCT	Malaysia	Patient Dengue fever or Dengue hemor-rhage stage I or II	228 (111/117)	18 - 60 years old	3 days of inter-vention	50 gr Carica papaya leaf + Standard treatment	Standard Treat-ment	Total of platelet count	69.0 (22.6) / 66.4 (22.8). 10^3 /µL	8–48 hours Mean Difference −7.703 (−14.055, 1.351) / −16.764 (−24.566, −8.964)
6	Vijeth S. B. (2018)	RCT	India	Dengue patient	83 (40/43)	>18 years old	7 days of inter-vention	CPLE + Supportive treatment	Support-ive treatment	Total of platelet count and total of red blood cells	98470 / 95247/µL (mean)	36920 / 77770/µL (mean)

Thrombocytopenia is one of the most common haematological features and prognostic indicators in patients with dengue disease.[15,16] There are 6 randomized controlled trials that reported the potency of *Carica papaya* as a treatment for thrombocytopenia in dengue patients which included in this study.

In a study conducted by Gadhwal et al[17], 400 participants were divided using the odd even method into 2 groups: the control and intervention groups. the intervention group was given CPLE 500 mg together with supportive treatment which consisted of paracetamol, normal saline and antiemetics, while the control group was only given supportive treatment. The results of this study showed an accelerated increased average number of platelets in the intervention group compared to the control group.[17] In another study by Sathyapalan et al[18] and S.B. et al[19], a significant improvement ($p<0.05$) of the mean platelet count was also found in the intervention group which given CPLE compared to the control group.[18,19] Ability of *Carica papaya* extract in increasing platelets count for patients with dengue was also stated by Srikanth et al[12], a total of 285 children with dengue fever and dengue hemorrhagic fever in phase 1 and phase 2 were grouped into intervention group and control group. CPLE then administered to patients from intervention group, while standard therapy was given to control group. The platelets count then measured in the third and fifth days after intervention and the result showed higher amounts of platelets in

intervention group than in control group.[12] A similar result was also reported in a study conducted by Subenthiran et al[14], where an enhancement of the mean platelet count was observed in the intervention group compared to the control group in 9 to 48 hours after intervention.[14]

Carica papaya leaf have been proven by many studies to have many benefits such as antidiabetic, antitumor, antioxidant and antimicrobial, also platelets enhancer effect for patients with dengue fever. Increased platelets due to *Carica papaya* which was found in several trials is potentially caused by the effect of papain, a natural compound derived from leaf of *Carica papaya*, that stimulates the thrombopoietic cytokine, especially IL-6. Papain that contained in papaya leaf will stimulate the production and secretion of IL-6 by hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC). Higher number of IL-6 then stimulate the proliferation of common myeloid progenitors, leading to increased levels of mature megakaryocytes, resulting in an increase in the number of platelets. Besides that, IL-6 also acts on hepatocyte which will stimulate thrombopoietin production which will stimulate megakaryopoiesis and thrombopoiesis, resulting in an increase the number of platelets.[20] (Figure 4).

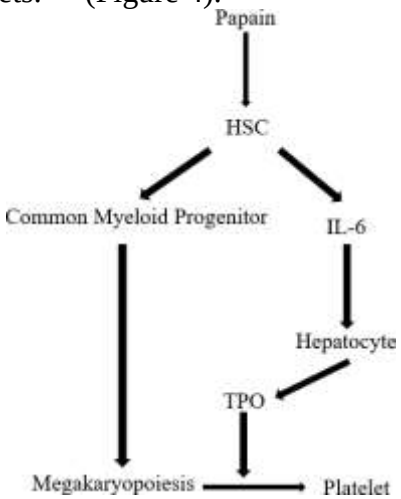

Figure 4. Platelet enhancer mechanism of papain in C*arica papaya*[20]

Certain genes have an important role in modulating platelet production. Arachidonate 12-lipoxygenase (ALOX-12) is a gene which highly expressed in megakaryocytes and responsible for the production of 12-Hydroxyeicosatetraenoic acid (12-HETE). This gene is associated with increased megakaryocytes and its conversion into platelet by 12-HETE, thus increased activity of this gene will result in increased platelet production. In a study by Subenthiran et al, it was found that *Carica papaya* leaf was able to increase the activity of ALOX-12 gene which can be possible to be the thrombopoiesis enhancer mechanism of *Carica papaya* leaf.[14]

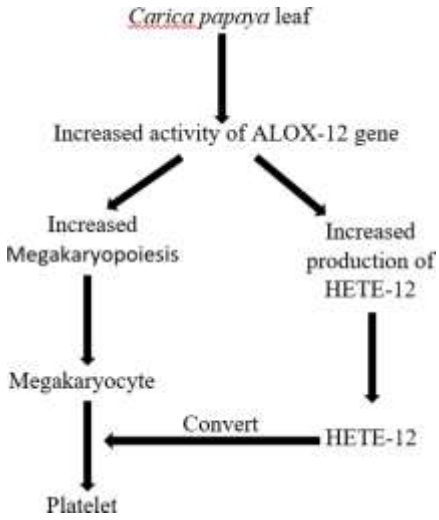

Figure 5. C*arica papaya* increase the activity of ALOX-12 gene and increase the amount of platelet[14]

Thrombopoietin (TPO) is a substance that have a crucial role in platelet production. TPO will modulate megakaryopoiesis and thrombopoiesis by activate its receptor, c-mpl, leading to increased production of platelet. In certain study, treatment with *Carica papaya* leaf was able to enhance the amount of TPO, discovering the potential mechanism of *Carica papaya* leaf in increasing thrombocyte.[21]

Another thrombocyte-enhancer mechanism of *Carica papaya* leaf is by escalate the expression of CD110 (Cluster Differentiation 110) which is a transmembrane protein that plays an important role in thrombopoiesis and acts as ligand for thrombopoietin. Leaf of *Carica papaya* has been discovered to have an effect in increasing the expression of CD110, indicating the possible mechanism of *Carica papaya* leaf in escalating the platelet.[22]

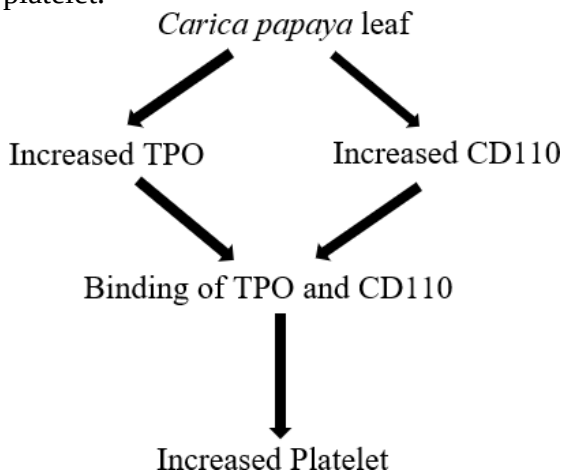

Figure 6. C*arica papaya* enhance platelet by increasing TPO and its ligand, CD110[21,22]

Based on its various mechanism in increasing the number of platelets, *Carica papaya* leaf have a therapeutical potency for dengue and improve the prognosis of the patients. However, this systematic review still has several limitations, such as only focusing in platelet count as disease improvement indicator, exclusion of patients with phase 3 and 4 DHF from sample populations in several reference studies, and a lack of human studies on this potency of *Carica papaya*. Therefore, further studies of *Carica papaya* leaf are still needed to find out other beneficial mechanism of *Carica papaya* leaf for treatment of dengue and its effectivity for patients with phase 3 and 4 of DHF.

CONCLUSION

Based on this systematic review, it can be concluded that *Carica papaya* leaf have a potency to be a therapy for thrombocytopenia for patients with dengue hemorrhagic fever.

RECOMMENDATIONS

Further comprehensive studies with larger human populations are still needed to evaluate *Carica papaya* capability in increasing the number of platelet and discover other beneficial mechanisms of *Carica papaya* for patients with dengue hemorrhagic fever.

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