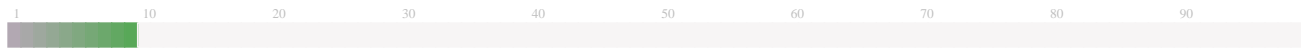


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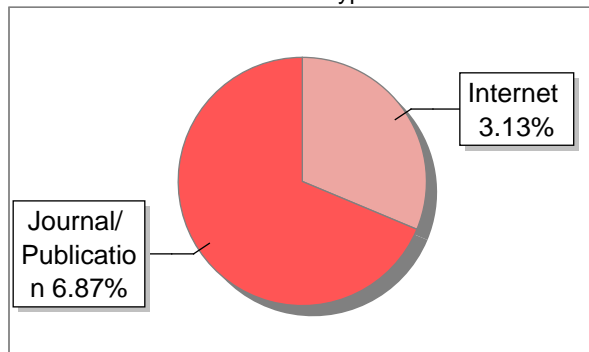
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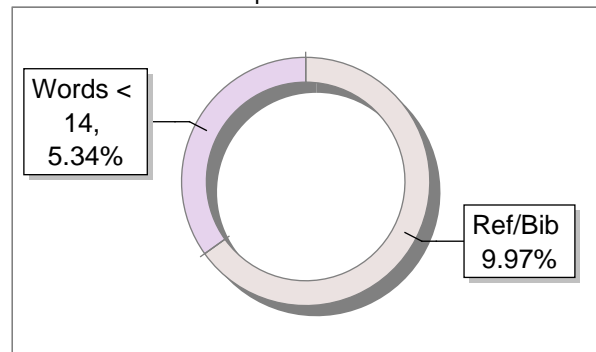
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Research Paper

## An evaluation the use of guava leaf extract capsules (*Psidium guajava* Linn) on the thrombocyte level and length of hospital stay of dengue fever or dengue hemorrhagic fever patient's at private hospital in Indonesia

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### ABSTRACT

Dengue hemorrhagic fever (DHF) is one of ten most common diseases of hospitalized patients in Indonesia with 30,232 male and 28,883 female patients. There were 34 cases with incidence rate (IR) of 4.4 per 10,000 inhabitants in Wonosobo regency in 2015. The leaf of guava is reported to contain many phytochemical compounds useful to cure DHF. The aim of this study is to evaluate the effect of guava leaf extract capsules on the thrombocyte level and length of stay (LOS) of dengue fever (DF) or dengue hemorrhagic fever (DHF) patient's at private Hospital in Indonesia. This is a cohort retrospective study. There are 107 DF/DHF patient's divided into 2 groups. The first group was given by capsules of guava leaf extract (n=52) 500 mg two capsules three times daily. The second group was given with placebo (n=55). The results of the thrombocyte level and the LOS between two groups were compared by t-test and chi-square. The differences on the two groups are analyzed using unpaired t-test and chi-square. The results showed that there was no significant difference both of group ( $p > 0.05$ ). During fever, the average level of thrombocyte was found that there was a significant difference of both groups in the 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, and 7<sup>th</sup> day of fever condition ( $p < 0.05$ ). The average level of thrombocyte in placebo group higher than the treatment groups. Based on the LOS, there was no significant difference on the two groups ( $p > 0.05$ ). Guava leaf extract capsules do not significantly effect on the thrombocyte level and LOS of DF/DHF patient's at private Hospital in Indonesia

**KEYWORDS:** dengue fever, dengue hemorrhagic fever, guava leaf extract capsules (*Psidium guajava* Linn.), thrombocyte level, length of stay.

Received 20 September, 2021; Revised: 03 October, 2021; Accepted 05 October, 2021 © The author(s) 2021. Published with open access at [www.questjournals.org](http://www.questjournals.org)

### I. INTRODUCTION

Dengue Fever (DF) or Dengue Hemorrhagic Fever (DHF) is a disease caused by the Dengue virus from the genus Flavivirus, Family Flaviviridae. This disease is often found in tropical and sub-tropical countries. The World Health Organization (WHO) noted that since 1968-2009 Indonesia was the country with the highest DHF cases in Southeast Asia with a mortality rate of 41.4% in 1968 and continued to decline to 0.89% in 2009<sup>1</sup>. Guava leaf (*Psidium guajava* Linn) is a plant that is reported to contain various efficacious compounds to treat DHF. Quercetin and tannins which are compounds of the flavonoid group are compounds that are declared efficacious. These compounds work by inhibiting the enzyme reverse transcriptase mechanism so that it can inhibit the development of the Dengue virus. Guava leaf extract is also reported to have activity in increasing the number of megakaryocytes in the bone marrow, so that it can increase the number of platelets in the blood<sup>2</sup>.

Preclinical research shows that guava leaf ethanol extract can increase the number of megakaryocytes in the bone marrow so that it can increase the number of platelets in the blood of mice. If viewed from the aspect of immunology in this study occurs through the mechanism of increasing the number of cytokines, GM-CSF (granulocyte macrophage colony stimulating factor), IL (interleukin). Furthermore, the stimulation of proliferation and differentiation which is controlled by TNF (tumor necrosis factor-alpha) and IL 3 can increase

the number of platelets in the blood<sup>3</sup>. In vitro test, showed an effect in inhibiting the growth of dengue virus<sup>4</sup>. Other research showed that guava leaf extract could inhibit viral replication up to 92.6% in vitro<sup>5</sup>. Based on clinical trials conducted at RSUP. DR. M. Jamil Padang in 2013, it is known that the supplementation of guava leaf extract (*P. guajava*) significantly increased the number of platelets in the treatment group compared to the control group<sup>2</sup>. Another study conducted at the hospital. Dr. Soetomo Surabaya, HasanSadikin Hospital Bandung, and CiptoMangunKusumo Hospital Jakarta in 2006-2007 showed that administration of guava leaf extract syrup in DHF patients significantly increased the number of platelets in<sup>67</sup> treatment group compared to the control group<sup>6</sup>. The guidelines for the management of Dengue Fever or Dengue Hemorrhagic Fever state that the therapy used in the management of Dengue Fever or Dengue Hemorrhagic Fever is the use of crystalloid or colloid isotonic fluids.

The use of paracetamolantiperetic if fever and avoid the use of other NSAIDs such as ibuprofen and aspirin and the administration of antiemetic's if necessary<sup>1</sup>. he use of adjuvant therapy such as the use of guava leaf extract has not been officially regulated in the guidelines for the treatment of Dengue Hemorrhagic Fever or Dengue Hemorrhagic Fever, but based on previous research studies have shown a positive effect on length of stay and platelet value, so it is important to prove it through this study. Parameters that will be observed are increased levels of platelets and decreased length of stay of patients.

## II. LITERATURE REVIEW

### 1. Dengue Hemoragic Fever dan Dengue Fever

Dengue is a disease caused by one type of the dengue virus. Dengue virus has 4 serotypes namely Dengue Virus-1 (DEN-1), Dengue Virus-2 (DEN-2), Dengue Virus-3 (DEN-3), Dengue Virus-4 (DEN-4) (Tirtha, 2008). . Dengue virus is a small nucleated RNA virus, equipped with an envelope and is a member of the Flaviviridae family of the Flavivirus genus. This virus is transmitted through the bite of the *Aedes aegypti* mosquito. Dengue fever is generally presented with fever, muscle aches, joint pain, headache, rash, leukopenia and thrombocytopenia. The bad condition of Dengue Fever is Dengue Hemorrhagic Fever which can cause death. Dengue Hemorrhagic Fever is often characterized by a fever of 2-7 days accompanied by bleeding<sup>1</sup>

### 2. Pathophysiology of Disease

Dengue Hemorrhagic Fever is a type of infection caused by the dengue virus which is mostly transmitted by the female *Aedes aegypti* mosquito. The virus that enters the body through the mosquito bite will then multiply in the reticuloendothelial system and will then be followed by viremia for 5-7 days. Furthermore, the virus in the blood will be captured by macrophages and process it into APC (Antigen Presenting Cell). Antigen attached to these macrophages will activate helper T cells and attract other macrophages to phagocytize more viruses. The virus also activates B cells which will release antibodies and mediators of inflammation such as anaphylactocin, histamine and serotonin, thereby increasing the permeability of the capillary walls of blood vessels resulting in extravasation of intravascular fluid. This results in reduced plasma volume, hypotension, and hypoproteinemia. In addition, the release of various inflammatory mediators in the body will cause symptoms such as fever, joint pain, muscle malaise and others. In severe cases of DHF even the total plasma volume in the body can be reduced by >20%. Hemostatic changes in patients with DHF are caused by 3 factors: vascular changes, thrombocytopenia and coagulation disorders. After the incubation period, this disease will be followed by 3 stages, namely the fever (febrile) stage on days 1-3 where day 2 is the peak of the fever, a critical period / shock bleeding (on days 4-6) and a recovery period (Recovery Phases). ) on days 7-10<sup>7</sup>.

### 3. Guava Leaves (*P. guajava*.)

Guava leaves have traditionally been used as a remedy for diarrhea. Micro-lac-induced diarrhea in experimental rats can be inhibited using guava leaf extract with a narcotic-like mechanism, proving that guava leaves have anti-cough and antimicrobial properties<sup>47</sup><sup>1,8</sup>. Guava leaf extract contains flavonoid compounds quercetin and tannins which have the property of inhibiting the activity of the reverse transcriptase enzyme which was tested using reverse transcriptase in mice. It was concluded that guava leaf extract could help inhibit the growth of RNA (ribonucleic acid) core viruses. Previously, it was investigated the efficacy of the tannin content of guava leaf extract, it was stated that the tannin from guava leaf extract could inhibit the activity of the reverse transcriptase enzyme from tumor RNA viruses using polyadenylic acid-oligotymidylic acid primers and could even inhibit DNA-polymerase enzyme activity although its activity was higher low, because DNA (deoxyribonucleic acid) is considered more stable than RNA. Oral administration of guava leaf extract can help in the treatment of viral infections, both those with RNA nuclei, such as Dengue, hepatitis A, hepatitis C, HIV (human immunodeficiency virus), as well as those with DNA nuclei such as hepatitis B, dengue, influenza, and others<sup>9,10</sup>.

Several pre-clinical studies have shown that standardized ethanol extract of guava leaves shows that in mice used as research subjects, guava leaf extract can increase the number of megakaryocytes in the bone<sup>46</sup>

marrow so that it can increase the number of platelets in the blood. If viewed from the aspect of immunology in this study occurs through the mechanism of increasing the number of cytokines, GM-CSF (granulocyte macrophage colony stimulating factor), IL (Interleukin). Furthermore, the stimulation of proliferation and differentiation which is controlled by TNF (tumor necrosis factor) and IL 3 can increase the number of platelets in the blood<sup>3</sup>. Based on the in vitro test, it showed an effect in inhibiting the growth of dengue virus<sup>4</sup>. Research conducted by Guntur et al (2017) also showed that administration of guava leaf extract can stimulate thrombopoietin so that it is useful in increasing platelets in dengue fever patients<sup>6</sup>.

Based on some of the results of the bioactivity test above, it shows that the possibility of the truth of the hypothesis, that the administration of guava leaf extract is able to stimulate the formation of platelets, is able to reduce vascular permeability, has activity against Dengue virus infection so that it is expected to be able to prevent the occurrence of thrombocytopenia which leads to shock and death. Some results of acute toxicity tests related to the use of guava leaves (Psidiumguajava Linn) stated that in preclinical acute toxicity tests carried out on wistar rats using water extract at a dose of 10-50 mg/100 grams showed no harmful effects after 72 hours<sup>11</sup>. Another study stated that wistar rats given guava leaf (P. guajava) water extract at a dose of 5 g/kg did not produce toxicity and LD50 appeared at doses > 5 g/kg. In the extract using ethyl acetate, the dose did not produce toxicity at a dose of 1.4 g/kgBW and the ethanol extract at 2.05 g/kgBW did not show any signs of toxicity<sup>11,12</sup>.

Several studies to look at the potential side effects of guava leaves (Psidium folium) have shown that until now there have been no reports of side effects from the use of guava leaves and the use of guava leaves as therapy is declared safe<sup>11,13</sup>.

### III. METHOD

#### Materials

Capsules of guava leaf extract given to DF/ DHF patient's in 2015-2017 at PKU Muhammadiyah Wonosobo Hospital.

#### Study subjects

Study design: this is an observational study with cohort retrospective design. The instruments of the study are obtained from the secondary data of medical records at Medical Record Unit of PKU Muhammadiyah Wonosobo Hospital in the period of 2015 to 2017.

#### Study Setting

this study took place in PKU Muhammadiyah Wonosobo Hospital. PKU Muhammadiyah Wonosobo Hospital is a type C hospital and is the 2<sup>nd</sup> level health facility.

Study Subject: the subjects of this study are patient's fulfilling inclusion and exclusion criteria. The inclusion criteria are that the patients are diagnosed with DF/DHF with ICD A90 or A91 in the age of  $\geq 18$  years old. The exclusion criteria are patient's with hematology disorders, heart or lung diseases, in salicylic acid or aspirin therapy, incomplete thrombocyte test, in other therapy containing other form of guava leaf extract (e.g. sachet). As many as 107 DF/DHF patients are divided into 2 groups, i.e. the one given guava leaf extract capsules (n=52) and the other one without guava leaf extract capsules/placebo (n=55).

#### Data analysis

Characteristic test is done using univariate analysis. The statistical test for non-paired categorical imperative hypothesis test is conducted using chi-square for nominal data. chi-square is used to analyze the characteristic of patient's gender and symptom. The paired numerical comparative hypothesis test is done using unpaired t-test for interval data. The unpaired t-test is used to analyze age, temperature, initial thrombocyte level, and fever days.

### IV. RESULTS AND DISCUSSION

#### Patient's Characteristics

The patient's characteristics observed in this study are gender, age, temperature, initial thrombocyte level, fever days, and patient's symptom. The data is divided into two groups, i.e. the group with guava leaf extract capsules (n=52) and the other group without guava leaf extract capsules/placebo (n=55) and reported in mean: mean $\pm$ SD, number (n) or frequency (%). p value shows the statistical significance of both groups. The Characteristics of DF/DHF Adult Patient's hospitalized at PKU Muhammadiyah Wonosobo Hospital described in table 1. Based on the gender, it is found that there are more male patient's than the female ones, i.e. 56 male (52.34%) and 51 female patient's (47.66) with  $p > 0.05$ . A study in South India on 641 Dengue Fever atau Dengue Hemorrhagic Fever patient's finds that there are 54% male patient's and 46% female patient's (10). A research conducted by Zumaroh (2015) finds that among 57 DHF cases in Puskesmas Putat Jaya, there are 54% male patients and 46% female patient's (11).

**Table I.** Characteristics of adult DF/DHF patients hospitalized PKU Muhammadiyah Wonosobo 2015-2017.

Patient's Characteristics	guava leaf extract capsules (n=52)	Placebo (n=55)	p value
Male (n%)	28 (53.85)	28 (50.91)	0.761
Age (mean±SD)	40,90±13.481	37,98±15.542	0.302
Temperature (mean±SD)	37.26±0.933	37.34±1.06	0.672
Initial Thrombocyte Level (mean±SD)	75.71±41.83	88.21±37.49	0.106
Fever Days (mean±SD)	3.85±1.66	3.64±1.91	0.547
Symptom			
Fever (n%)	43 (83.33)	44 (80.95)	0.342
Nausea, vomiting (n,%)			
Headache (n,%)			
Heartburn (n,%)	32 (61.90)	39 (71.43)	
Joint pain (n,%)			
Faint (n%)	21 (40.48)	16 (28.57)	
Bleeding (n%) (scurvy, melena, hematuria, red spots)	10 (19.05)	10 (19.05)	
	9 (16.67)	9 (16.67)	
	6 (11.90)	6 (11.90)	
	1 (2.38)	3 (4.76)	

\*unpaired t-test, chi-square

The average age of *Dengue Fever* or *Dengue Hemorrhagic Fever* patient's with guava leaf extract capsules in this study is 41 years old while the average age of patient's in group placebo is 38 years old. It shows that there is no significant difference on patient's age in the two groups,  $p > 0.05$ . A previous study shows that 95% DHF cases involve patient's in the age of 15-44 years old and 3.64% cases involve patient's around the age of >45 years old (12). A research by Zumaroh (2015) finds that among 57 DHF cases at Puskesmas Putat Jaya, the percentage of 0-11 month-old patient's is 11%, 1-5 years old is 33%, 6-12 years old is 33%, 13-18 years old is 11%, and 19 to >50 years old is 12%<sup>14</sup>.

Based on the data on table 1, it is found that the base line score of the initial thrombocyte average level of patient's with guava leaf extract capsules is 75.71 ( $\times 10^3/\mu\text{L}$ ). Meanwhile, the initial thrombocyte average level of patient's without guava leaf extract capsules is 88.22 ( $\times 10^3/\mu\text{L}$ ). The initial thrombocyte average level of the two groups do not differ significantly showed ( $p > 0.05$ ). Viewed from the DF/DHF patient's illness phase, it is found that their thrombocyte level decreases starting on the 2<sup>nd</sup> day of the fever with the lowest thrombocyte level in the 4<sup>th</sup>-6<sup>th</sup> day. On the other hand, the peak of fever happens in the 2<sup>nd</sup> day. Afterwards, the patient's body temperature gradually decreases.

Based on the data on table 1, it is found that DF/DHF patient's mostly symptom on fever (82.14%), nausea-vomiting (66.67%), headache (34.52%), abdominal pain (19.04%), joint pain (16.67%), faint (11.90%), bleeding (scurvy, melena, hematuria) (3.57%). The symptom are in line with the clinical symptoms of DF/DHF mentioned by WHO (2012) i.e. fever, rash, hemorrhagic manifestations, heartburn related to the increase of aspartate aminotransferase (AST) and nausea-vomiting<sup>1</sup>.

Based on the data of patient's characteristics, it is found that there are not significant differences of all variables between the two groups ( $p > 0.05$ ). There is no difference between patient's with guava leaf extract and placebo, showed that there is similar characteristics of the patient's involved in this research.



**The Analysis of Thrombocyte Level and Length of Stay**

**Table 2.** The Difference on the Thrombocyte Level of Both Groups based on Fever Days at PKU MuhammadiyahWonosobo Hospital in 2015-2017.

Fever Day	guava leaf extract capsules (n=52)	placebo (n=55)	p value
Fever Day 1 mean±SD n (%)	95.00±76.98 7 (36.84)	73.58±39.14 12 (63.16)	0.429
Fever Day 2 mean±SD n (%)	68.60±37.56 10 (37.04)	74.47±30.29 17 (62.96)	0.660
Fever Day 3 mean±SD n (%)	78.48±36.42 21 (48.84)	75.71±29.64 21 (51.16)	0.780
Fever Day 4 mean±SD n (%)	68.24±27.57 33 (51.56)	84.87±33.77 31 (48.44)	0.034
Fever Day 5 mean±SD n (%)	60.39±30.07 41 (51.90)	89.87±41.63 38 (48.10)	0.001
Fever Day 6 mean±SD n (%)	63.25±33.65 44 (55.00)	80.33±29.63 36 (45.00)	0.020
Fever Day 7 mean±SD n (%)	68.76±42.76 38 (51.35)	87.94±38.21 36 (46.85)	0.046
Fever Day 8 mean±SD n (%)	84.14±38.07 28 (53.85)	94.84±42.18 24 (46.15)	0.341
Fever Day 9 mean±SD n (%)	91.85±31.29 13 (54.17)	95.64±48.52 11 (45.83)	0.819
Fever Day 10 mean±SD n (%)	184.33±122.16 (66.67)	73.67±29.37 3 (33.33)	0.178
Fever Day 11 mean±SD n (%)	181.5±27.57 2 (66.67)	65.00±00.00 1 (33.33)	0.180

\*unpaired t-test

Based on the data on table 2, the unpaired t-test shows that there is a significant difference on the thrombocyte level of both groups in the 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, and 7<sup>th</sup> day of fever ( $p < 0,05$ ). The average thrombocyte level of patient's without guava leaf extract capsules is better than the ones with guava leaf extract capsules.

**Table 3.** The Difference on Patient's Average Thrombocyte Level in Both Groups during Hospital Stay at PKU MuhammadiyahWonosobo Hospital 2015-2017.

Group	N	Mean	Std.Deviation	Std.Error Mean	P value
Guava leaf extract capsules	42	77.47	28.90	4.00	0.13
Placebo	42	86.32	31.00	4.18	

\*unpaired t-test

Unpaired t-test shows that there is no significant difference on the average level of thrombocyte between patients's with guava leaf extract capsules and the patient's without guava leaf extract capsules ( $p > 0.05$ ).

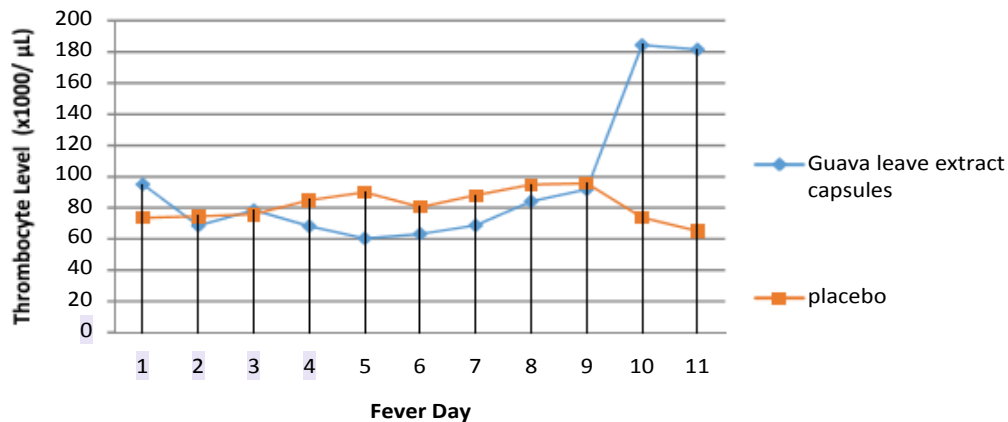
**Table 4.** The Difference on Patient’s Length of Stay at PKU MuhammadiyahWonosobo Hospital 2015-2017.

Group	N	Mean	Std.Deviation	Std.Error Mean	P value
Guava leaf extract capsules	52	4.62	1.05	0.15	0.67
Placebo	55	4.25	0.96	0.13	

\*unpaired t-test

Based on the table, unpaired t-test shows no significant difference on the length of stay (LOS) of patient’s with guava leaf extract capsules and the placebo ( $p > 0.05$ ).

Based on Figure 1, it is found that there is significant difference on the average level of thrombocyte in the 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup>, and 7<sup>th</sup> day in which the average thrombocyte level of patient’s without guava leaf extract capsules is higher than that of patient’s with guava leaf extract capsules ( $p < 0,05$ ).



**Figure 1.** The Difference on Average Thrombocyte Level based on Patient’s Fever Days

Bleeding manifestations in DF/DHF patients are mostly in the form of red spots on the skin. Meanwhile, severe bleeding symptoms which might appear are gastrointestinal bleeding, hematemesis, and melena. Bleeding in DF/DHF occurs in some mechanisms, i.e. vasculopathy, trombopathia, and thrombocytopenia, coagulopathy, dan disseminated Vascular Coagulation (DIC) (14). Vasculopathy is marked by hemoconcentration, pleura effusion or ascites which is the characteristic of blood leaking in DHF<sup>15</sup>. Trombopathy and thrombocytopenia might be caused by the descreasing of thrombocyte production by bone marrow, the increasing damage of thrombocyte in Reticulo Endothelial System (RES), and excessive thrombocyte aggregation in damaged vascular endothelium might cause excessive usage of thrombocyte<sup>16</sup>. Coagulopathy happens because the activation of continuous coagulation system and fibrinolysis which result in the decreasing of many coagulation factors such as fibrinogen II, V, VII, VIII, IX and X as well as plasminogen<sup>7</sup>. Disseminated Vascular Coagulation (DIC) is a clinical syndrome signed by the vast activation of coagulation system which result in the formation of intravascular fibrin and thus the thrombocyte in the blood veins cause the decreasing of blood flow to the organs and cause organ failures. Due to excessive coagulation deficiency of thrombocyte and other coagulation factors, severe hemorrhage might occur<sup>16</sup>.

The release of inflammation mediators in the body, *Dengue Fever* or *Dengue Hemorrhagic Fever* patient’s might experience fever, joint pain, and malaise muscle. The increase of blood veins permeability will cause hemostasis due to vascular change, thrombocytopenia, and coagulation disorders. The symptoms on *Dengue Fever* or *Dengue Hemorrhagic Fever* patient’s appear after virus incubation period. The fever phase (febrile) will occur around 3 days in which the peak of fever is in the 2<sup>nd</sup> day. The critical period/shock bleeding will happen in the 4<sup>th</sup>-6<sup>th</sup> day followed by recovery phase in day 7-10<sup>16</sup>. Based on the phases, *Dengue Fever* or *Dengue Hemorrhagic Fever* is a disease that will naturally recover in which the amount of thrombocyte will automatically increase in day 7-10. If the patient is able to withstand after the 24-48 hours of critical phase,

gradual reabsorption of extravascular fluid compartment will occur in 48-72 hours. During this phase, the hemodynamic status will be stable, health will recover, appetite will come back, gastrointestinal symptom will decrease, and the amount of leukocyte and thrombocyte will increase. However, the increase of thrombocyte level will not be as fast as leukocyte. The amount of patient's thrombocyte will naturally increase up to more than 150.000/ $\mu$ L in 2-3 days after the critical period. During the recovery period, there should be fluid intake restriction to prevent fluid overload<sup>17</sup>. A research by Sari *et al.* (2017) on the pattern of thrombocyte level of patient's infected with dengue shows that the average thrombocyte level of DHF patient's with the critical period in the 3<sup>rd</sup> day is 52.382 sel/mm<sup>3</sup> and it starts to increase in day 7<sup>18</sup>.

The pathogenesis of thrombocytopenia is not fully known. It might happen due to many factors related to apoptosis mechanism as well as the existence of lysis due to the involvement of complement system and platelet antibody. Another mechanism is the occurrence of complex antigen-antibody between virus and with antibody which later activate coagulation system<sup>11</sup>. Thrombocytopenia can also happen due to the occurrence of antithrombocyte antibody increase marked by the formation of IL-6 which stimulates excessive activation of cell B to form antibody. The reaction is antithrombocyte autoantibody with the peak in the 5<sup>th</sup> day of fever<sup>2</sup>. Other than IL-6, some inflammation mediators related to dengue shock are cytokinin, IL-2, and TNF  $\alpha$ . The working mechanism of those inflammation mediators are as mediator in natural immunity caused by the stimulus of infectious substances as a regulator which control activation, proliferation, lymphocyte differentiation, non-specific inflammation cell activator, growth stimulator, and mature leukocyte differentiation<sup>10</sup>. Thrombocyte caused by the increase of vascular permeability might also happen due to the activation of complement system, i.e. the release of C3a and C5a which are strong anaphylatoxin in increasing vascular permeability. The demolition of platelets done by complement activation as a chain between thrombocyte with the fragments and antigens of dengue virus, or it might also happen due to direct attack to thrombocyte without dengue fever through immune response<sup>8</sup>.

The extract of guava leaf contains flavonoid compounds, i.e. tannin and quercetin which works in DF/DHF disease through the mechanism of reverse transcriptase enzyme tested using reverse transcriptase pre-clinically to help inhibit RNA virus<sup>9,10,19</sup>. Some pre-clinical studies show that in standardized ethanol extract of guava leaf in mice as the subject of research, the extract of guava leaf can increase the amount of megakaryocyte in bone marrow which at the end can increase the amount of thrombocyte in blood. Viewed from immunology aspect, it happens through the mechanism of cytokinin increasing amount, GM-CSF, IL. Next, proliferation stimulus and differentiation controlled by TNF  $\alpha$  and IL 3 can increase the amount of thrombocyte in blood<sup>3</sup>.

A pre-clinical research conducted by Hasimet *et al.* (2015) using Sprague-Dawley rats induced with quinine. Quinine is a medication often used for malaria and can cause thrombocytopenia. This research shows that the use of 70% ethanol extract of guava leaf with the dose of 50 mg/kg of rat's weight p.o combined with red yeast rice extract with the dose of 400 mg/rat's weight p.o for 14 days can increase the amount of rat's thrombocyte level<sup>20</sup>. The conversion dose of guava leaf extract from rat to human dose is 2000 mg (2 gram). However, it should be combined with the extract of red yeast rice. A research conducted by (2004) on the effect of 70% ethanol extract of guava leaf on the amount of megakaryocyte of rats finds that 3 of the tested ethanol extract doses are dose 1: 107.927 mg extract (containing 2.655 mg quercetin), dose 2: 215.854 mg extract (containing 5.31 mg quercetin) and dose 3: 431.708 mg (containing 10.62 mg quercetin). It is known that the 3 doses are significantly different in increasing the amount of megakaryocyte compared to the control group in which the 431.708 mg of extract dose (containing 10.62 mg quercetin) is the best dosage in increasing the rat megakaryocyte amount<sup>21</sup>.

The medication procedures of DF/DHF based on WHO (2012) are such as through the intake of crystalloid isotonic solution such as NaCl 0,9% or ringer lactate, paracetamol intake if the patient experiences fever by avoiding other NSAID which may cause the decreasing of thrombocyte amount and cause severe bleedings. The administration of antiemetic might also be done. Other supportive therapies that can be done are such as the distribution of oral rehydration solutions (ORS), fruit juice, as well as drinks containing electrolyte and sugar. Based on medication guideline of DF/DHF by WHO, there is no suggestion to implement additional supplements such as the capsules of guava leaf extract. The success key of DF/DHF therapy is maintaining the fulfillment of patient's fluid needs during critical period. If the patient can bear after 24-48 hours of critical period, a gradual reabsorption of extravascular compartment fluid will occur in 48-72 hours. During recovery phase, hemodynamic status will be stable, health gets better, appetite returns, gastrointestinal symptoms decrease, the amount of leukocyte as well as thrombocyte increases. The amount of patient's thrombocyte will increase up to 150,000/ $\mu$ L in 2-3 days after the critical phase<sup>1</sup>. The increase in platelets during the recovery period occurs through a mechanism whereby the bone marrow of DHF patients who show bone marrow hyperplasia at the onset of fever with inhibition of maturation of all hemopoiesis systems, especially megakaryocytes. After day 5 to day 8 fever there is a rapid increase in erythropoiesis and hypercellularity and is mainly filled with erythropoiesis with the formation of highly active platelets<sup>6</sup>.

## V. CONCLUSION

The guava leaf extract addition to the standard therapy in treating DF/DHF patient's in private hospital in Indonesia is not affecting the platelet count and length of stay.

**Ethical Clearance:** The ethical clearance was taken from research committee of Ahmad Dahlan University, Yogyakarta, Indonesia.

**Source of Funding:** This research was funded privately and did not receive funding from any party.

**Conflict of Interest:** The author confirm that there are no conflicts of interest to disclose.

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