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Original Article

Effect of *Sterculia quadrifida* R. Br Stem Bark on Hematological Profile and Thrombopoietin Levels in DENV-3-infected Wistar Rats

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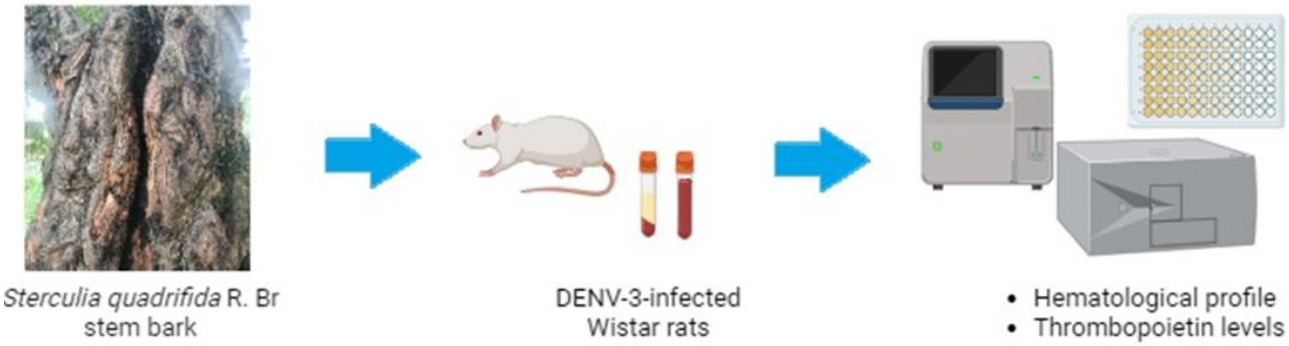
ABSTRACT

Dengue is an infectious disease that induces various alterations in the hematological profile and THPO levels that correlate to the disease severity. This study aims to investigate the effect of *Sterculia quadrifida* R. Br stem bark extract on the hematological parameters and THPO levels of DENV-3-infected Wistar rats. A total of 27 male rats were divided into three groups: healthy, dengue, and treatment (dengue and extract). The extract was orally delivered at a 1500 mg/KgBW dose once daily for seven days. Blood samples were collected on days 1 (healthy group), 5, and 8 (dengue and treatment group). The platelet, MCV, MCH, and MCHC in the dengue and treatment group showed no significant difference ($p>0.05$) on days 5 and 8 compared to the normal values, 876 ± 44.11 10^3/mm^3, 56.34 ± 1.42 fL, 18.56 ± 0.54 pg, and 32.88 ± 0.56 g/dL, respectively. Compared to the healthy group, hematocrit, leukocyte, hemoglobin, and erythrocyte in the dengue and treatment group displayed significant differences on both days and RDW-CV on day eight alone. Post-hoc test on the fifth day revealed that the treatment group showed significant differences in hematocrit and leukocyte levels compared to the dengue group. THPO levels on day five in the dengue and treatment group were displayed at 30.28 ± 6.72 pg/ml and 35.75 ± 28.55 pg/ml, respectively, showing statistical difference ($p<0.05$) compared to the healthy group, 40.32 ± 7.72 pg/ml. The results showed that *S. quadrifida* can reduce leukocytosis and hemoconcentration and might also have the potential to increase THPO levels during dengue infection. This study was the first to report dengue-infected Wistar rats' hematological profiles and THPO levels.

GRAPHICAL ABSTRACT



Introduction

Dengue is a viral infection typically prevalent in regions characterized by tropical and subtropical climates and spread by the bite of the Aedes mosquito. Dengue virus (DENV), an RNA virus composed of four serotypes (DENV1-DENV4), is responsible for the development of a disease characterized by a range of clinical symptoms ranging from moderate to severe [1]. Dengue infections occasionally emerge as epidemics characterized by a seasonal pattern, where the frequency of infections escalates during and after the rainy season. Thus far, the current estimate suggests that between 100 and 400 million people worldwide are annually infected with the disease. According to the World Health Organization (WHO), there has been a significant increase in the number of reported cases of dengue fever over the past two decades. Specifically, the reported cases have risen from 505.430 in 2000 to over 2.4 million in 2010 and 4.2 million in 2019, with 70% of patients in the Asian region [2]. The diagnosis of dengue fever can be established by evaluating clinical symptoms and performing several laboratory examinations, including hematology analysis and several specific tests such as the viral antigen test (NS-1 protein), antibody testing, and genomic sequencing [3, 4]. The hematological profile reported in dengue typically indicates thrombocytopenia, leukopenia, and elevated hematocrit levels [1, 4]. Thrombocytopenia is a commonly used clinical parameter to evaluate the severity of dengue infections. The mechanism of thrombocytopenia in dengue infection remains incompletely elucidated. However, it is thought to result from bone marrow suppression induced by DENV. This suppression leads to damage in progenitor cells, destruction of megakaryocytes, and alterations in regulatory processes within the bone marrow. An approach to evaluate this suppression is by analyzing thrombopoietin (THPO) levels, a cytokine that regulates megakaryocyte and platelet formation by activating the c-MPL receptor. Thrombopoietin was discovered to elevate as a compensatory mechanism in response to decreased platelet count [5, 6]. At present, there is no specific therapy for the management of dengue. The treatment employed for dengue is solely supportive and symptomatic, aimed at treating the clinical symptoms. Consequently, utilizing traditional plants (natural medicine) as the primary resource for dengue therapy is highly imperative. Developing countries, particularly in Asia and Africa, continue to rely on traditional medicine as their primary means of preventing and treating numerous diseases. This tradition has been perpetuated and transferred from ancient times to today [7]. *Sterculia quadrifida* R. Br, commonly referred to as peanut tree, is a medicinal plant frequently used by the people of Timor Island, Indonesia (local name: Faloak), to treat several diseases, such as hepatitis, rheumatism, and to recover stamina.

This is thought to be due to the presence of flavonoids, alkaloids, terpenoids, phenolics, and saponins [8]. Previous studies have discovered several specific compounds, including (+)-catechin [9], epicatechin [10], and scopoletin [11]. The stem bark of *S. quadrifida* also has been found to possess potent antioxidant properties [12, 13], and hepatoprotective activity causes its ability to inhibit all stages of the hepatitis C virus (HCV) life cycle *in vitro* [10]. HCV and DENV share several features as they belong to the Flaviviridae family. These two viruses display several similarities [14-16].

The thorough study of Wistar rats as an animal model for dengue remains lacking. A comprehensive review of the literature revealed that there is limited research obtainable on the topic of dengue infection in Wistar rats. The only study identified was conducted by Triyono [17], which investigated the effects of *Monascus jmbA* rice on cytokine profiles and platelet counts in Wistar rats infected with DENV-3. Hence, this study aims to investigate the characteristics of Wistar rats infected with dengue and assess the effects of *S. quadirifida* stem bark extract on the hematological profiles and THPO levels of Wistar rats infected with DENV-3.

Materials and Methods

Ethical statement

All treatments and experimental protocols have been approved by the Ethics Committee of the Faculty of Medicine-Public Health and Nursing, Gadjah Mada University, with no. KE/FK/1452/C/2022.

Plant material

The stem bark of *S. quadrifida* was collected from a tree indigenous to Kupang City, East Nusa Tenggara, Indonesia. The infusion method is used to extract the stem bark due to its easy preparation and applicability in the community. The simplicia is dissolved in distilled water and heated to a temperature of 90 ˚C for 15 minutes [18]. The procedure is carried out singularly. After 15 minutes, the resultant infusion filtrate was collected and dried by freeze-drying to get a crude extract.

Cell culture and virus propagation

C6/36 cells (derived from *Aedes albopictus*) were cultured at 28 ˚C incubator in 10% Minimum Essential Medium/MEM (Sigma Aldrich) supplemented with 10% Fetal Bovine Serum/FBS (Sigma Aldrich), 2% Penicillin-streptomycin (Sigma Aldrich), and 0.5% Amphotericin B (Gibco). Cells were grown and maintained in T-25 flasks. Cell development was observed for 1-2 days using an inverted microscope until the cells were 90-95 % confluent. Once confluent, the medium was removed and 300 µl of the DENV-3 was inoculated and incubated for 1 hour (rock gently the T25 flask every 15-20 minutes). Subsequently, 2% MEM complete (MEM-2 % FBS, 2 % Penicillin-streptomycin, 0.5% Amphotericin B) was added and incubated for 5-7 days in a 28 ˚C incubator while observing the Cytopathic Effect (CPE) [19, 20]. The virus underwent passages four times on C6/36 cells, with each passage having an incubation period of 5-7 days.

Plaque assay

Plaque assay was used to determine the concentration of dengue virus in plaque form units (pfu). C6/36 cells with a density of 1.5 x 10^5 were cultured on 24-well plates in 10% MEM and incubated at 28 ˚C for 1-2 days until 90-95% confluent. After confluence, the medium was removed, and a 6-fold dilution of the virus was added to 2% MEM complete. Each well was inoculated with 200 µl virus dilution and incubated for 2 hours in a 28 ˚C incubator (rock plates gently every 15-20 minutes). Subsequently, discard the virus, and then a mixture of medium was added with 1% CMC and incubated for 4-6 days until plaque forms. After incubation, all the CMC overlay was removed and fixation was done using 3.7% formalin for 35 minutes. After 35 minutes, each was washed well with tap water, and then stained with 400 µl 1% crystal violet for 15-30 minutes. After staining, the crystal violet was discarded with tap water and incubated at room temperature overnight. The viral titers were expressed as pfu/ml [21].

Dengue infection

The first phase of experiments was administering the dengue infection to three rats to optimize the viral dosage and injection route. The evaluation of infections includes the assessment of the NS-1 protein using antigen rapid test method (Right Sign NS-1 Antigen Rapid Test). Rats were injected with DENV-3 via the intraperitoneal method with a titer of 1 x 10^5 pfu at a dose of 0.8 cc [17,22]. Blood samples were collected on days 1 and 3 through the retro-orbital vein. NS-1 was determined to be positive on the third day. The virus dose and injection route in this stage were then used as a protocol in the main study for the dengue and treatment (dengue and extract) groups.

Animal treatment

A total of 27 male Wistar rats weighing 200-300 grams aged 2-3 months were divided into three groups, including the healthy group, the dengue group, and the treatment group (dengue and extract). The rats underwent a week-long acclimation period in controlled conditions, with temperatures between 20-24 ˚C and humidity levels within 30-70%. Ad libitum food and drink was supplied during the adaptation phase. The lighting was regulated using a 12-hour cycle of brightness and darkness. The extract was administered orally with a 1500 mg/kgBW dose dissolved in 3 cc of distilled water. The determination of the extract dose in this investigation was established through reference to prior research conducted by Noviyanah *et al.* [23] about the acute toxicity assessment of *S. quadrifida* stem bark extract, that research reported an LD50 >2000 mg/kg, indicating a low toxicity category and the mortality absence in mice. The extract was given once a day for seven days.

Blood collection

Blood collection was carried out on the first day in the healthy group, while the dengue and treatment groups were carried out on the fifth and eighth day (via a retro-orbital vein and cardiac puncture, respectively). Rats were anaesthetized first using 0.5 cc/KgBW ketamine via the IM route before blood was taken. On day 5, blood collection was carried out via retro-orbital vein using a micro-capillary tube, and on days 1 and 8, it was carried out by cardiac puncture using a 23G needle. The amount of blood taken was 0.5-1 cc. After taking the blood on days 1 and 8, the rats were anaesthetized and euthanized by cutting the aorta.

Hematology analysis

The blood samples were collected in EDTA microtubes (0.5 cc/vial, EDTA K3). All samples were analyzed using the flow cytometry method using an automated hematology analyzer, Sysmex KX-21. The hematological profile undergoing evaluation included platelet, hematocrit, leukocyte, hemoglobin level, erythrocyte, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width-coefficient of variation (RDW-CV).

Thrombopoietin analysis

Serum levels of THPO were analyzed using an Enzyme-Linked Immunosorbent Assay (ELISA) using kits from ABclonal™ (Company ABclonal Inc, Woburn, USA), catalogue number RK06279. The cytokine concentration is determined using a standard curve.

Statistical analysis

Statistical analysis used one-way ANOVA (if data distribution was normal and homogenous) or Kruskal-Wallis (abnormal distribution), followed by a post-hoc analysis using the LSD test (Least Significant Difference) or Pairwise Comparison (Kruskal-Wallis) test using SPSS version 26 software. All the results are represented by the mean value ± standard deviation (SD). A value of $p < 0.05$ was considered statistically significant.

Results and Discussion

Effect of S. quadrifida on hematological profiles

The statistical tests conducted in this study, consisting of ANOVA or Kruskal-Wallis, and post-hoc test using LSD or pairwise comparison to

analyze changes in the hematological profile of each parameter are presented in Table 1. Significant differences between the groups were observed solely in the hematocrit levels, leukocytes, hemoglobin, and erythrocytes. Meanwhile, the other parameters resembled the values observed in the healthy group, and no significant differences were detected.

Platelets

This study determined that the platelet counts in the dengue group indicated a decrease on the fifth day compared to the healthy and treatment group. However, statistical analysis did not show a significant difference between the groups ($p>0.05$). On the eighth day, the platelet values in both groups increased compared to the healthy group. However, no statistically significant difference, as indicated in Table 1.

According to previous studies, thrombocytopenia is generally observed in mice with several conditions, such as infected with high titer virus 10^7-10^9 pfu [24, 25], and mice with specific conditions, such as immunocompromized (AG129 and G129 mice) and humanized mice [26]. Furthermore, it has been discovered that mice showed a higher degree of resistance to dengue infection due to the diminished IFN signaling, particularly to type-1 IFN, in contrast with humans, who exhibit higher susceptibility to IFN [27]. This research study aligns with the outcomes of Ferreira *et al.* [28], who conducted a study of C57BL/6 mice infected with DENV-3 titers ranging from 10^2-10^5 pfu. Their study likewise reported that platelet values remained within the normal range and exhibited no significant differences. A study by Triyono [13] also indicated that platelet levels in Wistar rats infected with DENV-3 were within the normal range and showed no significant alterations compared to rats in the healthy group.

The study results indicated that administering *S. quadrifida* stem bark did not significantly impact platelet count elevation. This phenomenon is thought to be related to the incapacity of Wistar rats to manifest clinical manifestations of thrombocytopenia in the context of dengue infection within the current research model, as well as the insufficiency of the extract itself.

Hematocrit

Dengue infection generally elevates hematocrit levels, indicating vascular leakage due to the inflammation response [29].

Table 1: Hematological findings on the healthy, dengue, and treatment groups

Parameters	Groups (Mean ± SD)				
	Day 1	Day 5		Day 8	
	Healthy	Dengue	Treatment	Dengue	Treatment
Platelet (10^3/mm^3)	876 ± 44.11	767.78 ± 210.71	887 ± 95.46	927.22 ± 124.93	937.33 ± 115.18
Hematocrit (%)	42.03 ± 1.05	48.78 ± 0.99[a*]	46.26 ±1.05[a, b]	35.01 ± 2.21[a]	35.94 ± 1.95[a]
Leukocyte (10^3/mm^3)	5.25 ± 2.33	14.4 ± 2.23[a]	11.06 ± 2.31[a, b]	6.42 ±1.89[a]	6.85 ± 2.25[a]
Hemoglobin (g/dL)	14 ± 0.49	15.42 ± 0.91[a]	15.28 ± 0.34[a]	11.54 ± 0.65[a]	11.68 ± 0.59[a]
Erythrocytes (10^3/mm^3)	7.55 ± 0.34	8.53 ± 0.43[a]	8.46 ± 0.4[a]	6.2 ± 0.62[a]	6.35 ± 0.42[a]
MCV (fL)	56.34 ± 1.42	55.36 ± 1.51	55.23 ± 2.00	56.91 ± 2.59	56.64 ± 1.72
MCH (pg)	18.56 ± 0.54	18.12 ± 0.77	18.11 ± 0.92	18.74 ± 1.07	18.42 ± 0.94
MCHC (g/dL)	32.88 ±0.56	32.77 ± 0.62	32.66 ± 0.81	33.11 ± 0.73	32.44 ± 0.83
RDW-CV (%)	13.73 ± 0.63	13.45 ± 1.143	13.74 ± 1.48	15.75 ± 1.62[a]	14.66 ± 1.14[a]

*[a] Significant difference compared to the healthy group alone ($p < 0.05$); [a, b] Significant difference compared to the healthy and dengue group ($p< 0.05$); * biased data is excluded based on the criteria established by Day and Underwood (2002); treatment group: dengue and extract; SD: Standard Deviation; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW-CV: red cell distribution width-coefficient of variation*

In this study, the hematocrit values in the groups infected with dengue and treatment exhibited a statistically significant rise on the fifth day after infection compared to the healthy group. Meanwhile, on the eighth day following infection, both dengue and treatment groups observed a significant decrease in hematocrit levels compared to the healthy group (Table 1).

The study further observed that hemoconcentration levels in the treatment group on day five post-infection were comparatively lower than those affected by dengue and were seen as significantly different (Table 1). The findings indicate that *S. quadrifida* could decrease hemoconcentration, which is thought to be caused by vascular leakage due to increased inflammatory responses. *S. quadrifida* bark exhibits immunomodulatory properties and contains catechin derivative chemicals with significant anti-inflammatory effects [9-11, 30]. On the eighth day post-infection, a significant decrease in hematocrit levels was observed in the dengue and treatment groups compared to the healthy group. This phenomenon is thought to be caused by the blood collection procedure on the fifth day.

Leukocyte

The leukocyte counts in the dengue and treatment groups showed a statistically significant increase on day five post-infection, followed by a significant return to normal amounts through day 8. The leukocyte values on day 5 in the treatment group indicated a decreased and statistically significant difference as opposed to the dengue group, as presented in Table 1.

Dengue commonly induces leukopenia in humans; nevertheless, there have been incidences where leukocytosis has been observed [31]. This study observed an evident elevation in leukocyte levels within the dengue and treatment groups compared to the healthy group. However, it is noteworthy that the leukocytosis seen in the treatment group was relatively lower and indicated a significant difference compared to the dengue-only group. The stem bark of *S. quadrifida* was discovered to contain flavonoid compounds, including (+) catechin [9] and epicatechin [10]. These two compounds are catechin derivatives with anti-inflammatory properties. In addition, a study conducted by Munawaroh *et al.* [11] showed that *S. quadrifida* stem bark contains scopoletin, which has immunomodulatory activity by enhancing macrophage phagocytosis and increasing nitric oxide production, thereby suppressing inflammatory reactions.

Hemoglobin and erythrocyte

The hemoglobin and erythrocyte levels in the dengue and treatment groups exhibited an initial increase on day 5, followed by a subsequent drop on day 8, compared to the healthy group. Nevertheless, no statistically significant alterations were observed in the levels of these two parameters between the dengue group and the treatment group ($p > 0.05$) (Table 1).

It has been shown that hemoglobin levels tend to elevate in individuals with dengue infections. The elevation in hemoglobin levels appears to be correlated with an increase in plasma leakage related to the severity of the underlying disease [32, 33]. Furthermore, it has been discovered that dengue infection has been linked to a raised level of erythrocytes [33]. On the eighth day, a significant decrease was observed in both parameters. However, this reduction may be attributed to the blood sampling procedure conducted on the fifth day.

MCV, MCH, MCHC, and RDW-CV

In this study, MCV, MCH, and MCHC values in the dengue and treatment groups decreased on the fifth day. However, no statistically significant differences were seen between the two groups, as indicated in Table 1. The values of these three parameters tend to remain within the usual range. These results align with the research undertaken by Hidayat *et al.* [34], which indicates that all three parameters exhibit a normal range and do not show statistically significant differences in primary and second dengue infections. In addition, Advani *et al.* [35] have also said that MCHC is the parameter that exhibits the most minor change during dengue infection.

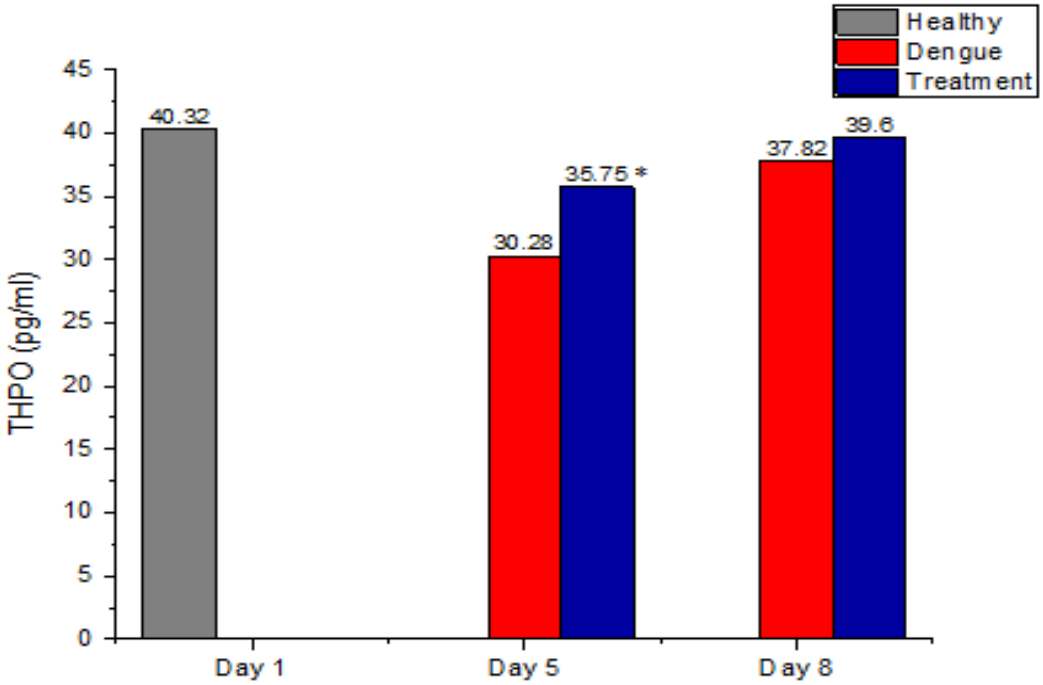


Figure 1: The THPO levels were measured in three groups: the healthy, dengue, and treatment group (dengue & *S. quadrifida*). THPO levels in the healthy group were used as reference values. On day five post-infection, there was a statistically significant difference between these three groups with a p-value < 0.05 (0.019). However, on day 8, no significant difference was displayed (p-value > 0.05 (0.659). *Biased data is excluded based on the criteria established by Day and Underwood [40]

Table 2: Post-hoc used Pairwise Comparison on day five following infection on THPO levels

No.	Groups	Mean ± SD (pg/ml)	*P-value*
1	Treatment	35.37 ± 28.55	0.659
	Dengue	30.28 ± 6.72	
2	Treatment	35.37 ± 28.55	0.008*
	Healthy	40.32 ± 7.72	
3	Dengue	30.28 ± 6.72	0.041*
	Healthy	40.32 ± 7.72	

**p-value < 0.05: statistically significant difference; SD: Standard Deviation*

On the fifth day following infection, the RDW-CW values exhibited similar levels across the three groups. However, on the eighth day, these values were observed to have increased significantly across the groups ($p<0.05$). The RDW-CV value in the dengue group exhibited a statistically significant difference compared to the healthy group. However, no significant differences were seen between the healthy group with the treatment group and the dengue group with the treatment group (Table 1). The increase in RDW-CV on the eighth day is thought to be due to the blood collection process on the 5th day.

Effect of S. quadrifida on THPO levels

The results of THPO levels can be seen in Figure 1 and Table 2. The THPO levels in the dengue and treatment groups decreased in day five compared to the healthy group and then increased in day eight after infection (Figure 1). Table 2 summarizes the significant differences discovered on day five following infection, analysed by post hoc tests using pairwise comparison. Significant differences were seen only between the healthy group and the treatment group, as well as between the healthy group and the dengue group. Compared to the dengue group, the treatment group exhibited an

elevation in THPO levels, although no statistically significant difference was seen (Table 2).

THPO is a cytokine that regulates the generation of platelets (megakaryocytopoiesis) by initiating a series of internal signalling cascades. The interaction will activate the Janus Kinase (JAK) pathway, specifically JAK2, signal transducer, and activator of transcription (STAT), which will subsequently undergo phosphorylation to promote megakaryopoiesis for platelet production, hence increasing the platelet count [6].

The study observed a reduction in THPO levels in both the dengue and treatment groups on day 5, followed by a slight rise on day 8. These findings align with a study conducted by Matondang *et al.* [36] that reported a decline in THPO levels during dengue infections in humans, followed by a subsequent increase to normal levels on days 8 and 9 during the recovery phase. A study conducted by Diansyah *et al.* [37] also found a decrease in THPO levels in dengue infection patients. This decline seems to result from the normal progression of dengue infection, which is associated with inflammation and platelet counts. Furthermore, Figure 1 demonstrates that the dengue group exhibited a lower THPO decrease than the treatment group on the 5th and 8th days following infection. This suggests that the extract from *S. quadrifida* stem bark might have the ability to enhance THPO levels, although the difference is not statistically significant. This is thought to be due to the stem bark of *S. quadrifida* containing catechin compounds that are known to have antiviral activity in several Flaviviridae family viruses [9, 10, 38]. A study by Yi *et al.* [38] showed that catechin has antiviral activity catechin against all DENV serotypes. Catechin can interfere with the post-entry stage in the replication cycle, disrupt protein translation, and decrease the DENV titer. Furthermore, the stem bark of *S. quadrifida* has been identified to contain flavonoids and exhibit potent antioxidant properties [12, 13]. Flavonoids, an antioxidant class of substances, have been observed to elevate THPO levels in cases of drug-induced thrombocytopenia (busulfan and cyclophosphamide) [39].

The present study is the first investigation into THPO levels in Wistar rats infected with dengue and examines the effect of *S. quadrifida* stem bark extract on THPO. The results of this study are expected to provide further insight into the utilization of experimental animal models for dengue infection in Wistar rats, thus facilitating future research attempts.

Conclusion

The findings of this study indicate that the extract derived from the stem bark of *Sterculia quadrifida* R. Br effectively decreases hemoconcentration and leukocytosis in dengue infections. However, it does not significantly impact an increase in platelet count. In addition, the stem bark of *S. quadrifida* might have the potency to enhance THPO levels during dengue infections, specifically on day five post-infection. The occurrence is thought to be related to the presence of flavonoids and catechin compounds, which are related to its anti-inflammatory and antiviral activity.

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