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## THE POTENTIAL OF RED DRAGON FRUIT PEEL YOGURT TO IMPROVE PLATELET LEVELS IN HEPARIN-INDUCED THROMBOCYTOPENIA IN WISTAR RATS

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### ABSTRACT

Patients infected with the dengue virus will develop thrombocytopenia which can cause bleeding and complications. One of the materials that contain antioxidants and have potential as a functional food is red dragon fruit peel. This peel can be processed into yogurt as a way to increase antioxidant function which ultimately supports the immune system of its users. This study analyzed the effect of red dragon fruit peel yogurt on the platelet levels of thrombocytopenic Wistar rats. It used a pre-post-test control group design. Male Wistar rats were randomly assigned into seven groups: K-; K+; and five treatment groups that received dragon fruit peel yogurt at doses of 5% (K1); 10% (K2); 15% (K3); 20% (K4); and 25% (K5). Thrombocytopenia was induced by 0.1 mL.100g<sup>-1</sup> BW of heparin for 3 days. The intervention was carried out for 28 days. The result showed that all groups had significant differences before and after the intervention ( $p < 0.05$ ). Tukey analysis showed that there were significant differences in all groups ( $p < 0.05$ ). Yogurt containing 25% red dragon fruit peel provides an effective dose for improving platelet levels in thrombocytopenic rats.

**Keywords:** platelets; red dragon fruit peel; thrombocytopenia; Wistar; yogurt

### INTRODUCTION

Dengue virus infection is one of the infections caused by mosquitoes. It is spread over all geographic areas and causes 100 million dengue infections every year. Deaths due to infectious diseases decreased from 2005 to 2015, but deaths due to the dengue virus increased by 48% (Malavige and Ogg, 2017). Infection caused by the dengue virus can cause dengue haemorrhagic fever (DHF). Phases in a patient with dengue include the febrile phase, the critical phase, and the recovery phase. The febrile phase occurs after an incubation process of 3 to 7 days and the patient can recover without experiencing complications. The febrile phase is an early phase characterized by an increase in body temperature to  $\geq 38.5$  °C, headache, vomiting, myalgia, joint pain, and transient macular rash. The critical phase is characterized by persistent vomiting, increased pain in the abdominal area, tender hepatomegaly, increased levels of haematocrit that coincide with a rapid decrease in platelet count, serous effusions, mucosal bleeding, and lethargy or restlessness. The recovery phase is characterized by changes in vascular permeability and occurs throughout 48 – 72 h (Simmons et al., 2012).

Dengue virus infection (DENV) occurs through the transmission of the DENV serotype (DENV 1 – 4) by the *Aedes aegypti* mosquito. These four serotypes allow for asymptomatic infection or classic symptoms of dengue

fever. Platelets are an important blood component in the coagulation process. Patients infected with DENV will develop thrombocytopenia which can cause bleeding and complications in the organs of the body. DENV will suppress bone marrow and decrease platelet production, and directly infect megakaryocytes (Castilho et al., 2020).

Studies show that there are haematological changes in patients with dengue. These include thrombocytopenia, leukopenia, lymphocytosis, and lymphocytopenia (de Azeredo, Monteiro and de Oliveira Pinto, 2015). Patients with dengue infection may develop iatrogenic complications. Patients who have severe dengue infection should routinely have haematocrit measurements including fluid monitoring. An alternative approach to control the *A. aegypti* vector is to use sterilized male mosquitoes to control the female mosquito population by reducing egg production so that the transmission of the dengue virus can be suppressed. This strategy involves the intracellular bacterium *Wolbachia* (Candra, 2010).

Food intake plays a role in maintaining immunity for people with dengue infection. Food and fluids are non-pharmacological therapies to prevent and improve various risk factors associated with infectious manifestations due to dengue. Nutritional therapy related to changes in haematological conditions can be an alternative to prevent worsening of the condition of people with dengue infection.

A symbiotic product can be classed as a functional food due to its content of probiotic and prebiotic bacteria. Intestinal microflora can be affected by food products containing probiotics in appropriate doses so that they can act as antioxidants. Microbiota, both facultative and strict anaerobes including streptococci, bacteroides, lactobacilli, and yeasts, can be found from the mouth to the colon. Prebiotics can act as a growth stimulator and support probiotic activity such as by having biofunctionality in improving intestinal health, improving immunity, and even reducing the risk of inflammation (Mofid et al., 2019).

One of the fruits that contain antioxidants and have potential as a functional food is red dragon fruit (*Hylocereus polyrhizus*) (Joshi and Prabhakar, 2020), a variety of dragon fruit that has red flesh and peel, is oval in shape, and has a sour to sweet taste. It is rich in nutrients and minerals such as vitamin B1, B2, B3, C, carbohydrates, crude fibre, niacin, flavonoids, phenolics, betacyanins, lycopene, polyphenols, and phytoalbumin (Choo et al., 2019). Red dragon fruit peel is very underutilized because it is only considered as waste. It accounts for up to 33% of the total weight of the fruit (Nurliyana et al., 2010). The peel contains betacyanin compounds including betanin, isobetanin, phyllocactin, isophyllocactin, betanidin, isobetanidin, and hylocerenin. Betacyanins are identified as the main pigment in red dragon fruit peel which is purplish red. Pectin, triterpenoids, and steroids are also found in red dragon fruit peel (Phongtongpasuk, 2016; Choo et al., 2018). The content of phenolic compounds, antioxidant activity and dietary fibre in red dragon fruit peel is higher than that in the flesh of the fruit (Nurliyana et al., 2010). Red dragon fruit peel has high antioxidant activity so that it has the potential to be developed as a natural antioxidant and even functional food.

Red dragon fruit peel can be processed into yogurt as a way to increase its economic value (Figure 1). Red dragon fruit peel yogurt is an alternative processed fermented drink to increase antioxidant function which ultimately supports the immune system of its users. Yogurt was chosen as the vehicle for processed red dragon fruit peel; because patients with dengue infection accompanied by fever need fluid intake to help restore homeostatic conditions. Also, yogurt is also easier to consume. This study aims to determine the potential of red dragon fruit peel yogurt as an alternative functional drink to improve haemoglobin, haematocrit, and platelet levels in heparin-induced thrombocytopenia in Wistar rats.

### Scientific Hypothesis

Red dragon fruit peel yogurt can improve haemoglobin, haematocrit, and platelet levels in heparin-induced thrombocytopenia (HIT) in Wistar rats.

## MATERIAL AND METHODOLOGY

### Samples

This study used male Wistar rats, weighing 160–200 g and aged 12–16 weeks. A total of 42 Wistar rats were randomly divided into seven groups.

### Chemicals

Thrombocytopenia in this study used Heparin ammonium salt, Merck, Sigma-Aldrich, form powder (biological source from porcine intestinal mucosa).

### Animals and Biological Material

This study used *Rattus norvegicus*, strain Wistar from House of Experimental Rats, Center for Food and Nutrition Studies (CFNS), Universitas Gadjah Mada, Yogyakarta, Indonesia.

The isolated culture for the red dragon fruit peel are *Lactobacillus bulgaricus* FNCC 0041 and *Streptococcus thermophilus* FNCC 0040 from CFNS, Universitas Gadjah Mada, Yogyakarta, Indonesia.

### Instruments

Hematology Analyzer, Sysmex KX-21, Kobe, Japan.

### Laboratory Methods

The automated hematology analyzer (AHA) was used to measure hemoglobin, hematocrit, and platelet levels (Whitehead et al., 2019).

### Description of the Experiment

**Sample preparation:** Whole blood was obtained from each Wistar rats and stored with anticoagulant for the measurement of the haemoglobin, haematocrit, and total platelets.

**Number of samples analyzed:** Blood samples from 42 Wistar rats were collected from the retroorbital vein (before and after intervention).

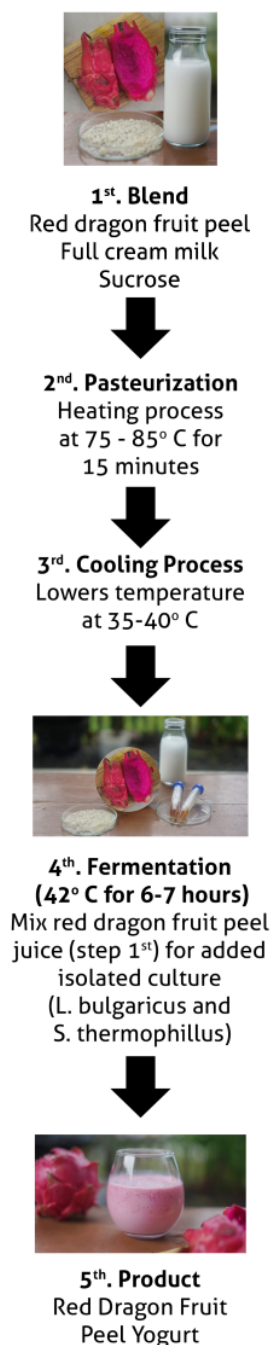
**Number of repeated analyses:** duplo

**Number of experiment replication:** duplo

Facilities and handling of the experimental animals during the study were managed based on the Guidelines for Care and Use of Laboratory Animals of CFNS, Universitas Gadjah Mada, and were approved by the Committee on the Ethics of Health, Universitas Negeri Semarang (permission number: 077/KEPK/EC/2020). The experimental animals were obtained from the House of Experimental Rats, CFNS, Universitas Gadjah Mada, Yogyakarta, Indonesia. This study used male Wistar rats, weighing 160–200 g and aged 12–16 weeks. A total of 42 Wistar rats were randomly divided into seven groups consisting of six rats per group: negative control (K-); positive control (K+); and five treatment groups that received dragon fruit peel yogurt at doses of 5% (K1), 10% (K2), 15% (K3), 20% (K4) and 25% (K5) respectively. The cage environment had a light:dark cycle of 12:12 h, room temperature of 25 ± 1 °C and humidity that was always maintained. Cage cleanliness and sanitation were also maintained to reduce stress on the experimental animals during treatment. Rats were placed in individual cages made of stainless steel. Each Wistar rat received 20 g per day standard feed and ad libitum water. The experimental animals were acclimatized for 7 days before the treatment.

**Induction of thrombocytopenia.** Thrombocytopenia was induced in the experimental animals by a single intraperitoneal injection of 0.1 mL.100g<sup>-1</sup> BW of heparin from Merck. Three days after the heparin injection, the rats experienced thrombocytopenia and received up to 200 mL yogurt containing dragon fruit peel at various concentrations for 28 days. Administration of the red dragon fruit peel yogurt was carried out in the morning.

**Experimental design.** This study used a randomized controlled pre-test post-test design in which a total of 42 Wistar rats were divided randomly into seven groups consisting of six rats each: K-, the negative control group (non-thrombocytopenic rats that did not receive any treatment); K+, the positive control group



**Figure 1** Red dragon fruit peel yogurt procedure.

(thrombocytopenic rats that did not receive any treatment); K1, thrombocytopenic rats that received 5% red dragon fruit peel yogurt; K2, thrombocytopenic rats that received 10% red dragon fruit peel yogurt; K3, thrombocytopenic rats that received 15% red dragon fruit peel yogurt; K4, thrombocytopenic rats that received 20% red dragon fruit peel yogurt; K5, thrombocytopenic rats that received 25% red dragon fruit peel yogurt.

The red dragon fruit peel yogurt; made based on the research conducted by Mardiana and Putriningtyas (Mardiana Budiono and Putriningtyas, 2020; Putriningtyas and Wahyuningsih, 2017) and, was administered orally through gastric intubation once daily for 28 days. The composition of red dragon fruit peel yogurt is full cream milk, fresh red dragon fruit peel, isolated culture (*L. bulgaricus* and *S. thermophilus*) and sucrose. After 7 hours of incubation at 42 °C, the yogurt formed was stored at 4 °C.

The rats' body weight was monitored weekly. The rats were euthanized by cervical decapitation after 28 days of intervention, then burned using an incinerator. Blood samples were collected from rats before and after the intervention.

Parameters analyzed. Blood samples were collected from the retroorbital vein and measurements of haemoglobin, haematocrit, and platelets were done using whole blood. Whole blood was obtained from each animal and stored with anticoagulant for the measurement of the haemoglobin, haematocrit, and total platelets. The parameters were measured using a automated haematology analyzer. The experiment was done in duplicate in two biological replication.

#### Statistical Analysis

The mean  $\pm$  standard deviation (SD) was calculated for each group of six rats. As all data were normally distributed, the significance of differences before and after treatments was determined using the pair t-test. The significance of differences between the groups were assessed by one-way analysis of variance (ANOVA), calculated by the SPSS version 20 program, with a significance level of  $p < 0.05$  by the Tukey HSD test.

#### RESULTS AND DISCUSSION

Table 1 shows the vitamin C and flavonoid content of red dragon fruit peel yogurt, measured using spectrophotometry. The analysis showed that the increase in vitamin C levels was not proportional to the increase in the amount of red dragon fruit peel. The flavonoid analysis also showed the same result as that for vitamin C. Flavonoids are bioactive compounds that act as antioxidants. Red dragon fruit peel is a source of phenolic antioxidants. Water-based dragon fruit peel extract has more attractive colour and better antioxidant activity (Jamilah et al., 2011). Total phenolic content in dragon fruit peel extracted using ethanol and water solvents is in the range of  $1.193 \pm 0.011 - 1.351 \pm 0.021 \mu\text{g.mL}^{-1}$  (Lourith and Kanlayavattanukul, 2013). Fermentation of milk by lactic acid bacteria can increase the nutritional content of yogurts, such as vitamins and phenols.



Table 1 Nutritional content of red dragon fruit peel yogurt.

Materials	Nutritional content	
	Vitamin C (mg.100g <sup>-1</sup> )	Total Flavonoid (mg.100g <sup>-1</sup> )
5% red dragon fruit peel yogurt	22.379	38.519
10% red dragon fruit peel yogurt	10.612	48.485
15% red dragon fruit peel yogurt	6.515	22.209
20% red dragon fruit peel yogurt	11.024	42.349
25% red dragon fruit peel yogurt	20.072	43.277

Table 2 Mean body weight of Wistar rats.

Group	Body weight (g)				
	Pre-injection	Pre	Post	Δ	p*
K-	184.17 ±4.49	189.83 ±4.58	214.67 ±4.97	24.83 ±0.75 <sup>b,c,d</sup>	0.001
K+	186.50 ±5.61	190.83 ±5.38	206.00 ±5.51	15.17 ±0.75 <sup>a,c,d,e,f,g</sup>	0.001
K1	190.00 ±4.90	194.17 ±4.71	214.17 ±4.79	20.00 ±0.63 <sup>a,b,e,f,g</sup>	0.001
K2	187.83 ±2.86	191.50 ±3.27	211.50 ±3.62	20.00 ±0.89 <sup>a,b,e,f,g</sup>	0.001
K3	184.17 ±6.97	188.17 ±7.06	212.50 ±7.31	24.33 ±0.82 <sup>b,c,d</sup>	0.001
K4	185.17 ±3.82	189.67 ±3.78	213.83 ±3.76	24.17 ±0.75 <sup>b,c,d</sup>	0.001
K5	186.00 ±4.78	190.17 ±4.96	214.33 ±5.24	24.17 ±0.98 <sup>b,c,d</sup>	0.001

Note: Sampling was done 3 days after induction of thrombocytopenia and 28 days after the start of the treatment. K-: negative control; K+: thrombocytopenia; K1: thrombocytopenia treated with 5% red dragon fruit peel yogurt; K2: thrombocytopenia treated with 10% red dragon fruit peel yogurt; K3: thrombocytopenia treated with 15% red dragon fruit peel yogurt; K4: thrombocytopenia treated with 20% red dragon fruit peel yogurt; K5: thrombocytopenia treated with 25% red dragon fruit peel yogurt. Values represent the mean ± SD for observations made on six rats in each group. Statistical analysis: \*paired t-test, significant difference ( $p < 0.05$ ); one-way analysis of variance (ANOVA); where significant, post hoc testing (least significant difference) was done for intergroup comparisons.

<sup>a</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K- values.

<sup>b</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K+ values.

<sup>c</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K1 values.

<sup>d</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K2 values.

<sup>e</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K3 values.

<sup>f</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K4 values.

<sup>g</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K5 values.

Lactic acid bacteria can grow and carry out fermentation activities maximally by utilizing sugars or carbohydrates in the media to form lactic acid and cause a decrease in pH (Hanzen, Hastuti and Lukiati, 2016; Bintari et al., 2017).

The static bodyweight of the rats was assessed weekly (Biosep-In Vivo Research Instrument, USA) to determine rats' development during the study (Table 2).

The result of the data analysis shows that there were significant differences in each group before and after the intervention ( $p < 0.05$ ). In all treatment groups, all Wistar rats gained weight; the group with the highest weight gain was the negative control group.

Weight gain in the treatment groups was probably due to the consumption of red dragon fruit peel yogurt. Fermentation using *Bacillus lactis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* can stimulate the production of metabolites such as butyrate, reducing pathobionts that cause inflammation and impair intestinal barrier function (Veiga et al., 2014).

Thrombocytopenia is a complication caused by heparin, commonly referred to as HIT. HIT can be characterized by venous and arterial thrombosis, decreased platelets, and platelet aggregation. Heparin can function to bind antithrombin as the main inhibiting protein for the coagulation process (Mulyadi and Soemarsono, 2007).

Table 3 shows that there were differences in haemoglobin, haematocrit, and platelet levels before and after treatment in all treatment groups: levels increased in the treatment groups that received red dragon fruit peel yogurt and decreased in the control group. The biggest increases were found in the group that received 25% red dragon fruit peel yogurt: 5.61 ±0.02, 13.71 ±0.10, and 192.96 ±4.53 mg.dL<sup>-1</sup> respectively. Results of the post hoc analysis showed that there were significant differences in all groups ( $p < 0.05$ ).

Thrombocytopenia is one of the criteria used by the World Health Organization as a potential indicator for dengue infection. Thrombocytopenia is associated with pro-oxidant conditions in dengue infection.

Table 3 Mean levels of haemoglobin, haematocrit and platelets in Wistar rats.

Group	Parameters tested		
	Hemoglobin (g.dL <sup>-1</sup> )	Hematocrit (mL %)	Platelets (× 10 <sup>3</sup> .μL <sup>-1</sup> )
<b>K-</b>			
Pre	14.92 ± 0.50	47.82 ± 0.21	321.12 ± 3.73
Post	14.73 ± 0.47	46.93 ± 0.26	312.54 ± 3.45
Δ	-0.19 ± 0.10 <sup>b,c,d,e,f,g</sup>	-0.88 ± 0.06	-8.58 ± 0.64
p	0.001*	0.005*	0.001*
<b>K+</b>			
Pre	9.07 ± 0.20	30.32 ± 0.72	97.13 ± 3.96
Post	8.95 ± 0.21	29.40 ± 0.71	96.03 ± 4.06
Δ	-0.12 ± 0.04 <sup>b,c,d,e,f,g</sup>	-0.93 ± 0.02	-1.11 ± 0.60
p	0.001*	0.001*	0.001*
<b>K1</b>			
Pre	9.00 ± 0.22	30.24 ± 0.49	99.21 ± 0.48
Post	10.87 ± 0.15	36.05 ± 0.49	133.37 ± 0.90
Δ	1.87 ± 0.07 <sup>a,b,c,d,e,f,g</sup>	5.82 ± 0.01 <sup>a,b</sup>	34.16 ± 0.46 <sup>a,b</sup>
p	0.001*	0.001*	0.001*
<b>K2</b>			
Pre	9.13 ± 0.36	29.20 ± 0.90	97.95 ± 0.41
Post	12.24 ± 0.34	39.05 ± 0.91	195.34 ± 2.20
Δ	3.12 ± 0.05 <sup>a,b,c</sup>	9.85 ± 0.04 <sup>a,b,c</sup>	97.39 ± 2.14 <sup>a,b,c,d,e,f,g</sup>
p	0.001*	0.001*	0.001*
<b>K3</b>			
Pre	8.67 ± 0.13	29.81 ± 0.66	98.12 ± 0.45
Post	13.61 ± 0.13	40.60 ± 0.62	238.06 ± 3.92
Δ	4.94 ± 0.05 <sup>a,b,c,d</sup>	10.78 ± 0.08 <sup>a,b,c,d</sup>	139.94 ± 3.95 <sup>a,b,c,d,e,f,g</sup>
p	0.001*	0.001*	0.001*
<b>K4</b>			
Pre	8.56 ± 0.20	29.80 ± 0.34	97.95 ± 0.43
Post	13.92 ± 0.20	42.61 ± 0.44	279.24 ± 5.08
Δ	5.36 ± 0.27	12.81 ± 0.52	181.29 ± 4.87 <sup>a,b,c,d,e,g</sup>
p	0.001*	0.001*	0.001*
<b>K5</b>			
Pre	8.63 ± 0.19	29.90 ± 0.41	98.03 ± 0.43
Post	14.24 ± 0.20	43.60 ± 0.46	290.99 ± 4.78
Δ	5.61 ± 0.02	13.71 ± 0.10	192.96 ± 4.53 <sup>a,b,c,d,e,f</sup>
p	0.001*	0.001*	0.001*

Note: Sampling was done 3 days after induction of thrombocytopenia and 28 days after the start of the treatment. K-: negative control; K+: thrombocytopenia; K1: thrombocytopenia treated with 5% red dragon fruit peel yogurt; K2: thrombocytopenia treated with 10% red dragon fruit peel yogurt; K3: thrombocytopenia treated with 15% red dragon fruit peel yogurt; K4: thrombocytopenia treated with 20% red dragon fruit peel yogurt; K5: thrombocytopenia treated with 25% red dragon fruit peel yogurt. Values represent the mean ± SD for observations made on six rats in each group. Statistical analysis: \*paired t-test, significant difference ( $p < 0.05$ ); one-way analysis of variance (ANOVA); where significant, post hoc testing (least significant difference) was done for intergroup comparisons.

<sup>a</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K- values.

<sup>b</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K+ values.

<sup>c</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K1 values.

<sup>d</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K2 values.

<sup>e</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K3 values.

<sup>f</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K4 values.

<sup>g</sup>Statistically significant difference ( $p < 0.05$ ) when compared with K5 values.

Oxidative stress can increase when there is an imbalance of oxidants and antioxidants due to internal or external exposure to stressors such as viruses (Ahmed et al., 2014). Dengue virus can induce oxidative stress in humans due to its release of proinflammatory cytokines which also influence the immunopathogenic mechanism (Chandra et al., 2013). Thrombocytopenia is also associated with lipid peroxidation.

Red dragon fruit peel yogurt contains vitamin C, a water-soluble vitamin also known as ascorbic acid which can stimulate immune function and has a role as an antioxidant (Rammohan et al., 2019). Vitamin C can increase the platelet count by modulating the platelet oxidative state and because platelets have vitamin C transporters (SVCT2) which will influence the platelets to activate vitamin C intracellularly so that it can ultimately improve cells' lipid

peroxidation condition (Safwan and Asar, 2017). Vitamin C can alter the oxidative state of thrombocytopenia by inhibiting the expression of CD40L, a transmembrane protein that is produced in both proinflammatory and prothrombotic conditions (Mohammed et al., 2017). Vitamin C content is also related to haemoglobin status (Ahmed et al., 2014). Previous studies have shown that the consumption of 25 – 1000 mg ascorbic acid added to a liquid formula containing 4.1 mg of nonheme iron can increase iron absorption by 0.8 – 7.1%, thereby improving haemoglobin status (Safwan and Asar, 2017).

Endothelial damage in DENV is caused by the dengue virus itself. Thrombocytopenia is responsible for bleeding in patients. The condition of thrombocytopenia can be influenced by various factors such as reactive immune response and decreased platelet production, activation, and apoptosis (Mutiara et al., 2019). Dengue virus can bind directly to prothrombin, thus inhibiting its conversion to thrombin and decreasing coagulation activation, thrombin formation, and associated bleeding complications.

Yogurt can release bioactive peptides and bacteriocins.  $\beta$ -Casein-derived peptides released from yogurt can trigger goblet cells to secrete mucin either in vitro or in vivo. The lactic acid bacteria found in yogurt can break down simple carbohydrates to produce lactate, acetate, or propionate (El-Said et al., 2014). These bacteria can affect the breakdown of carbohydrates, alter the metabolic output, and provide an important substrate that supports the development of intestinal microbes (Fernandez et al., 2017).

The increase in haemoglobin, haematocrit, and platelet levels after consumption of red dragon fruit peel yogurt could be due to its phenolic, flavonoid, and anthocyanin content. Phenolics, also called phenols, are found in various tropical plants (Kapcum, Uriyapongson and Uriyapongson 2020). Flavonoids in dragon fruit peel have an antioxidant action that can affect immunity. Flavonoids also have antiviral activity against several RNA viruses (Clain et al., 2019); this will probably not change the genotoxic effect on several mammalian cells, including human primary cells which are compatible with arboviral infection. Flavonoids also have a stimulant effect on blood cell production and may also trigger platelet production and platelet aggregation through arachidonate 12-lipoxygenase (ALOX 12), also known as platelet-type lipoxygenase as well as platelet activation factor receptor (PTAFR). Increased activity of this gene is required for platelet production and activation. The ALOX 12 gene is expressed in megakaryocytes and is responsible for the production of 12 hydroxyeicosatetraenoic acid (12-HETE) from platelets. The PTAFR gene is also a precursor for platelet production (Agustina, 2019).

Red dragon fruit peel yogurt is made using *L. bulgaricus* and *S. thermophilus*. The fermentation process not only creates a distinctive aroma and taste but can increase the antioxidant potential of the drink. Research has shown that the level of betanin in fermented red dragon fruit peel drink (1.42%) is more than that of the flesh (0.23 – 0.39%) (Stintzing, Schieber and Carle, 2002; Choo et al., 2018).

Compounds other than flavonoids contained in red dragon fruit peel are betacyanins and betalains, the content of which in red dragon fruit peel is higher than in the fruit flesh. Betalains are water-soluble polyphenolic pigments

composed of yellow betaxanthins and purplish-red betacyanins. Betacyanins consist of betalamic acid and an acyclic amine group which is excellent electron donors which enables them to scavenge free radicals. The red-purple betacyanin pigments in red dragon fruit peel have recently been suggested as a potential betalain source (Liaotrakoon et al., 2013).

The increases in haemoglobin, haematocrit, and platelet levels were directly proportional to the dose of dragon fruit peel given. This mechanism is possible because flavonoids are also known to be able to capture and neutralize free radicals such as ROS or RNS, which are associated with phenolic OH groups so that they can repair damaged tissue or inhibit the inflammatory process (Schwartz et al., 2010).

The flavonoids in red dragon fruit peel are catechin, epicatechin, quercetin, myricetin, and kaempferol, of which catechins have the highest concentration in red dragon fruit peel. Catechin is thought to inhibit DENV infection (Simon, Sutherland and Pryzdial, 2015). The dragon fruit peel contains flavonoids in the form of catechin polyphenol active compounds: epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC) (Morais et al., 2019). The mechanism by which virus entry to the host is inhibited by EGCG begins in the early stages of the viral replication cycle. The EGCG in red dragon fruit peel yogurt can inhibit the virus adherence to the cell surface through direct interaction with the outer membrane of dengue virus particles (Clain et al., 2019). Flavonoids are also thought to increase granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3), stimulating megakaryopoiesis to increase platelet levels (Wiyasihati, Wigati and Wardani, 2013).

## CONCLUSION

Red dragon fruit peel yogurt is effective for improving haemoglobin, haematocrit, and platelet levels in HIT in rats. Yogurt containing 25% red dragon fruit peel provides an effective dose for improving haemoglobin, haematocrit, and platelet levels in thrombocytopenic rats.

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