

Exploration of the Analgesic and Antipyretic Effects of Mangosteen Peel Methanol Extract (*Garcinia mangostana* L) in Male Wistar Rats

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Abstract: Analgesic-antipyretic is a compound that is often used to reduce pain and fever. A natural plant that has the potential as an antipyretic analgesic compound is mangosteen fruit (*Garcinia mangostana* L). This study aims to find out the analgesic and antipyretic effects of mangosteen peel methanol extract on male Wistar rats. This type of research is experimental, design Post-Test Only Control Group Design. The research was conducted at the Pharmaceutical Laboratory of the University of North Sumatra Medan, January - March 2021. The test was conducted using 25 mice divided into 5 groups. Data analysis uses SPSS test one-way ANOVA if the data does not distribute normal Kruskal-Wallis. The results of the study 5 hours after treatment, the body temperature of the mice experienced a significant change, the value of $P < 0.05$ (Value $P = 0.004$). Where the methanol extract group of mangosteen skin III showed the lowest body temperature 5 hours after treatment which was $36.14 \pm 0.12^\circ\text{C}$ and the methanol extract group Mangosteen-III skin also showed a significant difference to the control group that showed the highest body temperature of $37.36 \pm 0.46^\circ\text{C}$. The least amount of geliat found in the mangosteen-III skin methanol extract group was 5.22 ± 1.91 and this number showed a significant difference with the mangosteen- I skin methanol extract group (12.81 ± 3.12) and the control group (11.10 ± 1.91). In conclusion, the results of mangosteen skin testing have antipyretic and antipyretic effects, found at 5 hours after treatment and the highest dose is 750 mg/ kgBB. Meanwhile, the results of the hematologic examination showed a significant decrease in line with the increase in the dose of mangosteen skin methanol extract given.

Keywords: mangosteen skin; analgesic; antipyretic; hematologic

I. Introduction

The use of folk remedies is now trending again, this is because of their low cost and low side effects (Salmerón-Manzano, Garrido-Cardenas and Manzano- Agugliaro, 2020). Plants that can potentially be antipyretic analgetic compounds are mangosteen fruit (*Garcinia mangostana* L) (Puspitaningrum, Kusmita and Setyani, 2014); (Ponggele, 2013). Analgetic-antipyretic is a compound that is often used by humans of all ages to reduce pain and fever due to various things. In general, analgesic is divided into two, opioid and nonopioid anaesthy ((Hilal- Dandan and Brunton, 2013); (Pathan and Williams, 2012)). Most analgesic drugs also provide antipyretic effects, and vice versa antipyretics can also reduce the pain suffered by patients (Ferreira and Lopes, 2016). Windarini research results, et al, stated that methanol extract of mangosteen peel (*Garcinia mangostana* L.) contains saponin compounds, alkaloids, flavonoids, triterpenoids, tannins, and polyphenols ((Windarini, Astuti and Wardani, 2011); (Bahri, Pasaribu and Sitorus, 2012)). Flavonoids in mangosteen peel can inhibit prostaglandins so that they have antipyretic effects (Suwertayasa, Bodhy and Jaya Edy, 2013). Mangosteen peel is also considered an

anti-inflammatory by inhibiting nitric oxide (NO), prostaglandin E2 (PGE2) production, and can suppress COX-2 expression (Parmita, In and Armyanti, 2017). According to Jinsrat (1992) in Putri (2015), some of the main compounds of mangosteen peel content that are reportedly responsible for some pharmacological activities are the xanton group. Identified xanton compounds are 1,3,6-trihydroxy-7-methoxy-2,8-bis (3methyl2-butenyl) - 9H-xanten-9-on and 1,3,6,7-tetrahydroxy-2,8-bis(3-methyl-2-butenyl)-9Hxanten-9-on. Both are better known as alpha-mangostin and gammamangostin ((Putri, 2015) : (Putra SR, 2012).¹⁰ Parmita, In and Armyanti, 2017)).

Various injuries and diseases most often appear with pain and fever. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually prescribed for their treatment but significant gastrointestinal complications such as perforation, bleeding, (Subedi, Rahman and Akbar, 2016). Paracetamol or acetaminophen has been widely used since 1955, but improper use because this drug is over a counter drug can have various negative effects in the body. Dorji et al. (2018) reported outpatients at Phuentsholing General Hospital, (India) out of 441 outpatients, as many as 72.1% had used paracetamol in the past 1 year (Dorji, Gyeltshen and Pongpirul, 2018). The use of paracetamol in Indonesia is also quite high, Surya et al., Surya et al. (2018) reported that of the 50 parents of students in Like Kumara Kindergarten, 34 people (68%) tended to choose paracetamol as a choice of fever medicine (Surya, Artini and Ernawati, 2018). Drug abuse is also not uncommon among sports professionals, to reduce pain due to athletic activities or as prophylaxis before exercise (Esh et al., 2017). Prolonged administration of the drug, impaired kidney function, increased blood pressure, and increased incidence of heart infarction, as well as at high doses (7.5-15 grams/24 hours), causing hepatotoxic (Bebenista dan Nowak, 2014), the second ¹⁵ most common cause of liver transplantation in the United States (Khosravi et al., 2011). Although paracetamol is a safe and inexpensive analgesic, the analgesic effect is considered by many health workers to be lower than NSAIDs (Hung et al., 2018).

From the above facts, it becomes important to develop herbal remedies. Mangosteen peel is a shell that is discarded by consumers or can be called agricultural waste. The use of mangosteen p²³ for treatment in Indonesia is still not much, especially as an antipyretic analgesic. Thus, this study was design¹⁴ to find out the analgesic and antipyretic effects of mangosteen peel methanol extract on male Wistar rats.

II. Research Methods

This study is an experimental study with the Design Post-Test Only Control Group ⁸esign study that aims to explore the antipyretic and analgesic effects of mangosteen peel. This research was conducted at the Pharmaceutical Laboratory of the University of North Sumatra Medan in January - March 2021.

2.1 Tool

³⁰ EDTA tube research tool, Spuit 5 cc, Spuit 3 cc, Spuit 1 cc, Digital thermometer, 100 ml measuring pumpkin, 10 ml measuring gourd, filter paper, merang paper, analytical scales, blender, macerator vessel, rotary evaporator, test tube, improved Neubauer counting chamber, and hemometer.

2.2 Material

Ingredients such as Methanol, Brewer yeast, Normal Saline, chloroform, NA-CMC, Paracetamol, Mangosteen Peel, Glacial acetic acid, aqua dest, FeCl3, HCl, amyl alcohol, Sulfuric acid, magnesium powder, zinc powder, ammonia.

2.3 Research Steps

Identification of the plant is carried out at the Herbarium Denaense FMIPA USU. Mangosteen peel that has been collected, washed thoroughly with running water, lined Dry ingredients from mangosteen peel smoothed into powder, and form simplistic (Kosasih et al., 2019). Simplisia weighed 200 grams each, extracted, maceration technique with 400 ml of 98% methanol solvent (Vasanthakumar D et al., 2015). Phytochemical tests use fans worth method modifications consisting of identification of phenols, steroids/triterpenoids, terpenoids, saponins, flavonoids, tannins and alkaloids (Widowati et al., 2016, 2017, 2018).

Identification of Flavonoids, Alkaloids, determination of total flavonoid levels is determined by the following formula: (Louis et al., 2017)

$$TFC = \frac{\text{Quersetin equivalence} \times \text{Volume of solvent extract}}{\text{Quersetin Equality}} = \frac{\text{Quersetin Equality}}{\text{Concentration}}$$

The determination of the total tannin rate is determined by the following formula: (Septiana, 2014)

$$TTC = \frac{\text{Tanic Acid Equivalence} \times \text{Volume of extract solvent}}{\text{Extract Mass}} = \frac{\text{Tanic Acid Equivalence}}{\text{Concentration}}$$

The determination of total phenolic levels is determined by the following formulas: (Bouyahya et al., 2016)

$$TPC = \frac{\text{Error Acid Equivalence} \times \text{Volume of extract solvent}}{\text{Extract Mass}} = \frac{\text{Error Acid equivalence}}{\text{Concentration}}$$

2.4 Analgesic Activity Testing

- Evaluation of the analgesic activity of this study was conducted using 25 mice grouped into 5 different groups:
- Control: Mice in this group were given 1 ml of Na-CMC 0.5% and after 15 minutes were given an injection of 10 ml/kgBB of an acetic acid solution of 0.7%. After 5 minutes of injection, the calculation of the amount of writhing (writhing) in mice for 20 minutes.
- Standard (150 mg/kgBB): Mice in this group were given a 10 ml/kgBB paracetamol oral suspension and after 15 minutes were given a 10 ml/kgBB injection of an acetic acid solution of 0.7%. After 5 minutes of injection, the calculation of the amount of writhing (writhing) in mice for 20 minutes.
- Mangosteen Skin Extract-1 (250 mg/kgBB): Mice in this group were given an oral suspension of mangosteen peel dose of 2.5 ml/kgBB and after 15 minutes were given an injection of 10 ml/kgBB of an acetic acid solution of 0.7%. After 5 minutes of injection, writhing was calculated in mice for 20 minutes.
- Mangosteen Skin Extract-2 (500 mg/kgBB): Mice in this group were given an oral suspension of Mangosteen Peel dose of 5 ml/kgBB and after 15 minutes were given an injection of 10 ml/kgBB of an acetic acid solution of 0.7%. After 5 minutes of injection, the calculation of the amount of writhing (writhing) in mice for 20 minutes.
- Mangosteen Skin Extract-3 (750 mg/kgBB): Mice in this group were given an oral suspension of mangosteen peel dose of 7.5 ml/kgBB and after 15 minutes were given an injection of 10 ml/kgBB of an acetic acid solution of 0.7%. After 5 minutes of injection, the calculation of the amount of writhing (writhing) in mice for 20 minutes.

The parameter measured to assess the analgesic activity of the sample was the amount of writhing after 5 minutes of injection of an acetic acid solution of 0.7% for 20 minutes. In addition, it can also be calculated the average inhibition of abdominal writhing by sharing the difference between the average number of writhing in the control group and the sample group tested against the average number of geliat (writhing) in the control group multiplied by 100% (Saini and Singha, 2012).

2.5 Anti-Pyretic Activity Testing

Antipyretic activity testing in this study was conducted with the Yeast-Induced method. Brewer's Yeast solution is made from a 15% form of brewer yeast suspension. The suspension is made by dissolving 15 grams of brewer's yeast into a normal 100 ml of saline. Then, 25 grams of the suspension is then dissolved with 100 ml of aqua dest to make a 20% brewer's yeast solution. This 20% brewer's yeast solution is induced by subcutaneous injection at a dose of 10 ml/kgBB. Before and 24 hours after induction, the mice's body temperature was measured rectally with a digital thermometer (Saini and Singha, 2012; Sivamurugan et al., 2016; Veronica et al., 2017).

This evaluation of antipyretic activity was conducted in 25 mice that had been induced by the Yeast-Induced method. These mice were then grouped into 5 groups:

- Control: Test animals are given 1 ml of 0.5% Na CMC suspension after 24 hours of induction. Food and drink are given in ad libitum.
- Standard (150 mg/kgBB): Test animals are given a 10 ml/kgBB oral paracetamol suspension after 24 hours of induction. Food and drink are given in ad libitum.
- Mangosteen Skin Extract-1 (250 mg/kgBB): Test animals were given Mangosteen Peel extract doses of 2.5 ml/kgBB after 24 hours of induction. Food and drink are given in ad libitum.
- Mangosteen Skin Extract-2 (500 mg/kgBB): Test animals are given Mangosteen Peel extract doses of 5 ml/kgBB after 24 hours of induction. Food and drink are given in ad libitum.
- Mangosteen Skin Extract-3 (750 mg/kgBB): Test animals were given 7.5 ml/kgBB mangosteen peel extract after 24 hours of induction. Food and drink are given in ad libitum.

2.6 Data Analysis

Data analysis in this study was conducted with descriptive statistical analysis, inferential statistical analysis in accordance with the results of the data normality test using Shapiro-Wilk. If normally distributed data uses parametric statistical analysis in the form of one-way ANOVA, if the distributed data is not normal then data transformation is carried out. However, if the data is still distributed abnormally, then an alternative test is carried out with non-parametric statistical analysis in the form of Kruskal-Wallis.

III. Discussion

3.1. Results

a. Characteristics of Extract

After extraction by maceration method of mangosteen skin samples found the following characteristics of the extract.

Table 1. Characteristics of Mangosteen Peel Methanol Extract (*Garcinia Mangostana* L)

Characteristic	Value
Fresh Simplisia Weight (gr)	500 gr
Dry Simplisia Powder Weight (gr)	212 gr
Solvent Volume (ml)	2120 ml
Extract Weight (gr)	15,55 gr
Yield (%)	7.33%

From the table data above, it can be seen that from 500 grams of mangosteen skin samples found an extract of 15.55 grams. Thus, the amount of yield obtained from mangosteen peel methanol extract is 7.33%.

b. Phytochemical Screening

The results of phytochemical screening on samples of mangosteen peel methanol extract can be seen in the following table.

Table 2. Phytochemical Screening Results of Mangosteen Peel Methanol Extract

Fitokimia	Reaksi	Hasil
Alkaloid	Bouchardart	+
	Mayer	+
	Dragondroff	-
	Wagner	+
Saponin	Aquadest + Alcohol 96%	-
Flavonoid	FeCl ₃ 5%	+
	Mg (s) + HCl (p)	-
	NaOH 10%	-
	H ₂ SO ₄ (p)	-
Tanin	FeCl ₃ 1%	+
Steroid dan Terpenoid	Salkowsky	-
	Liberman Bouchard	+

From the table data above, it can be seen that mangosteen peel methanol extract contains several phytochemical compounds including Alkaloids, Saponins, Flavonoids, Tannins, as well as Steroids and Terpenoids.

c. Weight

The mice's weight data analyzed their normality with Shapiro-wilk. From table 4.3 data it can be seen that the entire weight of the mice used in this study has a value of $P > 0.05$ meaning normal distribution. The analysis was then continued by normality data from bodyweight to compare the weight of mice between groups. The results of the comparison are displayed in the following table.

Table 3. Comparison of Early Weight of Mice in The Entire Treatment Group

Treatment Group	Weight (gram)	Value P
Control	172.40 ± 12.33	0.955
Standard	176.20 ± 14.02	
Mangosteen Peel Methanol Extract -I	170.60 ± 13.72	
Mangosteen Peel Methanol Extract -II	170.10 ± 20.20	
Mangosteen Peel Methanol Extract -III	175.30 ± 10.67	

The data is displayed as Mean ± SD. The P-value has obtained from the One Way ANOVA analysis.

From the table data above can be seen the value of $P > 0.05$ (Value $P = 0.955$) which means there is no significant difference to the initial weight of the mice used in this study.

d. Antipyretic Effects

Measurement of body temperature in 7 different observation times, namely: before induction, after induction (24 hour, 1 hour, 2 hours, 3 hours, 4 hours, and 5 after treatment. All parameters are then analyzed for normality with Shapiro-wilk and the results of the analysis can be seen in the following table.

Table 4. Body Temperature Comparisons in The Entire Treatment Group

Treatment Group	Body Temperature (°C)						
	Before induction *	After induction **	1 hours**	2 hours*	3 hours*	4 hours*	5 hours*
Control	36.30 ± 0.37	38.11 (0.40)	37.70 (1.40)	37.72 ± 0.61	37.62 ± 0.46	37.36 ± 0.63	37.05 ± 0.45 ^a
Standard	36.32 ± 0.27	38.00 (0.50)	37.60 (1.40)	37.46 ± 0.49	37.20 ± 0.26	37.02 ± 0.46	36.72 ± 0.22 ^{ab}
Mangosteen Peel Methanol Extract - I	36.18 ± 0.31	38.30 (0.50)	38.20 (0.90)	37.64 ± 0.42	37.34 ± 0.38	37.24 ± 0.30	36.90 ± 0.32 ^a
Mangosteen Peel Methanol Extract - II	36.34 ± 0.21	37.80 (0.40)	37.60 (0.80)	37.48 ± 0.61	37.00 ± 0.28	36.84 ± 0.23	36.60 ± 0.24 ^{ab}
Mangosteen Peel Methanol Extract - III	36.20 ± 0.19	38.00 (1.20)	38.10 (1.20)	37.58 ± 0.36	37.36 ± 0.46	36.86 ± 0.36	36.14 ± 0.12 ^b
P-Value	0.982	0.184	0.281	0.917	0.104	0.167	0.004

*The data is displayed as Mean ± SD. The value of P is obtained from the one-way ANOVA analysis; **Data is displayed as Median (Range). The value of P is derived from the Kruskal-Wallis analysis; Different superscripts in the same column show significant differences.

From the table data above, it can be seen that the entire body temperature of mice at the time before induced was uniform, this is reflected in the value of $P > 0.05$ (Value $P = 0.982$). After 24 hours of induction, the rat's body temperature remained uniform, this can be seen from the value of $P > 0.05$ (Value $P = 0.184$). However, the body temperature of mice after usually induced increased compared to before induction. Before induction the rat's body temperature had a tendency between 36.24-36.34°C and increased by a range of 37.90-38.30°C after 24 hours of induction.

After 24 hours of induction, the entire group of mice was given treatment according to the treatment group. The body temperature of the mice 1-4 hours after treatment showed no significant differences between the treatment groups. This can be seen from the P-value of the rat's body temperature every hour which is greater than 0.05. However, at the end of the observation that is 5 hours after treatment, the body temperature of the mice experienced a significant change, this is reflected in the value of $P < 0.05$ (Value $P = 0.004$). Where the methanol extract group of mangosteen skin III showed the lowest body temperature 5 hours after treatment which was 36.14 ± 0.12°C and the methanol extract group Mangosteen-III skin also showed a significant difference to the control group that showed the highest body temperature of 37.36 ± 0.46°C. An overview of changes in the body temperature of mice can also be seen in the following line diagram image.

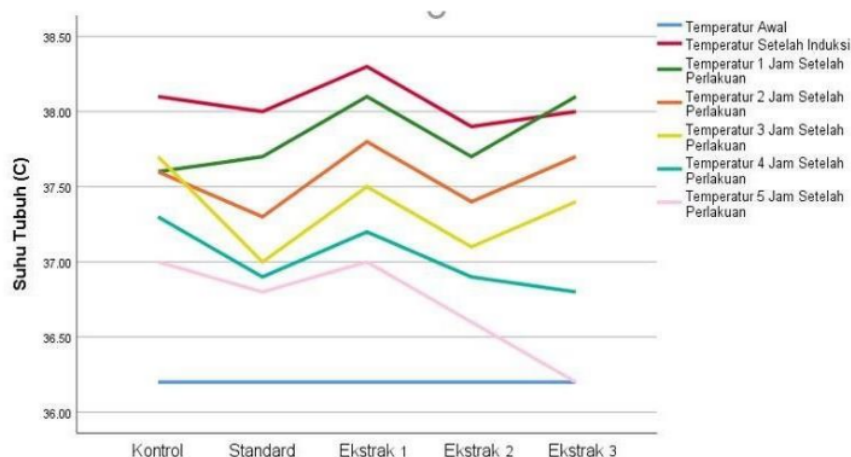


Figure 1. Diagram of The Body Temperature Line of the Entire Treatment Group During the Observation Period

From the diagram image above, it can be seen that the body temperature of mice before treatment is the lowest temperature of all rats, while the highest body temperature of rats is the highest body temperature of rats. Meanwhile, the mice's body temperature a few hours after treatment ranged between the body temperature range before and after induction. Gradually, the body temperature of mice 1-5 hours of treatment decreased. However, after 5 hours of treatment, the mice's body temperature decreased, the most significant and near-normal decrease could be seen in the mangosteen-I skin methanol extract group and followed by the mangosteen- II skin methanol extract group, the standard group, mangosteen-I skin methanol extract, and finally the control group.

e. Analgesic Effect

From table 5 data it can be seen that the value $P < 0.05$ (Value $P = 0.003$). This suggests that there is a significant difference in the number of geliat between treatment groups. The least amount of geliat found in the mangosteen-III skin methanol extract group was 5.22 ± 1.91 and this number showed a significant difference with the mangosteen-I skin methanol extract group (12.81 ± 3.12) and the control group (11.10 ± 1.91).

The results of the comparison of the number of geliat in the entire group of mice can be seen in the following table.

Table 5. Comparison of The Number of Geliat (Writhing) in All Treatment Groups

Treatment Group	Number of Geliat (Writhing)	Value P
Control	11.10 ± 1.91^a	0.003
Standard	8.82 ± 3.26^{ab}	
Mangosteen Peel Methanol Extract -I	12.81 ± 3.12^a	
Mangosteen Peel Methanol Extract -II	8.83 ± 3.36^{ab}	
Mangosteen Peel Methanol Extract -III	5.22 ± 1.91^b	

The data displayed as Mean \pm SD. The value of P is obtained from the one-way ANOVA analysis; Different superscripts in the same column show significant differences.

The comparison of the number of geliat between treatment groups can be seen in the following bar diagram image.

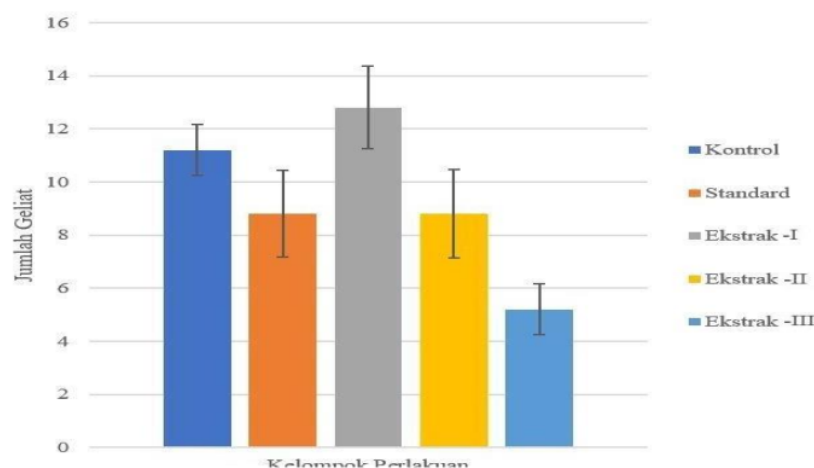


Figure 2. Bar Diagram of The Number of Geliat in The Entire Treatment Group

From the picture above it can be seen that the largest amount of geliat found in the mangosteen-I skin methanol extract group, then followed by the control group, standard, methanol extract mangosteen-II skin, and the lowest group of methanol extract mangosteen-III skin.

f. Hematology Evaluation

The hematological parameters evaluated in the study include Hemoglobin, erythrocyte count, leukocytes, and platelets. Before further analysis of the hematology parameters, the analysis of the normality of the data with Shapiro-wilk and the results of the analysis can be seen in the following table.

Table 6. Comparison of Hematological Parameters across Treatment Groups

Treatment Group	Hematologic			
	Hb* (gr/dL)	RBC** (x 10 ⁶ /μL)	WBC* (x 10 ³ /μL)	PLT* (x 10 ³ /μL)
Control	14.53 ± 4.02	7.64 (6.35)	8.31 ± 1.14 ^a	867.60 ± 214.14
Standard	14.01 ± 1.85	7.67 (2.95)	3.06 ± 1.01 ^b	650.62 ± 366.56
Mangosteen Peel	12.50 ± 1.32	7.25 (2.60)	6.75 ± 0.42 ^a	800.61 ± 97.55
Methanol Extract -I				
Mangosteen Peel	14.31 ± 3.19	7.76 (5.20)	5.09 ± 0.17 ^c	867.40 ± 423.06
Methanol Extract -II				
Mangosteen Peel	12.92 ± 0.60	7.05 (0.98)	3.35 ± 1.07 ^b	624.65 ± 242.11
Methanol Extract -III				
Value P	0.649	0.512	< 0.05	0.523

*The data is displayed as Mean ± SD. The value of P is obtained from the one-way ANOVA analysis; **Data is displayed as Median (Range). The value of P is derived from the Kruskal-Wallis analysis; Different superscripts in the same column show significant differences.

From the table data above, it can be seen that both hemoglobin levels, erythrocyte counts, and platelet counts do not show significant differences between treatment groups. The range of hemoglobin, erythrocytes, and platelet counts in the entire group of mice was 12.50-14.31 gr/dL, 7.05-7.76 x 10⁶/μL, and 624.65-867.40 x 10³/μL. Only the

number of leukocytes showed significant differences between treatment groups, this was reflected in the P-value of < 0.05 . The standard group ($3.06 \pm 1.21 \times 10^6/\mu\text{L}$) and mangosteen-III skin methanol extract ($3.35 \pm 1.07 \times 10^6/\mu\text{L}$) showed significant differences with other treatment groups. The group with the highest number of leukocytes was the control group, followed by the methanol extract group Mangosteen-I, II, III, and Standard Skin. However, in the mangosteen-I skin methanol extract group ($6.75 \pm 0.42 \times 10^6/\mu\text{L}$) and the control group ($8.31 \pm 1.14 \times 10^6/\mu\text{L}$) there was no significant difference in the number of leukocytes.

3.2 Discussion

The results of this study show that mangosteen peel has potential antipyretic and analgesic effects. This shows that mangosteen peel in the form of methanol extract obtained by maceration has antipyretic effects after 5 hours of administration of the extract. Antipyretic effects were mainly observed at the two highest doses: 500 mg/kgBB and 750 mg/kgBB. However, the analgesic effect of mangosteen peel is found at the highest dose of 750 mg/kgBB. Meanwhile, the results of the hematologic examination showed a significant decrease in line with the increase in the dose of mangosteen skin methanol extract given.

Pain is an unpleasant subjective experience in one part of the body as a result of harmful stimuli. There are types of pain, namely neurogenic and peripheral pain. Peripheral pain is activated through resistance to the nociceptive afferent neurons while neurogenic pain by pain sensitization through afferent input of pain sensation. To evaluate the analgesic effect of neurogenic pain is done through the hot plate method while intraperitoneal injection of acetic acid is performed to evaluate the analgesic effect of peripheral pain (Nitave, Chougule and Koumaravelou, 2018; Sharma et al., 2020).

The sensation of pain induced by acetic acid is a local inflammatory response caused by acetic acid injected into the peritoneum. This local inflammation occurs through the metabolism of arachidonic acid from phospholipids in tissues through the cyclooxygenase pathways (PGE2 and PGE2 α) and lipoxygenase. So that products from cyclooxygenase pathways such as PGE2 and PGE2 α as well as various products from the lipoxygenase pathway will be abundant in peritonium search. Products of this cyclooxygenase and lipoxygenase pathway that cause swelling through cumulative permeability of capillaries and the release of various endogenous mediators that will stimulate pain in the nerve endings of the nociceptor (Afsar et al., 2015).

Fever is a rise in body temperature shown by various living things in response to invasion from infecting agents. Brewer yeast is a lipopolysaccharide (exogenous pyrogen) that is a cell wall component of gram-negative bacteria. When pyrogens such as lipopolysaccharides (LPS) or brewer yeast enter the body by damaging the natural barrier. Brewer yeast then binds to an immunological protein called Lipopolysaccharide Binding Protein (LBP). This binding encourages the synthesis and release of various endogenous cytokines such as IL-1, IL-6, TNF α . These endogenous cytokines easily pass through the blood-brain barrier and work on the preoptic/anterior hypothalamus, thus activating the arachidonic acid pathway resulting in the synthesis and release of prostaglandin E2. PGE2 is produced from the cyclooxygenase-2 pathway causing a rise in body temperature (Santra et al., 2014; Eldahshan and Abdel-Daim, 2015).

The antipyretic and analgesic effects of mangosteen peel are related to the content of phenols and flavonoids present in mangosteen peel. Various studies have reported analgesic effects possessed by alkaloid compounds, phenols, and flavonoids. Flavonoids can inhibit the biosynthesis of prostaglandins involved in immunological responses and

are also the end product of the cyclooxygenase and lipoxygenase pathways. In addition, flavonoids also affect protein kinase which is one of the regulatory enzymes that can inhibit the inflammatory process (Eldahshan and Abdel-Daim, 2015). In addition to flavonoids, Gaichu et al. (2017) also reported that alkaloid compounds as phytochemical compounds also inhibit prostaglandin synthesis which is one of the products of the cyclooxygenase pathway (Gaichu et al., 2017). So it can be concluded that the analgesic and antipyretic effects of mangosteen peel are due to the presence of alkaloids, phenols, and flavonoids.

These phytochemical compounds will inhibit prostaglandin biosynthesis thereby preventing the cascade of inflammation and will eventually produce analgesic and antipyretic effects. Several previous studies supported the results of this study. One of them (Puspitaningrum, Kusmita and Setyani, 2014) conducted a similar study, with the results of mangosteen peel ethanol extract (*Garcinia mangostana* L) proven to have antipyretic analgesic effects with an effective dose of 50 mg / kgBB of mice. Research (Ongele, 2013), which conducted a study of mangosteen skin analgesic tests, stated that mangosteen peel extract has analgesic effects that begin to be seen in the 30th to 120th minutes with the maximum effect seen at the 90th minute, with a concentration of 10% in Swiss mice.

IV. Conclusion

Mangosteen skin methanol extract contains various phytochemicals namely Alkaloid, Saponin, Flavonoids, Tannins, as well as Steroids and Terpenoids: Mangosteen skin methanol extract has a significant antipyretic effect (Value $P = 0.004$) after 5 hours of administration with an optimal dose of 750 mg / kgBB: Mangosteen skin methanol extract has a significant analgesic effect (Value $P = 0.003$) against nociceptive pain with an optimal dose of 500-750 mg / kgBB.

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