BirEx JOURNAL
Budapest International Research in Exact Sciences
Medical, Biological, Argiculture, Engineering
Science and other related areas
e-ISSN : 2655-7827
p-ISSN : 2655-7835
http://www.bircu-journal.com/index.php/birex

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

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**Abstract:** *Analgetic-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 ± 0.12oC 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 ± 0.46oC. 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, anlagesic 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 Warditiani, 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) :(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 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 peel for treatment in Indonesia is still not much, especially as an antipyretic analgesic. Thus, this study was designed 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 Design 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

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)

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

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

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

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

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

## 2.4 Analgesic Activity Testing

a. Evaluation of the analgesic activity of this study was conducted using 25 mice grouped into 5 different groups:
b. 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.
c. 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.
d. 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.
e. 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.
f. 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, 20 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:

a. 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.
b. 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.
c. 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.
d. 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.
e. 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 foundthe 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 mangosteenskin 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 | Pereaksi | Hasil |
|---|---|---|
| Alkaloid | Bouchardart | + |
| | Mayer | + |
| | Dragondroff | - |
| | Wagner | + |
| Saponin | Aquadest + Alcohol 96% | - |
| Flavonoid | FeCl3 5% | + |
| | Mg $_{(s)}$ + HCl $_{(p)}$ | - |
| | NaOH 10% | - |
| | H2SO4 (p) | - |
| Tanin | FeCl3 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 hours), 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 ± 0.12b |
| 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 usualy induced increased compared to before induction. Before induction the rat's body temperature had a tendency between 36.24-36.34oC and increased by a range of 37.90-38.30oC 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 ± 0.12oC 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 ± 0.46oC. An overview of changes in the body temperature ofmice can also be seen in the following line diagram image.

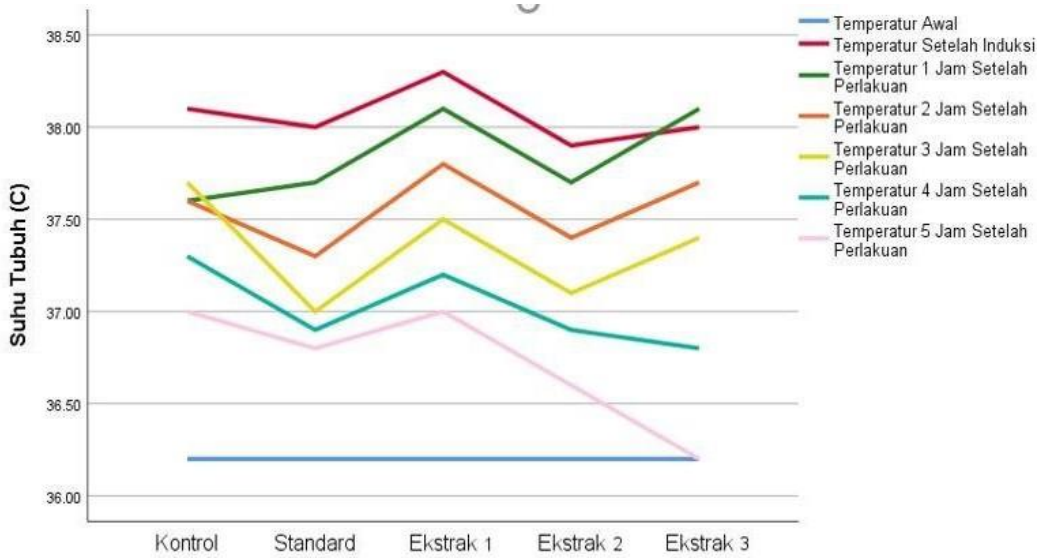


***Figure 1.*** *Diagram of The Body Temperature Line of the Entire Treatment Group During theObservation Period*

From the diagram image above, it can be seen that the body temperature of micebefore 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 | $11.10 \pm 1.91^{a}$ | |
| Standard | $8.82 \pm 3.26^{ab}$ | |
| Mangosteen Peel Methanol Extract -I | $12.81 \pm 3.12^{a}$ | 0.003 |
| Mangosteen Peel Methanol Extract -II | $8.83 \pm 3.36^{ab}$ | |
| Mangosteen Peel Methanol Extract -III | $5.22 \pm 1.91^{b}$ | |

The data is displayed as Mean ± 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 geliats between treatment groups can be seen in the following bar diagram image.

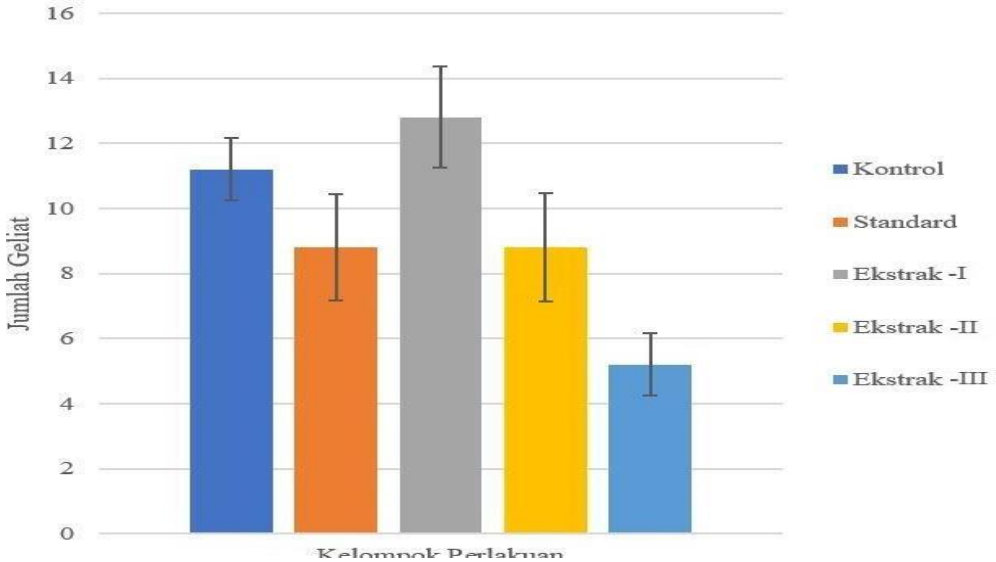


***Figure 2.*** *Bar Diagram of The Number of Geliat in The Entire Treatment Group*

From the picture above it can be seen that the largest amount of geliat foundin 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-wilkand 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 Methanol Extract -I | 12.50 ± 1.32 | 7.25 (2.60) | 6.75 ± 0.42 [a] | 800.61 ± 97.55 |
| Mangosteen Peel Methanol Extract -II | 14.31 ± 3.19 | 7.76 (5.20) | 5.09 ± 0.1 7[c] | 867.40 ± 423.06 |
| Mangosteen Peel Methanol Extract -III | 12.92 ± 0.60 | 7.05 (0.98) | 3.35 ± 1.07[b] | 624.65 ± 242.11 |
| **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 ± 1.01 x 106/μL) and mangosteen-III skin methanol extract (3.35 ± 1.07 x 106/μL) 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 ± 0.42 x 106/μL) and the control group (8.31 ± 1.14 x 106/μL) 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 PGE2α) and lipoxygenase. So that products from cyclooxygenase pathways such as PGE2 and PGE2α as well as various products from the lipooxygenase pathway will be abundant in peritonium search. Products of this cyclooxygenase and lipooxygenase 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 lipopolisakarisa (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, TNFα. 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 lipooxygenase 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 analgetic effects with an effective dose of 50 mg / kgBB of mice. Research (Ponggele, 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.

## References


Afsar, T. et al. (2015) ‘Antipyretic , anti-inflammatory and analgesic activity of Acacia hydaspica R . Parker and its phytochemical analysis’, BMC Complementary and Alternative Medicine, 15(136), pp. 1–12. doi: 10.1186/s12906-015-0658-8.

Azwanida, N. N. (2015) ‘A Review on the Extraction Methods use in Medicinal Plants,Principles,Strength and Limitation’, Medicinal aromatic plants. doi: doi:10.4172/2167-0412.1000196.

Bahri, S., Pasaribu, F. and Sitorus, P. (2012) ‘Uji Ekstrak Etanol Kulit Buah Manggis (Garcinia Mangostana, L) Terhadap Penurunan Kadar Glukosa Darah’, Journal of Pharmaceutics and Pharmacology, 1(1), pp. 1–8.

Bouyahya, A. et al. (2016) ‘Determination of Phenolic Contents, Antioxidant and Antibacterial Activities of Strawberry Tree (Arbutus unedo L.) Leaf Extracts’, British Biotechnology Journal, 14(3), pp. 1–10. doi: 10.9734/bbj/2016/26488.

Dorji, T., Gyeltshen, K. and Pongpirul, K. (2018) ‘Rational use of paracetamol among out-patients in a Bhutanese district hospital bordering India: A cross-sectional study’, BMC Research Notes, 11(1), pp. 1–6. doi: 10.1186/s13104-018-3764-0.

Eldahshan, O. A. and Abdel-Daim, M. M. (2015) ‘Phytochemical study, cytotoxic, analgesic , antipyretic and anti-inflammatory activities of Strychnos nux- vomica’, Cytotechnology, 67, pp. 831–844. doi: 10.1007/s10616-014- 9723-2.

Esh, C. J. et al. (2017) ‘Acetaminophen (paracetamol): Use beyond pain management and

dose variability', Frontiers in Physiology, 8(DEC), pp. 1–7. doi: 10.3389/fphys.2017.01092.
Ferreira, T. R. and Lopes, L. C. (2016) 'Analysis of Analgesic, Antipyretic, and Nonsteroidal, Anti-Inflammatory Drug Use in Pediatric Prescriptions', Jornal de Pediatria, 92(1), pp. 81–87.
Gaichu, D. M. et al. (2017) 'Phytochemical screening and antipyretic activities of dichloromethane-methanolic leaf and stem bark extracts of Ximenia americana in rat models', Journal of Herbmed Pharmacology, 6(3), pp. 107–113.
Gupta, A. et al. (2012) 'Modern extraction methods for preparation of bioactive plant extracts', International Journal of Applied and Natural Sciences.
Hilal-Dandan, R. and Brunton, L. (2013) Goodman and Gilman Manual of Pharmacology and Therapeutics. United State: McGraw Hill Professional.
Hung, K. K. C. et al. (2018) 'Oral paracetamol and/or ibuprofen for treating pain after soft tissue injuries: Single centre double-blind, randomised controlled clinical trial', PLoS ONE, 13(2), pp. 1–13. doi: 10.1371/journal.pone.0192043.
Khosravi, S. et al. (2011) 'Non-alcoholic fatty liver disease and correlation of serum alanin aminotransferase level with histopathologic findings', Hepatitis Monthly, 11(6), pp. 452–458.
Kosasih, E. et al. (2019) 'Hepatoprotective Effect of Citrus Sinensis Peel Extract Against Isoniazid and Rifampicin-induced Liver Injury in Wistar Rats', Majalah Obat Tradisional, 24(3), pp. 197–203. doi: 10.22146/mot.45762.
Louis, H. et al. (2017) 'Determination of Total Phenolic Content and some Selected Metals in Extracts of Moringa oleifera, Cassia tora, Ocimum gratissimum, Vernonia baldwinii and Telfairia occidentalis Plant Leaves', World News of Natural Sciences, 11(2017), pp. 11–18.
Nitave, S. A., Chougule, N. B. and Koumaravelou, K. (2018) 'Phytochemical Investigation, Analgesic and Antipyretic Activities of Ethanolic Extract of Kariyat', International Journal of Pharmaceutical Sciences and Research, 9(3), pp. 1035–1043. doi: 10.13040/IJPSR.0975-8232.9(3).1035-43.
Pandey, A. and Tripathi, S. (2014) 'Concept of Standarization, Extraction and Pre Phytochemical Screening Strategies for Herbarl Drug', Journal of Pharmacognosy and Phytochemestry.
Parmita, R. I., In, M. and Armyanti, I. (2017) 'Uji Efek Antiinflamasi Kombinasi Astaxanthin dan Ekstrak Kulit Manggis ( Garcinia mangostana Linn ) pada Tikus Putih Galur Wistar Abstrak PENDAHULUAN Inflamasi merupakan suatu respon protektif yang ditujukan drug / NSAID ) namun memiliki efek samping yang', 3, pp. 689–696.
Pathan, H. and Williams, J. (2012) 'Basic opioid pharmacology: an Update', British Journal of Pain, 6(1), pp. 11–16.
Ponggele, R. M. (2013) 'Uji Efek Analgesik Ekstrak Kulit Manggis (Garcinia Mangostana L.) Pada Mencit Swiss (Muss Musculus)', Jurnal e-Biomedik, 1(2), pp. 796–801. doi: 10.35790/ebm.1.2.2013.3245.
Puspitaningrum, I., Kusmita, L. and Setyani, W. (2014) 'Efek Analgetik Antipiretik Ekstrak Etanol Kulit Buah Manggis (Garcinia mangostana L.) PADA TIKUS PUTIH JANTAN GALUR WISTAR', e-Publikasi Ilmiah Fakultas Farmasi Unwahas Semarang, 11(1), pp. 18–24. Availableat:http://www.publikasiilmiah.unwahas.ac.id/index.php/ilmuFarmasidanklin ik/article/view/1284.

Putra SR (2012) Rahasia-Rahasia Keajaiban Kulit Buah Manggis. Cetakan 1. Jogjakarta: Diva Press.
Putri, I. P. (2015) 'Effectivity Of Xanthone Of Mangosteen (Garcinia mangostana L.) Rind As Anticancer', J Majority │, 4, p. 33.
Rabiu, A. R. and Haque, M. (2020) 'Preparation of Medicinal Plants : Basic Extraction and Fractionation Procedures for Experimental Purposes', Journal of Pharmacy & Bioallied Sciences, 12(1), pp. 1–10. doi: 10.4103/jpbs.JPBS.
Saini, N. K. and Singha, M. (2012) 'Anti-inflammatory, analgesic and antipyretic activity of methanolic Tecomaria capensis leaves extract', Asian Pacific Journal of Tropical Biomedicine, 2(11), pp. 870–874. doi: 10.1016/S2221- 1691(12)60245-7.
Salmerón-Manzano, E., Garrido-Cardenas, J. A. and Manzano-Agugliaro, F. (2020) 'Worldwide research trends on medicinal plants', International Journal of Environmental Research and Public Health, 17(10). doi: 10.3390/ijerph17103376.
Santra, S. et al. (2014) 'Antipyretic effect of Azadirachta indica leaf extract (Neem Leaf Extract) on albino rats', Research Journal of Pharmaceutical, Biological and Chemical Sciences, 5(6), pp. 669–673.
Sasidharan, S. et al. (2011) 'Extraction, isolation and characterization of bioactive compounds from plants' extracts', African Journal of Traditional, Complementary and Alternative Medicines, 8(1), pp. 1–10.
Septiana, D. (2014) 'Analisis Kadar Alkaloid dan Tanin Tumbuhan Beluntas (Pluchea indica Less.) pada Lahan Salin di Desa Asingi Kecamatan Tinanggea dan Non Salin di Desa Lambodijaya Kecamatan Lalembuu Sulawesi Tenggara', Biowallacea, 1(2), pp. 82–89.
Sharma, V. C. et al. (2020) 'Analgesic , anti-inflammatory and antipyretic activities of ethanolic extract of stem bark of Anogeissus latifolia Roxb', Clinical Phytoscience, 6(11), pp. 1–9.
Sivamurugan, V. et al. (2016) 'Analgesic, Anti-inflammatory and Antipyretic Activity of the Methanol Extracts of Brown Alga Lobophora variegata (JV Lamouroux) Womersley ex EC Oliveir', American Journal of Phytomedicine and Clinical Therapeutics, 4(2), pp. 42–57.
Subedi, N. K., Rahman, S. M. A. and Akbar, M. A. (2016) 'Analgesic and Antipyretic Activities of Methanol Extract and Its Fraction from the Root of Schoenoplectus grossus', Evidence-based Complementary and Alternative Medicine, 2016. doi: 10.1155/2016/3820704.
Surya, M. A. N. I., Artini, I. G. A. and Ernawati, D. K. (2018) 'Pola Penggunaan Parasetamol atau Ibuprofen sebagai Obat Antipiretik Single Therapy pada Pasien Anak', E-Jurnal Medika, 7(8), pp. 1–13.
Suwertayasa, M., Bodhy, W. and Jaya Edy, H. (2013) 'Uji Antipiretik Ekstrak etanol Daun Tembelekan (Lantana Camara L.) pada Tikus Putih Jantan Galur Wistar', Pharmacon Jurnal Ilmiah Farmasi, 2(3), pp. 45–49.
Vasanthakumar D et al. (2015) 'Antibacterial activity of Rosa damascena petal extracts against the fish pathogen Aeromonas hydrophila', European Journal of Experimental Biology, 5(8), pp. 56–59.
Veronica, S. A. et al. (2017) 'Antiinflammatory , analgesic and antipyretic effects of dichloromethane stem bark extract of Acacia mellifera', The Journal of Phytopharmacology, 6(4), pp. 239–246.
Widowati, W. et al. (2016) 'Antioxidant and Anti Aging Assays of Oryza sativa Extracts, Vanillin and Coumaric Acid', Journal of Natural Remedies, 16(3), pp. 88–99. doi: 10.18311/jnr/2016/7220.

Widowati, W. et al. (2017) ‘Antioxidant and antiaging assays of Hibiscus sabdariffa extract and its compounds’, Natural Product Sciences, 23(3), pp. 192–200. doi: 10.20307/nps.2017.23.3.192.
Widowati, W. et al. (2018) ‘Antioxidant and antiaging activities of Jasminum sambac extract, and its compounds’, Journal of Reports in Pharmaceutical Sciences, 7(3), pp. 270–285.
Windarini, L. G. ., Astuti, K. W. and Warditiani, N. K. (2011) ‘Skrining Fitokimia Ekstrak Metanol Kulit Buah Manggis (Garcinia mangostana Linn.)’, SpringerReference, 1.