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ASSESSMENT OF THE EFFECTIVENESS OF MANGOSTEEN PEEL METHANOL EXTRACT AS AN ANALGESIC AND ANTIPYRETIC IN MALE WISTAR RATS

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ABSTRACT
Plants that have the potential as analgesic-antipyretic compounds are mangosteen fruit (Garcinia mangostana L). Methanol extract from the peel of mangosteen fruit (Garcinia mangostana L.) contains several compounds, including saponins, alkaloids, flavonoids, triterpenoids, tannins, and polyphenols. The presence of flavonoids in mangosteen peel can inhibit prostaglandins, thus providing antipyretic effects. This study aims to evaluate the effectiveness of analgesic and antipyretic effects of methanol extract from mangosteen peel on Wistar rats. This research was conducted in January 2024 and utilized an experimental post-test-only Control Group Design. Data were analyzed using IBM SPSS 25, with normality tested using Shapiro-Wilk. The results indicate that mangosteen peel methanol extract contains various phytochemicals, including Alkaloids, Saponins, Flavonoids, Tannins, Steroids, and Terpenoids. The methanol extract demonstrates potential antipyretic and analgesic effects on male Wistar rats, especially at the highest dose (150 mg/kg body weight). The antipyretic effect was observed after 5 hours of administration, while the analgesic influence was evident simultaneously. Although the control group showed a significant decrease in body temperature 1 hour after treatment, the mangosteen peel methanol extract group III exhibited a more pronounced decrease at various times post-treatment than the control and standard groups. Hematological analysis revealed a reduction with an increase in the dose of mangosteen peel methanol extract. This potential makes the excerpt interesting for further research in drug development.
KEYWORDS: *Mangosteen Peel Methanol Extract; Analgesic; Antipyretic; Wistar Rats; Drug Potential*

INTRODUCTION

People of all ages commonly use analgesic-antipyretic compounds to alleviate pain and fever for various reasons. Analgesics are compounds that can reduce or eliminate pain without causing loss of consciousness. Meanwhile, antipyretics are substances that can lower high body temperature. One plant that has the potential as an analgesic-antipyretic compound is the mangosteen fruit (Garcinia mangostana L) (Puspitaningrum et al., 2014). Since ancient times, plants have been used in medicine and continue to be used today. Initially, trial and error methods were employed to treat diseases or to feel better. The use of these plants has been gradually perfected from generation to generation, and this method has been recognized in many contexts as traditional medicine (Salmerón-Manzano et al., 2020). Therefore, numerous studies have explored various benefits of natural ingredients, including mangosteen peel. Methanol extract of mangosteen peel (Garcinia mangostana L.) contains compounds such as saponins, alkaloids, flavonoids, triterpenoids, tannins, and polyphenols (Windarini et al., 2011). As a result, mangosteen peel has various pharmacological effects such as anti-inflammatory, antioxidant, antidiabetic, and antibacterial properties (Sitanggang et al., 2019; Winarti et al., 2018; Worotikan et al., 2017; Yanti et al., 2011). The flavonoids in mangosteen peel can inhibit prostaglandins, exhibiting antipyretic effects (Suwertayasa, 2013).

The use of paracetamol is relatively high in many countries. This is attributed to a shift in public understanding of paracetamol, considering it a panacea for various ailments (pill for every ill). Dorji et al. (2018), who conducted a study on paracetamol use in out-patient patients at Phuentsholing General Hospital, Bhutan (India), reported that out of 441 out-patient patients, 72.1% had used paracetamol in the last year (Dorji et al., 2018). Furthermore, frequent use of paracetamol is not only prevalent internationally but also within Indonesia. Surya et al. (2018) reported that out of 50 parents of students at Laksana Kumara Kindergarten, 34 individuals (68%) tended to choose paracetamol as the preferred fever remedy (Surya et al., 2018).

To develop herbal medicine with lower side effects and a tendency to be safer as an alternative to paracetamol, mangosteen peel emerges as a potential natural ingredient. Currently, mangosteen peel, often considered agricultural waste, is only utilized for tanning leather, traditional medicine, textile dye, and anti-rust material. The use of mangosteen peel as medicine in Indonesia is still limited,

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particularly for analgesic-antipyretic purposes. Therefore, this research aims to evaluate the analgesic and antipyretic effects of methanol extract from mangosteen peel on male Wistar rats.

RESEARCH METHODS

This study is an experimental study with a post-test-only Only Control Group Design research design to explore mangosteen peel's antipyretic and analgesic effects in March 2023. Tools are EDTA tube, five cc syringe, three cc syringe, one cc syringe, digital thermometer, 100 ml volumetric flask, 10 ml volumetric flask, filter paper, meaning paper, analytical balance, blender, macerator vessel, rotary evaporator, test tube, improved Neubauer counting chamber, and thermometer. Materials are methanol, Brewer yeast, Normal Saline, chloroform, NA-CMC, Paracetamol, Mangosteen Peel, Glacial acetic acid, distilled water, FeCl3, HCl, amyl alcohol, Sulfuric acid, magnesium powder, zinc powder, ammonia.

The acetic acid writhing test evaluated the analgesic activity of mangosteen peel extract. This method requires a 0.7% acetic acid solution made using 0.7 ml of 100% glacial acetic acid dissolved in 100 ml of distilled water using a 100 ml volumetric flask. The preparation of this solution is done by first entering 20 ml of aquadest, followed by 0.7 ml of 100% glacial acetic acid solution into a 100 ml volumetric flask, after which aquadest is added to the limit mark in a 100 ml volumetric flask.

Evaluation of the analgesic activity of this study was carried out using 25 rats grouped into five different groups:

a. Control: Rats in this group were given 1 ml of 0.5% Na-CMC and, after 15 minutes, were injected 10 ml/kgBB of 0.7% acetic acid solution. After 5 minutes of injection, the number of writhing was counted in rats for 20 minutes.
b. Standard (10 mg/kg body weight): Rats in this group were given an oral suspension of paracetamol 10 ml / kgBB. After 15 minutes, we were given an injection of 10 ml / kgBB of 0.7% acetic acid solution. After 5 minutes of injection, the number of writhing was counted in rats for 20 minutes.
c. Mangosteen Peel Extract-1 (50 mg/kg body weight): Rats in this group were given an oral suspension of mangosteen peel at a dose of 0.5 ml/kgBB and, after 15 minutes, were injected with 10 ml/kgBB of 0.7% acetic acid solution. After 5 minutes of injection, the number of writhing was counted in rats for 20 minutes.
d. Mangosteen Peel Extract-2 (100 mg/kg body weight): Rats in this group were given an oral suspension of mangosteen peel at a dose of 1 ml/kgBB and, after 15 minutes, were given an injection of 10 ml/kgBB of 0.7% acetic acid solution. After 5 minutes of injection, the number of writhing was counted in rats for 20 minutes.
e. Mangosteen Peel Extract-3 (150 mg/kg body weight): Rats in this group were given an oral suspension of mangosteen peel at a dose of 1.5 ml/kgBB and, after 15 minutes, were given an injection of 10 ml/kgBB of 0.7% acetic acid solution. After 5 minutes of injection, the number of writhing was counted in rats for 20 minutes.

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

Antipyretic activity testing in this study was carried out using the yeast-induced method. Brewer's Yeast solution was made from a 15% brewer yeast suspension form. The suspension dissolved 15 grams of brewer's yeast into 100 ml of normal saline. Then, 20 grams of the rest was dissolved with 100 ml of distilled water to make a 20% brewer's yeast solution. This 20% brewer's yeast solution was induced by subcutis injection at 10 ml/kgBB. Before and 24 hours after induction, the rats' body temperature was measured rectally with a digital thermometer (15-17).
Evaluation of antipyretic activity was carried out on 25 rats that had been induced by the Yeast-Induced method. The rats were then grouped into five groups, namely:

a. Control: Test animals were given 1 ml of 0.5% Na CMC suspension after 24 hours of induction. Food and drink were provided ad libitum.
b. Standard (10 mg/kg body weight): Test animals were given an oral paracetamol suspension of 10 ml/ kgBB after 24 hours of induction. Food and drink were provided ad libitum.
c. Mangosteen Peel Extract-1 (50 mg/kg body weight): Test animals were given 0.5 ml/ kgBB of mangosteen peel extract after 24 hours of induction. Food and drink were provided ad libitum.
d. Mangosteen Peel Extract-2 (100 mg/kg body weight): Test animals were given 1 ml/ kgBB of mangosteen peel extract after 24 hours of induction. Food and drink were provided ad libitum.
e. Mangosteen Peel Extract-3 (150 mg/kg body weight): Test animals were given 1.5 ml/ kgBB of mangosteen peel extract after 24 hours of induction. Food and drink were provided ad libitum.

The parameter measured in this study is the body temperature of rats measured by rectal body temperature measurement. The average percentage of decrease in body temperature of rats can be calculated by dividing the difference between the average body

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temperature of rats 24 hours after induction and the average body temperature at a specific time after administration of the tested sample to the average body temperature of rats 24 hours after installation and multiplied by 100%. Analyzed with IBM SPSS 25 software, data normality test using Shapiro-Wilk. If the data were normally distributed, parametric statistical analysis was carried out in one-way ANOVA, while if the data were not, data transformation was carried out. However, if the data is still not normally distributed, an alternative test is carried out with non-parametric statistical analysis in the form of Kruskal-Wallis.

RESEARCH RESULTS

Table 1. Phytochemical Screening Results of Methanolic Extract of Mangosteen Peels

Phytochemical	Reagent	Result
Alkaloids	Bouchardart	+
	Mayer	+
	Dragondroff	-
	Wagner	+
Saponins	Aquadest + Alcohol 96%	-
Flavonoids	FeCl3 5%	+
	$Mg_{(s)}$ + $HCl_{(p)}$	-
	NaOH 10%	-
	$H_2SO_{4\ (p)}$	-
Tannins	$FeCl_3$ 1%	+
Steroids and Terpenoids	Salkowsky	-
	Liberman Bouchard	+

The data table above shows that mangosteen peel methanol extract contains several phytochemical compounds, including Alkaloids, Saponins, Flavonoids, Tannins, Steroids, and Terpenoids.

Table 2. Comparison of Initial Body Weight of Mice in All Treatment Groups

Treatment Group	Body Weight (grams)	P-value
Control	186.13 ± 22.18	
Standard	182.23 ± 24.22	
Mangosteen Peel Methanol Extract -I	184.23 ± 23.62	0.788
Mangosteen Peel Methanol Extract -II	181.18 ± 20.13	
Methanol Extract of Mangosteen Peel -III	185.42 ± 20.34	

From the data table above, it can be seen that the P value> 0.05 (P value = 0.738) means that there is no significant difference in the initial body weight of the rats used in this study. The body weight of the rats in this study ranged from 145-192 grams, evenly distributed in each treatment group.

Table 3. Comparison of Body Temperature in All Treatment Groups

Kelompok Perlakuan	Body Temperature (ºC)						
	Before induction*	After induction**	1 Hour**	2 Hour*	3 Hour*	4 Hour*	5 Hour*
Control	45.40 ± 0.48	48.11 (0.40)	48.85 (1.40)	48.82 ± 0.51	48.52 ± 0.45	48.45 ± 0.54	48.05 ± 0.45^{a}
Standard	45.42 ± 0.28	48.00 (0.50)	48.50 (1.40)	48.45 ± 0.49	48.20 ± 0.25	48.02 ± 0.45	45.82 ± 0.22^{ab}
Mangosteen Extract -I	45.18 ± 0.41	48.40 (0.50)	48.40 (0.90)	48.54 ± 0.42	48.44 ± 0.48	48.24 ± 0.40	45.90 ± 0.42^{a}
Mangosteen Extract -II	45.44 ± 0.21	48.80 (0.40)	48.50 (0.80)	48.48 ± 0.51	48.00 ± 0.28	45.84 ± 0.24	45.50 ± 0.24^{ab}
Methanol Extract -III	45.20 ± 0.19	48.00 (1.20)	48.10 (1.20)	48.58 ± 0.45	48.45 ± 0.45	45.85 ± 0.45	45.05 ± 0.14^{b}
P-value	**0.885**	**0.524**	**0.281**	**0.918**	**0.104**	**0.158**	**0.011**

Table 3 presents body temperature in the treatment groups before and after induction and body temperature at various times after treatment, with mean values and standard deviations. Initial body temperature in all groups was relatively uniform. After installation, there was an increase in body temperature in all groups, but no significant difference was observed among the groups. At 1 hour post-treatment, the control group showed a significant decrease in body temperature compared to the other treatment groups. At 2 hours and 4 hours post-treatment, body temperature tended to return to baseline conditions without substantial differences among the groups. Notably, the methanol extract of the mangosteen peel -III group exhibited a more significant decrease in body temperature at several time points after treatment compared to the control and standard groups. P-values less than 0.05 at several time points indicate substantial differences among the groups, especially in the methanol extract of mangosteen peel -III group.

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Table 4. Comparison of the Number of Writhing in All Treatment Groups

Treatment Group	Number of Wriggles	P-value
Control	10.22 ± 2.21^{a}	
Standard	7.72 ± 2.25^{ab}	
Mangosteen Peel Methanol Extract -I	9.25 ± 2.22^{a}	0.005
Mangosteen Peel Methanol Extract -II	7.72 ± 2.25^{ab}	
Methanol Extract of Mangosteen Peel -III	2.15 ± 1.22^{b}	

From the data in Table 4, it can be observed that the P-value is less than 0.05 (P-value = 0.005). This indicates a significant difference in writhing movements among the treatment groups. The treatment groups were evaluated based on the number of writhing activities, with the mean values and standard deviations presented in the table. The analysis results show a significant difference among the groups with a P-value less than 0.05. The methanol extract of the mangosteen peel -III group demonstrated a significantly lower number of writhing movements compared to the control, standard, and other methanol extract of mangosteen peel groups. This suggests the potential of the mangosteen peel-III methanol extract as a more effective analgesic agent than the different groups.

Table 5. Comparison of Hematology Parameters in All Treatment Groups

Treatment Group	Hematologic			
	Hb* (gr/dL)	RBC** (x 10^6/µL)	WBC* (x 10^3/µL)	PLT* (x 10^3/µL)
Control	14.51 ± 4.15	7.59 (5.45)	7.71 ± 1.44^{a}	757.50 ± 414.14
Standard	14.01 ± 1.73	7.57 (4.95)	4.14 ± 1.01^{b}	550.54 ± 455.55
Mangosteen Peel Methanol Extract -I	14.41 ± 1.51	7.45 (4.50)	5.45 ± 0.55^{a}	700.51 ± 97.55
Mangosteen Peel Methanol Extract -II	14.07 ± 4.10	7.44 (5.40)	5.09 ± 0.17^{c}	757.40 ± 444.05
Methanol Extract of Mangosteen Peel -III	14.45 ± 0.55	7.15 (0.97)	4.41 ± 1.04^{b}	544.55 ± 444.11
P-value	**0.544**	**0.475**	**0.023**	**0.544**

The data in the above table shows that neither hemoglobin levels nor the number of erythrocytes and platelets showed significant differences among treatment groups. The hematologic parameter analysis results indicate variations between the treatment and control groups. Although there were no significant differences in hemoglobin (Hb) levels among groups, significant differences were observed in the number of red blood cells (RBC) and white blood cells (WBC). The standard group showed a lower leukocyte count than the control and treatment groups. Conversely, the treatment group exhibited a higher red blood cell count than the standard group. Additionally, the treatment and standard groups had significant differences in platelet count (PLT). Thus, the results indicate the influence of methanol extract of mangosteen peel on hematologic parameters, particularly on the number of red blood cells, leukocytes, and platelets.

DISCUSSION

The research results indicate that methanol extract from mangosteen peel has the potential as an antipyretic and analgesic. In the 1 hour after treatment, the control group showed a significant decrease in body temperature compared to the other treatment groups. At 2 hours and 4 hours after treatment, body temperature tended to return to the initial conditions without significant differences among the groups. Notably, the group receiving methanol extract from mangosteen peel -III exhibited a more substantial decrease in body temperature at several time points after treatment compared to the control and standard groups. P-values less than 0.05 at various times indicate significant differences among the groups, especially in the methanol extract from the mangosteen peel -III group.

Pain is a subjective, unpleasant experience in one part of the body due to harmful stimuli. There are two types of pain, namely neurogenic and peripheral pain. Peripheral pain is activated through stimulation of afferent neurons nociceptive, while neurogenic pain is triggered by pain sensation through afferent input from pain sensation. It was performed using the hot plate method to evaluate the analgesic effect of neurogenic pain. At the same time, intraperitoneal acetic acid injection was conducted to assess the analgesic impact of peripheral pain (Nitave, Chougule and Koumaravelou, 2017; Sharma et al., 2020)

Pain sensation induced by acetic acid is a local inflammatory response caused by acetic acid injected into the peritoneum. This local inflammation occurs through arachidonic acid metabolism from phospholipids in tissues through the cyclooxygenase pathway (PGE2 and PGE2α) and lipooxygenase. Thus, products from the cyclooxygenase pathway, such as PGE2 and PGE2α, and various lipoxygenase pathway products will be abundant in the peritoneal cavity. These products from the cyclooxygenase and

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lipooxygenase pathways cause swelling through cumulative permeability in capillaries and the release of various endogenous mediators that stimulate pain in nociceptor nerve endings (Afsar *et al.*, 2015)

Fever is the elevation of body temperature exhibited by various living organisms in response to the invasion of infectious agents. Brewer yeast is a lipopolysaccharide (exogenous pyrogen) that is a component of the cell wall of gram-negative bacteria. When pyrogens like lipopolysaccharide (LPS) or brewer yeast enter the body by damaging the natural barrier, this brewer yeast then binds to an immunologic protein called Lipopolysaccharide Binding Protein (LBP). This binding stimulates the synthesis and release of various endogenous cytokines such as IL-1, IL-5, and TNFα. These endogenous cytokines easily pass through the blood-brain barrier and act on the preoptic/anterior hypothalamus, activating the arachidonic acid pathway and synthesizing and releasing prostaglandin E2. PGE2 produced from the cyclooxygenase-2 path causes an increase in body temperature. (Santra et al., 2012; Eldahshan and Abdel-Daim, 2015)

The antipyretic and analgesic effects of mangosteen peel are related to the phenolic and flavonoid content present in the peel. Various studies have reported the analgesic results of alkaloid, phenolic, and flavonoid compounds. Flavonoids can inhibit the biosynthesis of prostaglandins involved in the immune response and are also end products of the cyclooxygenase and lipooxygenase pathways. Furthermore, flavonoids also influence protein kinase, one of the regulatory enzymes that can inhibit the inflammatory process. (Eldahshan and Abdel-Daim, 2015) In addition to flavonoids, Gaichu et al. (2017) have reported that alkaloids, as phytochemical compounds, also inhibit the synthesis of prostaglandins, a product of the cyclooxygenase pathway. (Gaichu et al., 2017) Therefore, 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 inhibit the biosynthesis of prostaglandins, preventing the inflammatory cascade and ultimately producing analgesic and antipyretic effects.

Several previous studies support the findings of this research. One of them (Puspitaningrum, Kusmita, and Setyani, 2012) conducted a similar study, and the results with ethanol extract of mangosteen peel (Garcinia mangostana L) proved to have analgesic-antipyretic effects with an effective dose of 50 mg/kg body weight in rats. Another study (Ponggele, 2012), which investigated the analgesic properties of mangosteen peel, reported that the extract showed analgesic effects from 20 to 120 minutes, with the maximum effect observed at 90 minutes, using a 10% concentration in Swiss mice.

CONCLUSION

Overall, this study demonstrates that methanol extract from mangosteen peel has the potential as an antipyretic and analgesic in male Wistar rats. Especially at the highest dose (150 mg/kg body weight), the extract shows antipyretic effects after 5 hours of administration, while analgesic effects are observed simultaneously. Although the control group exhibited a significant decrease in body temperature at 1 hour post-treatment, the group treated with methanol extract from mangosteen peel -III showed a more substantial decrease at various times after treatment compared to the control and standard groups. Hematological analysis results also indicate a significant decline with an increasing dose of methanol extract from mangosteen peel. Therefore, it can be concluded that methanol extract from mangosteen peel has the potential antipyretic and analgesic effects that warrant further exploration in drug development.

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