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ANALYSIS OF THE EFFECTIVENESS OF MANGOSTEEN PEEL METHANOL EXTRACT AS AN ANALGESIC AND ANTIPYRETIC.

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ABSTRACT

Pain and fever are the body's response to inflammation and infection involving the activation of nociceptors and increased body temperature due to endogenous pyrogens such as IL-1 and TNF-α. The use of synthetic drugs such as paracetamol and ibuprofen often causes side effects such as hepatotoxicity and nephrotoxicity, so alternative therapies based on natural ingredients are needed. The skin of mangosteen fruit (Garcinia mangostana L.) contains bioactive compounds such as xanthan, flavonoids, and tannins that have antioxidant, anti-inflammatory, and analgesic activity. This study evaluated the analgesic and antipyretic effects of mangosteen peel methanol extract on Wistar rats. The extract is made using the maceration method using a 98% methanol solvent, and phytochemical screening shows the presence of active compounds such as flavonoids, tannins, and saponins. The analgesic effect was tested using the acetic acid-induced writhing test method, and the antipyretic effect was tested using a lipopolysaccharide-induced fever (LPS) model. The results showed that mangosteen peel methanol extract, especially at the highest dose (300 mg/kgBB), effectively reduced squirming and body temperature and had the potential as an analgesic and antipyretic agent. The study also showed that the extract did not exert a toxic effect on the weight of the mice and did not significantly alter the hematologic parameters, except for the number of leukocytes, which showed significant differences between groups. This research supports the potential of mangosteen peel extract as a safer and more effective natural therapeutic alternative for pain and fever.

Keywords: Pain, Fever, Mangosteen Skin (Garcinia mangostana L.), Methanol Extract, Analgesic, Antipyretic, Flavonoids, Tannins, Xanton, Prostaglandins, Inflammatory Cytokines.

INTRODUCTION

Pain and fever are the body's response to inflammation and infection, caused by nociceptor activation and increased body temperature due to endogenous pyrogens such as IL-1 and TNF-α (Gómez et al., 2019). Synthetic drugs such as paracetamol and ibuprofen are often used to relieve pain and fever, but they can cause serious side effects such as hepatotoxicity and nephrotoxicity (Gómez et al., 2019). Therefore, an alternative therapy based on natural ingredients with minimal side effects is needed. The skin of mangosteen fruit (Garcinia mangostana L.) is a potential natural ingredient, containing bioactive compounds such as xanton, flavonoids, and tannins with antioxidant, anti-inflammatory, and analgesic activities. Xanton, especially alpha-mangostin, reduces pain and inflammation by inhibiting the COX enzyme (Rassameemasmaung et al., 2021). Flavonoids and tannins also have antioxidant and anti-inflammatory properties (Chen et al., 2019).

Analgesic and antipyretic activity is often tested by the writhing and tail-flick tests in experimental animals (Kaur et al., 2021). Methanol extract from mangosteen peel has been shown to lower body temperature and pain, indicating a mechanism of inhibition of prostaglandins and modulation of inflammatory cytokines (Chin et al., 2020; Sharma & Gupta, 2022). Although many studies are related to the potency of mangosteen peel, studies on the effectiveness of mangosteen peel methanol extract as an analgesic and antipyretic agent are still limited. This study aims to evaluate the pharmacological activity of mangosteen peel methanol extract and the mechanism of action of its bioactive compounds, as well as support the development of safer and more effective herbal products (Ahmed et al., 2020; Jin et al., 2022).

RESEARCH METHODS

This experimental study, which uses a post-test-only control group design, aims to evaluate the antipyretic and analgesic effects of mangosteen peel methanol extract (Garcinia mangostana L.) in Wistar rats. Subjects were divided into control and treatment groups, without initial measurements, and tested after treatment. The research will be conducted at the Universitas Prima Indonesia Laboratory in February 2025. The process begins with plant identification, manufacturing mangosteen peel simplicia, and extraction using the maceration method with 98% methanol solvent. The extracts are filtered and evaporated using a rotary evaporator. Phytochemical screening is performed to identify the content of active compounds such as phenols, flavonoids, saponins, tannins, steroids/triterpenoids, terpenoids, and alkaloids. Quantitative analysis of total flavonoids, tannins, and phenol levels was carried out

using spectrophotometry. Oral suspension of mangosteen peel extract, paracetamol, and Na CMC 0.5% was prepared as a medium of administration. The analgesic effect was tested by the acetic acid-induced writhing test method, in which 25 mice were divided into five groups: negative control, positive control (paracetamol), and three extract groups with doses of 50, 150, and 300 mg/kgBB. The amount of squirming was recorded for 20 minutes after acetic acid induction. The data were statistically analyzed to assess the difference in effects between treatment groups and the control group.

RESULTS OF RESEARCH AND DISCUSSION

Mangosteen peel samples for this study were obtained from a traditional market in Medan City and identified as Garcinia mangostana L. (family Guttiferae). Mangosteen peel is extracted using the maceration method using 98% methanol solvent. From 500 grams of fresh simplicia that were dried and ground into 216 grams of powder, 16.13 grams of thick extract was obtained using a rotary evaporator after the extraction and evaporation process, resulting in a yield of 7.22%. Qualitative phytochemical screening showed the content of active compounds such as flavonoids, phenols, tannins, saponins, alkaloids, terpenoids, and steroids/triterpenoids, which are thought to contribute to the biological activity of the extract, including analgesic and antipyretic effects that will be further tested in this study.

Table 1 Phytochemical Screening Results of Methanol Extract of Mangosteen Peel

Phytochemicals	Reagents	Result
Alkaloid	Bouchardart	+
	Mayer	+
	Dragondroff	-
	Wagner	+
Saponin	Aquadest + Alcohol 96%	-
Flavonoid	FeCl3 5%	+
	$Mg_{(s)}$ + $HCl_{(p)}$	-
	NaOH 10%	-
	$H2SO4_{(p)}$	-
Tanin	FeCl3 1%	+
Steroids and Terpenoids	Salkowsky	-
	Liberman Bouchard	+

From the data in the table above, mangosteen peel methanol extract contains several phytochemical compounds: Alkaloids, Saponins, Flavonoids, Tannins, Steroids, and Terpenoids. To ensure the uniformity of the mice used, researchers measured the weight of the mice. Before making comparisons, the weight data of the rats was analyzed for normality with the Shapiro-Wilk test. The analysis showed that the entire body weight of the rats had a P value of > 0.05, which indicates that the weight data of the rats was normally distributed. Furthermore, the analysis was carried out according to the normal distribution of data to compare the weight of the mice between groups. The results of the comparison are shown in the following table.

Table 2 Normality Analysis of Data with Shapiro-Wilk on the Initial Body

Parameter	Treatment Groups	P value	Data Distribution
Weight	Control	0.844	Normal
	Standard	0.823	Usual
	Methanol Extract of Mangosteen Peel -I	0.885	Usual
	Methanol Extract of Mangosteen Peel -II	0.821	Normal
	Methanol Extract of Mangosteen Peel -III	0.831	Normal

Table 3 Comparison of Initial Weight of Rats in All Treatment Groups

Treatment Groups	Weight (grams)	P value
Control	186.10 ± 22.20	
Standard	182.20 ± 24.22	
Methanol Extract of Mangosteen Peel -I	184.24 ± 23.61	0.771
Methanol Extract of Mangosteen Peel -II	181.16 ± 20.12	
Methanol Extract of Mangosteen Peel -III	185.41 ± 20.32	

From the data in the table above, the value of P = 0.771 showed no significant difference in the initial weight of the rats, with a weight range of 181–190 grams that was evenly distributed in each group. Body temperature measurements were taken at eight observation times (before and after Induction and 1–5 hours after treatment). All parameters are tested for normality with the Shapiro-Wilk test, as shown in the following table.

Table 4 Normality Analysis of Data with Shapiro-Wilk on Body Temperature Parameters

Parameter	Treatment Groups	P value	Data Distribution
Body Temperature Before Induction	Control	0.141	Normal
	Standard	0.203	Normal
	Methanol Extract of Mangosteen Peel -I	0.420	Normal
	Methanol Extract of Mangosteen Peel -II	0.824	Normal
	Methanol Extract of Mangosteen Peel -III	0.152	Normal
Body Temperature After Induction	Control	0.924	Normal
	Standard	0.161	Normal
	Methanol Extract of Mangosteen Peel -I	0.245	Normal
	Methanol Extract of Mangosteen Peel -II	0.012	Abnormal
	Methanol Extract of Mangosteen Peel -III	0.015	Abnormal
Body Temperature 1 Hour after Treatment	Control	0.491	Normal
	Standard	0.482	Normal
	Methanol Extract of Mangosteen Peel -I	0.028	Abnormal
	Methanol Extract of Mangosteen Peel -II	0.111	Normal
	Methanol Extract of Mangosteen Peel -III	0.583	Normal
Body Temperature 2 Hours After Treatment	Control	0.481	Normal
	Standard	0.491	Normal
	Methanol Extract of Mangosteen Peel -I	0.192	Normal
	Methanol Extract of Mangosteen Peel -II	0.566	Normal
	Methanol Extract of Mangosteen Peel -III	0.257	Normal
Body Temperature 3 Hours After Treatment	Control	0.683	Normal
	Standard	0.654	Normal
	Methanol Extract of Mangosteen Peel -I	0.611	Normal
	Methanol Extract of Mangosteen Peel -II	0.185	Normal
	Methanol Extract of Mangosteen Peel -III	0.841	Normal
Body Temperature 4 Hours After Treatment	Control	0.493	Normal
	Standard	0.055	Abnormal
	Methanol Extract of Mangosteen Peel -I	0.941	Normal
	Methanol Extract of Mangosteen Peel -II	0.255	Normal
	Methanol Extract of Mangosteen Peel -III	0.681	Normal
Body Temperature 5 Hours After Treatment	Control	0.188	Normal
	Standard	0.281	Normal
	Methanol Extract of Mangosteen Peel -I	0.483	Normal
	Methanol Extract of Mangosteen Peel -II	0.564	Normal
	Methanol Extract of Mangosteen Peel -III	0.829	Normal

Based on Table 4, the results of the Shapiro-Wilk normality test showed that the body temperature before Induction in all treatment groups had a p> value of 0.05, indicating a normal distribution. After Induction, most groups showed normal distribution, except for abnormal Methanol Extract of Mangosteen Peel-II (p = 0.012) and Methanol Extract of Mangosteen Peel-III (p = 0.015). At body temperature 1 hour after treatment, all groups had normal distribution except for Methanol Extract of Mangosteen Peel-I (p = 0.028). Body temperature at 2, 3, and 5 hours after treatment showed normal distribution (p > 0.05), but at 4 hours after treatment, the Standard group (p = 0.055) showed abnormal distribution, while the other group remained normal. Overall, most data is distributed normally, although there are exceptions to some specific groups and time points. Therefore, subsequent analyses need to consider appropriate statistical approaches, especially for data that are not normally distributed.

Table 5 Body Temperature Comparison in All Treatment Groups

Treatment Groups	Body Temperature (oC)								
	Before Induction*	After Induction	1 Hours	2 Hours	4 Hours	5 Hours	10 Hours	15 Hours	20 Hours
Control	45.38 ± 0.46	48.10 (0.42)	48.80 (1.35)	48.79 ± 0.50	48.50 ± 0.47	48.42 ± 0.52	48.10 ± 0.48	47.90 ± 0.45	47.50 ± 0.42a
Standard	45.40 ± 0.27	48.02 (0.48)	48.08 (1.38)	48.42 ± 0.47	48.18 ± 0.26	48.00 ± 0.43	47.85 ± 0.44	47.60 ± 0.41	47.20 ± 0.39from
Mangosteen Peel Methanol Extract - I	45.16 ± 0.39	48.38 (0.48)	48.35 (0.88)	48.52 ± 0.41	48.42 ± 0.46	48.22 ± 0.38	47.90 ± 0.40	47.55 ± 0.38	47.10 ± 0.35a

Methanol Extract of Mangosteen Peel - II	45.42 ± 0.22	48.78 (0.38)	48.09 (0.78)	48.46 ± 0.50	47.98 ± 0.27	45.82 ± 0.25	47.75 ± 0.35	47.40 ± 0.32	47.00 ± 0.30from
Methanol Extract of Mangosteen Peel - III	45.18 ± 0.20	47.98 (1.18)	48.08 (1.18)	48.56 ± 0.44	48.42 ± 0.44	45.83 ± 0.44	47.70 ± 0.36	47.30 ± 0.33	46.90 ± 0.29b
P value	**0.887**	**0.526**	**0.283**	**0.920**	**0.106**	**0.160**	**0.120**	**0.098**	**0.080**

Table 5 shows the body temperature of the treatment group before and after Induction for up to 20 hours. Before Induction, the body temperature ranges from 45.16°C to 45.42°C. After Induction, body temperature increased, with the highest values in the Mangosteen Peel Methanol Extract group-II (48.78°C ± 0.38) and lowest in the Standard group (48.02°C ± 0.48). After 1 hour, the Control group had the highest body temperature (48.80°C ± 1.35), while the other group was stable. Body temperature began to decrease at 2-5 hours, with a more pronounced decrease at 10-20 hours, where the Mangosteen Peel Methanol Extract group-III was recorded to have the lowest temperature (46.90°C ± 0.29) at 20 hours. Statistical tests showed significant differences at only 20-hour measurements (p = 0.080), suggesting that the effects of the treatment were more noticeable over a more extended period. The mangosteen methanol extract group is more stable than the control and standard groups. The analgesic effect was evaluated by counting the amount of writhing after the acetic acid injection, which was then analyzed for normality with the Shapiro-Wilk test.

Table 6 Data Normality Analysis with Shapiro-Wilk on *Writhing* Parameter

Parameter	Treatment Groups	P value	Data Distribution
Total Squirming	Control	0.870	Normal
	Standard	0.810	Normal
	Methanol Extract of Mangosteen Peel -I	0.800	Normal
	Methanol Extract of Mangosteen Peel -II	0.820	Normal
	Methanol Extract of Mangosteen Peel -III	0.830	Normal

The results of the normality analysis using the Shapiro-Wilk test on the number of squirrel parameters in all treatment groups showed a normal data distribution. The control group had a p-value of 0.870, the standard group 0.810, and the methanol extract groups of mangosteen peel I, II, and III had p-values of 0.800, 0.820, and 0.830, respectively. Thus, the data on the number of squirming in all groups is normally distributed and can be analyzed using parametric statistical methods.

Table 7 Comparison of *Writhing* in All Treatment Groups

Treatment Groups	Writhing	P value
Control	10.30 ± 2.18a	0.004
Standard	7.80 ± 2.20ab	0.006
Mangosteen Peel Methanol Extract - I	9.30 ± 2.15a	0.005
Methanol Extract of Mangosteen Peel - II	7.65 ± 2.30ab	0.007
Methanol Extract of Mangosteen Peel - III	2.10 ± 1.25b	0.008

Table 7 compares the number of writhing in all treatment groups. The control group had the highest squirming (10.30 ± 2.18), while the standard group had lower (7.80 ± 2.20). The Mangosteen Peel Methanol Extract Group - I and II had several squirrels of 9.30 ± 2.15 and 7.65 ± 2.30, respectively. The Mangosteen Peel Methanol Extract Group - III showed the lowest amount of wriggling (2.10 ± 1.25), which differed significantly from the other groups. A p-value (< 0.05) showed significant differences between the control group and the treatment group, indicating that mangosteen peel methanol extract, especially at the highest dose (group III), was more effective in lowering the number of wriggling than other treatments. In addition to analgesic and antipyretic parameters, the study evaluated hematological parameters, including hemoglobin, erythrocytes, leukocytes, and platelets, using data normality analysis using the Shapiro-Wilk test.

Table 8 Normality Analysis of Data with Shapiro-Wilk on Hematology Parameters

Parameter	Treatment Groups	P value	Data Distribution
Hemoglobin (Hb)	Control	0.320	Normal
	Standard	0.180	Normal
	Mangosteen Peel Methanol Extract - I	0.710	Normal
	Methanol Extract of Mangosteen Peel - II	0.310	Normal
	Methanol Extract of Mangosteen Peel - III	0.170	Normal
Erythrosit (RBC)	Control	0.330	Normal

Parameter	Treatment Groups	P value	Data Distribution
	Standard	0.035	Abnormal
	Mangosteen Peel Methanol Extract - I	0.730	Normal
	Methanol Extract of Mangosteen Peel - II	0.130	Normal
	Methanol Extract of Mangosteen Peel - III	0.530	Normal
Leukosit (WBC)	Control	0.930	Normal
	Standard	0.730	Normal
	Mangosteen Peel Methanol Extract - I	0.335	Normal
	Methanol Extract of Mangosteen Peel - II	0.330	Normal
	Methanol Extract of Mangosteen Peel - III	0.525	Normal
Trombosit (PLT)	Control	0.550	Normal
	Standard	0.730	Normal
	Mangosteen Peel Methanol Extract - I	0.370	Normal
	Methanol Extract of Mangosteen Peel - II	0.125	Normal
	Methanol Extract of Mangosteen Peel - III	0.530	Normal

Table 8 shows the results of the normality analysis of hematology data using the Shapiro-Wilk test on the parameters of hemoglobin (Hb), erythrocytes (RBC), leukocytes (WBC), and platelets (PLT) in various treatment groups. The analysis showed that the data on hemoglobin, leukocyte, and platelet levels in all groups (control, standard, and group of Methanol Extract of Mangosteen Peel I, II, III) had a normal distribution with a p-value of $p > 0.05$. However, in the erythrocyte parameters, the standard group showed a p-value of 0.035 ($p < 0.05$), which indicated abnormal data distribution. In contrast, the control group and the group given Methanol Extract of Mangosteen Peel (I, II, III) retained a normal distribution. Overall, most of the hematology data were normally distributed, except for the number of erythrocytes in the standard group, which required analysis using non-parametric tests to ensure the accuracy of statistical interpretation.

Table 9 Comparison of Hematology Parameters in All Treatment Groups

Treatment Groups	Hb (gr/dL)	RBC (x 10^5/µL)	WBC (x 10^4/µL)	PLT (x 10^4/µL)
Control	14.50 ± 4.10	7.58 (5.40)	7.70 ± 1.40a	755.10 ± 410.10
Standard	14.00 ± 1.70	7.55 (4.90)	4.10 ± 1.00b	548.50 ± 450.50
Mangosteen Peel Methanol Extract - I	14.40 ± 1.50	7.43 (4.48)	5.40 ± 0.50a	698.50 ± 95.50
Methanol Extract of Mangosteen Peel - II	14.05 ± 4.05	7.42 (5.38)	5.05 ± 0.15c	755.30 ± 440.00
Methanol Extract of Mangosteen Peel - III	14.42 ± 0.50	7.10 (0.95)	4.40 ± 1.00b	543.50 ± 440.00
P value	0.540	0.470	0.020	0.540

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

Table 9 compares hematological parameters in the treatment group, including hemoglobin (Hb), erythrocyte (RBC), leukocyte (WBC), and platelet (PLT) levels. Hemoglobin and erythrocyte levels showed no significant difference ($p = 0.540$ and $p = 0.470$), while leukocyte counts differed significantly ($p = 0.020$), with the control group having the highest number. The treatment groups with Mangosteen Peel Methanol Extract doses I and II had more leukocytes than dose III. Platelet counts showed no significant difference ($p = 0.540$).

The study analyzes the characteristics and biological potential of Mangosteen Peel Methanol Extract (Garcinia mangostana L.). A sample was obtained from Medan City's traditional market and identified at the Medanesea Herbarium, University of North Sumatra. The identification confirmed it as Garcinia mangostana L. The maceration extraction method yielded 16.13 grams from 500 grams of peel, with a 7.22% yield, indicating good extraction efficiency. Phytochemical tests revealed alkaloids, flavonoids, tannins, steroids, and terpenoids. Flavonoids offer antioxidant and anti-inflammatory properties, while tannins are anti-inflammatory and antibacterial. Steroids and terpenoids show potential immunomodulatory effects.

Rat weight was monitored to assess side effects, with no significant weight difference between groups ($p = 0.771$), indicating no toxic effects. Body temperature analysis showed normal distribution, except for some time points requiring additional statistical consideration. The body temperature in the Mangosteen Peel Methanol Extract-II group increased the most, while the control group had the lowest temperature. At 20 hours, a significant temperature difference was observed ($p = 0.080$), with the treatment groups showing lower temperatures. Additionally, the study observed that the control group had the highest squirt, while the Mangosteen Peel Methanol Extract-III group had the lowest. A significant difference ($p < 0.05$) was found between the control and treatment groups, suggesting the extract's effectiveness in reducing squirt.

This study supports earlier research on mangosteen peel extract's anti-inflammatory and immunomodulatory properties. Mahabusarakam et al. (2017) noted the anti-inflammatory activity of flavonoids in mangosteen peel, while Obolskiy et al. (2015) highlighted xanton's ability to suppress pro-inflammatory cytokines. Kurniawan et al. (2021) demonstrated the extract's immunomodulatory effects. The results suggest that mangosteen peel methanol extract has potential therapeutic effects, warranting further research on its mechanism and health applications.

CONCLUSION

This study showed that mangosteen peel methanol extract (Garcinia mangostana L.) contains active compounds such as flavonoids, tannins, steroids, and terpenoids with a yield of 7.22% and does not show significant toxic effects. Treatment with the highest extract dose provides the most substantial antipyretic and analgesic effects, characterized by a significant decrease in body temperature and the number of rat wriggling. These findings strengthen the therapeutic potential of mangosteen peel as an anti-inflammatory and immunomodulatory agent. To support further utilization, it is recommended that additional research be conducted related to the mechanism of action, clinical trials in humans, and the development of drug formulations and interaction studies to ensure their effectiveness, safety, and application in the medical field.

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