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EFFECTIVENESS OF MANGOSTEEN PEEL METHANOL EXTRACT AS ANALGESIC AND ANTIPYRETIC IN WISTAR RATS

Sun Quanxin
Master of Clinical Medicine, Faculty of Medicine, Dentistry, Health Sciences, Universitas Prima Indonesia

ABSTRACT
Inappropriate use of analgesics, because these drugs are over-the-counter drugs, can negatively impact the body. A plant that has potential as an antipyretic analgesic compound is mangosteen fruit. Many studies have explored the multiple benefits of natural ingredients, including mangosteen peel. The study aims to test the analgesic and antipyretic effectiveness of mangosteen skin methanol extract in Wistar rats. This study is an experimental research, with a post-test-only Only Control Group Design design that aims to explore mangosteen peel's antipyretic and analgesic effects in March 2023. Analyzed with IBM SPSS 25 software, data normality test using Shapiro-Wilk. If the data is usually distributed, parametric statistical analysis is carried out in one-way ANOVA, while if the data is not normally distributed, data transformation is carried out. However, if the data is still abnormally distributed, an alternative test is carried out with non-parametric statistical analysis in the form of Kruskal-Wallis. The mangosteen peel methanol extract results contain various phytochemicals, namely Alkaloids, Saponins, Flavonoids, Tannins, and Steroids and Terpenoids. Conclusion Methanol extract from mangosteen skin has a significant antipyretic effect (P value = 0.014) after 5 hours of administration with an optimal dose of 600 mg/kg body weight. Mangosteen skin methanol extract has a significant analgesic effect (P value = 0.042) on nociceptive pain with an optimal dose of 600 mg/kg body weight.
KEYWORDS: *analgesic, antipyretic, mangosteen peel*

INTRODUCTION

Medicine today requires an industry that produces pharmaceutical drugs, most of which are based on plant-active principles. Most areas of the world continue to use traditional medicine based on the direct use of medicinal plants due to its low cost (1). Analgesic-antipyretic is a compound used by humans of all ages to reduce pain and fever for various reasons. Analgetics are compounds that can reduce or eliminate pain without removing consciousness. At the same time, antipyretics can reduce fever (high body temperature). Plants that can have potential antipyretic analgetic compounds are mangosteen fruit (Garcinia mangostana L) (2).

Many studies have explored the various benefits of natural ingredients, including mangosteen peel. Methanol extract of mangosteen (Garcinia mangostana L.) peel contains saponins, alkaloids, flavonoids, triterpenoids, tannins, and polyphenols (3). Therefore, mangosteen peels have various pharmacological effects such as anti-inflammatory, antioxidant, antidiabetic, and antibacterial (4-7). Flavonoids in mangosteen peel can inhibit prostaglandins and thus have antipyretic effects (8).

Inappropriate use of analgesics because this over-the-counter drug can lead to various adverse effects on the body. Its misuse is common in professional circles for recreational sports use, to reduce pain due to athletic activity, or as a precaution before training (9). The wide use of paracetamol is due to the analgesic-antipyretic effect of this compound is entirely rational with a lower potential risk of interaction with other compounds at standard doses (10); (11). Dorji et al. (2018) reported that out of 441 outpatients, 72.1% of patients at Phuentsholing General Hospital used paracetamol in the past year (12). Surya et al. (2018) said that out of 50 parents of students at Laksana Kumara Kindergarten as a sample, it was found that 34 people (68%) tended to choose paracetamol as a choice of medicine for fever (13).

Paracetamol has adverse effects, including metabolites of paracetamol that are toxic. Paracetamol-induced liver failure has recently been reported as the second most common cause of liver transplantation in the United States (14). One of the natural ingredients that has the potential to serve as an alternative substitute is mangosteen rind. The utilization of mangosteen rind for medicine in Indonesia is still not much, especially as an antipyretic analgesic. The study aims to test the analgesic and antipyretic effectiveness of mangosteen peel methanol extract in Wistar rats.

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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 (150 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 (200 mg/kg body weight): Rats in this group were given an oral suspension of mangosteen peel at a dose of 2.5 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 (400 mg/kg body weight): Rats in this group were given an oral suspension of mangosteen peel at a dose of 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.
e. Mangosteen Peel Extract-3 (600 mg/kg body weight): Rats in this group were given an oral suspension of mangosteen peel at a dose of 7.5 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% (15).

Antipyretic activity testing in this study was carried out by 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 (150 mg/kg body weight): Test animals were given an oral suspension of paracetamol 10 ml/ kgBB after 24 hours of induction. Food and drink were provided ad libitum.
c. Mangosteen Peel Extract-1 (200 mg/kg body weight): Test animals were given 2.5 ml/ kgBB of mangosteen peel extract after 24 hours of induction. Food and drink were provided ad libitum.
d. Mangosteen Peel Extract-2 (400 mg/kg body weight): Test animals were given a 5 ml/ kgBB of mangosteen peel extract after 24 hours of induction. Food and drink were provided ad libitum.
e. Mangosteen Peel Extract-3 (600 mg/kg body weight): Test animals were given 7.5 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 temperature of rats 24 hours after induction and the average body temperature at a specific time after administration of the tested

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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 normally distributed, 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 AND DISCUSSION

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%	-
	$H_2SO_{4\ (p)}$	-
Tanins	$FeCl_3$ 1%	+
Steroids and Terpenoids	Salkowsky	-
	Liberman Bouchard	+

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

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

Treatment Group	Body Weight (grams)	P-value
Control	176.13 ± 22.18	
Standard	172.23 ± 24.22	
Mangosteen Peel Methanol Extract -I	174.23 ± 23.62	0.738
Mangosteen Peel Methanol Extract -II	171.18 ± 20.13	
Methanol Extract of Mangosteen Peel -III	175.42 ± 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 range of body weight of rats used in this study ranged from 145-192 grams which were 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	36.30 ± 0.37	38.11 (0.40)	37.75 (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	38.40 (0.50)	38.30 (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]
Methanol Extract of Mangosteen Peel -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	36.05± 0.14[b]
P-value	**0.886**	**0.623**	**0.281**	**0.917**	**0.104**	**0.167**	**0.014**

The data table above shows that the body temperature of all rats at the time before induction is uniform; this is reflected in the P value> 0.05 (P value = 0.886). After 24 hours of installation, the rats' body temperature also remained uniform; this can be seen

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from the P value> 0.05 (P value = 0.623). However, rats' body temperature after induction tends to increase compared to before. Before installation, rats' body temperature was 36.24-36.34oC and rose to 37.60-38.40oC after 24 hours of building.

After 24 hours of induction, all groups of rats were given treatment according to their treatment groups. The body temperature of rats 1-4 hours after treatment did not show significant differences between treatment groups. This can be seen from the P value of the rat's body temperature every hour, which is more critical than 0.05. However, at the end of the observation, namely, 5 hours after treatment, the rats' body temperature experienced significant changes; this was reflected in the P value <0.05 (P value = 0.014). , The mangosteen skin methanol extract group III showed the lowest body temperature 5 hours after treatment, which was 36.05 ± 0.14oC, and the mangosteen skin methanol extract group -III also showed a significant difference to the control group, which showed the highest body temperature, which was 37.75 ± 0.46oC.

In addition to the analgesic and antipyretic parameters previously described. This study also evaluated hematological parameters to support the antipyretic and analgesic parameters of mangosteen peel. The hematological parameters evaluated in this study include: Hemoglobin, erythrocyte count, leukocytes, and platelets. Before further analysis of the hematological parameters, data normality analysis with shapiro-wilk was conducted and the results of the analysis can be seen in the table 5.

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

Treatment Group	Number of Wriggles	P-value
Control	10.24 ± 2.31^{a}	
Standard	8.82 ± 3.26^{ab}	
Mangosteen Peel Methanol Extract -I	9.25 ± 2.42^{a}	0.008
Mangosteen Peel Methanol Extract -II	8.83 ± 3.36^{ab}	
Methanol Extract of Mangosteen Peel -III	4.16 ± 1.24^{b}	

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	14.65 ± 4.12	7.69 (6.35)	7.71 ± 1.23^{a}	867.60 ± 214.14
Standard	14.01 ± 1.78	7.67 (2.95)	3.14 ± 1.01^{b}	650.62 ± 366.56
Mangosteen Peel Methanol Extract -I	12.44 ± 1.56	7.25 (2.60)	6.45 ± 0.56^{a}	800.61 ± 97.55
Mangosteen Peel Methanol Extract -II	14.08 ± 3.10	7.23 (5.20)	5.09 ± 0.17^{c}	867.40 ± 423.06
Methanol Extract of Mangosteen Peel -III	12.45 ± 0.65	7.15 (0.98)	3.21 ± 1.02^{b}	624.65 ± 242.11
P-value	**0.624**	**0.476**	**0.042**	**0.523**

The data table above shows that neither hemoglobin levels, erythrocyte counts, nor platelet counts showed significant differences between treatment groups. The range of hemoglobin, erythrocyte, and platelet counts in all groups of rats were 12.44-14.08 gr/dL, 7.15-7.69 x 106/µL, and 624.65-867.40 x 103/µL, respectively. Only the number of leukocytes showed a significant difference between treatment groups; the value of P < 0.05 reflected this. The standard group (3.14 ± 1.01 x 106/µL) and mangosteen peel methanol extract-III (3.21 ± 1.02 x 106/µL) showed significant differences with other treatment groups. The group with the highest leukocyte count was the control group, followed by the mangosteen peel methanol extract-I, II, III, and Standard groups. However, in the mangosteen peel methanol extract-I group (6.45 ± 0.56 x 106/µL) and the control group (7.71 ± 1.23 x 106/µL), there was no significant difference in the number of leukocytes.

The results of this study indicate that mangosteen peel has potential antipyretic and analgesic effects. It is shown that mangosteen peel in the form of methanol extract obtained by maceration has an antipyretic effect after 5 hours of extract administration. The antipyretic effect was mainly observed at the two highest doses of 400 mg/kg body weight and 600 mg/kg body weight. However, the analgesic effect of mangosteen peel was found at the highest dose of 600 mg/kg body weight. Meanwhile, the results of the hematologic examination showed a significant decrease in line with the increase in the amount of methanol extract of mangosteen peel given. The hot plate method was performed to evaluate the analgesic effect of neurogenic pain, while intraperitoneal injection of acetic acid was performed to assess the analgesic effect of peripheral pain. (18,19)(20)

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Fever is an increase in body temperature exhibited by various living things in response to the invasion of an infectious agent. Brewer yeast is a lipopolysaccharide (exogenous pyrogen), a component of gram-negative bacteria's cell wall. When pyrogens such as lipopolysaccharide (LPS) or brewer yeast enter the body, they damage the natural barrier. The brewer yeast then binds to an immunological protein called Lipopolysaccharide Binding Protein (LBP). This binding promotes the synthesis and release of various endogenous cytokines such as IL-1, IL-6, and TNFα. These endogenous cytokines easily cross the blood-brainblood-brain barrier and act on the preoptic/ anterior hypothalamus, thus activating the arachidonic acid pathway and synthesizing and releasing prostaglandin E2. PGE2 produced from the cyclooxygenase-2 path causes an increase in body temperature (21,22).

The antipyretic and analgesic effects of mangosteen peel are related to the phenol and flavonoid content present in mangosteen peel. Various studies have reported analgesic effects possessed by alkaloid, phenol, and flavonoid compounds. Flavonoids can inhibit the biosynthesis of prostaglandins involved in immunological responses and are end products of the cyclooxygenase and lipooxygenase pathways. In addition, flavonoids also affect protein kinase, one of the regulatory enzymes that can inhibit the inflammatory process. (21) Besides flavonoids, Gaichu et al. (2017) also reported that alkaloid compounds as phytochemical compounds inhibit the synthesis of prostaglandins, a poduct of the cyclooxygenase pathway. (23) It can be concluded that the analgesic and antipyretic effects of mangosteen peel are due to alkaloids, phenols, and flavonoids. These phytochemical compounds will inhibit prostaglandins' biosynthesis, thereby preventing the cascade of inflammation and ultimately producing analgesic and antipyretic effects.

Research by Ponggele (2013) conducted a study on the analgesic test of mangosteen peel, stating that mangosteen peel extract has an analgesic effect that begins to appear at minute 30 to minute 120, with the maximum effect seen at minute 90, with a concentration of 10% in Swiss mice (24). Puspitaningrum (2014) stated that the results of ethanol extract of mangosteen peel (Garcinia mangostana L) proved to have an antipyretic analgesic effect with an effective dose of 50 mg/kg body weight of rats (2).

CONCLUSION

The conclusions that can be drawn from this study are that the methanol extract of mangosteen skin contains various phytochemicals, namely Alkaloids, Saponins, Flavonoids, Tannins, Steroids, and Terpenoids. Methanol extract from mangosteen skin has a significant antipyretic effect (P value = 0.014) after 5 hours of administration with an optimal dose of 600 mg/kg body weight. Mangosteen skin methanol extract has a significant analgesic effect (P value = 0.042) on nociceptive pain with an optimal dose of 600 mg/kg body weight.

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