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Analgesic and Antipyretic Effects of Red Dragon Fruit (*Hylocereus polyrhizus*) Peel Extract in White Male Rats

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ABSTRACT

Red dragon fruit (*Hylocereus polyrhizus*) is a tropical fruit that is currently cultivated in all tropical parts of the world. It is popular to consume its fruit flesh, while the peel is often thrown away. This red dragon fruit peel (RDFPE) is known to possess lots of phytochemical compounds with multitudes of usage, amongst them as an analgesic and antipyretic. Therefore, the active compounds of RDFPE play an important role in the natural product. This study aims to observe and analyze the analgetic and antipyretic activity possessed by red dragon fruit peel. This study is an in-vivo experiment on 25 white male rats divided into five groups, in which each group receive Na CMC, acetaminophen, and the other three groups will receive three different doses of RDFPE (500 mg/kg, 750 mg/kg, and 1000 mg/kg), respectively. Acetic acid writhing and tail immersion methods were performed to induce inflammation and Brewer's yeast injection performed induced pyrexia. In the investigation of the acetic acid writhing test, the intervention was administered before induction, and for the tail immersion test, induction was given before and after the intervention was administered. Meanwhile, in brewer's yeast-induced pyrexia, the rectal temperature was measured before induction, 24 hours after induction, and each hour for five four after the intervention; intervention was administered 24 hours after induction. This study found that RDFPE at the dose of 750 mg/kg and 1000 mg/kg are effective as an analgesic by reducing the average writhing and delaying the tail retraction of the experiment subject and also effective as an antipyretic by reducing the elevated temperature of the experiment subject ($p<0.05$). This study concludes that RDFPE possesses analgesic and antipyretic activity, especially at the higher dose. Phytochemical compounds such as alkaloids and flavonoids are most likely responsible for this analgesic and antipyretic activity by inhibiting inflammation activity.
Keywords: Red dragon fruit peel; analgesic; antipyretic; in-vivo study; phytochemicals

INTRODUCTION

Red dragon fruit (*Hylocereus polyrhizus*), which is also known as pitaya or pitahaya is a tropical fruit from the Cactaceae family which is well known for its distinct red-scaly look peels (Li et al., 2022). While it is originally from South and Central America, nowadays, red dragon fruit is cultivated all around the tropical part of the world (Luu et al., 2021; Saenjum et al., 2021).

The pulp of red dragon fruit is the part that is commonly utilized, while the peels are generally discarded. This practice is considered wasteful since red dragon fruit peels account for about 30-35% of the total weight of the fruit (Li et al., 2022).

Research and experiments into red dragon fruit peels utilization found red dragon fruit peels contain a large multitude of phytochemicals such as betacyanin, phenols, flavonoids, triterpenoids, steroids, tocopherols, vitamins, and carotenoid (Joshi and Prabhakar, 2020; Khuzaimah and Millati, 2022; Hendra et al., 2019; Kaul et al., 2020; Liana et al., 2019; Luu et al., 2021). These large multitudes of phytochemicals gave red dragon fruit peels great potential as a phytopharmaceutical agent. Flavonoids compound are known to have anti-inflammatory properties by inhibiting the COX and LOX pathways (Kaul et al., 2020), hence making them a potential analgesic agent.

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METHODOLOGY

Materials

The specimen used in this study was the red dragon fruit, procured from a local traditional market in Medan, North Sumatera, and identified by Herbarium Medanense of North Sumatera University. The Herbarium Medanense of Mathematic and Natural Science Faculty of the University of Sumatera Utara confirmed the specimen through letter number 17/MEDA/2022 to be red dragon fruit (*H. polyrhizus*).

Animal subject

In this study, 25 white male Wistar rats (*Rattus norvegicus*) were divided into 5 distinct groups, each group will receive similar induction, but with different interventions. The first group was the negative control group, which only

received suspension base intervention. The second group was the positive control group, which received a paracetamol suspension (150 mg/kg) intervention. Meanwhile, the third, fourth, and fifth groups received dragon fruit peel extract suspension intervention, with 500 mg/kg, 750 mg/kg, and 1000 mg/kg dosages, respectively. The experiment protocol was approved by the Health Research Ethical Committee of Prima Indonesia University through ethics declaration number 029/KEPK/UNPRI/III/2022.

Extraction of red dragon fruit peel extract

Fresh red dragon fruit was peeled and the peels were collected in a clean container and cut into pieces, dried, and turned into powder. Extraction was conducted by maceration method using methanol as the solvent. In the maceration jar, 500 grams of red dragon fruit peel powder was mixed with 1.5 liters of methanol. This mix was then stirred every 30 minutes for 6 hours and kept in a dark chamber for three days. After three days, the mix was filtered using filter paper, the filtrate was kept in a separate container, while the residue was returned to the maceration jar, and into it added another 1.5 liters of methanol, and kept in the dark chamber for another three days (re-maceration). This re-maceration process was conducted twice. In the end, about 4.5 liters of the filtrate were produced. This filtrate then evaporated in a rotary evaporator until most of the solvent evaporate. This concentrated filtrate was then reduced further in a water bath until it produced a thick consistent extract.

Phytochemical screening of red dragon fruit peel extract

Red dragon fruit peel extract (RDFPE) was undergone qualitative phytochemical screening for the presence of alkaloid, steroid, triterpenoid, saponin, flavonoid, tannin, and glycoside compounds. This screening was conducted by the Organic Chemistry Laboratory of the Mathematic and Natural Science Faculty of the University of Sumatera Utara.

Preparation of oral suspension

The base for the oral suspension is 0.5 grams of carboxymethyl cellulose sodium (Na CMC), which is put into the mortar with 10 mL of hot distilled water. After 15 minutes, the water and Na CMC mix were ground using a pestle until became a gel. The gel was then moved into a 100 mL volumetric flask, then diluted into 100 mL volume, which produced 0.5% Na CMC suspension.

Making RDFPE suspension start with adding 1 gram of RDFPE into the mortar, followed by adding Na CMC 0.5% suspension whilst grinding to homogenize it. The mix was then transferred into a 10 mL volumetric flask and diluted into a 10 mL volume, producing 10% RDFPE suspension.

To produce paracetamol suspension, 150 mg of paracetamol was ground with mortar and pestle, then into it added Na CMC 0.5% suspension whilst continuing grinding until a homogenized mix was produced. The mix was then transferred into a 10 mL volumetric flask and diluted into a 10 mL volume, producing 1.5% paracetamol suspension.

Evaluation of analgesic activity of RDFPE

Evaluation of the analgesic activity of RDFPE is conducted using two methods, the tail immersion method, and the acetic acid writhing method.

The tail immersion method was conducted an hour before and after administering the suspension by putting the animal subject into a restrainer, fixating its tail, and putting a marking line 3 cm from the distal part of the tail. The tail was then immersed in the 55ºC water up to a 3 cm marking line. The time between the tail immersed up to the line to the moment the subject animal withdrew its tail is called reaction time. Using this reaction time, the maximum possible analgesia (MPA) was calculated using the formula:

$$MPA: \frac{Dragon\ Fruit\ Peel\ Extract\ Reaction\ Time - Control\ Reaction\ Time}{15\ seconds - Control\ Reaction\ Time} x\ 100\%$$

Acetic acid writhing methods began by diluting 0.7 mL glacial acetic acid into 20 mL aquadest inside a 100 mL volumetric flask, then adding aquadest until it reaches 100 mL volume, hence producing 0.7% acetic acid solution. Each experiment subject then receives intervention according to their group. Fifteen minutes after receiving the intervention, induction by injecting 0,7% acetic acid solution into the peritoneal cavity was performed. Five minutes after induction, the experiment subject was observed for 20 minutes for writhing activity. The average abdominal writhing inhibition percentage was then calculated using the formula (Ye et al., 2021):

$$\%\ of\ Inhbition = \frac{Control\ Mean\ Writhing\ Count - Test\ Mean\ Writhing\ Count}{Control\ Mean\ Writhing\ Count} x\ 100\%$$

Evaluation of the antipyretic activity of RDFPE

Antipyretic activity in this study was investigated through a yeast-induced method. Preparation of yeast solution began by mixing 20 grams of brewer yeast into 100 mL aquadest to produce 20% yeast solution. This 20% brewer's

Table I. Phytochemical screening of RDFPE

Secondary Metabolites Compounds	Reagent(s)/Method(s)	Result
Alkaloids	Bouchardat's	+
	Mayer's	+
	Dragendorff's	+
	Wagner	+
Steroid and Triterpenoid	Salkowski	-
	Lieberman-Burchard	-
Saponin	Aquadest + Alcohol 96%	+
Flavonoids	$FeCl_3$ 5%	+
	$Mg_{(s)}$ HCl $_{(p)}$	-
	NaOH 10%	-
	$HaSO_{4(p)}$	+
Tannin	$FeCl_3$ 1 %	+
Glycosides	Molisch's	-

*+: a secondary metabolite of the compound detected; -: secondary metabolites of the compound not detected.

yeast solution was then injected into the experiment subject subcutaneously. Before and 24 hours following the pyrexia induction, the experiment subject's rectal temperature was measured using a digital thermometer (Veronica et al., 2017; Sivamurugan et al., 2016; Saini and Singha, 2012).

After temperature measurement after induction, every experiment subject receive intervention according to their group and the temperature was measured every hour for five consecutive hours after the intervention.

After the temperature record are completed, the experiment subject was then sacrificed following ketamine anesthesia, and an intracardiac blood sample was taken and put into a blood tube with EDTA. The blood routine examination was then conducted by the Health Laboratory of the Health Department of North Sumatra (Chiuman, 2019; Mutia and Chiuman, 2019).

There are two parameters used to determine antipyretic activity in this study, temperature and leukocyte count alteration following the intervention. The average percentage of experiment subject temperature alteration is calculated by using the formula (Saini and Singha, 2012):

$$\%℃\ Alteration = (PreInt\ Temperature - PostInt\ Temperature) \times 100\%$$

where %ºC Alteration is the percentage of rectal temperature change, PreInt Temperature is the rectal temperature before the intervention, and PostInt Temperature is the rectal temperature after the intervention.

RESULT AND DISCUSSIONS

Result

Phytochemical screening

Phytochemical screening in this study found that there is the presence of alkaloid, saponin, flavonoid, and tannin compounds in the RDFPE (Table I).

Analgesics activity

Analgesic activity by tail immersion method conducted in this study found that administration of RDFPE was effective at delaying tail retraction reaction in experiment subjects, especially at higher doses compared to the negative control. On average, the negative and positive control group's average reaction time is 4.54 seconds and 13.09 seconds, respectively. The group that received 750 mg/kg and 1000 mg/kg RDFPE average reaction times are 10.84 seconds and 12.83 seconds, respectively. Meanwhile, at 500 mg/kg dose, the average reaction time is even lower compared to the negative control or even compared to the reaction time before its intervention.

Amongst all of the groups, the group with the highest maximum possible analgesia (MPA) is the positive control group, which received acetaminophen. Meanwhile, the two highest doses of RDFPE (750 mg/kg and 1000 mg/kg) MPA is 60.22% and 79.25%, respectively (Table II).

One-way ANOVA analysis of this data found that there is a significant mean difference between the groups. Further analysis (post-hoc: Bonferroni) found that there is a significant mean difference between the negative control and positive control and two highest doses groups

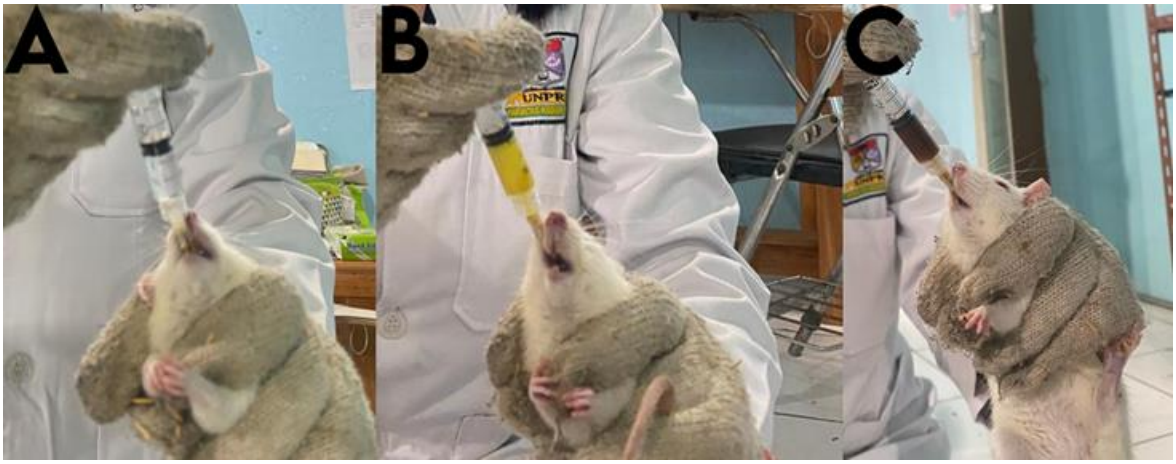

Figure 1. Administration of Different Intervention Into Different White Male Rats. The First Rat Receive Suspension Syrup Base/Clear Syrup (A), the Second Rat Receive Paracetamol Syrup/Yellow Syrup (B), and the Third Rat Receive 750 mg/kg RDFPE Syrup/Brown Syrup.

Table II. Effect of RDFPE on tail immersion reaction time

Group	Average Tail Immersion Reaction Time (seconds)		MPA
	Before Intervention	After Intervention	
NCG	4.13	4.54	0%
PCG	3.80	13.09	81.74%
RDFPE-1	4.43	4.40	-1.34%
RDFPE-2	4.00	10.84	60.23%
RDFPE-3	4.11	12.83	79.25%

*NCG: Negative Control Group; PCG: Positive Control Group; RDFPE-1: 500 mg/kg dosage group; RDFPE-2: 750 mg/kg dosage group; RDFPE-3: 1000 mg/kg dosage group; MPA; Maximum Possible Analgesia

Table III. Effect of RDFPE on Acetic Acid-induced Writhing

Group	Average Writhing per 20 minutes	Relative Writhing Reduction
NCG	33.8	-
PCG	12	48.89%
RDFPE-1	20	22.96%
RDFPE-2	15	73.33%
RDFPE-3	9.6	64.44%

*NCG: Negative Control Group; PCG: Positive Control Group; RDFPE-1: 500 mg/kg dosage group; RDFPE-2: 750 mg/kg dosage group; RDFPE-3: 1000 mg/kg dosage group

($p<0.05$), but no significant mean difference with 500 mg/kg dose group ($p>0.05$).

Meanwhile, analgesic activity by writhing methods conducted in this study found that administration of RDFPE was effective at reducing the writhing in the experiment subject. At the dose of 1000 mg/kg, RDFPE even reduces the writhing better compared to acetaminophen (positive control). On average, the negative control group's average writhing in 20 minutes is 33.8 times, whilst the positive control group is 12 times. Meanwhile, the group that received 1000 mg/kg of RDFPE averaged writhing in 20 minutes only 9.6 times (Table III). Further data analysis found that there is a significant mean difference between the negative control and all other groups ($p<0.05$). However, the 1000 mg/kg dose is the only one with no significant mean difference compared to acetaminophen ($p>0.05$).

Antipyretic Activity

Twenty-four hours after induction with brewer's yeast, all experiment subject experienced fever, indicated by increasing rectal temperature.

Table IV. Effect of RDFPE on Brewer's Yeast-induced Pyrexia

Group	Before Induction	After Induction	Rectal Temperature After Intervention in ºC (% difference)				
			1h	2h	3h	4h	5h
NCG	36.96±0.57	38.96±0.44	39.1±0.44 (-0.36%)	38.92±0.30 (0.10%)	39.06±0.22 (-0.26%)	39.04±0.12 (-0.21%)	38.62±0.30 (0.87%)
PCG	36.66±0.36	38.24±0.51	37.72±0.48 (1.36%)	37.22±0.80 (2.67%)	36.74±0.77 (3.92%)	36.46±0.69 (4.65%)	36.26±0.48 (5.18%)
RDFPE-1	36.68±0.48	38.6±0.43	38.58±0.36 (0.05%)	38.34±0.34 (0.67%)	38.14±0.27 (1.19%)	38.14±0.38 (1.19%)	38.06±0.26 (1.40%)
RDFPE-2	36.46±0.33	38.82±0.53	38.72±0.44 (0.26%)	38.52±0.41 (0.77%)	38.28±0.38 (1.39%)	37.9±0.40 (2.37%)	37.46±0.40 (3.50%)
RDFPE-3	36.54±0.54	38.26±0.53	38.16±0.63 (0.26%)	38.14±0.42 (0.31%)	37.58±0.40 (1.78%)	37.22±0.35 (2.72%)	36.76±0.33 (3.92%)

*NCG: Negative Control Group; PCG: Positive Control Group; RDFPE-1: 500 mg/kg dosage group; RDFPE-2: 750 mg/kg dosage group; RDFPE-3: 1000 mg/kg dosage group; negative percentage indicates increasing temperature compared to after induction temperature.

All experiment subjects then received intervention according to the group they belong to. Antipyretic activity in this study was observed through the rectal temperature difference between pre-intervention and post-intervention every hour for five hours as shown in Table IV.

One hour after the intervention, there is no meaningful temperature decrease across all groups, except the positive control group. Post-hoc analysis has shown that compared to the negative control group, the positive control group is the only one that had a significant mean difference ($p<0.05$), while all three RDFPE groups had no significant mean difference ($p>0.05$). However, compared to the positive control group, the group with 750 mg/kg and 1000 mg/kg dosages also had no significant mean difference.

However, five hours following the intervention, the analysis has shown that the negative control group compared to the positive control and the two highest RDFPE dosage groups had significant mean differences ($p<0.05$). Meanwhile, compared to the positive control group, the 750 mg/kg and 1000 mg/kg dosage groups have no significant mean difference ($p>0.05$).

Comparing the leukocyte count between all experiment subjects among all groups suggested that there is no mean difference between all groups ($p>0.05$).

Discussion

Multiple studies on red dragon fruit peel have determined that red dragon fruit peel is rich in phytochemical compounds such as phenolics, flavonoids, alkaloids steroids, triterpenoids, fatty acids, and betacyanin (Joshi and Prabhakar, 2020; Luo et al., 2014; Eldeen et al., 2020; Le, 2022; Som et al., 2019; Lin et al., 2021). This study also found the presence of alkaloids, flavonoids, tannins, and saponin compounds in red dragon fruit peels. However, this study failed to detect the presence of steroids and triterpenoids in the red dragon fruit peel, despite a study by Luo *et al.* (2014) found that triterpenoids constitute 29.77% of phytochemicals in red dragon fruit peel, while steroids constitute another 16,46%, making it the two most dominant compounds in red dragon fruit peel. The discrepancy between these findings might be the result of the different detection techniques. In Luo *et al.* study, the phytochemical analysis was conducted with gas chromatography-mass spectrometry, hence the quantitative results, meanwhile this study only conducted qualitative analysis, which detection depends on the technique sensitivity. Eldeen et al. (2020) review of dragon fruit studies was one of the most complete studies on dragon fruit from the flowers to the fruits. It compiles the broadest phytochemical content of dragon fruit, from its flesh, peel, seed, and flowers, to the seed oils. However, none of these studies found the presence of alkaloids in red dragon fruit, except for Lin *et al.* (2021).

This in-vivo experiment on white male rats using multiple doses of RDFPE found that red dragon fruit peel possesses an analgesic and anti-pyretic potential.

Based on two analgesic activity tests (acetic acid writhing and tail immersion test), two results suggested that RDFPE has strong analgesic activity,

especially at higher doses. In this study, administration of RDFPE at the dose of 750 mg/kg or 1000 mg/kg manage to decrease the writhing activity and delay the tail retraction on the experiment subject compared to the experiment subject that only received Na CMC. Further analysis even found that there is no difference between the administration of acetaminophen, which is a known NSAID, and the administration of 1000 mg/kg of RDFPE. This analgesic activity is possibly due to the anti-inflammatory effect possessed by phenolics (Som et al., 2019), betalains (Joshi and Prabhakar, 2020; Luo et al., 2014; Le, 2022), steroids (Wahdaningsih et al., 2021) and, flavonoids (Liana et al., 2019), and alkaloids (Lin et al., 2021). These multitudes of phytochemicals work as analgesics in various ways. Betalains for example work as an anti-inflammatory by reducing tumor necrosis alpha (TNF-α) expression or by its strong antioxidant properties which scavenge the free radicals that are known to propagate inflammation (Le, 2022). Another study also found that the administration of RDFPE lowered IL-1β expression (Eka et al., 2017). Steroids in RDFPE, especially β-sitosterol also known to inhibit the inflammatory response by inhibiting the NF-κB pathways (Sun et al., 2020).

Meanwhile, antipyretic activity tested in this study found that RDFPE was only effective at lowering the temperature but not effective at significantly lowering the white blood count. This study found that at the dose of 750 mg/kg and 1000 mg/kg, RDFPE work as effectively as paracetamol in lowering the experiment subject temperature. While paracetamol already presented effective antipyretic activity one hour after administration, RDFPE was only shown to present significant antipyretic activity 3 hours after administration. Administration of brewer's yeast solution cause pyrexia associated with increased TNF-α, IL-1β, and interferon-c in the plasma. Immune cells then responded to this increase and the presence of pathogens by expressing pro-inflammatory cytokines. These cytokines, which later give the signal to the thermoregulator part of the brain will cause fever (Mumtaz et al., 2018). The activity of RDFPE as anti-inflammatory through its multitudes of phytochemical constituents then controls the inflammation in the area, hence reducing the elevated temperature. Suppressions of TNF-α by flavonoid compounds like baicalin and inhibition of prostaglandin E2 synthesis by alkaloid compound (Mumtaz et al., 2018). Another compound that is possibly responsible for lowering this elevated temperature is β-sitosterol, which is known to have antipyretic properties (Wahdaningsih et al., 2021).

CONCLUSION

According to the findings in this study and further discussion, it can be concluded that red dragon fruit (*Hylocereus polyrhizus*) peel extract possessed analgesic and antipyretic properties, especially at higher dosages (750 mg/kg or 1000 mg/kg). These analgesic and antipyretic properties are most likely due to alkaloids and flavonoid compounds in the red dragon fruit suppressing the inflammatory activity.

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