



Anti-Inflammatory Effect of Red Dragon Fruit (*Hylocereus polyrhizus*) Peel on Male White Rat

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Abstract

Background: The side effects of synthetic anti-inflammatory drugs have become a known problem in medicine as well as in the general public. These side effects problems drive patients to seek alternatives to common anti-inflammatory drugs, especially natural alternatives. Phytochemicals such as flavonoids, alkaloids, and many different others have been identified as potential anti-inflammatory agents. Red dragon fruit (*Hylocereus polyrhizus*) is one source of such phytochemicals. Whilst the consumption of the flesh of red dragon fruit is very common, utilization of the peel is very rare and often becomes waste. **Objective:** This study aimed to explore the potential of red dragon fruit peel as an anti-inflammatory agent. **Methods:** This experimental study with a control group post-test-only design. This study involved in-vitro (protein denaturation inhibition using bovine serum albumin) and in-vivo (carrageenan-induced inflammation on an air-pouch model on 25 white rats) experiment. **Results:** This study showed that the red dragon fruit peel extract contains flavonoid, alkaloid, saponin, and tannin compounds. Administration of red dragon fruit peel extract suspension was found to be effective at inhibiting protein denaturation and reducing white blood count in the inflammation exudates, and the effectiveness is increasing along with the dose. **Conclusion:** It can be concluded that the red dragon fruit peel extract was effective as an anti-inflammatory agent, especially at a higher dose.

Keywords: dragon fruit peel, anti-inflammatory, phytochemicals, flavonoid

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INTRODUCTION

Hylocereus polyrhizus, which is commonly known as red dragon fruit (in English-speaking countries) or *pitaya* or *pitahaya* (in Mexico, Central, and South America) or *buah naga* (in Malaysia and Indonesia) is a plant from the cactus family, Cactaceae (Saenjum et al., 2021; Muhammad et al., 2020). This plant is native to Central and South America, and Mexico in North America but is currently being cultivated in almost every tropical part of the world (Luu et al., 2021; Saenjum et al., 2021). Red dragon fruit (*H. polyrhizus*) got its name from the distinct red color of the fruit flesh, with pink-to-red peel (Luu et al., 2021; Saenjum et al., 2021). The part of red dragon fruit that people commonly consumed is the flesh or pulp of the fruit, while the peel is usually thrown away and becomes waste due to a lack of understanding of its utility value (Niah and Baharsyah, 2018; Paramita et al., 2015; Muhammad et al., 2020).

The potency of dragon fruit peel in the food industry as well as its pharmaceutical properties have been explored (Muhammad et al., 2020; Liana et al., 2019; Saenjum et al., 2021; Luu et al., 2021). For pharmaceutical use, the phytochemical content of the dragon fruit, including its peel already shows a positive sign. Multiple studies found that red dragon fruit peel has several phytochemical compounds such as betacyanin, flavonoid, phenol, terpenoid, carotene, phytoalbumin, vitamins B1, B3, B6, and B12, and vitamins A, C, and E (Hendra et al., 2019; Kartikawati et al., 2020; Muhammad et al., 2020; Saenjum et al., 2021; Liana et al., 2019; Luu et al., 2021; Sinaga et al., 2015). This large multitude of phytochemicals has many different effects on the physiological process in humans. For example, betacyanin (the compound responsible for the red color of the dragon fruit peel) is known to be an effective protective agent for cells and tissue from damage by free radicals and oxygen-reactive species and thus works as analgetic (Kartikawati et al., 2020). Meanwhile, flavonoid compounds work as anti-inflammatory agents by inhibiting cyclooxygenase and lipoxygenase (Hendra et al., 2020). Meanwhile, another study found that dragon fruit peel extracts are effective as an anti-inflammatory agent through the inhibition of hyaluronidase by the phenolic and flavonoid compounds of the extract (Liana et al., 2019). The dragon fruit possess great potency as anti-inflammatory agent by inhibiting the cyclooxygenase and lipoxygenase, as well as the hyaluronidase by its multiple compounds. Both studies also only use the peel of the red dragon fruit. One study found that red

dragon fruit peel contains more flavonoid and phenolic content compared to the flesh (Saenjum et al., 2021).

MATERIALS AND METHODS

Material

A fresh specimen in the form of fresh red dragon fruit procured from a traditional market in Medan and then identified by Herbarium Medanense at the Faculty of Mathematics and Natural Sciences of Sumatera Utara University to be *H. polyrhizus* through identification number 018/MEDA/2022.

Animal subject

For *in vivo* experiment in this study, 25 white male rats of Wistar strain, aged 5 months old, with the weight between 160-200 grams were divided into 5 separate groups, where each group received the same induction, but different interventions according to their group. All rats were put into an acclimatization state for 14 days and fed with food pellets and water. The first group was the negative control group (1 mL of suspension base), the second group was the positive control group (10 mL/kg of diclofenac sodium suspension), and the other three groups were the extract group with three different doses (500 mg/kg, 750 mg/kg, and 1000 mg/kg suspension). After the study was finished, all rats were euthanized using carbon dioxide gas inside a sealed chamber. The carcasses were disposed of per the Integrated Laboratory of Prima Indonesia University guidelines. This study and its experiment protocol were reviewed and approved by the Health Research Ethical Committee of Prima Indonesia University through ethics declaration number 027/KEPK/UNPRI/III/2022.

Methods

Extraction

Following cleaning the red dragon fruit under running water, the fruit was peeled and the peel was then cut into cubes, dried, and powdered. The extraction method used in this study was the maceration method which began by weighing 500 grams of powdered red dragon fruit peel and putting it into a glass container and mixing it with 1.5 liters of methanol, stirred, sealed, and kept in the dark chamber for three days. After three days, the mix was filtered and the filtrate was kept in a separate container while the residue was put back into the extraction jar. The extraction process was repeated twice using the residue. All the filtrate is then combined into a total volume of ~4.5 liters. This filtrate was then evaporated using a rotary evaporator to remove most of the methanol and increase the concentration of the extract, followed by further reduction with a water bath

until it turned into red dragon fruit peel extract (RDFPE) with a thick consistency.

Phytochemical screening

In this study, only qualitative phytochemical screening was conducted. This phytochemical screening was conducted to screen the presence of alkaloids, flavonoids, saponins, tannins, glycosides, steroids, and triterpenoid compounds. In order to detect the presence of alkaloid compounds, four different detection methods using four different reagents were carried out, Boucharat's test, Mayer's test, Dragendorff's test, and Wagner's test. Each of these tests was conducted by adding each corresponding reagent into a sample of the filtrate inside a test tube. The presence of alkaloids is signified by the color of the precipitate, which is colored differently according to the reagent used in the test. The color of the precipitates in the Boucharat's, Mayer's, Dragendorff's, and Wagner's tests was brownish-black, yellow, red, and reddish-brown, respectively (Egbuna et al., 2019). To detect steroids, the aqueous extract was mixed with chloroform and H_2SO_4 (Salkowski test). The formation of red chloroform layer and a greenish-yellow acid layer showed the presence of steroids (Egbuna et al., 2019). Liebermann-Burchard's test was carried out to detect the presence of triterpenoid by mixing the extract with ethanol, acetic anhydride, and H_2SO_4 to produce a pink to violet color, signified the triterpenoid presence in the extract (Egbuna et al., 2019). To detect the presence of saponin, in a test tube, the extract and distilled water were mixed and shaken to produce froth. If the froth stable/persist for at least 10 minutes and did not diminish after HCl was added, then there was saponin in the extract. Just like alkaloid screening, flavonoid screening is also carried out using four different methods, each using a different reagent, $FeCl_3$, $Mg_{(s)}HCl_{(p)}$ (Shinado's test), NaOH, and H_2SO_4 . For the $FeCl_3$, NaOH, and H_2SO_4 test, each reagent was added to the extract and if the flavonoid was present, the mixture will change color into a bluish-black, yellow to orange color which turn colorless upon the addition of HCl, and orange color, respectively. Meanwhile, for Shinado's test, a mix of the extract, magnesium, and hydrochloric acid was heated to boil for 5 minutes and red coloration indicates the presence of flavonoid (Egbuna et al., 2019). For tannin detection, if the extract changes color into brownish-green or blue-black upon the addition of ferric chloride, then tannin was present (Egbuna et al., 2019). Meanwhile, to detect the presence of glycoside, the Molisch test was carried out. The Molisch test began by mixing the extract with the Molisch reagent, followed by adding sulfuric acid

through the test tube wall to prevent mixing. If a purple ring formed, then glycoside was present (Elzagheid, 2018). This phytochemical screening was conducted by the Laboratory of Organic Chemistry of Mathematics and Natural Sciences Faculty of Sumatera Utara University.

Preparation of control, standard, and extract solution

The control was prepared by adding 50 μ L of methanol into a volumetric flask and then added with 0.2% BSA solution until 5 mL volume was achieved. Meanwhile, the standard was prepared by mixing 125 mg of diclofenac sodium with methanol by adding methanol into a volumetric flask to achieve 25 mL volume to produce the main standard with a 5000-ppm concentration. This main standard was then diluted into 100 ppm, 200 ppm, 400 ppm, 800 ppm, and 1600 ppm concentrations. To prepare the extract solution, 200 mg of red dragon fruit peel extract was dissolved in 10 mL methanol to create the main extract solution with 20000 ppm. This main extract solution was then diluted into 1000 ppm, 2000 ppm, 4000 ppm, 8000 ppm, and 16000 ppm concentrations, respectively (Abidin et al., 2019; Rahmawati et al., 2020).

Preparation of Oral Suspension

The base of the oral suspension used in this study was carboxymethyl cellulose sodium (Na CMC). This base was prepared by adding 10 mL of hot distilled water into 0.5 grams of Na CMC powder inside a mortar and letting it sit for 15 minutes and grinded until it turned into a gel mass. The Na CMC gel mass was then transferred into a 100 mL volumetric flask and diluted into 100 mL volume to produce 0.5% Na CMC suspension. This base act as an excipient for the positive control and the red dragon fruit peel extract and also as the negative control. To prepare the red dragon fruit peel extract suspension (ES), 1 gram of red dragon fruit peel was added into the mortar, and into it added the suspension base and grinded with a pestle to homogenize it and then transferred into a 10 mL volumetric flask. The mix was then diluted into a 10 mL volume to produce 10 % ES suspension.

To prepare the diclofenac sodium suspension, 1 mL of suspension base was added into 100 mg of diclofenac sodium powder in the mortar whilst grinding. After the diclofenac sodium and the suspension were mixed, it was transferred into a 10 mL volumetric flask and diluted to 10 mL volume to give 1% sodium diclofenac suspension.

Preparation of bovine serum albumin (BSA)

Preparation of BSA started by making tris buffer saline (TBS) solution. It was done by dissolving 0.87

grams of sodium chloride (NaCl) and 0.121 gram of tris base in 100 mL aquadest. This TBS solution pH was then measured and adjusted with glacial acetate acid to achieve a pH of around 6.2-6.5. Inside a volumetric flask, 0.2 grams of BSA powder dissolved into 100 mL TBS solution to give 0.2% BSA solution.

In vitro anti-inflammation activity evaluation

The anti-inflammation activity of red dragon fruit peel extract in this study was evaluated by protein denaturation assay. Into seven test tubes, 5 mL of 0.2% BSA solution was added. 50 µL of control was added to the first test tube, 50 µL of the standard into the second tube, and extract solution with different concentrations (10 ppm, 20 ppm, 40 ppm, 80 ppm, and 160 ppm) into the third to the seventh tubes respectively, then incubated at room temperature for 30 minutes followed by heating for 45 minutes at 100°C temperature and let it sit for another 25 minutes at room temperature. After that, the test tube vortexed, and the absorbance was measured using UV-Vis Spectrophotometry at 660 nm wavelength. This absorbance measurement was conducted three times (Abidin et al., 2019; Rahmawati et al., 2020; Sriarumtias et al., 2020). The anti-inflammatory activity was calculated using the following equation:

$$\%denaturation\ inhibition = \frac{Control\ absorbance - Extract\ solution\ absorbance}{Control\ absorbance} \times 100\%$$

In vivo anti-inflammatory activity evaluation

Carrageenan induced air-pouch model was chosen to induce inflammation in the experiment subject in this study. In each experiment subject, 20 mL of air was injected subcutaneously into the intrascapular region under anesthesia. On the third and sixth days after the

20 mL air injection, another 10 mL of air was injected into the same area to keep the space air-filled. On the sixth day, 2 mL of 1% carrageenan solution was injected into the air pocket to induce inflammation. Two hours prior to carrageenan injection, each experiment subject was given intervention according to their group and repeated 24 hours after induction. Forty-eight hours after induction, a small incision was made on the carrageenan pocket to aspire the exudates and the total white blood cell was counted using a hemocytometer. The white blood count was then used to calculate the white blood cell recruitment inhibition using the formula: $(1-T/C) \times 100\%$, where T corresponds to the intervention white blood count and C corresponds to the negative control white blood count (Leite et al., 2022).

RESULTS AND DISCUSSION

Phytochemical screening of RDFPE in this study revealed the presence of alkaloid, saponin, tannin, and flavonoid compounds, while steroid, triterpenoid, and glycoside were not detected. Complete screening methods and the result are presented in Table 1. In this study, methanol was used as an extraction solvent because a study has shown that methanol was an optimal extraction solvent to obtain high content of phytochemical constituents, as well as high *in-vitro* anti-inflammatory constituents (Truong et al., 2019). While methanol is toxic for humans and can lead to blindness or even death, most of the methanol used in the extraction process was evaporated using a rotary evaporator and on the water bath, which leaves the extract with only residual methanol. This residual methanol is also regulated and should not be more than 3000 ppm (European Medicines Agency and Committee for Human Medicinal Products, 2019).

Table 1. Phytochemical Screening of Red Dragon Fruit Peel Extract (RDFPE)

Secondary Metabolite	Reagent/Methods	Result
Alkaloid	Boucharat's	Detected
	Mayer's	Detected
	Dragendorff's	Detected
	Wagner's	Detected
Steroid dan Terpenoid	Salkowski test	Not Detected
	Liebermann-Burchard	Not Detected
Saponin	Distilled water + HCl	Detected
	FeCl ₃ 5%	Detected
Flavonoid	Mg _(s) HCl _(p)	Not Detected
	NaOH 10%	Not Detected
	H ₂ SO _{4(p)}	Detected
Tannin	FeCl ₃ 1 %	Detected
Glycoside	Molisch	Not Detected

In-vitro testing of the anti-inflammatory effect of RDFPE showed positive inhibition of protein (BSA) denaturation. *In-vitro* testing in this study found that higher concentration RDFPE has higher capability in inhibition of protein denaturation. However, the protein denaturation inhibition capability is not linear with concentration. This meant that doubling the concentration did not double the protein denaturation inhibition. For example, dragon fruit peel extract with 160 ppm concentration has average protein denaturation inhibition of 36.22%, while at 10 ppm concentration, the average protein denaturation inhibition is only about 8.19%. The average protein denaturation inhibition between the two was approximately 4 times, while the concentration difference between the two is 16 times greater. The complete percentage of protein denaturation inhibition amongst different concentration are shown in Table 2 and Figure 1. Different concentrations showed that each concentration compared to the other was significantly inhibit the denaturation of the protein and a higher concentration was significantly better at inhibiting protein denaturation ($p < 0.05$). Denaturation inhibition greater than 20% is considered to be a potential anti-inflammatory agent (Drăgan et al., 2016), hence, only

extract with 80 ppm and 160 ppm concentration have potential anti-inflammatory activity.

In-vivo testing on white Wistar rats (*Rattus norvegicus*) showed that oral administration of dragon fruit peel extract suspension effectively works as an anti-inflammatory agent. Oral administration of dragon fruit peel extract suspension decreased the amount of total white blood cells (WBC) in exudates from the carrageenan induction and the effectivity was increased along with the dose. These findings are presented in Table 3. In the highest dose given (1000 mg/kg), dragon fruit peel extract suspension even outperformed diclofenac sodium in white blood count reduction. However, administration of 500 mg/kg dragon fruit extract suspension has no significant difference with Na CMC in the reduction effect of white blood counts. In Tukey HSD post-hoc test, there was no evidence to reject the null hypothesis between Na CMC and RDFPE 500 mg/kg and between diclofenac sodium and RDFPE 1000 mg/kg ($p > 0.05$) (Table 4). This study has found that RDFPE at 1000 mg/kg dosage manages to inhibit white blood cell recruitment up to 71,84%, higher than the diclofenac sodium inhibition of 64,83%. Some studies suggest inhibition of more than 50% fulfilled the requirement as an anti-inflammation agent (Zaini et al., 2016; Astika et al., 2022).

Table 2. Percentage of Protein Denaturation Inhibition Between Different Concentrations of RDFPE

Concentration (ppm)	Average Absorbance*	Average Absorbance Standard Deviation	Average Inhibition Percentage
Control	0.828067	0.006232	0
10	0.760200	0.005940	8.19±0.71
20	0.733300	0.005650	11.43±1.18
40	0.680400	0.007700	17.82±1.43
80	0.629800	0.002000	23.93±0.45
160	0.527200	0.005710	36.32±0.92

*Acquired from the mean of three absorbance measurement replications.

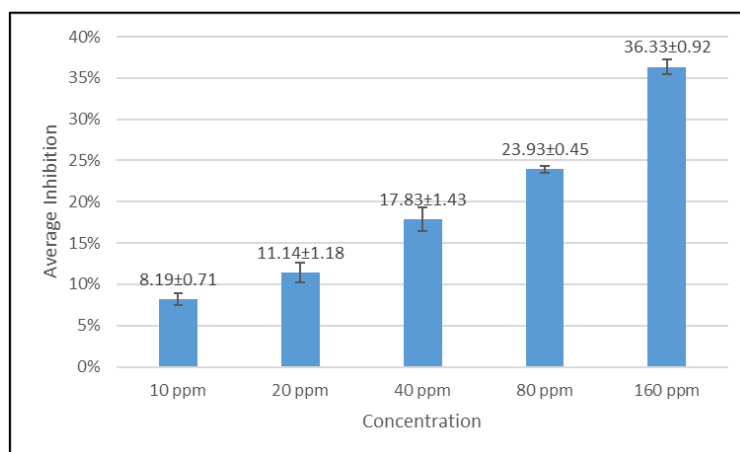


Figure 1. Protein Denaturation Inhibition Effectivity of Red Dragon Fruit Peel Extract in Different Concentrations. Represented as means ± SD of three replicates.

Table 3. Average White Blood Cell Count in Exudates in Different Groups

Group	n	Average Total WBC	Inhibition (%)
(-) Control	5	9,840.00±383.08	
(+) Control	5	3,460.00±736.04	64.83
RDFPE 1	5	9,130.00±719.03	7.21
RDFPE 2	5	7,820.00±646.72	20.52
RDFPE 3	5	2,770.00±757.13	71.84

(-) Control: Na CMC; (+) Control: Diclofenac sodium; RDFPE 1: 500mg/kg dose; RDFPE 2: 750mg/kg dose; RDFPE 3: 1000mg/kg dose.

Table 4. Mean Difference of Total White Blood Cells Between Different Groups

	(-) Control	(+) Control	RDFPE 1	RDFPE 2	RDFPE 3
(-) Control		-6380.00*	-710.00	-2020.00*	-7070.00*
(+) Control	6380.00*		5670.00*	4360.00*	-690.00
RDFPE 1	710.00	-5670.00*		-1310.00*	-6360.00*
RDFPE 2	2020.00*	-4360.00*	1310.00*		-5050.00*
RDFPE 3	7070.00*	690.00	6360.00*	5050.00*	

(-) Control: Na CMC; (+) Control: Diclofenac sodium; RDFPE 1: 500mg/kg dose; RDFPE 2: 750mg/kg dose; RDFPE 3: 1000mg/kg dose. *Significant mean difference

Many studies had found that red dragon fruit peel contains flavonoid, alkaloid, saponin, tannin, steroid, triterpenoid, and glycoside in varying concentrations (Ragab et al., 2018; Luo et al., 2014; Saenjum et al., 2021; Zain et al., 2019; Le, 2022). The difference in findings between this study and the other multiple studies is due to different methods of phytochemical analysis. Studies by others (Ragab et al., 2018; Luo et al., 2014; Saenjum et al., 2021; Zain et al., 2019; Le, 2022) were quantitative analyses, using different methods, whilst this study only uses qualitative screening and using a simple reagent, thus when the amount of the compound was not high enough for the reagent to detect, the result was negative.

This study finding is in accordance with findings by Nur et al, where dragon fruit extract was found to be effective in inhibiting BSA denaturation with 64,32±0,81 to 84,97±0,81% inhibition compared to the control group (Nur et al., 2022). Nur et al. study also found that different solvent of the extract affects the effectiveness of the protein denaturation inhibition effect. Aqueous extract (water solvent) is more effective at inhibiting protein denaturation compared to extract with ethanol or ethyl acetate solvent (Nur et al., 2022). These study findings are far lower compared to the findings by Nur et al (2022). However, the study by Nur et al. (2022) was using the whole fruit (peel, stem, and flesh), instead of just the dragon fruit peel like this study. While the peel contains a higher concentration of flavonoid content compared to the flesh when extract derived from peel, stem, and flesh will result in an extract with even higher flavonoid content. However, the effect of the difference can not be determined since

Nur et al. study did not specify the ratio of the different parts (Nur et al., 2022).

Eldeen et al. found that dragon fruit extract has an anti-inflammatory effect by involving both lipoxygenase and cyclooxygenase pathways (Eldeen et al., 2020). The extract effects on both lipoxygenase and cyclooxygenase pathways mean that the extract works lead to blockage of leukotriene and prostaglandin pathways (Eldeen et al., 2020). In their study, Eldeen et al. also found that dragon fruit extract with a higher concentration of betalains has higher anti-inflammatory potency. However, Eldeen et al. study was using white dragon fruit (*Hylocereus undatus*) instead of red dragon fruit (*Hylocereus polyrhizus*) like this study. This difference in dragon fruit species does not have a big difference in phytochemical contents, both generally contain similar phytochemical contents with a different concentration between the two species (Luo et al., 2014). Aside from betalains, flavonoid and tannin compounds in red dragon fruit peel most likely act as an anti-inflammatory, since both are known to have anti-inflammatory properties (Onyekere et al., 2019). However, since this study method of analysis of the phytochemical content of red dragon fruit peel was a qualitative analysis, this study cannot name a specific flavonoid or tannin compound which responsible for this anti-inflammation action.

CONCLUSION

This study has found that red dragon fruit contains alkaloids, saponins, tannins, and flavonoids. These multiple compounds have the potential as an anti-inflammatory agent, as an alternative to synthetic anti-inflammatory drugs. However, the dose at which this

extract work as an anti-inflammatory agent is way too high (1000 mg/kg), meanwhile the toxicity of this extract is still unknown. Further study to identify a specific compound that is responsible for this anti-inflammatory action and further action to isolate the compound(s) can reduce the dosage needed to perform effectively as an anti-inflammatory agent.

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