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Antiinflammatory Activity of Bangle Rhizome (*Zingiber purpureum* Roxb) Ethanol Extract on Rat Carrageenan Induced and Erythema Method

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Abstract

***Background**: Inflammation is a physiological response triggered by cellular damage, typically characterized by symptoms such as edema. **Objective**: This study was conducted to evaluate the anti-inflammatory activity of the ethanol extract of Bangle rhizome (Zingiber purpureum Roxb.) using the carrageenan-induced paw edema method and the UVB-induced erythema method. The most effective dose demonstrating significant anti-inflammatory activity was also determined. **Methods**: The bangle rhizome (Zingiber purpureum Roxb) was subjected to maceration using 96% ethanol. A total of 25 rats were randomly divided into five groups: negative control (0.5% CMC-Na), positive control (diclofenac sodium at 0.9 mg/200 g body weight), and treatment groups receiving ethanol extract of bangle rhizome at doses of 5, 10, and 20 mg/200 g body weight. In the carrageenan-induced method, the edema volume in the rat paw was measured following the administration of 0.8% lambda-carrageenan. In the erythema method, the degree of inflammation was assessed using UVB-induced erythema scoring. **Results** and **Conclusion**: Anti-inflammatory activity was observed at doses of 5, 10, and 20 mg/200 g body weight in the carrageenan model and at doses of 10 and 20 mg/200 g in the erythema model. The most potent anti-inflammatory effect was recorded at the dose of 20 mg/200 g body weight, which was comparable to the positive control in both models. The presence of flavonoids and steroids in the extract may contribute to the observed anti-inflammatory activity.*

***Keywords**: Anti-inflammatory, bangle rhizome extract, carrageenan-induced edema, UVB-induced erythema*

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INTRODUCTION

Inflammation is the body's reaction to damage or contamination (Bachtiar *et al*., 2021). Inflammation occurs due to a nearby response from tissues or cells to the stimulus for the release of certain chemicals that will stimulate tissue changes in the reaction, including histamine, serotonin, bradykinin, leukotrienes, and prostaglandins (Garakia *et al*., 2020). Inflammation is often thought of as a disease, when in fact it is the work of an immune response. The response that occurs is characterized by symptoms such as rubor (redness), calor (heat), dolor (pain), and tumor (swelling), so that inflammation often interferes with activities. Inflammation affects the membranes, causing leukocytes to secrete lysosomal enzymes, arachidonic acid, and various eicosanoids (Cowin 2008). The treatment of inflammation has two main goals: to relieve pain, which is the first visible symptom, and to sluggish or restrict the process of tissue destruction. Anti-inflammatory drugs have a common mechanism of action, which is inhibiting prostaglandin synthesis via the inhibition of the enzyme cyclooxygenase. Cyclooxygenase is responsible for prostaglandin biosynthesis. Based on the mechanism of action, anti-inflammatory drugs are divided into 2 groups, namely steroid groups that work by inhibiting the release of prostaglandins and their source cells, and nonsteroidal groups (NSAIDs) that work through the mechanism of cyclooxygenase inhibition that plays a role in prostaglandin biosynthesis. Drugs used as anti-inflammatories are the nonsteroidal group (AINS) and corticosteroids, where both groups have the potential to suppress signs and symptoms of irritation, but both groups of medicine regularly cause detrimental and dangerous outcomes together including gastrointestinal harm, nephrotoxicity, and hepatotoxicity (Garakia *et al*., 2020).

In addition to drugs of the NSAID class, many plants are used as anti-inflammatories whose use is still widely favored by the community. Indonesia itself has many types of flora that may be used as a supply of herbal medicinal materials and are widely used by the community for generations to overcome health problems. One of the natural ingredients that is empirically effective as an anti-inflammatory drug is the bangle rhizome. Bangle belongs to the Zingiberaceae family and has been widely used in traditional medicine. Bangle rhizome is useful as a medicine for fever, abdominal pain, constipation, wind, worms, and gout (Ministry of Health RI 2001). The results of the phytochemical screening test of bangle rhizomes by Astarina *et al*. (2013) and Padmasari *et al*. (2013) showed that bangle rhizomes contain essential oil Compounds, flavonoids, saponins, triterpenoids, alkaloids, and tannins. Based on (Bachtiar *et al*., 2021), bangle rhizomes contain bioactive compounds that are useful as medicines, one of which is essential oil.

The main components of the bangle rhizome essential oil (*Zingiber purpureum* Roxb.) consist of sabinene (48.1%), *terpinen-4-ol* (25.1%), *α-terpinene* (4.3%), and *α- phellandrene and Phenylmethylene* (2.7%). The utilization of plants that have anti-inflammatory activity is very necessary, especially to get alternative treatments that have small side effects, especially in efficacy as an anti-inflammatory, so in this study, tests will be carried out on the anti-inflammatory activity of ethanol extract of bangle rhizome which will be tested on male rats with two methods, namely carrageenan induction and UV radiation. The carrageenan induction method is a measurement of the volume of artificial edema in the leg of rats induced with lambda carrageenan, while the UV radiation induction method shows redness on the back of test animals due to UV light irritation, resulting in vasodilation followed by increased vascular permeability and local leukocytosis, commonly called erythema. The solvent used was 96% ethanol because it can dissolve compounds that are polar and non-polar, and is more selective. 96% ethanol can be used to remove impurities of amino acids, minerals, and proteins, which cannot be dissolved at low ethanol levels.

MATERIALS AND METHODS

Materials

The sample material used was a bangle rhizome. The chemicals used include distilled water, 96% ethanol, CMC-Na, and diclofenac sodium. The check animals used male white rats of stress with an age of 2-3 months and a body weight of about 150-300 grams.

Preparation of the ethanol extract of the bangle rhizome

The preparation of the ethanol extract of the bangle rhizome was accomplished through the maceration method using 96% ethanol solvent with a ratio of 1:10. As much as 1 kg was put into a maceration bottle, and then 96% ethanol was added to as much as 7.5 L. The maceration bottle was maintained at room temperature and was avoided while stirring repeatedly. After 5 days, the results of soaking were filtered with a flannel cloth and filter paper, then the pulp plus 96% ethanol as much as 2.5 L was filtered with flannel cloth and filter paper, and then the liquid extract was concentrated in a *rotary evaporator at 40°C* until a viscous extract was obtained.

Chemical content identification of the bangle rhizome extract

Flavonoid test. Flavonoid identification was done by dissolving 5 ml of concentrated extract of bangle rhizome into a test tube and adding 0.1 gram of Mg

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powder and 5 drops of concentrated HCL, 2 ml of amyl alcohol, then shaking and letting it separate. If there is a red, yellow, or orange color in the amyl alcohol layer, the flavonoids are positive (Ciulei 1984). **Saponin test.** Identification of saponins was done by dissolving 0.05 mg of bangle rhizome sample into 20 ml of water, then.

Heat and filter, add 1 drop of HCL 2 N, shake vigorously for 10 seconds, and then leave for 10 seconds (Ciulei 1984). **Tannin Test**. A total of 0.05 mg of bangle rhizome powder was dissolved in 20 mL of distilled water. The solution was subsequently heated and filtered. To the obtained filtrate, 2–3 drops of 1% ferric chloride ($FeCl_3$) solution were added. The presence of tannins was indicated by the formation of a green or bluish-black coloration (Ciulei, 1984). **Essential oil**. A precipitate was formed by pipetting 1 mL of the test solution and then letting it evaporate in a porcelain cup. The positive effects of essential oils are indicated by the unique smell that the plant residue produces (Ciulei 1984). **Alkaloid Test**. Alkaloids were identified using the Mayer and Dragendorff methods. A mixture was prepared by combining 0.5 grams of concentrated bangle rhizome extract with 1 mL of 2 M hydrochloric acid (HCl) and 9 mL of distilled water. The mixture was then boiled for two minutes, allowed to cool, and subsequently filtered. The resulting filtrate was divided into three portions, and Mayer and Dragendorff reagents were added to each portion. A positive result for alkaloids was indicated by the formation of a white precipitate with the Mayer reagent and a light brown to yellow precipitate with the Dragendorff reagent (Ciulei, 1984).

Preparation of the solution

CMC-Na mucilago 0.5%. Weigh 500 mg of CMC-Na, and put 100 mL of hot water into a vaporizer cup. CMC-Na powder is sprinkled over the hot water little by little while stirring until homogeneous.

Diclofenac sodium suspension preparation 1%.

CMC-Na was weighed at 100 mg and then put little by little into a mortar containing hot water while stirring until homogeneous and fluffy. Diclofenac sodium was weighed at 100 mg, put into a mortar containing CMC-Na mucilage, and crushed while adding distilled water to a volume of 10 mL.

Preparation of the test preparations.

The extract test preparations were prepared by weighing 500 mg of CMC-Na and then sprinkling it into a vaporizer cup containing hot water and stirring until it expands. Bangle rhizome extract was weighed at 1 gram, then crushed in a mortar to shrink the particles, after which CMC-Na mucilago was added to a volume of 50 mL and stirred until homogeneous.

Anti-inflammatory test

Diclofenac sodium dose determination. The average human body weight of a 70-kg dose of diclofenac sodium is 50 mg/kg BW. The conversion factor from humans weighing 70 kg to rats with an average body weight of 200 g is 0.018, so the dose of diclofenac sodium for rats is 0.9 mg/200g BW of rats.

Anti-inflammatory test procedure of the rat paw edema method.

In this study, 5 animals were used in each experimental group. The anti-inflammatory test procedure is that rats are fed 8 hours before testing and, are still given drinking water. The rats were weighed and grouped randomly. 25 rats were divided into 5 groups. The left hind paw of each rat to be induced was marked at the ankle, then the volume was measured first by inserting the sole of the rat's foot into mercury until the mark limit. Each rat was treated according to its group. Group 1 with negative control treatment (CMC-Na), group 2 positive control (diclofenac sodium), dose of 0.9 mg/200 g BW, groups 3, 4, and 5 of the extract dose of 5 mg, 10 mg, and 20 mg/200 g BW. One hour later, a 0.8% lambda carrageenan solution was induced on the left hind paw with a volume of 0.2 ml. The volume of the paw was measured at 0.5, 1, 2, 3, 4, 5, 6, and 24 hours after lambda carrageenan induction; the paw of the rat was inserted into the seismometer until the limit mark. The DAI of the test drug is indicated by its ability to inhibit the volume of paw edema produced due to lambda carrageenan induction (Winter *et al.,* 1962). All data obtained were statistically analyzed on the volume of paw edema, and the proportion of edema inhibition was calculated.

Anti-inflammatory test procedure of the erythema method.

The mice were depilated with a size of 1.5 x 2.5 cm on the back for 18 hours. Test animals were treated orally 30 minutes before UV irradiation. The apparatus was heated for 30 minutes before use. Mice were irradiated with UV light at a distance of 10 cm for 5 hours, then the erythema formed was observed at 6, 12, 24, 48, and 72 hours.

Data Analysis

Carrageenan induction method. The effect of the administration of 96% ethanol extract of bangle rhizome on the anti-inflammatory effect with the carrageenan induction method was determined by calculating the volume of the edema.

$Vu = Vt – Vo$

Description:

Vu: The extent of edema rat paw on every occasion

Vt: Edema extent of the rat paw after stretching with 0.8% carrageenan at the time(t)

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Vo: Edema volume of rat paw before 0.8% carrageenan

After obtaining the edema volume data, a comparison curve of edema volume versus time was made. Then the AUC (Area under the curve) is calculated, which is the average area under the curve, representing the relationship between the average edema volume per unit time. With the formula:

$$AUC^{n-1} = \frac{Vt_{n-1} + Vt_{n}}{2} (t_n - t_{n-1})$$

Description:

Vt_{n-1}: average edema volume in t n −1

Vt_{n}: average volume at t n

The anti-inflammatory power can be calculated using the following formula:

$$DAI = \frac{AUC_k - AUC_p}{AUC_k} x100\%$$

Description :

AUC_k: AUC curve of the mean edema volume against time for the negative control.

AUC_p: AUC curve of the mean edema volume versus time for each treatment group.

The data obtained is then analyzed with the *Kolmogorov-Smirnov test* to examine the distribution of facts and analyzed with the Levene check to peer the homogeneity of the statistics. If the facts are typically allotted and homogeneous, it's typically analyzed with a one-way analysis of variance (ANOVA) test with a 95% confidence level and continued with the LSD test to determine whether or not there is a significant difference. If a condition for the ANOVA test is not met, the *Kruskal-Wallis* test is performed to determine if there is a difference. If there is a significant difference, the Mann-Whitney test is conducted to determine the difference between the treatment groups.

RESULTS AND DISCUSSION

The extraction of bangle rhizome powder was carried out by maceration with 96% ethanol as a solvent because it can dissolve polar and non-polar compounds. The macerate was obtained and then concentrated with a *rotary evaporator* at 40˚C. The thick extract was 153.6 grams with a yield of 15.36%.

Identification of the chemical content of extracts and powders of bangle rhizomes aims to establish the truth of the chemical content contained in bangle rhizomes. The identification of compounds was carried out on flavonoids, saponins, tannins, essential oils, alkaloids, triterpenoids, and steroids. Analytical Chemistry Laboratory of the Faculty of Pharmacy, Bumigora University. The identification results can be seen in Table 1

Table 1. Compound content identification results of the bangle rhizome extract and powder

Name of Compound	Description	Extract	Powder
Flavonoid	The orange color that forms on the amyl alcohol layer shows flavonoid compounds (Ciulei 1984).	+	+
Saponin	The generation of foam for up to 10 seconds indicates saponin compounds (Ciulei 1984).	+	+
Tanin	The formation of a bluish-black shade suggests the presence of tannin compounds (Ciulei 1984).	+	-
Minyak atsiri	The generation of a characteristic odor by residues from the plant indicates essential oils (Ciulei 1984).	+	+
Alkaloid	Characterized by the formation of mild brown to yellow color precipitates on the *Dragendorff* reagent and white precipitates on the Mayer reagent (Ciulei 1984).	+	+
Triterpenoid	The formation of a brown ring (Ciulei 1984).	+	+
Steroid	Formation of a blue-green ring (Ciulei 1984).	-	-

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Description :
+: Compounds were detected
-: Compounds were not detected.

The results of identifying the compound content of bangle rhizome extracts and powders showed that bangle rhizomes contain flavonoids, saponins, tannins, triterpenoids, essential oils, and alkaloids. According to Astarina, N. W. G., Astuti, K. W., Warditiani (2012), and Padmasari *et al*. (2013), bangle rhizomes are positive for flavonoids, saponins, tannins, triterpenoids, alkaloids, and essential oils. According to Safira *et al*. (2012) and Burdah (1996), the flavonoid compounds in the Bangle rhizomes are flavonol groups, aurones, and isoflavone. The essential oils in bangle rhizomes contain butyl phenols such as (E)-1-(3,4-*dimethoxyphenyl*) *butadiene* (DMPBD), *terpinen 4-ol,* and terpenoid groups (Jeenapongsa *et al.* 2003; Pattanaseree 2005).

Anti-inflammatory effect test using the carrageenan induction method

The anti-inflammatory effect test was conducted using the rat paw edema approach by injecting 0.8% λ-carrageenan as a great deal as 0.2 ml. This approach is one of the simplest, easiest to perform, and most frequently used methods of testing anti-inflammatory activity. The inflammation formed by carrageenan induction also does not cause tissue damage. The edema quantity was measured before and after management of the check substance using a plethysmometer. This test used 25 rats divided into 5 test groups, namely negative control, positive control, and ethanol extract of bangle rhizome with dose variations obtained from the orientation results, namely 5 mg/200g BW, 10 mg/200g BW, and 20 mg/200g BW. Data were obtained from observations in a subplantar volume of rats in the form of the subplantar volume of rat after the hours 0.5 to 6 hours and 24 hours after carrageenan induction

Table 2. Average edema volume

Treatment	Mean volume (mL) of edema ± SD								
	T0	T0,5	T1	T2	T3	T4	T5	T6	T24
Negative control (CMC-Na)	0±0	0.024± 0.003	0.028± 0.002	0.032± 0.003	0.036± 0.002	0.040± 0.001	0.0616± 0.00167	0.0446± 0.001	0.0398± 0.002
Extract dose 5 mg/kg BW	0±0	0.019± 0.002	0.023± 0.003	0.026± 0.005	0.031± 0.004	0.033± 0.004	0.034± 0.003	0.0328± 0.002	0.022± 0.002
Extract dose 10 mg/kg BW	0±0	0.018± 0.002	0.022± 0.003	0.026± 0.003	0.028± 0.004	0.030± 0.002	0.031± 0.001	0.031± 0.002	0.021± 0.002
Extract dose 20 mg/kg BW	0±0	0.018± 0.002	0.020± 0.0007	0.023± 0.001	0.025± 0.002	0.026± 0.002	0.026± 0.002	0.025± 0.002	0.013± 0.002
Na Diklofenak	0±0	0.017± 0.001	0.018± 0.002	0.020± 0.002	0.023± 0.002	0.024± 0.002	0.023± 0.002	0.022± 0.002	0.012± 0.0008

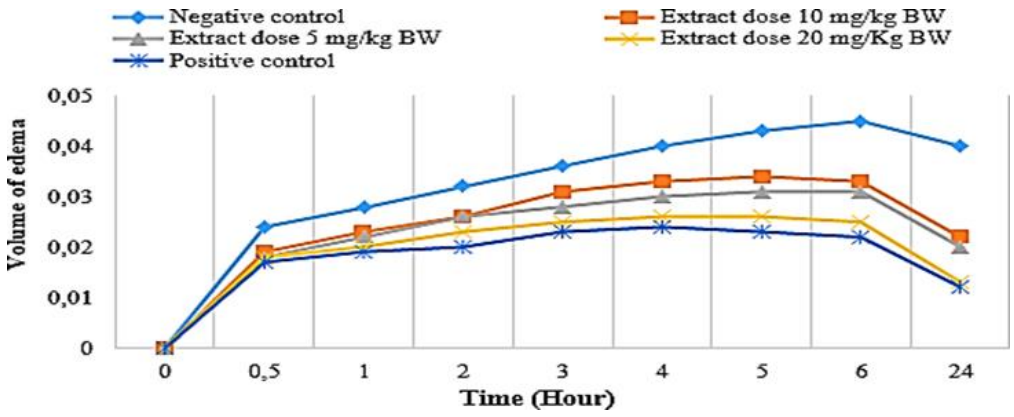

Figure 2. Results of the anti-inflammatory effect test with the carrageenan induction method

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The negative control group given CMC Na experienced an increase in edema volume starting from hour 0.5, which was able to last for 6 hours due to the absence of an inhibitory process in the three processes of inflammation by carrageenan and decreased 24 hours later, where the largest edema volume formed occurred at hour 6. Based on the average edema volume in rat feet, it is known that the edema volume increases 30 minutes after induction with λ-carrageenan. According to Moris 2003), the formation of edema due to carrageenan induction consists of 3 phases. The primary segment involves the discharge of histamine and serotonin and lasts for ninety minutes. The second section involves the discharge of bradykinin and occurs 1.5-2.5 hours after induction. The 1/3 segment occurs three hours after induction, and the release decreases for up to 24 hours. The positive control group given diclofenac sodium in a dose of 4.5 mg/kg BW increased slowly, starting from hour 0.5, where the volume of leg edema formed was highest at hour 4, then the volume decreased from hour 5 to hour 24. This shows that diclofenac sodium provides a good therapeutic effect in the form of edema inhibition that occurs at hour 4. Diclofenac sodium is a phenyl acetate derivative belonging to the AINS group with the strongest anti-inflammatory power. This drug works to inhibit cyclooxygenase, which is relatively non-selective and reduces the bioavailability of arachidonic acid (Tjay and Rahardja 2002). Diclofenac sodium is absorbed quickly and completely; its bioavailability is about 50%, with 99% bound to plasma proteins, and has a half-life of 1-3 hours, an onset of 30 minutes, and 8 hours (Katzung 2007).

The ethanol extract treatment group from the bangle rhizome increased the the edema volume at hour 0.5 after being induced with carrageenan. In the treatment group given ethanol extract of bangle rhizome as much as 5 mg/kg body weight, the increase in edema continued until the 5th hour and decreased again at the 6th hour. In the treatment of ethanol extract of bangle rhizome at a dose of 10 mg/kg BW and 20 mg/kg BW, it increased until the 4th hour and lasted until the 5th hour with a constant volume, indicating edema inhibition and decreased starting from the 6th hour. At the 6th hour, when a decrease in edema volume was experienced, the anti-inflammatory effect of the test compound could be seen through changes in edema volume.

Table 3. Average AUC total and average DAI (%)

Group	Mean AUCtotal ± SD	Mean percentage % DAI ± SD
Negative control (CMC-Na)	0.965±0.033b	-
Extract dose 5 mg/kg BW	0.654±0.062ab	32.36±5.867b
Extract dose 10 mg/kg BW	0.627±0.043ab	34.96±4.142b
Extract dose 20 mg/kg BW	0.495±0.061ab	48.71±5.569
Na Diklofenak	0.430±0.031a	54.65±3.738

Description:

a: Significantly different from the poor management group based on the LSD test ($p < 0.05$)

b: Significantly different from the effective management group based on the LSD test ($p < 0.05$)

The anti-inflammatory activity is expressed in the anti-inflammatory power. Based on the results of DAI (anti-inflammatory power) of ethanol extract of bangle rhizome at a dose of 20 mg/kg BW, it is assumed that this dose has more active compound content and the amount absorbed is more so that it can provide a better anti-inflammatory effect than doses of 10 mg and 5 mg/kg BW. The results of compound identification in the ethanol extract of bangle rhizome contain steroids, flavonoids, and tannins, according to previous studies. The compounds that provide anti-inflammatory effects are flavonoids and steroids, so in this study, the suspected anti-inflammatory compounds are flavonoids and steroids. Flavonoid compounds can inhibit COX and lipooxygenase enzymes (Narayana *et al*. 2001). Inhibition of the COX and lipooxygenase pathway directly also leads to the inhibition of eicosanoid and leukotriene biosynthesis, and flavonoids can inhibit leukocyte accumulation in inflammatory areas (Panda *et al*. 2009; Kumbhare & Sivakumar 201, referenced in Zaini *et al*. 2016). The anti-inflammatory effect is also supported by its action as an antihistamine, histamine is one of the inflammatory mediators whose release is stimulated by pumping calcium into cells, flavonoids can inhibit the release of histamine from mast cells, and another mechanism of flavonoids is stabilizing Reactive Oxygen Species (ROS) reacting with reactive compounds from radicals so that the radicals become

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inactive (Nijveldt *et al*. 2001, referenced in Zaini *et al*. 2016). Steroids work by inhibiting phospholipase activity, thereby preventing the release of arachidonic acid and blocking the release of arachidonic acid and blocking the cyclooxygenase and lipooxygenase pathways so that inflammatory mediators cannot be formed (Katzung 2002). Steroids inhibit the production of many important inflammatory factors such as interleukins, cytokines, and chemotaxis agents. Decreased release of these agents leads to decreased secretion of lipolytic and proteolytic enzymes, resulting in reduced leukocyte cell migration to the inflamed area (Grover *et al*. 2007).

Test of the anti-inflammatory effect with the erythema method

This study was conducted to prove the anti-inflammatory effect of ethanol extract of bangle rhizome on the back of rats characterized by the mean erythema score. This method is based on the visual observation of erythema on the skin of rats that have been shaved on the back. Erythema is formed due to UV light irritation. UV-causing erythema is an experiments for inflammatory reactions used to evaluate compounds that have anti-inflammatory activity both topically and systemically in test animals (Thompson 1990). The inducer used was an Exoterra UV B lamp

Table 4: Mean erythema score

Group	Mean ± SD erythema score				
	T6	T12	T24	T48	T72
Negative control	1.8 ± 0.836	2.6 ± 0.547	3.4 ± 0.547[b]	3.8 ± 0.447[b]	3.2 ± 0.447[b]
Extract 5 mg/200g BW	1.6 ± 0.894	2.4 ± 0.547	3.4 ± 0.547[b]	3.2 ± 0.836[b]	2.6 ± 0.547[b]
Extract 10 mg/200g BW	1.4 ± 0.547	2.6 ± 0.547	3.2 ± 0.447	2.8 ± 0.836[b]	2.2 ± 0.836[ab]
Extract 20 mg/200g BW	1.4 ± 0.547	2.2 ± 0.836	2.6 ± 1.140	2 ± 1.000[a]	1.2 ± 0.836[a]
Positive control	1.6 ± 0.547	2.2 ± 0.836	2.4 ± 0.547[a]	1.6 ± 0.547[a]	0.6 ± 0.547[a]

Description:
a : Substantially unique from poor management
b : Substantially specific from effective management

Based on the graph above, erythema in mice appeared 6 hours after irradiation with UVB lamps. In the negative control group given CMC Na, erythema began to increase until 48 hours after irradiation with UVB lamps and decreased after 72 hours. This is to the research of Ito *et al.* (2015) that UVB-induced erythema responds after 2-24 hours of exposure, where, according to Kobayashi (2006), at 12-24 hours after induction, there is swelling and bullous formation. UVB directly damages the DNA chain, resulting in the formation of pyrimidine dimers and causing mutations. The reaction caused by UVB radiation results in the release of inflammatory mediators such as histamine, serotonin, and prostaglandins that cause the dilation of capillaries, leading to erythema and edema. UVB radiation can activate small molecules, such as melanin, tryptophan, riboflavin, and porphyrin, to form reactive oxygen species (ROS), which indirectly cause oxidative stress and activate cellular oxygen. In the positive control group given diclofenac sodium, erythema appeared 6 hours after UVB irradiation, increased until 24 hours of exposure, and was different from the negative control, so it can be said that diclofenac sodium can inhibit the formation of erythema. At 48 hours after exposure, the erythema score decreased. This shows that diclofenac sodium provides anti-inflammatory effects with the ability to reduce the mean erythema score. According to research by Kienzler *et al*. (2005), the administration of diclofenac sodium can reduce erythema and edema due to exposure to UVA and UVB rays 48 hours after irradiation. Diclofenac sodium works to inhibit the enzyme cyclooxygenase, which plays a role in the metabolism of arachidonic acid into inflammatory mediators such as prostaglandins, thromboxane, and prostacyclin. Inside the remedy organization of ethanol extract of the bangle rhizome, erythema formed at the 6th hour after UVB exposure. In the treatment group of ethanol extract of the bangle rhizome, doses of 5, 10, and 20 mg/200 g continued to increase after 24 hours, then decreased at 48 hours. Furthermore, the mean erythema score data were statistically tested to determine significant differences between the treatment groups.

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Table 5. Mean erythema score

Treatment group	Mean erythema score ± SD
Negative control (CMC-Na)	2.96 ± 0.77[b]
Positive control (Natrium diklofenak)	1.68 ± 0.70[a]
Extract dose 5 mg/200 g BW	2.64 ± 0.71[b]
Extract dose 10 mg/200 g BW	2.44 ± 0.68[ab]
Extract dose 20 mg/200 g BW	1.88 ± 057[a]

Description:

a: Significantly different from the negative control group based on the LSD test results.

b: Significantly different from the positive control group based on the LSD test results.

The statistical test results show that the mean erythema score data is normally distributed with a significance value (0.268 > 0.05) and homogeneous with a significance value (0.295 > 0.05). The outcomes of the only-manner ANOVA check confirmed that there were good-sized variations among treatment corporations with a significance value (0.000 <0.05), followed by the results of the LSD test, which showed that there were significant differences between the treatment groups. The results of the statistical tests showed that the ethanol extract of bangle rhizome at a dose of 10 mg/200 g BW and ethanol extract of bangle rhizome at a dose of 20 mg/200 g BW were significantly different from the negative control CMC Na, thus proving that bangle rhizome extract has an anti-inflammatory effect. Flavonoids work by inhibiting the activity of cyclooxygenase and lipoxygenase enzymes, eicosanoid biosynthesis, and neutrophil degranulation. Flavonoids inhibit the production of pro-inflammatory cytokines such as TNF-α (tumor necrosis factor-α), IL-1β (interleukin-1β), and IL-6 (interleukin-6). The flavonoid mechanism also inhibits the activation of transcription factors such as NF-κB (nuclear factor-κB), thereby interfering with the protein expression of iNOS and COX-2 (Nijveldt RJ *et al*.,2001). Steroids reduce inflammation by blocking phospholipase A2 activity, which stops the release of arachidonic acid. Arachidonic acid is a building block for the production of pro-inflammatory mediators such as prostaglandins and leukotrienes (Barnes, 2022).

CONCLUSION

Extract Ethanol of bangle rhizome showed anti-inflammatory interest using the carrageenin induction method at doses of 5, 10, and 20 mg/200 g bw and showed anti-inflammatory activity using the erythema method at doses of 10 mg/200 g bw and 20 mg/200 g bw, ethanol extract of bangle rhizome at a dose of 20 mg/200 g bw in rats showed the highest anti-inflammatory interest and comparable to effective management in each method. The molecular mechanisms underlying the anti-inflammatory properties of the ethanol extract of bangle rhizome should be further investigated, particularly at the most effective dose of 20 mg/200 g body weight. Pathways involving inflammatory mediators, such as pro-inflammatory cytokines, nuclear factor-kappa B (NF-κB), and cyclooxygenase-2 (COX-2), should be examined in greater detail. Furthermore, the identification and isolation of active compounds should be conducted to support the development of standardized phytopharmaceutical formulations. To comprehensively assess the extract's efficacy and safety, studies involving chronic inflammation models, subchronic or chronic toxicity evaluations, and long-term comparisons with conventional anti-inflammatory drugs are required. Clinical trials in humans may also be considered to determine the extract's translational potential for therapeutic application.

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