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Article

Evaluation of the Analgesic Potential of Bangle Rhizome (*Zingiber cassumunar* Roxb.) Extract in Mice (*Mus musculus*)

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Abstract

Bangle (*Zingiber cassumunar* Roxb.) is a medicinal plant traditionally used by local communities for various health conditions, including fever, stomach discomfort, constipation, and common cold symptoms. This study was conducted to evaluate the analgesic activity of bangle rhizome extract in mice, determine the most effective dose for producing an analgesic response, and compare its analgesic efficacy with aspirin. The experimental animals were randomly allocated into six groups consisting of a normal control group, a negative control group receiving 0.5% Na-CMC, a positive control group administered aspirin, and three treatment groups receiving bangle rhizome extract at doses of 150, 200, and 300 mg/kg body weight, respectively. Analgesic activity was assessed using a chemical pain induction model in which 1% acetic acid was administered intraperitoneally 30 minutes after oral administration of the respective treatments. The number of writhing responses was recorded at 10 minute intervals over a 60 minute observation period. The findings demonstrated that the bangle rhizome extract exhibited analgesic activity by reducing the frequency of writhing responses in mice. Among the tested doses, 200 mg/kg body weight produced the most favorable analgesic effect. Furthermore, the analgesic activity observed at this dose was comparable to that produced by aspirin, suggesting that bangle rhizome extract has promising potential as a natural analgesic agent.

Keywords: Acetic acid; Analgesic; Aspirin; Rhizome; *Zingiber cassumunar* Roxb

1. INTRODUCTION

The use of traditional (herbal) medicines for various ailments has been passed down from generation to generation by our ancestors. These traditional medicines tend to be safer because they do not cause significant negative side effects on the body, and they are relatively less expensive. The average prevalence of pain worldwide is quite high, at 30.3% [1]. Pain stimuli are classified into four types: chemical, mechanical, heat, and cold [2]. The mechanism of pain begins when peripheral nerves receive a stimulus from outside the body that exceeds a certain threshold. This stimulus triggers the synthesis

of prostaglandins (PG) and several other compounds by the phospholipid membranes of peripheral cells; the stimulus is then transmitted to the central nervous system, where it is perceived as pain [3].

Analgesics are medications that reduce pain by acting on the central nervous system or on peripheral pain mechanisms, but do not significantly alter consciousness. Analgesics can relieve pain without addressing its cause. Analgesic effects are achieved through the use of opioid medications that act on the central nervous system, as well as nonsteroidal anti-inflammatory drugs that act on the peripheral nervous system [4]. Analgesics, when used in excessive doses, can cause several side effects. Side effects of analgesics include gastrointestinal, kidney, and liver problems [5]. In addition, it is effective as a remedy for fever, stomachaches, constipation, colds, and gout [6]. One natural substance with analgesic effects is the bangle rhizome (*Zingiber cassumunar*). This plant belongs to the ginger family and has analgesic effects due to its active compounds, which work by reducing prostaglandin E2 (PGE2) and cyclooxygenase-2 (COX-2) expression [7]. A study conducted by (6) showed that bangle rhizome extract contains chemical compounds such as saponins, flavonoids, essential oils, alkaloids, tannins, and glycosides.

The bangle plant is one of the plants believed to have traditional medicinal properties among the people of South Sulawesi; it is consumed by chewing 1 gram of the plant. However, a lack of knowledge among the public has led to the indiscriminate consumption of bangle. Therefore, it is necessary to determine whether the use of bangle rhizome in the community has proven analgesic activity and whether it is being used at the appropriate dosage. Based on the above discussion, this study aims to determine the secondary metabolite content of bangle rhizome extract (*Z. cassumunar*), to identify the optimal dose of bangle rhizome extract (*Z. cassumunar*) as an analgesic, and to compare the analgesic efficacy of bangle rhizome extract (*Z. cassumunar*) with that of aspirin.

2. MATERIALS AND METHODS

2.1. Material

The materials used in this study included Bangle rhizomes (*Z. cassumunar*) found near residential areas in Sangatta, East Kalimantan. The samples were identified at the Faculty of Forestry, Mulawarman University, and processed into dry simplicia at the Research and Development Laboratory of "Farmaka Tropis" Pharmaceutical Sciences, Faculty of Pharmacy, Mulawarman University, Samarinda, East Kalimantan. In addition, other materials used included 0.5% Na-CMC, aspirin, mice, 70% ethanol, aquades, 0.9% NaCl, acetat acid, alcohol, 1% FeCl, 5% $FeCl_3$, HCl concentrated, HCl 1N, Dragendorff's reagent, Meyer reagent, Liebermann Burchad reagen, Wagner reagen.

2.2. Instrument

The tools used in the study include Rotary evaporator, hand grinder, Hotplate, Waterbirth, stirring rod, glass bottle, plastic bottle, glass funnel, desiccator, beaker, watch glass, filter paper, volumetric flask, mortar, spatula, glass jar, pipette, analytical balance, oven.

2.3. Method

2.3.1. Sample Preparation

Bangle rhizomes (*Z. cassumunar*) were collected from the Sangatta, East Kalimantan district, then sorted and cut into small pieces until the desired size was achieved, after which they were dried in an oven at 50°C for several days until fully dried. The dried plant material was weighed for the next process, which was extraction.

2.3.2. Extreaction Process

The rhizomes of *Z. cassumunar* were extracted using the maceration method. The extraction process began by macerating 200 grams of dried, finely ground *Z. cassumunar* rhizome powder in 1.5 liters of 70% ethanol at room temperature for 2–3 days, after which the mixture was filtered. The residue was re-macerated with 500 ml of 70% ethanol at room temperature for 2 days, then filtered, and the filtrate was concentrated using a rotary evaporator at 50°C until a thick extract was

obtained. The thick extract was weighed and suspended in CMC-Na and distilled water according to the predetermined dosage [8].

2.3.3. Preparation of Test Animals

A random selection methods use in which male, 2–3 months old, and weighed 25–35 grams. The mice were divided into 6 groups, each consisting of 4 male mice. Group 1 was the negative control group, Group 2 was the positive control group, Group 3 was the normal group, and Groups 4, 5, and 6 were the test groups. The mice were acclimated for 1 week to allow them to adjust to laboratory conditions. The cage is made of transparent polycarbonate plastic, has good air circulation and lined with rice husks. The cage measures 40 cm long, 30 cm wide and 18 cm high.

2.3.4. Aspirin Dosage Calculation

The aspirin dose is determined based on the human dose conversion factor. The standard aspirin dose is 500 mg. Dosing is based on the average adult body weight of 70 kg. The conversion from a human dose (70 kg) to a mouse dose uses a conversion factor of 20 g = 0.0026. Therefore, the aspirin dose for a 70 kg human = 500 mg. Thus, the conversion of human dose to mice is: human dose × conversion factor for a 20 g mouse = 500 × 0.0026 = 1.3mg/20gBW [9].

2.3.5. Determination of The Dose Series for Ethanol Extract of Bangle Rhizome

The determination of the dosage of bangle rhizome extract was based on previous research, which found that a dose of 200 mg/kg body weight had an analgesic effect; therefore, this study used a lower dose of 150 mg/kg body weight, a dose of 200 mg/kg body weight, and a higher dose of 300 mg/kg body weight. The concentrated extract obtained was weighed according to the predetermined doses, then suspended in 0.5% Na-CMC and stirred until homogeneous.

2.3.6. Analgesic Testing

The mice fasted for 18 hours while still being provided with drinking water, and their body weights were measured. The mice were divided into 6 groups; each group of 5 mice was marked and administered the following oral treatments:

a) Group I (0.5% Na-CMC): 0.5% Na-CMC solution (negative control)

b) Group II positive control (Aspirin): Aspirin solution (positive control suspended in 0.5% Na-CMC).

c) Group III normal control: No treatment administered

d) Group IV (Extract I): Administered bangle rhizome extract at dose I (150 mg/kg body weight)

e) Group V (Extract II): Administered bangle rhizome extract at dose II (200 mg/kg body weight)

f) Group VI (extract III): Administered bangle rhizome extract at dose III (300 mg/kg body weight)

After receiving a single oral dose, 30 minutes later the mice were administered 1% glacial acetic acid intraperitoneally; the number of writhing episodes was then observed and counted every 10 minutes for 60 minutes, and the writhing episodes were calculated using the % protection formula [10]. The role of Positive control to confirm that the testing method used is valid and that the test animals (mice) respond normally to the analgesic drug. The aspirin suspension serves as a standard control that has been proven to have pain-relieving (analgesic) effects. The role of negative control to determine the baseline level of maximum pain in the absence of the drug's active ingredient, while also testing the effect of the vehicle used. The role normally controls to serve as the definitive standard for assessing the normal physiological condition of mice without exposure to pain-inducing chemicals or test compounds.

2.3.7. Data Analysis

The research data, consisting of the cumulative number of twitches in each treatment group, were used to calculate the analgesic potency, expressed as the percentage of protection. The data obtained were analyzed using normality and homogeneity tests, followed by a one-way ANOVA comparison test and a post hoc least significant difference (LSD) test to determine significant differences among the groups.

2.3.8. Phytochemical Analysis

a. Alkaloid

Alkaloid testing was performed using the Mayer, Wagner, and Dragendorff methods. A 3 mL sample was placed in a porcelain dish, 2 mL of chloroform and 2 mL of ammonia were added, and the mixture was filtered; then, 3–5 drops of concentrated H_2SO_4 were added, and the mixture was shaken until two layers formed. The upper layer was transferred into three 2.5-mL tubes; each of the three solutions was analyzed with 4–5 drops of the Mayer, Dragendorff, and Wagner reagents, respectively. The reaction with the Mayer reagent produced a white precipitate; with the Dragendorff reagent, an orange-red precipitate formed; and with the Wagner reagent, a brown precipitate formed.

b. Flavonoid

Add 3 mL of the extract to 100 mL of hot water, boil for 5 minutes, then filter. To 5 mL of the filtrate, add 0.05 grams of magnesium powder and 1 mL of concentrated HCl, then shake vigorously. A positive test is indicated by the formation of a red, yellow, or orange color.

c. Saponin

Add 3 mL of the extract to 10 mL of distilled water while shaking for 1 minute, then add 2 drops of 1 N HCl. If the foam that forms remain stable for approximately 7 minutes, the extract is positive for saponins.

d. Steroid

Add 10 drops of CH_3COOH and 2 drops of concentrated H_2SO_4 to 3 mL of the extract. Shake the solution briefly and let it stand for a few minutes. A positive test is indicated by the formation of a blue or green color or a black ring.

e. Tannin

Add 10 drops of CH_3COOH and 2 drops of concentrated H_2SO_4 to 3 mL of the extract. Shake the solution briefly and let it stand for a few minutes. A positive test is indicated by the formation of a blue or green color or a black ring.

f. Triterpenoid

2 mL of the extract, add 10 drops of glacial CH_3COOH and 2 drops of concentrated H_2SO_4. Gently shake the solution and let it stand for several minutes. The presence of triterpenoids produces a red or purple color.

3. RESULT AND DISCUSSION

3.1. Extraction Process

The extraction of bangle rhizomes yielded a recovery rate of 10.53%, with an extract weight of 65.84 grams and a crude drug weight of 625 grams. An extract is said to have a good yield if its value is above 10%.

3.2. Phytochemical Analysis

Phytochemical testing is one method of qualitatively identifying the chemical composition of a plant. This test aims to determine the active compounds present in bangle rhizome extract. The identification of these compounds serves as a reference for determining which compounds are responsible for treating diseases. The results of the phytochemical tests are shown in the table 1.

The results obtained indicate that bangle rhizome extract contains alkaloids, flavonoids, tannins, triterpenoids, and saponins. This is also supported by research by Bajuber, et.al., 2020 [8], which found that bangle rhizome extract contains flavonoids, alkaloids, saponins, terpenoids, and phenols. Plants containing flavonoids are known to help reduce pain. Flavonoids and alkaloids are secondary metabolites found in bangle rhizome extract that are believed to have pharmacological effects as analgesic agents. In addition, flavonoids also act as diuretics, anti-inflammatories, antihistamines, antioxidants, antibacterials, and blood sugar-lowering agents. Flavonoids can reduce pain by inhibiting the development of inflammation. They work by blocking the activity of the cyclooxygenase enzyme, thereby reducing prostaglandin production in the arachidonic acid pathway, which prevents inflammation from forming and consequently reduces the onset of pain. In

addition to inhibiting the cyclooxygenase enzyme, flavonoids also halt neutrophil degranulation, thereby preventing the release of cytokines, free radicals, and enzymes involved in the inflammatory process. Another study also indicates that the flavonoid contained in bangle rhizome is quercetin. Quercetin acts as a potent hydrogen donor. It is possible that quercetin can inhibit the cyclooxygenase enzyme in the production of prostaglandin inhibiting this prostaglandin production process, the resulting pain response can be reduced [10]. Alkaloids act by blocking a key step in prostaglandin formation, specifically the cyclooxygenase (COX) pathway in the arachidonic acid pathway. Meanwhile, tannins work by stimulating the release of the enzyme lipomodulin, which inhibits the enzyme phospholipase, thereby disrupting the cyclooxygenase and lipoxygenase pathways and preventing the formation of their metabolites [10]. Phytochemical compounds serve as a fundamental link between the empirical claims of traditional medicine and the scientific validation of modern pharmacology. Through isolation, identification, and modification of chemical structures, phytochemical discoveries transform natural substances, which were originally used solely based on generations of experience, into standardized, safe, and scientifically sound pharmaceutical preparations.

Table 1. Secondary Metabolites in Bangle Rhizome Extract

Compound	Reagen	Colour	Result
Alkaloid	Mayer	yellowish white	+
	Wagner	reddish brown	+
	Dragendroff	brownish-orange	+
Flavonoid	Mg + Hcl	yellow	+
Saponin	Air Panas + HCl	foam forms	+
Steroid	Liebermann-Burchard	green/Blue	-
Tanin	FeCl3	greenish-black	+
Triterpenoid	Liebermann-Burchard	purple	+

Description:
+ = A compound was detected
- = A compound wasn't detected

3.3. Analgesic Activity of Bangle Rhizome Extract (Z. cassumunar)

This study aims to determine the analgesic activity of bangle rhizome extract (*Z. cassumunar*) in mice (*Mus musculus*) compared to aspirin. The number of movements by mice in the test group and the negative control group over a 60-minute period can be seen in the table 2.

Table 2. the number of movements by mice in the test group and the negative control group over a 60-minute period

Replication	The Number of Movement			
	Negative	150 mg/KgBW	200 mg/KgBW	300 mg/KgBW
1	47	40	13	21
2	41	19	16	27
3	53	24	11	27
4	52	18	35	22
Total	193	101	75	97
Average	48.25±5.50	25.25±10.17	18.75±11.02	24.25±3.20

Analgesic testing was conducted using the Siegmund method. This method involves the chemical induction of pain. Pain was induced using an irritant compound acetic acid which was injected intraperitoneally into mice. Acetic acid is a weak acid that irritates tissues, causing pain. Prostaglandins play a role in pain associated with tissue damage; thus, the presence of acetic acid, which can irritate tissues, sensitizes pain receptors. Prostaglandins induce a state of hyperalgesia—an exaggerated response to stimuli. Pain mediators such as bradykinin and histamine then stimulate these receptors, resulting in

noticeable pain. The resulting pain response manifests as writhing movements in mice. Writhing in mice refers to a stretching movement in the abdominal region, followed by stretching in one of the hindquarters [10]. Acetic acid is a weak acid that irritates tissues, causing pain. Prostaglandins play a role in pain associated with tissue damage; thus, the presence of acetic acid, which can irritate tissues, sensitizes pain receptors. Prostaglandins induce a state of hyperalgesia an exaggerated response to stimuli. Pain mediators such as bradykinin and histamine then stimulate these receptors, resulting in noticeable pain. The resulting pain response manifests as writhing movements in mice. Writhing in mice refers to a stretching movement in the abdominal region, followed by stretching in one of the hindquarters [10].

Table 2, which was conducted over 60 minutes, shows that the negative control group administered 0.5% Na-CMC exhibited a higher number of twitches. The bangle rhizome extracts at doses of 150 mg/kg body weight, 200 mg/kg body weight, and 300 mg/kg body weight did not produce a higher number of twitches than the negative control. This occurred because the mice induced with 0.5% Na-CMC were not administered test substances (aspirin and bangle rhizome extract) capable of reducing pain, so the healing process was aided solely by their own immune systems. The average twitch response in the test groups receiving doses of 150 mg/kg body weight, 200 mg/kg body weight, and 300 mg/kg body weight was nearly identical. This indicates that the bangle rhizome extract is capable of reducing the mice's twitch response through its analgesic effect. Meanwhile, the negative control group exhibited frequent writhing, indicating that the negative control used did not contain any active substances capable of reducing pain. The analgesic efficacy of bangle rhizome extract can be observed through a reduction in the frequency of writhing movements in mice. The effectiveness of an analgesic drug is assessed based on its ability to suppress or eliminate pain caused by chemical induction in test animals. In mice, pain is indicated by a writhing response. This response typically appears within about five minutes after induction [11].

The efficacy of the bangle rhizome extract obtained in this study is believed to be due to the presence of secondary metabolites in the bangle rhizome, namely alkaloids and flavonoids. Alkaloids function as inhibitors of a key step in prostaglandin biosynthesis [12]. The mechanism of action of alkaloids as analgesics is to inhibit a key step in prostaglandin biosynthesis, specifically the cyclooxygenase pathway in the arachidonic acid metabolic pathway [13]. Flavonoids can inhibit the activity of cyclooxygenase enzymes, resulting in reduced prostaglandin production from arachidonic acid and reduced pain; in addition, flavonoids also inhibit neutrophil degranulation, which in turn inhibits the release of cytokines, free radicals, and enzymes involved in inflammation. The analgesic mechanism of action of flavonoids involves inhibiting the enzymes cyclooxygenase (COX) and lipoxygenase (LOX) in the arachidonic acid pathway, thereby inhibiting the formation of pain mediators. Flavonoid compounds can act as analgesic agents by inhibiting the activity of the enzymes cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing prostaglandin production in the arachidonic acid pathway. This prevents the development of inflammation, which in turn reduces the onset of pain, stabilizes pain receptors, and determines the duration of pain [14].

Statistically, the normality test showed that the analgesic data were normally distributed p-value of 0.20 ($p > 0.05$). The homogeneity test showed that the data had homogeneous variances p-value of 0.06 ($p > 0.05$). The test group was compared with the negative control group using ANOVA, which yielded a p-value of 0,01 ($p < p\ 0.05$). Statistically, there was a significant difference in analgesic effects between the dose groups and the negative control group which yielded a p-value of 0,01 ($p < 0.05$) with a 95% confidence level, indicating that bangle rhizome extract has significant analgesic efficacy.

3.4. Optimal Dose of Bangle Rhizome Extract

In the test group treated with 150 mg/kg body weight of bangle rhizome extract, there was a decrease in the number of writhing movements following administration of the 150 mg/kg body weight dose of bangle rhizome extract; the total number of writhing movements in the mice was 101, with an average of 25.25 movements, and the percentage of analgesic efficacy was 59.44%. In the test group treated with 200 mg/kg body weight of bangle rhizome extract, there was a decrease in the number of writhing movements following administration of the 200 mg/kg body weight dose of bangle rhizome extract; the total number of writhing movements in the mice was 75, with an average of 18.75, and the percentage of

analgesic potency was 69.88%. In the test group treated with 300 mg/kg body weight of bangle rhizome extract, there was a decrease in the number of writhing movements following administration of the 300 mg/kg body weight dose of bangle rhizome extract; the total number of writhing movements in the mice was 97, with an average of 24.25 movements, and the percentage of analgesic efficacy was 61.07%.

The average analgesic potency in the test group treated with bangle rhizome extract is shown in Table 3 as follows:

Table 3. Average Analgesic Potency of the Test Group

Replication	Number of movements		
	150 mg/KgBW	200 mg/KgBW	300 mg/KgBW
1	40	13	21
2	19	16	27
3	24	11	27
4	18	35	22
Total	101	75	97
average	25.25±10.17	18.75±11.02	24.25±3.20

The percentage of analgesic potency of the bangle rhizome extract in the test group is shown in Table 4 below:

Table 4: Percentage of Analgesic Efficacy in the Test Group

Treatment Group	Analgesic Effect
Dose 150 mg/KgBW	59.44%
Dose200 mg/KgBW	69.88%
Dose 300 mg/KgBW	61.07%

Based on the mean and percentage of analgesic potency for each group, the 200 mg/kg body weight dose was found to have the highest analgesic effect compared to the other groups. The analgesic activity of a compound is considered effective if it can reduce mouse writhing by >50% compared to the negative control. The analgesic effect is thought to arise from the activity of flavonoids, which inhibit the COX enzyme, thereby inhibiting prostaglandin biosynthesis, while inhibition of the prostaglandin formation phase in the arachidonic acid metabolic pathway occurs due to the presence of alkaloids. Thus, the mechanism behind the high analgesic efficacy is thought to result from the combined action of several compounds that share the same mechanism of action: the inhibition of nonspecific pain mediator production [15].

3.5. Analgesic Potential of Bangle Rhizome Extract (Z.cassumunar) Compared to Aspirin

This stage aims to determine the potential of bangle rhizome extract to reduce pain in mice induced by 1% acetic acid administered intraperitoneally, as assessed by its analgesic efficacy at the optimal dose compared to a positive control group treated with aspirin. The average analgesic potency of the bangle rhizome extract at the optimal dose and the positive control is shown in Table 5 below:

Table 5: Average Analgesic Potency at the Optimal Dose and for the Positive Control

Group	Average Analgesic Potency	Analgesic Effect
Positive control	26.5±6.13	57.43%
Dose 200 mg/KgBB	18.75±11.02	69.88%

The average reduction in writhing in the positive control group was 25.6, with an analgesic potency of 57.43%. Aspirin works by inhibiting the cyclooxygenase (COX) pathway and prostaglandin synthesis. COX inhibition can reduce mucus and bicarbonate secretion, cause vascular damage, lead to leukocyte accumulation, and inhibit the differentiation of

prostaglandin (PGE2) cells [16]. In the 200 mg/kg body weight dose group, the average reduction in mouse writhing was 18.75, with an analgesic efficacy of 69.88%. This reduction in mouse writhing was due to the analgesic effects of several chemical components found in bangle rhizomes, namely alkaloids and flavonoids [10]. Based on the results of the comparison, bangle rhizome extract was found to have analgesic properties comparable to those of aspirin. This study successfully demonstrated that bangle rhizome extract has analgesic efficacy equivalent to that of aspirin, a synthetic pain reliever that is widely used in clinical practice.

5. CONCLUSION

Based on the results of this study Bangle rhizome extract (*Z. cassumunar*) has been found to contain alkaloids, flavonoids, saponins, tannins, and triterpenoids. The effective dose of bangle rhizome extract (*Z. cassumunar*) as an analgesic is 200 mg/kg body weight. The analgesic potency of bangle rhizome extract (*Z.cassumunar*) is comparable to that of aspirin. This elevates the potential of *Z.cassumunar* (bangle) from merely a traditional medicinal plant (jamu) to a candidate for a modern analgesic based on scientific evidence (evidence-based medicine). The testing still uses crude extract, so, it is not yet known specifically which single compound, among alkaloids, flavonoids, saponins, tannins, or triterpenoids, plays the most dominant role in producing the analgesic effect.

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