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# The Analgesic Effect and Toxicity of Red and White Ginger on Mus Musculus with the Acetate Writhing Test

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**Abstract:** Based on data from the World Health Organization in 2020, the incidence of dysmenorrhea was 1,769,425 (90%) women who suffered from dysmenorrhea, with 10-16% suffering from severe dysmenorrhea. The problem of pain is very disruptive to activities, so prevention and treatment of pain must be a concern. Ginger is a natural ingredient that grows in South Kalimantan and is empirically used to treat pain. The study aimed to determine the analgesic effects and toxicity of red and white ginger from Banjarmasin and Banjar Regency. The nutrient content profile of the soil where the ginger grew was analyzed, and it was determined by nitrogen content, cation exchange capacity, and soil pH. The content of active compound groups was analyzed using specific reagents to determine the presence of active compounds. Determination of total phenolic levels using a colorimetric method using a UV-Vis spectrophotometer. The instant ginger formula was optimized with organoleptic test result parameters. Acute toxicity tests using male Wistar rats with observations for 14 days. Analgesic tests were conducted on Mus musculus using the acetic acid writhing test. The results showed that the highest nitrogen (1,34%), cation exchange capacity (29.22 me/100 g), and soil pH levels (6,89) were in the soil where the ginger samples from Banjar Regency grew. The chemical compound content in all gingers contained the same phenolics, flavonoids, tannins, saponins, and terpenoids. The levels of marker compounds in succession from Banjarmasin red ginger, Banjarmasin white ginger, Banjar Regency red ginger, and Banjar Regency white ginger were 7.43%, 6.26%, 8.52%, and 7.12%, respectively. The results of formula optimization showed that all gingers had a sweet and spicy taste, a distinctive odor, powder form, and a reddish-brown color in red ginger and pale yellow in white ginger. The toxicity test results showed that at doses of 300 mg/Kg BW and 2000 mg/Kg BW, there was no toxic effect on the administration of ginger extract. Analgesic activity showed that all gingers had an analgesic effect at a dose of 200 mg/Kg BW. The analgesic effects from the strongest to the lowest were red ginger from Banjar Regency, red ginger from Banjarmasin, white ginger from Banjar Regency, and white ginger from Banjarmasin. This study concludes that red ginger from Banjar Regency has the most potent analgesic activity and no toxicity for all ginger.
**Keywords:** Analgesic; red ginger; white ginger; writhing test.

## INTRODUCTION

Based on data from the World Health Organization (WHO) in 2020, the incidence of dysmenorrhea was 1,769,425 (90%) women suffering from dysmenorrhea, with 10-16% suffering from severe dysmenorrhea (Yulianti & Susilowati, 2022). In Indonesia, dysmenorrhea is 64.25%, consisting of 54.89% primary dysmenorrhea and 9.36% secondary dysmenorrhea. Over the past 50 years,

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75% of women have experienced menstrual pain (Tsamara et al., 2020). Usually, symptoms of primary dysmenorrhea occur in women of productive age and women who have never been pregnant. Dysmenorrhea often occurs in women aged between 20 years or before 25 years. As many as 61% occur in unmarried women (Pattiiha et al., 2021).

Pain problems are very disruptive to activities, so prevention and treatment of pain must be a concern. Pain is a sensory and emotional state caused by actual and potential tissue damage (Bahrudin, 2018). Pain can occur in women, especially women who experience dysmenorrhea. Pain can be reduced or prevented with treatment. Treatment using synthetic drugs has side effects, namely peptic ulcers (Kuna et al., 2019). So, alternative treatments that come from natural ingredients are needed. Using natural ingredients can increase the economic value of the product, including supporting products downstream by government programs (Akhmadi, 2024).

Ginger is a natural ingredient that grows abundantly in South Kalimantan. Ginger is empirically used to treat pain (Sandy & Susilawati, 2021). Ginger is generally used as a spice, food supplement, and medicine. In Indonesia, there are three types of ginger, namely red ginger (Zingiber officinale var. rubrum), white ginger (Zingiber officinale var. amarum), and elephant ginger (Zingiber officinale var. officinale) (D. Sari & Nasuha, 2021). Ginger plants are adaptable to tropical areas so they can grow in lowlands or mountains at 1,500 m above sea level (ASL). However, to grow and produce optimally at 300-900 m altitude above sea level (Sartika et al., 2022). The higher the area, the lower the air temperature, and the intensity of the sun also decreases, thus affecting plants because the physiological processes of plants depend on sunlight (Adawiyah & Rizki, 2018). Differences in growing places will affect the nutrients in the soil, thus affecting the content of active compounds and pharmacological activity, including in ginger plants.

Such studies tested the analgesic effect of red ginger from Manado formed in nanoparticle preparations (Kaunang et al., 2020). Other studies tested the analgesic effect of white ginger infusion in significantly inhibiting pain (Dewi & Salim, 2018). The novelty in this study is that no research has been conducted on the compound content, comparing the analgesic effects of red and white ginger from Banjarmasin and Banjar Regency, especially in the form of instant powder preparations. The purpose of the research that has been carried out is to determine the analgesic and toxicity effects of red ginger and white ginger originating from Banjarmasin and Banjar district.

## MATERIALS AND METHODS

### Research Design

This research is experimental and includes analysis of nutrient content profile, active compound content, marker compound levels, formulation, toxicity test on male Wistar rats (*Rattus norvegicus*), and pharmacology test on mice (*Mus musculus*).

### Time and Place

The research will be conducted in two places, namely the Pucuk Sirih Banjarmasin, Indonesia, Herbal Medicine Factory Laboratory, which already has a certificate of Good Traditional Medicine Manufacturing Method, and the Banjarbaru Industrial Research and Standardization Center (Baristan).

### Research Ethics Test

Before this research begins, an ethics test will be conducted. The ethics test has been approved through the Ethics Committee at the Poltekkes Kemenkes Banjarmasin Indonesia with certificate number No.405/KEPK-PKB/2024.

**Sample Preparation**

The samples used are red ginger and white ginger from two different growing places. The sampling location for the highlands is in the Pengaron District, Banjar Regency, while for the lowlands, it is in the North Banjarmasin District, Banjarmasin City. Ginger samples were washed thoroughly with running water; the rhizome was taken. Next, the ginger was peeled, then washed again, and drained. Ginger samples were divided into fresh samples for making instant herbal formulas, toxicity tests, and pharmacology tests. In contrast, dry ginger was used to determine the content and levels of marker compounds.

**Soil Nutrient Content Profile**

The nutrient profile analyzed was nitrogen content, cation exchange capacity, and soil pH. Nitrogen levels were determined using the Kjeldahl method. Cation exchange capacity was determined using the Leaching method using 1 N Ammonium Acetate pH 7. Determination of soil pH using a calibrated pH meter (Suryani, 2014; Yuliani et al., 2017).

**Active Compound Content**

Dry ginger was ground with a blender, then 1 gram was taken, dissolved in 100 mL of pro-analysis ethanol, and filtered. The filtering results were separated and then analyzed. The active compound group content was analyzed using specific reagents to determine the presence of phenolics, tannins, flavonoids, saponins, terpenoids, and alkaloids (Rizki et al., 2021b).

**Quantitative Analysis of Marker Compounds**

Ginger extract 100 mg was dissolved in ethanol and then filtered. As much as 1 mL of the solution was put into a test tube, 2.5 mL of 5% Folin-Ciocalteau reagent was added, shaken, and left for 3 minutes. Then, each was added with 2 mL of 1M Na2CO3 solution, shaken until homogeneous, and left for 50 minutes. The solution was then read for its absorbance on a UV-Vis Spectrophotometer. The marker used was pure gallic acid as a standard compound. Sample and standard readings were carried out at a wavelength of 742 nm and an operating time of 30-40 minutes (Rizki et al., 2022).

**Instant Herbal Medicine Formulation**

Fresh ginger, as much as 1 kg, is cleaned from its skin and then blended with 500 mL of sterile water. The solution is then added with 4500 mL of sterile water and stirred until evenly distributed. The solution is then filtered using filter paper. The filtered solution is put into a large pan, adding 5 kg of granulated sugar. Then, heat it using a stove over low heat. Stirring is carried out continuously until the solution dries, the fire is turned off, and the mixture is stirred until cold and instant powder is formed. The instant powder formed is put into a tightly closed glass container.

**Acute Toxicity Test**

Toxicity tests were conducted using male Wistar rats. A total of 30 male rats were divided into five groups. The first to fourth groups were each given a herbal formula of red ginger from Banjar Regency, red ginger from Banjarmasin, white ginger from Banjar Regency, and white ginger from Banjarmasin. The fifth group was not given any treatment. Treatment was given twice a day, namely in the morning and evening. Forced feeding was carried out using a gastric tube. Observations of the emergence of behavioral changes, stress, and death were conducted on experimental animals for 14 days after treatment (BPOM RI, 2022).

**Analgesic Test**

The pharmacological activity test used female mice aged 2-3 months weighing 25-35 grams. The mice were acclimatized for 1 week to adjust to laboratory conditions.

Treatment: A total of 30 mice (*Mus musculus*) were grouped into 6 treatment groups, which were divided randomly, namely: (K-) negative control group with the treatment given 25 mL/kg BW of distilled water; (P1) Banjarmasin white ginger extract dose 200 mg/kgBW; (P2) Banjar Regency white ginger extract dose 200 mg/kg BW; (P3) Banjarmasin red ginger extract dose 200 mg/kg BW; (P4) Banjar Regency red ginger extract dose 200 mg/kgBW; (K+) aspirin positive group dose 91 mg/kgBW. Analgesic testing was only done for one day, so sampling was only done once. Each experimental animal was given a sample orally according to the type and dose that had been determined. Thirty minutes after the sample was given, the mice were induced with an intraperitoneal injection of 1% acetic acid volume 5 mL/kgBW. Before injection, the mice were anesthetized using ether to prevent severe pain in the mice during intraperitoneal injection. Acetic acid functions as a pain trigger in mice. The amount of wriggling indicates the pain parameters in mice. Then, the amount of wriggling began to be observed and counted 5 minutes later. The frequency of wriggling was measured every 10 minutes for one hour. Wriggling is characterized by a response in the form of a reflex arching the back, straightening the hind legs, and abdominal contractions (Goenarwo et al., 2011).

## RESULTS AND DISCUSSION

### Soil Nutrient Content

Soil samples were taken in the area where the ginger grows. The soil was then analyzed to determine the nitrogen content, cation exchange capacity, and acidity (pH). These three parameters will indicate the soil quality where the ginger grows. The results of the soil nutrient content test are presented in Table 1.

Table 1. Soil Nutrient Content Test Results

| No. | Parameter | Banjarmasin City | Banjar Regency |
|---|---|---|---|
| 1 | Nitrogen Levels | 0.87% | 1.34% |
| 2 | Cation Exchange Capacity | 18.34 me/100 g | 29.22 me/100 g |
| 3 | Soil Acidity (pH) | 6.06 | 6.89 |

The test results showed that the highest nitrogen content was found in the soil from Banjar Regency at 1.34%. The nitrogen content in the soil from Banjarmasin was relatively lower at only 0.87%. However, Banjar Regency and Banjarmasin soil remained above the nitrogen content standard. Nitrogen helps increase plant growth, including healthy leaf growth as a place for photosynthesis (Nopsagiarti et al., 2020). The cation exchange capacity parameter of the soil from Banjar Regency is also higher, at 29.22 me/100 g, compared to Banjarmasin, which is 18.34 me/100 g. The soil acidity (pH) from Banjar Regency is 6.89, the optimum pH level. The soil from Banjarmasin is relatively acidic, with a pH of 6.06, below the optimum soil pH standard, which is more than 6.6. The high acidity of the soil from Banjarmasin is because the Banjarmasin area is a swamp area, so it tends to have acidic properties like peat soil characteristics. Based on these results, the soil where the ginger used in this study grows is the most optimum soil from Banjar Regency.

### Active Compound Content

Specific reagents determined the content of active compounds in the four gingers. Ginger extract was dissolved in ethanol and then dripped with particular reagents. The test results are presented in Table 2.

Table 2. Active Compound Content Test Results

| No | Parameter | Red Ginger Banjarmasin | White Ginger Banjarmasin | Red Ginger Banjar Regency | White Ginger Banjar Regency |
|---|---|---|---|---|---|
| 1 | Phenolic | + | + | + | + |
| 2 | Flavonoid | + | + | + | + |
| 3 | Tannin | + | + | + | + |
| 4 | Alkaloid | - | - | - | - |
| 5 | Saponins | + | + | + | + |
| 6 | Terpenoid | + | + | + | + |

The test results showed that all ginger contains phenolic, flavonoid, tannin, saponin, and terpenoid compounds. There was no difference in the results between red ginger and white ginger, nor was there any difference between ginger from Banjarmasin and Banjar Regency. The content of compounds in the same type of plant is generally similar, even though they grow in different places. Qualitatively (existence), there will be no difference; later, the difference occurs typically quantitatively (amount) of the compounds contained. Phenolic is a compound that contains OH groups in massive amounts spread in plants, including ginger, with the ability to be an anti-pain, antioxidant, and antibacterial (Sukweenadhi et al., 2023). Flavonoids are compounds found in abundance in ginger with strong anti-pain abilities. These compounds will synergize with each other to produce efficacy. The uniqueness of a natural ingredient is that active compounds do not work alone, so the combination of the presence of phenolics, flavonoids, tannins, saponins, terpenoids, and alkaloids will provide strong efficacy in plants that work comprehensively on the body (Mao et al., 2019).

**Quantitative Analysis of Marker Compounds**

Marker compound levels were tested on the four gingers. The test used a spectrophotometric method based on total phenolic parameters with gallic acid standards. The results of marker compound levels testing in red and white ginger from Banjarmasin and Banjar Regency are presented in Table 3.

Table 3. Marker Compound Level Test Results

| No. | Sample | Total Phenolic Content |
|---|---|---|
| 1 | Red Ginger from Banjarmasin | 7.43% b/b |
| 2 | White Ginger from Banjarmasin | 6.26% b/b |
| 3 | Red Ginger from Banjar Regency | 8.52% b/b |
| 4 | White Ginger from Banjar Regency | 7.12% w/w |

The total phenolic content of all ginger can be seen in Table 3. The total phenolic content shows the content of all phenolic compounds contained in ginger. The total phenolic group also includes the flavonoid and tannin groups found in ginger. The test results showed that the highest total phenolics was found in red ginger from Banjar Regency at 8.52%. The total phenolic content of red ginger from Banjarmasin was in second place with a content of 7.43%. The difference in total phenolic content in red ginger is due to differences in the plants' growth. Plants that grow in optimum environmental conditions will produce optimum active compounds, which are indicated by high levels of marker compounds (Rizki et al., 2021a; A. K. Sari et al., 2020). The soil's nutrient content originating from Banjar Regency has the highest nitrogen content and cation exchange capacity, with an optimum pH approaching neutral pH. This soil is optimum for growing ginger (Nopsagiarti et al., 2020). In addition, ginger will grow optimally in higher plains, while the Banjarmasin area is a lowland. This causes differences in marker compound levels.

There is a difference in the levels of marker compounds when comparing red ginger and white ginger. Red ginger's total phenolic content is higher than white ginger's. The anthocyanin content marked by the red color in red ginger increases the total phenolic content contained (Lestari et al., 2024). In white ginger, the anthocyanin content is low, affecting the total phenolic content in white ginger (Sartika et al., 2022). The results show that red ginger is most widely used to treat diabetes problems. Red ginger has a higher price than white ginger because the benefits of red ginger are better.

**Formula Optimization**

The ginger formula in instant ginger powder was optimized. Each ginger was treated with the same additional ingredients and manufacturing methods. The results of making diamond powder were then tested organoleptically. The optimization results are shown in Table 4.

Table 4. Formula Optimization Results on Ginger

| No. | Instant Powder Sample | Organoleptic Optimization Results | | | |
|---|---|---|---|---|---|
| | | Flavor | Smell | Form | Color |
| 1 | Red Ginger from Banjarmasin | Sweet Spicy | Typical | Powder | Red Brown |
| 2 | White Ginger from Banjarmasin | Sweet Spicy | Typical | Powder | Pale Yellow |
| 3 | Red Ginger from Banjar Regency | Sweet Spicy | Typical | Powder | Red Brown |
| 4 | White Ginger from Banjar Regency | Sweet Spicy | Typical | Powder | Pale Yellow |

The results of the instant powder optimization show that all ginger can be formed into instant powder. All ginger has a sweet and spicy taste. The sweet taste comes from the granulated sugar used in making ginger powder. The use of granulated sugar aims to form instant powder crystals. The spicy taste comes from the active ingredients of ginger, which are phenolic compounds, namely gingerol and shogaol, in all types of ginger (Sa'diah et al., 2019). The spicy taste produced is distinctive because only ginger contains the compound. The odor produced by all powders is distinctive from the content of terpenoid essential oils in ginger. The color of red ginger is reddish brown, which comes from the characteristics of red ginger, which contains anthocyanin compounds from the flavonoid group (Wibawa & Tirta, 2021). White ginger powder does not contain dominant anthocyanins, so it has a pale yellow powder (Lestari et al., 2024).

**Acute Toxicity of Instant Herbal Medicine**

The study was guided by BPOM Regulation Number 10 of 2022 concerning Guidelines for In Vivo Preclinical Toxicity Testing (BPOM RI, 2022). The fixed doses method was used to test red ginger and white ginger extracts originating from Banjarmasin and Banjar Regency. The results of the acute toxicity test on ginger are presented in Table 5.

Table 5. Acute Toxicity Test Results of Ginger Extract

| No. | Instant Powder Sample | Introductory Dose (300 mg/Kg BW) | Test Dose (2000 mg/Kg BW) |
|---|---|---|---|
| 1 | Red Ginger from Banjarmasin | Non Toxic | Non Toxic |
| 2 | White Ginger from Banjarmasin | Non Toxic | Non Toxic |
| 3 | Red Ginger from Banjar Regency | Non Toxic | Non Toxic |
| 4 | White Ginger from Banjar Regency | Non Toxic | Non Toxic |

The acute toxicity test results at the preliminary dose showed that the mice did not experience any behavioral changes or deaths. This occurred in all samples: Banjarmasin red ginger, Banjarmasin white ginger, Banjar Regency red ginger, and Banjar Regency white ginger. A preliminary test must be conducted to see the possibility of toxic effects on the initial administration of low doses. If there are behavioral changes and deaths in mice at the preliminary dose, then the sample has a toxic effect at a low dose, so the test must be stopped. No testing is carried out at the test or high doses (Farisi et al., 2015). This study found no toxic effects on mice at low doses, so high-dose testing was carried out.

This study showed that Banjarmasin red ginger, Banjarmasin white ginger, Banjar Regency red ginger, and Banjar Regency white ginger did not have toxic effects on high or maximum doses. This aligns with empirical use, which shows that white and red ginger are safe to use (Syaputri et al., 2021). White ginger has no harmful effects when used according to the rules. Although no toxic effects appear in high-dose tests, it is necessary to be aware of the excessive use of ginger. The use of ginger for pregnant women in the first trimester remains a concern because the hot effects of ginger can cause problems for the fetus in the first trimester (Shawahna & Taha, 2017).

**Pharmacological Activity**

Table 6 shows the average cumulative number of rat wriggles every 10 minutes for 60 minutes. Based on the measurement time, the number of wriggles from the four treatment groups was compared with the control group. Table 6 also shows the average cumulative number of wriggles for 60 minutes for each mouse in each group.

Table 6. Results of Pharmacological Tests on Ginger

| No | Sample* | Average Number of Squirms | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 20 | 30 | 40 | 50 | 60 | Average |
| 1 | KN | 38.2 | 36.4 | 30.7 | 26.7 | 20.4 | 14.7 | 8.9 | 25.1 |
| 2 | KP | 26.3 | 17.5 | 14.6 | 10.6 | 8.8 | 7.1 | 3.7 | 12.6 |
| 3 | P1 | 30.1 | 23.5 | 20.8 | 18.4 | 15.7 | 12.7 | 6.8 | 18.3 |
| 4 | P2 | 29.4 | 19.6 | 16.5 | 15.6 | 13.4 | 11.4 | 5.9 | 15.9 |
| 5 | P3 | 28.5 | 18.7 | 15.4 | 12.7 | 10.8 | 9.5 | 4.1 | 14.2 |
| 6 | P4 | 27.2 | 16.5 | 13.4 | 9.5 | 7.4 | 6.4 | 2.5 | 11.8 |

KN: Negative Control, KP: Positive Control (Aspirin 91 mg/Kg BW), P1: (P1) Banjarmasin white ginger extract dose 200 mg/kg BW; (P2) Banjar Regency white ginger extract dose 200 mg/kg BW; (P3) Banjarmasin red ginger extract dose 200 mg/kg BW; (P4) Banjar Regency red ginger extract dose 200 mg/kg BW

The results of pharmacological tests on ginger showed that the administration of acetic acid caused pain in mice, which was indicated by the appearance of writhing in all groups. The difference between all groups was the treatment given, so there was a difference in writing. The negative control group, which was only given distilled water, had the highest average writhing in 60 minutes. Compared to the positive control, which was given an anti-pain drug, namely aspirin, which had an average writhing of 12.6, the administration of aspirin reduced the incidence of writhing in mice. This shows that the administration of positive control can reduce pain in mice (Goenarwo et al., 2011). The effect of pain continues to decrease over time, in line with the drug's entry into the mice's blood, thus providing an optimal effect at the 60th minute.

When comparing the negative control and all treatments using ginger, it can be seen that there is a decrease in the number of wriggles when ginger extract is given. White ginger and red ginger from Banjarmasin and Banjar Regency have properties that reduce wriggles. This shows that ginger when used empirically as an anti-pain, has been proven to reduce pain in animals (Srikandi et al., 2020). However, the decrease in wriggling in the treatment group with ginger varied. The highest decrease was in red ginger from Banjar Regency, with an average of 11.8, indicating that red ginger from Banjar Regency had the most substantial anti-pain effect compared to the others. When comparing red ginger from Banjar Regency with that from Banjarmasin, ginger from Banjar Regency had the most potent ability. The weakest effect occurred in white ginger from Banjarmasin, with an average wriggling of 18.3.

A similar study that tested the analgesic effect of red ginger from Manado formed in nanoparticle preparations found that red ginger can be an analgesic (Kaunang et al., 2020). Another study that tested the analgesic effect of white ginger infusion found that white ginger can significantly inhibit pain (Dewi & Salim, 2018). The results obtained are similar when compared between the two studies with this study similar. Both white ginger and red ginger can be analgesics. The results are in line with the soil nutrient content test results. The nutrients in the soil from Banjar Regency have the highest nitrogen content, the highest cation exchange capacity, and better soil acidity than those from Banjarmasin. This also aligns with the highest total phenolic content obtained in red ginger from Banjar Regency. High total phenolic content is directly proportional to the anti-pain activity of a material, so it has the most substantial anti-pain effect compared to other samples (Akbar & Rizki, 2015).

When compared between the positive control and the ginger tested, it can be seen that red ginger from Banjar Regency has anti-pain activity equivalent to aspirin. When the positive control is compared to white ginger from Banjarmasin and Banjar Regency, the positive control is still better. Red ginger from Banjarmasin is almost close to positive control, although its ability is still better than red ginger from Banjar Regency. Banjar Regency is the largest producer of white and red ginger in South Kalimantan. Red ginger grows optimally in highland areas (Effendi, 2000), so ginger from Banjar Regency is better than red ginger from Banjarmasin, which grows in the lowlands.

The limitation of this study is that analgesic testing was only carried out on test animals, not human subjects. The dose tested on the analgesic effect only used one dose, not using dose variations. The plants used only came from Banjarmasin City and Banjar Regency, so if plants from other areas were used, differences in research results might occur. The implicit suggestion from the results of this study is that stability testing should be carried out during the preparation. In addition, it should be continued with analgesic testing on human subjects. Other researchers can also make innovations in different forms of preparation.

## CONCLUSION

The analgesic effects from the strongest to the lowest were red ginger from Banjar Regency, red ginger from Banjarmasin, white ginger from Banjar Regency, and white ginger from Banjarmasin. This study concludes that red ginger from Banjar Regency has the most potent analgesic activity and no toxicity for all ginger.

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## CONFLICT OF INTEREST

All authors have no conflict of interest.

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