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ANALYSIS OF THE EFFECT OF GINGER (ZINGIBER OFFICINALE) EXTRACT AS A PAIN RELIEVER AND FEVER REDUCER IN MALE WISTAR RATS.

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ABSTRACT
A fever is an increase in body temperature above average, often due to the body's response to infection. Antipyretic drugs such as paracetamol or ibuprofen are used to reduce fever. Red ginger, with compounds such as gingerol and shogaol, can also help relieve fever. Red ginger contains compounds such as gingerol and shogaol that have anti-inflammatory and antipyretic properties, helping to reduce fever and pain. Experimental studies using Post-Test Only Control Group Design were conducted to test the antipyretic and analgesic effects of Ginger extract (Zingiber officinale) on male Wistar rats. Acetic acid writhing test, body temperature evaluation, and hematology analysis were performed with IBM SPSS 25. The results showed a significant decrease in body temperature after 5 hours of administration, especially in the ginger extract -III group (600 mg/kg body weight). Hematological analysis also showed a significant decrease along with increasing doses of the extract. These results confirm the potential of Ginger (Zingiber officinale) as an antipyretic and analgesic agent that can be explained through active compounds such as gingerol and shogaol that have anti-inflammatory and analgesic effects. Ginger can be a natural alternative in managing fever and pain in traditional herbs and warm compresses, with potential effects comparable to conventional antipyretic and analgesic drugs.
KEYWORDS: *Fever, Antipyretic drugs, Red ginger, gingerol and shogaol, Experimental research*

BACKGROUND

Fever is a condition that occurs when body temperature increases above its standard limit. The causes of fever can vary but are generally caused by the body's response to infection, whether by viruses, bacteria, or fungi (Fatkularini et al., 2015). When the body recognizes the presence of a pathogen, the immune system releases pyrogens, which are responsible for raising body temperature. This is done to create an unsuitable environment for pathogens so they cannot multiply. In addition, fever can also be caused by other conditions, such as abnormalities in the brain that regulate body temperature or exposure to toxic substances that affect the temperature regulation center in the brain. Abnormalities in the brain, such as tumors or head injuries that affect the function of the temperature regulation center can also cause fever. It is important to remember that fever itself is not a disease but rather a natural response of the body to a particular infection or stimulus. Treatment of fever usually aims to relieve symptoms such as pain and discomfort caused by increased body temperature. If other alarming symptoms accompany fever or last for an extended period, it is essential to consult a doctor for proper diagnosis and treatment (Safithri & Pravitasari, 2018); (Zelviani et al., 2020).

Fever management is carried out using antipyretic drugs (Purdaningtyas, 2018). This drug aims to restore body temperature to normal by inhibiting the release of prostaglandin E2, a chemical that mediates the effects of endogenous pyrogens in the hypothalamus. One commonly used antipyretic drug type is paracetamol or acetaminophen, which works by inhibiting the production of prostaglandin E2 (Fatan et al., 2023); (Surya et al., 2018). Other medications like ibuprofen are often used to lower fever and reduce inflammation. Although paracetamol is considered relatively safe if used at recommended doses, excessive use can increase the risk of liver damage or hepatotoxicity. Therefore, following the correct dosage rules per the doctor's instructions or drug label is very important. In addition, fever management also includes giving adequate fluids, adequate rest, and handling the cause of fever, such as infection, with antibiotics if needed.

The World Health Organization (WHO) encourages using traditional or herbal medicines as an alternative to maintaining public health. This is because conventional medicine is considered safer, with relatively minor side effects, if used according to the correct rules, as revealed in a 2013 WHO report. Traditional medicine often uses herbal ingredients in various forms, such as herbs or warm compresses. One example of a plant frequently used in conventional medicine is the rhizome of red ginger (Zingiber officinale Rosc. Var. Rubrum). Red ginger is known to have a variety of health benefits, including as an anti-inflammatory, antioxidant, and immune system boost (Pharmaceutics, 2019). The application of red ginger in the form of warm compresses can help relieve some symptoms, such as muscle and joint pain, reduce inflammation, and provide a sensation of relaxation in the affected area. Ginger, with active ingredients such as gingerol, shogaol, zingiberen, zingiberol, flavonoids, and essential oils, is effective in treating fever and relieving pain (Siregar et al., 2022) (Nadia, 2020). Gingerol and shogaol have anti-

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inflammatory properties that reduce body inflammation, while zingiberen and zingiberol help relieve pain. Ginger flavonoids have antioxidant and anti-inflammatory effects, protect body cells, and suppress inflammation.

Meanwhile, the essential oil in ginger, which contains borneol, Kampen, and cineol, has antipyretic and analgesic effects, helps lower body temperature, and relieves pain. Combining these ingredients makes ginger an effective and natural choice to overcome fever and pain in traditional herbs and medicinal products containing ginger extract. Thus, this study was designed to determine the analgesic and antipyretic effects of Ginger Methanol extract (Zingiber officinale) on male Wistar rats.

RESEARCH METHODS

This study is an experiment using Post-Test Only Control Group Design, which aims to investigate ginger's antipyretic and analgesic effects (Zingiber officinale). The analgesic activity of Ginger extract (Zingiber officinale) was evaluated using the acetic acid writhing test method. This method involves the preparation of a 0.7% acetic acid solution, which is prepared by mixing 0.7 ml of 100% glacial acetic acid with 100 ml of distilled water using a 100 ml measuring flask. The procedure for making this solution begins by pouring 20 ml of distilled water into a 100 ml measuring flask, then adding 0.7 ml of 100% glacial acetic acid solution into the flask, and finally adding distilled water until it reaches the limit mark on the 100 ml measuring flask. The evaluation of the analgesic activity of this study was carried out using 25 rats grouped into five different groups:

1. Control: Rats in this group were given 1 ml of 0.5% Na-CMC and, after 15 minutes, were given an injection of 10 ml/kgBB of 0.7% acetic acid solution. After 5 minutes of injection, the amount of writing was calculated on the rats for 20 minutes.
2. Standard (15 mg/kg body weight): Rats in this group were given an oral suspension of paracetamol 10 ml/kgBB and, after 15 minutes, were given an injection of 10 ml/kgBB 0.7% acetic acid solution. After 5 minutes of injection, the amount of writing was calculated on the rats for 20 minutes.
3. Ginger Extract (Zingiber officinale)-1 (200 mg/kg body weight): Rats in this group were given an oral suspension of Ginger (Zingiber officinale) dose 0.5 ml/kgBB and after 15 minutes, were given an injection of 10 ml/kgBB 0.7% acetic acid solution. After 5 minutes of injection, the number of *writhing* was calculated in rats for 20 minutes.
4. Ginger Extract (Zingiber officinale)-2 (400 mg/kg body weight): Rats in this group were given an oral suspension of Ginger (Zingiber officinale) dose of 1 ml/kgBB and after 15 minutes were given an injection of 10 ml/kgBB 0.7% acetic acid solution. After 5 minutes of injection, the amount of writing was calculated on the rats for 20 minutes.
5. Ginger Extract (Zingiber officinale)-3 (600 mg kg body weight): Rats in this group were given an oral suspension of Ginger (Zingiber officinale) dose of 1.5 ml/kgBB and after 15 minutes, were given an injection of 10 ml/kgBB 0.7% acetic acid solution. After 5 minutes of injection, the amount of writing was calculated on the rats for 20 minutes.

Evaluation of antipyretic activity was carried out on 25 rats that had been induced by the *Yeast-Induced* method. These rats were then grouped into five groups, namely:

1. Control: Test animals were given 1 ml 0.5% Na CMC suspension after 24 hours of Induction. Food and drink are provided ad libitum.
2. Standard (600 mg kg body weight): Test animals were given an oral suspension of paracetamol 10 ml/kgBB after 24 hours of Induction. Food and drink are provided ad libitum.
3. Ginger Extract (Zingiber officinale)-1 (200 mg/kg body weight): Test animals were given Ginger extract (Zingiber officinale) dose 0.5 ml/kgBB after 24 hours of Induction. Food and drink are provided ad libitum.
4. Ginger Extract (Zingiber officinale)-2 (400 mg/kg body weight): Test animals were given Ginger extract (Zingiber officinale) at a dose of 1 ml/kgBB after 24 hours of Induction. Food and drink are provided ad libitum.
5. Ginger extract (Zingiber officinale)-3 (600 mg kg body weight): Test animals were given Ginger extract (Zingiber officinale) 1.5 ml/kgBB after 24 hours of Induction. Food and drink are provided ad libitum.

After being given ginger methanol extract (Zingiber officinale), paracetamol as a standard control, and Na-CMC as a control, rats measured body temperature every hour for 5 hours post-treatment. The rats were then operated on to take blood samples intracardically using a three cc syringe and a 23 G needle after anesthesia with chloroform. The parameters observed included the mice's body temperature, as measured by a rectal thermometer, as well as the percentage decrease in body temperature calculated by dividing the difference in the rats' average body temperature 24 hours post-induction by the body temperature at a particular time after sampling, multiplied by 100%. All research data, including phytochemical screening, rat weight, writhing, and body temperature, were analyzed using IBM SPSS 25 with descriptive statistical analysis and inferential statistical analysis such as one-way ANOVA or Kruskal-Wallis according to the results of the data normality test.

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RESULTS OF RESEARCH AND DISCUSSION

Table 1. Comparison of Body Temperature in All Treatment Groups

Treatment Group	Body Temperature (°C)						
	Before Induction*	After Induction**	1 Jam**	2 Jam*	4 Jam*	4 Jam*	5 Jam*
Kontrol	45.34 ± 0.45	48.36 (0.40)	48.85 (3.40)	48.83 ± 0.33	48.22 ± 0.42	48.42 ± 0.24	48.02 ± 0.42[a]
Standard	45.23 ± 0.25	48.23 (0.50)	48.50 (3.40)	48.43 ± 0.49	48.20 ± 0.22	48.02 ± 0.42	42.82 ± 0.22ab
Extract Methanol Jahe (Zingiber officinale) -I	45.12 ± 0.41	48.43 (0.50)	48.40 (0.90)	48.34 ± 0.42	48.44 ± 0.48	48.24 ± 0.40	42.90 ± 0.42a
Ekstrak Metanol Jahe (Zingiber officinale) -II	45.44 ± 0.27	48.80 (0.40)	48.50 (0.80)	48.48 ± 0.33	48.00 ± 0.28	42.84 ± 0.24	42.20 ± 0.24ab
Ekstrak Metanol Jahe (Zingiber officinale) -III	45.20 ± 0.27	48.23 (2.20)	48.20 (2.20)	48.28 ± 0.42	48.42 ± 0.42	42.82 ± 0.42	42.02± 0.24B
P Value	**0.881**	**0.527**	**0.284**	**0.912**	**0.102**	**0.152**	**0.014**

*Data is displayed as Mean ± SD. P value obtained from One Way ANOVA analysis; **Data is displayed as Median (Range). The P value is obtained from the Kruskal-Wallis analysis. *Different superscripts* in the same column show significant differences

Table 1. Shows a comparison of body temperatures across treatment groups over time. Before the Induction of fever, the treatment group showed a relatively uniform body temperature. After fever induction, there was a rise in body temperature in all treatment groups, but there was no significant difference between the groups. At time intervals of 1, 2, and 5 hours after treatment, the body temperature of the control group and all other treatment groups showed uniformity. However, at 4 hours after treatment, significant differences were seen between treatment groups. This analysis provides a comprehensive picture of the body's temperature response to therapy at various times in the study.

Table 2. Comparison of *Writhing* in All Treatment Groups

Treatment Group	Jumlah Geliat (*Writhing*)	P Value
Control	10.43 ± 2.51a	
Standard	7.26 ± 2.53ab	
Extract Methanol Jahe (Zingiber officinale) -I	9.52 ± 2.53a	0.009
Ekstrak Metanol Jahe (Zingiber officinale) -II	7.56 ± 2.13ab	
Ekstrak Metanol Jahe (Zingiber officinale) -III	2.25 ± 1.44b	

The data is displayed as Mean ± SD. P value obtained from One Way ANOVA analysis; *Different superscripts* in the same column show significant differences

Table 2. presents a comparison of Writhing across treatment groups. The analysis showed that the control group had a wriggle amount of 10.43 ± 2.51, with a P value of 0.009. The standard group showed a wriggling amount of 7.26 ± 2.53, while the ginger methanol extract (Zingiber officinale)-I group had a writhing count of 9.52 ± 2.53a. The Ginger methanol extract (Zingiber officinale) -II group showed a wriggling amount of 7.56 ± 2.13ab, and the Ginger methanol extract (Zingiber officinale) -III group had the lowest wriggling amount of 2.25 ± 1.44b. Different superscripts in the same column showed significant differences between treatment groups. These results indicate that the Ginger-III methanol extract group has better analgesic potential than the control, standard, and methanol extract groups of Ginger-II.

Table 3. Comparison of Haematological Parameters in All Treatment Groups

Treatment Group	Hematologic			
	Hb*(gr/dL)	RBC**(x 205/µL)	WBC*(x 203/µL)	PLT*(x 203/µL)
Control	23.12 ± 3.11	7.59 (5.32)	7.65 ± 2.43a	757.50 ± 323.21
Standard	23.31 ± 2.42	7.57 (3.94)	3.23 ± 2.02b	561.53 ± 355.54
Extract Methanol Jahe (Zingiber officinale) -I	23.12 ± 2.43	7.35 (3.51)	5.35 ± 0.55 [a]	722.52 ± 97.52
Ekstrak Metanol Jahe (Zingiber officinale) -II	23.24 ± 3.42	7.33 (5.35)	5.09 ± 0.2 7[c]	757.12 ± 312.05
Ekstrak Metanol Jahe (Zingiber officinale) -III	23.32 ± 0.52	7.25 (0.91)	3.32 ± 2.07b	533.55 ± 333.26
P Value	**0.528**	**0.453**	**0.018**	**0.528**

*Data is displayed as Mean ± SD. P value obtained from One Way ANOVA analysis; **Data is displayed as Median (Range). The P value is obtained from the Kruskal-Wallis analysis. *Different superscripts* in the same column show significant differences.

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Table 3 compares hematological parameters between treatment groups given different types of treatment, including control, standardized, and three groups given ginger methanol extract (Zingiber officinale) in various doses. Hematological parameters observed include hemoglobin (Hb) levels, erythrocyte count (RBC), leukocytes (WBC), and platelets (PLT). The results showed no significant difference in hemoglobin levels between treatment groups ($P = 0.528$). However, there was a significant difference in leukocyte count between the treatment groups ($P = 0.018$), where the group given Ginger -II methanol extract showed a more substantial decrease in leukocyte count compared to the standard group. The analysis showed no significant difference between treatment groups on erythrocyte and platelet parameters ($P > 0.05$). Data presentation using Mean ± SD for Hb, RBC, WBC, and PLT, with P values obtained from One Way ANOVA analysis. Data for RBC are also shown as Median (Range), with P values obtained from Kruskal-Wallis analysis. Different superscripts in the same column showed significant differences between treatment groups.

Ginger rhizomes have various benefits, including being analgetic and anti-inflammatory. Chemical compounds that exert an anti-inflammatory effect on ginger rhizomes are Gingerol (6,8 and 10)-Gingerol and (6)-shogaol. Its mechanism of action occurs by inhibiting prostaglandin synthesis through inhibition of cyclooxygenase-2 (COX-2) enzymes. Prostaglandins, as mediators, have an essential role in the inflammatory process. The results showed that ginger methanol extract (Zingiber officinale) has the potential to be an antipyretic and analgesic. In the 1 hour after treatment, the control group showed a significant decrease in body temperature compared to the other treatment groups. At 2 hours and 2 hours after treatment, body temperature tended to approach baseline conditions with no significant differences between groups. It is important to note that the group that received the Methanol extract of Ginger (Zingiber officinale)-III showed a more substantial decrease in body temperature at some time after treatment compared to the control and standard groups. P values that are less than 0.05 at some time indicate significant differences between groups, especially in the Ginger Methanol extract (Zingiber officinale) -III group (Nurdyansyah & Widyastuti, 2022); (Pakpahan, 2015).

The results of this study are supported by Ainun (2018), stating that the administration of ginger infusion (Zingiber official Roscoe) with concentrations of 10% w/v, 20% w/v, and 30% w/v provides an analgetic effect on mice, and there is no difference with mefenamic acid suspension. (Ainun Rachmawati and Yuni Nurhamida, 2018). Research Mantiri (2013) states that squeezing red ginger rhizomes dose I 4 mg / 20 gr BB has an analgesic effect comparable to aspirin dose 0.4 mg / 20 gr BB. Squeezed red ginger rhizomes dose II 8 mg / 20 gr BB and dose III 16 mg / 20 gr BB have a more potent analgesic effect than aspirin dose 0.4 mg / 20 gr BB. The maximum impact of squeezing red ginger rhizomes is 8 mg / 20gr BB at dose II. The period of action of the analgesic effect of squeezing red ginger rhizomes is faster in the 30th minute than aspirin, which is in the 60th minute. (Mantiri et al., 2013).

Ginger (Zingiber officinale) is associated with its antipyretic and analgesic effects through its content of active compounds, especially gingerol and shogaol. Gingerol is the main compound in ginger that gives it its spicy and warm flavor. Gingerol is a phenolic compound that is the main component in ginger (Zingiber officinale). This compound provides ginger with a zesty and warm taste and has a wide range of pharmacological effects that benefit human health. Gingerols have been known to have anti-inflammatory, antioxidant, analgesic, anticancer, and antimicrobial properties. The anti-inflammatory effect of gingerol is mainly related to its ability to inhibit the COX-2 enzyme, which plays a role in the formation of prostaglandins so that it can relieve inflammation. In addition, gingerols may also help reduce pain in a similar way to nonsteroidal analgesic drugs (NSAIDs) such as aspirin, but with a lower potential for side effects. Gingerols also have anticancer activity due to their ability to inhibit the growth of cancer cells and stimulate apoptosis (cancer cell death). Overall, gingerols are natural compounds with a wide array of health benefits and continue to be the subject of exciting research in herbal medicine and pharmaceuticals. This compound has been shown to have anti-inflammatory properties that can reduce inflammation and inhibit prostaglandin synthesis, which in turn helps lower body temperature during fever and relieve pain (Sugiarti et al., 2011); (Srikandi et al., 2020).

In addition to gingerol, shogaol is an essential compound in ginger that has similar effects. Shogaol is an active compound found in ginger that has been heated or processed, and this compound has strong anti-inflammatory properties (Firdausni & Kamsina, 2018). Shogaol can reduce the production of inflammatory mediators in the body by inhibiting the activity of the enzyme COX-2, which is responsible for producing prostaglandins that cause inflammation and pain. In addition, this compound can also block pain pathways by reducing the sensitivity of pain receptors on nerves or interfering with the transmission of pain signals in the nervous system (Martina, 2012); (Siregar et al., 2022). Based on studies that have been conducted, the consumption of ginger-containing shogaol can provide benefits in overcoming various conditions associated with inflammation and pain, such as arthritis, joint pain, and other inflammatory conditions. Shogaol can reduce the production of inflammatory mediators and block pain pathways, thereby contributing to ginger's analgesic effects. The combination of these compounds, along with other components in ginger, such as zingiberen and zingeron, provides a scientific basis for the use of ginger in treating fever and pain in traditional and modern medicine (Dewi Sari, 2021).

CONCLUSION

This study revealed the potential of ginger methanol extract (Zingiber officinale) as an antipyretic and analgesic agent in male Wistar rats, specifically at the highest dose (600 mg/kg body weight). Antipyretic and analgesic effects begin after 5 hours of extract administration. The group that received ginger extract showed a more significant reduction in body temperature compared to the control group and the group that received the standard. The results of hematological analysis

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also showed a substantial decrease along with the increase in the extract dose given.

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