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Analgesic Efficacy Analysis of Cinnamon (Cinnamomum Verum) Extract in Wistar Model Rats

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Abstract
Body pain is a common problem that is often treated with analgesic drugs, such as mefenamic acid. However, the use of this kind of drug can cause side effects that need attention. As a safer alternative, cinnamon extract from Cinnamomum has shown potential as an effective pain treatment. This is due to the content of active compounds in cinnamon that have analgesic, anti-inflammatory, and antispasmodic properties. This research aims to explore the effects of natural analgesic remedies from cinnamon to develop more effective and safe solutions for pain management. The method used was an experimental Post-Test Only Control Group Design, in which the antipyretic and analgesic effects of cinnamon extract (Cinnamomum verum) were evaluated in experimental rats induced using the Yeast-Induced method. The results of data analysis using IBM SPSS 25 identified the potential of cinnamon as a natural analgesic remedy. Hematological parameters such as hemoglobin (Hb), erythrocytes (RBC), leukocytes (WBC), and platelets (PLT) were evaluated using the One Way ANOVA test between treatment groups. Although there were no significant differences in Hb (p = 0.504), there were substantial differences in RBC, WBC, and PLT (with p = 0.448, 0.004, and 0.504, respectively). Post-hoc analysis showed significant differences between treatment groups. In addition, cinnamon extract (Cinnamomum verum) also showed a substantial effect on the amount of vigor in rats, significantly reducing activity compared to the control group and standard group. The analgesic potential of cinnamon extract can be attributed to active compounds such as cinnamaldehyde, eugenol, coumarins, and flavonoids that interact with the nervous system in the body. This study provides a further overview of the benefits of using cinnamon as a natural analgesic remedy that can be a safer and more effective therapeutic option.

Keywords: *Cinnamon extract, Natural analgesic remedies, Cinnamon active compounds, Antipyretic and analgetic, Pain management*.

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I. INTRODUCTION

Pain in the body often felt in everyday life, such as cramps, bumps, or as a disease symptom, can be overcome by taking analgesic drugs. Analgesic drugs work to reduce or eliminate pain sensations by changing the way the body responds to the stimulus that causes pain (Wardoyo and Oktarlina 2019); (Purnomo and Tilaqza 2022). Several types of analgesic drugs are commonly used, such as paracetamol for mild to moderate pain, NSAIDs for pain and inflammation, and opioids for more severe pain. However, it is essential to consult a doctor before taking analgesic drugs to get the proper treatment according to the condition and level of pain experienced. Analgesic drugs are substances that can reduce pain without losing consciousness. Analgesic drugs are divided into two groups, namely narcotic analgesics and non-narcotic analgesics. Non-narcotic groups, such as paracetamol and ibuprofen, can be purchased freely without a doctor's prescription (Lara 2021). However, continued use can cause side effects, such as liver or stomach damage. Meanwhile, the narcotic group, including morphine and oxycodone, should only be used by prescription because of their potential dependence and severe side effects. In taking analgesic drugs, it is essential to adhere to the recommended dosage and consult a doctor for safe and effective treatment of the pain experienced.

One of the analgesic drugs that are often consumed by the public is mefenamic acid. Mefenamic acid is one of the analgesic drugs commonly used by the public to treat mild to moderate pain (Rusnaeni et al. 2016). This drug belongs to the category of NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) and works by reducing inflammation and relieving pain. Although effective in overcoming pain, continuous mefenamic acid can cause various side effects, such as nausea, vomiting, drowsiness, visual disturbances, diarrhea, and blood clotting problems, such as thrombocytopenia, eosinophilia, and granulocytopenia. Understanding and using traditional medicine wisely can not only provide effective alternative treatments but can also be a way to preserve local

knowledge and wisdom passed down from generation to generation. In addition, traditional medicine is also often considered to have fewer side effects than modern medicines, making it an attractive choice for some people dealing with various health conditions.

A plant that has potential as a pain treatment is cinnamon (Cinnamomum burmanii). Cinnamon (Cinnamomum burmanii) is a potential pain treatment plant (Maharianingsih and Poruwati 2021). This plant is known for its active compounds with analgesic properties, namely the ability to relieve pain. Compounds such as coumarin, Canela aldehyde, and eugenol present in cinnamon have been studied to have pain-relieving and inflammatory effects. In addition, cinnamon also has antispasmodic properties that can help reduce muscle spasms and relieve cramps associated with pain. Therefore, extracts or essential oils from cinnamon are often used in traditional medicine to treat various types of pain, including muscle pain, joint pain, and menstrual pain.

Nonetheless, it is essential to consult a health care professional before using cinnamon as a pain treatment, especially if you have certain medical conditions or are taking other medications. Cinnamon is not only used as a kitchen spice but also as an ingredient in herbal cosmetics. It has analgesic, antibacterial, anti-inflammatory, antioxidant, antithrombotic, and antidiabetic properties.

This study aimed to explore the potential of cinnamon (Cinnamomum burmanii) as a natural analgesic remedy based on its active compound content, such as essential oils, cinnamaldehyde, tannins, calcium oxalate, flavonoids, triterpenoids, and saponins. Cinnamic acid compounds in the cinnamon act as antioxidants that are effective against free radicals prevent oxidative damage, and repair damage that has occurred, while eugenol compounds also have analgesic properties that help reduce pain. This research is expected to provide a deeper understanding of the mechanism of action of cinnamon in overcoming pain, as well as contribute to the development of natural analgesic drugs that are effective and safe for human health.

II. RESULT METHODS

This experimental study uses Post-Test Only Control Group Design to explore the antipyretic and analgesic effects of cinnamon (Cinnamomum verum). The tools used in this study included EDTA tubes, five cc syringes, three cc syringes, one cc syringes, digital thermometers, 100 ml measuring flasks, 10 ml measuring flasks, filter paper, molten paper, analytical scales, blenders, macerator vessels, rotary evaporators, test tubes, improved Neubauer counting chambers, and hemometers. The research materials needed include methanol, Brewer yeast, Normal Saline, chloroform, NA-CMC, Paracetamol, Cinnamon (Cinnamomum verum), Glacial acetic acid, aquadest, FeCl3, HCl, amyl alcohol, sulfuric acid, magnesium powder, zinc powder, and ammonia.

The processing process of Cinnamon (Cinnamomum verum) in this study began with collecting and washing clean using running water. After that, the cinnamon is drained and spread on the molten paper until the water is absorbed. Then, the cinnamon is weighed, and the material is dried in a drying cabinet. The weight of the dried material is then weighed again. Next, the dry material of Cinnamon (Cinnamomum verum) is ground into powder and forms simplisia ready for further research (Kosasih et al. 2019). Cinnamon Simplisia (Cinnamomum verum) weighed 200 grams each and then extracted using the maceration technique with 400 ml of 98% methanol solvent. Maceration is carried out for one week with occasional stirring regularly. The filtrate is then evaporated using a *rotary vacuum evaporator* with a temperature of 50oC until a paste extract is obtained and stored at 20oC (Vasanthakumar D et al. 2015). In phytochemical test research using a modification of the Farnsworth method consisting of the identification of phenols, steroids/triterpenoids, terpenoids, saponins, flavonoids, tannins, and alkaloids (Widowati et al. 2016, 2017, 2018).

In this study, antipyretic activity testing was carried out using the Yeast-induced method. The Brewer's Yeast solution is made by taking a 15% brewer yeast suspension and dissolving it in normal saline to form a suspension. The suspension is then dissolved with aquadest in a ratio of 20 grams of suspension to 100 ml of aquadest, resulting in a 20% brewer's yeast solution. This 20% brewer's yeast solution was induced in rats by subcutis injection using a dose of 10 ml per kilogram of body weight. The rats' body temperature measurements were taken before and 24 hours after induction using a digital thermometer inserted into the rectum to obtain an accurate body temperature. This method was used to measure the effectiveness of cinnamon (Cinnamomum verum) in overcoming fever induced by brewer's yeast solution in experimental rats (Saini and Singha 2012; Sivamurugan et al. 2016; Veronica et al. 2017). This study involved 25 mice that had been induced using the Yeast-Induced method. The mice were grouped into five experimental 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. Cinnamon extract (Cinnamomum verum)-1 (200 mg/kg body weight): Test animals were given Cinnamon extract (Cinnamomum verum) dose 0.5 ml/ kgBB after 24 hours of induction. Food and drink are provided ad libitum.

4. Cinnamon Extract (Cinnamomum verum)-2 (400 mg/kg body weight): Test animals were given a Cinnamon extract (Cinnamomum verum) dose of 1 ml/kgBB after 24 hours of induction. Food and drink are provided ad libitum.
5. Cinnamon Extract (Cinnamomum verum)-3 (600 mg/kg body weight): Test animals were given Cinnamon extract (Cinnamomum verum) 1.5 ml/kgBB after 24 hours of induction. Food and drink are provided ad libitum.

After being given methanol extract of cinnamon (Cinnamomum verum), paracetamol as standard, and Na-CMC as a control, body temperature measurements were taken every hour for 5 hours after treatment on rats. Next, the mice were dissected to take blood samples intracardiac with a three cc syringe equipped with a 23 G needle, and the blood samples were inserted into EDTA tubes. Before the blood draw, the rats were anesthetized using chloroform. The parameters measured were the body temperature of the mice measured rectally, and the average percentage decrease in mouse body temperature was calculated by dividing the difference in the average body temperature of the mice 24 hours after induction with the body temperature at a particular time after giving the tested sample, then the results multiplied by 100%. Data analysis was performed using IBM SPSS 25 software, including descriptive statistical analysis for phytochemical screening results, rat weight, writhing, and body temperature. Inferential statistical analyses such as one-way ANOVA or Kruskal-Wallis are used according to the data distribution tested for normality using Shapiro-Wilk. If the data is usually distributed, parametric statistical analysis is performed. At the same time, if it is abnormal, the data will be transformed, or alternative tests will be carried out using Kruskal-Wallis non-parametric statistical analysis.

III. RESULTS AND DISCUSSION

Table 1. Phytochemical Screening Results of Cinnamon Methanol Extract (Cinnamomum verum)

Phytochemicals	Reagents	Result
Alkaloid	Bouchardart	+
	Mayer	+
	Dragondroff	-
	Wagner	+
Saponin	Aquadest + Alcohol 96%	-
Flavonoid	FeCl3 5%	+
	Mug $_{(s)}$ + Hakal $_{(p)}$	-
	NaOH 10%	-
	H2SO4 $_{(p)}$	-
Tannin	FeCl3 1%	+
Steroids and Terpenoids	Salkowsky	-
	Liberman Bouchard	+

From the table data above, it can be seen that Cinnamon Methanol extract (Cinnamomum verum) contains several phytochemical compounds, including Alkaloids, Saponins, Flavonoids, Tannins, as well as Steroids and Terpenoids.

To homogenize all the mice used in this study, researchers measured the body weight of the mice used. Before comparing the body weight of the mice used in this study, the rats' weight data were analyzed for normality with Shapiro-Wilk. The results of the data normality analysis can be seen in the following table.

Table 2. shows the results of data normality analysis using the Shapiro-Wilk test on body weight parameters in various treatment groups. The test results were conducted to evaluate the data distribution from each group. The following is a narrative of the results of the data normality analysis in the table:

Data normality analysis was performed using the Shapiro-Wilk test against body weight parameters in different treatment groups. In the control group, a p-value of 0.854 indicates that the distribution of body weight data in the control group can be considered normal. The same thing happened in the standard treatment group with a p-value of 0.843, indicating that the distribution of weight data in the standard group was also normal. Furthermore, in the treatment group with cinnamon methanol extract (Cinnamomum verum)-I, a p-value of 0.862 indicates that the distribution of body weight data in the group can be considered normal. Similarly, the cinnamon methanol extract (Cinnamomum verum) -II and -III treatment groups had p-values of 0.834 and 0.832, respectively, indicating that the distribution of body weight data in both groups was also normal. Overall, the normality data analysis results showed that the distribution of body weight data in all treatment groups, including control and treatment with cinnamon methanol extract, could be considered normal based on the p-value criteria of the Shapiro-Wilk test.

Table 2. Data Normality Analysis with Shapiro-Wilk on the Initial Body

Parameter	Treatment Group	P Value	Data Distribution
Weight	Control	0.854	Normal
	Standard	0.843	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -I	0.862	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -II	0.834	Normal
	Methanol Extract of Cinnamon (Cinnamomum verum) -III	0.832	Normal

Table 3. Comparison of Rats' Initial Body Weight in the Entire Treatment Group

Treatment Group	Weight Loss (grams)	P Value
Control	184.10 ± 22.13	
Standard	182.34 ± 24.12	
Cinnamon Methanol Extract (Cinnamomum verum) -I	184.50 ± 23.35	0.755
Cinnamon Methanol Extract (Cinnamomum verum) -II	181.10 ± 20.11	
Methanol Extract of Cinnamon (Cinnamomum verum) -III	185.31 ± 20.38	

The data is displayed as Mean ± SD. The P value is obtained from ANOVA's One-way analysis.

Table 3. compares the initial body weight of rats in all treatment groups, with the data results expressed as Mean ± SD. The control group had an average body weight of 184.10 grams ± 22.13 grams, while the standard treatment group and cinnamon methanol extract (Cinnamomum verum) -I, -II, and -III had an initial body weight of rats ranging from 181.10 grams to 185.31 grams. The results of One Way-ANOVA analysis showed a p-value of 0.755, indicating no significant difference in the initial body weight of mice between the control group and the other treatment groups. These results indicated homogeneity of the mice's initial body weight across treatment groups, including those receiving cinnamon methanol extract (Cinnamomum verum).

Table 4. Analysis of Data Normality with Shapiro-Wilk on Writhing Quantity Parameter

Parameter	Treatment Group	P Value	Data Distribution
Number of Squirms	Control	0.854	Normal
	Standard	0.824	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -I	0.811	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -II	0.872	Normal
	Methanol Extract of Cinnamon (Cinnamomum verum) -III	0.828	Normal

Table 4. presents the results of data normality analysis using the Shapiro-Wilk test on the parameters of the amount of writhing in various treatment groups. Each treatment group, including the control, standard, and treatment groups with methanol extracts of cinnamon (Cinnamomum verum)-I, -II, and -III, was analyzed to evaluate the data distribution. The p values of the Shapiro-Wilk test for each treatment group showed that the writhing data in all groups were standard, with p values of 0.854, 0.824, 0.811, 0.872, and 0.828, respectively. These results indicate that the writhing data in all treatment groups can be ascribed to a normal distribution based on the p-value criteria obtained from the Shapiro-Wilk test.

Table 5. Comparison of *Writhing* in All Treatment Groups

Treatment Group	Jumlah Geliat (*Writhing*)	P Value
Control	10.12 ± 2.50a	
Standard	7.43 ± 2.56ab	
Cinnamon Methanol Extract (Cinnamomum verum) -I	9.33 ± 2.56a	0.004
Cinnamon Methanol Extract (Cinnamomum verum) -II	7.51 ± 2.12ab	
Methanol Extract of Cinnamon (Cinnamomum verum) -III	2.24± 1.2	

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 5. presents a comparison of the number of writhing in all treatment groups and the analysis results using the One Way ANOVA test. The data is displayed as Mean ± SD, and the p-value is obtained from ANOVA's Way analysis. These results showed a significant difference in wriggling between treatment groups. The average amount of gel in the control group was 10.12 ± 2.50.

In contrast, in the standard group and the treatment group with control cinnamon extract (Cinnamomum verum) -I, -II, and -III, each had an average amount of gel was 7.43 ± 2.56, 9.33 ± 2.56, 7.51 ± 2.12, and 2.24 ± 1.2, respectively. The p-value of the One Way-ANOVA test was 0.004, indicating a significant difference in the amount of writhing between the treatment groups. Thus, it can be concluded that 198cinnamon control198 extract (Cinnamomum verum) affected the amount of writhing in rats in this writing test, compared to the 198control and standard groups. Superscript on the data showed significant differences between treatment groups based on post-hoc tests.

Table 6. Shapiro-Wilk Data Normality Analysis of Haematological Parameters

Parameter	Treatment Group	P Value	Data Distribution
Haemoglobin (Hub)	Control	0.325	Normal
	Standard	0.515	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -I	0.753	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -II	0.355	Normal
	Methanol Extract of Cinnamon (Cinnamomum verum) -III	0.523	Normal
Eritrosit (RBC)	Control	0.331	Normal
	Standard	0.035	Abnormal
	Cinnamon Methanol Extract (Cinnamomum verum) -I	0.731	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -II	0.535	Normal
	Methanol Extract of Cinnamon (Cinnamomum verum) -III	0.536	Normal
Lukosit (WBC)	Control	0.923	Normal
	Standard	0.738	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -I	0.337	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -II	0.333	Normal
	Methanol Extract of Cinnamon (Cinnamomum verum) -III	0.530	Normal
Platelet (PLT)	Control	0.555	Normal
	Standard	0.733	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -I	0.375	Normal
	Cinnamon Methanol Extract (Cinnamomum verum) -II	0.530	Normal
	Methanol Extract of Cinnamon (Cinnamomum verum) -III	0.535	Normal

Table 6. displays the results of data normality analysis using the Shapiro-Wilk test on hematological parameters, including hemoglobin (Hb), erythrocytes (RBC), leukocytes (WBC), and platelets (PLT), in various treatment groups. Each treatment group, such as the control, standard, and treatment groups with methanol extracts of cinnamon (Cinnamomum verum) -I, -II, and -III, was analyzed to evaluate the data distribution. The p values of the Shapiro-Wilk test for each hematological parameter and treatment group indicate that the hematological data in all groups are normal or abnormal, depending on the type of parameter and the treatment group. With significant p-values ($p < 0.05$), some groups showed abnormalities, such as erythrocytes (RBCs) in the standard group. Meanwhile, other parameters such as hemoglobin (Hb), leukocytes (WBC), and platelets (PLT) showed normal data distribution in all treatment groups.

Table 7. 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	23.02 ± 3.00	7.59 (5.32)	7.65 ± 2.43a	757.50 ± 323.20
Standard	11.30 pm ± 2.42 pm	7.57 (3.94)	3.23 ± 2.02b	560.53 ± 355.54
Cinnamon Methanol Extract (Cinnamomum verum) -I	23.02 ± 2.43	7.35 (3.50)	5.35 ± 0.55 [a]	722.52 ± 97.52
Cinnamon Methanol Extract (Cinnamomum verum) -II	23.24 ± 3.42	7.33 (5.35)	5.09 ± 0.2 7[c]	757.02 ± 302.05
Methanol Extract of Cinnamon (Cinnamomum verum) -III	23.32 ± 0.52	7.25 (0.90)	3.32 ± 2.07b	533.55 ± 333.26
P Value	**0.504**	**0.448**	**0.004**	**0.504**

*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 7. presents a comparison of hematological parameters, including hemoglobin (Hb), erythrocytes (RBC), leukocytes (WBC), and platelets (PLT), in all treatment groups along with the results of statistical analysis using the One Way-ANOVA test. Data is displayed as Mean ± SD for Hb and Mean (CV%) for RBC, WBC, and PLT. The p-value is obtained from ANOVA's One Way analysis. The results showed no significant difference in hemoglobin parameters between treatment groups, with a p-value of 0.504. However, there were substantial differences in erythrocyte (RBC), leukocyte (WBC), and platelet (PLT) counts between the treatment groups, with p values being 0.448, 0.004, and 0.504, respectively. Superscript on the data showed significant differences between treatment groups based on post-hoc tests.

The results of the writhing test analysis showed that cinnamon extract (Cinnamomum verum) significantly affected the amount of wriggling in rats compared to the control group and the standard group. This indicates that cinnamon extract has potential as an effective analgesic or pain-relieving agent, significantly reducing the pain response of mice to stimuli administered in writhing trials. The group that received cinnamon extract showed a significant reduction in the number of rats, with lower values than the control group and the group that received the standard treatment. Cinnamon extract (Cinnamomum verum) contains several active compounds that can interact with the peripheral and central nervous systems, thus providing analgesic effects. Cinnamaldehyde: This compound is a significant component in cinnamon essential oil and has been found to have anti-inflammatory and analgesic properties. Eugenol: This compound is also in cinnamon and has anti-inflammatory potential and pain relief effects. Coumarin is another compound found in cinnamon and has anti-inflammatory potential. Flavonoids: This group of compounds has anti-inflammatory properties and may contribute to the analgesic impacts. These compounds can affect nerve pathways involved in pain perception. There may be interactions with pain receptors, reduction of inflammation, or modulation of pain transmission pathways in the nervous system. Combining these active compounds in cinnamon extract might provide a holistic analgesic effect.

The results of this study are supported by Hafid (2023), that concentrations of 1%, 2%, and 3% can provide the most effective analgetic and concentration effects, namely 3% with a percentage of 38.32%. Cinnamon bark extract with a concentration of 3% is rated as the most effective because it contains the most essential oil compounds. This essential oil consists of various active compounds, such as cinnamaldehyde, eugenol, and others, known to have analgesic or pain-relieving effects. With a high concentration, this extract can be more effective in reducing pain in rat experiments in writhing tests. The higher content of active compounds in the 3% extract can provide a more robust response to pain stimuli, so this extract is considered more effective than lower concentrations (Hafid and Farid 2023).

According to Maryo Juan's research in Meisya (2023), cinnamon bark extract had the most effective analgesic effect on rats at 224 mg per 200 grams of body weight. This analgesic effect is triggered by the eugenol compounds present in the extract. Eugenol can inhibit the production of inflammatory mediators in the COX-1 and COX-2 pathways and the production of leukotrienes derived from the lipoxygenase pathway. These pathways act as mediators that trigger pain. Therefore, eugenol in cinnamon extract effectively reduces pain by suppressing the inflammatory response (Meisya Salsabila 2023).

The decrease in vigorous activity in rats given cinnamon extract can indicate that the extract has potential as an analgesic or pain reliever (Carolin et al. 2023). The reduced activity response in mice suggests that they feel a lack or decrease in pain sensation in response to stimuli that usually cause intense writhing or movement. This suggests that cinnamon extract can relieve or reduce pain in mice, indicating a potentially similar effect in humans. Although the exact mechanism has not been ascertained, there may be active compounds in cinnamon extract that interact with the peripheral or central nervous system, resulting in analgesic effects. These interactions may occur through various pathways, including reduction of pain receptors, modulation of neurotransmitters involved in pain signal transmission, or even reduction of inflammation that can affect pain perception. However, to understand this mechanism more deeply, more research is needed to identify the compounds in cinnamon extract responsible for its analgesic effects and their mechanism of action in reducing pain.

CONCLUSION

Cinnamon extract (Cinnamomum verum) significantly affected the amount of vigor in rats, considerably reducing wriggling activity compared to the control and standard groups. The analgesic potential of cinnamon extract can be attributed to active compounds such as cinnamaldehyde, eugenol, coumarins, and flavonoids that interact with the nervous system.

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