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# ANALGESIC POTENTIAL OF ETHANOL EXTRACT OF KETAPANG LEAVES (*Terminalia catappa* L.) ON MICE USING THE HOTPLATE METHOD

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## ABSTRACT

**Background:** Pain is a sensory experience from tissue damage that can occur over a certain duration. Pain management is generally carried out by administering analgesic drugs. Ketapang leaves have potential as a natural analgesic alternative. **Objective:** To evaluate the analgesic activity of ketapang leaf extract in male white mice. **Methods:** A total of 15 mice were divided into five groups: 0.5% Na CMC as a negative group, a positive control asetil salisilat acid 500 mg/KgBW, and three treatment groups given sampel at doses of 300 mg/KgBW, 400 mg/KgBW, and 500 mg/KgBW. The analgesic test was conducted using the hot plate methog, and the mice's response to heat stimulus was observed for 60 minutes after oral suspension administration. **Results:** Extract at various doses significantly increased the latency period of the mice compared to the negative control group. The highest latency period was shown by the 500 mg/KgBW dose, which was 9.39 seconds. This suspected activity is due to the content of flavonoid, alkaloid, saponin, and steroid compounds, which may blockade of the cyclooxygenase pathway. **Conclusion:** The extract of ketapang leaves possesses analgesic percentages of 33%, 36%, and 55%, respectively. The most effective dose was 500 mg/KgBW, with an analgesic percentage of 55%.

## ABSTRAK

**Latar belakang:** Nyeri merupakan pengalaman sensoris akibat kerusakan jaringan yang dapat dialami dalam durasi tertentu. Penanganan nyeri umumnya dilakukan dengan pemberian obat analgesik. Daun ketapang (*Terminalia catappa* L.) berpotensi sebagai alternatif analgesik alami. **Tujuan:** mengevaluasi aktivitas analgesik ekstrak daun ketapang pada mencit putih jantan. **Metode:** Sebanyak 15 ekor mencit dibagi menjadi lima kelompok, yaitu kelompok kontrol negatif (CMC Na 0,5%), kontrol positif (Aspirin 500 mg/KgBB), serta tiga kelompok perlakuan yang diberi ekstrak etanol daun ketapang dengan dosis 300 mg/KgBB, 400 mg/KgBB, dan 500 mg/KgBB. Uji analgesik dilakukan dengan metode *hot plate*, dan respons terhadap rangsang diamati selama 60 menit setelah pemberian suspensi secara oral. **Hasil:** Pemberian ekstrak pada dengan variasi dosis secara signifikan meningkatkan waktu latensi

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mencit dibandingkan kelompok kontrol negatif. Waktu latensi tertinggi ditunjukkan oleh dosis 500 mg/KgBB yaitu sebesar 9,39 detik. Dugaan aktivitas ini diakarenakan kandungan senyawa flavonoid, alkaloid, saponin, dan steroid dengan berbagai mekanisme kerja memblokir jalur siklooksigenase. **Simpulan:** Ekstrak etanol daun ketapang pada ketiga dosis tersebut memiliki aktivitas analgesik dengan persentase daya analgesik secara berturut-turut sebesar 33%, 36%, dan 55%. Dosis yang paling efektif adalah 500 mg/KgBB dengan persentase daya analgesik sebesar 55%.

## INTRODUCTION

Pain is often a common symptom associated with many medical conditions. Pain is an unpleasant physical sensation caused by strong or potentially damaging stimuli, such as stubbing your toe or the pain of applying alcohol to a wound. Pain is a sensory and emotional experience associated with actual or potential tissue damage occurring within the body at a specific time (Yusuf et al., 2020). The causes of pain include tissue damage caused by chemical, mechanical, and physical (heat or electrical) stimuli.

To reduce pain, people generally use analgesic drugs. Analgesics are drugs that can eliminate and/or reduce pain without causing loss of consciousness. These drugs are used to help relieve pain, often intentionally or unintentionally, for example, when experiencing a headache or toothache. Many of the medications we take often contain analgesic or analgesic ingredients (Sari & Nayoan, 2023). Non-opioid analgesics mechanism directly by inhibiting the central nervous system enzymes that catalyze prostaglandin biosynthesis. Examples of non-opioid drugs include mefenamic acid, acetylsalicylic acid, acetaminophen, and ibuprofen (Dipiro, 2008).

Many attempts to treat various diseases using traditional and natural herbal remedies derived from plants obtained from the environment around the home have been carried out and have reached the stage of development and scientification of herbal medicine. Traditional or natural medicines are believed to be safer or non-toxic. This is not necessarily true, especially when herbal medicine is consumed together with prescription drugs, over-the-counter drugs, or mixed with other herbal medicines. The empirical use of kumis kucing (*Orthosiphon grandiflora*) and keji beling (*Strobilanthes crispus*) was common in the 1970s, used in families as a remedy for frequent urination, sirih hijau leaves (*Piper betle* L.) is believed to stop bleeding during nosebleeds with a simple application: the leaves are rolled up and inserted into the bleeding nostril. The use of these plants is evidence of a tradition of using plants as raw materials for medicines that began in the home environment. The use of these plants is greatly influenced by culture and ethnicity (Anugroho et al, 2024).

The plant used as a medicinal ingredient is the ketapang leaf. The contain compounds including alkaloids, flavonoids, saponins, quinones, and phenolics in

the leaves, fruit, and bark (Herli & Wardaniati, 2019). From these compounds, it is known that ketapang leaves have analgesic mechanism (Lee, 2019).

The novelty of this study is the use of the hot plate analgesic test method. The advantages of the hot plate method are consistent and uniform temperature control across the entire surface of the plate and a cut-off time that protects the test animals so that the risk of injury can be controlled (Hafizh et al., 2021). Based on this background, the researcher will conduct research related to testing the analgesic activity of *Terminalia catappa* L. leaf ethanol extract using the hot plate method. The results of this study are expected to provide information on ketapang leaf simplisia containing active compounds that can be used as traditional medicine or analgesic drugs.

## METHOD

### Extract Preparation

The extraction of ketapang leaves (*Terminalia catappa* L.) was carried out using the maceration method. The extract was prepared by weighing 100 grams of ketapang leaf (*Terminalia catappa* L.) and soaking it in 1000 ml of 70% ethanol solvent (1:10), then the container was tightly closed and left for three days, stirring occasionally. The macerate is then filtered using a funnel lined with filter paper, and the resulting filtrate is concentrated using a waterbath at 50°C until a thick ketapang leaf extract is obtained. The resulting product is then weighed and the extract yield is calculated (Depkes, 2000).

### Phytochemical Screening

#### Flavonoids

0.5 g of Ketapang leaf extract is added to 5 drops of HCl and magnesium powder (Mg). A positive result for the presence of flavonoid compounds is indicated by a color change to green, red, yellow, and purple (Hasan et al., 2022).

#### Alkaloids

0.5 g of Ketapang leaf extract was added to 5 drops of HCl in 3 different tubes. Tube A was added with 4 drops of Dragendorff reagent, tube B was added with 4 drops of Mayer reagent, and tube C was added with 4 drops of Wagner reagent. A positive reaction for alkaloids is indicated by the formation of an orange precipitate (Dragendorff), a white precipitate (Mayer), and a brown precipitate (Wagner) (Surahmaida et al., 2020).

#### Saponins

0.5g of ketapang leaf extract was reacted with distilled water, heated, and shaken. The presence of saponin compounds was indicated by the formation of foam (Hasan et al., 2022).

**Steroids**

0.5 g of ketapang leaf extract was reacted with 2 ml of ethyl acetate and Liebermann-Burchard reagent was added. A positive result for steroid compounds was indicated by a green color change (Hasan et al., 2022).

**Analgesic Test**

Test animals (mice) were adapted to the same cage and feed conditions for 7 days. Before the treatment, the mice were fasted for 8 hours but were still given water (ad libitum). They were then given negative control, positive control, and ketapang leaf ethanol extract treatments. Analgesic activity was tested at 15, 30, 45, and 60 minutes with a cut-off time of 15 seconds to observe the analgesic response after treatment. Analgesic testing was performed using the heat induction method with a hot plate at a temperature of 50-55°C. Then, the pedal was pressed to turn on the automatic stopwatch on the hot plate when the mice began to touch the hot plate and observed until the mice showed a pain response, indicated by licking their paws or jumping. The time of the pain response was recorded when the mice first licked their paws or jumped.

**Data Analisys**

The data obtained was the latency time of mice to heat stimuli from a hot plate, which was measured by licking the soles of their feet and jumping from each treatment group. The percentage of analgesic potency was calculated and presented in a bar chart. If the pain percentage showed a potency of 50% or more compared to the negative control group, it was considered effective as an analgesic (Keswara & Handayani, 2019). The calculation of the percentage of analgesic effect using the formula:

$$\% \text{ Analgesic effect} = \frac{\text{T-K}}{\text{C-K}} \times 100$$

Explanation:

T = Latency time of the positive control group or the ketapang leaf extract group

K = Latency time of the negative control group

C = Cut-off time (15 seconds)

**RESULT**

The determination of ketapang leaf plants showed that the samples used were confirmed to be *Terminalta catappa* L., also known as ketapang leaves. Organoleptic testing of ketapang leaf simplisia showed that the samples had a distinctive aroma, a slightly bitter taste, and a green powder color. Meanwhile, the organoleptic test results for ketapang leaf extract showed a thick texture, a blackish-green color, and a distinctive aroma.

**Table 1.** Results of Organoleptic Testing of Ketapang Leaf Simplisia

| Organoleptic | Material simplisia | Extract |
|---|---|---|
| Form | Powder | Thick |
| Color | Green | Dark Green |
| Smell | Specific aroma | Specific aroma |
| Taste | Slichtly bitter | Bitter |

The extraction of ketapang leaves yielded an extract weight of 14.95 grams with a yield of 14.95% w/w, from a powder weight of 100 grams. The yield is considered good if the value is more than 10%. The results of phytochemical screening tests of ketapang leaf ethanol extract were positive for flavonoids, alkaloids with Dragendroff, Mayer, and Wagner reagents, saponins, and steroids.

Table 2. Results of Phytochemical Screening Tests of Ketapang Leaf Extract

| Chemical Content | Reagen | Test Result |
|---|---|---|
| Flavonoids | Concentrated HCl + Mg Powder | Yellow color reaction |
| Alkaloid | Dragendorff | Orange precipitate reaction (+) |
| | Mayer | White precipitate reaction (+) |
| | Wagner | Brown precipitate reaction (+) |
| Saponin | Hot water shaken vigorously | Foam forms (+) |
| Steroid | Acetic acid 2 ml + Liebermann Burchard | Green color forms (+) |

The data represent that administration of the extract at various doses (300, 400, and 500 mg/kgBW) significantly increased the latency time of mice compared to the negative control group, with a clear dose-dependent effect pattern. The highest dose group (500 mg/kgBW) showed efficacy equivalent to the positive control group (acetylsalicylic acid 500 mg/kgBW). There was a consistent pattern of increased latency time with increasing observation time in all treatment groups.

**Table 3.** Average Latency Time of Mice in Each Group

| Treatment Group | Latency Time ± SD | | | | Average Latency Time ± SD |
|---|---|---|---|---|---|
| | 15th min | 30th min | 45th min | 60th min | |
| K(-) CMC Na 0,5% | 2,41 ± 0,14 | 3,35 ± 0,14 | 2,20 ± 0,62 | 1,75 ± 0,56 | 2,42 ± 0,26 |
| K (+) Asam asetil salisilat 500 mg/KgBB | 8,12 ± 2,35 | 8,81 ± 2,62 | 10,14 ± 2,83 | 11,32 ± 1,33 | 9,59 ± 0,66 |
| Dose I 300 mg/KgBB | 3,85 ± 0,55 | 5,34 ± 0,77 | 7,73 ± 0,41 | 9,23 ± 0,53 | 6,53± 0,15 |

| Treatment Group | Latency Time ± SD | | | | Average Latency Time ± SD |
|---|---|---|---|---|---|
| | 15th min | 30th min | 45th min | 60th min | |
| Dose II 400 mg/KgBB | 4,45 ± 0,06 | 5,39 ± 0,22 | 8,15 ± 0,61 | 9,93 ± 0,34 | 6,98 ± 0,23 |
| Dose III 500 mg/KgBB | 6,90 ± 0,73 | 9,10 ± 0,63 | 9,78 ± 0,87 | 11,79 ± 0,60 | 9,39 ± 0,12 |

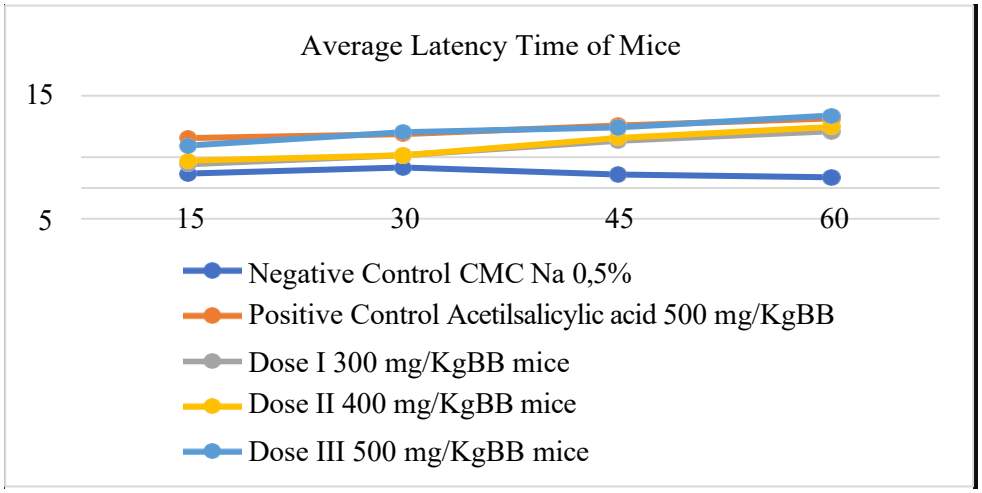


**Figure 1** Graph of The Average Latency Time of Mice In Each Group Given Treatment During 60 Minutes of Observation at 15-Minute Intervals

The results of the analgesic potency percentage obtained from the average latency time of mice were as follows: the positive control group with acetylsalicylic acid was 57%, the dose I group (300 mg/kgBW) was 33%, the dose II group (400 mg/kgBW) was 36%, and the last group, dose III (500 mg/kgBW), was 55%. These results indicate that the Ketapang leaf extract at dose III (500 mg/kgBW) has an analgesic effect that is almost the same as the positive control group treated with acetylsalicylic acid. An analgesic efficacy percentage of 50% or greater than the negative control group is considered effective as an analgesic (Keswara & Handayani, 2019).

**Tabel 3. Result of Analgesic Efficacy Percentage**

| Treatment Group | % Analgesic Effect |
|---|---|
| Positive control acetylsalicylic acid | 57 % |
| Dose I (300mg/KgBW mice) | 33 % |
| Dose II (400mg/KgBW mice) | 36 % |
| Dose III (500mg/KgBW mice) | 55 % |

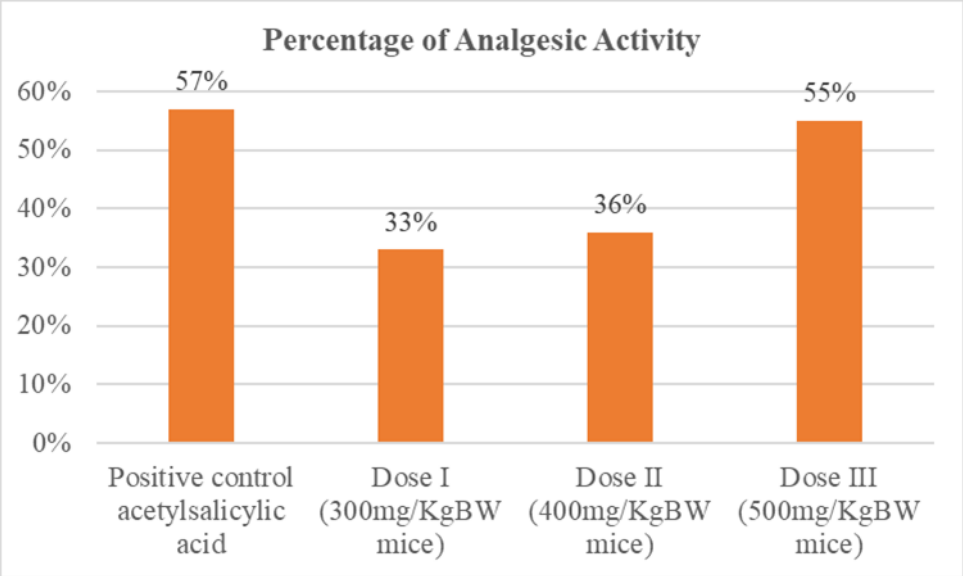


**Figure 2.** Graph of Analgesic Potency Percentage Results for Each Group

## DISCUSSION

The analgesic activity of ketapang leaf extract in mice was tested by measuring the latency time after administration of the test compound. Observations on the test animals were conducted every 15 minutes for up to 60 minutes. Observations in the negative control group treated with 0.5% CMC Na showed a low latency time with an average of 2.42 seconds; the results of this treatment did not show any analgesic effect. Based on these results, it was identified that 0.5% CMC Na does not contain active compounds that can affect pain in mice.

The positive control group of acetylsalicylic acid (500 mg/kg BW) showed an increased latency time with an average of 9.59 seconds at 15 minutes, approximately 8.12 seconds, to 11.32 seconds at 60 minutes. This increase in latency time indicates that acetylsalicylic acid is effective as an analgesic that can increase the ability of mice to tolerate pain. Acetylsalicylic acid was used as a positive control because it belongs to the non-steroidal anti-inflammatory drug (NSAID) class, which has strong analgesic activity (Rahmadanita et al., 2019). Acetylsalicylic acid can inhibit the cyclooxygenase enzyme, better known as COX-1 and COX-2, thereby inhibiting the biosynthesis of prostaglandins and thromboxanes from arachidonic acid. COX-1 is known to have a cytoprotective effect with a protective mechanism on the gastric mucosa. If COX-1 is inhibited, side effects will appear in the gastrointestinal tract. Meanwhile, if COX-2 is inhibited, prostaglandin production will decrease. Prostaglandins are mediators of pain, fever, and anti-inflammation. Therefore, if acetylsalicylic acid inhibits prostaglandins, it will cause a decrease in pain.

Dose I of ketapang leaf extract (300mg/kgBW) showed an increase in latency time from 3.85 seconds at minute 15 to 9.23 seconds at minute 60. At this

dose, an analgesic effect was already evident, although not as strong as the positive control. At dose II of ketapang leaf extract (400 mg/kg BW), the latency time at 15 minutes increased to 4.45 seconds and at 60 minutes to 9.93 seconds. The increase in latency time was slightly higher than that observed at dose I, indicating an increase in the analgesic effect. At dose III of ketapang leaf extract (500 mg/kg BW), the latency time at 15 minutes increased from 6.90 seconds to 11.79 seconds at 60 minutes. The highest dose of ketapang leaf extract showed a significant increase. Based on the data from the graph, it shows that ketapang leaf extract has an analgesic effect based on the dose given to mice. The higher the dose of extract given, the greater the increase in latency time, which indicates an increase in the ability of mice to tolerate pain.

The percentage of analgesic potency was calculated based on the average latency time of mice per treatment group. The analgesic potency percentage in the positive control group of acetylsalicylic acid was 57%, dose I of ketapang leaf ethanol extract (300 mg/kg BW mouse) was 33%, dose II of ketapang leaf ethanol extract (400 mg/kg BW mouse) was 36%, and dose III of ketapang leaf ethanol extract (500 mg/kg BW mouse) was 55%. This shows that the analgesic potency of dose III of ketapang leaf ethanol extract 500 mg/kg BW mouse has an analgesic effect that is almost the same when compared to the positive control of acetylsalicylic acid. A pain inhibition percentage of 50% or greater than the negative group is considered effective as an analgesic (Keswara & Handayanı, 2019) Dose III of 500 mg/kg body weight of ketapang leaf ethanol extrant was more effective than doses I and II because dose III had an active substance concentration that reached the effective dose, resulting in a stronger analgesic effect, whereas in doses I and II, the amount of active substance entering the body may not have been sufficient to reach the effective concentration.

In each treatment group observed for 60 minutes, there was an increase in latency time caused by the hot plate as a pain mediator. Based on these results, it shows that ketapang leaf ethanol extract can provide an analgesic effect by inhibiting pain (Lee, 2019). The body can adapt to pain stimuli because there are natural analgesics in the body called endorphins. This causes the body to experience an increase in defense to overcome pain (Wulan et al., 2017).

Ethyl alcohol extract of ketapang leaves contains flavonoids, alkaloids, saponins, and steroids. This is supported by previous research by Lee (2019). Ketapang leaf extract has the ability to relieve pain due to its flavonoid and alkaloid content, which work by inhibiting the cyclooxygenase enzyme in the arachidonic acid pathway, thereby inhibiting prostaglandin biosynthesis and reducing pain (Samiun et al., 2020). Furthermore, there are also saponin compounds that have a mechanism of action that inhibits the formation of prostaglandins, thereby reducing pain (Sentat et al., 2018) and also with the same mechanism of action, namely inhibiting the 5-lipoxygenase pathway and the COX-2 pathway that produces pain

mediators. This also occurs due to the presence of flavonoid and alkaloid compounds (Hesturini et al., 2017). Another compound found in Ketapang leaf extract is steroids, which work by stimulating the biosynthesis of lipodulin protein, which can inhibit the action of phospholipase enzymes, an enzyme involved in the release of arachidonic acid and its metabolites (prostaglandins, leukotrienes, prostacyclins, thromboxanes, glucocorticoids) that block the cyclooxygenase and lipoxygenase pathways (Keswara & Sri, 2019). Based on this explanation, ethanol extract of ketapang leaves does indeed contain bioactive compounds such as flavonoids, alkaloids, saponins, and steroids, and at doses 1 300mg/KgBW, dose II 400mg/KgBW, and dose III 500mg/KgBW, mice exhibited analgesic activity after testing.

## CONCLUSION

The 70% ethanol extract of ketapang leaves (Terminalia catappa L.) was found to have analgesic activity with an effective dose of 500 mg/kg body weight and an analgesic efficacy of 55%.

## RECOMMENDATIONS

Further research is needed on the development of analgesic testing methods such as chemical stimulation or tail-flick methods. Analgesic activity will need to be supplemented with blood testing and organ sampling to determine tissue damage and isolate compounds suspected of having analgesic activity.

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