

Analgesic And Antipyretic Activity Test Of Dill Leaf (*Anethum Graveolens*) Ethanol Extract

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Abstract

Fever is a common health condition, usually caused by infection, characterized by an increase in body temperature ($>37.5\text{ }^{\circ}\text{C}$) and often accompanied by pain. Dill leaves are known as medicinal plants with potential analgesic and antipyretic effects. This study aimed to evaluate the analgesic and antipyretic activity of ethanol extract of dill leaves in mice. Five groups of test animals were used, induced with 1% acetic acid to produce pain and 4% peptone to induce fever. After 30 minutes, the positive control group was given paracetamol, the negative control group received CMC Na, while the test groups treated with dill leaf extract at doses of 400, 500, and 600 mg/KgBW. Observations included activity assessment and body temperature reduction, with using one-way ANOVA. Findings indicated a significant difference in the analgesic test ($p = 0.00$; $p < 0.05$), while the antipyretic test showed no significant difference ($p = 0.575$; $p > 0.05$). Further Tukey testing confirmed that the positive control group did not differ the 600 mg/KgBW group. That dose is effective as an analgesic to paracetamol.

Keywords: Analgesic, Antipyretic, Dill Leaves

1. INTRODUCTION

Pain is an unpleasant sensory and emotional experience that arises from actual or potential tissue damage. It is a subjective sensation, and the pain threshold varies among individuals. The limit of pain caused by constant temperature occurs at $44\text{--}45\text{ }^{\circ}\text{C}$. Acute pain accounts for 37% of cases in developed countries, while in developing countries the rate is higher, reaching 41%. The use of analgesics is one of the approaches to relieve pain. Analgesics, commonly known as pain relievers, are substances that can reduce pain without affecting consciousness.

At present, fever remains one of the most common health problems throughout medical history. Fever occurs due to a normal response to an infection in the body, infection occurs when microorganisms in the form of viruses or bacteria enter the body. Fever may result from brain disorders or toxins that affect the body's regulatory center. The primary cause of fever is infectious disease, including infections by viruses, bacteria, rickettsia, chlamydia, and parasites. Fever is characterized by an increase in body temperature above $37.5\text{ }^{\circ}\text{C}$. The Indonesian Pediatric Association defines normal body temperature in children as ranging between $36.5\text{ }^{\circ}\text{C}$ and $37.5\text{ }^{\circ}\text{C}$. The harmful effects of fever in children include

dehydration, oxygen deficiency, neurological damage, and febrile convulsions. Proper management of fever is necessary to minimize these adverse effects.

One of the drugs that can be used as both an analgesic and antipyretic is paracetamol. “Antipyretic” literally means a drug that reduces fever without altering normal or biologically elevated body temperature. Its mechanism of action involves inhibiting the cyclooxygenase enzyme to prevent prostaglandin formation, which usually occurs in the central nervous system. The side effects of one of the antipyretics are gastrointestinal disorders, kidney dysfunction, cardiovascular system disorders, liver system disorders, and hematological system disorders.

The potential risk of side effects from synthetic chemical drugs has prompted people to turn to alternative treatments using natural ingredients, including medicinal plants. Dill leaves (*Anethum graveolens*) are one such traditional remedy. Dill leaves (*Anethum graveolens*) show significant therapeutic potential for various human diseases and can also function as a natural preservative in the food industry (Hadi et al., 2024). Fennel is increasingly recognized as an important culinary and medicinal plant and as a source of valuable bioactive compounds. Fennel is cultivated as a vegetable and a source of essential oil. This essential oil is used as a raw material in the telon oil industry to enhance the flavor and aroma of medicinal ingredients. Medicinally, fennel functions as an antispasmodic, carminative, diuretic, stimulant, and stomachic. This was added by Yousaf and Shahid (2020), who stated that *Anethum graveolens* has various pharmacological activities, including anticancer, gastroprotective, anti-inflammatory, antioxidant, antimicrobial, antispasmodic, antisecretory, and mucosal protective effects. Fennel is an herb that contains many specific compounds extracted from the roots, leaves, and flowers of the plant, including phenolic acids, α -phellandrene, triterpenes, flavonoids, and coumarins. These bioactive compounds contribute to its pharmacological activity. Furthermore, this plant has long been used to treat gastrointestinal ailments, reduce bad breath, and increase breast milk production. This plant is also considered a hypolipidemic agent. Dill leaves (*Anethum graveolens*), in the form of dill tablets, has been used as a hypolipidemic agent consisting of several important constituents, such as dill leaves (*Anethum graveolens*), chicory (*Cichorium intybus*), fumitory (*Fumaria parviflora*), and lime (*Citrus aurantifolia*).

Flavonoids, in addition to their anti-inflammatory effects, are also believed to provide analgesic and antipyretic benefits. Flavonoids and alkaloids are thought to inhibit the synthesis of prostaglandin E-2, a peripheral fever mediator, by blocking prostaglandin

synthesis, particularly endoperoxides. This assertion is corroborated by a study conducted by Wijaya and Lina (2023), which demonstrates that flavonoids and alkaloids manifest antipyretic activity by impeding prostaglandin biosynthesis through the suppression of cyclooxygenase-2 (COX-2) enzyme activity, consequently reducing body temperature. Research on the use of dill leaves (*Anethum graveolens*) as an alternative treatment to relieve pain and lower body temperature in mice has not yet been conducted either in vivo or in vitro. Based on this, the researcher carried out an analgesic and antipyretic activity test of dill leaves in male mice.

2. METHOD

The experiment evaluating the analgesic and fever-reducing properties was performed in March 2025 at the Natural Product and Pharmacology laboratories of the Pharmacy Program, Institute of Science and Health Technology RS dr. Soepraoen, located on Sudanco Supriyadi Street No. 22, Sukun District, Malang, East Java.

The equipment used included a rotary evaporator set (IKA RV10®), blender (Philips®), glass jars, horn spoons, porcelain dishes, watch glasses, glass rods (Pyrex®), syrup bottles, glass funnels (Pyrex®), beaker glass (Pyrex®), analytical balance (Ohaus®), thermometer (Onemed®), mori cloth, mortar and pestle, syringe (Onemed®), aluminum foil, and oral gavage.

The materials employed were dill leaf leaves, 96% ethanol (Onemed®), acetic acid solution, peptone, paracetamol® tablets, 1% Na-CMC, and distilled water. The sample used was the dill plant (*Anethum graveolens*), specifically its leaves. Samples were obtained from Jantur Hamlet, Gunungsari Village, Batu City, East Java, and were taxonomically identified at Materia Medica, Batu City.

2.1. Extraction Process

A total of 400 grams of powdered simplicia was soaked in 96% ethanol for seven days to extract its active components. After the soaking process, the mixture was separated using a mori cloth and glass funnel to collect the liquid portion. This liquid extract was then evaporated with a rotary evaporator until it formed a dense dill leaf extract. The final extract was weighed, and its yield percentage was computed in relation to the initial sample weight.

2.2. Preparation of samples

Preparation of 1% v/v Acetic Acid Solution

Glacial acetic acid (100%) 0.5 ml was added to 50 ml of distilled water.

Preparation of 4% Peptone Induction Solution

Two grams of peptone were weighed, dissolved in distilled water, stirred until homogeneous, and transferred into a 50 ml volumetric flask. The volume was adjusted with distilled water to the calibration mark.

Preparation of Negative Control Na-CMC Solution

One gram of Na-CMC was weighed and gradually added into 50 ml of hot distilled water (70 °C) while stirring until a transparent gel mass formed, then the volume was adjusted with distilled water to 20 ml.

Preparation of Paracetamol Suspension

Paracetamol suspension was prepared by weighing the drug according to dose conversion calculations, then dispersing it in 1% Na-CMC solution.

Analgesic Testing

In this experiment, 25 male Wistar mice weighing between 20–30 grams and aged approximately 6–8 weeks were employed to assess the pain-relieving effect of dill leaf extract. Before testing began, all animals were maintained for one week in controlled laboratory conditions to ensure adaptation, with access to a normal diet and water. The subjects were then grouped into five categories: one group received 1% Na-CMC as a neutral control, another was treated with 500 mg/kgBW paracetamol as a standard reference, and three additional groups were administered dill leaf extract at concentrations of 400, 500, and 600 mg/kgBW. After half an hour of treatment, a 1% acetic acid solution was injected into the peritoneal cavity to provoke a pain response. The number of abdominal constrictions was observed and recorded every five minutes over a 30-minute period, followed by the computation of inhibition percentages to determine the extract's analgesic capacity.

$$\% \text{ Analgesic Activity} = [100 - (P/K)] \times 100\%$$

Where:

P : Cumulative number of writhes in the treatment/drug group

K : Cumulative number of writhes in the control group

Antipyretic Testing

The antipyretic activity test was conducted on 25 male Wistar mice aged 6–8 weeks weighing 20–30 grams. The mice were acclimatized for one week and given standard feed and water. The animals were divided into five groups: group 1 received 1% Na-CMC solution as the negative control, group 2 received paracetamol suspension 500 mg/kg BW as the positive control, and groups 3, 4, and 5 were given extract suspensions at doses of 400 mg/kg BW, 500 mg/kg BW, and 600 mg/kg BW, respectively. Rectal temperatures were measured before induction. Then, 4% peptone solution was administered intramuscularly to induce fever. Thirty minutes later, rectal temperature was measured again, followed by sample administration according to group treatment. Rectal temperature measurements were repeated every 30 minutes for 120 minutes.

2.3. Data Analizes

The data on temperature reduction and writhing counts were analyzed using SPSS one-way ANOVA, followed by Tukey's test to identify group differences.

3. RESULTS AND DISCUSSION

This study was conducted to evaluate the analgesic and antipyretic activities of dill leaves using mice as test animals. The dill leaves were first processed through maceration extraction. Maceration is a method of isolating chemical compounds without heating, thereby maintaining the stability of heat-sensitive compounds throughout the extraction process. The maceration method is influenced by temperature, time, and the type of solvent used.

In this research, maceration was carried out using 96% ethanol as the solvent to obtain a concentrated extract, which is easier for further identification. Ethanol was chosen as the solvent because it is volatile, inexpensive, widely available, and relatively safe. The inhibitory effect produced by the 96% ethanol extract was greater compared to other solvents, as ethanol is highly polar and can extract compounds with higher polarity. Additionally, 96% ethanol penetrates plant cell walls more effectively than lower concentrations, thus producing a denser extract.

The extraction of dill leaves yielded 47.2 grams of extract, equivalent to a rendement percentage of 11.8% from 400 grams of simplicia, with a dark green viscous appearance. According to Husna, Effendi, & Maheshwari (2016), rendement calculation is used to determine the amount of compounds extracted by the solvent but does not identify their types.

A higher rendement value indicates a greater concentration of active compounds within the sample.

The obtained extract was then tested for analgesic and antipyretic activities in mice (*Mus musculus*). For the analgesic test, a chemical stimulus method was applied by inducing acetic acid and observing the writhing responses. This method is considered simple, practical, and sufficiently sensitive to detect compounds with even low analgesic activity. Acetic acid was chosen as an inducer because the pain it causes originates from acute local pain, namely the release of arachidonic acid from phospholipid tissue through the cyclooxygenase pathway, producing prostaglandin E2 (PGE2) and prostaglandin F2a (PGF2a) in the peritoneal fluid.

In the analgesic test, after the administration of the extract, the animals were injected intraperitoneally with 1% acetic acid as a pain inducer. Acetic acid causes local pain in the abdominal cavity that is easily observable. This pain occurs due to a decrease in abdominal pH, leading to tissue irritation. The damage activates phospholipase enzymes, resulting in prostaglandin formation and the sensation of pain. The tissue damage caused by acetic acid is temporary, and the stimulus is transmitted to the brain and interpreted as peripheral pain by C-type nerve fibers. Pain responses are displayed through writhing movements, with both hind legs retracted, the body stretched, and the abdomen touching the surface floor. In this chemical stimulation method, a sample is considered to have analgesic activity if it inhibits writhing by more than 50%. Inhibition above 70% indicates a strong analgesic effect, whereas less than 70% reflects a weak analgesic effect.

The percentage of writhing was calculated based on the number of responses recorded every 5 minutes over a 30-minute observation. The test results showing the reduction in writhing frequency by the analgesic activity of dill leaf extract are presented in the graph in Figure 1

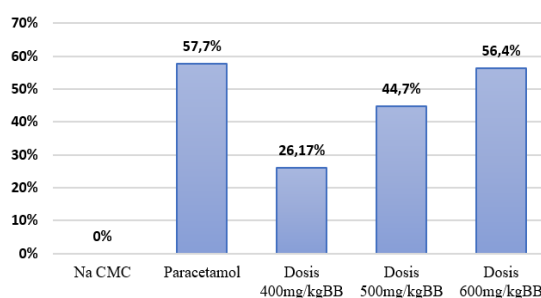


Figure 1. Graph of the analgesic activity test results

From the observations summarized in Figure 1, differences in pain relief responses are clearly visible among the various test groups. Mice given Na CMC as a negative control showed a response value of 0, confirming that this control substance has no analgesic properties. In contrast, the group given paracetamol achieved an analgesic percentage of 57.7%, reinforcing its proven role as a pain reliever. These results are consistent with the pharmacodynamic action of paracetamol, which involves inhibition of the cyclooxygenase (COX) pathway to suppress prostaglandin synthesis in the brain and spinal cord. This is in line with previous research stating that paracetamol is a non-narcotic analgesic that works by inhibiting prostaglandin synthesis, especially in the central nervous system (Khulun & Zukhruf, 2019, in Nurfadhila et al., 2023).

Meanwhile, treatment using ethanol extracts of dill leaves produced varying effects depending on the administered concentration. A dose of 400 mg/kgBW generated an analgesic response of 26.17%, indicating weak protection and minimal pain-relief potential since the percentage was below 50%. Increasing the dose to 500 mg/kgBW improved the effect to 44.7%, and a further increase to 600 mg/kgBW produced 56.4%. These outcomes demonstrate that the highest dose (600 mg/kgBW) displayed a measurable analgesic effect, with efficacy closest to that of paracetamol. The activity is believed to stem from the presence of flavonoid constituents in dill leaves, which may act to hinder COX enzyme activity and, consequently, limit the biosynthesis of prostaglandins responsible for pain sensation. This biochemical process resembles the mechanism by which paracetamol alleviates discomfort.

Table 1. Normality Test Results

		Kolmogorov-Smirnov ^a			Shapiro-Wilk		
Kelompok mencit		Statistic	df	Sig.	Statistic	df	Sig.
Jumlah geliat	Kontrol Negatif	.184	5	.200*	.978	5	.921
	Kontrol positif	.200	5	.200*	.935	5	.627
	Uji dosis 1	.207	5	.200*	.967	5	.853
	Uji dosis 2	.300	5	.161	.922	5	.543
	Uji dosis 5	.193	5	.200*	.984	5	.955

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

The statistical evaluation conducted through SPSS using a one-way ANOVA revealed that the analgesic test data displayed a significant variation, with a p-value of 0.00 ($p < 0.05$), confirming the presence of a real difference among the tested groups. A follow-up analysis using the Tukey method showed that the comparison between the positive control and the 600 mg/kgBW treatment group produced a p-value of 0.962 ($p > 0.05$). These findings indicate

that the 600 mg/kgBW dose exhibits an analgesic effect comparable to paracetamol, which functioned as the positive control and is widely acknowledged for its pain-relieving capability.

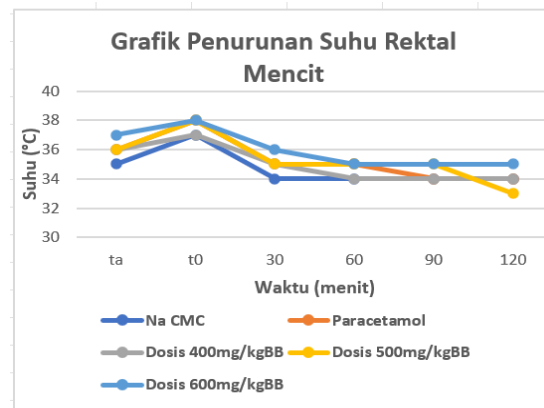


Figure 2. Graph of Rectal Temperature Reduction in Mice

In the antipyretic test, the procedure began with the administration of 4% peptone induction to the experimental mice. Based on the graph above, the average rectal temperature of the mice before treatment ranged between 35–37°C, and after intraperitoneal administration of 4% peptone it ranged between 36–37°C. This indicates that there was an increase in body temperature of the mice from the initial temperature to the post-induction temperature of about 1–2°C. This increase shows that the experimental animals experienced a fever condition. When a rise in body temperature of at least 0.6°C from the baseline occurs, the test animal is considered to have developed fever. Induction with peptone, which is a protein substance, functions as a pyrogen that can trigger an elevation in body temperature (fever) but is not toxic. This is consistent with the study by Yovita, Mercya et al. (2024), which found that peptone is an effective fever inducer in laboratory animals. Fever occurs due to the activity of pyrogens, which stimulate the synthesis of prostaglandins and thereby raise body temperature (Blomqvist & Engblom, 2018)

After 60 minutes of treatment, all groups showed a reduction in body temperature to varying degrees. In the group administered dill leaf extract, the decrease in body temperature demonstrated a direct correlation with the increase in dosage, meaning that the higher the dose, the stronger the antipyretic effect observed. This is consistent with previous research indicating that plant extracts possess antipyretic properties due to their content of secondary metabolites such as flavonoids, alkaloids, saponins, tanins, and steroids, which play a role in inhibiting prostaglandin synthesis (Amalia, 2022; Purwasih et al., 2023)

The active component contained in dill leaves, namely picronin, was able to exert an antipyretic effect. Picronin is an alkaloid compound that works in a manner similar to synthetic antipyretic drugs. In addition, dill leaves (*Anethum graveolens*) are known to contain various chemical compounds that offer numerous pharmacological effects and have the potential to be developed as natural remedies for treating human diseases due to their effectiveness and safety.

Dill leaves also contain alkaloids that act by inhibiting prostaglandin synthesis, which in turn prevents the onset of fever. Meanwhile, the positive control group that received paracetamol exhibited the most optimal reduction in body temperature. The antipyretic mechanism works by inhibiting the elevation of prostaglandin concentration in the central nervous system and cerebrospinal fluid, which is triggered by proteins from pyrogens that induce fever.

Table 2. ANOVA Results of Mice Temperature Reduction

ANOVA					
penurunansuhu	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1.254	4	.314	.742	.575
Within Groups	8.456	20	.423		
Total	9.710	24			

The statistical assessment of the antipyretic experiment yielded a p-value of 0.575, surpassing the 0.05 level, which implies that variations among the treatment groups were not significant. Even though every administered dose tended to lower the mice's body temperature, the reductions recorded did not demonstrate any significant difference when compared statistically.

4. CONCLUSION

The results of this study revealed a significant difference in the analgesic test ($p=0.00$; $p<0.05$), whereas the antipyretic test did not reveal a significant difference ($p = 0.575$; $p > 0.05$). in the antipyretic evaluation, the administration of dill leaves at doses of 400, 500 and 600 mg/kg BW caused a marked decrease in the rectal temperature of rats after 120 minutes of observation. Therefore, it can be concluded that dill leaves extract has analgesic properties, with the optimal effect observed at dose of 600 mg/kg BW. Futher analysis using Turkey's

test confirmed that the positive control group did not differ significantly from the 600 mg/kg BW group. This dose is as effective as paracetamol.

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