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RESEARCH ARTICLE OPEN ACCESS

ANALGESIC EFFECT OF EXTRACT ETHYL ACETATE OF MANGO LEAVES (mangifera indica L.) ON MALE MICE WITH ACETIC ACID INDUCTION

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ABSTRACT

Pain is an emotionally and sensory exhausting ordeal accompanied by painful physical injury. Mefenamic acid is one example of a substance that can be used to administer pain medications. On the other hand, side effects can occur with continuous and long-term use. The analgesic effect is provided by tannins, alkaloids, saponins, and flavonoids found in mango leaves (Mangifera Indica L.). This study aims to determine the analgesic effect of ethyl acetate extract of mango leaf (*Mangifera Indica* L.) in male mice induced by acetic acid 1 %. Experimental setting in a controlled environment with male mice randomly placed in one of five groups. Providing negative control (CMC Na), positive control (mefenamic acid 65 mg/kgBW), and EEADM (doses 100 mg/kgBW, 200 mg/kgBW, and 300 mg/kgBW) orally were used. Only 30 minutes remained. Next, 1% acetic acid is inserted intraperitoneally. After the first 30 minutes, check the squirrels every 5 minutes. Data on squirming and percentage of protection were subsequently examined using the ANOVA SPSS test, which had a significance rate of 95% ($p < 0.05$). Next, an LSD test was performed. In the results of the squirming test and the percent protection test using *the ANOVA test* , a significance value of < 0.05 was obtained, followed by the LSD test. The results of the LSD test by comparing the positive control of mefenamic acid 65 mg/kgBW with the EEADM dose of 300 mg/kgBW which showed that there was no difference in significance, this indicates that the EEADM dose of 300 mg/kgBW can be used as an analgesic. Based on the results of the study with a discussion that is known that the dose that has a faster reduction in pain is EEADM dose of mg/kgBW.

Keywords : Acetic acid; Analgesics; Ethyl acetate extract of mango leaves; Mice

INTRODUCTION

Pain involves the five senses and emotions, as well as being painful and potentially harmful to the body (Gultom *et al.,* 2023). Unpleasant sensations that cause pain, such as sharp pain, burning pain, electrocution, etc., can have a significant impact on the life of the sufferer (Gultom *et al.,* 2023). Pain is a common health problem that is experienced by an estimated 20% of the world's population each year, half of whom experience chronic pain (Hartono *et al.,* 2024). Based on the prevalence of back pain in Indonesia of 18% (Koesyanto, 2013). Osteoarthritis sufferers in Indonesia reach 20-60% (Indimeilia *et al.,* 2023). The incidence of rheumatic pain in Indonesia reaches 23.6-31.3%.

Meanwhile, in a study in the United States in 2012, 6.6 million adults had mild pain and 25.5 million experienced moderate to severe pain. (Setyaningsih et al., 2022)

A mechanism by which pain occurs is through four processes, namely the transduction process with the receipt of pain stimulus by the nociceptor which is then converted into an electrical implus. The term transmission describes a chain reaction that begins in the peripheral part and ends in the cerebral cortex after running through the dorsalis cornea of the spinal cord, thalamus, and spinothalamic tract. Modifications to the transmission of pain impulses may increase or decrease the intensity of those impulses; This process is known as modulation. Perception is the end result that can cause a feeling of pain (Nugraha *et al.,* 2023). Treatment of a pain medication can use medications such as analgesics (Sujana *et al.,* 2023). To relieve pain without the potential for addiction, many people opt for non-opioid analgesics such as paracetamol, aspirin, or mefenamic acid. Unfortunately, there are certain negative effects that can occur with long-term and continuous use. Such negative effects include gastrointestinal problems, hypersensitivity responses, and, in extreme cases, damage to the kidneys and liver. According to Kumontoy D *et al.* (2023), traditional medicinal plants can be defined as a combination of plant, animal, mineral, or extract preparations (galenica) or a combination of these elements used for therapy. In contrast to factory-produced medicines, traditional medicinal herbs are associated with fewer side effects (Sujana et al ., 2023). In the research of Eri Kurniawan and Susi endrawati, 2023 mango leaves *Mangifera indica* L.) contain flavonoids, phenols, tannins, terpenoids, quinones that have analgesic effects. In previous studies, mango leaves contain compounds in the form of tannins, flavonoids, saponins, triterpenoids, steroids, phenolics, alkaloids and mangiferins. (Anisa *et al.,* 2019)

Depending on the number or placement of the hydroxyl group, flavonoids of different types exhibit varying degrees of polarity. The formation of glycosides by flavonoids and sugars makes these compounds highly soluble in polar solvents. The glycon form of the flavonoids found in mango leaves has fewer polar characteristics, so it is able to dissolve polar and non-polar molecules, so that the use of ethyl acetate can be extracted more effectively (Dewa *et al.,* 2019). The choice of solvent using ethyl acetate is because there are secondary metabolite compounds contained in mango leaves (*Mangifera indica* L), namely flavonoids (Dewa *et al.,* 2019). This compound has extensive pharmacological activity, which has analgesic-like bioactivity (Kurrota Ayyun *et al.,* 2023). One of the ways flavonoids exert their analgesic effects is by inhibiting the enzyme cyclooxygenase. Reducing prostaglandin synthesis by inhibiting the enzyme cyclooxygenase can relieve pain. As a result of its action on the arachidonic acid metabolic pathway, the alkaloids inhibit an important step in the formation of prostaglandins. Steroids inhibit phospholipase, which prevents the formation of pain mediators, and triterpenoids, which can inhibit the oxidation of arachidonic acid, are two classes of saponin chemicals (Sa'adah *et al.,* 2022). Additionally, tannins can suppress the formation of prostaglandins by inhibiting COX enzymes (Tamimi *et al.,* 2020). The analgesic effect of mangiferin is attributed to mango leaves. Mango leaves are safe to eat because their effectiveness has been shown in scientific research (Kardiansyah & Endrawati, 2023).

Based on the above background description, the purpose of the study was to determine the analgesic effect of Ethyl acetate extract of mango leaves (*Mangifera indica* L) in male mice induced by acetic acid 1%.

MATERIAL AND METHOD

Research Place

The research was conducted at the Integrated Laboratory of dr. Soebandi University Jember.

Tools and Materials

The equipment used in this study is an analytical scale, *beaker glass* (*pyrex*), test tube (*pyrex*), 1 ml injection syringe, oral probe, oven, blender, filter cloth, droppipette, volume pipette, *stopwatch*, measuring cup (*pyrex),* petri dish measuring cup, *rotary evaporator*, permanent marker, gloves (*Safe Glove*), mortar and stamper. The ingredients used are ethyl acetate extract of mango leaves, CMC Na 0.5%, analgesic drugs (Mefenamic acid 500 mg), Acetic acid 1%, hydrochloric acid 2 N, *dragendorff reagents*, magnesium powder, concentrated hydrochloric acid, FeCl3 1%, *aquadest*.

Plant Determination

In the laboratory of the Jember State Polytechnic, researchers were able to positively identify the species of mango leaves by collecting leaves and other elements from the plant (*Mangifera Indica* L.) and belongs to the *Anacardiaceae family.* The results show that mango leaves belong to the species of (*Mangifera Indica* L) with the family *Anacardiaceae*

Sample Making of Mango Leaf Simplicia

The manufacture of simplicia goes through several stages including simplicia collection, wet sorting, washing, drying, dry sorting, smoothing or sieving, and packaging and storage (Seran *et al.,* 2023). The mango leaves used as much as 2 kg are then wet sorted and dried in direct sunlight, finally heating the process using an oven at 40°C until the leaves are dry. After the leaves are dry, they are then mashed using a 40 mesh sieve so that the mango leaf simplicia powder can be obtained (Seran *et al.,* 2023)

Manufacture of Ethyl Acetate Extract of Mango Leaves

The sample of mango leaf simplicia powder consisted of 200 g of powder, 1000 ml of ethyl acetate solvent, a tightly closed container, and stirring every six hours. The soaking process is carried out in a shady place for three days. The concentrated extract is made by combining the results of the macerated and re-immersion filtrate, then evaporated in a rotary evaporator at a temperature of 45 °C.(Islamiyati *et al.,* 2024)

Test Solution Manufacturing

The manufacture of a test solution of ethyl acetate extract of mango leaves for a dose of 100 mg/kgBB weighted as much as 100 mg, a dose of 200 mg/kgBB weighed as much as 200 mg, a dose of 300 mg/kgBB weighed as much as 300 mg. after that, dissolve each weighed extract into each CMC Na 0.5 % as much as 10 ml then grind until homogeneous (Dhinda Lara *et al.,* 2021).

Manufacture of 1% Acetic Acid Solution

1% acetic acid is made by diluting, as much as 1 ml of acetic acid is added to aquadest up to a volume of 100 ml (Prambudi, 2020).

Manufacturing of CMC Na 0.5% Solution

As much as 0.5 grams of CMC Na is weighed and added to a mortar filled with hot water little by little until it rises. Then grind and add little by little 100 ml of aquadest, stir until homogeneous (Dhinda Lara *et al.,* 2021).

Mefenamic Acid Suspension Manufacturing

Mefenamic acid tablets are weighed one by one and crushed in a mortar until smooth, then the fine mefenamic acid tablets are re-weighed as much as 84.253 mg after which they are dissolved into CMC Na 0.5% suspension as much as 10 ml. (Erni Anikasari *et al.,* 2022)

Induction of Acetic Acid

The acetic acid used is 1 % with a dose of 50 mg/kgBB [18] Acetic acid injection is carried out intraperitoneally. So that the administration of acetic acid is carried out in IP (intraperitoneal) so that it can be absorbed quickly and the pain produced in mice is long enough so that mice can be easily observed (Zulkifli & Eka Octaviany, 2019)

Analgesic Activity Test

Animal Preparation

This study used 25 mice that were previously adapted for 7 days, mice were divided into 5 treatment groups each consisting of 5 mice, namely in group 1 negative control (CMC Na), group 2 positive control (mefenamic acid 65 mg/kgBB) and EEADM group 3 (dose 100 mg/kgBB), EEADM group 4 (dose 200 mg/kgBB) and EEADM group 5 (dose 300 mg/kgBB). After that, mark the tail of the mice and weigh each mouse according to the treatment group. The mice that have been weighed are then given orally according to the treatment group and wait 30 minutes, after 30 minutes the mice are induced with acetic acid interperitoneally and observe the mice's squirming every 5 minutes for 60 minutes (Desiani *et al.,* 2022).

Examination of Tickling in Mice

Examination of squirrels in mice was carried out by observing the squirming of a mouse, namely by watching the rats bend over, their stomachs attached to each other, and their legs pulled back until their bellies touched the floor. We calculated how many times each mouse wriggled after 60 minutes of observation, which happened every 5 minutes. Then, we calculated the average number of squirrels in each group (Sa'adah *et al.,* 2022).

Percent Protection Against Mouse Tickling

The ability of the experimental substance to reduce pain in mice caused by acetic acid is known as percentage protection (Anwar *et al.,* 2019). To determine the analgesic effect, the following formula is used:

% protection = 100 - (P/K x 100)

Information:

P = Cumulative amount of squirming in analgesic drugs

K = Cumulative number of mice given CMC-Na (control)

After that, the results of the percentage protection of each mouse are summed, then

the average number of mice per group and the elementary school score are calculated. The data results of each treatment group were first tested for normality and homogeneity. It is said that the data is distributed normally and homogeneously if it shows a p-value (sig) value of >0.05. If the data is distributed normally and homogeneously, the test is continued using *the one way ANOVA* parametric test.If the p-value (sig) is <0.05, the test is continued to LSD to find out whether there are significant and significant differences between each treatment group. The LSD test uses the help of program software, namely SPSS 24.

Research Ethics

This research, ethics was carried out at dr. Soebandi University through the ethics committee at dr. Soebandi University Jember with no. 590/KEPK/UDS/XIII/2024

RESULTS AND DISCUSSION

Mango Leaf Ethyl Acetate Extraction

"The determination of plants was carried out at the Jember State Polytechnic with number 206/PL17.8/PG/2024. The determination results showed that the sample used was a mango leaf which has the Latin name *Mangifera indica* L with the family name *Anacardiaceae*. In this study, a maceration process was carried out and the next process was condensation using *a rotary evaporator* at a temperature of 45°C. The yield obtained is 7.06% (Table 1) In the results of the calculation of the extract yield, it is said to be very good if the value obtained is more than 10% (Saerang *et al.,* 2023).

Phytochemical Screening

Phytochemical screening of mango leaves contains tannins, alkaloids, saponins, flavonoids similar to this study and is seen in Table 2 of the results of phytochemical screening of ethyl acetate extract of mango leaves. This indicates that alkaloids have sediment, flavonoids form an orange color, tannins form a blue color, and saponins produce foam.

Mango Leaf Analgesic Test

This study used 25 mice, then the mice were divided into 5 groups that would receive treatment. Previously, mice were given orally according to the treatment group, namely in group 1 negative control (CMC Na), group 2 positive control (mefenamic acid 65 mg/kgBB) and EEADM group 3 (dose 100 mg/kgBB), EEADM group 4 (dose 200 mg/kgBB) and EEADM group 5 (dose 300 mg/kgBB). Then each group of mice was left alone for 30 minutes. After 30 minutes each treatment group was given intraperitoneally 1% acetic acid induction to induce pain. Observe the amount of squirming that appears every 5 minutes for 60 minutes. The results obtained were data on mice for 60 minutes. The results of the number of squirrels can be seen in Figure 1.

Based on figure 1 above, it can be seen that the average squirting of the CMC-Na group is 120.8 ± 10.98 squirting, the mefenamic acid group with a dose of 65 mg/kgBB is 50.6 ± 11.34 squirting, the mango leaf ethyl acetate extract group at a dose of 100 mg/kgBB produces 75 ± 7.58 squirrels, the 200 mg/kgBB dose produces 67.5 ± 4.61 squirrels, and the 300 mg/kgBB dose produces 49.5 ± 4.39 squirrels. The table above shows that EEADM at a dose of 300 mg/kgBB has the smallest amount of squirming compared to EEADM at doses of 100 mg/kgBB and 200 mg/kgBB. In Appendix 6, it is

shown that the results of the significance value are 0.585 > 0.05 which means that EEADM 300 mg/kgBB has no difference in significance value with the positive control of mefenamic acid 65 mg/kgBB.

Observation of the amount of squirming to determine analgesic activity occurred in mice. The acetic acid given to the mice aims to stimulate pain in mice so that it can cause squirming which is a sign that the mice are experiencing pain (Parmadi et al ., 2020). The mechanism of action of acetic acid is to trigger the release of *arachidonates* from a phospholipid network with the *Cyclooxygenase* pathway and produce *prostaglandin* E2 (PGE2), *prostaglandin* F2a (PGF2a). These prostaglandins cause a sense of pain (Triswanto *et al.,* 2018). Acetic acid indirectly works by pushing *prostaglandins* as a result of *cylooxygenase* into the *peritoneum* so that pain will occur in mice (Rahimah *et al.,* 2023). Based on the graph (Figure 2), it can be seen that the most wriggling occurred in the CMC Na negative control group of 0.5% because it had no analgesic effect and the least wriggling occurred in the mefenamic acid positive control group of 65 mg/kgBB which decreased at the 15th and 40th minute which was not much different from the EEADM dose of 300 mg/kgBB which decreased in the 40 to 60 minutes. This is because mefenamic acid 65 mg/kgBB has an action mechanism by inhibiting the enzyme cyclooxygenase so that it can reduce or decrease pain. While the content of EEADM at doses of 100 mg/kgBB, 200 mg/kgBB, 300 mg/kgBB contains alkaloids, flavonoids, tannins and saponins. However, the highest reduction in pain occurred at EEADM at a dose of 300 mg/kgBB. The decrease did not have a significant difference to mefenamic acid 65 mg/kgBB so that EEADM at a dose of 300 mg/kgBB had an analgesic effect close to the mefenamic acid group.

Percentage Protection Calculation

After obtaining the average of each treatment group. Then it is continued by calculating the percentage of analgesic protection. The percentage of protection is a test material to reduce mouse squirming caused by acetic acid. The percentage of protection of an analgesic is calculated by comparing the percentage of analgesic protection of the test compound group to the percentage of analgesic protection of the positive control group. In this study, the percentage of analgesic protection was calculated to determine the effectiveness of the analgesic EEADM dose (100, 200, 300 mg/kgBB). The results of the calculation of the protection percentage can be seen in table 3.

In the data table above, it can be seen that the data result of the percentage protection of EEADM 300 mg/kgBB is 58.83% and for the positive control group of mefenamic acid 65 mg/kgBB is 58.10%. The negative control of CMC Na 0.5 % had no effect on pain because it had no analgesic effect while in the use of mefenamic acid as a positive control is an analgesic drug that is commonly used in the community in treating pain with weak to moderate levels of pain and has been proven to have a strong analgesic effect compared to negative control, so mefenamic acid is used as a comparison to positive control.

In the results of the calculation obtained, the percentage of protection is known to be EEADM 300, which is 58.83% while Mefenamic Acid 65 mg/kgBB is 38.10 percent. The result of this protection percentage is higher than the research of Eri Kurniawan and Susi Endrawati (2023) who found that mango leaf extract (Mangifera Indica L) doses of 25 mg/kgBB, 50 mg/kgBB, and 100 mg/kgBB had analgesic effects of 22.14%, 22.46%, and 25.31%, respectively. This is different because the different solvents used in this

study are using ethyl acetate solvents which can affect several active compounds contained in it that can cause analgesic effects, one of which is flavonoids. The dosage used is also different, while in the previous study by Eri Kurniawan and Susi Endrawati (2023), 96% ethanol solvent was used.

The results of phytochemical screening showed that EEADM contains alkaloid compounds, flavonoids, tannins, and saponins. This is in line with the results of Kurota Ayyun's (2023) research which found that the analgesic effect of the ethyl acetate extract compound of mango leaves is accurate. The analgesic effects of flavonoids are due to their ability to inhibit the enzyme cyclooxygenase. Reducing prostaglandin synthesis, as is possible with cyclooxygenase enzyme inhibitors, can relieve pain. Although alkaloids are beneficial because they inhibit the cyclooxygenase pathway in the metabolism of arachidonic acid, which is an important step in the formation of prostaglandins. Analgesic saponin chemicals are categorized as steroids or triterpenoids (Sa'adah *et al.,* 2022). Tannins have the ability to inhibit pain with the mechanism of action of enzymes involved in inflammation, the most important of which are the arachidonic metabolic pathway, and the prostaglandin synthesis pathway (Tamimi *et al.,* 2020).

The results of the LSD test showed that the EEADM group of 300 mg/kgBB had a non-significant difference with the positive control of mefenamic acid 65 mg/kgBB with a significance value of 0.811. In these results, EEADM 300 mg/kgBB is a very effective extract for analgesic treatment. So that the determination of dose effectiveness can be selected from the difference between a treatment group and a positive control. The analgesic effect is proportional to the concentration of the extract. In contrast to the 65 mg/kgBB positive control, the EEADM doses of 100 and 200 mg/kgBB showed statistically significant changes. A significance value of 0.139, which is greater than the significance level of 0.05, indicates that there was no significant difference between EEADM doses of 100 mg/kgBB and 200 mg/kgBB; However, there was a significant difference with positive controls, which have been shown to have analgesic effects.

Because mefenamic acid is known to inhibit the enzyme cyclooxygenase through its involvement in prostaglandin synthesis, and because it is effective in reducing pain, the findings suggest that a positive control of 65 mg/kgBB of this compound provides 58.10 percent protection. One of the groups of pain mediators responsible for inflammation and tissue pain is prostaglandins. When the enzyme cyclooxygenase is inhibited, prostaglandin synthesis decreases, there by reducing discomfort (Dhinda Lara *et al.,* 2021). The percentage protection results of the EEADM group at a dose of 100 mg/kgBB of 37.91%, 200 mg/kgBB of 44.08%, 300 mg/kgBB of 58.83% which showed the best analgesic effect was the EEADM group of 300 mg/kgBB was a treatment group that had an analgesic effect almost equivalent to the positive control group of mefenamic acid of 65 mg/kgBB. The larger the dose used, the more the analgesic effect will be increased (Dhinda Lara *et al.,* 2021).

CONCLUSION

Based on the results of the study with a discussion that is known that EEADM is proven to be used as an analgesic with the doses used, namely EEADM doses of 100 mg/kgBB, 200 mg/kgBB, and 300 mg/kgBB and the dose that has a faster reduction in pain, namely EEADM doses of 300 mg/kgBB.

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TABLE AND FIGURE

Table 1 Yield Results of Mango Leaf Extract

Sample	Weight Simplification (grams)	Weight of the extract (grams)	Yields (%)
Mango Leaf	200 grams	14,13 grams	7,06 %

Table 2 Phytochemical Screening Results

Compound	Reagents	Research results	Literature results	Conclusion
Alkaloids	HCL and *Dragendroff*	There is a deposit	There are deposits (Winata *et al.*, 2023)	+

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Compound	Reagents	Research results	Literature results	Conclusion
Flavonoids	Mg Powder and HCL Concentrate	Formed red-orange color	Formed reddish-orange (Winata *et al.*, 2024)	+
Tannins	Water and FeCl3	Formed a blue-black color	Formed a blackish-blue color (Winata *et al.*, 2024)	+
Saponins	Hot water and HCl Concentrated	Foam	Foam arises (Winata *et al.*, 2024)	+

Table 3 Percent protection calculation

Group	% SD ± Protection
Mefenamic Acid 65 mg/kgBB	58.10 ± 7.58 [a]
EEADM 100 mg/kgBB	37.91 ± 6.27 [b]
EEADM 200 mg/kgBB	44.03 ± 3.82 [bc]
EEADM 300 mg/kgBB	58.83 ± 3.63 [a]

Remarks: the same letter shows no different significance or no different meaning p > 0.05, different letters show different significance or different meaning p > 0.05

Figure 1. Graph of the average amount of twitching in an hour

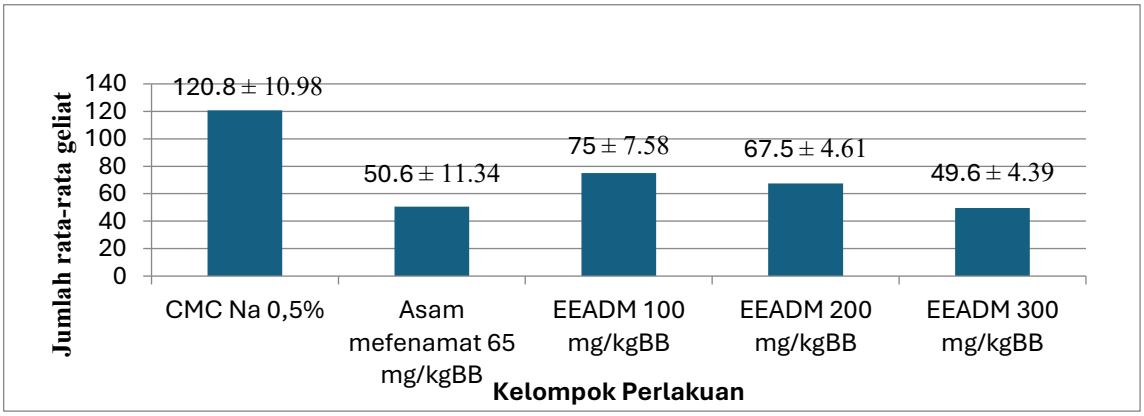

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Figure 2. Graph of the number of mice squirming every 5 minutes for 60 minutes