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Analgesic and Antipyretic Effects of Jamblang (Syzygium cumini (l). Skeel) Leaves Ethanol Extract

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ABSTRACT

Analgesic-antipyretic is a compound used to reduce pain and fever. This study aims to determine whether the ethanol extract of Syzygiumium cumini leaves has analgesic and antipyretic activity in mice (Mus musculus) induced by acetic acid and peptone. The method used was the Writhing method with acetic acid induction fanalgesiasic and the rectal temperature measurement method for antipyretic testing. This research was started by extracting Syzygium cumini (L.) Skeels leaves with 70% ethanol solvent by maceration. Syzygium cumini (L.) Skeels leaves extract was then tested in 5 groups the s, positive control growth as up given paracetamol for antipyretic testing and mefenamic acid for analgesic testing, negative control group (Na.CMC suspension), a dose of 6 mg/Kg, 9 mg/Kg and 12 mg/Kg of body weight. The results indicate that the ethanol extract Syzygiumium cumini leaves has analgesic and antipyretic activity at all treatment doses and the most effectivect is at a dose of 6 kg BW

Keywords *: Syzygium cumini (L) Skeels, Mice, Analgesic, Antipyretic*

INTRODUCTION

Analgesic-antipyretic is a compound that is used to reduce pain and fever due to various reasons. Analgesics are compounds that can reduce or eliminate pain without losing consciousness. While antipyretics are compounds that can reduce fever (Tjay& Rahardja, 2008).

One of the most widely used analgesic-antipyretic drugs is paracetamol. Paracetamol acts centrally by inhibiting the synthesis of prostaglandins and cyclooxygenase enzymes, as well as inhibiting signal transmission through the descending erotogenic system in the spinal cord (Boesoirie, *et al*., 2015). Paracetamol is one of the drugs that cause acute liver failure (ALF) in the United States and Europe (Tittarelli, *et al*., 2017). Paracetamol also has side effects, namely causing blood disorders and long-term use can cause liver damage (Tjay & Rahardja, 2008; Ozougwa&Eyo, 2015).

Many side effects caused by synthetic analgesic and antipyretic drugs have prompted various studies to develop medicinal products from natural ingredients that are safer. One of the plants commonly used by the community is *Syzygium cumini* (L.) Skeels. The methanolic extract of *Syzygium cumini (L.) Skeels leaves* contain secondary metabolites in the form of flavonoids, alkaloids, tannins, and terpenoids, which are used in medicine, among others, for anti-inflammatory, pain relief, and anti-fungal (Gafur, M. *et al.*, 2011). Flavonoids are

known to have antipyretic effects due to their ability to inhibit prostaglandin biosynthesis reactions through the mechanism of inhibition of the *cyclooxygenase-2 enzyme* (Samiun, A, *et al*., 2020). Flavonoids are known to have analgesic, anti-inflammatory, and antioxidant properties. These effects are related to the inhibition of NF-κB-dependent pro-inflammatory cytokines, VEGF, ICAM-1, STAT3, and activation of antioxidant transcription factor Nrf2 (Borghi, SM, *et al*., 2017; Chang *et al*., 2007). Previous research has proven that *Syzygium cumini* leaves can have an anti-inflammatory effect at a concentration of 80% (Wahyuni & Dewi, S.R, 2018).

MATERIAL AND METHODS

Materials and Instrument

The instruments and materials used include: a stirring rod, blender, canula, beaker (pirex®), rotary evaporator (IKA®RV10, Germany), stopwatch, syringe, test tube (pyrex®), digital thermometer (ThermoONE®), analytical balance, *Syzygium cumini* leaves, ethanol 70%, acetic acid solution 1%, aquadest, mefenamic acid, Na CMC 0.05%, peptone and paracetamol.

Extraction

Syzygium cumini (L.) Skeel leaf powder weighed as much as 400 grams, extracted by maceration using 70% ethanol. Remaceration was carried out to obtain a thick extract. The extract that has been obtained is continued by conducting a preliminary phytochemical screening (including the test for alkaloids, saponins, flavonoids, terpenoids, steroids, and tannins) to determine the content of bioactive compounds contained.

A test of polyphenols was carried out by taking 1 ml of extract was added with 1 % $FeCl_3$ reagent. The reaction is positive if a black or dark blue color is formed. For the flavonoid test, take 1 ml of Jamblang extract and add a few drops of 10% NaOH, the reaction will show a positive flavonoid if occurs specific color change. Test of alkaloids using Wagner's reagent and saponins is done using 1 ml of extract added to hot water and shaken. The positive reaction of saponins is when the foam is formed durable. Test for Terpenoids: Liebermann – Burchard Test: 1ml of the extract was treated with chloroform, and acetic anhydride and a few drops of H_2SO_4 were added and observed the formation of dark green color indicates of the presence of terpenoids.

Screening Test of Analgesic Activity in Mice (Mus musculus)

Twenty-five mice (grouped) into 5 groups, every 5 mice, before the treatment fasted for 8 hours. The positive control used mefenamic acid and the negative control used Na.CMC. Mice as test animals were given ethanol extract of *Syzygium cumini* (L) Skell leaves orally which was divided into 3 doses, namely 6 mg/30gBW, 9 mg/30gBW, and 12 mg/30gBW. After 30 minutes the treatment was continued with pain induction with 1%

acetic acid intraperintorially. The number of stretches was calculated in each treatment group. One stretch was marked by the mouse's legs being pulled forward and backward with the abdomen touching the floor. The stretches of each group were averaged and compared between the treatment and control groups.

Screening test of Antipyretic Activity in Mice (Mus musculus)

wenty-five mice (grouped) into 5 groups, 5 mice each, before the treatment fasted for 8 hours then the rectal temperature was measured initially using a digital thermometer, then 12.5% peptone was induced subcutaneously with a dose of 1 mL/BW after 30 minutes later, the rectal temperature was measured again, then for group I, Na.CMC was given as a negative control. Groups II, III, and IV were given ethanol extract of jamblang leaves at a dose of 6mg/30gBW,9mg/30gBW and 12 mg/30gBW and after 30 minutes later, the rectal temperature was measured again. Meanwhile, for group V, paracetamol suspension was given as a positive control.

RESULTS AND DISCUSSION

Based on the results of phytochemical screening on the ethanolic extract of jamblang leaves, flavonoids, alkaloids, saponins, tannins and terpenoids were detected. This is to the results of research conducted by Gafur, M, *et al.*(2011) which reported that extracts contain flavonoids, alkaloids, tannins, and terpenoids.

In this study, the writhing method was used, which is a chemical method used to test the analgesic activity of a compound. The mechanism of this method is to observe the writhing response that occurs due to pain stimulation by an irritant. This irritant was administered by injecting acetic acid as an intraperitoneal pain inducer in mice. The analgesic activity of this compound was determined based on the decrease in the frequency of stretching (Gawade, 2012). Acetic acid causes inflammation of the wall of the abdominal cavity, causing a writhing response in the form of contraction of abdominal muscles or stretching. The emergence of a writhing response will appear a maximum of 5-20 minutes after administration of acetic acid and usually writhing will reduce for one hour (Puente, *et al*, 2015).

Syzygium cumini(L.) Skeels leaves extract group (figure 1) showed a decrease in the amount of stretching at a dose of 6 mg/kg BW which indicated an analgesic effect from the administration of ethanol extract of *Syzygium cumini*(L.) Skeels leaves. The ability of the extract in overcoming pain is due to the presence of flavonoids. Flavonoids act as analgesics with the mechanism of action of inhibiting the cyclooxygenase enzyme. Through the inhibition of this cyclooxygenase enzyme, the production of prostaglandins as a pain mediator is also inhibited (Pandey, *et al.*, 2013).

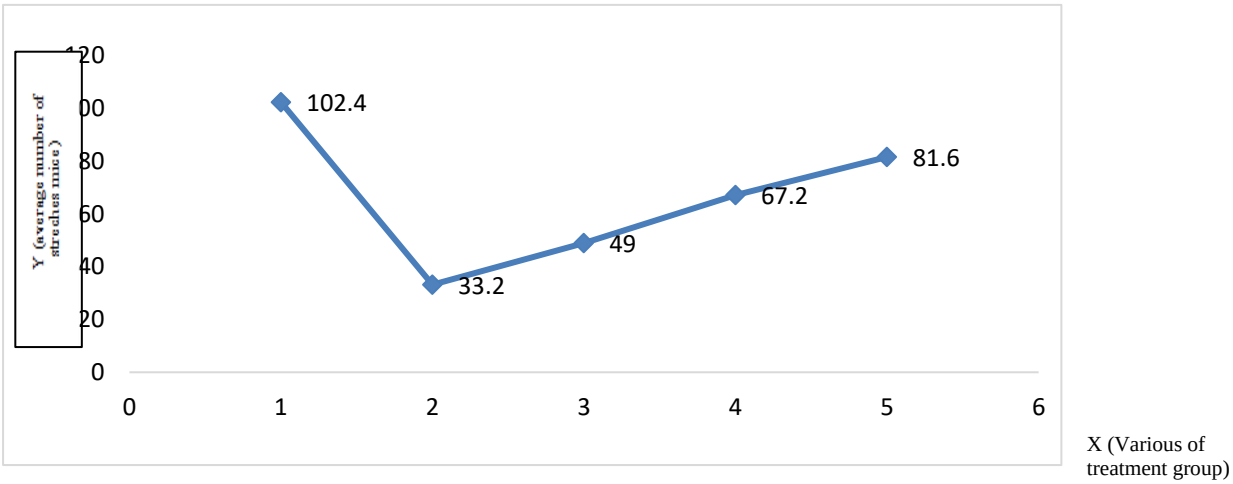

Figure 1. The stretches profile of mice in each group after treatment

Based on the results of the average amount of stretching (Figure 1), the percentage of analgesic effect was obtained (Figure 2). It can be seen that the dose of ethanol extract of *Syzygium cumini* leaves 6 mg/KgBW haors an analgesic effect of 61% which is almost close to the positive control (61%). It can be assumed that the extract dose of 6 mg/KgBW has a potential effect in relieving pain.

The results of statistical analysis using one-way ANOVA with a 95% confidence level showed a significant difference ($p>0.05$) between the positive control group and the 6, 9, and 12 mg/KgBW dose groups. This stated that the 6, 9, and 12 mg/KgBW doses had analgesic activity.

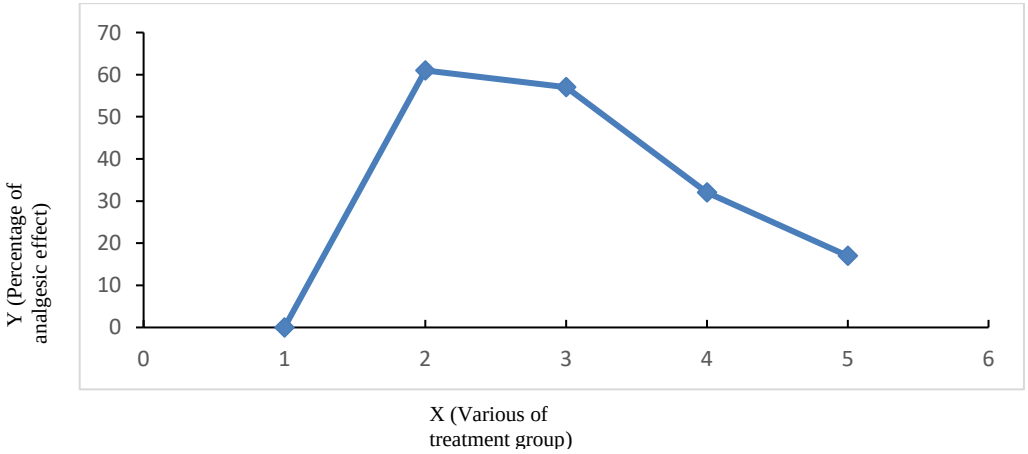

Figure 2. The percentage analgetic effect of mice in each group

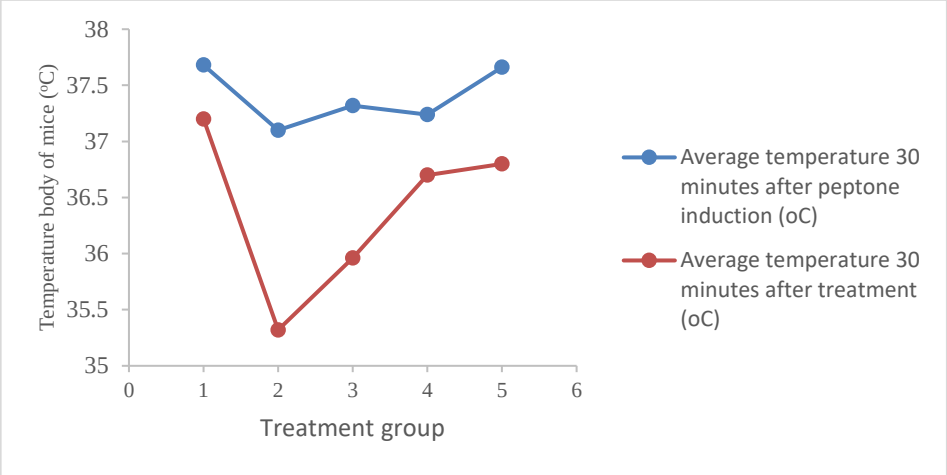

Figure 3. The temperature body profile of mice in each group after induction and treatment

The results of this study indicate that the decrease in temperature that occurs varies between treatment groups which are observed for 30 minutes (see figure 3). The negative control group was the group that experienced the smallest decrease in temperature compared to the other treatment groups.

The antipyretic activity caused by the ethanolic extract of *Syzygium cumini* leaves is most likely influenced by the content of the compounds present in it. Phytochemical analysis of the ethanol extract of jamblang leaves showed that the extract contain alkaloids, flavonoids, steroids, phenolics, and saponins (Gafur, M, *et al*., 2011). The active compounds of alkaloids, flavonoids, and saponins can potentially reduce fever (Hidayati, 2008). Flavonoid compounds have various kinds of bioactivity, one of which is antipyretic. Flavonoids affect cyclooxygenase (COX) inhibitors which function to trigger the formation of prostaglandins. It plays a role in the inflammatory process and increases body temperature. If prostaglandins are not inhibited, the body temperature will increase which will cause fever (Suwertayasa, 2013). Additionally, alkaloid compounds also have an antipyretic effect (Syifa, *et al*., 2011; Styawan&Budiman, 2015).

In addition to alkaloids and flavonoids, saponins are also compounds resulting from secondary metabolism in some plants that have surface tension-lowering, antipyretic, and diuretic activity (Maya, 2015). The action mechanism of flavonoid and alkaloid compounds as antipyretics by inhibiting the cyclooxygenase enzyme to prevent the formation of prostaglandins will be inhibited. Fever is a common response to inflammation and infection. The mechanism involves prostaglandin E_2 (PGE_2)-EP3 receptor signaling in the hypothalamus, which raises the set point of the hypothalamic thermostat for body temperature (Kita, *et al*., 2015). Saponins can decrease body temperature, possibility by inhibiting the bond between exogenous pyrogens that enter the body with their receptors (Suwertayasa, *et al*., 2013).

CONCLUSION

The ethanol extract of *Syzygium cumini* (L.) Skeels has an analgesic and antipyretic effects and the most optimal dose at 6 mg/kgBW.

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