Anti-inflmatory Activity Test of Ethanol Extract of Betel Leaves Green (Piper betle L.*) Against White Male Rats Carrageenan Induced*

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ABSTRACT

Background: *Inflammation is an attempt by the body to eliminate invading organisms, preparation for tissue preparation, and to eliminate irritants. The use of anti-inflammatory drugs can reduce the symptoms of inflammation. One of the natural ingredients as an alternative treatment that can be used as an anti-inflammatory is green betel leaves (Piper betle L.).*
Purpose: *To determine the most effective dose (100, 200, and 400 mg/kgBB) of green betel leaf ethanol extract (EEDSH) as an anti-inflammatory based on the volume of edema in the feet of white male rats induced by carrageenan.*
Methods : *The extract was made by maceration method using 70% ethanol solvent. The research used was a laboratory experiment using white male rats as test animals divided into 5 groups, namely negative control (CMC Na), positive control (Sodium Diclofenac), EEDSH treatment group with doses of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/KgBW with 1% carrageenan induction. Anti-inflammatory activity was analyzed by % anti-inflammatory power calculated based on measurements of edema volume. Analysis of research data using SPSS 25 using One Way ANOVA (p <0.05).*
Results: *The results of the percentage of anti-inflammatory power of positive control, EEDSH doses of 100 mg/KgBB, 200 mg/KgBB, and 400 mg/KgBB were 29.13%, 31.43%, 32.66%, 31.45%. The results of statistical testing obtained a value of 0.366 (P>0.05) which means there is no significant difference.*
Conclusions: *Ethanol extract of green betel leaves has anti-inflammatory activity against white male rats induced by carrageenan with the most effective dose being a dose of 100 mg/KgBW which has an anti-inflammatory effect that is not significantly different from the positive control*

Key words: *anti-inflammatory; green betel leaves; carrageenan; white male rat*

INTRODUCTION

Inflammation is the body's attempt to eliminate invading organisms, prepare to repair tissue, and eliminate irritants (Dewi & Wahyuni, 2017). The body's defense mechanism known as the inflammatory process allows the body to neutralize and destroy harmful substances at the site of damage and prepare conditions for tissue healing such as viruses, bacteria, antigens, and protozoa (Wijaya *et al.,* 2017). Inflammation occurs due to swelling (edema), redness, pain, changes in function, and heat (Dewi & Wahyuni, 2017). Stimuli that can cause the emergence of substances, namely histamine, prostaglandin, bradykinin and serotonin, can cause vasodilation and increased capil

permeability (Anggitasari *et al.,* 2023). In Indonesia, the prevalence of diseases involving inflammatory processes in Indonesia is very high, some of which are joint diseases of 7.3%, asthma 2.4%, tumors or cancer of 1.8%, and hepatitis of 1.2%. Among these diseases, tumors and cancer are the highest causes of death in Indonesia (Wicaksono *et al.,* 2021).

Anti-inflammatory drugs are divided into two groups, namely Steroidal Anti-inflammatory Drugs (SAID) and Nonsteroidal Anti-inflammatory Drugs (NSAID (Indri Ilmiyatul Hasanah, 2023). Side effects caused by the use of SAIDs and NSAIDs can be a major concern for users of anti-inflammatory drugs. These side effects can come from synthetic drugs so they can be a treatment. for example, drugs derived from plants (Pramitaningastuti, 2017).

It is known that 30.6% of herbal plants are owned by Indonesian people as alternative medicine. Green betel leaf (*Piper betle* L.) is one of the plants that has an effect as an anti-inflammatory (Anwa*r et al.,* 2015). Green betel leaf plants can be used as protection against pathogenic microbes, anti-inflammatory, antioxidant, analgesic, antimutagenic and carcinogenic which are flavonoid compounds (Pujaningsih *et al.,* 2021). The anti-inflammatory activity test of red betel leaf extract showed a decrease in inflammation of 77.58% for acetosal, 72.3% for 25 mg/kgBW extract, 85.60% for 50 mg/kgBW extract, and 81.02% for 100 mg/kgBW extract. The 50 mg/kgBW dose had the greatest anti-inflammatory effect of all doses tested (Fitriyani *et al.,* 2011).

Based on this background, further testing is needed to determine the anti-inflammatory activity of green betel leaf extract (Piper betle L.) so that the research can help find the benefits of betel leaf ethanol extract as an anti-inflammatory drug.

MATERIAL AND METHODS

Research ethics

All research procedures for anti-inflammatory activity testing on mice have been carried out through the Chairman of the Ethics Commission of Dr. Soebandi University with No. 275 / KEPK / UDS / IV / 2024 stating that the research has passed ethical standards.

Plant Determination

Before conducting research on green betel leaves (Piper betle L.), it is necessary to determine the plant to identify the type of plant and ensure the truth of the simplicia. Plant determination was carried out at the Biology Laboratory of the University of Science and Applied Technology, Ahmad Dahlan University, Yogyakarta.

Tools & Materials

The tools used in this study were analytical balance (sartorius), 1 cc syringe, test tube, test tube rack, beaker glass (pyrex), rotary evaporator (IKA® RV 10 basic), measuring cup (pyrex), stirring rod, marker, hol plate, mortar and stamper, sonde needle, mercury plethysmometer, animal drinking place, animal feeding place, cleaning tool, and mouse cage.

The materials used in the study were ethanol extract of green betel leaves (Piper betle L.) at doses of 100, 200, and 400 mg/kgBW, carrageenan, CMC Na, 50 mg sodium diclofenac, Mg powder, dragendorff reagent (chemical nitrate), concentrated HCL, FeCl3 reagent, and distilled wat

Green Betel Leaf Extraction

Making green betel leaf extract (Piper betle L.) in 70% ethanol solvent using maceration method. Dry powder of green betel leaf is weighed as much as 300 mg into a container, then added 70% solvent as much as 1.5 liters covered with aluminum foil. The maceration process is carried out for 3x24 hours, then stirred once every 24 hours for 5 minutes. The yield results are collected in a container and put into a Rotary evaporator until a thick extract is obtained and then the yield percentage is calculated (Andriani & Murtisiwi, 2018).

Screening of Green Betel Leaf Extract

Phytochemical screening of green betel leaf ethanol extract was carried out qualitatively using the color reaction method (test tube) aimed at determining the secondary metabolite compounds contained in green betel leaves by observing changes in color. Testing for tannin compounds was carried out by adding 8 drops of H2SO4 and dripping with 3 drops of dragendroff, the presence of tannin compounds was indicated by a change in orange color. Testing for alkaloid compounds was added with 8 drops of H2SO4 and dripping with 3 drops of dragendroff, indicated by showing orange deposits. Testing for flavonoid compounds was added with Mg powder and HCL, indicated by a change in orange to red color. And testing for saponin compounds was added with 2 drops of 1% FeCl3 reagent, indicated by a change in dark blue or solid black color (Putri & Madiun, 2023).

Anti-inflammatory Activity Test of Green Betel Leaf Ethanol Extract

25 mice were randomly divided into 5 groups, adapted for 7 days. Each animal was weighed first, then the weight of the mouse was recorded, weighed, the mouse was marked on the ankle and put into a large tube until the mark was visible, put the mouse's foot into a small tube to measure the initial fluid volume (Vo) using a plethysmometer. At the initial volume of the mouse's foot after being measured, then induced with 1% carrageenan as much as 0.1 ml intraplantarly in 5 treatment groups, then in the first hour the edema volume was re-measured after being induced. All groups were treated orally with a suspension of green betel leaf ethanol extract at doses of 100, 200, and 400 mg/kgBW. Then given 0.5% CMC Na as a negative control and 4.5 mg/kgBW sodium diclofenac as a positive control. Then the mice were left for 1 hour. The mouse's foot was then measured the volume of the foot after treatment (final volume) (Vt) was measured using a plethysmometer. Measurements were carried out for 360 minutes every 60 minutes. Each mouse was measured for the volume of edema on the soles of the mouse's feet. Observations lasted for 6 hours to obtain the maximum effect of reducing edema, then calculated, the percentage of edema inhibition, and anti-inflammatory power.

Analisis Data

The data collected in this study, namely the decrease in edema volume, can be calculated using the following formula:

$$\% \text{ edema} = \frac{Vt-V0}{V0} x\ 100\%$$

Note : Vt : volume of edema after carrageenan injection

V0 : initial foot volume before carrageenan induction

Then calculate the % edema inhibition using the following formula

$$\% \text{ inhibisi} = \frac{a-b}{a} \times 100\%$$

Note :

a : average percentage of edema in the negative control group after carrageenan injection

b : average percentage of edema in the treatment group after carrageenan injection

Then calculate the relationship between the percentage of edema and time and calculate AUC0-6 using the following formula :

$$AUC_{tn_{-1}}^{tn} = \frac{Vt_n + Vt_n}{2} (t_n - t_{n-1})$$

$$\% \text{ daya antiinflamasi} = \frac{AUC_k - AUC_p}{AUC_k} \times 100\%$$

Note :

Vtn-1 = Average edema volume at tn-1

Vtn = Average edema volume at tn

AUCk = Average edema volume curve versus time for negative control

AUCp = Average edema volume curve versus time for treatment

Analysis of research data using IBM SPSS 25. Normality test was conducted using the Shapiro-Wilk method, while homogeneity test was conducted using the Levene method. If the test results show a significance value ($p>0.05$), then the analysis can be continued with One Way Anova, with a confidence level of 95% and a value criterion ($p<0.05$) then all treatment groups have different anti-inflammatory activities, if a p value> 0.05 is obtained then all treatment groups are said to have anti-inflammatory activity.

RESULT AND DISCUSSION

Plant Determination

Before the extraction of green betel leaves (Piper betle L.) using 70% ethanol solvent, plant determination was carried out first. Plant determination in this study was carried out at the Biology Laboratory of the Faculty of Applied Science and Technology, Ahmad Dahlan University, Yogyakarta. The results of plant determination with letter number 150 / Lab.Bio / B / III / 2024 showed that green betel leaves (Piper betle L.) were the part used in this study.

Green Betel Leaf Extraction

In this study, green betel leaves (Piper betle L.) were extracted to produce ethanol extract using the maceration extraction technique. One of the easy-to-do cold extraction techniques is maceration extraction((Puspitasari & Prayogo, 2017)). According to the working principle of maceration, polar compounds will dissolve with polar solvents and non-polar compounds will dissolve with non-polar solvents. These solvents can penetrate cell walls and enter plant cells that contain active substances((Badaring et al., 2020)). Green betel leaf extraction was carried out using the maceration and remaceration methods using 70% ethanol solvent. Remaceration was carried out to obtain the results of a single maceration process, the re-maceration process can allow more compounds to remain in one maceration process (Septiana, 2018).

The yield percentage of the ethanol extract from green betel leaves (Piper betle L.) that has been thickened is then calculated. The yield percentage is the ratio between

the weight of the extract produced and the weight of the simplex (Alfauzi *et al.,* 2022). In this study, a yield percentage of 22.86% was produced, which can be seen in Table 1.

The percentage of yield is relative to the number of secondary metabolite compounds reacted, because the higher the yield, the more secondary metabolite compounds are extracted. The requirement for good yield is a yield of not less than 10% (Rusman *et al.,* 2023). In this study, the yield value of 22.86% was obtained, which can be said to be good because it has met the yield requirements. In previous studies, the extraction of green betel leaves obtained extraction results using 70% ethanol with a value of 22.8% (Haryanti *et al.,* 2020). If we look at the % yield results obtained in previous studies with the % yield results with the current study, they almost produce the same extraction value. This is because they use the same solvent and extraction method.

Phytochemical Screening of Ethanol Extract of Green Betel Leaves

Pada penelitian ini untuk mengidentifikasi senyawa yang terkandung pada tanaman yang akan diteliti perlu dilakukan skrining fitokimia terlebih dahulu. Skrining fitokimia dilakukan dengan pengujian pada warna menggunakan pereaksi warna. Hasil skrining fitokimia ekstrak etanol daun sirih hijau dapat dilihat pada tabel 2.

Based on table 3. above shows the image of the results of phytochemical screening obtained flavonoid and tannin compounds in the ethanol extract of green betel leaves. While the green betel leaf extract is negative for containing saponin and alkaloid compounds. This occurs because saponins and alkaloids have low concentrations so that they cannot be detected in the ethanol extract of green betel leaves. If the flavonoid compound changes to red or orange, it can be said to be a positive change. This occurs because the flavonoid compound is reduced with magnesium and concentrated HCL to maximize the red or orange color (Sulistyarini *et al.,* 2019). Flavonoids have several types, namely flavonols, flavanols, isoflavones, flavanonols, and flavans (Husna *et al.,* 2022). Flavonoid compounds are used as anti-inflammatories because they can inhibit the cyclooxygenase enzyme and can inhibit accumulation in the area, thus becoming anti-inflammatory (Manurung & Sumiwi, 2016). If the tannin compound changes color to blackish blue, it can be said to be positive. The change is caused by the reaction between the tannin compound group and the 10% FeCl reagent which causes the compound extract to change color to blackish blue. Tannin has anti-inflammatory properties that can reduce inflammation. Tannin compounds can also stimulate the formation of new cells and increase the formation of blood vessels that can help the healing process *(Meilina et al.,* 2022).

In previous research, results were obtained that it contains tannin, alkaloid, flavonoid and saponin compounds (Putri & Madiun, 2023). The difference between this study and previous studies is that no saponin and alkaloid compounds were found. Differences in research solvents, sampling and environmental factors in the study can affect different phytochemical screening results.

Measurement Data and Edema Percentage Results

Data obtained from measuring the volume of rat paw edema every hour in 5 groups, each treatment group consisted of 5 rats. The marked rat feet were then measured on a mercury plesthymometer to the limit mark. The initial volume of the rat feet (V0) was not given any treatment, then the rat feet were given carrageenan induction intraplantarly and waited for 1 hour, given carrageenan suspension treatment, sodium diclofenac suspension, and green betel leaf ethanol extract at a dose of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW orally. then record the decrease in edema in the ra

feet every hour for 60 minutes. Changes in the decrease in edema volume can be seen in Figure 1.

In the positive control group, data on the results of the decrease in edema volume were obtained at 1 hour after administration of sodium diclofenac suspension given orally. The decrease in edema volume continued at 1 hour to 6 hours, which was the last. Previous studies using sodium diclofenac as a positive control stated that sodium diclofenac has anti-inflammatory properties because it can stop or prevent carrageenan-induced edema. This is in accordance with the mechanism of action of sodium diclofenac which works by inhibiting the formation of prostaglandins which are inflammatory mediators.

Meanwhile, the negative control group given CMC Na suspension did not result in a decrease in edema that had been induced by carrageenan. This is because CMC Na has a neutral nature, meaning that CMC Na is only a solvent that has no effect. This occurs because the work of carrageenan processed by mice to eliminate inflammatory mediators is starting to be less effective as an inflammatory inducer((Hardani, 2015)). The increase in edema volume occurs due to carrageenan induction, resulting in the release of inflammatory mediators. When carrageenan is induced into the body of mice, the body of the mouse will consider carrageenan as a foreign substance, so that the body can release inflammatory mediators such as prostaglandins which can cause responses such as swelling, pain, and other responses. In this study, it can be said to be in accordance with the theory in previous studies, where the negative control group did not experience a decrease in edema volume in the legs of mice.

Table 3. The average results of the percentage of edema volume in the negative control group obtained the highest percentage among the other treatment groups with a value of 84.53% compared to the other treatment groups. The administration of EEDSH 100 mg/KgBB showed a decrease in edema volume that began in the second hour and gradually decreased in the sixth hour. The treatment group of EEDSH dose 100 mg/KgBB obtained an average value of 21.45%. In EEDSH dose 200 mg/KgBB there was an average decrease in edema volume of 17.40%, while in EEDSH dose 400 mg/KgBB the average result value was 19.75%. Administration of EEDSH 200 mg/KgBB obtained the largest decrease in edema volume compared to other doses. This study obtained greater results compared to previous studies, namely green betel leaf ethanol extract dose 200 mg/KgBB with a value of 16.35%.

On the Percentage of Inhibition Results on Rat Feet

The inhibition percentage can be used to determine the ability of sodium diclofenac as a positive control in inhibiting carrageenan-induced rat paw edema within 60 minutes. If the percentage value of edema volume is smaller, the percentage of drug inhibition is greater. The percentage of inhibition in each treatment group can be seen in table 4.

the average percentage of edema volume produced in the 100 mg/KgBB group of green betel leaf ethanol extract with a value of 74.63% is almost comparable to the positive control group, namely with a value of 72.31%. These results can be said that the percentage of inhibition of the group with a dose of 100 mg/KgBB has greater anti-inflammatory and edema inhibition activity compared to the ethanol extract of green betel leaves at doses of 200 mg/KgBB and 400 mg/KgBB with average values of 79.42% and 78.33%. In Andayani's study (2020) it was stated that it produced sodium diclofenac as a positive control with a value of 72.95%. While in this study, the percentage of inhibition in the positive control group was 72.31%. It can be said that the percentage of inhibition of previous studies with this study is almost similar to the results of previous studies. This

can show how much potential edema inhibitory activity is formed in the feet of mice. These results indicate the potential for edema inhibition activity in rat feet, this is because diclofenac sodium is included in the group of non-selective anti-inflammatory drugs that have anti-inflammatory effects and large working mechanisms. Non-selective inhibition of COX1 and COX2 against inflammatory processes has been proven as a non-steroidal anti-inflammatory drug clinically (Rahmi *et al.,* 2019).

AUC and DAI Percentage Data Results

The AUC (Area Under Curve) value is the area under the curve that represents the ratio of edema thickness for each mouse at each time unit((Rahajeng et al., 2020)). If the AUC value is greater, the anti-inflammatory activity of the drug in reducing edema volume is smaller (Ihsan *et al.,* 2021). The research results can be seen in table 5.

The average AUC0-6 in each group, the highest value was obtained by the negative control with a value of 2.10 and the smallest value was obtained by the EEDSH treatment group with a dose of 200 mg/KgBB of 1.42. EEDSH with a dose of 100 mg/KgBB has a similar value to EEDSH with a dose of 400 mg/KgBB. While in the positive control group, sodium diclofenac has a higher AUC value, namely 1.48 compared to EEDSH with a dose of 100 mg/KgBB and a dose of 400 mg/kgBB.

After the AUC calculation results can be continued with the calculation of the percentage of anti-inflammatory power (DAI) to determine the value of how much green betel leaf extract is effective in reducing edema in the feet of male rats. The average DAI percentage data can be seen in table 6.

The percentage of anti-inflammatory power can be obtained from the percentage of decrease in edema volume in the soles of the rat's feet. In the graph above, the highest percentage value of anti-inflammatory power was obtained in the EEDSH 200 mg/kgBW group with a value of 32.66%. Furthermore, the highest value was obtained by the EEDSH treatment group with a dose of 100 mg/KgBW with a value of 31.43% and the EEDSH treatment with a dose of 400 mg/KgBW with a value of 31.45%. While the smallest value was obtained by the positive control group with a DAI value of 29.13%.

The data from the DAI percentage that has been obtained is then subjected to One Way ANOVA statistical analysis using SPSS 25 which is used to see significant differences in the anti-inflammatory activity test in each treatment group. The series of One Way ANOVA tests begins with a normality test and a homogeneity test, with the requirement of normal data distribution and the same data variance, namely with a p value> 0.05. After these requirements are met, it can be continued with One Way Anova with a P value <0.05, then in all treatment groups the treatment has different anti-inflammatory effectiveness, if the P value> 0.05 then in all treatment groups it has the same anti-inflammatory effectiveness.

From the data normality test using Shapiro Wilk, it was found that the data was normally distributed with a value of P> 0.05. Furthermore, a homogeneity test using Levene obtained the result of 0.985 (p> 0.05) so it can be said that the data varies homogeneously. So it can be continued with the One Way ANOVA test, from the test it got a value of 0.328 or p> 0.05. It can be concluded that there is no difference between treatment groups one, two, and three with a positive control, namely sodium niclofenac, which means that all treatment groups have the same anti-inflammatory activity.

From these results it can be said that there is anti-inflammatory activity produced from the ethanol extract of green betel leaves, where it can be seen that green betel leaves contain flavonoid and tannin compounds. Compounds that play a role in stopping the release of anti-inflammatory mediators such as prostaglandins and histamine. Flavonoids have an anti-inflammatory working mechanism through COX1 an

lipoxygenase inhibitors, inhibiting white blood cells, and inhibiting histamine *(Audina et al.,* 2018). While tannin compounds can inhibit the release of antihistamines, which are inflammatory mediators. Histamine can also affect vasodilation, edema, and pain so that tannins can help reduce symptoms of inflammation (Arifah *et al.,* 2017).

CONCLUSION

Based on this study, it can be concluded that the yield of ethanol extract of green betel leaves is 22.86%. Green betel leaves in this study have flavonoid and tannin compounds. In the ethanol extract of green betel leaves at doses of 100 mg/KgBB, 200 mg/KgBB, and 400 mg/KgBB, it can reduce the volume of edema in the soles of the feet of mice.

The statistical test results obtained a value of 0.366, which means that all treatment groups were not significantly different. In this study, it can be concluded that all treatment groups have anti-inflammatory activity as indicated by the results of statistical tests. The most effective dose as an anti-inflammatory against white male rats induced by carrageenan obtained from the percentage data of anti-inflammatory power is at a dose of 100 mg/KgBW which was obtained in statistical tests.

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TABLE AND FIGURE

Table 1. Yield of Ethanol Extract of Betel Leaves

Sample	Sample Weight	Weight of Thick Extract (g)	Extract Yield (%)
Green betel Leaf	300	68,6	22,86

Table 2. Phytochemical Screening

Compound	Reagent	Changes That Occurred	Results
Tanin	H_2SO_4 + *Dragendrof*	There is a blue-black color change	+
Alkaloid	H_2SO_4 + *Dragendroff*	No sediment formed	-
Flavonoid	Mg + HCL	There is a red color change	+
Saponin	HCL + aquadest	There is no foam	-

information : (+) = there is a compound content
(-) = no compound content

Table 3. Average Percent of Edema in Rat Feet

Treatment group	Mean ± SE
Control Negatif (CMC Na)	84,53 ± 2,111
Control Positif (Na Diklofenak)	23,41 ± 1,755
EEDSH 100 mg/kgBB	21,45 ± 1,570
EEDSH 200 mg/kgBB	17,40 ± 0,625
EEDSH 400 mg/kgBB	19,73 ± 2,178

Table 4. Average Percentage of Inhibition

Treatment group	Mean % inhibition ± SE
Control Positif (Na Diklofenak)	72,31 ± 2,007
EEDSH 100 mg/kgBB	74,63 ± 1,859
EEDSH 200 mg/kgBB	79,42 ± 0,738
EEDSH 400 mg/kgBB	78,33 ± 2,576

Table 5. Mean AUC0-6

Treatment group	Mean AUC_{0-6} ± SE
Kontrol Negatif (CMC Na)	2,10 ± 0,334
Kontrol Positif (Natrium Doklofenak)	1,48 ± 0,031
EEDSH (100 mg/KgBB	1,44 ± 0,030
EEDSH (200 mg/KgBB)	1,42 ± 0,026
EEDSH (400 mg/KgBB)	1,44 ± 0,026

Table 6. Average Percentage of Anti-Inflammatory Power

Treatment group	Mean % DAI ± SE
Control Positif (Na Diklofenak)	29,13 ± 1,49
EEDSH 100 mg/kgBB	31,43 ± 1,45
EEDSH 200 mg/kgBB	32,66 ± 1,34
EEDSH 400 mg/kgBB	31,45 ± 1,24

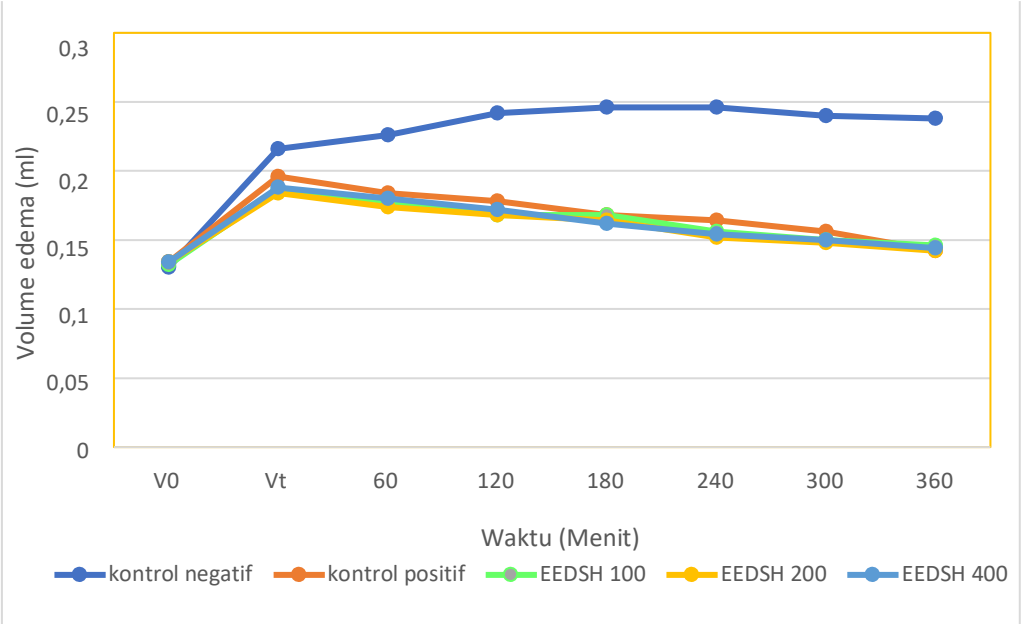

Figure 1. Average Edema Volume Measurement in Each Grooup