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The Anti-Inflammatory Potential of a Combination of *Centella asiatica* Leaf and *Caesalpinia sappan* Wood Ethanol Extracts

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ABSTRACT

Introduction: *Inflammation is the body's response to infection and tissue damage by sending the body's cells and defense molecules from the bloodstream to the location needed to eliminate the cause of the damage. Centella asiatica L. and Caesalpinia sappan L. contain tannin, phenolic, and flavonoid compounds that are effective as anti-inflammatories.* ***Objective***: *This study aimed to test the anti-inflammatory potency and effective dose of Centella asiatica leaves and Caesalpinia sappan wood, in male rats (Rattus norvegicus).* ***Methods***: *20 wistar rats were divided into five treatment groups: a negative control group (CMC Na 1%), a positive control group (Diclofenac Sodium), and three combination groups of a combination Centella asiatica leaves and Caesalpinia sappan wood ethanol extracts (EEPS) with dose variations of 250:375 mg/kgBW, 200:400 mg/kgBW, and 150:425 mg/kgBW. Intraplantar edema induction with lambda carrageenan. parameter measured of edema volume with a plethysmometer and edema thickness with a caliper.* ***Results***: *The combination of ethanol extract showed anti-inflammatory effects at all doses, which showed a decrease in the volume and thickness of edema at 180 to 360 minutes. At the dose 150:425 mg/kgBW shows total inflammatory response during the observation period is seen from the area under curve (AUC) value where AUC value of edema volume of 21.50 and an AUC value of edema thickness of 46.70. In addition, at this dose, percentage of anti-inflammatory activity (%DAI) where the value of %DAI at edema volume is 34% and %DAI at edema thickness is 22%.* ***Conclusion***: *The combination of ethanol extract has an anti-inflammatory effect, as well as an effective dose to reduce the volume and thickness of edema in male rats (Rattus norvegicus), namely a dose of 150:425 mg/kgBW.*

KEYWORDS: *Anti-inflammatory, ethanol extract, Centella asiatica L., Caesalpinia sappan L., carrageenan.*

INTRODUCTION

Inflammation is the body's response to infection and tissue damage by sending the body's cells and defense molecules from the bloodstream to the location needed to eliminate the cause of the damage. Inflammation is usually characterized by redness, swelling, heat, and pain (Kumar et al., 2020). Inflammation plays an important role in the healing process, but it can also play a role as a cause of various chronic diseases. These chronic diseases include diabetes mellitus, cancer, cardiovascular disease, and neurodegenerative diseases. If chronic inflammation is not treated properly it can lead

to tissue damage and exacerbation of these diseases (Setiawan & Ernawati, 2024).

One way to minimize an overreaction from inflammation is to use anti-inflammatory drugs, the most commonly used of which are steroids and nonsteroidal anti-inflammatory drugs (OAINS) (Sriarumtias et al., 2020). Nonsteroidal anti-inflammatory drugs are most commonly used for the treatment of acute and chronic pain. However, OAINS can cause various side effects such as gastrointestinal bleeding, kidney disorders, and cardiovascular disease (Acebo et al., 2018). Based on empirical experience, the plant that is thought to have an anti-inflammatory effect is *Centella asiatica* L. and *Caesalpinia sappan* L.

Centella asiatica L. and *Caesalpinia sappan* L. have opportunities as medicinal plants. The compound content in *Centella asiatica* leaves consists of alkaloids, saponins, tannins, flavonoids, terpenoids, and glycosides. Tannin and flavonoid compounds can function as antioxidants that can neutralize free radicals in the body (Sadik & Anwar, 2022). Meanwhile, *Caesalpinia sappan* wood contains alkaloids, flavonoids, tannins, brazilin, phenylpropane, and terpenoids. The highest antioxidant activity is obtained from the wood trunk which also has the highest content of phenolic compounds (Salsabila & Fuadi, 2023).

Previous research (Thirza et al., 2021) stated that the optimal dose of *Centella asiatica* leaf ethanol extract of 100 mg/kgBB had an anti-inflammatory effect in indomethacin-induced rats. In research (Widowati, 2011) states that Secang wood extract has strong antioxidant activity at a concentration of 6.25-100 µg/ml of 80.46-89.13%. Research that has been conducted by (Putri et al., 2021) that the antioxidant activity of IC_{50} in combination with ethanol extracts of secang wood and *Centella asiatica* produced the strongest activity with a ratio of 1:1 resulting in an IC50 value of 59.431 ppm with a strong category. The low IC_{50} value (50−100 ppm**)** is a good early indicator for screening that the substance has great potential to have anti-inflammatory effects (Legasari et al., 2023).

The role of antioxidants in relieving inflammation centers on the neutralization of *Reactive Oxygen Species* (ROS) By neutralizing free radicals, antioxidants directly reduce inflammatory triggers and inhibit pro-inflammatory signaling pathways (Zuo et al., 2019).

The combination of the active compounds of the Centella asiatica leaf and the sappan wood allows for complementary pathways to provide a more optimal anti-inflammatory effect, as the active compounds of the brazilian from the sappan wood (Puspitadewi, 2023)and the asiatic acid of the Centella leaf (Diniz et al., 2023) work on different but synergistic targets and mechanisms as anti-inflammatory. These two plants have complementary mechanisms of action to fight the two root causes of metabolic and chronic diseases:

inflammation and free radicals (Ikrima et al., 2020).

MATERIALS AND METHODS

Material

The materials used in this study were aluminum foil, carrageenan λ 1%, aquadest, *Centella asiatica* L leaves, *Caesalpinia sappan* L. wood, 96% ethanol, 1% Na-CMC, 50 mg diclofenac sodium. The instruments used are a maceration jar, rotary vacuum evaporator (ika™ rv 10 v), analytical balances (kern), Plethysmometer, and Vernier calipers.

Sample Processing

The samples used were the leaves of the *Centella asiatica* L. and *Caesalpinia sappan* L wood has been determined by the Plant Determination Unit of the UMI Makassar Pharmacognosy-Phytochemistry Laborato- ry. Both samples are cleaned with running water, then dried. Then the two samples were dried sorted and then simplisia were finely ground into a powder for further processing (F. Salsabila et al., 2025)

Extract Preparation

The extraction method used is maceration. Both plants weighed as much as 700 grams. Divorce leaves *Centella asiatica* L. macerated using 96% ethanol solvent in a 1:9 ratio for 4 days. Meanwhile, *Caesalpinia sappan* L. macerated using 96% ethanol in a 1:9 ratio for 5 days. Both plants are macerated at room temperature, stirring occasionally. Then filtering is carried out, the pulp of the two plants is remacerated. Furthermore, the obtained filtrate is vaporized at a temperature of 60°C at a speed of 100 rpm using *rotary evaporator* until a thick extract is obtained (Putri et al., 2022).

Preparation of Carrageenan λ 1%

Karagenan L weighed by 1 gram and then added 50 mL of 0.9% sodium chloride in a 100 mL measuring flask, homogenized and then sufficient volume (Maulana et al., 2020).

Preparation of Suspension Variations of Ethanol Extract of *Centella asiatica* Leaves and *Caesalpinia sappan* Wood

The ethanol extract suspension of *Centella asiatica* L. and *Caesalpinia sappan* L. wood is made by dissolving each extract into a 1% b/v Na-CMC suspension. For each variation the dosage of *Centella asiatica* L leaves is 250, 200, and 150 mg/kgBW, while *Caesalpinia sappan* wood is 375, 400, and 425 mg/kgBW. For each variation *Centella asiatica* leaf extract was weighed at 500 mg, 400 mg, and 300 mg, while *Caesalpinia sappan* wood extract was 750 mg, 800 mg, and 850 mg, respectively, then dissolved in 10 mL of 1% Na-CMC until homogeneous (Hasty Martha Wijaya, 2021)

Treatment and Testing of Anti-Inflammatory Effects in Test Animals

Anti-Inflammatory activity assay has received approval from the ethics committee (Number: UMI012503136). The test animals are adapted to a laboratory environment for a

week in a cleanly cage environment. Before being given treatment, the test animals were weighed and fasted for ±18 hours while still being given water (Suryandari et al., 2021). Initial volume (Vo) and initial thickness (Ko) measurements were taken on the soles of the rat's feet before induction. Then, each test animal was injected with carrageenan L 1% intraplantarly, and then the measurement of induction volume (Vi) and induction thickness (Ki) was carried out. After two hours, each group of test animals was given an oral treatment of test extract: group I (negative control) was given 1% CMC Na, group II (positive control) was given 50 mg of Diclofenac Sodium, group III, IV, V was given a combination suspension of *Centella asiatica* and *Caesalpinia sappan* wood ethanol extract (EEPS) with consecutive dose variations of 250:375 mg/kgBW, 200:400 mg/kgBW, and 150:425 mg/kgBW. The volume and thickness of the rat's legs were measured using a plestimometer and caliper every 30 minutes after the administration of the comparator or test extract for 6 hours (Ma & Zhang, 2015)

Data Analysis

The data obtained consisted of the volume and thickness of edema in the test animals. The data was statistically analyzed parametric for normality, followed by One-way ANOVA and Bonferroni post hoc test.

RESULTS AND DISCUSSION

The parameters in this study are the volume of edema measured with a plethysmometer and the thickness of edema with a caliper device. The plethysmometer works on the principle of measurement based on Archimedes' law, which is that an object inserted into a liquid substance will exert upward force or pressure. Meanwhile, the caliper device aims to measure the thickness of the edema on the soles of the feet of test animals (Azizah & Azhairi, 2017).

The data obtained from the measurement of the edema volume of rat legs using a plethysmometer every minute in each group was then averaged and tabulated in Table 1 and Figure 1.

Based on Table 1 and Figure 1 above, group I (CMC Na 1%) as a negative control experienced a considerable increase in edema volume over time. Group II (Diclofenac sodium) and combination extract group (EEPS) with different dosage variations had the same trend, namely an increase in edema volume up to 150 minutes and a decrease in edema volume from 180 minutes to 360 minutes, which showed effectiveness as an anti-inflammatory.

Data obtained from measuring the edema thickness of rat legs using calipers every minute in each group were then averaged and tabulated in Table 2 and Figure 2.

Based on Table 2 and Figure 2 above, it shows that group I (CMC Na 1% b/v) as a negative control experienced a significant increase in edema thickness over time. Group II (Diclofenac Sodium) and combination extract group (EEPS) with different dosage variations have the same trend, namely an

Table 1. Average measurement results of edema volume (mm^3)

Treatment	Vo	Vi	Average Edema Volume After Treatment (Minutes) ±SD						
			30	60	120	180	240	300	360
Group I CMC Na 1%b/v	1.02± 0.04	1.15± 0.08	1.45± 0.07	1.72± 0.14	2.21± 0.07	2.89± 0.06	3.41± 0.19	3.88± 0.27	4.38± 0.40
Group II Diclofenac sodium	1.04± 0.05	1.14± 0.10	1.21± 0.08	1.56± 0.06	1.98± 0.43	2.25± 0.12	1.98± 0.08	1.85± 0.17	1.65± 0.03
Group III EEPS 250:375 mg/kgBW	1.05± 0.10	1.16± 0.10	1.39± 0.17	1.69± 0,27	2.09± 0.13	2.4± 0.34	2.18± 0.18	2.01± 0.09	1.87± 0.10
Group IV EEPS 200:400 mg/kgBW	1.03± 0.03	1.11± 0.03	1.29± 0.13	1.64± 0.15	2.05± 0.15	2.37± 0.13	2.12± 0.16	1.96± 0,06	1.81± 0.04
Group V EEPS 150:425 mg/kgBW	1.06± 0.05	1.12± 0.03	1.25± 0.06	1.58± 0.19	2.03± 0.19	2.33± 0.03	2.05± 0.14	2.9± 0.03	2.76± 0.04

V_0 : Initial edema volume
Vi : Induced edema volume

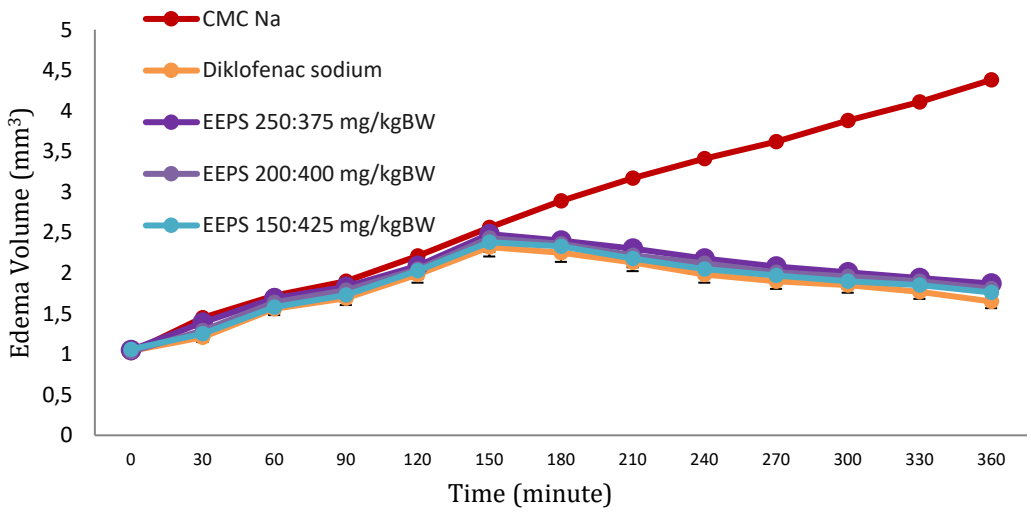

Figure 1. Average measurement results of edema volume (mm^3)

increase in edema thickness up to 150 minutes and a decrease in edema thickness from 180 minutes to 360 minutes. Overall, both in terms of measurement of edema volume and edema thickness, the administration of EEPS showed an anti-inflammatory effect, with effectiveness dependent on the dose.

From the results of the measurements that have been carried out (Tables 1 and 2), quantitative data is then made in the form of Area Under Curve (AUC) ($AUC=\int_{t0}^{t\ end}$ Volume/edema (t) dt).

AUC is a value that describes the area under the curve obtained from a graph of the relationship between the average inflammatory volume or thickness and the time of observation. The smaller the AUC value, the lower the volume/thickness of the inflammation and/or the shorter duration, which indicates the stronger the antiinflamato-

Table 2. Average measurement results of edema thickness (mm)

Treatment	T0	Ti	Average edema thickness after treatment (minutes) ±SD						
			30	60	120	180	240	300	360
Group I CMC Na 1%	2.06± 0.14	3.69± 0.92	3.78± 1.61	4.38± 1.55	4.95± 1.07	5.38± 1.05	5.83± 0.83	6.14± 1.00	6.43± 0.83
Group II Diclofenac sodium	2.69± 0.15	3.58± 0.52	3.64± 1.23	4.09± 1.41	4.84± 1.01	4.62± 1.17	4.04± 0.61	3.49± 0.48	2.88± 0.20
Group III EEPS 250:375 mg/KgBW	2.53± 0.29	3.86± 1.41	3.92± 1.64	4.42± 1.85	5.01± 0.93	5.05± 0.38	4.52± 0.47	3.99± 0.46	3.51± 0.44
Group IV EEPS 200:400 mg/KgBW	2.58± 0.38	3.8± 1.28	3.77± 1.62	4.39± 1.63	4.98± 0.80	4.88± 0.47	4.38± 0.61	3.8± 1.03	3.28± 0.96
Group V EEPS 150:425 mg/KgBW	2.65± 0.21	3.69± 0.99	3.7± 1.44	4.2± 1.24	4.86± 0.67	4.73± 0.40	4.22± 0.37	3.69± 0.68	3.15± 0.25

T_0 : Initial edema thickness
To : : Induced edema thickness

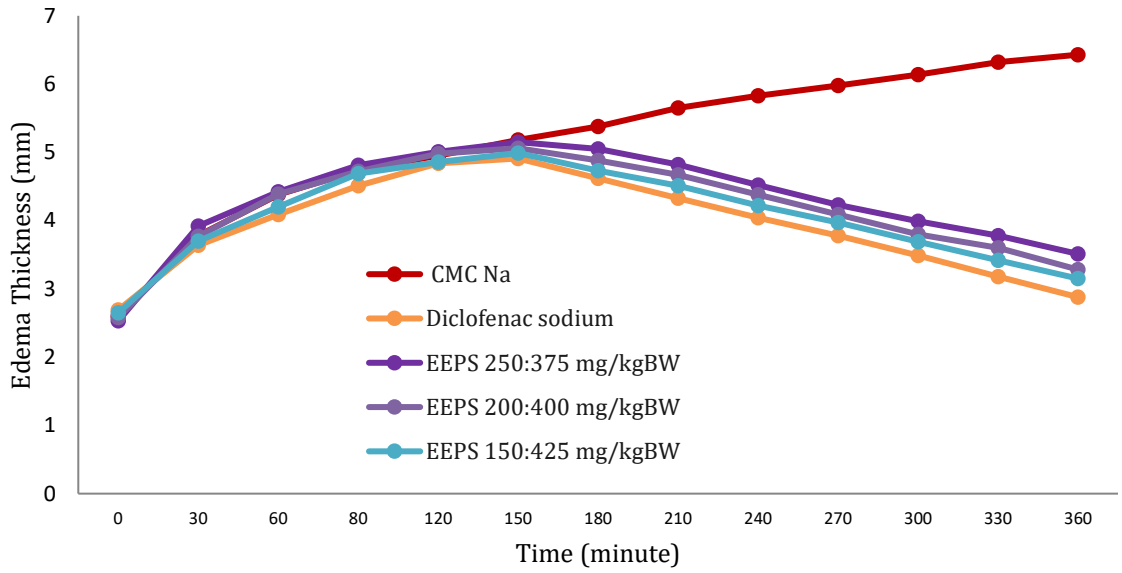

Figure 2. Average measurement results of edema thickness (mm)

ry activity of the test compound. The greater the AUC value, meaning the higher the volume/thickness of the inflammation and/or the longer duration, which indicates less or even no anti-inflammatory activity (Apridamayanti et al., 2018; Safitri et al., 2023)) from the average edema curve to time (minutes) and continues with the calculation of the percentage of anti-inflammatory activity (% DAI).

$$\% \, DAI = \frac{AUCcontrol - AUCtreatment}{AUCcontrol} \times 100$$

Anti-Inflammatory Potency (DAI) is the percentage of a compound's effectiveness in inhibiting or lowering inflammation and is calculated based on a comparison of the AUC value of the treatment group with the AUC of the negative control group (Pramitaningastuti & Anggraeny, 2017).

The higher the % DAI value, the greater the ability of the test compound to reduce the

Table 3. AUC and % DAI measurement results for edema volume (mm3)

Treatment	Considering	AUC value after treatment (minutes)							AUC	%DAI
		30	60	120	180	240	300	330	0-330	
Group I CMC Na 1% b/v	0.13	1.59	1.81	2.38	3.03	3.52	4	4.24	32.38	0%
Group II Diclofenac Sodium	0.1	1.38	1.62	2.15	2.19	1.94	1.81	1.71	20.85	36%
Group III EEPS 250:375 mg/kgBW	0.12	1.54	1.76	2.28	2.35	2.13	1.97	1.9	22.61	30%
Group IV EEPS 200:400 mg/kgBW	0.08	1.46	1.71	2.24	2.29	2.06	1.93	1.85	22	32%
Group V EEPS 150:425 mg/kgBW	0.06	1.41	1.65	2.2	2.26	2.01	1.88	1.81	21.5	34%

volume/thickness of inflammation, which means that its anti-inflammatory activity is greater (Apridamayanti et al., 2018; Safitri et al., 2023).

The quantitative data of the study are in the form of AUC (Area Under Curve) and % DAI from the average curve of the edema volume in Table 3.

Based on Table 3 above, the 1% b/v CMC Na treatment group had the highest AUC value of 33.28 with the lowest % DAI of 0%. This shows that CMC Na 1% does not have anti-inflammatory effects on the soles of the feet of mice because the negative control group was only given 1% b/v CMC Na suspension which was unable to inhibit the formation of edema (Suryandari et al., 2021).

In the treatment group, Diclofenac sodium had a low AUC value of 20.85 and a high %DAI of 36%, indicating that Diclofenac sodium had an anti-inflammatory effect on the soles of the feet of rats. Diclofenac sodium is a class of non-steroidal anti-inflammatory drugs that reduce inflammation by stopping the production of prostaglandins. Diclofenac sodium is also bound to plasma proteins by 97% and accumulates in synovial fluid after administration in test animals (Azizah & Azhairi, 2017; Kresnamurti et al., 2021).

In the test preparation group, the combination of ethanol extracts showed low AUC values and high % DAI at each dose variation. The lowest AUC value of 21.50 and a high % DAI of 34% at the EEPS dose of 150:425 mg/kgBW indicate the presence of anti-inflammatory activity produced by the combination of ethanol extract because it is assumed to contain secondary metabolite compounds that have anti-inflammatory effects.

Quantitative data were also made for the study in the form of AUC (Area Under Curve) and %DAI from the average curve of edema thickness in Table 4.

Based on Table 4 above, it shows that the 1% b/v CMC Na treatment group had an AUC value of 59.64 and the lowest % DAI of 0%. The Diclofenac Sodium treatment group had a

Table 4. The results of the AUC and %DAI measurements of udem thickness (mm).

Treatment	Ku	AUC value after treatment (minutes)							AUC 0-360	%DAI
		30	60	120	180	240	300	330		
Group I NaCMC 1%	1,09	4,08	4,56	5,06	5,52	5,91	6,23	6,37	59,64	0%
Group II Sodium Diclofenac	0,89	3,86	4,30	4,87	4,47	3,91	3,33	3,03	45,03	24%
Group III EEPS 250:375 mg/kgBB	1,32	4,17	4,61	5,08	4,93	4,37	3,88	3,64	49,46	17%
Group IV EEPS 200:400 mg/kgBB	1,22	4,08	4,56	5,02	4,77	4,24	3,70	3,44	48,09	19%
Group V EEPS 150:425 mg/kgBB	1,04	3,95	4,45	4,92	4,62	4,10	3,55	3,28	46,70	22%

lower AUC of 45.03 and a high %DAI of 24% indicating the strongest anti-inflammatory effect. In the treatment group, the combination of ethanol extract showed low AUC values and high %DAI in each dose variation. This shows that EEPS has a significant anti-inflammatory effect. EEPS dose of 150:425 mg/kgBW had a low AUC value of 46.70 and %DAI of 22% compared to other doses.

The results of the One-Way ANOVA test showed significantly different values on the decrease in volume and thickness of the edema ($P < 0.05$). Then a follow-up test was carried out using the Post Hoc test, namely the Bonferroni test to see the differences between treatment groups. The results of the Bonferroni test on the decrease in volume and thickness of edema showed that the 1% CMC Na group against all treatment groups showed significantly different results ($P < 0.05$).

In the Diclofenac sodium treatment group against all treatment groups, EEPS showed no significant difference ($P > 0.05$). In each of the EEPS groups with dose variations, there was no significant difference in value ($P > 0.05$). This showed that Diclofenac sodium and the EEPS group with dose variations had the same effect in decreasing the volume and thickness of edema on the soles of the feet of rats.

Based on the results of the research that has been conducted, it is shown that the combination of ethanol extracts of Centella asiatica leaves and Caesalpinia sappan wood has an anti-inflammatory effect allegedly because contains the main active compounds. *Centella asiatica* has main content belong to a group of triterpenes such as asiatic acid, asiacoside, and madecoside which have anti-inflammatory activity with reported mechanisms including inhibition of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) levels, as well as the expression of cyclooxygenase-2 (COX-2) protein and the production of prostaglandin E2 (PGE2). These compounds may also enhance anti-inflammatory mediators such as interleukin-10

(IL-10) that mediate tissue protection (Sun et al., 2020; (Hernayanti et al., 2021;(Diniz et al., 2023).

Secang wood has the main content of the phenolic group, namely Braziline which has an anti-inflammatory effect through the mechanism of inhibiting protein denaturation caused by oxidative stress so as to help protect cells from damage that triggers an inflammatory response and reduce the expression of inflammatory cytokine mRNA such as IL-6 and TNF-α. These mechanisms include a decrease in COX-2 and iNOS expression as well as regulation of the NF-κB pathway which plays a role in inflammation while increasing anti-inflammatory mediators such as IL-10 (Mueller et al., 2016; Asevedo et al., 2024; Wirawati et al., 2025).

CONCLUSION

Based on the results of this study, the combination of ethanol extract of *Centella asiatica* L. leaf and *Caesalpinia sappan* L.wood had an anti-inflammatory effect in male rats (*Rattus norvegicus*) with an effective dose in reducing the volume and thickness of edema with an effective dose of 150:425 mg/kgBW which produced an AUC value of 21.50 and %DAI of 34% in the measurement of edema volume. In addition, it produced an AUC value of 46.70 and %DAI of 22% in the measurement of edema thickness.

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