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ANTIBACTERIAL ACTIVITY TEST OF BREADFULNESS LEAF EXTRACT PLASTER PREPARATION (*Artocarpus altilis*) *IN VITRO* AND *IN VIVO* IN THE TREATMENT OF MICE CUT WOUNDS

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ABSTRACT

The skin is the largest organ in the human body. One of the problems that often occurs in the skin is wounds. Wounds are damage or loss of tissue in the body caused by a factor, one type of wound is a cut wound. Cuts occur due to friction with objects causing linear tears in the skin and underlying tissue. Cuts can cause infections due to bacteria. Breadfruit leaves (Artocarpus altilis) contain flavonoid compounds that can regenerate the skin by increasing collagen in the skin and have bactericidal properties. This study aims to determine the optimal concentration in the activity of breadfruit leaf extract formulated in the form of plasters against in vitro and in vivo tests in the treatment of cut wounds in mice. This study used the maceration method in making the extract using 96% ethanol solvent. Breadfruit leaf extract was formulated into a plaster preparation with various concentrations F1: EEDS 10%, F2: EEDS 15%, F3: EEDS 20%, and F4: EEDS 25%. The plaster preparation was evaluated to determine the physical properties and compounds of the wound dressing material by conducting thickness tests, humidity tests, pH tests, organoleptic tests, FTIR tests, activity tests of the preparation against in vitro tests and in vivo tests. The results showed that the concentration of EEDS 25% with a value of 24.35 against the in vitro test using Staphylococcus aureus bacteria with a Hansaplast plaster comparator with a value of 16.35. In the in vitro test in the treatment of mouse cuts, it was stated that the concentration of EEDS 25% with a healing day of 10.6 days was close to the healing day of the Hansaplast plaster comparator with a healing day of 9.3 days.

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Introduction

The skin has a function to cover the entire outer part of the body and is called the body's protector against foreign objects, chemicals that can damage body parts, exposure to ultraviolet rays found in sunlight and protect the body from attacks by bacteria or microorganisms and maintain the body's balance from environmental changes that occur. The skin can be affected by several problems such as pale skin, changes in skin color to yellowish, or reddish and also an increase in skin temperature and shows abnormalities in the body or skin disorders caused by certain diseases (Aminuddin, M., 2020)

A wound is a damage or loss of body tissue caused by a factor that can cause disruption to the body's protective system. One example of a wound is a cut wound. Cut wounds occur due to linear tears in the skin and the tissue underneath caused by sharp surfaces. In cuts, wound care is needed to promote healing, prevent skin damage, and reduce the risk of infection. (Marlinawati, IT, 2022).

Wound care is a form of a series of actions carried out in an effort to prevent trauma or when injured on the skin. In general, the care carried out on wounds is carried out simply and is also generalized by using a certain pattern depending on the condition and also the problem of the wound experienced. Optimal care that is carried out plays a very important role in the wound healing process so that it can take place perfectly. (Wintoko, R., 2020).

Efforts made in wound healing must pay attention to the condition of the wound, because wounds are very susceptible to bacterial infection. One of the bacteria that infects wounds is *Staphylococcus aureus bacteria* . This bacteria is known to survive in environmental conditions that have high salt concentrations. *Staphylococcus aureus bacteria* are also known to be able to easily reproduce because they can grow at an optimal temperature of 30 ° C and cannot survive without oxygen (Magani, 2020).

In this wound healing therapy, plaster preparations are very suitable for use. Plasters are one of the preparations that are practical in their use and are able to cover wounds well compared to wound medicines with other forms of preparations such as creams, ointments, lotions or other liquid preparations. Plasters can also prevent friction or external threats that can be removed (Rahayu, DM, 2022).

Plasters can be elastic and will follow every curve of the skin so that they can cover wounds from dirt and bacteria, are waterproof, sterile, and do not stick to the wound. Breadfruit (*Artocarpus altilis*) is a versatile plant that is widely used because it has many benefits for humans. One of the benefits of the breadfruit plant *(Artocarpus altilis)* is that it is used as a traditional medicine because it contains secondary metabolite compounds. The presence of phenolic groups in flavonoids and tannins makes the plant potentially an antioxidant (Kurniawati, 2021).

The results of Ningrum's research, ID (2023) showed that the gel formulation from breadfruit leaf extract (*Artocarpus altilis*) was able to accelerate the healing process of cuts in *New Zealand White rabbits* . In this wound healing therapy, breadfruit leaves will be used. The reason for using breadfruit leaves is because breadfruit leaves are one type of medicinal plant that can be used for wound healing therapy. Breadfruit leaves have various types of secondary metabolite compounds,

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namely flavonoids, tannins, saponins, and polyphenols. The saponin content in breadfruit leaves can function as a wound cleanser and is also able to trigger the formation of collagen which plays a very important role in the wound healing process (Setyowati, DA, 2023).

Materials and Methods

Tool

Maceration bottle, rotary evaporator, hotplate, beaker glass, ose needle, vernier caliper, incubator, disposable razors, desiccator, autoclave, FT-IR tool, acrylic plate.

Material

Crushed breadfruit leaves, 96% ethanol, distilled water, chitosan, glycerin, tapioca flour, CH_3COOH, Nutrient Agar, *Mueller Hinton Agar* (MHA),

Processing of Simple Powder

The obtained breadfruit leaves are cleaned of dirt on the leaves, then the leaves are separated from the leaf stems, then shredded, then weighed for their wet weight and then air-dried until the breadfruit leaves are dry. Then, the weight of the dried breadfruit leaves is weighed. The process of drying breadfruit leaves is done by smoothing them by blending and filtering. Then, the weight of the dry powder is weighed and stored in a glass bottle and tightly closed.

Phytochemical Screening

Phytochemical screening was carried out by testing for alkaloids, flavonoids, tannins, saponins and steroids.

\Making Plaster Preparations

Preparation of 1% CH_3COOH Solution

Pipette 1 ml of glacial CH_3COOH solution , then put it into a 100 ml measuring flask, and dilute it using distilled water until it reaches the boundary line.

Making 2% Chitosan Solution

The procedure for making 2% chitosan is done by weighing 1 g of chitosan and putting it into a 100 ml beaker glass. Then, 50 ml of a 1% CH_3COOH solution that has been made is added and left at room temperature until all the soaked chitosan dissolves.

Making Plasters from Tribal Leaf Extract

Weigh 6 grams of tapioca flour, then put into a 100 ml glass beaker and dissolved with 35 ml of distilled water and stirred using *a stirring bar* until homogeneous on *a magnetic stirrer* using a temperature of ±70 ° C. The stirring process is carried out until it thickens. After thickening, breadfruit leaf extract is added according to the concentration of the preparation and then stirred again until homogeneous on *a magnetic stirrer* . Then add 50 ml of 2% chitosan solution and 2 ml of glycerin solution. Stir again until homogeneous on *a magnetic stirrer* and leave to mix evenly. The mixture is poured onto an acrylic plate and leveled. Then put into the oven and heated in the oven using a temperature of ±40 ° C for 24 hours.

Evaluation of Plaster Preparations

Plaster Thickness Measurement

Plaster thickness measurements were carried out at five different points, namely at the lower right corner, lower left corner, upper right corner, upper left corner and the middle. The tool used to measure the

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thickness of the plaster is a vernier caliper. Then the calculation is carried out on the average thickness of the plaster from the five measurement points.

Moisture Absorption Test

In testing the moisture absorption capacity of plaster, the plaster is weighed first, then stored at room temperature in a desiccator for 24 hours, then stored again in the chamber for 24 hours, then reweighed and the percentage of moisture absorption capacity is calculated using the following formula:

$$\%\text{Humidity} = \frac{\text{berat awal} - \text{berat akhir}}{\text{berat awal}} x\ 100\%$$

pH Test

In the pH test that will be carried out on the breadfruit leaf extract plaster preparation by first dissolving the preparation using a solvent. The pH measurement must be in accordance with the pH of the skin, which is between 4.5 and 6.5. The pH measurement is carried out using a benchtop pH meter. The breadfruit leaf extract plaster sample is dipped into 10 ml of distilled water solvent first, left until the distilled water solution changes color to green. Furthermore, the pH measurement is carried out using a benchtop pH meter.

Organoleptic Test

In the organoleptic test that will be done by observing the preparation with the naked eye. The observations made are odor, color and texture.

***Fourier Transform Infra Red*) Analysis**

FTIR analysis was conducted to determine the group of compounds contained in the preparation of breadfruit leaf extract plaster (*Artocarpus altilis*). Then compare the compounds contained in the breadfruit leaf extract (*Artocarpus altilis*).

Media Creation

Making Na Media (*Nutrient Agar*)

Nutrient Agar media , namely by weighing 28 g of *Nutrient Agar* (Na) powder. The results of the weighing are then dissolved into aquadest solution by pouring slowly until the volume is sufficient to 1 L using the help of *a magnetic stirrer* until all the powder is completely dissolved. Furthermore, sterilization is carried out using an autoclave for 15 minutes at a temperature of 121 ° C.

Making MHA (*Mueller Hinton Agar*) Media

Mueller Hinton Agar media by weighing 19 g of MHA powder, it is put into an Erlenmeyer which will be dissolved using 500 ml of distilled water and heated on *a magnetic stirrer* until dissolved and boiling. then sterilized using an autoclave for 15 minutes at a temperature of 121 ° C (Sari L, 2019).

Making Media Slanted and Bacterial Culture Stock

In the process of making slant agar media, 3 ml of nutrient agar media is inserted into a test tube. Then it is left in a slanted position at room temperature until solidification occurs. The *Staphylococcus aureus bacterial culture* found in the main strain is then taken using a sterilized ose needle, then inoculated on the surface of the slant nutrient agar media by scratching the surface area, then incubated for 18-24 hours using a temperature of 35 ° C (Sari L, 2019)

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Preparation of Microbial Suspensions

In the process of making a culture of *Staphylococcus aureus bacteria* by first inserting 10 ml of distilled water into a test tube that has been sterilized first. Furthermore, sterilization is carried out using an autoclave for 15 minutes at a temperature of 121 ° C. then vortex is carried out to obtain the suspension results. (Yanti, NA, et al. 2020)

Antibacterial Test of Plaster Preparations

Antibacterial Test Procedures for plaster preparations were carried out *In Vitro* and also *In Vivo.*

In Vitro* Test of Breadfruit Leaf Extract Plaster Preparation Against *Staphlyococcus aureus Bacteria

Vitro Test which is done using *Staphylococcus aureus bacteria. Take* 15 ml of MHA (*Muller Hinton Agar)* media solution and put it into a previously lined petri dish, then leave it to solidify at room temperature. Next, scratch the *Staphylococcus aureus bacterial inoculum* into the petri dish continuously, and incubate at a temperature of 28-29 ° C for 25 hours. Then, a paper disc is placed on the MHA media that has solidified and contains the bacterial inoculum. The paper disc is first soaked in a plaster solution with a concentration of 10%: 15%: 20%: 25% and also control + with control -. Repetition is done 3 times.

***In Vivo* Test of Breadfruit Leaf Extract Plaster on Healing of Cut Wounds in Mice**

In the *In Vivo test* conducted using mice as experimental animals. Mice used as many as 18 where the preparation therapy was repeated 3 times. Mice that will be used as test animals are first shaved until only mouse skin remains. Then, an incision/cut wound is made parallel to the spine on the mouse with a wound diameter of 1 cm and a wound depth of 1 mm, or it can be said to be deep to the subcutaneous tissue. In the area of the incision, it is first wiped with 70% alcohol to clean dirty skin and prevent continuous bleeding. The plaster is then attached with a plaster of different variations, both control + and control -. During the application of treatment using the plaster preparation, the area must not be washed or exposed to water. The plaster is changed once a day. Observation of the incision wound was carried out and measuring the diameter of the incision wound closure for 15 days, namely on day 1, day 3, day 6, day 9, day 12, day 13, day 14, and day 15. The plaster was changed every day.

Data analysis

Observation data on the preparation of breadfruit leaf plaster in pH testing, plaster tensile strength testing, plaster thickness testing, plaster organoleptic testing were analyzed descriptively by considering the comparison of which concentration meets the requirements of the incision wound, then the measurement results were made in table form. And the results of *In Vitro testing* and *In Vitro testing* on mice were analyzed using the One Way Anova (*Analysis of variant*) test using a confidence level of 95% ($\alpha = 0.05$).

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Results and Discussion

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Phytochemical Screening

Based on the phytochemical screening examination that has been carried out on the breadfruit leaf simplex samples, the results obtained are as shown in Table 1

Table 1. Results of phytochemical screening tests of breadfruit leaves

Compound Groups	Reagent	Results	Conclusion
Steroid	H_2SO_4 is purple and red or changes to green/blue	At first it was purple, then the color changed to green.	(+) Steroid
Alkaloid	Meyer's reagent (yellow/white precipitate)	A white precipitate forms	(+) Alkaloid
	Dragendorff's reagent (brick red precipitate)	No sediment formed	
	Bouchardat reagent (blackish brown precipitate)	A blackish brown precipitate is formed	
Flavonoid	Addition of 0.1 Mg powder, 1 ml HCL (P), 2 ML Amyl alcohol	An orange ring forms on the amyl alcohol layer	(+) Flavonoid
Tannin	Addition of FeCl3 solvent (blue or blackish green color)	A blackish green color is formed	(+) Tannin
Saponins	Addition of distilled water solvent and shake vigorously. Then, Addition of 1-2 drops of 2N HCl	Foam/foam forms when shaken using hot distilled water	(+) Saponin

Breadfruit leaves contain secondary metabolite compounds, namely flavonoids, alkaloids, tannins, saponins, and steroids. Research on secondary metabolites in wound healing of medicinal plants in the wound healing process, this shows the importance of the role of secondary metabolites, especially using in vivo and/or in vitro (cell culture) evaluations, has enabled the identification of pure compounds that work in one or more phases of the healing process. Phytochemicals enhance wound healing especially during the proliferation and inflammation phases. Phytochemicals work at multiple levels through the regulation of different signaling pathways. Therefore, these compounds provide many therapeutic effects. These secondary metabolites can act as antioxidants and modulate inflammation and the sequence of phases in the healing process. Furthermore, phytochemicals have the potential to enhance tissue regeneration and restore skin function, which is important in chronic diseases. (Santoz, et.al. 2023)

Evaluation of Stock

Thickness Measurement

The results of the thickness measurements obtained for the plaster preparations are, control - with a plaster thickness of 0.1 mm, 10% concentration with a thickness of 0.2 mm, 15% concentration with a thickness of 0.2 mm, 20% concentration with a thickness of 0.1 mm and 25% concentration

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with a thickness of 0.1 mm. from the results of the plaster thickness measurement, the plaster has met the thickness requirements with a plaster thickness requirement of <1 mm (Yulianti T, 2021).

Moisture Test of Plaster Preparations

Based on the results of the humidity test on the plaster preparation which has been stored for 48 hours that the control - with a humidity percentage of 1.25%, a concentration of 10% with a percentage of 1.58%, a concentration of 15% with a percentage of 1.52%, a concentration of 20% with a percentage of 1.38% and a concentration of 25% with a percentage of 1.69%. The results of the humidity test have met the requirements with the condition that the humidity test is <10%.

pH test of plaster preparation

The results of the pH test that has been carried out on the plaster preparation that the pH obtained for the plaster with the control - is 4.53, 10% concentration with pH 4.66, 15% concentration with pH 4.79, 20% concentration with pH 4.97, 25% concentration with pH 5.02. From the results obtained that the plaster preparation has met the pH test requirements, namely at the skin pH requirements of 4.5 - 6.5.

Organoleptic test of plaster preparations

The results of organoleptic tests on the plaster preparation in the control - that the odor produced is the odor that comes from CH_3COOH and also the odor of tapioca flour base. The odor produced in the 10% concentration plaster is the odor of breadfruit leaf extract and also the odor of CH_3COOH. Likewise, the odor produced by the 15%, 20%, and 25% concentration plaster. The higher the concentration of the plaster preparation, the more the odor of breadfruit leaf extract will be felt and the odor of CH_3COOH will not be felt.

FTIR Test

Based on the results of the FTIR test, the results of the FTIR analysis of breadfruit leaf extract are shown in Figure 1

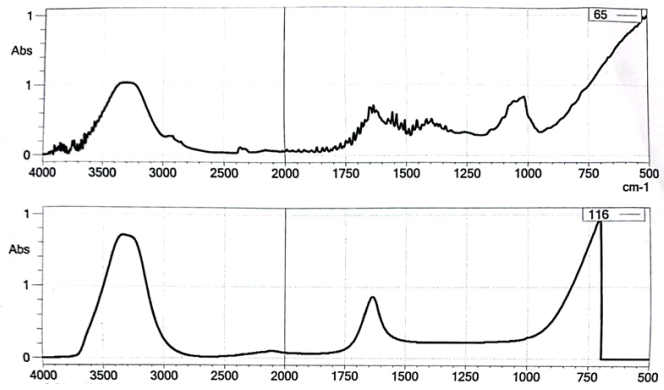

Figure 1. FTIR Test Results of Breadfruit Leaf Extract

The presence of the OH functional group in ethanol is at a wavelength of 3230–3550 cm $^{-1}$. Absorption on the CH bond will be slightly below 3000 cm $^{-1}$ and there is absorption in the 1000–1150 cm $^{-1}$ region which comes from the CO bond. Furthermore, the presence of the NH-amine

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group is at a wavelength of 3628 cm $^{-1}$. The NH-amine group is a group found in alkaloid compounds. The -C=C aromatic group is at a wavelength of 1591-1604. The -C=C aromatic group is a functional group found in a compound of flavonoids. The presence of the -CO ketone functional group is at a wavelength of 1678-1719 cm $^{-1}$. The -CO ketone group is a functional group found in saponins. The presence of the -CH alkane group is at a wavelength of 2855-2963 cm $^{-1}$. The -CH alkane group is a functional group found in steroids. The presence of a group, namely C=O, which is found at a wavelength of 1715 cm $^{-1}$.

In the FTIR test of the breadfruit leaf extract plaster preparation, the presence of the CO functional group increased in the wavelength region of 1200-900 cm $^{-1}$. The sharp increase occurred because of the CO group contained in chitosan. The addition of acetic acid caused a high value of the adsorption capacity of the extract and chitosan. The functional group contained in tapioca flour is OH which is found at a wave number of 3500-3000 cm $^{-1}$ (Figure 2).

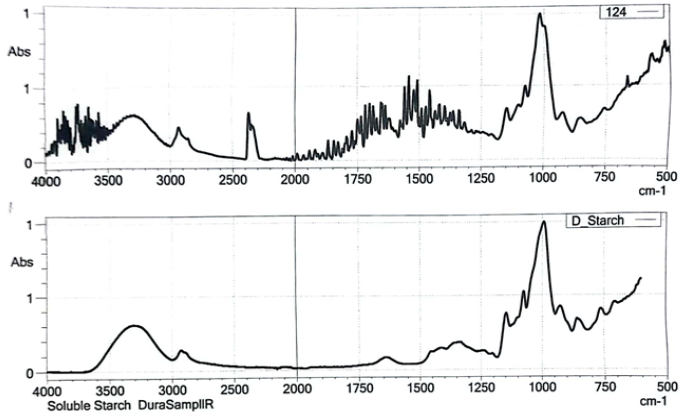

Figure 2. FTIR Test Results of Breadfruit Leaf Extract Plaster

Activity Test of Breadfruit Leaf Plaster Preparation

***In Vitro* Test of Breadfruit Leaf Extract Plaster Preparation**

In Vitro tests were carried out on *Staphylococcus aureus bacteria* and the *In Vitro Test data* that was obtained can be seen in Table 2 which shows the average results of measuring the area of the inhibition zone of *Staphlylococcus aureus bacteria* :

Table 2. Results of measuring the inhibition zone of *Staphylococcus aureus bacteria*

Kel	Repeated antibacterial activity *of Staphylococcus aureus*			Average (mm)
	P1	P2	P3	
K+	12.10	17.45	19.50	16.35
K -	0	0	0	0
P1	12.90	9.85	11.45	11.4
P2	13.40	15.70	15.95	15.01
P3	20.45	16.10	11.50	16.01
P4	21.40	24.85	26.80	24.35

The results of the measurement of the inhibition zone of *Staphylococcus aureus bacteria* that the measurement obtained by K+ as a comparison with the average

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measurement result is 16.35. The measurement of the inhibition zone produced by K- is 0 in each repetition. Thus it can be stated that K- does not have an antibacterial inhibition zone against *Staphylococcus aureus bacteria.*

The measurement results carried out using a 10% concentration plaster (P1) obtained that the average measurement was 11.4. In the 15% concentration plaster (P2) with an average measurement of 15.01. In the 20% concentration plaster (P3) with an average measurement of 16.01. In the 25% concentration plaster (P4) with an average measurement of 24.35. Thus, the plaster with a concentration of 25% has the widest inhibition zone against *Staphlyococcus aureus bacteria.*

In vitro test on *Staphylococcus aureus bacteria* that there is inefficient workmanship so that the results of measuring the bacterial inhibition zone in each repetition produced are very different. However, it can be stated that the breadfruit leaf extract plaster has an antibacterial inhibition zone against *Staphylococcus aureus bacteria.*

From the results of data analysis that has been done using normality data analysis according to value requirements (P>0.005) and the results obtained in Control + with a sig value of 0.519, 10% concentration plaster with a sig value of 0.946, 15% concentration plaster with a value of 0.170, 20% concentration plaster with a sig value of 0.969 and 25% concentration plaster with a sig value of 0.696. That the results of the normality test have met the requirements. The results of the homogeneity test obtained with a sig value. 0.136 with the requirements of the Homogeneity test value (P>0.05). The results of the *One Way Anova test data analysis* were obtained with a sig value. 0.00 with the requirements of the *One Way Anova test* is value (P<0.05).

In Vivo Test of Breadfruit Leaf Extract Plaster Preparation

In Vivo tests were conducted on the treatment of cut wounds in mice. *and the In Vivo* Test data that has been obtained can be seen in table 3 below which displays the average results of measuring the area of the inhibition zone of *Staphlylococcus aureus bacteria* .

Table 3. Average time (days) for the wound to completely close

Kel	Repeated incision wounds in mice			Average (days)
	P1	P2	P3	
K+	10	9	9	9.3
K -	15	15	15	15
P1	14	13	14	13.6
P2	13	12	13	12.6
P3	12	11	10	11
P4	10	10	12	10.6

Data analysis conducted on the *In Vivo test* of plaster preparation in mouse cut wound therapy is by analyzing the *Homogeneity test data* obtained with a significance value of 0.106 with the *Homogeneity test requirements* being P (*Value*)> 0.05 with the value obtained then the *Homogeneity test* has met the *Homogeneity test requirements.* In this study, breadfruit leaf extract plaster has a faster healing process with an average wound healing of 10.6 days

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and the results of data analysis using *Tukey HSD analysis* obtained a value of 10.67.

Conclusion

All variants of breadfruit leaf extract plaster (*Artocarpus altilis*) can be formulated into plaster preparations and have met the requirements for evaluating preparations. The results of the study showed that the right variation of the *In Vitro Test* as an antibacterial against *Staphylococcus aureus bacteria* was owned by breadfruit leaf extract plaster with a concentration of 25% and the average area of the bacterial inhibition zone was 24.35 mm, the results of the study showed that the right variation of the *In Vivo Test* on healing of mouse cuts with the fastest total healing days was 10.6 days using breadfruit leaf extract plaster with a concentration of 25%.

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