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Effectiveness Of Ethanol Extract From Sea Pandan (Pandanus Tectorius) On Hydroxyproline Levels As A Parameter For Collagen Formation In The Healing Process Of Incision Wounds In Male Rattus Norvegicus

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ABSTRACT
This study aims to determine the effectiveness of ethanol extract gel of sea pandan fruit on hydroxychlorine levels as a parameter for collagen formation in the healing process of incisional wounds of male white rats (Rattus norvegicus). This study is laboratory experimental research with a post-test only control group design. The experimental animals used were male white rats which were divided into negative control groups (Gel Base), positive control (Bioplacenton®), and treatment groups with marine pandan ethanol extract gel concentrations of 10%, 20%, and 30%. The treatment was carried out for 10 days at the Integrated Biomolecular and Hyperbaric Laboratory, Faculty of Medicine, Hang Tuah University, Surabaya. The measured parameter was the level of hydroxyproline of skin tissue. The results showed that there was a significant difference in hydroxyproline levels between treatment groups ($p=0.032$). Post-hoc Duncan test revealed that the 20% concentration group (575.46 ± 20.84 µg/ml) showed significantly higher hydroxyproline levels compared to the negative control (440.09 ± 48.76 µg/ml, $p<0.05$), although not significantly different from the positive control (591.75 ± 29.9 µg/ml). The 20% concentration provides the most optimal effect with the highest average hydroxyproline levels and the narrowest data distribution, signaling more consistent fibroblast stimulation and collagen deposition. A concentration of 10% indicates high variability so the effect is less stable, while a concentration of 30% provides a moderate effect that may be affected by mild irritation. The conclusion of this study is that sea pandan fruit ethanol extract gel has the potential to accelerate the healing of incision wounds through increasing hydroxyproline levels as an indicator of collagen formation.
Keywords: Pandanus Tectorius; Hydroxyproline; Collagen; Wound Healing; Ethanol Extract Gel.

INTRODUCTION

Wound healing remains a significant global health challenge, with chronic wounds affecting approximately 2% of the global population and imposing substantial economic burdens on healthcare systems worldwide (Abdelhakim & Ogawa, 2025). The wound care market is projected to reach USD 22 billion by 2026, reflecting the urgent need for effective therapeutic interventions (Criollo-Mendoza et al., 2023). Hydroxyproline, as a specific amino acid found predominantly in collagen, serves as a gold standard biochemical marker for assessing collagen synthesis during wound healing. Elevated hydroxyproline levels correlate directly with enhanced collagen deposition, which is critical for restoring tissue integrity and mechanical strength (Lipatov et al., 2024). This parameter has been extensively validated in wound healing research globally, making it an essential indicator for evaluating therapeutic

efficacy in experimental wound models (Dwicahyani et al., 2018; Jeschke et al., 2020; Lotfollahi, 2024).

Indonesia is a country that has very abundant biodiversity, so it has great potential for the development and utilization of traditional medicine. In the medical world, many efforts are made to speed up wound healing, one of which is by using natural ingredients that contain bioactive compounds (Dwicahyani et al., 2018; Irwandi et al., 2021; Juang & Liang, 2020; Maxwell, 2024; Mollie, 2023). Sea pandan fruit (Pandanus tectorius) has been used in traditional medicine because it is known to contain various active compounds as anti-inflammatory, antioxidant, and increase collagen synthesis, thus potentially accelerating the wound healing process (Andriani et al., 2015).

The sea pandan plant (Pandanus tectorius) is found growing wild along the north coast of Java Island, the Thousand Islands, Sumatra, and several other islands. Although many of the benefits of Pandanus tectorius have been reported, scientific evaluation of the potential benefits of Pandanus tectorius fruit is still limited, so the utilization of this resource is still not optimal. Sea pandan fruit is known to contain active compounds such as flavonoids, saponins, phenolics, terpenoids, steroids, and glycosides (Elfiah et al., 2022; Gardeazabal & Izeta, 2024; Luthfi et al., 2020). Flavonoids are bioactive compounds that function as anti-inflammatory, antioxidant, and antimicrobial agents, and also play a role in accelerating the formation of new epithelial layers in wound tissue (Buyantogtokh et al., 2020; Febiati, 2016; Kasmadi et al., 2024). Saponins play a role in the wound healing process through the stimulation of collagen synthesis which is important in wound regeneration. Sea pandan fruit also contains antioxidant compounds that help accelerate the regeneration of epithelial tissue in wound tissue (Lubis et al., 2020; Lallo et al., 2020). These bioactive compounds have demonstrated wound healing properties in various plant species, yet their specific mechanism and optimal dosage in sea pandan fruit for collagen synthesis stimulation have not been systematically investigated.

A wound is a disturbance in tissue continuity or loss and damage to part of the body's tissue. This condition is caused by various factors such as trauma from sharp and blunt objects, temperature fluctuations, contact with chemicals, explosions, electric shocks, and animal bites (Panda et al., 2023). An incision wound is a type of wound that occurs due to a sharp object incision, with relatively regular and clear edges of the wound. These incision wounds are generally found in surgical procedures, as well as daily trauma such as knife incisions or other sharp objects. Incision wounds are one of the most commonly used types of wounds in experimental research because they have uniform characteristics, controlled wound depth, and a healing process that can be observed systematically. Physiologically, the healing process of incision wounds takes place through four main stages: hemostasis, inflammation, proliferation, and remodelling (Lestari et al., 2023). Incision wounds are highly dependent on the process of adequate collagen formation, especially in the proliferation phase. Collagen plays a role in providing the stability of the wound tissue. An imbalance in collagen synthesis can cause wounds to be difficult to close. Therefore, incision wounds are the right model to evaluate the effectiveness of a therapy in stimulating collagen formation objectively (Lipatov et al., 2024).

One of the biochemical parameters that has been carried out to evaluate the formation of collagen in the wound healing process is hydroxyproline levels (Fauziah & Soniya, 2020; Irwandi et al., 2021; Mollie, 2023). Hydroxychlorine is a derivative of the amino acid proline that is specifically found in the structure of collagen, so the level of hydroxychlorine in tissues reflects the amount of collagen formed during the wound healing process. Measurements of hydroxychlorine levels can represent collagen synthesis activity, especially in the proliferation phase, which is the phase when fibroblast activity increases and collagen formation takes place most intensively (Addis et al., 2020). Therefore, the measurement of hydroxychlorine levels is considered an objective and sensitive method to assess the effectiveness of therapy in accelerating wound healing, particularly in incision wounds (Lipatov et al., 2024; Baldea et al., 2023).

Wounds are a condition that cannot be underestimated, because if not treated properly, they can cause infection and potentially harm the body. Wound healing is a natural mechanism of the body, but this process can be accelerated with the use or combination of certain medications (Criollo-Mendoza et al., 2023). Wound care with medications, such as Bioplacenton, is considered difficult to access by certain groups of people, especially those living in coastal areas with low levels of well-being (Youlanda & Susilawati, 2023). Geographical factors are also obstacles in the availability of these drugs (Triwahyuni et al., 2020). Increasing awareness of the potential risks of chemicals has driven people's preference for natural products that are considered safer and more environmentally friendly, so that the demand for organic products is increasing (Obahiagbon et al., 2023). This shift towards natural products underscores the urgency of developing evidence-based phytotherapeutic alternatives that are not only accessible and affordable but also scientifically validated for wound healing efficacy.

Several studies have explored the wound healing potential of various Pandanus species and related plant extracts. Don et al. (2018) demonstrated that herbal extracts at 10-30% concentrations effectively promoted wound closure in animal models. Ranti et al. (2024) reported that plant-based gel formulations enhanced fibroblast proliferation and collagen deposition during the proliferation phase of wound healing. Repent et al. (2024) found that topical gel preparations containing bioactive compounds at 20% concentration showed optimal penetration and therapeutic effects without causing skin irritation. However, none of these studies specifically investigated the effects of Pandanus tectorius fruit extract on hydroxyproline levels as a quantitative marker of collagen synthesis in incision wound models. This represents a significant research gap, as hydroxyproline measurement provides direct biochemical evidence of collagen formation, which is the cornerstone of effective wound healing (Mathew-Steiner et al., 2021).

The novelty of this research lies in three key aspects: (1) it is the first study to quantitatively evaluate the effect of Pandanus tectorius fruit ethanol extract on hydroxyproline levels as a direct marker of collagen synthesis in incision wounds; (2) it systematically compares three concentration levels (10%, 20%, and 30%) to determine the optimal therapeutic dosage; and (3) it validates the efficacy of sea pandan fruit extract against a commercially available wound healing agent (Bioplacenton®), providing practical clinical relevance. By establishing the dose-response relationship between sea pandan extract

concentration and collagen formation, this study fills a critical knowledge gap and provides a foundation for developing evidence-based, accessible, and cost-effective wound healing therapies derived from locally available natural resources.

Based on the above background description, it is known that research using sea pandan fruit extract gel (Pandanus tectorius) on hydroxychlorine levels as a parameter for collagen formation in the incision wound healing process has never been carried out. The researcher will conduct a study entitled "The Effectiveness of Ethanol Extract of Sea Pandan Fruit (Pandanus tectorius) on Hydroxychlorine Levels as a Parameter for Collagen Formation in the Incision Wound Healing Process in Male Rattus norvegicus". This study used a white rat experiment that will be made an incision wound to see the potential of ethanol extract of sea pandan fruit (Pandanus tectorius) in healing incision wounds.

METHOD

The type of research used is purely *In Vivo* experimental research conducted in the laboratory, with *a Post Test Control Group* research design.This research model uses randomly selected experimental animals to test the potential of sea pandan fruit extract in healing incision wounds in male white rats

Research Methods

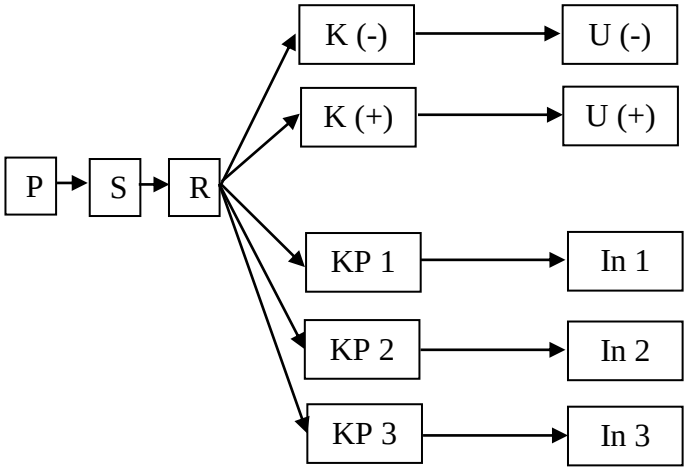

Figure 1. Research Method Design

Description:

P: Population

S: Samples of male white rats (*Rattus norvegicus)* taken from the population and randomized and have met the inclusion criteria

R: Randomization

K (-): Negative control group, which is a group of experimental animals that were given a standard diet and then on day 8 were incised wounds and given gel-based treatment

K (+): Positive control group, which is a group of experimental animals that were given a standard diet and then on day 8 were incised wounds and given Bioplacentone gel treatment.

KP 1: Treatment group one, namely a group of experimental animals that were given a standard diet and then on the 8th day were wounded and given a 10% concentration of sea pandan ethanol extract gel

KP 2: Treatment group two, namely the group of experimental animals that were given a standard diet and then on the 8th day were injected with wounds and given a gel treatment of ethanol extract of sea pandan fruit with a concentration of 20%

KP 3: Treatment group three, namely the group of experimental animals that were given a standard diet and then on the 8th day were incised wounds and given a gel treatment of ethanol extract of sea pandan fruit with a concentration of 30%

U (-): Measurement of hydroxycycline levels in rats on day 10 of gel-based treatment

U (+): Measurement of hydroxychlorine levels in rats on day 10 of Bioplacenton gel treatment

U 1: Measurement of hydroxychlorine levels in rats on day 10 of the gel treatment of ethanol extract of sea pandan fruit with a concentration of 10%

U 2: Measurement of hydroxychlorine levels in rats on day 10 of the ethanol extract gel treatment of sea pandan fruit concentration 20%

U 3: Measurement of hydroxycycline levels in rats on day 10 of the ethanol extract gel treatment of sea pandan fruit with a concentration of 30%

Population and Sample

The experimental animal population used was a male white rat (*Rattus norvegicus)* of the Wistar strain.

The sample used in this study was a male white rat (*Rattus norvegicus)* of the Wistar strain in a healthy physical condition aged 8 to 12 weeks with a body weight of about 125 to 250 grams.

Inclusion criteria:

1. Types of white rats (*Rattus norvegicus*) strain Wistar with male sex
2. Age 8 to 12 weeks and adapted for at least 1 week
3. Weight 125 - 250 grams
4. The physical condition of the animal is healthy, namely active movement, complete anatomy, and good appetite.

Exclusion criteria:

1. Weight less than 125 grams or more than 250 grams
2. Pain during adaptation
3. Disability or death during adaptation

Drop-Out Criteria

1. Animals try to get sick or die during the research process

Large Sample

To calculate the sample size in this study, the formula used Federer, as follows:

$$(t - 1)\,(n - 1) \geq 15$$

Description:

n : number of samples per treatment group

t : number of treatment groups

So:

$$(t - 1)(n - 1) \geq 15$$
$$(5 - 1)(n - 1) \geq 15$$
$$4(n - 1) \geq 15$$
$$(n - 1) \geq 3.75$$
$$n \geq 3.75 + 1$$
$$n \geq 4.75 \text{ (rounded to 5)}$$

So the minimum number of samples per group is 5 rats, to avoid the possibility of the animal trying to die, a correction is made by 1/(1-f) where f is the proportion of the dead experimental animals.

Dead test animals (f) ± 20%, thus:

Number of samples $= 1/(1 - 0.2) \times 5$
$= 6.25$
$= 6$ (large sample is rounded)

So the sample size is 5 with 1 spare mice, so the minimum sample per group is 6 mice. The total sample used in this study was 30 male white rats (*Rattus novergicus*).

Sampling Techniques

Sampling was carried out using *the Simple Random Sampling method* by being randomly taken that had entered the inclusion criteria, namely a male white rat (*Rattus norvegicus*) aged 8 to 12 weeks, a body weight of 125 to 250 grams, the physical condition of the experimental animal was healthy during adaptation, characterized by active movement, complete anatomy, and good appetite to be randomly placed into 5 research groups.

Research Variables

a) Independent Variables

1. Bioplacenton
2. Ethanol Extract Gel Dosage Sea Pandan Fruit Gel Preparation Concentration 10%
3. Ethanol Extract Gel Dosage Sea Pandan Fruit Gel Preparation Concentration 20%
4. Ethanol extract gel dosage of sea pandan fruit gel preparation concentration 30%

a) Bound Variables

Collagen formation of rat skin tissue assessed with hydroxychlorine levels

b) Variable Control

1. Types of test animals
2. Sex, age, and weight of the rat
3. Size and method of making incisions
4. Experimental animal cage
5. Standard feed
6. Time used for treatment

Operational Definition

Table 1. Research Operational Definition

Variable	Operational Definition	Measuring Instruments	Way Measurement	Scale
Independent	Sea pandan fruit extract through maceration extraction	Neraca analytics	1 gram with a concentration of 10%, 20%, 30%	Ratio

	with 96% ethanol solvent for topical gel preparations 2 times a day at 8.00 and 16.00			
	Bioplacenton	Neraca analytics	1 gram	Ratio
They depend				
	Hydroxyproline levels of skin tissue	UV-Vis spectrophotome-ter and hydroxychlorine standard curve	Measurement of hydroxychlorine levels from skin tissue using UV-Vis spectrophotometer test and hydroxychlorine standard curve	Ratio

Research Tools

1. Experimental animal cage size D 40 cm x W 30 cm x H 20 cm
2. Where to eat and drink try animals
3. Scales
4. Neraca analytics
5. Razor
6. *Scalpel*
7. *Handscoon*
8. Spectrophotometer
9. *Rotary vacuum evaporator*
10. Filter paper
11. Mix
12. Syringe
13. Alumunium foil
14. Oven
15. Kuvet
16. Calipers

Research Materials

1. Experimental animals male white rats (*Rattus norvegicus*) strain Wistar
2. Sea pandan fruit (*Pandanus tectorius)*
3. Standard feed of rats
4. Larutan Ethanol 96%
5. Aquades
6. Bioplacenton
7. Basis Gel
8. CMC-Na
9. Glycerin
10. Asam benzoat
11. Ketamin 10 mg/kg

12. Alcohol 70%
13. Larutan hydroxyproline
14. Larutan 4-dimethylaminobenzaldehid
15. Larutan HCL
16. NaOH Solution
17. Larutan Nacl
18. Larutan CuSO4,
19. H2O2 solution,
20. H2SO4 Solution

Place and Time of Research

The research location for the manufacture of sea pandan fruit extract and gel preparations at the Pharmaceutical Laboratory, Faculty of Pharmacy, Hang Tuah University. The maintenance and termination of experimental animals was carried out at the Biomolecular Integrated Laboratory, Faculty of Medicine, Hang Tuah University. The analysis of the preparation was carried out at the Biochemistry Laboratory, Faculty of Medicine, Hang Tuah University.

This research was carried out from April to June 2025 for theoretical data collection, theoretical foundation preparation, and administrative preparation and research proposals. From July to December 2025, the treatment stage of experimental animals to the preparation of a thesis was carried out.

Making Sea Pandan Fruit Extract (*Pandanus tectorius*)

Thick ethanol extract of sea pandan *(Pandanus tectorius)* is made using fresh ingredients weighing about 10 kg obtained from Pangandaran Beach, Pangandaran District, Pangandaran Regency, West Java Province. Sea pandan fruit samples were first taxonomic tested at the Laboratory of Plant Bioscience and Technology, Department of Biology, Faculty of Natural Sciences, Sepuluh Nopember Institute (ITS) and the extraction process was carried out at the Pharmaceutical Laboratory, Faculty of Pharmacy, Hang Tuah University.

Method of making sea pandan fruit extract *(Pandanus tectorius)* carried out in several stages. A sample of 10 kg of sea pandan fruit is first cleaned and cut into small pieces. Then, the sample is dried using an oven at 50°C for 12 hours. After drying, the fruit is macerated using 96% ethanol for 3 x 24 hours with periodic stirring, then the resulting filtrate is filtered using filter paper. All the obtained filtrates are then combined and stirred until homogeneous. It is then vaporized using *rotary vacuum evaporator* until a thick extract is obtained.

Screening Phytochemistry

Phytochemical screening was carried out at the Pharmaceutical Laboratory, Faculty of Pharmacy, Hang Tuah University. Phytochemical screening of sea pandan fruit extract was carried out to identify secondary metabolite compounds such as glycosides, saponins, triterpenoids, flavonoids, steroids, and phenolics. The method used is to add reagents to each compound analyzed.

Manufacture of Sea Pandan Fruit Extract Concentration

The extracted sea pandan fruit is then diluted using aquades to produce a solution with concentrations of 10%, 20%, and 30%, respectively. This dilution process is carried out based on concentration calculations using the weight per volume formula (b/v). To obtain a 10% solution, as much as 10 grams of extract is dissolved in 100 ml of aquades. The 20%

concentration is made by dissolving 20 grams of the extract into 100 ml of aquades, while the concentration of 30% is obtained by mixing 30 grams of the extract into 100 ml of aquades. The entire solution is then homogenized until evenly mixed.

The selection of concentrations of 10%, 20%, and 30% is based on scientific considerations that the ranges are safe for topical application in experimental animals, are often used in natural material-based research, and allow for evaluation of dose-response relationships. The 10% concentration was chosen as a low dose which could theoretically already provide an initial pharmacological effect because the bioactive compound content of the extract is still quite high even in small amounts. A concentration of 20% was chosen as a medium dose to evaluate the proportional improvement of the biological response without increasing the risk of tissue irritation. Meanwhile, the concentration of 30% was chosen as a high dose because it is the maximum concentration limit that is still physically stable and does not interfere with the texture or distribution of the preparation. In addition, some studies of plant extracts for wound healing in mice have used a concentration range of 10-30% and shown optimal therapeutic effects before reaching the plateau point. Thus, concentrations of 10%, 20%, and 30% were chosen to ensure that there was a wide enough dose variation to observe the dose-response relationship, but remained within a safe, stable, and formulationally feasible range for topical use in experimental animals (Don *et al*., 2018; Ranti *et al*., 2024; Repent *et al*., 2024)

Preparation of Sea Pandan Fruit Ethanol Extract Gel Preparation (*Pandanus tectorius*)

The gel preparation is made by mixing CMC-Na with glycerin, benzoic acid, and aquades, then adding sea pandan fruit extract (*Pandanus tectorius)* until a gel formulation with concentrations of 10%, 20%, and 30% is obtained (Astanti *et al*., 2022).

Table 2. Sea Pandan Fruit Ethanol Extract Gel Formula

Ingredients	Formula			Function
	I	II	III	
Sea pandan fruit extract (b/v)	10%	20%	30%	Active substances
The CMC (b/f)	3,5%	3,5%	3,5%	*Gelling Agent*
Asam Benzoat (b/v)	0,2%	0,2%	0,2%	Preservatives
Gliserin (b/f)	5%	5%	5%	Humectant
Aquadest	ad 100 g	ad 100 g	ad 100 g	Missing Pens

Preparation of Experimental Animals

The preparation of experimental animals begins with an adaptation process for 7 days so that the rats can adjust to the laboratory environment, thereby minimizing stress events in the rats. The mice were placed separately in a 40 x 30 x 20 cm plastic cage made of wood powder and divided into 5 groups at random. The enclosure is placed in a room with adequate air circulation and light saturation, not damp, not exposed to direct sunlight, and free from noise. The cleanliness of the cage is maintained by cleaning every two to three days. Feed and drink are placed in bottles with pipes. Weight weighing was carried out 1 time, namely before entering the adaptation period. Mice will be excluded from the study if they become ill or die during or after the adaptation process.

Incision Wound

Incision is carried out on the 8th day after the adaptation. The wound incision procedure is by anaesthesia rats using ketamine before being given an incision wound. The hair of the test animal in the incision area is shaved first with a size of 3 x 2.5 cm to facilitate the incision process. Before the incision is made, disinfectant using alcohol is carried out on the area of the skin that has been shaved. The wound was incised using *a sterile scalpel* with a length of 2 cm and a depth of 0.2 cm parallel to the *Os Vertebrae*.

Stages of Treatment

The rats were divided into 5 groups and each group was put in a different cage. The treatment of groups 1, 2, 3, 4, and 5 is as follows:

1. Group 1: negative control, i.e. mice were given incision wounds and gel base topically twice a day
2. Group 2: positive control, i.e. mice were given incision wounds and then treated with standard drug Bioplacenton twice a day.
3. Group 3: concentration I, namely rats were given incision wounds and then treated with 10% marine pandan *(Pandanus tectorius)* ethanol extract gel topically twice a day
4. Group 4: concentration II, namely rats were given incision wounds and then treated with 20% marine pandan *(Pandanus tectorius)* ethanol extract gel topically twice a day
5. Group 5: concentration III, namely rats were given incision wounds and then treated with 30% marine pandan *(Pandanus tectorius)* ethanol extract gel topically twice a day

Hydroxychlorine Levels Measurement

Hydroxycrolin levels were measured to evaluate collagen formation in the skin tissue of incision wounds of male rats (*Rattus norvegicus*) after the administration of sea pandan *fruit extract gel (Pandanus tectorius).* The procedure begins with the manufacture of a standard solution of hydroxyproline, which is by dissolving 50 mg of pure hydroxyproline into 50ml of aquades so that a parent solution with a concentration of 1000 ppm is obtained. From this solution, a hydroxychlorine solution with a concentration of 100 ppm is made by taking 5 ml of the parent solution and adding aquades to the entire volume to 50 ml.

To determine the maximum absorbance wavelength, a 100 ppm solution is diluted to 9 ppm by mixing 0.9 ml of a standard 100 ppm solution with aquades to a final volume of 10 ml. A total of 1 ml of 9 ppm solution was reacted with 1 ml of CuSO4, 1 ml of NaOH, and 1 ml of H_{2O2} and then incubated in an oven at 80^{oC} for 5 minutes. After cooling the solution is added 2 mL of 2-dimethylaminobenzaldehyde and 4 ml of $H_{2SO4,}$ then reheated at 70^{oC} during with a UV-Vis spectrophotometer in the wavelength range of 200-800 nm to determine the maximum wavelength.

The next stage is the making, a standard curve of hydroxychlorine as a reference to determine hydroxychlorine levels in the skin of rats. From a 100 ppm solution, six variations of hydroxyproline solution concentration were made, namely 9, 18, 27, 36, 45, and 54 ppm. Each is made by pipetting a 100 ppm parent solution of 0.9; 1,8; 2,7; 3,6; 4.5 and 5.4 ml are then diluted by adding aquades to a final volume of 10 ml.

Each concentration was pipetted with 1 ml and reacted with 1 ml of $CuSO_4$ 0.01 N, 1 ml of NaOH 2.5 N, and 1 ml of 6% H_2O_2. The mixture is heated in the oven at 80°C for 5 minutes. After cooling, the solution is given 4 ml of 3M H_2SO_4 and 2 ml of 5% 2-dimethyl-aminobenzaldehyde solution, then reheated at 70°C for 16 minutes. The absorbance of each

solution was measured using a UV-Vis spectrophotometer at a maximum wavelength of 560 nm. The results of absorbance measurements from six concentration variations were used to construct a standard curve, which was then used as a reference in determining hydroxychlorine levels in rat skin tissue.

The procedure for analyzing hydroxychlorine levels begins with sampling the scar skin tissue with a biopsy. The sample is put in aluminum foil and dried in an oven at 60°C for 12 hours. The dry sample was hydrolyzed using HCS 6 N solution for 24 hours in an oven at 110°C. After hydrolysis, the solution is neutralized with NaOH until it reaches pH 7 and stabilized with a datar solution. The solution is added 1 ml of $CuSO_4$, NaOH, and H_2O_2 each, then heated in the oven at 80°C for 5 minutes. After cooling, 4 ml of $3M_{H2SO4}$ and 2 ml of 2-dimethyl-aminobenzaldehyde are added and then ovened at 70°C for 16 minutes. Once it reaches room temperature, the absorbance is measured with a UV-Vis spectrophotometer at a predetermined wavelength. The value of hydroxyproline levels in rat skin was determined using a linear regression equation obtained from the hydroxyproline standard curve.

Data Management

This study uses data management in the form of:

1. Data Capture
2. Data Collection
3. Data Analysis

Data Analysis

Data analysis in this study was focused on the evaluation of hydroxychlorine levels of rat skin tissue after the administration of *Pandanus tectorius fruit ethanol extract gel.*The absorbance data obtained from the spectrophotometer were substituted into the linear regression equation of the standard curve result (y = a + bx) to obtain the hydroxycycline level values of each sample.

The values of hydroxychlorine levels that have been obtained are then analyzed using *the Shapiro-Wilk normality test and* the Levene *variance homogeneity test* to ensure that the parametric assumptions are met. If both assumptions are met, the analysis is followed by a *One-Way Analysis of Variance* (ANOVA) test to determine the difference in hydroxychlorine levels between treatment groups. If ANOVA shows a significant difference ($p < 0.05$), then a *post-hoc Duncan follow-up test* is carried out to identify a significantly different group.

RESULT AND DISCUSSION

Research Results Data

This research was carried out at the Biomolecular and Hyperbaric Laboratory, Faculty of Medicine, Hang Tuah University for 17 days. This study aims to determine the potential of *ethanol extract of Pandanus tectorius* in increasing hydroxycrolin levels as a parameter for collagen formation in the process of healing rat incision wounds by using 30 male white rats of the Wistar strain divided into 5 groups, namely:

1) K (-) : Negative control group, i.e. white rat group (*Rattus norvegicus*) adult male strain Wistar who is given incision wounds and gel base topically twice daily
2) K (+) : Positive control group, i.e. white rat group (*Rattus norvegicus*) adult male Wistar strain was given an incision wound and then treated with the standard drug Bioplacenton twice a day.

3) KP1 : Treatment group I, i.e. the white rat group (*Rattus norvegicus*) adult male strain of Wistar who was given an incision wound and then treated with a sea pandan fruit ethanol extract gel *(Pandanus tectorius)* 10% topically twice a day
4) KP2 : Treatment group II, namely the white rat group (*Rattus norvegicus*) adult male strain of Wistar who was given an incision wound and then treated with a sea pandan fruit ethanol extract gel *(Pandanus tectorius)* 20% topically twice a day
5) KP3 : Treatment group III, namely the white rat group (*Rattus norvegicus*) adult male strain of Wistar who was given an incision wound and then treated with a sea pandan fruit ethanol extract gel *(Pandanus tectorius)* 30% topically twice a day

Hydroxychlorine Levels Testing

Based on the standard curve made from 6 variations in hydroxyproline solution concentration, a linear regression equation y = 0.0051x + 0.0012 with a correlation coefficient r = 0.9939 was obtained. The value shows an excellent level of linearity because it is close to the number 1. This regression equation was then used to determine hydroxychlorine levels in skin tissue samples of mice that had been treated for 10 days.

The calculation of hydroxychlorine levels is carried out by substituting the absorbance value of the sample into the variable y in the regression equation so that an x value, which is the level of hydroxychlorine in skin tissue, will be obtained. The results of the measurement of hydroxychlorine levels from all treatment groups are as follows:

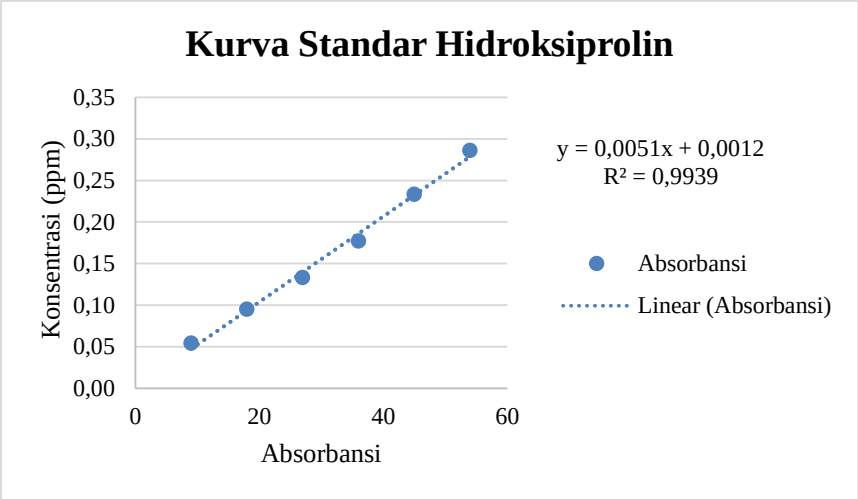

Figure 1. Hydroxychlorine Standard Curve

Table 3. Hydroxychlorine Levels from Rats' Skin Tissue

Treatment Groups	When hydroxyproline (µg/ml) ± SEM
K(-)	440.09 ± 48.76
K(+)	591,75 ± 29,9
KP 1	536,42 ± 34,37
KP 2	575,46 ± 20,84
KP 3	504,72 ± 35,67

Based on the results of the measurement of hydroxychlorine levels of rat skin tissue in Table 3, in the negative control group (K(-)) it was 440.09 ± 48.76 µg/ml, while in the positive control group (K(+)) it was 591.75 ± 29.9 µg/ml. In the ethanol extract gel treatment

group for sea pandanus, the concentration of 10% (KP1) was 536.42 ± 34.37 µg/ml, the concentration of 20% (KP2) was 575.46 ± 20.84 µg/ml, and the concentration of 30% (KP3) was 504.72 ± 35.67 µg/ml.

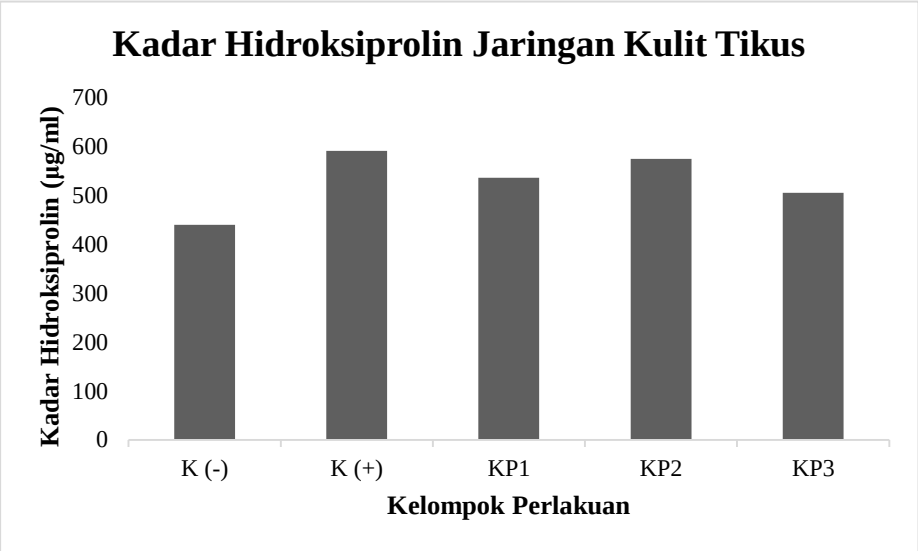

Figure 2. Hydroxychlorine Levels Histogram of Rat Skin Tissue

The results are also presented in Figure 3, which shows the differences in hydroxychlorine levels between treatment groups. KP2 had relatively higher levels of hydroxychlorine than the other treatment groups, although it was lower than the positive control group. This indicates that ethanol extract gel for sea pandanus has the potential to increase collagen synthesis in rat skin tissue during the healing process of incision wounds.

Shapiro-Wilk *Normality Test Results*

Before determining the appropriate type of statistical analysis, a normality test is carried out first on the research data. This study used the *Shapiro-Wilk* Normality Test because the number of samples in each group was less than 50. If the test results show a normal data distribution ($p > 0.05$), then the analysis is continued with the variance homogeneity test. Normality tests were carried out on all groups, namely negative control group, positive control, treatment group 1 (KP1), treatment group 2 (KP2), and treatment group 3 (KP3). The results of the normality test from each group are presented in Table 4 below:

Table 4. Normality Test Results

Treatment Groups	*p-value*	Distribution
K(-)	0,838	Normal
K(+)	0,785	Normal
KP 1	0,319	Normal
KP 2	0,121	Normal
KP 3	0,819	Normal

Shapiro-Wilk *test description*:

a. If the significance of $p > 0.05$, then the data distribution is normal (H0 is accepted).

b. If the significance of p < 0.05, then the data distribution is abnormal (H0 is rejected).

Based on the results of the *Shapiro-Wilk* normality test on the hydroxychlorine levels of rat skin tissue, *a p-value* was obtained in all treatment groups greater than 0.05. The *p-value* in the negative control group (K(-)) was p = 0.838, the positive control (K(+)) was p = 0.785, treatment group 1 (KP1) was p = 0.319, treatment group 2 (KP2) was p = 0.121, and treatment group 3 was p = 0.819 (KP3).

Because the whole value *p-value* > 0.05, the hydroxychlorine level data in all groups is normally distributed, so the zero (H0) hypothesis is accepted. Thus, the data meet the assumption of normality and can be attributed to the Homogeneity of Variance test (*Levene Test).*

Results of the Variance Homogeneity Test (*Levene Test)*

The variance homogeneity test was carried out using *the Levene Test* in each group, namely negative control group, positive control, treatment group 1 (KP1), treatment group 2 (KP2), and treatment group 3 (KP3). If the test results show that the variance between groups is homogeneous, then the analysis can be continued with a parametric statistical test, while if the variance is not homogeneous, then a non-parametric statistical test is used. The results of the variance homogeneity test are presented in Table 5 below:

Table 5. Variance Homogeneity Test Results

Variable	*Levene Statistic*	Sig. (*p-value)*	Remarks
Up to Hydroxyproline	0,449	0,772	Homogeneous

Levene Statistic *variance homogeneity test description*:

a. If the significance > 0.05 then the variance of the data is homogeneous.

b. If the significance < 0.05 then the data variance is not homogeneous.

The results of the variance homogeneity test in Table 5.5 show that the significance value obtained is p = 0.772 (p > 0.05). This indicates that the variance of data between groups is homogeneous. Then the analysis can be continued using a parametric statistical test, namely the *One-Way ANOVA test.*

ANOVA One-Way *Test Results*

The *One-Way ANOVA* test is a parametric statistical test used to determine whether there is a difference in the average hydroxyproline level between the negative control group, positive control, treatment group 1 (KP1), treatment group 2 (KP2), and treatment group 3 (KP3). The selection *of One-Way ANOVA* was based on the number of study groups that were more than two, the measurement of hydroxycycline levels performed once after 10 days of treatment, and the fulfillment of the assumptions of normal distribution and homogeneity of variance in the study data.

Hypothesis:

H0 : Ethanol extract gel of sea pandan *fruit (Pandanus tectorius)* has no effect on hydroxyproline levels as a parameter of collagen formation in the incision wound healing process in male *Rattus norvegicus*.

H1: Ethanol extract gel of sea pandan *fruit (Pandanus tectorius)* has an effect on increasing hydroxychlorine levels as a parameter for collagen formation in the incision wound healing process in male *Rattus norvegicus*.

Table 6. ANOVA One-Way Test Results

Variable	*p-value (*ANOVA)	Remarks
Hydroxyproline	0,032	Signifikan

The Anova One-Way *test description* is:
a. If the significance of p > 0.05 then H0 is accepted, H1 is rejected.
b. If the significance of p < 0.05 then H0 is rejected, H1 is accepted.

Based on the results of *the One-Way ANOVA test* in Table 7, the hydroxychlorine levels of rat skin tissue between treatment groups showed a significance value of p = 0.032 (p < 0.05). These results indicate that there was a statistically significant difference in the hydroxychlorine levels of rat skin tissue between the treatment groups. Thus, the zero hypothesis (H0) is rejected and the alternative hypothesis (H1) is accepted, which means that the administration of the treatment has an effect on the hydroxychlorine levels of the rat skin tissue.

Because the results of the One-Way ANOVA test showed significant differences, the analysis was continued with a post *hoc* test to find out the group pairs that had significant differences in hydroxychlorine levels.

Duncan Post-Hoc *Test*

Because the results of the One-Way ANOVA test showed a significant difference between the treatment groups (p < 0.05), the analysis was continued with the *Post-Hoc Duncan test.* The *Duncan* test was used to find out which groups had significant differences in hydroxychlorine levels after the administration of Pandanus *tectorius fruit ethanol extract gel.*The results of the follow-up test are presented in Table 8 below:

Table 7. Duncan Post-Hoc Test Results

Treatment Groups	N	Subset 1	Subset 2	Notasi
K(-)	6	440,09		a
KP3	6	504,72	504,72	off
KP 1	6	536,42	536,42	off
KP 2	6		575,46	b
K(+)	6		591,75	b
Say.		0,069	0,110	

The results of *the Duncan* test showed that the treatment group was divided into two homogeneous subsets. The first subset (notation a) consists of K(-), KP3, KP1, which show no significant difference from each other (p = 0.069. The second subset (notation b) consists of KP3, KP1, KP2, and K(+), which also do not differ significantly from each other (p = 0.110). This suggests that groups in the same subset do not have statistically significant differences in hydroxychlorine levels.

The KP3 and KP1 groups showed an *intermediate position,* namely the average value of hydroxycroline levels in KP3 and KP1 was between groups with lower and higher hydroxycroline levels, so that the groups experienced *overlap* between homogeneous subsets.

Meanwhile, the KP2 and K(+) groups were in the subset with higher average values of hydroxychlorine levels than the other groups. This suggests that both groups had a greater tendency to increase hydroxycroline levels, although in *the Duncan* test not all pairs showed statistically significant differences.

This study aims to determine the effectiveness of administering ethanol extract gel of sea pandan fruit (Pandanus tectorius) for 10 days in increasing hydroxychlorine levels as a parameter for collagen formation in the healing process of Rattus norvegicus' incision wounds. The results of this study showed that the positive control group showed the highest results, followed by the treatment group 2. This indicates that the administration of 20% concentration of sea pandan fruit ethanol extract gel can stimulate collagen formation more effectively than other treatments. This study shows that sea pandan ethanol extract gel can be an effective alternative in the process of healing incision wounds.

Hydroxychlorine is a collagen-specific amino acid used as a quantitative indicator of tissue collagen formation. Increased hydroxychlorine levels reflect increased collagen synthesis during the wound healing process, especially in the proliferation phase.

The results of the measurement of hydroxycycline levels of rat skin tissue stated that the best concentration was in the group of mice given Pandanus tectorius ethanol extract gel with a concentration of 20%. Increased wound healing effectiveness can be seen from the extract concentration of 10% to a concentration of 20%. However, the 30% concentration extract did not show a significant improvement over the 20% concentration, indicating that the healing effect reached the optimum point at the 20% concentration. A concentration of 30% indicates a moderate response, possibly due to too high a dose, mild irritation that inhibits tissue regeneration, or a gel extract formulation that is too concentrated so that absorption to the skin is not optimal. This suggests that increasing the dosage of the extract does not always provide additional effects after reaching optimal concentrations.

The acceleration of wound healing in the treatment group is related to the content of bioactive compounds in the Pandanus tectorius fruit, such as flavonoids, alkaloids, saponins, and terpenoids that act as antioxidants, anti-inflammatories, and tissue regeneration stimulants (Ningsih, Chatri and Advinda, 2023). Flavonoids have the ability to reduce oxidative stress and accelerate the resolution of inflammatory phases, increase the expression of transforming growth factor-beta (TGF-β) which plays a role in the proliferation phase, and stimulate fibroblasts to increase collagen formation (Amfotis, Suarni and Arpiwi, 2022). Flavonoids play an important role in activating wound healing pathways through the modulation of various cellular mediators. Flavonoids can promote the proliferation and migration of fibroblasts, which are responsible for collagen synthesis in the proliferation phase of wound healing. The activation of fibroblasts occurs through increased expression of transforming growth factor-beta (TGF-β), followed by fibroblast differentiation and stimulation of extracellular matrix deposition, including collagen types I and III. This increased synthesis is then reflected in increased levels of tissue hydroxychlorine as a biochemical marker of collagen formation. In addition, the antioxidant properties of flavonoids help lower excessive ROS (Reactive Oxygen Species) in the wound area, thereby preventing cell damage and allowing the collagen synthesis process to take place more optimally (Zulkefli et al., 2023). Thus, the flavonoid content in the ethanol extract of the

Pandanus tectorius fruit contributes directly to improving the quality of wound tissue through stimulation of collagen formation.

The progression of wound healing is also influenced by the selection of topical drug preparations in the form of gels that have the advantage of drying easily, having a cool sensation, very stable, maintaining skin moisture because they remain in the wound tissue for a long time, and do not irritate the skin, so they are easy to use (Astanti et al., 2022). This affects the penetration ability of the gel on soft tissue wounds which affects the anti-inflammatory, antioxidant, antibacterial, and stimulant properties of collagen synthesis contained in the Pandanus tectorius fruit extract compound used (Lubis et al., 2020; Lallo et al., 2020).

The effects observed in this study show that ethanol extract of sea pandan fruit has the potential to increase collagen formation, which can be seen from hydroxycrolin levels as a major biochemical marker. These results are in line with the findings of Bâldea et al. (2023), who report that gel preparations containing bioactive compounds with high antioxidant activity are able to accelerate collagen synthesis and wound tissue regeneration. Overall, this study shows that the ethanol extract gel of sea pandanus fruit (Pandanus tectorius) has a positive effect on the healing process of incision wounds in male white rats (Rattus norvegicus). The effect was demonstrated through increased hydroxychlorine levels in the treatment group, which signaled stimulation of fibroblast activity and increased collagen desposition.

This study has several limitations that need to be considered, namely the relatively short duration (10 days) so that it only represents the inflammatory phase and the proliferation phase, and the evaluation is only carried out at one point in time (day 10). In addition, the results of the study were limited to the incision wound model with the use of Bioplacenton® as the only positive control. Therefore, further research is needed with a larger sample size, assessment at several points in time, and variations of several concentrations of sea pandan fruit extract to find out other concentrations that are more optimal and safe.

This discussion can conclude that the speed of wound healing can be influenced by several factors, such as the psychological condition of the test animal, the environment, and the therapy given. This study showed that the treatment group with a concentration of 10%, 20%, and 30% of sea pandan ethanol extract gel had a higher wound healing speed than the negative control group. This can be seen from hydroxyproline levels, where the treatment group showed faster wound healing and increased hydroxyproline levels as an indicator of collagen formation. The most optimal effect was seen in the 20% concentration group, which had the narrowest distribution and the highest hydroxycroline levels, indicating a more consistent collagen deposition compared to other concentrations ($p=0.032$). Based on the results of the One-Way ANOVA test followed by the Post Hoc Duncan test, no significant difference was found between the specific treatment group and the positive control group (Bioplacenton®), which interpreted that the ethanol extract gel of sea pandan fruit had an effectiveness comparable to therapy in healing incision wounds.

CONCLUSION

Based on the results of a study on the effectiveness of ethanol extract of sea pandan fruit (Pandanus tectorius) in increasing hydroxyproline levels as a parameter for collagen formation in the process of healing incision wounds in Rattus norvegicus, it can be concluded that the administration of marine pandan fruit ethanol extract with a concentration of 10% indicates an increase in hydroxyproline levels, although the effect is still limited. Administration of the extract with a concentration of 20% gives the most optimal results, which shows increased hydroxychlorine levels and better collagen formation in the wound healing process. However, the administration of the extract at a concentration of 30% did not provide a higher increase in hydroxychlorine levels compared to a concentration of 20%. Therefore, the dose of marine pandan fruit ethanol extract that has the most potential to increase hydroxycrolin levels in the healing of incision wounds in rats is a form of topical preparation with a gel concentration of 20%.

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