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ORIGINAL ARTICLE

Effectiveness of green betel leaf extract cream in healing cut wounds

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Abstract

Green betel leaf (*Piper betle* L.) is widely used in the healing of cut wounds. The aim of this study was to investigate the efficacy of green betel leaf extract cream in the healing of cut wounds on the skin of white Wistar rats. The design employed was a pre-test post-test with a control group design and a sample size of 20 white rats divided into four groups. Betel leaf extract was prepared using the maceration method, while a cream preparation of betel leaf extract was prepared using the oil-in-water emulsion type (M/A). Macroscopic histopathological evaluation was performed by examining fibroblast growth. A one-way analysis of variance (ANOVA) test ($p < 0.05$) was used to determine the difference between groups, and a post hoc least significant difference (LSD) test was used to analyze which treatment group had the greatest efficacy. Technical terms were explained upon first use, and the language used was clear, objective, and value-neutral to improve academic quality. The text was free from grammatical errors, spelling mistakes, and unnecessary jargon. A one-way analysis of variance (ANOVA) test ($p < 0.05$) was used to determine the difference between groups, and a post hoc least significant difference (LSD) test was used to analyze which treatment group had the greatest efficacy. The study revealed a substantial difference in the average wound healing rates between the control group (P0) and treatment groups P1, P2, and P3. This is due to the lack of active substances in the control group (P0), which aids in accelerating the wound healing process. Notably, the 15% green betel leaf extract cream demonstrated superior efficacy in healing wounds in white rats compared to the 10% and 25% green betel leaf extract creams. The results indicated no significant difference between the application of 15% and 25% green betel leaf extract cream. This is due to the fact that secondary metabolite compounds present in the extract produce a healing effect on wounds at these particular levels. However, lower concentrations only act as microorganism inhibitors, rendering them less effective for promoting wound healing.

Keywords: green betel leaf extract cream, cut wounds, wistar rat

Introduction

The skin is the outermost organ of the body and functions in protection, absorption, excretion, body temperature regulation, pigment formation, vitamin D, and creatination.[1,2] It also has the most contact with the outside world, making it susceptible to injury. A wound can be defined as damage to a part of the body that occurs on the skin in the form of a tissue that is cut, torn, or damaged. Wounds also take different forms, depending on the cause, such as open wounds (if there is a tear) or closed wounds (if there is no tear). One example of an open wound is a cut or slash wound.[3–5] Cuts are wounds that can be caused by sharp objects. Its characteristics include open wounds and pain, and the length of the wound is greater than its depth. A cut is a type of wound that can result from the scratching of a rough surface. This type of wound is not very deep but can cause the injured skin surface to be very wide.[6] Open wounds such as cuts are very susceptible to infection, especially by bacteria, and can be an entry point for systemic infection. Infected wounds are slower to heal and often result in exudates and toxins being produced along with the death of regenerating cells.[7,8] Therefore, stimulation of healing and restoration of normal function of the injured body part is required to prevent infection.[9]

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The wound-healing process is important because the skin is the only organ that is frequently exposed to the outside world. When the skin loses its continuity, functions such as protective, sensory, thermoregulatory, metabolic, and sexual signaling will not be able to run as they should. Therefore, the wound healing process requires proper handling and treatment so that the wounded area does not become infected and does not cause chronic wounds.[9–11] The proliferation phase is one of the important stages in wound healing and occurs after the inflammatory phase.[12] The proliferation phase occurs 2 to 10 days after the wound and is characterized by angiogenesis, collagen deposition, granuloma tissue formation, wound contraction, and epithelialization.[13]

Wound care can be performed by administering drugs topically or systemically (orally), or it can be a combination of both in the wound care process.[14] Topically administered drugs can maximize patient compliance because they are easier to use and have lower risks. Topical preparations consisted of creams, lotions, ointments, and gels. Creams are semi-solid emulsions of either water-in-oil or oil-in-water type. The advantage of cream preparations over other topicals is that creams are easier to spread evenly on the surface of the skin.[15,16] Healing and wound care using plants or natural ingredients have been widely used. One such plant or plant that is in the surrounding environment and is widely used in the wound healing process is the green betel leaf (*Piper betle* L.). Green betel plants are widely used for treatment. The part of the betel plant that is widely used as a medicine is the leaf, because it has antiseptic, anti-inflammatory, and skin cooling properties.[17]

Green betel leaves have various properties because their chemical content in betel leaf is very high. Betel leaf in pharmacology can be used as an analgesic, antibisul, antibacterial, antilava, antidiabetic.[18] Betel leaf also contain various bioactive molecules such as saponins, tannins, essential oils, flavonoids, phenols, and hydroxychavicol, which have the ability to help the wound healing process and contain nutrients needed for wound healing, such as vitamin A and vitamin C.[19] Saponins, flavonoids, and tannins can help in the wound healing process because they function as antioxidants and antimicrobials that affect wound splicing and accelerate epithelialization. Betel leaf ethanol extract at a concentration of 10% topically applied on sliced wounds for 14 days can increase the speed of healing of sliced wounds.[20] Betel leaf are often used by the community to eliminate bad breath, treat wounds, stop bleeding gums, thrush, and eliminate body odor. Betel leaf contain 1-4.2% volatile oil and phenol compounds and their derivatives, such as hydroxy cavicol, cavibetol, eugenol, methylugenol, carvacrol, terpenes, sesquiterpenes, phenyl-propanes, and tannins. Kavikol has activity as a bactericide 5 times stronger than phenol.[21]

Several studies have shown that green betel leaf extract can heal wounds. Research by Rinaldi et al.[22] showed that 20% green betel leaf extract gel (using 70% ethanol solvent) was more effective in healing burns in male rabbits than 10% betel leaf extract gel and gel base (control). Nuryahya et al.[23] showed that green betel leaf extract and red betel leaf were effective in treating second-degree burns, where red betel leaf extract was more effective, even though both were equally able to increase the thickness of granulation tissue in the treatment of second-degree burns in male white Wistar rats. Zar'ah et al.[24] showed that green betel leaf extract (using a 95% ethanol solvent) had an effect on wound healing in mice. The 30% concentration was more influential on its use as a wound medicine than the other concentrations (20%, 40%, and distilled water extracts). Research by Afrylyani et al.[25] showed that a mixture of kenikir and green betel leaf extracts had an effect on wound healing in mice with the most effective concentration being the concentration of 7.5% kenikir leaf extract + 7.5% green betel. Gantriani et al.[26] showed that an ethanol extract of green betel leaves at a concentration of 10% was effective in accelerating the healing time of incision wounds in male white Wistar rats compared to other therapy groups (concentrations of 20%, 40%, and povidone iodine). The study of the benefits of betel leaves in wound healing based on the results of previous research is an important reason for researchers to study the effectiveness of green betel leaves in healing cuts. The purpose of this study was to examine the effectiveness of green betel leaf extract cream in the wound healing process on the skin of white wistar rats.

Method

This study used pre test post test design with control group. The samples of this study were 20 adult wistar male white rats divided into 4 (four) groups, consisting of control group (cream base), treatment groups 1, 2, and 3 (betel leaf extract cream 10%; 15% and 25% respectively). The tools used in this study

include minor surgical tools (stainless steel tray, scalpel, blade, scissors and tweezers), scales, sterile gloves, cotton bad, gauze, rat cages, rat feed containers, stationery, markers and calipers. The materials used include green betel leaf, glycerin, triethanolamine (TEA), ethyl alcohol, acetic acid, methyl paraben, propyl paraben, distilled water, sterile tampons, anaesthesia (ketamine), xylasin, wistar white rats, rat food and drink.

The preparation of green betel leaf extract in this study was carried out by maceration using 90% ethanol solvent. The results of previous studies related to the manufacture of green betel leaf extract mostly used 70% ethanol solvent[17,22], 95% ethanol solvent[24], 96% ethanol solvent[18,21,27], distilled water solvent[28], dan methanol solvent[29]. Based on the results of previous studies, to distinguish with the research to be carried out, the manufacture of green betel leaf extract used 90% ethanol solvent. In addition, ethanol is a universal solvent that can dissolve polar and nonpolar compounds. Ethanol is considered as a distiller because it is more selective than water, difficult to grow microbes in 20% ethanol and above and has several other advantages, namely non-toxic, neutral, good absorption, mixes with water in all comparisons, improves the stability of dissolved medicinal materials, and does not require high heat for concentration.

The process of making extracts begins with drying betel leaves using an oven at a temperature of 50-60^{o}C. After drying the betel leaves are blended until they become simplisia (powder). Furthermore, the simplisia or betel leaf powder is immersed in a maceration vessel separately, then given 90% ethanol solvent until the betel leaf powder is completely submerged. The maceration vessel was then closed tightly and allowed to stand for ± 5 (five) days while stirring 1 (one) time every day. The results obtained were then filtered and repeated 3 (three) times, then collected in a bottle. The extract obtained was then evaporated with a rotary evaporator at 70^{o}C with the aim of evaporating ethanol so that a thick extract of green betel leaf was obtained.

Preparation of betel leaf extract cream using oil-in-water (M/A) emulsion type. Type M/A is very good and suitable for topical application on wounds including cuts because it can absorb water. The oil phase ingredients, namely stearic acid (emulsifier), cetyl alcohol (emulsifier and thickener), and propyl paraben (preservative), were separated from the water phase, namely TEA (emulsifier), glycerin (humectant), methyl paraben (preservative) distilled water (solvent). The ingredients of the oil phase and water phase were then heated to a temperature of 55^{o}C until everything melted. Next, the green betel leaf extract was dissolved in a portion of distilled water, then put into the water phase and stirred until homogeneous, then put the oil phase little by little into the water phase, mixed and stirred constantly until room temperature and a cream base or cream was formed. The cream is then put in a container. All ingredients were weighed according to the desired concentration or dose (Table 1).

The F0 dose was prepared by adding distilled water until the total weight of the ingredients reached 100 g (without green betel leaf extract). Preparation of dose F1 (10% cream) was done by including 10 g of betel leaf extract, F2 (15% cream) included 15 g of green betel leaf extract, and F3 (25% cream) required 25 g of green betel leaf extract. All doses were added to the ingredients as shown in Table 1, and distilled water was added until the total weight of the ingredients was 100 g.

Tabel 1. Green betel leaf extract preparation formula

Materials	Formula/cream dose (gram)			
	F0	F1	F2	F3
Green betel leaf extract	0	10	15	25
Setil alkohol	4	4	4	4
Gliserin	15	15	15	15
TEA (trietanolamin)	3	3	3	3
Asam stearat	12	12	12	12
Metil paraben	0,2	0,2	0,2	0,2
Propil paraben	0,02	0,02	0,02	0,02
Aquades	100	100	100	100

Prior to wounding, the fur around the wound area (back) of the rats was shaved according to the desired incision area. After shaving, the rats were deprived of consciousness using a combination of ketamine (80 ml/kg BW) and xylasin (5 ml/kg BW) so that they did not feel pain and avoided excessive movement that would be caused by the rats when making the incision wounds. The mice were then wounded by cutting with a scalpel blade along ± 2 cm to the dermal layer. After the incision wound was made, treatment was given based on the wound care protocol and continued according to the treatment group that had been determined: 1) Control group (P0): The wound was treated with a cream base (0% betel leaf extract) and covered with gauze; 2) Treatment group 1 (P1): the wound was treated with 10% green betel leaf extract cream and then covered with gauze; 3) Treatment group 2 (P2): the wound was

treated with 15% green betel leaf extract cream and then covered with gauze; and 4) Treatment group 3 (P3): the wound was treated with 25% green betel leaf extract cream and then covered with gauze.

Wound treatment of white rats was carried out twice a day, namely in the morning and evening, for 14 days. Wound healing in white rats was observed by measuring the average length of the wound every day from the first day of wounding until day 14. Observations were made for up to 14 days according to the length of the normal wound healing process to reach the proliferation phase, which lasted around days 3 and 14 after the wound. After 14 days, all rats were euthanized by inhalation of excess technical chloroform.

Histopathological evaluation was performed macroscopically by examining fibroplast cell growth. The procedure started with excision of 2 × 2 cm of mouse skin at the midline of the back. Skin tissue was cut transversely to determine the number of fibroblasts. Wistar rat skin tissue was stored in a urine pot, soaked in 10% formalin, and stained with hematoxylin and eosin (H&E) at the Microbiology Laboratory of the University of North Sumatra. The number of fibroblast cells was counted using a digital analysis method, and each preparation was photographed with a camera and microscope at 400x magnification, photographed at 4x and stored. Photographic analysis of the number of fibroblast cells was carried out using Image Raster 3 software. Fibroblast cell tissue that appeared from the results of the histological examination was recorded as a red pixel by the software. Tissues with different colors were selected and recorded as other tissue pixels. The number of fibroblasts was calculated as the percentage of fibroblasts visible in the field of view.

The data were analyzed using SPSS. To test for differences between groups, one-way ANOVA was used ($p < 0.05$). To analyze which treatment group was most effective, a post-hoc test was conducted using the LSD technique.

Results

From the results of the phytochemical test of green betel leaf extract carried out, the phytochemical content in the extract found is flavonoids, saponins, tannins and alkaloids. Flavonoid content was found in green betel leaf extracts treated with ethyl acetate, n-hexane, and 90% alcohol. Flavonoids dissolve in polar solvents such as alcohol, resulting in the highest flavonoid content in extracts obtained using 90% alcohol solvents. After the addition of magnesium powder, positive results were indicated by changes in the color of the solution to red, yellow, and orange in the amyl layer. Examination of saponins in green betel leaf extract yielded positive results using n-hexane and distilled water reagents. The foam was stable after administration of HCL 2N. Tannin testing showed that tannin was present in the green betel leaf extract with ethyl acetate solvent and iron (III) Chloride or FeCl3 reagent, as indicated by the blackish-green test results. For alkaloids, this test produces a brown precipitate that is produced slightly because the wagner reagent used is only a little.

Observation of incision wound healing was performed every 2 days for 14 days in the four treatment groups. In the P2 treatment group, there was a better average percentage of incision wound healing (0.99 cm), which was calculated from the average healing from the first to the 14th day. In the P0, P1, and P3 groups, the average incision wound healing was 1.30 cm, 1.20 cm and 1.10 cm respectively. In groups P0, P1, and P3, the average reductions in wound length that occurred in each group from the initial condition were 1.36 cm, 1.63 cm and 1.89 cm. It can be concluded that the healing of incision wounds in group P2 or the group given green betel leaf extract cream with 10% levels occurred faster, followed by group P3 with similar results. The slowest wound healing occurred in the control group (P0) and the group that did not receive any treatment.

Table 2. Average wound healing (cm)

Day	P0	P1	P2	P3
2	1.96	1.86	1.78	1.94
4	1.68	1.75	1.51	1.71
6	1.55	1.50	1.30	1.50
8	1.31	1.21	1.15	1.21
10	1.11	0.99	0.76	0.76
12	0.87	0.71	0.34	0.47
14	0.64	0.37	0.10	0.11
Average	1.30	1.20	0.99	1.10

The results of the one-way ANOVA test show that the variance of the data on the results of the research variables of the control group (P0), P1, P2, and P3 are homogeneous or come from a population with the same variance of 0.801 (($p>0.05$). There was a significant difference in the average width of the in

Table 3. Post hoc LSD results

(I) Group	(J) Group	p
P0	P1	0.000
	P2	0.000
	P3	0.000
P1	P0	0.000
	P2	0.163
	P3	0.000
P2	P0	0.000
	P1	0.163
	P3	0.000
P3	P0	0.000
	P1	0.000
	P2	0.000

cision wound (cm) among all observation groups ($p<0.05$). Therefore, it is necessary to conduct a post- hoc test to determine which groups are different. The test results showed a difference in the mean per-centage of incision wound healing between the groups.

The healed wounds in the four groups were observed for 14 days based on the condition of wound healing by observing the pre-sence or absence of redness (erythema), swelling, and wound closure. As shown in Table 5, the disappearance of erythema (redness) in the control group (P0) occurred from day 9 to day 11, and the fastest disappearance was observed in experimental rats 1, 4, and 5. Treatment group 1 (P1), which occurred from day 8 to day 9, was the fastest in experimental rats 1, 2, and 3. In treatment group 2, which occurred from days 6 to 8, the fastest occurred in experimental rat 1. In treatment group 3 (P3), which occurred on days 6 to 7, the fastest occurred in experimental rat 5. In the control group (P0), the fastest disappearance of swelling was experienced by experimental rats 1, 4, and 5 on day 7. In treatment group 1 (P1), the fastest was experienced by experimental rats 1, 2, and 3 on day six. In treatment group 2 (P2), the fastest was experienced by experimental rat 1 on day four. In treatment group 3 (P3), the fastest was experienced by the experimental rats 5 on day 4.

Table 4. Physiological observation results of the incision wound

Group	Rat-	Wound condition on day-													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
P0	1	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt
	2	Mb	Mb	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt
	3	Mb	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt
	4	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt
	5	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km
P1	1	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km
	2	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km
	3	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt	Km
	4	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km
	5	Mb	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km
P2	1	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km	-	-
	2	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt	Km	Km
	3	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km
	4	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt	Km
	5	Mb	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km
P3	1	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt	Km	Km
	2	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Kt	Km	Km
	3	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km	-
	4	Mb	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km	-
	5	Mb	Mb	Mb	M	M	Kt	Kt	Kt	Kt	Kt	Km	Km	-	-

Exp: Mb (red swollen), M (red), Kt (dry open), Km (dry close)

Figure 1 shows that the number of fibroblast cells in the treatment group treated with 10% green betel leaf extract cream (P1) was higher and denser than that in the control group (P0), 15% green betel leaf extract (P2), and 25% green betel leaf extract (P3). In the control group, fibroblast cells were numerous and rather dense, while in the treatment groups given 15% green betel leaf extract and 25% green betel leaf extract, fibroblast cells were few and sparsely distributed. Fibroblast cell proliferation occurs during this phase. Fibroblasts play a large role in the repair process, which is responsible for the preparation of protein structure products that will be used during the tissue reconstruction process. The activity of flavonoids in increasing the number of fibroblasts is supported by research that concluded that the increase in the number of fibroblasts is caused by flavonoid compounds.[30] At the beginning of healing, fibroblasts have contractile ability and are called myofibroblasts, which will cause the edges of the wound to be attracted and then come closer, so that the two edges of the wound will be attached. As healing progresses, the number of fibroblasts increases. These cells produce collagen, resulting in granulation tissue that will then accumulate connective tissue matrix progressively, eventually resulting in dense fibrosis.[31]

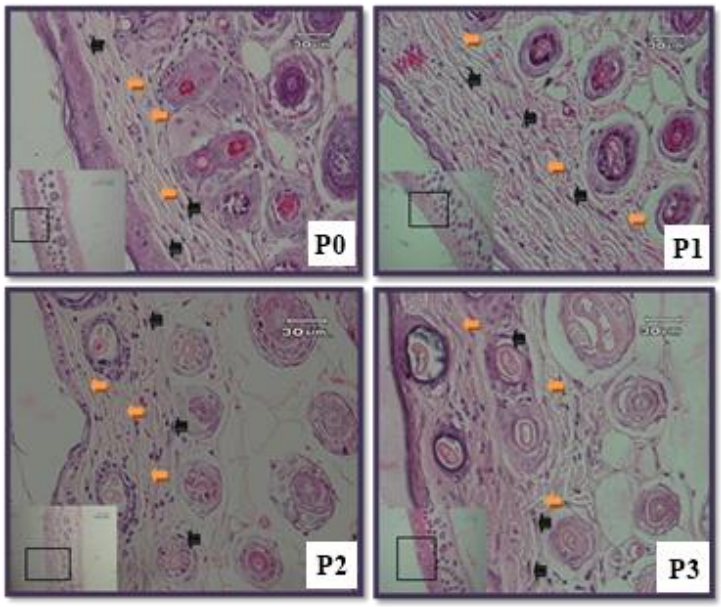

Figure 1. Fibroblasts proliferating on day 14 (magnified 400x)
: fibroblast cell : collagen

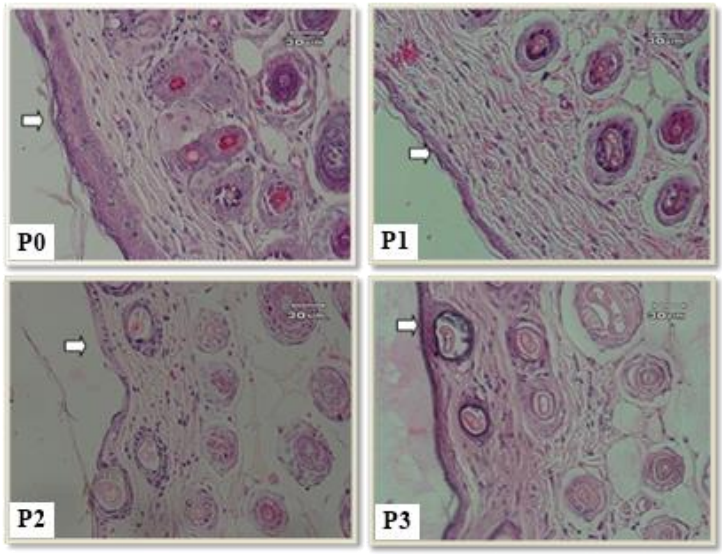

Figure 2. Collagen density on day 14
: Epithelialised wound edges

Discussion

In this study, the wound-healing effect was tested based on the reduction in wound length. The extract used in this study was green betel leaf. The solvent used was ethanol, which meets the requirements for extracting extracts. Ethanol is a universal solvent that can dissolve almost all substances, both polar and non-polar.[32] Then green betel leaf extract is processed into a cream preparation. The amount of solvent used affects the yield because the greater the amount of solvent, the greater the yield.

In this study, the wound was treated with plasters and gauze to prevent infection. However, at the time of the treatment of the incision wound, there were obstacles; namely, the plaster used could not adhere to the skin of the mice so that the plaster was detached and the mice often bit the plaster and gauze. Therefore, the incision wound was treated without plasters and gauze. The incision wound was cut to a length of 2 cm and depth of 0.2 cm, but the widening of the wound was more than 0.2 cm. This occurred because during induction, the rats moved even though they had been administered a local anesthetic, chloroform. The incision wounds were treated daily and the incision wounds were measured daily using a caliper for 14 days. The parameters assessed in this study were the presence of erythema, swelling, and wound closure. Redness (erythema) is the first thing that is seen in areas of inflammation due to the presence of blood clots, which is a reaction to activated platelets and fibrinogen proteins that are released by blood vessels.[33]

Based on the results of visual observations during the ring the study, out of 20 white rats with cuts, erythema and swelling were observed on days 1 to 3 after treatment with concentrations of 10%, 15%, 25%, and no treatment. However, on the 4th day, the P2 and P3 groups experienced a proliferation phase where the tissue formation process returned and did not experience erythema, while the P1 group and no treatment (P0) still experienced erythema. The fastest incision wounds experienced the maturation phase, namely in the 15% extract concentration treatment group (P2) and the 25% extract concentration treatment group (P3), where the 5th rat on the 10th day had closed completely and only had an imprint. In the P1 group and the group without treatment P0, the incision wound has experienced wound closure but has not closed perfectly, forming a scab (scab), which is the proliferation phase. This indicates that the growth of new cells occurred with docking of the wound edges. The formation of this scab indicates that the inflammatory phase ends and is the initial process of the proliferation phase, and the maturation phase is the perfect skin process.

The average wound healing phase on the first day to the 4th day in the group administered betel leaf extract cream, P2 (15%), and P3 (25%) groups, there was an inflammatory phase that showed a faster reduction in wound length than the P1 (10%) group and the control group (K), which experienced an inflammatory phase until the 6th day. This is due to the content of bioactive substances from lemongrass in the form of flavonoids, which can stop bleeding in wounds and act as anti-inflammatory substances that affect the production of inflammatory cells in the inflammatory phase of wound healing. Tannin, as an astrigen, can reduce mucosal permeability, and the bond between the mucosa becomes strong, preventing irritation. Indirectly, tannins affect mucosal permeability and bacterial walls, causing bacteria to shrink and die. Phenolic acid content in lemongrass plays a role in preventing cell damage caused by free radicals to prevent inflammatory processes and inflammation.

In this study, the group treated with 15% green betel leaf extract cream (P2) was more effective than the other groups. However, the treatment group with 25% green betel leaf extract cream (P3) also gave a good healing impact after the P2 treatment group on wound healing in white rats compared to the group giving 10% green betel leaf extract cream and those without treatment (P0). This is because at concentrations of 15% and 25%, secondary metabolite compounds in green betel leaf extract already have an effect on wounds, but at low concentrations only inhibit microorganisms, so they are less effective in wound healing. This is in accordance with the research of Purbowati et al.[34] which concluded that when antibacterial agents are used at small concentrations, they are only inhibitory (bacteriostatic), but when used at high concentrations, they kill microorganisms. The use of cream preparations as an extract formulation is because green betel leaf cream has good physical stability during storage at room temperature for 14 days, marked by no organoleptic changes, pH, adhesion, spreadability, and viscosity, and meets the requirements of the cream dosage form. In addition, the use of cream preparations is easier to apply and is also preferred.[35]

Another factor that can also affect the results of this study is that the number of samples used was less than that in previous studies, where in this study the samples used were only 20 white rats or five rats/group. The number of samples used affects the study because the greater the number of samples used, the smaller the chance of generalisation error.[36] Stress experienced by rats cannot be ignored because it can affect the wound healing process. Stress can trigger an increase in cortisol, which suppresses cellular immunity and can slow wound healing.[37]

Conclusion

The phytochemical test results showed that the green betel leaf extract has phytochemical content that can be utilized as a medicinal substance because it contains high levels of antioxidant compounds. The average wound healing of the control group (P0) compared to that of the treatment groups P1, P2, and P3 was very different. This is because the control group (P0) did not contain active substances that could help accelerate the healing process of the cuts. The 15% green betel leaf extract cream was more effective for wound healing in white mice than the 10% and 25% green betel leaf extract creams. However, the outcome of administering 25% green betel leaf extract cream was not significantly different from that of 15% green betel leaf extract cream. This is because at concentrations of 15% and 25%, the secondary metabolite compounds in green betel leaf extract already have an effect on wounds, but at low concentrations, they only inhibit microorganisms, so they are less effective in wound healing.

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