RESEARCH ARTICLE

Histopathological Evaluation of Second-Degree Burn Healing in Wistar Rats Treated with Aloe vera and Snail Mucus Gel Formulations

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ABSTRACT
Burns are complex dermatological injuries requiring innovative therapeutic approaches. This study tested the hypothesis that Snail Mucus and *Aloe vera* gel combinations could enhance the healing of second-degree burns more effectively than treatments using Bioplacenton as a comparative control. The experiment was conducted with 25 Wistar rats, divided into five groups, each treated with different gel formulations: 10% *Aloe vera* with 10%, 15%, and 20% Snail Mucus, a placebo, and Bioplacenton as the positive control. Second-degree burns were induced, and treatments were applied twice daily for 21 days. Healing progress was monitored through measurements of wound diameter and colour changes. Histopathological evaluation was carried out to see the presence of macrophages and fibroblasts and assess the number of fibroblasts, epithelialization, and expression of Platelet-Derived Growth Factor-Beta (PDGF-BB). Statistical analysis was done using ANOVA and Kruskal-Wallis tests to determine real differences. All Snail Mucus and *Aloe vera* gel formulations significantly accelerated wound healing compared to the placebo. The 20% Snail Mucus formulation exhibited the most rapid healing rates, comparable to the Bioplacenton control. Statistical analysis showed significant differences ($p<0.05$) in wound healing rates, increase in fibroblast activity, epithelialization and PDGF-BB expression between treated and control groups, with the highest concentration gel mirroring the positive control's efficacy. Snail Mucus and *Aloe vera* gels are potent agents in accelerating the healing of second-degree burns, with the 20% Snail Mucus formulation performing on par with Bioplacenton.
Keywords: *Aloe vera*, Burn Healing, Histopathological Analysis, Snail Mucus, PDGF-BB expression, Epithelialization, Fibroblasts.
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INTRODUCTION

The field of dermatological therapy is continually evolving, with recent research increasingly highlighting the efficacy of natural products in wound management. Among these, snail mucus and *Aloe vera* are particularly promising due to their unique properties and constituents facilitating rapid and effective wound healing, especially in burn cases [1,2]. Snail mucus, sourced from the species *Achatina fulica*, has attracted the scientific community's attention due to its powerful healing properties. This natural secretion is rich in several important bioactive compounds or wound-healing processes [2]. Beta agglutinin, one of its main components, helps coagulation during the hemostasis phase and facilitates the formation of thromboplastin, which is important for blood clotting. In addition, snail mucus contains the protein achatin, inhibiting the growth of bacteria and accelerating the inflammatory response, thereby improving the body's natural wound management. Other important constituents include glycoconjugates and acharan sulfate, which are important for binding and storing fibroblast growth factors that promote granulation tissue development. This tissue plays a role in replacing fibrin clots in wounds, providing a scaffold for regenerating new tissue [3,4]. The animal protein content in snail mucus has high biological value in healing and inhibiting inflammatory processes. Improves that snail mucus can be used in healing second-degree burns. Improves that snail mucus influences the number of fibroblasts in healing cut wounds. Based on the results of research conducted by Shoviantari et al., 2021 it is proven that the optimal formulation in healing burns is a 10% concentration of snail mucus [5]. In line with snail mucus, *Aloe vera* has been widely studied for its properties in wound healing. Previous research shows that *Aloe vera* extract can treat wounds more quickly. Based on several studies, the wound healing process will heal faster after applying *Aloe vera* to the skin's surface. *Aloe vera* has moisturizing, wound healing, anti-inflammatory, and antibacterial/ antifungal/ antiviral effects. *Aloe vera* will protect blood clots in the injured area, thereby speeding up wound healing and preventing infection. *Aloe vera* will stimulate epidermal growth factors, maximize the function of fibroblasts (found in connective tissue) and form new

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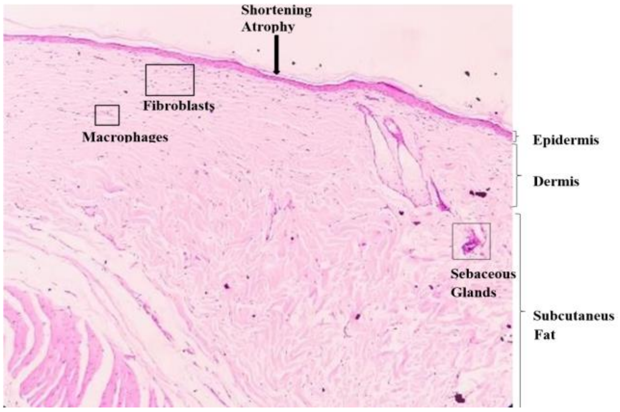

Figure 1. Representative photomicrographs of histopathology for F0

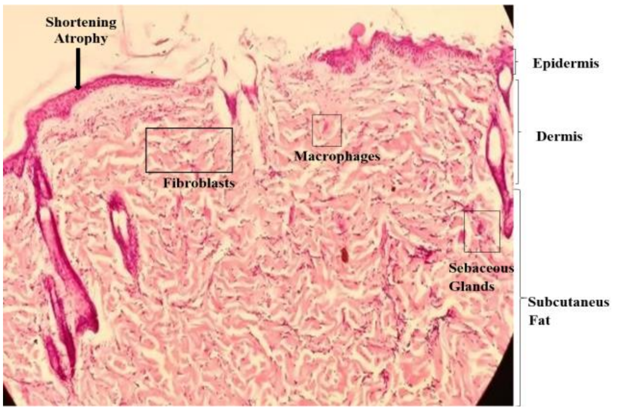

Figure 2. Representative photomicrographs of histopathology for F1

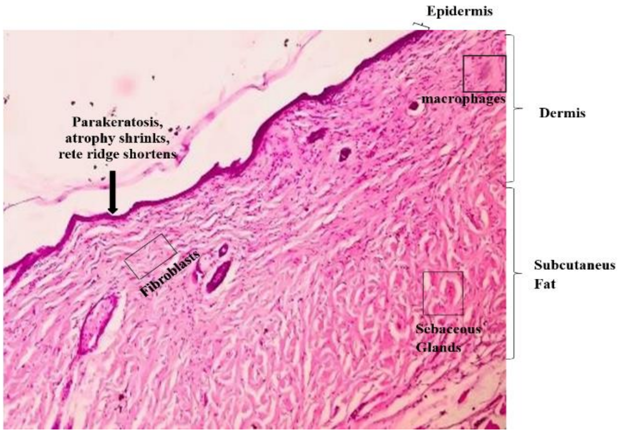

Figure 3. Representative photomicrographs of histopathology for F2

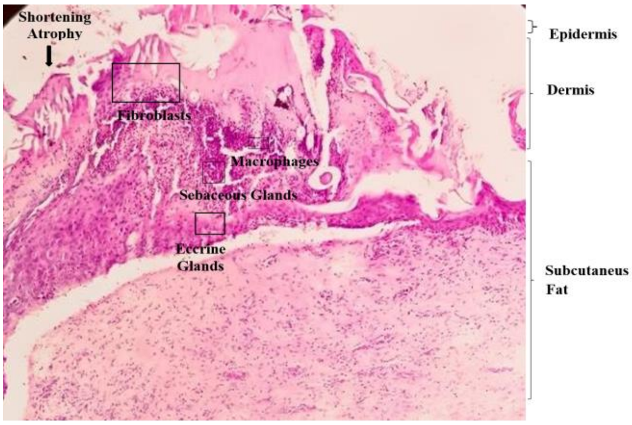

Figure 4. Representative photomicrographs of histopathology for F3

skin tissue [6–8]. The active substance content in *Aloe vera* is approximately two hundred types of active components that are effective in treatment in the form of vitamins (vitamins A, B1, B2, B3, B6, B12, C, E, and F, folic acid, tocopherol, and choline), enzymes (aliases, alkaline phosphatase, amylase, bradykinase, carboxypeptidase, catalase, cellulase, lipase, creatine phosphokinase, nucleotidase, proteolytase, and peroxidase), minerals (calcium, phosphorus, iron, chromium, copper, selenium, magnesium, manganese, potassium, sodium, chromium, and zinc), amino acids (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, valine, aspathic acid, glutamic acid, alanine, arginine, cystine, glycine, histidine, hydroxyproline, proline, serine, tyrosine), fatty acids (cholesterol, campesterol, beta-sisosterol, and lupeol), sugars (glucose, fructose, glucomannan), anthraquinones (aloin and edmodin), hormones (auxin and gibberellins), other components (salicylic acid, lignin, saponins, glycoproteins, c-glucosyl choroman) [9,10].

The active components of *Aloe vera* in wound healing include the enzyme bradykinin (reduces inflammation when used topically on the skin), zinc (improves tensile strength and wound healing), mannose-6-phosphate (has strong wound healing activity and anti-inflammatory effects), anthraquinone (acts as an analgesic, antibacterial and antiviral), fatty acids (have antiseptic and analgesic capabilities), amino acids (reduce inflation and synthesize collagen), salicylic acid (has anti-inflammatory and antibacterial capabilities), lignin (has a more penetrating effect high), saponin (has a cleansing and antiseptic effect), c-glucosyl choroman (functions as an anti-inflammatory) [11,12].

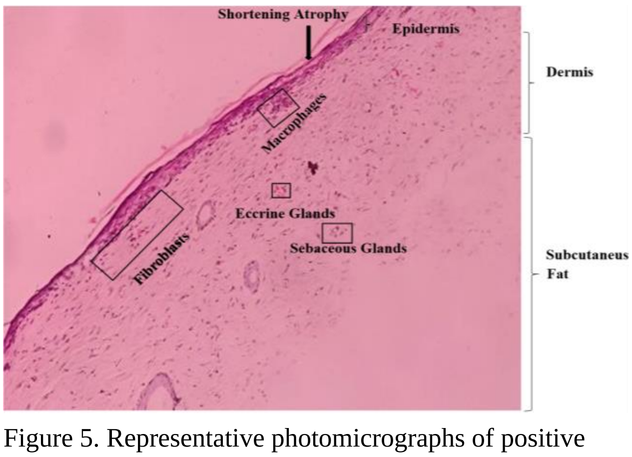

Figure 5. Representative photomicrographs of positive controls

Clinical studies have shown that *Aloe vera* gel can effectively treat burns, improve wound healing, and improve skin regeneration quality. For example, pure *Aloe vera* gel with a concentration of 10% has significantly improved the results of treating second-degree burns [13]. Burns are complex dermatological injuries that require immediate and effective treatment to prevent long-term morbidity. Burn wound healing is a multifaceted process

Table 1: Gel preparation formula

Ingredient	F0	F1	F2	F3
Aloe vera	-	10%	10%	10%
Snail Slime	-	10%	15%	20%
Carbopol	1.5%	1.5%	1.5%	1.5%
Glycerin	10%	10%	10%	10%
Nipagin	0.3%	0.3%	0.3%	0.3%
Nipasol	0.6%	0.6%	0.6%	0.6%
TEA	0.5%	0.5%	0.5%	0.5%
Propylene glycol	10%	10%	10%	10%
Aquadest ad	100	100	100	100

Table 2: Phytochemical screening of snail mucus and *Aloe vera*

S.No	Compound Classes	Snail Slime	*Aloe vera*
1	Flavonoid	+	+
2	Saponin	+	+
3	Alkaloid	+	-
4	Glycosides	-	+
5	Tannin	+	+

involving several stages: inflammation, proliferation, re-epithelialization, and maturation. Effective treatment modalities that can address these stages are critical in reducing the public health burden of burns, which remains a significant medical challenge globally [14]. Given the promising results observed with Snail Mucus (*Achatina fulica* (Ferussac, 1821)) and *Aloe vera* (*Aloe vera* (L) Burm.F.), our research aimed to develop a gel formulation that exploits the synergistic effects of these natural ingredients. This study will explore the impact of the agent on various aspects of burn wound healing, including wound contraction, fibroblast activity, epithelialization, and the presence of Platelet-Derived Growth Factor (PDGF) antibodies, thereby providing a comprehensive analysis of its potential as an effective therapeutic agent. in the treatment of burns [15].

MATERIALS AND METHODS

Preparation of sample

The samples used in this research were Snail Mucus (*Achatina fulica* (Ferussac, 1821)) family Achatinidae and *Aloe vera* (*Aloe vera* (L) Burm.F.) family Asphodelaceae which were obtained from the city of Pematang Siantar, North Sumatra, then Snail Mucus was identified in animal systematics laboratory (112/UN5.2.1.11/KRK/2022). *Aloe vera* was identified in the Medanese Herbarium (MEDA), Faculty of Mathematics and Natural Sciences, University of North Sumatra (6769/MEDA/2022). For the collection of Snail Mucus and *Aloe vera*. Snails weighing 20-40 g are used to obtain the slime. Snail slime is collected by cutting the end of the shell base. After that, place the shell upside down so the mucus can flow out. The mucus that comes out is immediately collected in a test tube and put into a centrifuge to separate the mucus and dirt. Meanwhile, wash the *Aloe vera* with running water until it is clean and then drain it until it is dry. Separate the skin and flesh from the *Aloe vera* plant. Then, the meat is blended until smooth and filtered. Mucus from Snail Mucus and *Aloe vera* was then carried out by phytochemical screening to see the secondary metabolites contained.

Gel Formulation

The gel preparation used carbopol as the gelling agent and consisted of three variations: F1 (10% *Aloe vera* and 10% snail mucus), F2 (10% *Aloe vera* and 15% snail mucus), and F3 (10% *Aloe vera* and 20% snail mucus). These formulations were adapted from our previous study, which focused solely on burn wound healing. We expanded the evaluation to include wound contraction, fibroblast activity, epithelialization, and Platelet-Derived Growth Factor (PDGF) antibody expression[15]. These additional parameters provide a more comprehensive understanding of the healing mechanisms. The detailed formulations are shown in Table 1.

Preparation of test animals

The population used in this study was 25 Wistar rats (*Rattus norvegicus*). Characteristics of the population used are male white mice, healthy, 2-3 months old, with a body weight of 180-250 grams. In the initial stage, the test animal is covered on the back with a width of 3x3 cm, then disinfected with an alcohol swab and anaesthetized using an anaesthetic cream containing Lidocaine and Prilocaine [16]. Burns are made using a metal plate with a diameter of 1 cm and a thickness of 1 mm. Based on several pieces of literature, the burns' degrees are grouped into first-degree, second-degree (II A and II B), and third-degree. In this study, the researchers wanted to create degree II A burns. Degree II A burns were characterized by a reddish colour marked by water bubbles (bullae) on the skin of male white mice. The process of making burns is by dipping the wound-making tool in hot water at 100 0 C and then placing it on the back of the test animal for 30 seconds until a second-degree burn is formed [16].

Treatment of animals

Test animals that have been injured will be given treatment using various formulations. F0 used a placebo gel, F1 was a control group that used a combination gel of *Aloe vera* and snail mucus with a concentration ratio of 10%:10%, F2 was a control group that used a combination gel of *Aloe vera* and snails with a concentration ratio of 10%:15%, F3 was the control group used a combination gel of *Aloe vera* and snail mucus in a ratio of 10%:20% and the positive control used bioplacenton. The gel preparation can be applied twice daily in the morning and evening using a thinly and evenly cotton bud, as much as 0.5 g.

Observe burns

Observation of burn wounds includes changes in burn diameter and wound colour. Measure the diameter of the burn wound using a calliper. Usually, wound measurements are carried out once every three days with one repetition. Meanwhile, observations of colour changes were carried out for 21 days, once every three days. Observation of colour intensity is observed visually (by eye) with the classification of burn wounds having been given a score, including (0) normal, (1) white-red, (2) mild redness, (3) moderate redness, (4) severe redness [17].

Histopathology test

Table 3: Average data on wound diameter measurement result.

Days	F0		F1		F2		F3		Positive control	
	Wound Diameter (cm)	C	Wound Diameter (cm)	C	Wound Diameter (cm)	C	Wound Diameter (cm)	C	Wound Diameter (cm)	C
0	2.00±0.00	5	2.00±0.01	5	2.00±0.01	5	2.00±0.01	5	2.00±0.01	5
3	1.85±0.11	5	1.50±0.12	4	1.54±0.12	4	1.25±0.24	4	1.26±0.09	3
6	1.79±0.17	4	1.39±0.19	4	1.26±0.06	4	0.69±0.12	2	0.50±0.05	2
9	1.65±0.15	4	1.11±0.08	4	0.87±0.09	3	0.40±0.15	2	0.18±0.04	1
12	1.50±0.12	4	0.89±0.08	3	0.56±0.06	2	0.16±0.08	1	0.00±0.00	0
15	1.23±0.04	4	0.68±0.08	2	0.35±0.06	1	0.00±0.00	0	0.00±0.00	0
18	0.81±0.08	3	0.29±0.08	1	0.00±0.00	0	0.00±0.00	0	0.00±0.00	0
21	0.52±0.03	3	0.00±0.00	0	0.00±0.00	0	0.00±0.00	0	0.00±0.00	0

Table 4: Calculation of the number of fibroblasts, epithelialization and PDGF-BB expression

Parameter	Group	Observation day			
		Day 3	Day 7	Day 15	Day 21
Number of fibroblasts	F0	45.4±4.03	73.8±5.71	61.4±6.22	44.8±3.70
	F1	26.4±6.73	37.4±4.28	62.8±4.82	39.8±2.39
	F2	41.8±9.60	73.2±6.91	51.2±7.19	26.6±7.92
	F3	57.2±6.98	77.8±5.40	46.8±5.40	17.6±3.36
	Positive control	64±4.18	83.4±5.17	45±4.84	12.2±1.78
Epithelialization	F0	13±2.13	20.7±1.30	48.7±2.65	79.2±2.82
	F1	18.3±2.67	26.3±2.63	66.7±5.26	90.8±2.76
	F2	32.38±2.47	56.4±4.45	84.2±3.38	112.3±2.46
	F3	31.8±3.45	68.9±2.72	127.6±4.16	175.2±6.52
	Positive control	35.6±2.20	87.6±1.77	139.4±3.28	206.6±8.63
PDGF-BB expression	F0	75.8±5.45	88.8±5.45	111.2±7.19	135.2±7.79
	F1	95.2±6.76	114±1.32	137.2±1.95	160.2±3.05
	F2	127.2±1.52	144.4±9.63	163.8±2.76	181.2±1.69
	F3	134.6±7.09	152.2±9.78	171.4±1.36	191±3.81
	Positive control	148.6±8.56	167.6±7.37	187.4±7.70	211.4±4.28

Histopathological observations began by taking the rat's skin by excision of the back that had been burned with a size of 3 x 3 cm2. The parts of the skin were the outer skin (epidermis) and part of the dermis, where skin tissue was taken on the 21st day per treatment group. The burn wound healing examination parameters carried out in this study were the observation of Representative photomicrographs of histopathologic for the presence of macrophages and fibroblasts as well as calculating the number of fibroblasts, the amount of epithelialization and the amount of PDGF-BB antibodies as indicators of wound healing.

Statistical analysis

The results of the observations will be analyzed using the IBM SPSS Statistics 25 program to observe burn wound diameter analysis data. The data analysis used was the Shapiro-Wilk normality test to determine whether the data was normally distributed ($p \geq 0.05$), then continued with Levene's homogeneity test to determine whether the data was homogeneous ($p \geq 0.05$). If the data is normally distributed, a parametric One-Way Anova test is carried out to compare the differences between all groups. It is said to be significant if $p<0.05$. Next, a post hoc Least Significant Difference (LSD) test was carried out to determine which groups were significantly different ($p<0.05$). The non-parametric Kruskal-Wallis test will be carried out if the data is not normally distributed. It is said to be significant if $p<0.05$ [18].

RESULTS AND DISCUSSION

The gel formulations in this study used Carbopol as a gelling agent, combined with 10% *Aloe vera* and various concentrations of Snail Mucus (10%, 15%, and 20%). The formulations showed consistent organoleptic properties, with colours ranging from light brown to dark brown and the odour of Snail Mucus effectively masked by *Aloe vera*. All gels showed homogeneity, pH stability (ranging from 5.77 to 6.27), and adequate spreadability (5.70 to 6.30 cm), facilitating easy application. The viscosity values (5,600 to 7,600 cps) ensured good adhesion to the wound site. These results align with findings from previous studies, which showed that the 10% *Aloe vera* and 20% Snail Mucus formulations had formulation and evaluation requirements [15].

Phytochemical screening

The results from taking snail mucus obtained 60 g from 80 snails with a yield of 2.37%. Meanwhile, 80 g of *Aloe vera* was obtained from 270 g of *Aloe vera* with a yield of 29.63%. The small yield of *Aloe vera* is due to the fact that more *Aloe vera* is wasted when removing the skin. Then, a phytochemical screening test was carried out on the sample. The results of the phytochemical screening of simplicia and extracts can be seen in Table 2.

Observe burn

The healing process of burn wounds is normal, as can be seen from changes in the diameter of the wound, which gets smaller, and changes in the colour of the wound. When observing, the colour of burn wounds is observed visually (eyes), with the classification of burn wounds being given a score, including (0) normal, (1) white-red, (2) mild redness, (3) moderate redness, (4) reddish heavy. After the mice were given treatment, there were changes in behaviour, such as sleeping more, decreasing appetite and increasing drinking intensity. This is caused by the pain experienced by mice in the back, so they experience stress. Average data on burn wound observations can be seen in Table 3. The results of the observations regarding the average reduction indicated that wound closure decreased until the wound healed. A comparison of the three groups of mice (F1, F2, and F3) was able to heal burn wounds starting on day 15 for the combination gel with a concentration of 10%:20% (F3). This follows visual colour observations in group 3, where the skin on the mice's backs had returned to normal, marked by faded colour and no scabs, whereas on the 12th day, group 4, whose skin had returned to normal first [14,17]. There is a difference in healing between the combination of pure *Aloe vera* and snail mucus because the gel preparation with a concentration of 10%:20% (F3) is optimal for healing burns, comparable to the positive control (bioplacenton). In contrast, the gel preparation with a concentration of 10%: 15% (F2) is not optimal for healing burns, and in gel preparations with a concentration of 10%:10% (F1), the burn wound healing process takes longer because the gel preparation has low adhesion to the skin, thus affecting the longer therapeutic effect. Based on research results, a combination gel preparation of 10% *Aloe vera* mucus and 20% snail mucus has the same efficacy as bioplacenton in healing burns. As a natural ingredient to treat burns, Aleo vera mucus has been proven to heal wounds faster. *Aloe vera* gel provides satisfactory results on burns due to its anti-inflammatory potential. It has been proven that pure *Aloe vera* gel with a concentration of 10% is used as an alternative for healing second-degree burns. Therefore, researchers took an *Aloe vera* concentration of 10% [19–21] and mixed it with snail mucus, which has been proven to be used in healing second-degree burns. This affects the number of fibroblasts in healing incision wounds. It also proves that the optimal formulation in healing burns is a 10% snail mucus concentration. Therefore, researchers took mucus concentrations of 10%, 15%, and 20% as new research. Based on statistical analysis, it was found that there were significant differences in activity between the five groups in healing burn wounds and all groups in this study had significant differences [7,22].

Histopathology test

The histopathological examination was carried out to see the presence of macrophages, the number of fibroblasts, the amount of epithelialization, and the number of PDGF antibodies in each group after being given different treatments. On examination of the histological structure of the F0 epidermis layer, the epidermis experienced parakeratosis, atrophy was reduced, and the rete ridge was shortened. Meanwhile, the condition of the histological structure of the epidermis layers in groups 1, 2, 3, and 4 with the administration of gel containing a combination of 10% *Aloe vera* mucus and 10% snail mucus (F1), 15% (F2), and 20% (F3) experienced shortened atrophy.

The condition of the histological structure of the F0 dermis can be seen in Figure 1. In the dermis tissue, sebaceous glands were still found but were not found, and sebaceous glands, macrophages, and fibroblasts were found in minimal numbers. Meanwhile, the histological structure of the F1 dermis can be seen in Figure 2. The dermis tissue has structures such as sebaceous glands, which are still found but were not found, and sebaceous glands, macrophages, and fibroblasts found in minimal numbers. In F2, it can be seen in Figure 3 that the dermis tissue has structures such as sebaceous glands, which are still found, the presence of sebaceous glands, macrophages and fibroblasts are found in minimal numbers.16,24 In F3, it can be seen in Figure 4 that the dermis tissue has structures such as sebaceous glands, which were still found but were not found, there were sebaceous glands, eccrine glands were found, and fibroblasts and macrophages were dominant. Blood vessel proliferation. The loose stroma consists of fibro collagen. This is the same as the positive control bioplacenton in Figure 5. The dermis tissue has a structure such as the presence of sebaceous glands, eccrine glands, fibroblasts and macrophages are dominant. Blood vessel proliferation. The loose stroma consists of fibro-collagen [17,24]. Histopathological observations of the presence of macrophages and fibroblasts align with the values for the number of fibroblasts, epithelialization and PDGF antibodies, which can be seen in Table 4. Based on the results of calculating the average number of fibroblasts, the F3 group was the group with the best increase in the number of fibroblast cells on the 7th day of 77.8 ± 5.40 and experienced a significant decrease on the following day until the 21st day, the results shown in the F3 group showed no difference significant compared to the positive control group with almost the same increase in fibroblasts. When fibroblast cells actively synthesize collagen and extracellular matrix, proliferating fibroblast cells and new blood vessels will decrease, resulting in increased extracellular matrix deposition. The decrease in the number of fibroblasts was also because, in the treatment group given the 10%:20% (F3) formula, there was better wound healing, where the need for collagen produced by fibroblasts was optimal and would not increase any further in line with the formation of new connective tissue. Fibroblasts will stop producing collagen when collagen synthesis reaches its peak and granulation tissue rich in fibroblasts is replaced by scar tissue so that the number of fibroblasts will begin to decrease on day 7 [25]. Based on the results of observations of epithelialization on days 3, 7, 15, and 21, it is clear that the epithelialization process occurs in wounds, especially when administering the 10%:20% (F3) formula, this shows that the 10%:20% (F3) formula can increase the epithelialization process in test mice. The increase in the average wound epithelialization of hyperglycemic mice by administering a 10%:20% formula (F3) significantly differed from the negative control (F0) and positive control. Epithelialization, the process of returning the epidermis to its original state, is one of the important physiological changes in tissue regeneration after injury. Epithelialization begins from the wound edges within a few hours after the injury. A single layer of cells initially forms over the wound, accompanied by a marked increase in mitotic activity in epithelial cells around the wound edges. When advancing epithelial cells encounter each other, migration stops, and a basement membrane forms [26,27]. The calculation results of PDGF BB expression on days 3, 7, 15, and 21 show an increase in the expression of the PDGF BB growth factor, which supports the repair of damaged cells. This can be seen by a significant increase in expression on the 21st day, occurring in the 10%:20% (F3) formula of 191 ± 3.81. The higher the PDGF BB expression score value, the greater the cell proliferation so that damaged cells experience improvement. In general, the results of this study show that administering the 10%:20% (F3) formula can increase the expression of PDGF BB. This is related to the content of *Aloe vera* and snail mucus in the 10%:20% (F3) formula so that it accelerates the wound healing process and can be well tolerated by fibroblasts accompanied by a synergistic response from growth factors such as PDGF, which play an important role in the angiogenesis process and stimulate fibroblast cell proliferation. PDGF BB plays a role in increasing proliferation and fibroblasts, increasing collagen production, triggering angiogenesis, and helping the chemotaxis process of neutrophils and macrophages so that wounds can heal more quickly [26,27].

CONCLUSION

This study conclusively demonstrated that gel formulations containing Snail Mucus and Aloe vera combinations significantly accelerated the healing process in second-degree burns among Wistar rats. Treatment groups receiving the highest concentration of combined gels (20% Snail Mucus and 10% *Aloe vera*) exhibited superior outcomes in terms of wound contraction, reduction in inflammation, and overall healing time compared to lower concentrations and control groups. Notably, the group treated with the highest concentration formula showed comparable healing efficacy to the positive control group treated with Bioplacenton, a recognized therapeutic agent in burn management. Histopathological analyses revealed increased fibroblast activity and enhanced PDGF-BB expression, particularly in the group treated with the 20% concentration, which paralleled the results observed with Bioplacenton treatment. These findings affirm the potential of Snail Mucus and *Aloe vera* as effective alternatives to traditional treatments, highlighting their synergistic effects in optimizing wound healing processes. This research provides a promising foundation for further exploration into bioactive compounds in dermatological applications, particularly for burn treatment protocols, offering a viable alternative to established pharmacological interventions.

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