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Research Article

Effectiveness of *Auricularia polytricha* Extract Gel on Burn Wound Healing in Male White Rats

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ABSTRACT

The number of burn cases in Indonesia has increased to 0.6% to 1,3% cases in January-august 2022. One way to address this issue is by inhibiting *Staphylococcus aureus* bacteria, which can otherwise impede the wound healing process. One of the herbal plants known for its efficacy in wound healing is the *Auricularia polytricha*. *A. polytricha* is known to contain flavonoid compounds that are potentially beneficial in wound healing. This study aims to evaluate the effectiveness of *A. polytricha* extract gel in healing burn wounds on white rats, using concentrations of 5%, 7.5%, and 10%. The gel was applied once a day for 14 days. Burns were created using an electric solder with a round metal plate tip of 1 cm in diameter. The solder was connected to an electric current for 5 minutes, then applied to the rats' skin for 5 seconds to create second-degree burns, followed by the application of topical *A. polytricha* extract gel. Macroscopic and microscopic data were analyzed using SPSS. The results showed that the administration of *A. polytricha* extract gel accelerated the healing of burn wounds in white rats. Macroscopic observations indicated that the 10% concentration of *A. polytricha* extract gel showed the best healing percentage compared to other groups. Microscopic observations revealed that the 10% *A. polytricha* extract gel scored 6.3, placing it in the good category.

Keywords: *Auricularia polytricha*; burn wounds; gel; male white rat; wound healing

INTRODUCTION

The skin has an important role as a body protector. The skin is an organ that covered and shields the body from several threats such as hazardous chemicals, pathogenic microorganisms, physical threat and UV radiation (Verma et al., 2024). Skin is extremely vulnerable to harm. Physical damage to the skin brought on by heat or force is called an injury and causes various changes in the skin. Depending on their cause, injuries can be classified as either open or closed wounds. One type of open wound is a burn (Fakouri et al., 2024).

A burn is tissue damage caused by contact with a hot source, such as boiling water, fire, chemicals, electricity, or radiation, whether accidental or intentional (Warghane et al., 2024). One of the basic processes of burn wound healing is epithelialization. Epithelialization occurs during the proliferation phase, which is typically observed by the presence of B and T cells and characterized by repetitive, uninterrupted cycles of cell division. At the wound's margins, epithelial cells start to multiply and keep continue to regain a normal or typical characteristics (Md Fadilah et al., 2024). Burn wounds have a high prevalence rate,

a high risk of morbidity and mortality, and require significant cost (Shah et al., 2024).

The prevalence of burn injuries in Indonesia remains high. According to the World Health Organization (WHO), approximately 180.000 individuals die each year due burn injury including including exposure to fire and flames, chemicals, electric shock, and other heat sources (WHO, 2023). When the wound is infected with bacteria, the healing process is impeded. Multiple types of bacteria can increase pathogenicity and destroy tissue in chronic wounds. Chronic wounds are characterized by bacterial colonization, and infection happens when there are more than 1×105 CFU/g of tissue (Withycombe et al., 2017). The microorganism that commonly make burns worse is *Pseudomonas aeruginosa* and *Staphylococcus* species (Azez et al., 2024).

Burn wounds require prompt treatment to prevent delays in healing and infection. Conventional burn treatments typically involve topical antimicrobials such as silver sulfadiazine (Sharma & Ahuja, 2024). Silver sulfadiazine is commonly used as a topical agent for burn wounds. While effective in treating burns, silver sulfadiazine do not have antioxidant effect (John et al., 2024). Antioxidants are essential for the healing of burn wounds because they reduce oxidative stress and encourage tissue restoration. An excess of Reactive Oxygen Species (ROS) is frequently produced as a result of burn injuries, which can further harm tissue. Antioxidants lessen oxidative stress and stop cellular damage by neutralizing these ROS (Hristova, 2024). One of the antibacterials and antioxidant from natural ingredients can come from h (JingWen et al., 2018).

The *A. polytricha* extract was chosen as a wound healing ingredients due to the capability of its active alkaloid compounds in inhibiting MRSA (Methicillin-Resistant *Staphylococcus aureus*). Other active compounds in *A. polytricha* with antibacterial properties include flavonoids, which enhance cell membrane permeability and form complexes with extracellular proteins, disrupting bacterial cytoplasmic membrane integrity (Permatasari et al., 2018). The phenol and flavonoid content in A. polytricha has the potential to be a natural antioxidant for wound healing (Packialakshmi et al., 2016; Teoh et al., 2018).

Previous research has formulated *A. polytricha* extract in a gel form with a concentration of 7.5% which was able to provide a repair effect on burn wound. Gels are preparations that contain a lot of water and have better drug delivery. They are often used for burn wound healing due to their good stability, ease of application, cooling sensation, moisture retention, good absorption, and non-irritating properties. Gels also have additional advantages such as absorbing light to heavy exudates, promoting quicker drying of burn wounds, and not leaving an oily residue on the skin, which reduces the risk of inflammation (Cook et al., 2022). Based on the literature review above, the research aims to prepare a gel formulation from *A. polytricha* extract and test its effectiveness on rats with burn wounds.

METHODS

Tools and Materials

The tool used is an analytical scale (Durascale, model DAB- E223, Indonesia), pH meter (Thermo Fisher Scientific), viscometer Brokfield (AMETEK RV, DV1 Digital Viscometer, USA), rotary evaporator (IKA laboratories, RV 3 V-C, China), electric soldering iron (Stanley, 69-033B, Singapore).

The materials used is an *A. polytricha* from Donowarih village, Malang district with determination number: 0184/UN.37/SHP/Lab. Taksonomi Tumbuhan/IV/2024,. Carbopol 940 (NF Polymer, Lubrizol, USA), triethanolamine (Emplura, Merck, Germany), metil paraben (MedChemExpress, USA), aquadest (Laboratory Reagent, Water One OneMed, Indonesia) etanol 70% (Teknis, PT. Palapa Muda Perkasa Depok, Indonesia), silver sulfadiazine (Burnazine, Cr 500g 10mg/g, Indonesia), chloroform (Honeywell, Germany).

Extraction and Formulation

A 70% ethanol solvent was used to macerate 500 grams of *A. polytricha* dry powder at a ratio of 1:5. The filtrate using Whatman paper no. 1, the process was repeated three times to ensure all compounds are extracted A rotary evaporator was used to obtain thick or concentrated extract. The yield was determined by weighing the result. The gel was formulat was shown in Table 1.

Table 1. Gel Formulation of *A. polytricha* Extract

Ingredients	Function	Formula numbers / content (%w/w)		
		1	2	3
Broccoli Dry Extract	Active substance	23.75	23.75	23.75
Crospovidone	Superdisintegrant	5	4.5	4
Ac-Di Sol	Superdisintegrant	2	2.5	3
PVP K-30	Blinder	2.5	2.5	2.5
Magnesium stearate	Lubricant	0.5	0.5	0.5
Talc	Glidant	1	1	1
Aspartame	Sweetener	4	4	4
Essence coffee	Flavor	2	2	2
Mannitol ad	Filler	100	100	100

Physical Characteristics Test and Anesthesia of Test Animal

The gel was tested to evaluate its physical characteristics such as organoleptic, pH, spreadability, and viscosity before being applied on animal models using tissue hispathology method. The test animal is put to sleep following the completion of the physical characteristics examination. The Health Research Ethics Committee Universitas Ahmad Dahlan granted ethical feasibility for this study (number 022404045). To anesthetize is necessary one milliliter of chloroform was used to soak a clean cloth, then put in a closed container to anesthetize the rats. The rat then left to die in the container.

Preparing The Burn Wounds in Rat

After the rats were anesthetized, second-degree burns were made. The location of the burns was determined on the back of the rat. 1-3 cm of fur was shaved around the injured area. The burns were made using an electric soldering iron that had a round metal plate tip measuring 1 cm. The solder was connected to an electric current for 5 minutes, then the tip of the solder was attached to the rat's skin for 5 seconds until a second-degree burn was formed (Zakiah et al., 2017). Thermal, chemical, electrical, or friction damage can result in second-degree burns. The wound is characterized by blistering and red skin (Balqis et al., 2014; Xiao et al., 2014).

Effectiveness Test of *A. polytricha* Extract Gel on Rat Burns

The research procedure involved the use of male Wistar rats divided into six treatment groups. Group 1 is the normal group, the test animals were not given burns and were not given topical preparations. Group 2 is the negative control, the test animals were given burns and were not given topical preparations. Group 3 is the positive control, the test animals were given burns and given 1 g silver sulfadiazine ointment. Test animals in group 4 were given burns and given 1 g formula 1 gel preparation (F1). Test animals in group 5 were given burns and given 1 g formula 2 gel preparation (F2). Test animals in group 6 were given burns and given 1 g formula 3 gel preparation (F3). Each treatment group was observed for 14 days, with macroscopic measurements of the wounds carried out on the 7th and 14th days, followed by microscopic observation of the skin tissue after the rats were sacrificed. Microscopic observation involved histological analysis using hematoxylin and eosin staining to measure the thickness of granulation tissue, which serves as an indicator of wound healing.

Macroscopic Observation of Wounds

On the first day following burn wound, as well as on days seven and fourteen, measurements were made. Using a caliper, the wound's side was measured at four diameters. The percentage of wound closure was then calculated by averaging the measurements (Azizah & Qomariyah, 2022). The following is the formula for calculating the percentage of burns:

Percentage of burns healing (initial wound – final wound)/(initial wound) x 100%

Microscopic Observation of Wounds

Skin tissue was collected for histological preparations on the fourteenth day. Using an optical microscope with a field of view at an objective magnification of 40 x10 and the Image system application, microscopic observation in the form of histological observation of skin tissue was performed to observe burn wounds microscopically reviewed from the thickness of granulation tissue. Histological observation of the wound healing process, particularly of granulation tissue in skin tissue, was made possible by the parameters examined, and the results were

interpreted in a semi-quantitative manner (Dwita et al., 2020). The rating range for microscopic observations is 0–2 for poor, 3–4 for less good, and 5-7 for good (Nazhiifah & Sofyanita, 2023).

Analysis of Data

Data analysis is conducted using relevant statistical methods, such as Shapiro-Wilk for normality testing, Repeated Measure ANOVA for macroscopic observations, and One Way ANOVA or Kruskal-Wallis test for microscopic observations, depending on data distribution. Results from physical and histological evaluations are used to assess the effectiveness of the black ear fungus extract gel in burn wound healing, focusing on significant differences between treatment groups. The data are interpreted descriptively and semi-quantitatively, providing a comprehensive overview of the therapeutic potential of black ear fungus in gel formulation for burn treatment.

RESULTS AND DISCUSSION

Extraction of *A. polytricha* and Results of Physical Characteristics

The yield of *A. polytricha* extract obtained was 13.227%. The physical characteristics of the gel formulation were tested to determine its suitability, including organoleptic tests, pH tests, viscosity tests, and spreadability tests. In this study, a gel formulation was prepared using *A. polytricha* extract at concentrations of 5%, 7.5%, and 10%. The organoleptic test aims to observe the color, odor, and form of the prepared formulation. The organoleptic test results for F1, F2, and F3 are shown in Table 3.

Based on Table 3, the organoleptic test results for the *A. polytricha* extract gel formulation showed that F1 had a clear brown color, resulting from a 5% concentration, with a characteristic mushroom odor and semi-solid form. F2 had a brown color, resulting from a 7.5% concentration, with a characteristic mushroom odor and semi-solid form. F3 had a dark brown color, resulting from a 10% concentration, with a characteristic extract odor and semi-solid form. The addition of extract affects the color and odor of the gel formulation, changing the color from clear brown to dark brown, and as the concentration increases, the mushroom odor becomes more distinct.

Table 2. Results of Organoleptic Test

Formulas	Organoleptic		
	Color	**Odor**	**Form**
F1 (Gel *A. polytricha* extract 5%)	 Clear brown	Distinctive odor of the extract	Semi-solid
F2 (Gel *A. polytricha* extract 7.5%)	 Brown	Distinctive odor of the extract	Semi-solid
F3 (Gel *A. polytricha* extract 10%)	 Dark brown	Distinctive odor of the extract	Semi-solid

Table 3. Physical Characteristic of *A. polytricha* extract gel

Physical Characteristics Test	Desired Specifications	F1	F2	F3
pH	4.5-6.5 (Irianto et al., 2020)	5.94	5.86	5.77
Viscosity (cps)	4000-40.000 cps (Zainal et al., 2023)	17.200	17.080	16.720
Spreadibility (cm)	5-7 cm (Chandra & Rahmah, 2022)	5.4	5.62	5.71

The results in the form of pH, viscosity, and of physical characteristic *A. polytricha* extract gel spreadability are in Table 4. The pH test was conducted to observe the acidity level of the formulation to ensure it does not cause skin irritation. Based on Table 4, the pH results for F1 showed a pH value of 5.94, F2 had a pH of 5.86, and F3 had a pH of 5.77. The pH test results indicate that the addition of extract in varying formulas caused a decrease in pH. The more extract used, the lower the pH value of the formulation, due to the acidic nature of *A. polytricha* extract, which has a pH value of 3.83 and contains acidic saponins. This is consistent with previous studies that showed that as the extract concentration increases, the pH value decreases (Thomas et al., 2022). Although the pH value decreased, all three formulas still had pH values between 4-6, which is considered safe (Mayangsari et al., 2022).

The viscosity test was conducted to determine the thickness of the gel formulation. Viscosity indicates the resistance of a liquid to flow. Gel viscosity is usually proportional to the amount and molecular weight of the thickening agent added; the higher the viscosity, the thicker the gel (Anggun et al., 2020). Based on Table 4, the viscosity results for the three formulas showed that F1 had a viscosity of 17.200 cPs, F2 had a viscosity of 17.080 cPs, and F3 had a viscosity of 16.720 cPs. Although there is a decrease in viscosity due to differences in extract concentration, each formula still met the specified viscosity requirements. As the concentration of the extract increases, the pH also falls, which affects the viscosity value. The gel mass will contract more when the preparation is more acidic, allowing the liquid to flow and lowering its viscosity (Larasati et al., 2024). Besides that, gel viscosity can also be affected by stirring and mixing during the gel base and humectant preparation process, as the shearing force during mixing can cause changes in the physical properties of the formulation, such as viscosity, and the amount of extract used can also affect the viscosity of the resulting formulation (Malaka et al., 2022).

The spreadability test aims to observe the ability of the formulation to spread on the skin. A gel with good spreadability will ensure better drug distribution, making the treatment more effective (Sugihartini et al., 2020). Based on Table 4, the spreadability test results showed that F1 had a spreadability of 5.40 cm, F2 had a spreadability of 5.62 cm, and F3 had a spreadability of 5.71 cm. All formulations had spreadability values within the required range of 5-7 cm (Chandra & Rahmah, 2022). Increasing the extract concentration tends to increase the gel's spreadability. A good formulation is one that easily spreads on the skin without requiring significant pressure. The spreadability is influenced by the components of the formulation, the more liquid components, the larger the spread diameter, and vice versa. Additionally, the more evenly the active ingredient is spread on the skin, the more optimal its effect will be (Malaka et al., 2022). The higher the spreadability diameter, the faster the gel spreads, increasing the contact of the drug with the skin surface. This is because high-viscosity gels have a smaller spread diameter, while low-viscosity (thinner) gels flow easily, resulting in a larger diameter (Sartika et al., 2023).

Results of Macroscopic Observation

Average Wound Diameter

Macroscopic observation involved visually examining burn wounds every day. The healing of burn wounds was observed on days 1, 7, and 14 by measuring the wound diameter on white rats. The results of burn wound healing are shown in Table 5.

Table 5. Average of Wound Diameter

Days	Normal Group	Negative Group (cm)	Positive Group	F1 (5%)	F2 (7.5%)	F3 (10%)
1	0	1.15 ± 0.384	0.81 ± 0.015	0.83 ± 0.212	1.24 ± 0.441	1.61 ± 0.110
7	0	0.68 ± 0.315*	0.57 ± 0.045*	0.52 ± 0.106	0.77 ± 0.213	0.85 ± 0.043*
14	0	0.45 ± 0.142*	0.44 ± 0.035*	0.34 ± 0.049#	0.38 ± 0.047	0.38 ± 0.060*#

Based on Table 5, the negative control group showed a significant difference on days 7 and 14 compared to day 1, after statistical analysis using repeated measure ANOVA, which had a significance value of p<0.05. This was attributed to psychological factors, as stress due to wounds can increase nutritional needs, which must be met to affect the wound healing process (Laguliga et al., 2021). The positive control group showed a significant difference on days 7 and 14 compared to day 1, after statistical analysis using repeated measure ANOVA, which had a significance value of <0.05. This was due to silver sulfadiazine, a standard topical gold drug in the sulfonamide class, which prevents bacterial folic acid synthesis due to its antibacterial properties and can induce macrophages to release growth factors and cytokines to accelerate the wound healing process (Fuadi et al., 2015).

The F1 group showed a significant difference on day 14 compared to days 1 and 7, after statistical analysis using repeated measure ANOVA, which had a significance value of <0.05. The F2 formula did not show a significant time difference, after statistical analysis using repeated measure ANOVA, which had a significance value of >0.05. This was due to the rats being very active, causing the wound dressing/bandage to come off, leaving the wound exposed and allowing bacterial contamination from outside. The F3 group showed a significant difference on days 7 and 14, after statistical analysis using repeated measure ANOVA, which had a significance value of <0.05. The F1 group showed a significant difference on day 14 compared to days 1 and 7, after statistical analysis using repeated measure ANOVA, which had a significance value of <0.05.

When measured by wound proportion, the negative control group had the lowest wound healing diameter compared to the other groups. The group given *A. polytricha* extract gel with a 10% concentration had the best wound healing diameter compared to the other groups, as the higher the extract concentration, the better the healing.

Table 6. Percentage of Wound Healing in Groups of Rat

Groups	Averages (%)
Normal control	0
Negative control	45 ± 0.040
Positive control	60 ± 0.043#
F1 (5%)	55 ± 0.126#
F2 (7.5%)	66 ± 0.127*#
F3 (10%)	76 ± 0.050*#

Based on the analysis of wound healing using SPSS (Table 6), the normality test results for the sample groups showed normally distributed data, as indicated by a significance value of >0.05. The one-way ANOVA test result was 0.011, with a significance value of <0.05, indicating a significant difference. The Tukey post-hoc test for further analysis showed that the negative control had a significant difference with groups F2 and F3 but not with the positive control and F1. The positive control showed a significant difference compared to F2 and F3. Group F1 showed a significant difference compared to groups F2 and F3 but no difference with the positive control and negative control. Group F2 showed a time difference with the positive control, negative control, and F1. Group F3 showed a significant time difference with the positive control, negative control, and F1.

The test results above showed that the application of *A. polytricha* extract gel at a 10% concentration had the highest wound healing percentage of 76% and was more effective than the other groups. The higher the concentration of *A. polytricha* extract, the greater the wound healing effect, due to the active ingredients in the *A. polytricha* extract that have wound healing activity. These include quercetin and oleanolic acid, which act as anti-inflammatory agents by activating TGF-β, regulating, proliferating, migrating, and differentiating cells (Frangogiannis, 2020). TGF-β acts as a pro-inflammatory agent by influencing the inflammatory response, angiogenesis, granulation tissue formation, reepithelialization, extracellular matrix deposition, and remodeling, leading to wound healing (Barrientos et al., 2008). The positive control had a higher wound healing percentage compared to

the negative control, at 60%, and was comparable to the F1 and F2 groups. The negative control group had the lowest wound healing percentage, at 45%.

Results of Microscopic Observation

Microscopic observation was carried out using a microscope with 40 x10 objective magnification. Wound healing can be observed from the thickness of the granulation tissue, interpreted semi-quantitatively by calculating the field of view and scoring the thickness of the granulation tissue. Granulation tissue thickness scoring and histological observation results from various groups are shown in Table 7.

Table 7. Scoring of Granulation Tissue Thickness

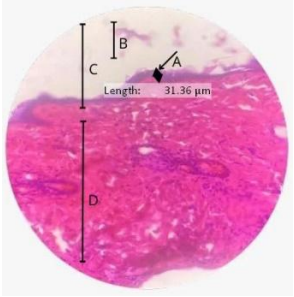
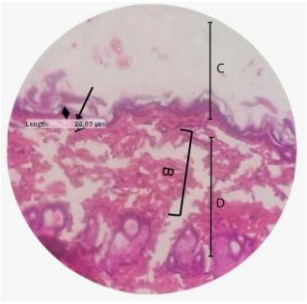
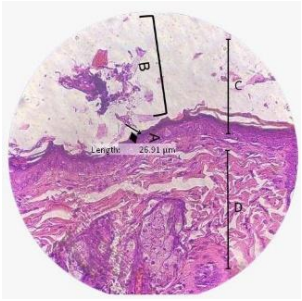
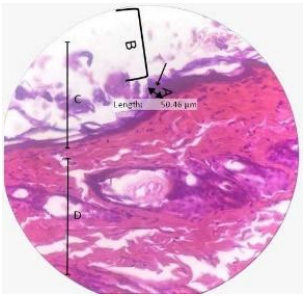
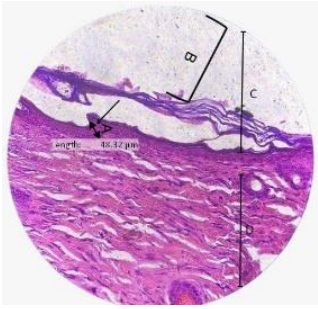
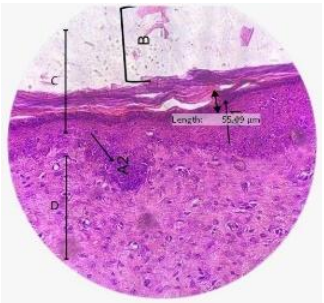
Groups	Average Field of View
Normal group	-
Negative control	2.9 ± 0.115
Positive control	5.3 ± 0.115
F1 (5%)	4.0 ± 0.115^{abde}
F2 (7,5%)	4.7 ± 0.115^{abce}
F3 (10%)	6.3 ± 0.115^{abcd}

a = Significant difference with negative control
b = Significant difference with positive control
c = Significant difference with F1
d = Significant difference with F2
e = Significant difference with F3

The SPSS analysis results showed that the normality test for the sample groups in the negative control, positive control, F1, and F3 did not have normally distributed data, as indicated by a significance value of >0.05. The Kruskal Wallis Test result was 0.009, with a significance value of <0.05. The data showed a significant difference, and the Mann-Whitney test result was 0.043, indicating a significant difference with a significance value of <0.05. The negative control had a significant difference with F1, F2, and F3, as the negative control had the lowest scoring value compared to the other groups, at 2.9, falling into the "not good" variable category. This indicated that the negative control did not have an accelerating effect on burn wound healing because it was not given any formulation. F1 had a scoring of 4.0, and F2 had a scoring of 4.7, falling into the "less good" variable category, with a difference from the positive control, which had a scoring of 5.3, falling into the "good" variable category. This indicated that the positive control given silver sulfadiazine ointment had the most effective wound healing activity compared to F1, which was given 5% *A. polytricha* extract, and F2, which was given 7.5% *A. polytricha* extract. F3 had the highest scoring compared to the other groups, at 6.3, falling into the "good" variable category. This indicated that the wounds given 10% *A. polytricha* extract gel were more effective compared to the other groups, as the higher the *A. polytricha* extract content, the greater the wound healing effect.

From the histopathology images in Table 8, it can be seen that in the negative control, epithelialization was slight, with no rete ridge or crust. The negative control received a scoring of 2. The positive control group showed perfect epithelialization, but there was no rete ridge or crust, and it received a scoring of 6. In the F1 group, which was given 5% *A. polytricha* extract, moderate epithelialization was observed, with no rete ridge or crust, and it received a scoring of 4. The F2 group, which was given 7.5% *A. polytricha* extract, also showed moderate epithelialization, with no rete ridge or crust, and it received a scoring of 4. In the F3 group, which was given 10% *A. polytricha* extract, perfect epithelialization was observed, with the presence of rete ridge but no crust, and it received a scoring of 7. The higher the extract concentration, the higher the wound healing scoring, and the better the tissue repair (Prasongko et al., 2020).

Table 8. Histological Observation Results of Burn Wound Skin Tissue in Rats

No	Groups	Histological Results	Information
1	Normal control		A. Perfect epithelialization and granulation tissue, no rete ridges. B. No crusts C. Epidermis D. Dermis
2	Negative control		A. Epithelialization and granulation tissue are few, there are no rete ridges. B. There are no crusts. C. Epidermis D. Dermis
3	Positive control		A. Perfect epithelialization and granulation tissue, but no rete ridges. B. No crusts. C. Epidermis D. Dermis
4	F1		A. Moderate epithelialization and granulation tissue, no rete ridges. B. No crusts. C. Epidermis D. Dermis
5	F2		A. Moderate epithelialization and granulation tissue, no rete ridges. B. No crusts C. Epidermis D. Dermis
6	F3		A1. Perfect epithelialization and granulation tissue, A.2 There is a rete ridge B. There is no crust. C. Epidermis D. Dermis

CONCLUSION

The gel formulations containing *A. polytricha* extract at concentrations of 5%, 7.5%, and 10% have met the physical characteristic test requirements. This indicates that the gel formulations are consistent with the expected physical properties such as pH, spreadability, and viscosity. The gel has proven effective in healing burn wounds in white rats, as observed macroscopically. This effectiveness is reflected in the percentage of wound healing and wound diameter, with significant differences noted between the treatment groups over time. The gel with a 10% extract concentration demonstrated the best wound healing, achieving a healing percentage of 76% compared to the negative and positive controls. 10% extract gel showing the highest healing score of 6.3.

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