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Wound healing and antimicrobial activities of a spray gel of banana (*Musa paradisiaca* L.) peel extract in rabbit (*Oryctolagus cuniculus*) models

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ABSTRACT

Introduction: *Musa paradisiaca* peel has inhibited microbial growth and enhanced wound healing in animal models. However, the study on its effect as a dosage form is lacking. In the present study, the antimicrobial and wound-healing effects of a spray gel of *M. paradisiaca* peel extracts were evaluated in rabbits.

Methods: The antimicrobial and wound healing activities of a spray gel were tested at different concentrations (10%, 15%, and 20%) of banana peel extract, categorized as low concentration (SGL), medium concentration (SGM), and high concentration (SGH) groups, respectively. The antimicrobial effects against *Escherichia coli* and *Staphylococcus aureus* were investigated by measuring inhibition zone diameters. Burns were inflicted on the back area of rabbits using hot steel. Macroscopic and microscopic examinations were performed.

Results: The spray gel containing banana peel extract exhibited inhibition zone diameters of 14.2 ± 0.38 mm and 14.6 ± 0.21 mm against *Escherichia coli* and *Staphylococcus aureus*, respectively. SGH showed the strongest wound-healing activity of all the samples, which was comparable with bioplacenton (BG) as a positive control. The wounds healed on days 16, 16, 20, and 22 for bioplacenton, SGH, SGM, and SGL, respectively. There was a significant difference ($P<0.05$) in collagen density and epidermal thickness between the treatment groups and the negative control (1.2 % sodium carboxymethyl cellulose (Na-CMC)).

Conclusion: The result indicates that the spray gel of *M. paradisiaca* peel ethanolic extract possesses antimicrobial and wound-healing activities, emphasizing its potential to be developed as a wound healing agent.

Implication for health policy/practice/research/medical education:
The current study presents scientific evidence that supports the efficacy of a spray gel formulation containing banana peel extract as an antimicrobial agent. This particular spray gel formulation also promoted the faster healing of burn wounds in rabbits. As a result, the banana (*M. paradisiaca*) peel spray gel exhibits promising potential as an effective medicinal treatment for facilitating wound healing.

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Introduction

The agriculture and food sectors play a crucial role in economies worldwide. Indonesia, an agricultural country with rich biodiversity boasts diverse plant species across its regions. Bananas are cultivated in over 130 nations and encompass more than 50 different species, each characterized by unique leaves, stems, roots, and fruits (1). Bananas have a wide range of culinary uses, from simple consumption to inclusion in salads, sandwiches, desserts, and baked goods (2). Conversely, bananas are the lowest-priced sources of carbohydrates, potassium, vitamins, and minerals, so they are referred to as foods that produce energy (3).

Based on the data from the Indonesian Central Statistics Agency, Indonesia produced 8.1 million tons of bananas in 2020, with one of the varieties being the Barangan banana (*Musa paradisiaca* L.), native to North Sumatra. Barangan

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bananas have traditionally been used to treat dandruff and promote healthy skin (4,5). Banana peels, which are often discarded, have been employed as organic fertilizer and animal feed due to their high fiber content (6). Transformation of banana peels into high-value pharmaceutical preparations will provide advantages in the development of health products. Previous studies have demonstrated that the extracts of *M. paradisiaca* peel could inhibit microbial growth and enhance wound healing in animal models (7). Banana peels have bioactive compounds, according to recent research, which can be used to create products with health benefits like antimicrobial (8-10) and antioxidant (11-13) properties. Banana peel contains pharmacologically effective tannins, glycosides, flavonoids, and saponins that speed up the healing of burns (6,14,15). *M. paradisiaca* peels contained the highest total phenols, total flavonoids, and total tannins compared to the other eight bananas tested (16). It has been shown to have broad-spectrum antimicrobial activity and good efficacy against both Gram-positive and Gram-negative microorganisms (9). However, transforming banana peels into valuable pharmaceutical products could offer significant benefits for health product development.

Burns are integumentary system wounds that occur when the skin comes into contact with heat sources like fire, hot water, chemicals, electricity, or radiation resulting in tissue loss or damage (17). Burns cause many problems due to their high volume/risk and high cost. Firstly, burns result in a considerable number of deaths, with an estimated 180 000 fatalities occurring annually, predominantly in low- and middle-income countries (18). Secondly, burns can be financially burdensome with an average total cost of burn care, which was estimated to be $US 15 250 per patient in 2011 (19). Burn therapy aims to alleviate discomfort, protect against epithelial damage, and reduce the risk of bacterial or fungal infections. Numerous techniques, including genomics, transcriptomics, proteomics, and metabolomics, can enhance our understanding of the molecular mechanisms underlying the health-promoting effects of banana peel, enhancing our understanding of banana peel and its phytochemicals (20).

Although there are synthetic drug-based products available in the market, this study suggests exploring pharmaceutical products with natural resources that are non-toxic to enhance wound healing. Previous studies have primarily focused on the wound-healing properties of banana peels in cream, ointment, and gel forms, with no investigation into spray gel (21,22). In a world that is becoming more crowded with advancing technologies, practicality is essential. Developing a spray gel for burn treatment using natural ingredients offers enhanced ease of application and skin comfort. The spray gel should have a consistent and lightweight texture that is easily absorbed, leaving no heavy or sticky residue. It should also be non-irritating and designed to be user-friendly (23). Another advantage of the spray gel is the ability to apply it to the wound without using a cotton swab, reducing the risk of infection and ensuring longer drug skin contact time compared to other preparations (24,25). *Musa paradisiaca* peel has demonstrated broad-spectrum antimicrobial activity and efficacy against both Gram-positive and Gram-negative microorganisms, making it an effective antibacterial agent (9). This study aims to demonstrate the effectiveness of a spray gel containing banana peel extract against *Escherichia coli* and *Staphylococcus aureus*, as well as its potential for wound healing in rabbits.

Materials and Methods

Material

Sodium carboxymethyl cellulose (Na CMC) (Hexpharm Jaya, Indonesia), copovidone (Graha Jaya Pratama Kinerja, Indonesia), propylparaben (Graha Jaya Pratama Kinerja, Indonesia), methylparaben (Graha Jaya Pratama Kinerja, Indonesia), propylene glycol (Smart Lab, Indonesia), ethanol (Hexpharm Jaya, Indonesia), aquadest (Hexpharm Jaya, Indonesia), Bioplacenton® (Kalbe Farma, Indonesia), *Staphylococcus aureus* ATCC® 25923™ (Smart Lab, Indonesia), and *Escherichia coli* ATCC® 25923™ (Smart Lab, Indonesia) were used in this study.

Plant materials

The peels from banana collected in Binjai, North Sumatra, Indonesia were used. According to the Herbarium Medanese at the University of North Sumatera, this plant was a species of *M. paradisiaca*, belonging to the Musaceae family (920/MEDA/2022).

Preparation of banana peel extract

The peels of bananas were collected, cleaned with water, then cut into small pieces and dried. After drying, the banana peels were blended and stored in a plastic jar at room temperature until needed. Thereafter, the dried banana peel powder was macerated with ethanol. The solvent was then eliminated using a rotary evaporator to obtain Banana peel extract (26).

Formulation of spray gel

Copovidone was dissolved in 96% ethanol and stirred until completely dissolved (A). Na CMC was dissolved in 60°C purified water, allowed to stand for 30 minutes, and then stirred until completely dissolved and formed a clear gel (B). Mixture A was added thoroughly to mixture B and stirred to get homogeneous. Methyl paraben and propyl paraben were dissolved in 96% ethanol and then added to a mixture of A and B. Propylene glycol and extract were added to the mixture until completely dissolved. The remaining purified water was added until it reached a predetermined weight. The resulting spray gel was placed in a tightly closed container (27).

Antimicrobial activity

The Microbiology Laboratory of the Faculty of Pharmacy at the University of North Sumatra offered the

antimicrobial test. The disc diffusion method was used to evaluate antibacterial activity against *E. coli* and *S. aureus* (28). The microbial suspensions were prepared according to the guidelines of the National Committee for Clinical Laboratory Standards (CLSI 2009) by diluting them with sterile saline to achieve a turbidity level equivalent to 0.5 McFarland (approximately 1.5×10^8 CFU/mL) (29). The prepared suspensions were then stored at 4 °C. Petri plates containing 20 mL of sterile Nutrient Agar were used. A uniform inoculum suspension was swabbed onto the agar surface and allowed to solidify. Once solidified, sterile discs with a diameter of 6 mm were used to create wells on the agar plates. Each well was then filled with 100 µL of spray gel containing different concentrations (10%, 15%, and 20%) of banana peel extract. The plates were subsequently incubated at 37 °C for 24 hours. Each concentration was tested in triplicate under sterile conditions. After the incubation period, the antimicrobial activity was determined by measuring the diameter of the zone of inhibition surrounding the wells (30).

Animals

Six rabbits, with four burns area in each rabbit, were used in the study. Each burn represented one test animal. Hence, each group consisted of four test animals (31). There were six groups, including a positive control group (Bioplacenton (BG)), a group that received no treatment (NC), a 10% low concentration spray gel group (SGL), a 15% medium concentration spray gel group (SGM), a 20% high concentration spray gel group (SGH), and negative control administered with 1.2% Na-CMC (SG). The number of test animals was calculated using Frederer's formula (32). The procedure was approved by the University of North Sumatra's ethics committee (0596/KEPH-FMIPA/2022).

Wound healing activity

The back skin of the rabbits was shaved and lidocaine was injected intramuscularly to anesthetize them. A metal plate with a 20 mm diameter was heated using a blue flame for three minutes and then applied to each rabbit's back for five seconds to create burn wounds (32). Four burns were applied to each of the six healthy male rabbits, with a weight range of 1500 to 2000 g each (31,33). The rabbits were randomly divided into six treatment groups. To ensure equal immune reactions among the rabbits, they were subjected to the same environmental and food conditions during the 5-day acclimatization phase. The six treatment groups (BG, NC, SGL, SGM, SGH, SG) received topical treatments twice daily, in the morning and evening. The data obtained were then used to calculate the percentage of burn healing (34).

$$\text{Wound contraction } (\%) = \frac{\text{Wound size on the day 0} - \text{Wound size on a specific day}}{\text{wound size on day 0}} \times 100$$

The effectiveness of healing was assessed both macroscopically and microscopically. The macroscopic assessment involved examining healing time and wound contraction rate, while the microscopic assessment involved observing the histology of collagen density and epidermal thickness. Throughout the duration of the investigation, each rabbit was provided with pelleted food and water while housed in the animal testing facility.

Histological evaluation

Histological analyses were conducted to evaluate the healing rates for various therapies. Tissue samples were taken from the wound site at the end of the research to evaluate epidermal thickness and collagen density. ImageJ® software (section 105, National Institutes of Health, USA) was used to measure the epidermal thickness and collagen density under a microscope at three different sites. For the collagen density evaluation, five histologic fields (400x magnification) of each histological section were photographed, and a scoring procedure was employed to calculate the proportion of collagen-containing regions (35). The total healing score for each case was determined by summing the results for each category. Score 0 indicated no collagen fibers detected, score 1 indicated low (<10%) collagen fiber density, score 2 indicated intermediate (10–50%) collagen fiber density, score 3 indicated high (50–90%) collagen fiber density, and score 4 indicated highly dense (90–100%) collagen fiber density in the wound areas (36).

Statistical analysis

The study utilized the SPSS 26.0 program for data analysis. One-way ANOVA was used to compare the means between groups, and a post hoc test of Bonferroni was employed to compare each group. Significant differences in the control group were indicated at $P < 0.05$.

Results

Antimicrobial activity

Figure 1 shows the antimicrobial activity of the spray gel of banana peel extract. The zone of inhibition was measured in mm following a 24-hour incubation. The zone of inhibition, measured in millimeters following a 24-hour incubation, indicated the presence of antibacterial activity in the SGL (10%), SGM (15%), and SGH (20%) spray gel formulations containing banana peel extract. The average diameter of the inhibition zone for *S. aureus* in the spray gel preparations with extract concentrations of 10%, 15%, and 20% was 14.6 mm, 13.5 mm, and 12.3 mm, respectively. For *E. coli* in the spray gel preparations with the extract concentrations of 10%, 15%, and 20%, the average diameter of inhibition zones was 14.6 mm, 13.5 mm, and 12.3 mm, respectively. Statistical analysis with one way ANOVA in each group showed the inhibition zones in the sample groups were significantly different ($P < 0.05$).

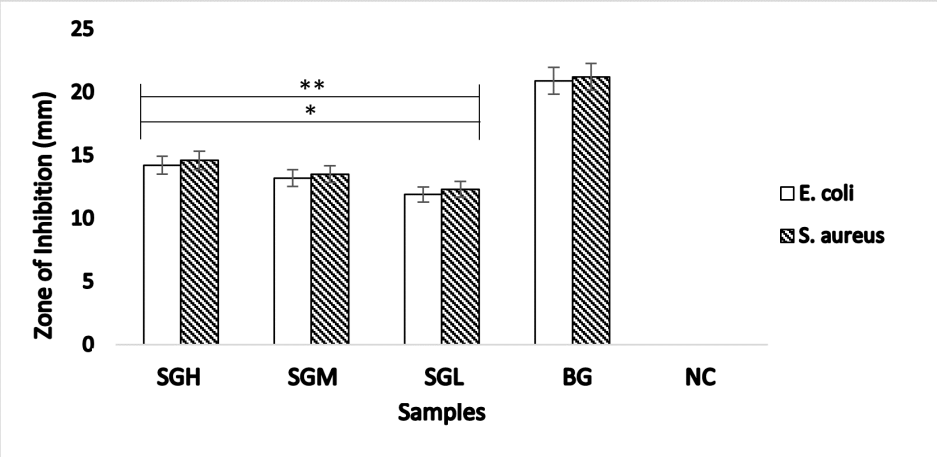

Figure 1. The antimicrobial effect of spray gel of banana (*Musa paradisiaca*) peel extract against *Escherichia coli* and *Staphylococcus aureus*. SGH: 20% high concentration spray gel group; SGM: 15% medium concentration spray gel; SGL: 10% a low concentration spray gel; BG: positive control group; NC: negative control group. Data are presented as mean ± SEM (n = 3). *Significant difference with the positive control group (P < 0.05). **Significant difference with the negative control group (P < 0.05), analysed with One way ANOVA and Bonferroni's post hoc tests.

Wound healing activity

The wound healing effects of the spray gel on six groups were analysed using one way ANOVA and post hoc analysis of Bonferroni. The spray gel of banana peel extract showed healing spectrum and treatment frequency, which were noticeably different from those of the control group (P < 0.05). The average healing times for BG and SGH were 16 days, for NC 26 days, for SG 24 days, for SGL 22 days, and for SGM 20 days (Figures 2A, 2B). Rabbits treated with the high-concentration of spray gel experienced noticeably greater prophylactic effects when compared to untreated rabbits. Furthermore, there was a significant (P < 0.05) decrease in wound size when compared the treated rabbits to the spray gel without extract and control groups.

Histological analysis

On the 26th day, the tissue samples were examined in the laboratory. In the area of mild injury (10% to 50% part

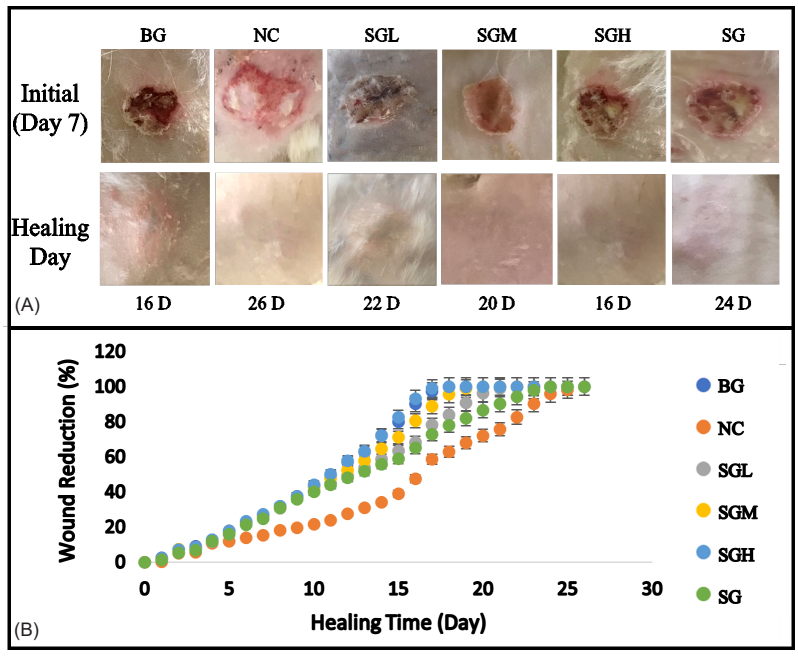

Figure 2. Wound healing activity of spray gel of banana (*Musa paradisiaca*) peel extract. (A) Burn wounds on the initial day and healing day (Day 26). (B) The percentage of wound reduction after treatment with spray gel. BG: Positive control group (Bioplacenton); NC: group, which received no treatment; SGL: 10% low concentration spray gel group; SGM: 15% medium concentration spray gel group; SGH: 20% high concentration spray gel group; SG: negative control administered with 1.2% Na-CMC. Data are presented as mean ± SEM (n = 4). *Significant differences of SGL and SG groups compared to the positive control group (P < 0.05). **Significant differences of SGL, SGM and SGH groups compared to the negative control group (P < 0.05) (analysed with One way ANOVA and Bonferroni's post hoc tests).

field of view), histological analysis revealed no difference ($P > 0.05$) in the density of collagen fibers between the NC and SG groups, as well as between the BG, SGL, SGM, and SGH groups. Similarly, in the area of tightly wound tissue (90% to 100% part field of view), there was no significant difference ($P > 0.05$) in the density of collagen fibers. The epidermis of SGL, SGM, and SGH had the same thickness as that of the positive control group ($P = 0.116$, $P = 0.860$, $P = 1.000$, respectively), and significantly different compared to the negative control group ($P = 0.024$, $P = 0.004$, $P = 0.002$, respectively). The tissue granulation was at its best, indicating outstanding treatment outcomes (Figure 3).

Discussion

Severe burns can lead to complications such as respiratory distress, extensive tissue damage, organ failure, and even death (17). As a result, many researchers have focused on developing suitable solutions to reduce the risk of wound infection and to shorten the recovery time for burn injuries. These therapies often involve the use of topical antibiotics. Compared to synthetic drugs, natural products are less hazardous (37). Numerous plants and plant-based products have been found to promote wound healing. Due to their lower cost burden and therapeutic benefits, the utilization of medicinal plants in wound care has become increasingly popular. Banana peel can serve as a barrier over the wound to inhibit microbial growth (8). Its immunological properties help reduce inflammation and accelerate the wound healing process (38).

The spray gel containing *M. paradisiaca* peel extract exhibited antimicrobial activity at all concentrations in a dose dependent manner. The spray gel containing extract at a concentration of 20% demonstrated a greater growth inhibition compared to a concentration of 10%. According to the results, the spray gel of banana peel extract was found to meet the criteria for the dormant state at a concentration of 10%, as well as the criteria for the moderately active state at the concentrations of 15% and 20% (39). The mechanism action of banana peel content involves interfering with bacterial cell metabolism of Gram-positive and Gram-negative bacteria, as well as reducing surface adhesion (40). In addition, it inhibits bacterial growth by blocking the bacterial adsorption of amino acids and carbohydrates (8).

The spray gel produced better results for *S. aureus*. This outcome may be attributed to structural variations in the cell wall of two bacteria. Gram-negative bacteria have an additional outer layer of membranes that is impenetrable to most chemicals, whereas Gram-positive bacteria only have one cell membrane (41). The diameter of inhibition zone may be increased due to the inclusion of additives like propylene glycol and ethanol, which may enhance the penetration of the active substance. The hydrophilic and hydrophobic groups of propylene glycol cause changes in permeability (42). Propylene glycol and ethanol function as cosolvents to increase the solubility of the active substance and modify the thermodynamic activity of stratum corneum by altering the intracellular lipid composition. As a result, the stratum corneum is quickly penetrated by the active component (43).

The wound area of each group was expanded in the early days. The extended area had a dazzling white tint compared to the burned region. This region, resembling a stasis area, turned white and necrotic. The wound area in all groups grew the following day; the newly formed region was whiter than the coagulated area. Thereafter, each group revealed a full red ring around the wound edge. This area corresponds to the hyperemic zone, where there is higher blood flow. On the seventh day, the BG and SGH developed a scar around the margin of the wound (Figure 2A).

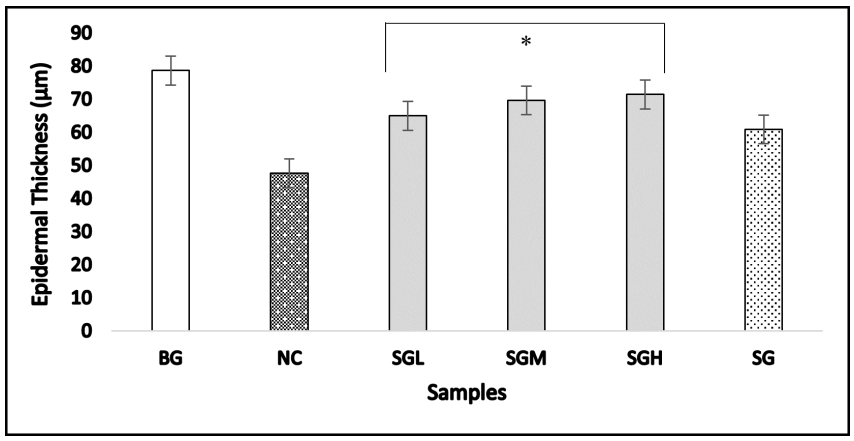

Figure 3. Epidermal thickness of rabbit skin after treatment with spray gel of banana (*Musa paradisiaca*) peel extract. BG: Positive control group (Bioplacenton); NC: group that received no treatment; SGL: 10% low concentration spray gel group; SGM: 15% medium concentration spray gel group; SGH: 20% high concentration spray gel group; SG: negative control administered with 1.2 % Na-CMC. Data are presented as mean ± SEM (n = 3). *Significant differences with the control group are expressed as $P < 0.05$ (analysed with ANOVA and Bonferroni's post hoc tests).

Banana peels contain a variety of bioactive compounds, including tannin, saponin, glycoside, terpenoid/steroid, and flavonoid, which have been linked to both direct and indirect antibacterial effects on the healing of wounds (44-46). During various stages of the healing process, these chemicals accelerate wound healing including inflammation, proliferation, and remodeling. Monocyte activity is induced by transforming growth factor β-1, vascular endothelial growth factor (VEGF), angiopoietin (Ang), tyrosine kinase (Tie), and later nuclear factor kappa B (NF-κB), which boosts interleukin-1 and interleukin-10 production and activates the nitric oxide pathway, matrix metalloproteinase (MMPs 2, 8, and 9), as well as Ras/Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase, c-Jun N-terminal kinase, and phosphoinositide 3-kinases/protein kinase B (Akt), all of which are essential for regulating the inflammatory response (38,47). The phenolic compounds in banana peels can change reactive oxygen species (ROS) generation, which may have antioxidant effects, in addition to lowering the expression of cyclooxygenase and lipoxygenase (48). The generation of ROS and other chemicals is what causes this. The primary growth factor, platelet-derived growth factor, encourages cell migration and division in the early stages of wound healing (49).

According to the histological study, the lower epidermis of the sample group had visible collagen fibers, suggesting a slower healing process. The skin's glandular structures were restored in the SGL group, although they had significantly fewer collagen fibers than those in the SGM group. SGH-treated wounds were found to have a thicker epidermis than the outcomes of all three treatments. It was determined that the epidermal thickness of 71.44 μm was better in the wounds treated with SGH (Figure 3). Re-epithelialization during the proliferative phase causes fibroblast migration to the transitory matrix. Maturating MMPs break down the matrix, speeding up tissue regeneration and wound healing (50). Barangan banana peel flavonoids can enhance keratinocyte migration and epithelial attachment that go along with it to the wound as well as increase VEGF, Ang-2, and Tie-1 production when compared to a control condition (38).

The findings of this study are also in line with those of Cheng et al (51), who investigated the effects of *M. paradisiaca* peel extract on wound healing, and Padilla-Camberos et al (52), who evaluated the effects of dehydrated *M. paradisiaca* peel in combination with solvents like methanol, hexane, and chloroform to treat burns. In this study, the use of a spray gel containing banana barangan peel extract showed higher efficacy with rapid absorption into the skin. The use of appropriate packaging also allowed easy and precise application when compared to previous studies using only the extract without pharmaceutical preparation, showing slower wound healing (11). Although this study demonstrated the effectiveness of a spray gel containing barangan banana peel extract compared to previous studies, its applicability to a range of wound types remains uncertain. To improve our understanding of the effectiveness of the spray gel, further research is needed, particularly involving comparative studies to evaluate its performance on different types of wounds.

Conclusion

The application of a spray gel formulation containing banana peel extract has shown potential in promoting the healing of burn wounds. The banana peel extract spray gel, particularly at the most effective concentration of 20%, exhibited significant antibacterial activity and accelerated the healing process of burn wounds. However, further studies are required to elucidate the effect on different types of wounds.

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Authors' contributions

The research and/or manuscript's idea and hypothesis were developed by all authors, and the procedures used to develop the hypothesis or arrive at the result were planned. RR prepared the biological materials and reagents, Y took responsibility for the logical interpretation and oversaw the project's or article's progression, and S handled the management of the data and the preparation of reports. All authors evaluated the finished manuscript before approving its publication.

Conflict of interests

None.

Ethical considerations

The animal treatments and procedures conducted in this study underwent evaluation by the Animal Research Ethics Committee/AREC, Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara, Medan, Indonesia. The committee approved the procedure performed in this study with approval number of 0596/KEPH-FMIPA/2022.

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References

1. Alzate Acevedo S, Díaz Carrillo ÁJ, Flórez-López E, Grande-Tovar CD. Recovery of banana waste-loss from

production and processing: a contribution to a circular economy. Molecules. 2021;26(17):5282. doi: 10.3390/molecules26175282.
2. Hailu M, Workneh TS, Belew D. Review on postharvest technology of banana fruit. Afr J Biotechnol. 2013;12(7):635-47.
3. Oguntoyinbo OO, Olumurewa JA, Omoba SO. Physico-chemical and sensory properties of cookies produced from composite flours of wheat and banana peel flours. J Food Stab. 2021;4(3):1-21. doi: 10.36400/J.Food.Stab.4.3.2021-0055.
4. Chandra F, Lister IN. Antifungal activity test of barangan banana peel (*Musa acuminata* Colla.) againts *Pityrosporum ovale* fungi. Biolink (Jurnal Biologi Lingkungan Industri Kesehatan). 2019;6(1):32-40. doi: 10.31289/biolink.v6i1.2211.
5. Cendana W, Diadora, Saragih AD, Martinus AR, Ikhtiari R. Potential effect of *Musa paradisiaca* peel extract on skin hydration. In: Proceedings of the International Conference on Health Informatics and Medical Application Technology (ICHIMAT 2019). Science and Technology Publications; 2020. p. 379-86. doi: 10.5220/0009515803790386.
6. Pathak PD, Mandavgane SA, Kulkarni BD. Valorization of banana peel: a biorefinery approach. Rev Chem Eng. 2016;32(6):651-66. doi: 10.1515/revce-2015-0063.
7. Loyola AB, Fernandes RV, Mendes JV, de Oliveira Neta NA, de Paiva LF, dos Anjos Mendonça AR, et al. Antimicrobial action and scaring of 10% green banana shell in chronic wounds. Open J Med Microbiol. 2018;8(3):47-55. doi: 10.4236/ojmm.2018.83005.
8. Kavitha V, Manonmani G, Devakumar J. Antimicrobial efficacy of fresh and dried banana peel extracts: an in vitro study. Drug Invent Today. 2019;11(5):1237-40.
9. Kapadia SP, Pudakalkatti PS, Shivanaikar S. Detection of antimicrobial activity of banana peel (*Musa paradisiaca* L.) on *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*: an in vitro study. Contemp Clin Dent. 2015;6(4):496-9. doi: 10.4103/0976-237x.169864.
10. Syakri S. Uji farmakologi sediaan plester patch dari limbah kulit pisang kepok (*Musa acuminata*) untuk penyembuhan luka bakar. J Kesehatan. 2019;12(1):58-62. doi: 10.24252/kesehatan.v12i1.7395.
11. Agarwal PK, Singh A, Gaurav K, Goel S, Khanna HD, Goel RK. Evaluation of wound healing activity of extracts of plantain banana (*Musa sapientum* var. *paradisiaca*) in rats. Indian J Exp Biol. 2009;47(1):32-40.
12. Mokbel MS, Hashinaga F. Antibacterial and antioxidant activities of banana (*Musa*, AAA cv. *cavendish*) fruits peel. Am J Biochem Biotechnol. 2005;1(3):125-31. doi: 10.3844/ajbbsp.2005.125.131.
13. Saryanti D, Setiawan I, Safitri RA. Optimization of M/A cream formula from kepok banana peel (*Musa acuminata* L.). Jurnal Riset Kefarmasian Indonesia. 2019;1(3):225-37. doi: 10.33759/jrki.v1i3.44.
14. Achmad H, Putri AP. Contents of banana peel extract as hemostasis in wound healing. Ann Rom Soc Cell Biol. 2021;25(1):4800-10.
15. Oboh G, Akinsanmi OA, Akinyemi AJ, Akinyemi AO. Phenolic extracts from plantain (*Musa paradisiaca*) peels inhibit angiotensin 1 converting enzyme - in vitro: possible antihypertensive benefits. Int J Plant Res. 2014;27(2):169. doi: 10.5958/2229-4473.2014.00027.5.
16. Bashmil YM, Ali A, Bk A, Dunshea FR, Suleria HAR. Screening and characterization of phenolic compounds from Australian grown bananas and their antioxidant capacity. Antioxidants (Basel). 2021;10(10):1521. doi: 10.3390/antiox10101521.
17. Kementerian Kesehatan RI. Keputusan menteri kesehatan republik Indonesia nomor HK.01.07/Menkes/555/2019 tentang pedoman nasional pelayanan kedokteran tata laksana luka bakar. 2019;52:1–5. https://yankes.kemkes.go.id/unduhan/fileunduhan_1610415947_843237.pdf.
18. World Health Organization (WHO). Burns. WHO; 2018. https://www.who.int/en/news-room/fact-sheets/detail/burns.
19. Sahin I, Ozturk S, Alhan D, Açikel C, Isik S. Cost analysis of acute burn patients treated in a burn centre: the Gulhane experience. Ann Burns Fire Disasters. 2011;24(1):9-13.
20. Broughton G 2nd, Janis JE, Attinger CE. Wound healing: an overview. Plast Reconstr Surg. 2006;117(7 Suppl):1e-S-32e-S. doi: 10.1097/01.prs.0000222562.60260.f9.
21. Mohd Zaini H, Roslan J, Saallah S, Munsu E, Sulaiman NS, Pindi W. Banana peels as a bioactive ingredient and its potential application in the food industry. J Funct Foods. 2022;92:105054. doi: 10.1016/j.jff.2022.105054.
22. Yusuf AL, Nugraha D, Sukma TA, Harun N. Activity test oinment extract ambon banana peels (*Musa paradisiaca* L.) with rabbit's (*Orycctolagus cuniculus*) combustio (minor burns). J Phys Conf Ser. 2020;1477(6):062006. doi: 10.1088/1742-6596/1477/6/062006.
23. Lamoudi L, Chaumeil JC, Daoud K. Swelling, erosion and drug release characteristics of sodium diclofenac from heterogeneous matrix tablets. J Drug Deliv Sci Technol. 2016;31:93-100. doi: 10.1016/j.jddst.2015.12.005.
24. Jáuregui KMG, Cabrera JCC, Ceniceros EPS, Hernández JLM, Ilyina A. A new formulated stable papin-pectin aerosol spray for skin wound healing. Biotechnol Bioprocess Eng. 2009;14(4):450-6. doi: 10.1007/s12257-008-0268-0.
25. Scales JT. Wound healing and the dressing. Br J Ind Med. 1963;20(2):82-94. doi: 10.1136/oem.20.2.82.
26. Ditjen POM, Depkes RI. Farmakope Indonesia Edisi Ketiga. Jakarta: Kementerian Kesehatan Republik Indonesia; 1979.
27. Bajaj S, Singla D, Sakhuja N. Stability testing of pharmaceutical products. J Appl Pharm Sci. 2012;2(3):129-38. doi: 10.7324/japs.2012.2322.
28. Zimbro MJ, Power DA, Miller SM, Wilson GE, Johnson JA. Difco™ & BBL™ manual: Manual of Microbiological Culture Media. Sparks, MD: BD (Becton, Dickinson and Company); 2009. p. 359-60.
29. Chalo DM, Lukhoba C, Fidahussein DS, Nguta JM. Antimicrobial activity, toxicity and phytochemical screening of selected medicinal plants of Losho, Narok County, Kenya. Asian J Nat Prod Biochem. 2017;15(1):29-43. doi: 10.13057/biofar/f150106.
30. Razmavar S, Abdulla MA, Ismail SB, Hassandarvish P. Antibacterial activity of leaf extracts of Baeckea frutescens against methicillin-resistant *Staphylococcus aureus*. Biomed Res Int. 2014;2014:521287. doi: 10.1155/2014/521287.
31. Manuja A, Raguvaran R, Kumar B, Kalia A, Tripathi BN. Accelerated healing of full thickness excised skin wound

in rabbits using single application of alginate/acacia based nanocomposites of ZnO nanoparticles. Int J Biol Macromol. 2020;155:823-33. doi: 10.1016/j.ijbiomac.2020.03.221.
32. Festing S, Wilkinson R. The ethics of animal research. Talking point on the use of animals in scientific research. EMBO Rep. 2007;8(6):526-30. doi: 10.1038/sj.embor.7400993.
33. Teoh L, Gnanasegaran N, Mohd Adnan AF, Taha RM. The comparative antimicrobial and anticancer of chemical extract from in vitro and in vivo *Peperomia pellucida* plantlet. J Appl Biol Biotechnol. 2021;9(2):115-23. doi: 10.7324/jabb.2021.9210.
34. Khiati B, Ahmed M. Comparison of efficacy of unheated and heat-treated Sahara honey on wound healing in rabbits. J Coast Life Med. 2015;3(2):162-5. doi: 10.12980/jclm.3.201514j91.
35. Balqis U, Rasmaidar, Marwiyah. Histopathological finding of burn healing using Ambarella leaf (*Spondias dulcis* F.) and coconut oil on rats (*Rattus norvegicus*). J Med Vet. 2014;8(1):31-6.
36. Ummah R, Monica WS, Sari DK, Adikurniawan YM, Amir MN. Effects of sugar and honey on the formation of collagen fibers in incision wound of domestic cat (*Felis domestica*). IOP Conf Ser Earth Environ Sci. 2020;575(1):012025. doi: 10.1088/1755-1315/575/1/012025.
37. Msomi NZ, Simelane MB. Herbal medicine. Builders PF, ed. Herbal Medicine. Rijeka, Croatia; IntechOpen; 2019. p. 215-27. doi: 10.5772/intechopen.72816.
38. Carvalho MTB, Araújo-Filho HG, Barreto AS, Quintans-Júnior LJ, Quintans JSS, Barreto RSS. Wound healing properties of flavonoids: a systematic review highlighting the mechanisms of action. Phytomedicine. 2021;90:153636. doi: 10.1016/j.phymed.2021.153636.
39. Silva AC, Santana EF, Saraiva AM, Coutinho FN, Castro RH, Pisciottano MN, et al. Which approach is more effective in the selection of plants with antimicrobial activity? Evid Based Complement Alternat Med. 2013;2013:308980. doi: 10.1155/2013/308980.
40. Kaczmarek B. Tannic acid with antiviral and antibacterial activity as a promising component of biomaterials-a minireview. Materials (Basel). 2020;13(14):3224. doi: 10.3390/ma13143224.
41. Tavares TD, Antunes JC, Padrão J, Ribeiro AI, Zille A, Amorim MTP, et al. Activity of specialized biomolecules against gram-positive and gram-negative bacteria. Antibiotics (Basel). 2020;9(6):314. doi: 10.3390/antibiotics9060314.
42. Carrer V, Alonso C, Pont M, Zanuy M, Córdoba M, Espinosa S, et al. Effect of propylene glycol on the skin penetration of drugs. Arch Dermatol Res. 2020;312(5):337-52. doi: 10.1007/s00403-019-02017-5.
43. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2012;64 Suppl:128-37. doi: 10.1016/j.addr.2012.09.032.
44. Rita WS, Asih IA, Swantara IM, Damayanti NL. Antibacterial activity of flavonoids from ethyl acetate extract of milk banana peel (*Musa x paradisiaca* L.). Hayati. 2021;28(3):223-31. doi: 10.4308/hjb.28.3.223.
45. Rao U, Ahmad B, Mohd K, Zin T. Antiulcer activity of *Musa paradisiaca* (banana) tepal and skin extracts in ulcer induced albino mice. Malays J Anal Sci. 2016;20(5):1203-16. doi: 10.17576/mjas-2016-2005-27.
46. Lewis DA, Fields WN, Shaw GP. A natural flavonoid present in unripe plantain banana pulp (*Musa sapientum* L. var. *paradisiaca*) protects the gastric mucosa from aspirin-induced erosions. J Ethnopharmacol. 1999;65(3):283-8. doi: 10.1016/s0378-8741(99)00005-7.
47. Adebayo SA, Dzoyem JP, Shai LJ, Eloff JN. The anti-inflammatory and antioxidant activity of 25 plant species used traditionally to treat pain in southern African. BMC Complement Altern Med. 2015;15:159. doi: 10.1186/s12906-015-0669-5.
48. Cheng H, Shi Z, Yue K, Huang X, Xu Y, Gao C, et al. Sprayable hydrogel dressing accelerates wound healing with combined reactive oxygen species-scavenging and antibacterial abilities. Acta Biomater. 2021;124:219-32. doi: 10.1016/j.actbio.2021.02.002.
49. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Curr Biol. 2014;24(10):R453-62. doi: 10.1016/j.cub.2014.03.034.
50. Baker EA, Leaper DJ. Profiles of matrix metalloproteinases and their tissue inhibitors in intraperitoneal drainage fluid: relationship to wound healing. Wound Repair Regen. 2003;11(4):268-74. doi: 10.1046/j.1524-475x.2003.11406.x.
51. Cheng YZ, Liu IM, Cheng JT, Lin BS, Liu F. Wound healing is promoted by *Musa paradisiaca* (banana) extract in diabetic rats. Arch Med Sci. 2019;16(1):1-9. doi: 10.5114/aoms.2020.92344.
52. Padilla-Camberos E, Flores-Fernández JM, Canales-Aguirre AA, Barragán-Álvarez CP, Gutiérrez-Mercado Y, Lugo-Cervantes E. Wound healing and antioxidant capacity of *Musa paradisiaca* Linn. peel extracts. J Pharm Pharmacogn Res. 2016;4(5):165-73.