Efficacy of Combined Bromelain and Hyaluronic Acid as an Enzymatic Debridement Agent for Full-Thickness Burn Wounds in Wistar Rats (*Rattus norvegicus*)

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HOW TO CITE:
Yesica, Iswinarno Doso Saputro, Lynda Hariani (2026). Efficacy of Combined Bromelain and Hyaluronic Acid as an Enzymatic Debridement Agent for Full-Thickness Burn Wounds in Wistar Rats (Rattus norvegicus). International Journal of Special Education, 41(19s), 1703 - 1713

ABSTRACT:

Background: Retained eschar delays healing of full-thickness burns, and the wound bed exposed by enzymatic debridement is vulnerable to desiccation. This study evaluated the effect of topical 10% bromelain, alone and combined with hyaluronic acid (HA), on burn wound healing in rats.

Methods: Twenty-four male Wistar rats with standardized 2 × 1 cm full-thickness dorsal burns were randomized into six groups receiving hydrogel control, 10% bromelain, or bromelain plus HA once daily, with endpoints on day 3 or day 7 (n = 4 per group). Epithelialized area was quantified by digital planimetry, neo-epidermal height by hematoxylin and eosin staining, and dermal collagen density by Masson trichrome with ImageJ. Kruskal-Wallis, Mann-Whitney, and Spearman tests were applied.

Results: Twenty-three rats completed the study. Day 7 epithelialized area reached 1.16 ± 0.39 cm^2 with bromelain and 1.07 ± 0.52 cm^2 with the combination versus 0.88 ± 0.39 cm^2 in controls. Neo-epidermal height was 3.4-fold greater with bromelain plus HA (232.99 ± 139.10 μm) than with bromelain alone (68.39 ± 136.77 μm), and three of four bromelain-only wounds showed no measurable epithelium. Day 7 collagen density was 40.50 ± 9.05% with the combination versus 32.39 ± 3.76% with bromelain alone, and bromelain produced the highest day 3 collagen density (44.92 ± 11.57%). Differences were not statistically significant (Kruskal-Wallis p = 0.145 to 0.323, Mann-Whitney p = 0.139 to 0.773).

Conclusion: Adding HA after bromelain debridement was consistently associated with thicker re-epithelialization and

preserved dermal collagen, supporting integrated enzymatic debridement with moisture-retentive wound bed care.

Keywords: bromelain, collagen density, enzymatic debridement, full-thickness burn, hyaluronic acid, re-epithelialization

INTRODUCTION

Burn injury remains a major global health problem, with an estimated 11 million new cases and approximately 180,000 deaths every year, most of which occur in low- and middle-income countries.[1-3] Full-thickness burns destroy the entire epidermis and dermis and leave a coagulated layer of denatured protein known as eschar.[4] Retained eschar acts as a mechanical barrier to keratinocyte migration, perpetuates the local inflammation that drives burn wound conversion, and provides a culture medium for invasive pathogens.[5,6] Rapid, effective, and safe eschar removal is therefore regarded as the cornerstone of full-thickness burn management.[7]

Surgical debridement by tangential excision remains the reference standard but is inherently non-selective, so viable dermis is frequently sacrificed together with necrotic tissue at the cost of substantial blood loss, contour deformity, and hypertrophic scarring.[8,9] Enzymatic debridement with bromelain, a complex of sulfhydryl proteolytic enzymes extracted from the stem of the pineapple plant (*Ananas comosus*), offers a highly tissue-selective alternative that dissolves denatured eschar proteins while preserving the viable wound bed.[10-12] Clinical studies of a bromelain-based debriding concentrate have documented rapid eschar clearance, fewer surgical excisions, and more accurate wound bed assessment in deep burns.[13-15]

An enzymatically debrided wound bed is nevertheless vulnerable to desiccation, and delayed re-epithelialization can follow when no moisture-retentive dressing is applied after debridement.[16] Hyaluronic acid, a linear glycosaminoglycan of the extracellular matrix, binds up to one thousand times its weight in water, modulates local inflammation, and stimulates keratinocyte proliferation, fibroblast activity, and angiogenesis through CD44-mediated signaling.[17,18] Most previous studies have evaluated either agent in isolation, without examining their dynamic interaction across the epidermal and dermal compartments of the acute wound. Combining selective enzymatic eschar removal with hyaluronic acid hydration is therefore biologically attractive, yet experimental studies that directly compare bromelain alone with bromelain plus hyaluronic acid in full-thickness burns remain scarce.[19]

This study aimed to evaluate the efficacy of topical 10% bromelain, alone and combined with hyaluronic acid, as an enzymatic debridement agent for full-thickness burn wounds in Wistar rats, assessed by macroscopic epithelialization, neo-epidermal height, and dermal collagen density.

MATERIALS AND METHODS

Study design and ethical approval

This true experimental study used a randomized post-test-only control group design and is reported in line with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines for animal research. The protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. Animal housing, wounding, and treatment were carried out at the Institute of Tropical Disease, Universitas Airlangga, beginning in February 2026.

Animals

Twenty-four healthy male Wistar rats (*Rattus norvegicus*) aged 3 to 4 months and weighing 250 to 300 g were used. Male animals

were selected to avoid the confounding effect of estrous-cycle hormonal fluctuation on wound healing. Health was confirmed by active movement, a dense coat, and clear eyes. Animals previously used in other experiments or showing any pre-existing skin lesion were excluded. Withdrawal criteria were weight loss above 10% during acclimatization, signs of illness, or death during the study. Rats were housed individually and received feed and drinking water of identical type and amount under controlled temperature and a regular light-dark cycle.

The minimum sample size was estimated with the two-mean formula recommended for animal studies, assuming a standard deviation of 14.27 and a between-group mean difference of 39.72 at $\alpha = 0.05$ and a power of 0.80, which yielded 2.02 animals per group.[20] This was rounded to three and multiplied by an attrition correction factor of 1.3, giving four animals per group and 24 animals for the six groups.

Full-thickness burn model

Anesthesia was induced with intramuscular ketamine 50 mg/kg combined with xylazine 5 mg/kg.[21] The dorsal fur was clipped, and the skin was disinfected with 10% povidone iodine followed by a chlorhexidine-cetrimide solution diluted 1:30 and a normal saline rinse. A 2 × 1 cm brass plate was immersed in water maintained at 100 °C for 5 minutes, verified with a thermometer, and applied to the dorsum for 10 seconds to create a standardized 2 cm^2 full-thickness burn (Figure 1).

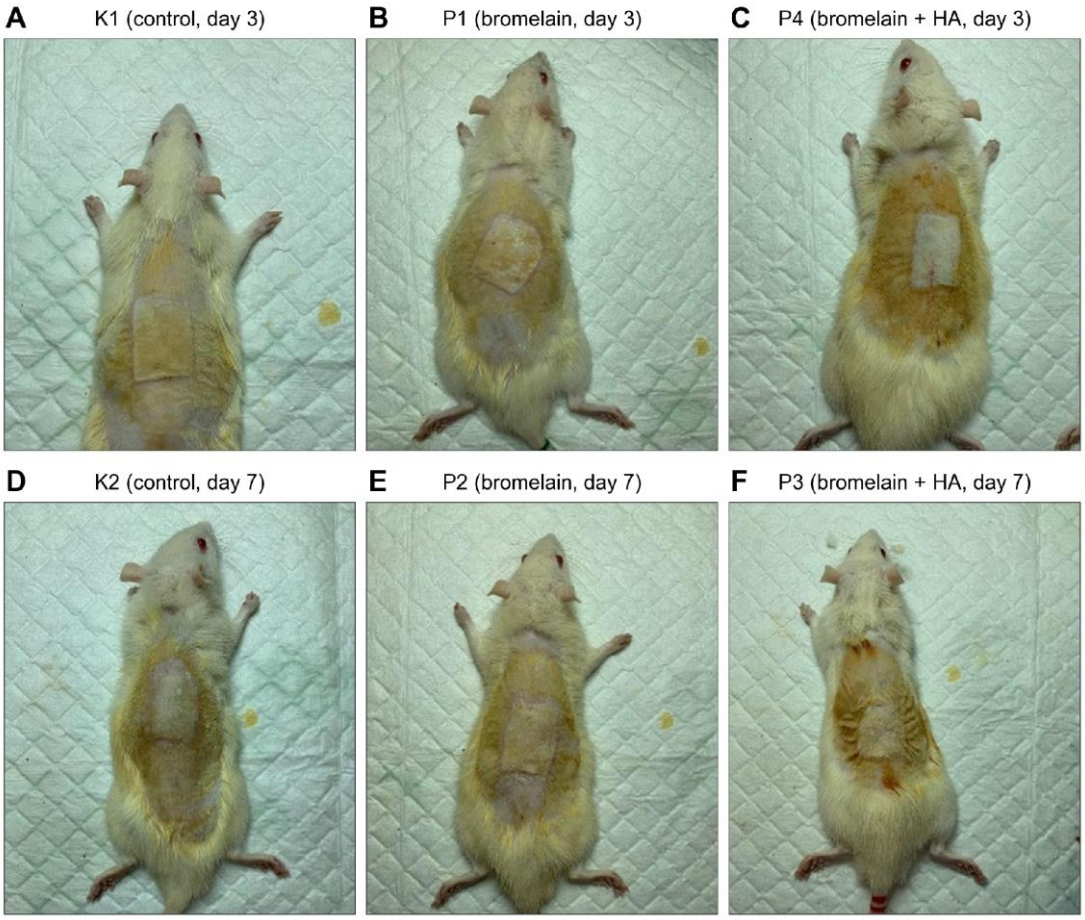

Figure 1. Representative standardized 2 × 1 cm full-thickness dorsal burn wounds on day 0 immediately after thermal induction and initial wound care. (A) Group K1. (B) Group P1. (C) Group P4. (D) Group K2. (E) Group P2. (F) Group P3. Groups K1 and K2 received hydrogel control, P1 and P2 bromelain

10%, and P3 and P4 bromelain 10% plus hyaluronic acid, with endpoints on day 3 (K1, P1, P4) or day 7 (K2, P2, P3). Photographs were cropped for presentation.

Groups and interventions

The rats were randomly allocated into six groups (Table 1). Control groups received plain hydrogel, bromelain groups received 10% topical bromelain cream, and combination groups received 10% bromelain followed by hyaluronic acid gel (0.2 to 0.4%) as a post-debridement dressing. The bromelain cream was compounded at the Faculty of Pharmacy, Universitas Airlangga, from pharmaceutical-grade bromelain powder incorporated into a hydrogel base at a final concentration of 10%, equivalent to 100 mg/mL. Each application delivered 0.2 g (0.2 mL) once daily, after which the wound was covered with a transparent film dressing. Groups K1, P1, and P4 were treated until day 3 and groups K2, P2, and P3 until day 7.

Table 1. Experimental groups and topical regimens

Group	Topical regimen	Endpoint	n randomized	n analyzed
K1	Hydrogel (vehicle control)	Day 3	4	4
K2	Hydrogel (vehicle control)	Day 7	4	4
P1	Bromelain 10%	Day 3	4	4
P2	Bromelain 10%	Day 7	4	4
P3	Bromelain 10% + hyaluronic acid	Day 7	4	4
P4	Bromelain 10% + hyaluronic acid	Day 3	4	3

All preparations were applied at 0.2 g (0.2 mL) once daily and covered with a transparent film dressing. One animal in group P4 died during the observation period. n, number of animals.

Macroscopic assessment

Wounds were photographed on days 0, 3, and 7 with a smartphone camera at a standardized distance of 20 cm with flash illumination. The epithelialized area (cm^2) was measured by non-contact digital planimetry with the ImitoMeasure application (imito AG, Zurich, Switzerland), tracing the boundary between dark necrotic tissue and pink viable epithelium on serial photographs.[22]

Histopathological examination

At the designated endpoint, each animal was euthanized with intraperitoneal pentobarbital 60 to 100 mg/kg. The wound and a 0.5 cm rim of healthy skin were excised down to a plane just above the fascia under aseptic conditions, fixed in 10% neutral buffered formalin, and embedded in paraffin. Sections were stained with hematoxylin and eosin (HE) for measurement of neo-epidermal height (μm) and with Masson trichrome (MT) for dermal collagen. Slides were examined under light microscopy at 400× magnification at the Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga. Collagen density was expressed as the percentage of dermal area occupied by collagen fibers, computed with ImageJ 1.48 (National Institutes of Health, Bethesda, MD, USA) at a constant color threshold of 160.

Statistical analysis

Analyses were performed with IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Distribution was tested with the Shapiro-Wilk test. Because several variables departed from normality, six-group comparisons used the

Kruskal-Wallis test, followed by focused Mann-Whitney tests for the predefined day 7 contrasts (P2 versus P3 and K2 versus P3). The relationship between collagen density and neo-epidermal height was examined with Spearman rank correlation. Data are presented as mean ± standard deviation (SD), and $p \leq 0.05$ was considered statistically significant.

RESULTS

Animals and burn model

Of the 24 randomized rats, one animal in the combination day 3 group (P4) died during observation, an attrition of 4.2%, leaving 23 animals for analysis. All induced wounds displayed the uniform pale, dry surface of full-thickness injury over the intended 2 cm^2 area.

Macroscopic epithelialization

On day 3, the epithelialized area remained below 0.30 cm^2 in 20 of 23 wounds, and every group median except that of P1 was 0.17 cm^2 or lower (Table 2, Figure 2A). The elevated P1 median of 0.63 cm^2 reflected two outlying wounds of 1.15 and 4.45 cm^2, the latter producing the largest single-group variance of this variable. Between day 3 and day 7, epithelialization rose steeply in every animal observed to day 7 except one control (Figure 2B). By day 7 the epithelialized surface corresponded to 57.8% of the original wound area in P2, 53.4% in P3, and 43.9% in K2.

Table 2. Macroscopic and histopathological outcomes of full-thickness burn wound healing

Group	n	Epithelialized area day 3 (cm^2)	Epithelialized area day 7 (cm^2)	Neo-epidermal height (μm)	Collagen density (%)
K1	4	0.17 ± 0.10	NA	347.26 ± 70.36	34.44 ± 6.55
K2	4	0.46 ± 0.72	0.88 ± 0.39	264.43 ± 99.06	36.21 ± 10.48
P1	4	1.45 ± 2.06	NA	319.13 ± 142.04	44.92 ± 11.57
P2	4	0.12 ± 0.14	1.16 ± 0.39	68.39 ± 136.77	32.39 ± 3.76
P3	4	0.07 ± 0.07	1.07 ± 0.52	232.99 ± 139.10	40.50 ± 9.05
P4	3	0.03 ± 0.03	NA	266.88 ± 52.79	31.28 ± 4.28

Values are mean ± SD. Histopathological variables were measured at each group endpoint (day 3 for K1, P1, and P4 and day 7 for K2, P2, and P3). Pooled values for the 23 analyzed wounds were 249.10 ± 137.55 μm for neo-epidermal height and 36.86 ± 8.78% for collagen density. NA, not applicable (animals terminated on day 3). Group definitions are given in Table 1. n, number of animals. SD, standard deviation.

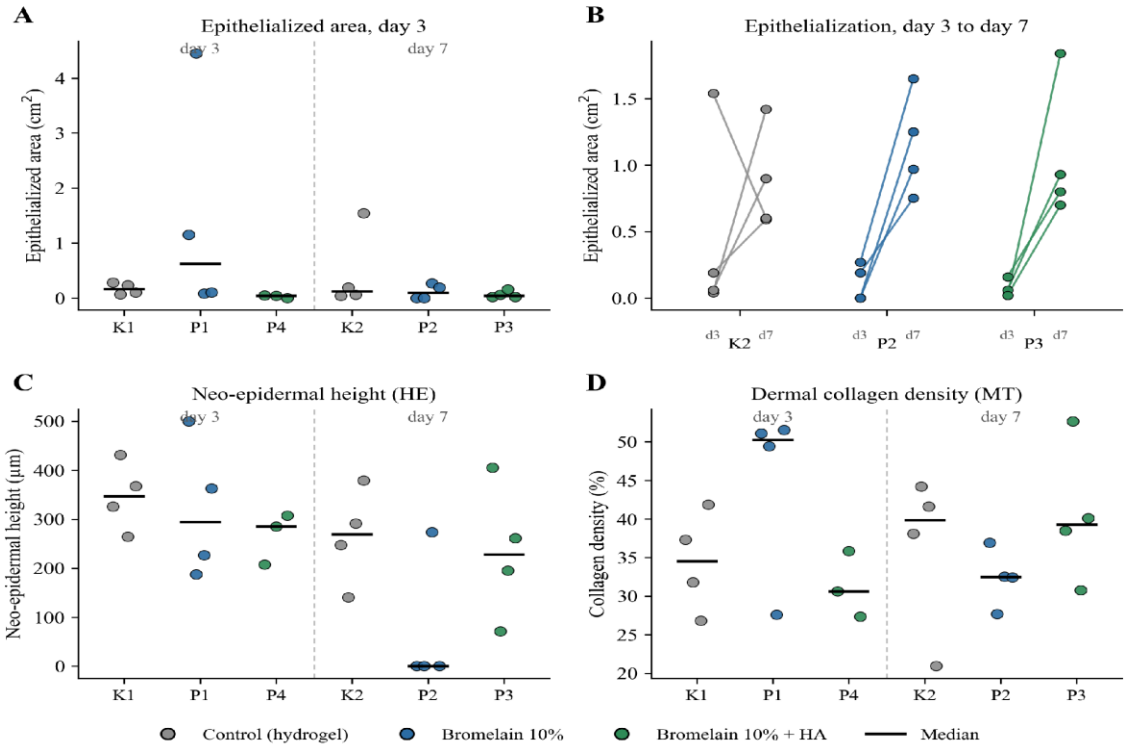

Figure 2. Individual-animal outcomes of full-thickness burn wound healing. (A) Epithelialized area on day 3 in all six groups. (B) Within-animal change in epithelialized area from day 3 (d3) to day 7 (d7) in the three groups observed to day 7. (C) Neo-epidermal height on hematoxylin and eosin sections at each group endpoint. (D) Dermal collagen density on Masson trichrome (MT) sections at each group endpoint. Dots represent individual animals and horizontal bars group medians. Groups K1 and K2 received hydrogel control, P1 and P2 bromelain 10%, and P3 and P4 bromelain 10% plus hyaluronic acid, with endpoints on day 3 (K1, P1, P4) or day 7 (K2, P2, P3).

Neo-epidermal Height

On day 3, mean neo-epidermal height was greatest in the control group K1, followed by the bromelain group P1 (Table 2). A marked divergence between the two active regimens appeared on day 7. Three of the four P2 wounds showed a neo-epidermal height of 0.00 µm, whereas all four P3 wounds were re-epithelialized and the P3 group mean was 3.4-fold higher than that of P2 (Figure 2C).

Dermal Collagen Density

Collagen density on day 3 was highest in P1, exceeding the parallel control K1 by 10.5 percentage points (Table 2, Figure 2D). Collagen density in the bromelain-only arm was 12.5 percentage points lower on day 7 than on day 3 (P2 versus P1), whereas the combination arm was 9.2 percentage points higher (P3 versus P4). On MT sections, day 7 combination wounds showed a more compact and organized collagen weave than the loose early matrix of bromelain-treated wounds on day 3 (Figure 3).

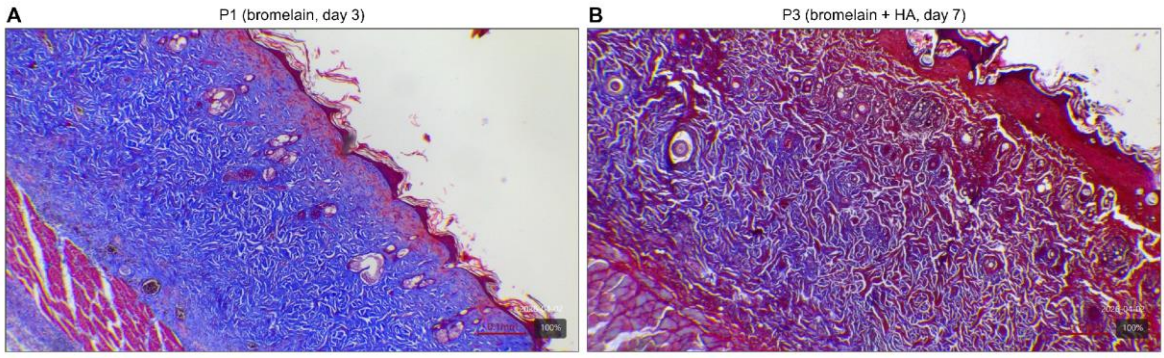

Figure 3. Representative Masson trichrome photomicrographs of the wound dermis. (A) Group P1 (bromelain, day 3) with early, loosely arranged collagen deposition (blue). (B) Group P3 (bromelain plus hyaluronic acid, day 7) with a more compact and organized collagen weave. Embedded scale bars represent 0.1 mm.

Statistical Comparisons

None of the simultaneous six-group comparisons reached statistical significance (Table 3). In the focused day 7 contrasts, P3 held a consistently higher mean rank than P2 for both histological outcomes, and the combination group performed comparably to the day 7 control (Table 4). Across the 23 analyzed wounds, collagen density was not correlated with neo-epidermal height (Spearman rho = 0.059, p = 0.788).

Table 3. Kruskal-Wallis comparison of healing variables across the six groups

Variable	Kruskal-Wallis H	df	*p* value
Epithelialized area day 3	8.212	5	0.145
Neo-epidermal height	7.751	5	0.171
Collagen density	5.833	5	0.323

Asymptotic two-tailed significance. df, degrees of freedom.

Table 4. Focused Mann-Whitney comparisons on day 7

Comparison	Variable	Mean rank	U	Z	*p* value
P2 vs P3	Neo-epidermal height	3.25 vs 5.75	3.000	-1.479	0.139
P2 vs P3	Collagen density	3.25 vs 5.75	3.000	-1.443	0.149
K2 vs P3	Neo-epidermal height	4.75 vs 4.25	7.000	-0.289	0.773
K2 vs P3	Collagen density	4.25 vs 4.75	7.000	-0.289	0.773

Mean ranks are given in the order of the listed comparison. Asymptotic two-tailed significance. U, Mann-Whitney statistic. Z, standardized test statistic.

DISCUSSION

The principal finding of this study is that the benefit of bromelain debridement depended strongly on how the wound bed was managed after eschar removal. Bromelain alone showed visibly faster eschar separation on serial photographs and produced the highest collagen density of any group on day 3, consistent with an

efficient transition from inflammation to early proliferation once necrotic tissue was removed.[10,23] By day 7, however, the same regimen was associated with the lowest neo-epidermal height in the study and the lowest day 7 collagen density, while the addition of hyaluronic acid preserved both parameters. Enzymatic debridement and post-debridement wound bed care therefore appear to be inseparable components of a single therapeutic strategy rather than independent interventions.[16,24]

The macroscopic behavior of the enzyme-treated wounds mirrors clinical experience with bromelain-based debridement. Controlled studies of the commercial concentrate report selective eschar dissolution with preservation of viable dermis and a reduced need for tangential excision and transfusion.[8,13] A systematic review spanning a decade of clinical use concluded that bromelain achieves complete debridement in most deep burns with acceptable safety and good long-term outcomes.[14] Accurate exposure of the wound bed also improves burn depth diagnosis after enzymatic debridement, which supports earlier and better-informed surgical decision making.[15] The visibly rapid eschar separation observed on serial photographs of the P1 and P4 groups, without bleeding or extension of necrosis, fits this clinical profile.

The collapse of re-epithelialization in the bromelain-only group on day 7, with three of four wounds showing no measurable neo-epidermis, most plausibly reflects desiccation of the exposed wound bed. A debrided surface that has lost its moisture barrier undergoes high transepidermal water loss, and the resulting local stress stimulates macrophages and fibroblasts to release matrix metalloproteinases, particularly MMP-1, MMP-2, and MMP-9.[25,26] Uncontrolled proteolysis of this kind lyses newly deposited collagen fibers, promotes fibroblast apoptosis, and arrests keratinocyte migration from the wound margin.[23,26] This mechanism would explain the paradoxical fall in collagen density from 44.92% on day 3 to 32.39% on day 7 when no secondary hydrating agent was provided.[16]

Hyaluronic acid appears to have counteracted these effects in the combination group. As the dominant glycosaminoglycan of the extracellular matrix, hyaluronic acid forms a strongly hygroscopic and highly hydrated pericellular matrix that maintains the moist microenvironment required for keratinocyte migration.[17,18] Through CD44-mediated signaling it stimulates basal keratinocyte proliferation, directs fibroblast recruitment, and supports angiogenesis, while exerting a dual immunomodulatory action that restrains excessive local inflammation.[17-19] Reviews of hyaluronic acid-based burn dressings likewise describe faster healing and better epithelial quality than conventional care.[16] These mechanisms are consistent with the 3.4-fold greater neo-epidermal height and preserved collagen density of P3 compared with P2.

The temporal design and the animal model deserve comment. Day 3 captures the peak of acute inflammation and the start of proliferation, whereas day 7 corresponds to maximal fibroblast activity and early matrix deposition in rodents.[2,6] Rodent skin is loose and contains a panniculus carnosus, so contraction closes wounds faster than the granulation and re-epithelialization that dominate healing of tight human skin.[21,27] Findings from this model therefore describe early biological trends rather than definitive closure times. Preclinical testing also remains obligatory for a compounded enzymatic product whose specific activity, pH, and stability have not been fully characterized before human exposure can be justified.[12,28]

From a translational perspective, the results support development of an integrated topical system that couples a debriding enzyme with a moisture-retentive macromolecule in a single delivery platform. Bromelain contributes selective proteolysis together with antimicrobial and anti-inflammatory activity, while hyaluronic acid maintains hydration of the newly exposed

dermis.[12,18,29] A ready-to-use combination could simplify dressing protocols, shorten hospitalization, and improve scar quality, which is particularly relevant for the low-resource settings that carry most of the global burn burden.[2,3] Because pineapple is cultivated widely in these regions, a locally compounded preparation could also be considerably cheaper than imported concentrates.[11] Safety surveillance should nevertheless accompany such development because bacteremia has been reported after enzymatic debridement of extensive burns.[30]

This study has limitations. Four animals per group limited statistical power, and wide biological variability, with standard deviations exceeding some group means, meant that clear descriptive trends did not reach statistical significance. Eschar area was not quantified, so debridement speed was assessed only qualitatively. Observation ended on day 7, before remodeling, complete closure, and scar quality could be evaluated. Only one bromelain concentration was tested, the enzymatic activity of the compounded cream was not assayed, and cytokines were not measured. Future studies should use larger groups, extend observation to days 14 through 28, test bromelain concentrations of 5% to 15%, quantify transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), and compare the combination with surgical debridement.

CONCLUSION

In this full-thickness burn model, topical 10% bromelain was associated with visibly faster early eschar separation and showed the highest day 3 collagen deposition, but without subsequent hydration it was followed by arrested re-epithelialization and loss of dermal collagen by day 7. Adding hyaluronic acid after debridement preserved collagen density and produced a 3.4-fold greater neo-epidermal height than bromelain alone, matching the healing profile of the hydrogel control while retaining the advantage of earlier enzymatic eschar removal. The combination of bromelain and hyaluronic acid therefore merits further preclinical optimization as an integrated debridement and wound bed care strategy for full-thickness burns.

DECLARATIONS

Ethical approval

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. All procedures complied with institutional guidelines for the care and use of laboratory animals.

Author contributions

Y contributed to conceptualization, methodology, investigation, data curation, formal analysis, and writing of the original draft. IDS contributed to conceptualization, methodology, supervision, and review and editing of the manuscript. LH contributed to validation, supervision, and review and editing of the manuscript. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this article and its supplementary material.

Acknowledgments

The authors thank the staff of the Institute of Tropical Disease and the Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga, for technical assistance, the Faculty of Pharmacy, Universitas Airlangga,

for compounding the study preparations, and Atikah, S.Si., M.Kes., for statistical guidance.

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