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BRIEF REPORT

Wound healing and anti-inflammatory effects of LAA, the *N*-acetyl-D-galactosamine-binding lectin from seeds of *Luetzelburgia auriculata* (Allemão) ducke

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Abstract

Cutaneous wounds represent a significant health concern, and effective treatment strategies are crucial for optimal healing. This study investigates the therapeutic potential of *Luetzelburgia auriculata* lectin (LAA), a plant-derived protein, in accelerating wound closure. Excisional wounds were created on the backs of mice, which were subsequently treated topically with LAA solutions at two concentrations (100 µg/mL and 200 µg/mL) or saline control. Wound healing was assessed through clinical observations, including wound area measurement and inflammatory score, as well as histopathological analysis and measurement of inflammatory cytokines. LAA significantly accelerated wound closure, reduced inflammation, and promoted tissue regeneration. Histological analysis revealed enhanced re-epithelialization, increased fibroblast proliferation, and improved collagen deposition in LAA-treated wounds compared with the control group. Furthermore, LAA treatment significantly reduced the levels of proinflammatory cytokines in wound tissues (interleukin-6, tumor necrosis factor-alpha, and monocyte chemoattractant protein-1). These findings suggest that LAA exerts its beneficial effects through a multifaceted mechanism, likely involving anti-inflammatory properties and stimulation of cellular processes crucial for tissue repair. This study provides preliminary evidence for the therapeutic potential of LAA in wound healing and warrants further investigation into its underlying mechanisms and clinical applications.

Keywords Plant lectins · Wound healing · Anti-inflammatory effects · Skin · Cytokines

Introduction

Wound healing is a complex and highly dynamic process. It involves an intricate series of interconnected cellular and molecular events meticulously orchestrated to restore the integrity and function of damaged skin tissue (Sorg and Sorg 2023). This process encompasses distinct yet overlapping phases, including hemostasis, inflammation, proliferation, and remodeling. Each phases involves specialized cellular and biochemical mechanisms working in harmony to achieve complete tissue repair and regeneration (Peña and Martin 2024). Disruptions to these events can impair tissue repair success, hindering the skin barrier's ability to maintain its initial function (Almadani et al. 2021; Kremer and Burkemper 2024).

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Several agents have been explored for their potential to promote wound healing; however, their efficacy is often limited (Freedman et al. 2023). Conventional wound healing therapies, such as topical antibiotics and dressings, can often fail to address the complex and dynamic nature of the wound healing process, leading to delayed or impaired tissue repair (Kolimi et al. 2022). Therefore, there is a pressing need to discover new bioactive compounds that can modulate various aspects of the wound healing cascade, including the regulation of inflammation, promotion of re-epithelialization, and enhancement of tissue remodeling (Ramalingam et al. 2021). These natural therapeutic agents have the potential to offer more comprehensive and effective solutions for the management of skin wounds (Kolimi et al. 2022).

Lectins represent a diverse class of carbohydrate-binding proteins that exhibit a wide range of biological activities, including anti-inflammatory, antimicrobial, and cell-stimulating properties, making them attractive candidates for wound healing applications (Konozy et al. 2022; de Sousa et al. 2023). *Luetzelburgia auriculata* (Allemão) Ducke, a tree species native to northeastern Brazil and belonging to the Fabaceae family, produces seeds that are rich in proteins and lipids. While some reports have suggested potential toxicity associated with seed consumption, *L. auriculata* seeds have been used to obtain bioactive compounds such as a *N*-acetyl-D-galactosamine-binding lectins (named as LAA) (Oliveira et al. 2002) and a Bowman–Birk Inhibitor (LzaBBI) (Martins et al. 2018).

LAA is a homotetrameric glycoprotein, which has a molecular weight of 123.5 kDa and exhibits anti-inflammatory efficacy in animal studies, reducing myeloperoxidase activity, inhibiting leukocyte adhesion and rolling, and suppressing the edematogenic effects of histamine and prostaglandins in models of peritonitis and paw edema (Alencar et al. 2010). LAA has also reported antimicrobial activity against phytopathogenic fungi (*Colletotrichum lindemuthianum*, *Fusarium solani*, and *Aspergillus niger*) (Melo et al. 2005). However, the potential of LAA to promote wound healing has not yet been investigated.

Given the well-documented anti-inflammatory properties of LAA, we hypothesized that it may exert beneficial effects on skin wound healing. We further postulated that LAA, by virtue of its specific binding to *N*-acetyl-D-galactosamine residues present on the surface of various cell types involved in wound healing, could modulate key aspects of the repair process. *N*-acetyl-D-galactosamine is a carbohydrate moiety commonly found on the surface of keratinocytes, fibroblasts, and other cells involved in wound healing. The binding of LAA to these residues may facilitate cell–cell interactions, stimulate crucial signaling pathways, and enhance the deposition of extracellular matrix components, such as collagen. These interactions could collectively contribute to reduced inflammation, accelerated cell proliferation and migration, and improved tissue remodeling. To test these hypotheses, the present study aims to investigate the wound healing and anti-inflammatory effects of LAA in a murine model of skin wounds.

Materials and methods

Purification of LAA

L. auriculata seeds were collected from plants located in Araripe, Ceará, Brazil. The plant was identified in the Herbarium Dárdano de Andrade-Lima at the Regional University of Cariri, number 13.480, and registered in SISGEN (Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional Associado, ID: A6D883E). The purification of the lectin from *L. auriculata* (LAA) was carried out as described by Oliveira et al. (2002). In brief, mature seeds were ground into a fine powder using a coffee mill. The resulting flour was diluted 1:10 (w/v) in NaCl 0.15 M and incubated at room temperature under continuous stirring for 4 h before centrifugation at 4000*g* for 20 min at 4 °C. The supernatant was then subjected to ammonium sulfate precipitation, and the resulting precipitate was resuspended in NaCl 0.15 M and applied to an affinity chromatography using Guar Gum column (1.0 cm × 3.5 cm) (Sigma Aldrich, St. Louis, MO, USA). The lectin was eluted with 0.1 M lactose in NaCl 0.15 M, dialyzed against distilled water, and lyophilized for storage. The purified LAA was subjected to 12% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) under denaturing conditions.

Animals and ethical conditions

The study was conducted in accordance with established guidelines and the experimental protocol previously approved by the animal facility at Universidade CEUMA (Protocol 00020/21). Adult Swiss mice (6–8 weeks old, both sexes) were obtained from the animal facility at Universidade CEUMA, where they were housed and monitored throughout the experiment under controlled temperature, humidity, and lighting conditions. The animals were provided with a specific rodent diet and water ad libitum. Swiss mice were chosen as the animal model for this study due to their widespread use in wound healing research, well-characterized biology, ease of handling, and availability.

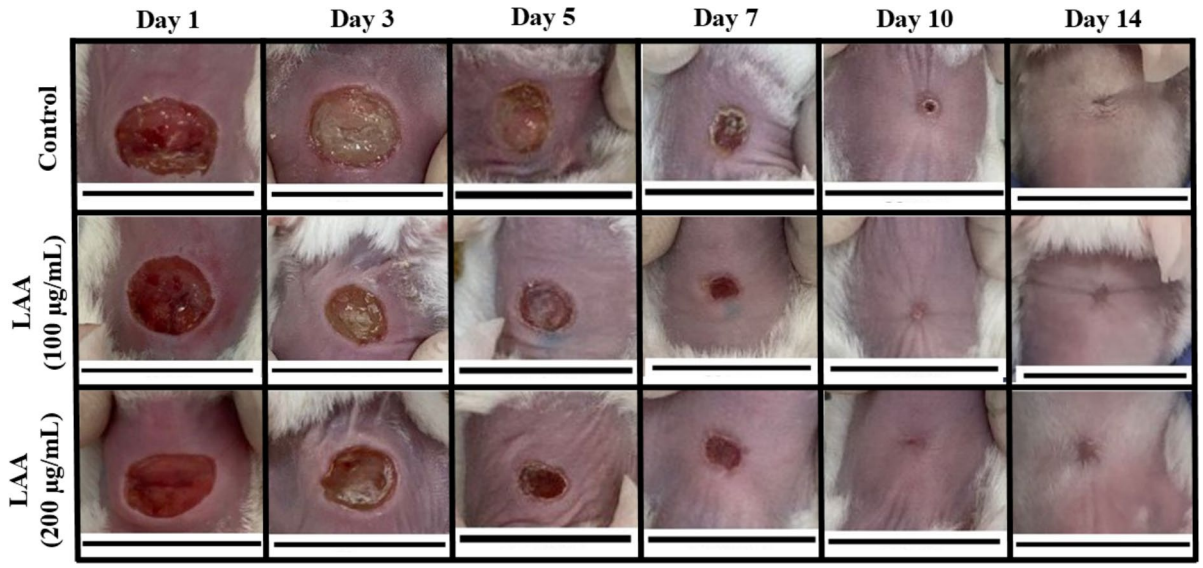

Fig. 1 Evolution of the tissue repair process over the respective days (1st, 3rd, 5th, 7th, 10th, and 14th) of cutaneous wounds. The images illustrate the progression of wound healing in the control group (treated with PBS) and the LAA-treated groups (100 µg/mL and 200 µg/mL). The scale bar below each image represents 20 mm

Wound healing model

Each animal was anesthetized with an intraperitoneal injection of xylazine hydrochloride (1 mg/kg) and ketamine hydrochloride (50 mg/kg). The dorsal thoracic region was shaved and cleaned with 70% ethanol. A full-thickness excisional wound (0.64 cm^2) was created using blunt-tipped scissors and dissecting forceps. The wound area was marked using a sterile template to ensure consistency in size and location.

The mice were randomly divided into three experimental groups ($n = 18$/group): (1) control: animals with wounds treated with 50 µL of saline solution (150 mM NaCl); (2) LAA100: animals with wounds treated with 50 µL of LAA solution at 100 µg/mL; and (3) LAA200: animals with wounds treated with 50 µL of LAA solution at 200 µg/mL. These dose (5 and 10 µg/wound/day) were chosen on the basis of previous reports with other lectins (Coriolano et al. 2014; dos Santos Silva et al. 2024).

The treatments were applied topically to the wound bed once daily for 14 days. The LAA solutions were prepared in saline without additional excipients or formulations. A total of 50 µL of the respective solutions were carefully applied using a micropipette to ensure even coverage of the wound area. For each sampling point (3rd, 7th, and 14th days of treatment), six animals were sacrificed, and the skin region where the wound was created was collected for cytokine level assessment and histopathological analyses.

Clinical evaluation

Wound healing was assessed through clinical observations, including wound area measurement and inflammatory score. The wounds were individually photographed and measured in diameter at days 1, 3, 5, 7, 10, and 14. The clinical parameters evaluated included wound area (0–7), amount of exudate (0–3), type of exudate (0–4), intensity of edema (0–3), color of surrounding skin tissue (0–4), and type of debrided tissue (0–3). Each parameter was scored, and the sum of the individual scores for each animal was used as an index of wound severity as described by Ferro et al. (2019).

Measurement of inflammatory mediators

The wounds collected on day 3 were transferred to sterile tubes and weighed. Each wound was macerated in 1 mL of phosphate-buffered saline (PBS) and homogenized by vortexing (five cycles of 30 s) to obtain wound lysates. A multiplex bead-based assay (CBA) was used to quantify cytokine levels (IL-6, IL-10, MCP-1, IFN-γ, TNF, and IL-12p70) using the BD™ Cytometric Bead Array (CBA) Kit (CBA; BD Biosciences, São Paulo, Brazil). The analysis was carried out in a BD Accuri C6® flow cytometer, following the manufacturer's instructions. The results were expressed in pg/mL.

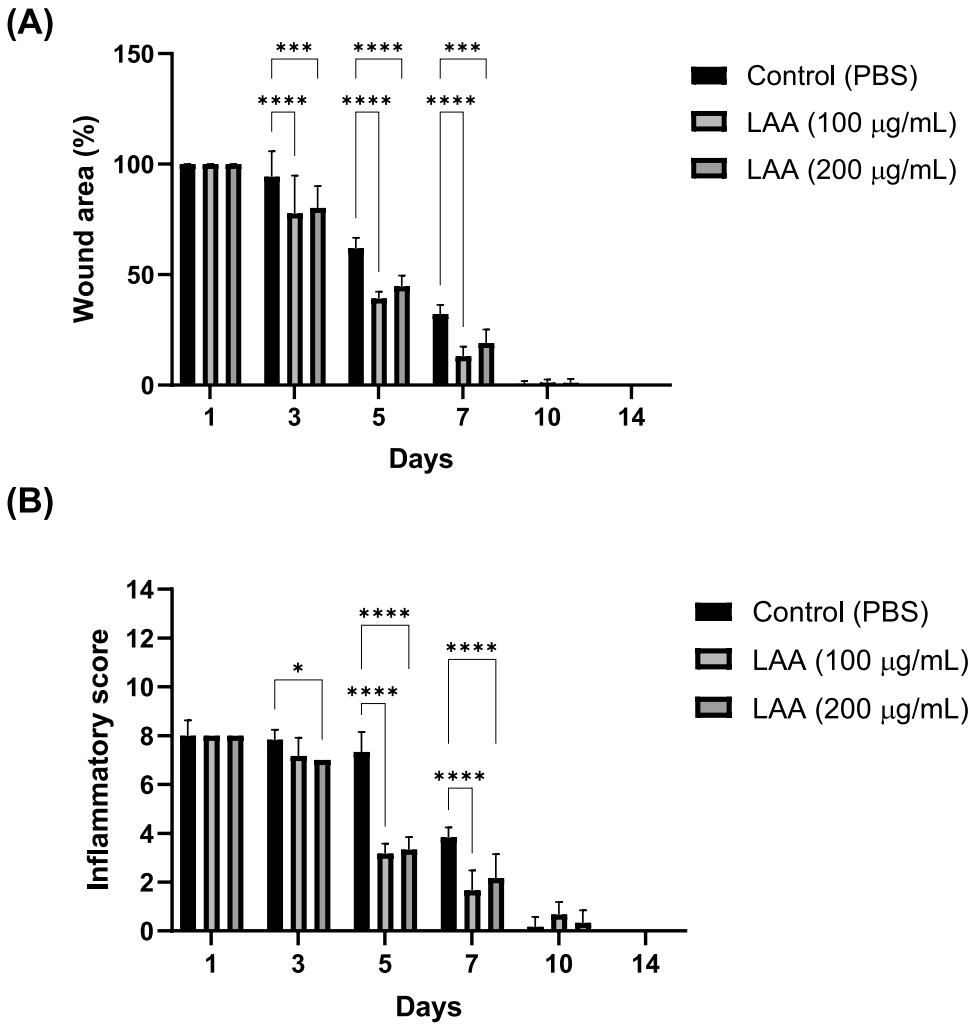

Fig. 2 Clinical evaluation of the healing effects of LAA. **a** Evaluation of wound area. **b** Inflammatory score. *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$

Histological analysis

The wound tissues of each animal were fixed in a 10% formaldehyde solution, processed through a series of alcohol and xylene baths, and embedded in paraffin. Sections of 5 µm thickness were cut using a microtome (Leica RM2245) and stained with hematoxylin and eosin (HE) for histopathological evaluation and Masson's trichrome for collagen visualization. The reagents used were purchased from DOLES (Goiânia, Brazil). The images were obtained using a Leica DM750 microscope equipped with a 4× achromatic objective lens (0.10 NA). The microscope was set to transmitted light–bright field (TL–BF) and fluorescence (FLUO) modes. Two independent researchers, blinded to the treatment groups, visually classified the histological results. The parameters evaluated in HE-stained tissues included cellular infiltration, fibroblast presence, and vascularization. Each parameter was scored as follows: absent (0), discrete (1), moderate (2), and accentuated (3). The images had dimensions of 2048 × 1536 pixels, with horizontal and vertical resolution of 96 dpi. ImageJ software was used to analyze the slides stained with Masson's trichrome. The parameters studied included the percentage of collagen area stained by Masson's trichrome, the mean intensity, and the sum of the pixel values in the stained area.

Statistical analysis

The data were analyzed using appropriate statistical tests. The normality of data was assessed using the Shapiro–Wilk test. For data that were normally distributed, parametric tests (analysis of variance (ANOVA) followed by Tukey's multiple comparison test) were used. For data that did not meet the assumption of normality, nonparametric tests (Kruskal–Wallis test followed by Dunn's multiple comparison test) were used. Nonparametric tests were chosen for data that did not follow a normal distribution because they do not assume normality and are more

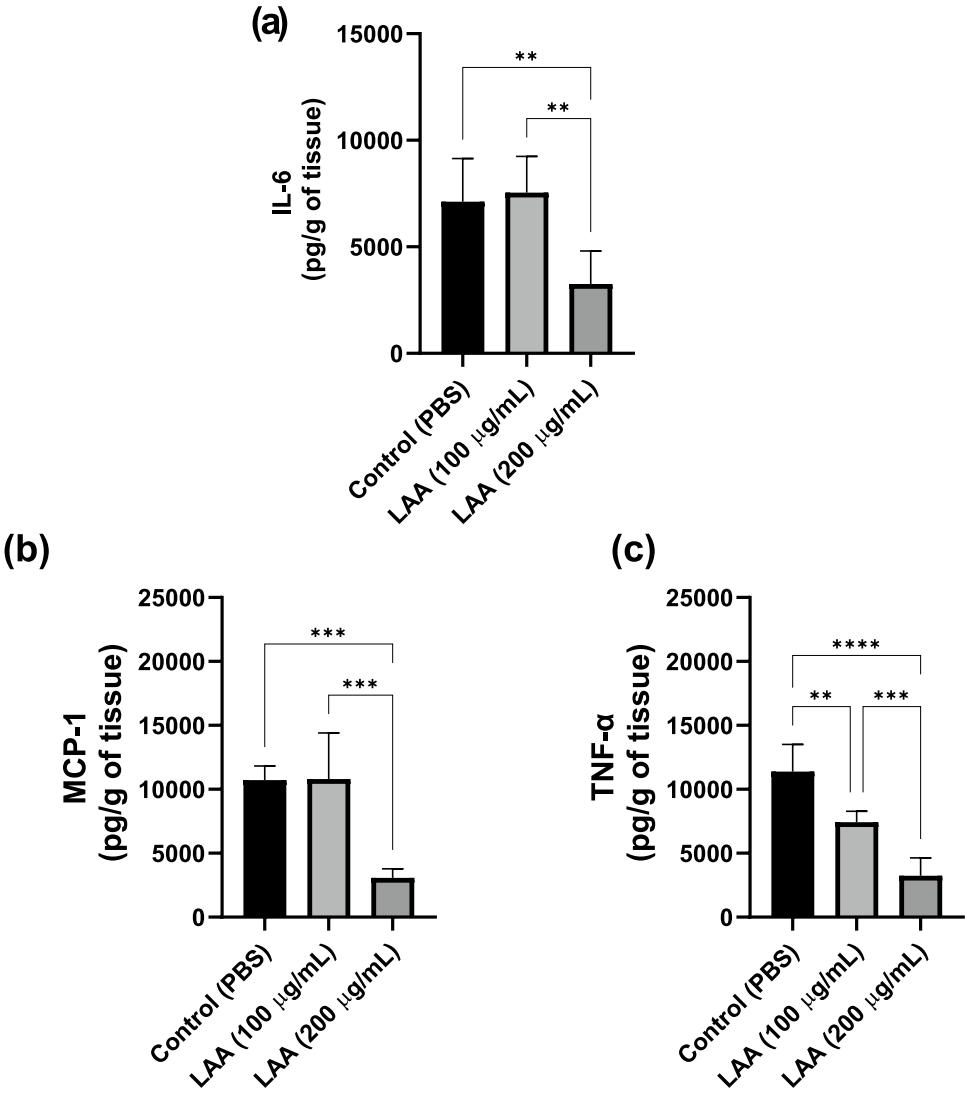

Fig. 3 Effects of LAA on the release of the inflammatory mediators. **a** Quantification of interleukin-6 (IL-6). **b** Quantification of monocyte chemoattractant protein-1 (MCP-1). **c** Quantification of tumor necrosis factor (TNF). $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$

robust for analyzing skewed data or data with outliers. A p value < 0.05 indicated statistical significance.

Results and discussion

Clinical evaluation of the lesion

Figure 1 illustrates the evolution and contraction of lesion areas over days 1, 3, 5, 7, 10, and 14. The clinical evaluation revealed the presence of edema in all groups during the inflammatory phase. The LAA-treated groups exhibited mostly mild exudate, which was more frequent than in the control group. Consequently, the initial inflammatory and reparative signs were less intense and resolved more quickly in the LAA treatment groups. No changes in lesion coloration were observed during this phase. Complete lesion closure was achieved by day 14 in the control group and by day 12 in the LAA-treated groups. Differences in contraction were observed between the LAA-treated groups and the control.

Figure 2a demonstrates that the wound areas in the groups treated with both concentrations of LAA were significantly smaller compared with the control group at days 3, 5, and 7 ($p < 0.05$). However, no notable difference was observed between the LAA100 and LAA200 groups. Regarding the inflammatory score, the LAA200 group exhibited lower values at days 3, 5, and 7 compared with the control group, while the animals treated with LAA at 100 µg/mL showed a lower score after 5 days of treatment (Fig. 2b).

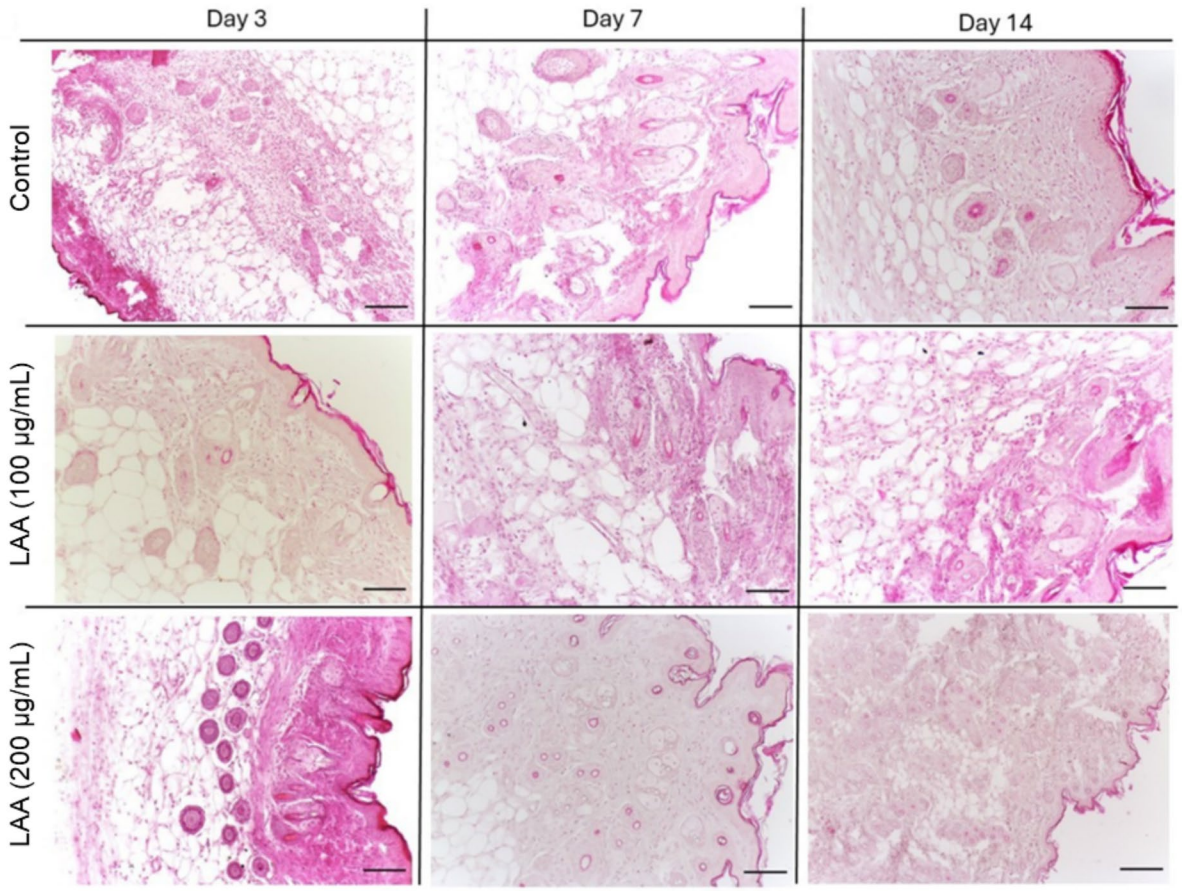

Fig. 4 Histopathological evaluation of the healing effects of topical administration of LAA using hematoxylin and eosin (HE) staining. The images show the degree of cellular infiltration, presence of fibroblasts, and vascularization. In the control group (PBS), there is a high level of inflammatory cell infiltration, with fewer fibroblasts and less vascularization. In contrast, the LAA-treated groups (100 and 200 µg/mL) exhibit reduced inflammatory cell infiltration, increased fibroblast presence, and enhanced vascularization. These changes indicate a more advanced stage of wound healing in the LAA-treated groups compared with the control. The scale bar represents 100 µM

These findings are consistent with previous reports on the beneficial effects of plant lectins on wound healing, which is associated with their ability of these proteins interact with specific carbohydrate moieties present in the wound microenvironment (de Sousa et al. 2023). The interactions between lectins and glycoconjugates can modulate the inflammatory response, promote the migration and proliferation of cells involved in the repair process, and stimulate the production of extracellular matrix components, such as collagen (Coelho et al. 2017; Carvalho et al. 2018; Mishra et al. 2019).

The reduction in inflammatory scores in LAA-treated wounds suggests that the healing action of lectin is should be associated with its anti-inflammatory effects (Alencar et al. 2010). Excessive inflammation can have detrimental effects on the wound healing process. Prolonged or excessive inflammation can lead to the release of inflammatory mediators that can damage surrounding tissues, impair re-epithelialization, and hinder collagen deposition. By mitigating inflammation, LAA may create a more favorable environment for tissue regeneration, allowing for a more efficient transition to the proliferative and remodeling phases of wound healing (Gao et al. 2024).

Measurement of inflammatory mediators

The IL-6, IL-10, MCP-1, IFN-γ, TNF, and IL-12p70 were quantified in the wound tissue samples; however, only the levels of IL-6, MCP-1, and TNF were detectable. The lowest levels of IL-6, MCP-1 and TNF, were observed in the group treated with the higher concentration of LAA (200 µg/mL) (Fig. 3a, b, and c). The topical treatment with LAA at 100 µg/mL only significantly decreased the levels of TNF, when compared with the control group (Fig. 3c).

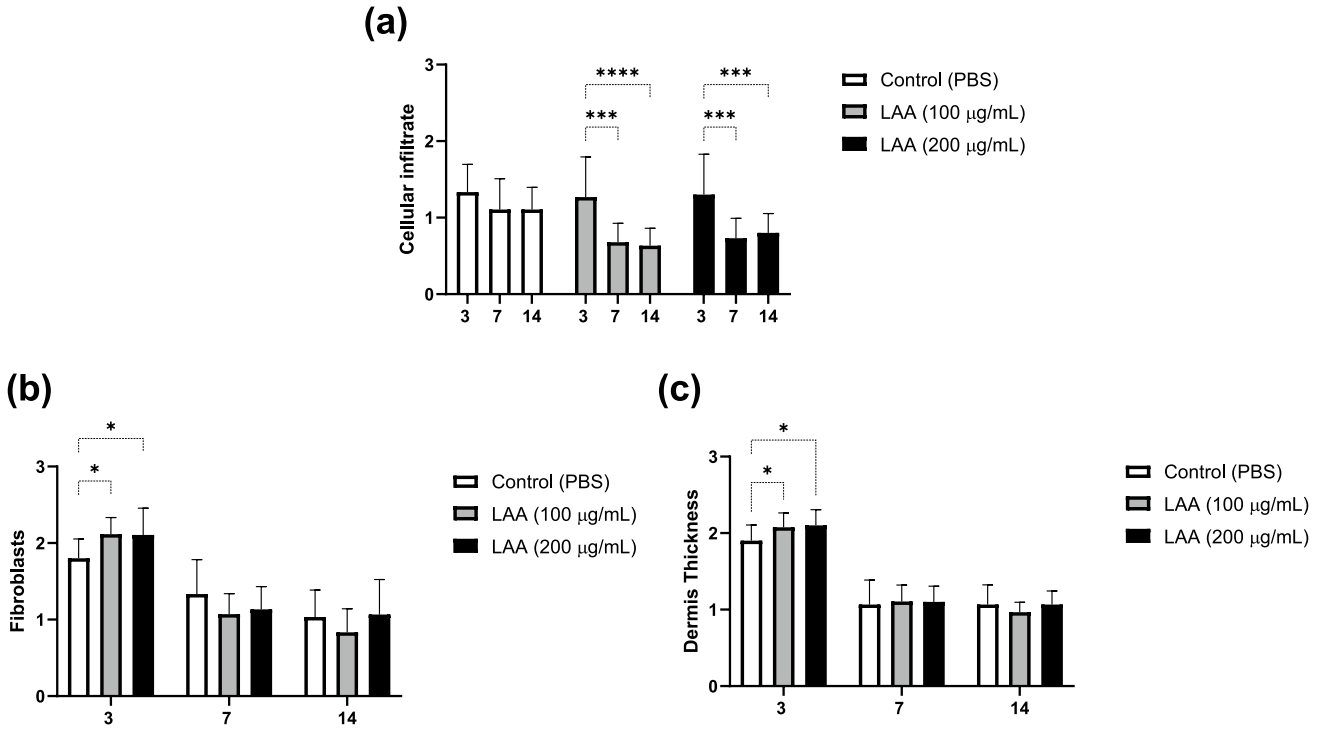

Fig. 5 Morphometric analysis of the healing effects of topical administration of LAA using hematoxylin and eosin (HE) staining. **a** Cellular infiltrate, **b** fibroblasts, and **c** dermis thickness. $*p<0.05$; $**p<0.01$; $***p<0.001$

High levels of L-6, MCP-1, and TNF are associated with the exacerbation of the inflammatory response and can delay wound healing (Behm et al. 2012). The observed reductions in the levels of these key inflammatory mediators (IL-6, MCP-1, and TNF) in the LAA-treated groups suggest that the lectin can effectively modulate the inflammatory response, creating a more favorable environment for tissue repair. The anti-inflammatory properties of LAA appear to have contributed to the enhanced healing dynamics observed in the clinical assessment. Several studies have shown that lectin-based therapies can modulate the inflammatory response and improve tissue repair (Alencar et al. 2010; Coelho et al. 2017). The anti-inflammatory effects of LAA may be mediated through various mechanisms, including inhibition of proinflammatory cytokine production, suppression of leukocyte adhesion and migration, and modulation of cellular signaling pathways. Further studies are needed to investigate the specific molecular targets and signaling pathways involved in LAA anti-inflammatory and wound healing effects.

Previous findings demonstrate that LAA can interfere with leukocyte migration, a crucial event in the inflammatory response. (Alencar et al. 2010) reported the ability of *L. auriculata* lectin to inhibit both leukocyte rolling and adhesion in in vitro and in vivo experimental models. However, the mechanisms underlying these effects have not been widely investigated. Our study fills this gap by demonstrating that LAA can suppress the expression of cytokines involved in leukocyte attraction, such as IL-6, MCP-1, and TNF (Raziyeva et al. 2021). Finally, these findings reinforce our hypothesis that LAA modulates inflammation, thereby contributing to improved wound healing.

Besides the evaluated cytokines (IL-6, IL-10, MCP-1, IFN-γ, TNF, and IL-12p70), other inflammatory markers also play crucial roles in wound healing. For instance, IL-1β is a proinflammatory cytokine that is rapidly produced in response to tissue injury and plays a pivotal role in the early stages of inflammation (Eming et al. 2017). IL-8 is a chemokine that attracts neutrophils to the wound site, facilitating the clearance of pathogens and debris (Pastar et al. 2014). TGF-β is a multifunctional cytokine that regulates cell proliferation, differentiation, and extracellular matrix production, and is essential for the later stages of wound healing, including tissue remodeling and scar formation (Eming et al. 2017). VEGF is a key factor in angiogenesis, promoting the formation of new blood vessels, which is critical for supplying nutrients and oxygen to the healing tissue (Shams et al. 2022). Future studies should investigate the effects of LAA on these and other inflammatory markers to provide a more complete understanding of its therapeutic potential.

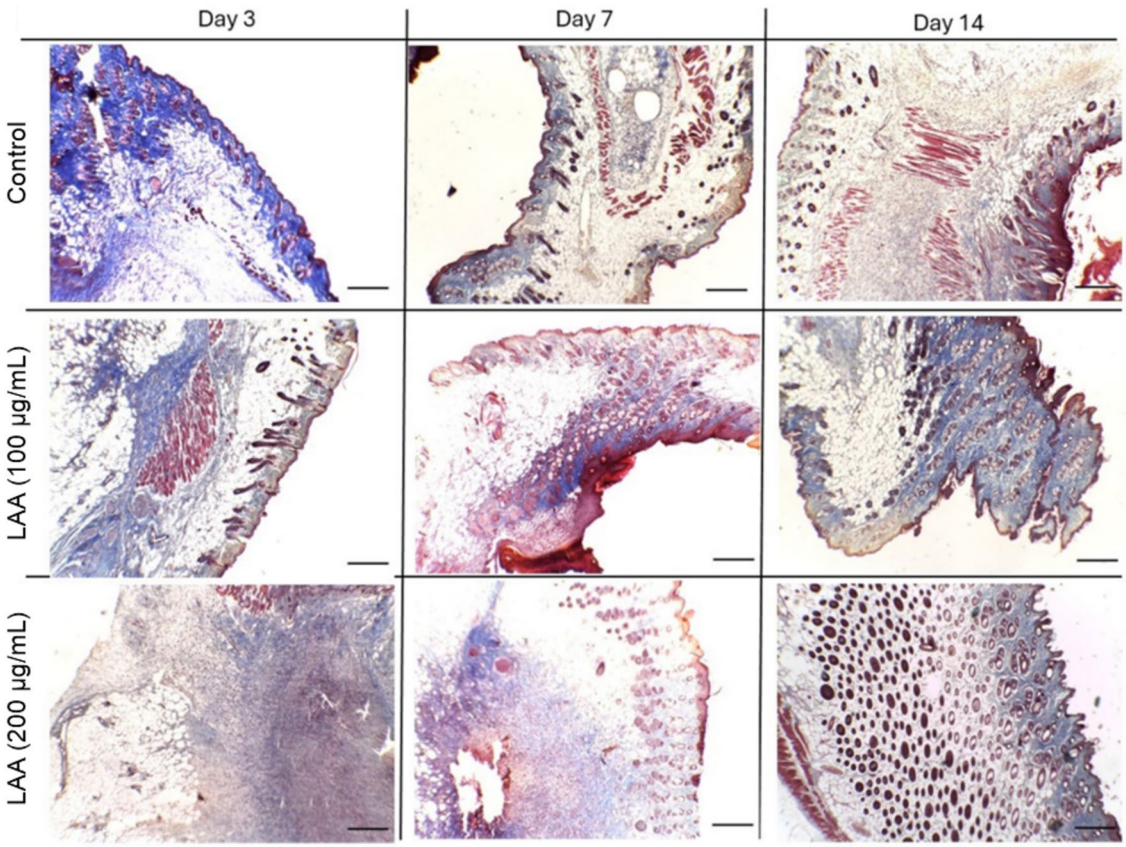

Fig. 6 Histopathological evaluation of the healing effects of topical administration of LAA using Masson's trichrome stain. The images show the degree of collagen deposition and organization in the wound tissues at different time points (day 3, 7, 14). The LAA-treated groups (100 and 200 µg/mL) exhibit increased collagen deposition and a more defined reticular pattern compared with the control group. The scale bar represents 100 µM

Histopathological analysis

Histopathological analysis revealed an acceleration of the wound healing process in LAA-treated groups compared with the control. LAA-treated wounds exhibited more organized and mature granulation tissue at all analyzed days (3, 7, and 14), characterized by increased vascularization and a higher density of fibroblasts. Re-epithelialization was also more rapid and extensive in LAA-treated wounds. Notably, the higher concentration of LAA (200 µg/mL) exerted a more pronounced effect on wound healing, with faster granulation tissue formation and more complete re-epithelialization compared with the lower concentration (100 µg/mL) and the control group. These findings suggest that LAA positively influences various stages of wound healing, promoting tissue regeneration and accelerating the overall repair process (Fig. 4).

The morphometric analysis confirmed the significant reduction on the number of inflammatory cells on days 7 and 14 compared with the control group (Fig. 5a). In addition, a significant increase in the number of fibroblasts and dermal thickness was observed in the treated groups at day 3 (Figs. 5b and c). These findings suggest that the anti-inflammatory properties of LAA may promote a more efficient transition between the phases of healing, especially between the inflammatory phase and the proliferative and remodeling phases. Thus, the stimulation of cell proliferation favors a more effective recovery of the injured tissue (Soliman et al. 2018).

The Masson's Trichrome staining analysis (Fig. 6) revealed a significant acceleration of the wound healing process in LAA-treated groups compared to the control. At all points, LAA-treated wounds exhibited a more organized and mature extracellular matrix, characterized by increased collagen deposition and a more defined reticular pattern. This was particularly evident in the higher concentration

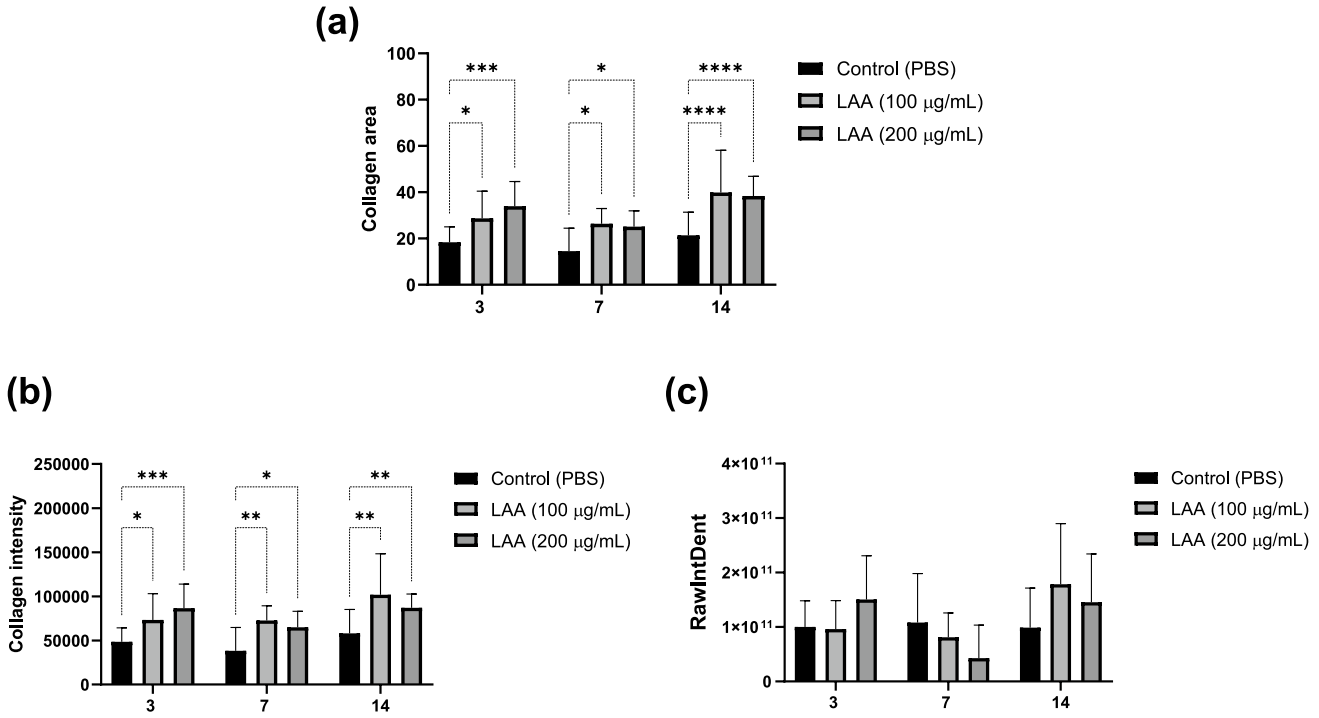

Fig. 7 Morphometric analysis of the healing effects of topical administration of LAA using Masson's trichrome stain. **a** Mean intensity of the area stained in blue by Masson's trichrome. **b** Masson's trichrome staining of the groups. **c** Millimeters of pixel values in area stained in blue by Masson's trichrome. $*p<0.05$; $**p<0.01$; $***p<0.001$; $****p<0.0001$

of LAA (200 µg/mL) group, where a denser and more organized collagen network was observed. These findings suggest that LAA not only promotes cellular aspects of wound healing but also enhances the deposition and organization of the extracellular matrix, crucial for tissue remodeling and mechanical strength.

Enhanced collagen production was observed, particularly after 14 days of treatment with both concentrations of LAA (Fig. 7a). These findings were further corroborated by the increase in collagen area intensity (Fig. 7b). However, no significant differences were observed in the sum of pixel values (RawIntDen) (Fig. 7c). These results indicate that the healing process of LAA-treated wounds was more effective, suggesting an increase in collagen deposition and stabilization, which is related to the formation of a more structured scar (Gardeazabal and Izeta 2024).

The data corroborated the clinical findings and suggested that the improved healing dynamics promoted by LAA treatment were associated with its anti-inflammatory properties (Alencar et al. 2010) and, thus, its ability to modulate the tissue repair process, including stimulating the production and organization of the extracellular matrix. In this context, LAA appears to promote a more favorable environment for tissue repair by mitigating inflammation and stimulating the proliferation of cells essential for the wound healing process, such as fibroblasts. The observed increase in collagen production, particularly during the later stages of treatment, further corroborates the positive influence of LAA on the regenerative phases of wound healing.

Conclusions

This study demonstrates the therapeutic potential of *L. auriculata* lectin (LAA) in accelerating cutaneous wound healing. Topical treatment with LAA significantly reduced wound area, decreased inflammatory scores, and modulated the levels of proinflammatory cytokines (IL-6, MCP-1, and TNF). Histopathological analyses revealed enhanced wound healing in LAA-treated groups, characterized by accelerated re-epithelialization, increased fibroblast proliferation, and enhanced collagen deposition and organization. These findings suggest that LAA exerts its beneficial effects through a multifaceted mechanism, including anti-inflammatory properties and the ability to stimulate key cellular processes involved in tissue repair.

This study provides novel evidence for the wound healing potential of LAA, a lectin with previously reported anti-inflammatory properties. Our findings contribute to the growing body of research supporting the use of plant-derived lectins as promising therapeutic agents for wound

management. However, further research is warranted to fully elucidate the underlying mechanisms of LAA action. Investigating the specific molecular targets and signaling pathways involved in LAA's anti-inflammatory and wound-healing effects is crucial. Moreover, future studies should evaluate the efficacy of LAA in treating chronic wounds, which represent a significant clinical challenge. In conclusion, this study provides valuable insights into the therapeutic potential of LAA for wound healing and opens avenues for the development of novel and effective strategies for wound management.

Author contributions K.L.R.B., L.S.S., I.S.S.S., M.Y.M.P., J.L.S.S., C.E.M.S., S.J.S.C.B., F.E.A.P., R.R.R., F.S.A.O., and C.G.C. conducted the investigation. K.L.R.B. and L.S.S. wrote the main manuscript text. P.M.G.P., C.G.C., C.S.T., and L.C.N.S. acquired funding and reviewed the manuscript. All authors reviewed the manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that they have no known competing commercial interests or personal relationships that could have appeared to influence the work reported in this paper.

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