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A preliminary study of cutaneous wound healing on the upper eyelid in a small Brazilian population using *Rhizophora mangle*-based cream

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Abstract: Plants used in traditional medicine offer an affordable new alternative in tissue repair therapy. This study aimed to evaluate the effectiveness of the 5% *Rhizophora mangle* cream compared to the 5% dexpanthenol cream in healing open surgical wounds on the upper eyelid. A total of 18 patients were submitted to the experiment and divided into 2 groups with 9 patients each who used topically and daily 5% dexpanthenol cream (control group) or 5% *R.mangle* cream (intervention group) for 7 days. Clinical, morphometric and histomorphometric analyses of wounds and surgical procedures for skin removal were performed. In the morphometric analysis, all wounds treated with *R.mangle* and dexpanthenol creams showed complete macroscopic scars, without inflammatory signs and infection free. The skin hydration values in pre and post application periods of the cream were 43.82 ± 43.93 and 62.12 ± 67.40 respectively. The histomorphometric study showed lower values of epithelium distance in *R. mangle* group and higher in dexpanthenol group with significant difference between groups ($p < 0.05$). The *R.mangle* 5% cream proved to be effective in healing wounds of human upper eyelid skin with a significant improvement in epithelization compared to dexpanthenol 5% cream.

Key words: Wound healing, Rhizophoraceae, Phytotherapy, Mangrove, Cream.

INTRODUCTION

Healing skin wounds is a vital function of the skin and functions as a biological, chemical, and physical barrier, representing an important step in the survival of the species. Its treatment has assumed a prominent place in modern science, with several modalities of regenerative medicine still in various phases of study but already showing promise; these include the use of embryonic cells, growth factors, and bioactive materials.

However, although this arsenal is experimentally well-described, it still presents poor clinical performance. Therefore, clinically efficient and cost-effective therapeutic methods are urgently needed (Gushiken et al. 2021). An authentic alternative to these treatments is offered by traditional therapies based on regional plants, which offer more accessible possibilities from both an economic and social perspective, thereby increasing the population's access to treatment and enabling the development of new drugs on a large scale (Moses et al. 2023).

As an example of such a traditional therapy, we have the *Rhizophora mangle*, a mangrove plant that presents several uses in Brazilian popular medicine, mainly as an adjuvant in the healing of cutaneous wounds (Silva et al. 2022).

The mangrove is a type of vegetation that grows in tropical and subtropical coastal regions, and presents polyphenolic compounds like tannins, which appears to be responsible for the mechanisms of skin re-epithelialization (Mitra et al. 2021, Silva et al. 2022). The effects attributed to *R. mangle* including antioxidant activity and antibacterial potential (Mitra et al. 2021), increased cell proliferation and the formation of new blood vessels on the wound (Silva et al. 2022) may be responsible for the improvement in the wound-healing response.

The objective of this study was to compare the efficacy of 5% *R. mangle* cream to 5% dexpanthenol cream in healing second-intention skin wounds in the upper-eyelid of human subjects.

MATERIALS AND METHODS

The methods used in this study, approved by the Research Ethics Committee (CEP) of UFPE with process number 69849417.6.0000.5208-CAE and registered in the Brazilian Clinical Trials Registry (REBEC) with process RBR-37HRF2, follow international ethical guidelines (Declaration of Helsinki, International Guidelines for Biomedical Research involving Human Beings – CIOMS) and Brazilian (Res. CNS 466/12 and complementary). Informed consent was obtained from all subjects involved in the study.

Rhizophora mangle

The leaves of *Rhizophora mangle* were collected in the mangrove forest of the city of Itamaracá, district of Vila Velha, in the state of Pernambuco, Brazil, at 7° 40' south latitude and 34° 50' west longitude. The botanical material was then identified by Prof. Dr. Marlene Barbosa, curator of the Herbarium of the Department of Botany, and deposited in the Herbarium of the Universidade Federal de Pernambuco (UFPE) under number UFPE: 69.655. The collection was authorized by the Pernambuco Environmental Pollution Control and Water Resources Administration Company under authorization from CA DFRB n° 120/2014. The leaves were previously dried at 35 °C for 72 h and ground to 0.177 mm in a Pulverisette 14 Classic Line knife mill (Fritsch).

Obtaining the aqueous extract of *Rhizophora mangle*

The aqueous extract was obtained by infusion (40 °C for 10 min) using 500 g of ground leaves in 2 L of distilled water. The material was then filtered and the liquid fraction dried in a freeze dryer (brand Liobras L101). After lyophilization, the extract was stored at 5 °C. The yield was calculated using Equation 1 (Oliveira et al.2023).

$$Yield\ (\%) = \left(\frac{Final\ mass(g)}{Initial\ mass\ (g)}\right)*100 \quad (1)$$

Preliminary characterization of the aqueous extract

The preliminary characterization of the phytochemical profile of the extract was initially carried out using the Thin Layer Chromatography (TLC) technique, using development systems and appropriate developers (Markhan 1982, Harbone 1984) to identify secondary compounds in order to identify and evaluate the presence or absence of coumarins, flavonoids, triterpenes and tannins.

The quantification of the main components present in the extract was carried out by UV/vis according to the methodology proposed by Albuquerque et al. (2022) with few modifications.

For this, the extract was solubilized in distilled water at a concentration of 1000 µg/mL.

The phenolic content was determined using 1mL of the Folin-Ciocalteau reagent (1/10 v/v) and 1mL of the extract, the system reacted for 10 min, then 2mL of sodium carbonate (Na_2CO_3) were added after 2 h of incubation, the Absorbance was determined at 765 nm on a UV-vis spectrophotometer (PERKIN ELMER, LAMBDA 650). The calibration curve was prepared with a standard solution of gallic acid, at concentrations of 7.5 to 150 µg/mL. Using the linear regression equation of the calibration curve, the total phenol content was calculated. The results were expressed in equivalent milligrams of gallic acid per gram of extract (mg EGA/g of extract).

The flavonoid content was measured using 1 mL of the extract solution + 1mL of the ethanol-aluminum chloride reagent (2%) for 1 h in the absence of light. Absorbance was determined on a UV-vis spectrophotometer (PERKIN ELMER, LAMBDA 650) at 425 nm. The calibration curve was prepared with a standard quercetin solution, at concentrations of 7.5 to 150 µg/mL. The results were expressed as equivalent milligrams of quercetin per gram of extract (mg QE/g of extract).

The flavonol content was determined using 2 mL of extract, 2 mL of ($AlCl_3$) and 3 mL of sodium acetate (50 g/L) for 30 min. After the test, absorbance was determined using a UV-vis spectrophotometer (PERKIN ELMER, LAMBDA 650) at 440 nm. The calibration curve was prepared with a standard quercetin solution, at concentrations of 7.5 to 150 µg/mL. The results were expressed as equivalent milligrams of quercetin per gram of extract (mg QE/g of extract).

Finally, the tannin content in the extract was determined, for this the following were used: 2 mL of extract; 3 mL of distilled water; 0.5 mL of Folin-ciocauteau reagent; 1.5 mL of 17% sodium carbonate (Na_2CO_3); 3 mL of distilled water – 10mL in total. The system was incubated for 30 min in the absence of light. After the test, absorbance was determined using a UV-vis spectrophotometer (PERKIN ELMER, LAMBDA 650) at 725 nm.The calibration curve was prepared with a standard tannic acid solution, at concentrations of 7.5 to 150 µg/mL. The results were expressed as equivalent milligrams of tannic acid per gram of extract (mg EAT/g of extract). All experiments were performed in triplicate.

Preparation of cream based on *Rhizophora mangle*

After obtaining and characterizing the extract, the cream was formulated according to the following formulation: ethylenediaminetetraacetic acid (EDTA) 0.06%, methylparaben 0.01%, propylbaraben 0.05%, propylene glycol 5%, distilled water qsp, lanette wax 14% , 1% sodium metabisulfite and 5% aqueous extract of *Rhizophora mangle*. Briefly, the cream components were heated to 65 ºC and homogenized in a Fisaton shaker at 600 rpm for 30 min. After this period, the cream was strained at 25 °C and finally the aqueous extract of *Rhizophora mangle* was added. At the end of preparation, the product obtained showed a yellowish color.

Healing trials using *Rhizophora mangle* cream

A randomized, non-inferiority, triple-blind clinical trial (evaluators, patients and statistician) was carried out at Fundação Santa Luzia and at the Universidade Federal de Pernambuco (UFPE), from January to April 2018.

A convenience sample of 18 volunteer patients was used considering both eyelids in a total of 36 eyelids, with diagnosis of upper blepharoclalasis (excess eyelid skin often related to aging or weight loss). Each of the subjects,

aged between 18 and 65 years and without contraindications to surgery and who signed the informed consent form, would be submitted to upper blepharoplasty surgery (removal of excess eyelid skin) at Fundação Santa Luzia, Recife.

The exclusion criteria were the existence of an infectious process at the site of the procedure to be performed; previous diagnosis of cancer, kidney disease, liver disease, hematological disease, immunological disease and/or diabetes mellitus; and the use of corticosteroids or immunosuppressants. Randomization was carried out by draw by the Santa Luzia Foundation secretariat, which delivered the creams without apparent external identification that could be perceived by patients.

The measurement of melanin concentration in the skin of the left forearm (anterior face) was carried out with a Konica Minolta CM-700d spectrophotometer, with an average of three shots. To evaluate the moisturizing power of the 5% *Rhizophora mangle* cream, a comparison was made with the dexpanthenol cream.

Ten measurements were taken on the mid-lower portion of the forearms, averages were calculated and expressed in corneometric units with the Corneometer® equipment. After administration of local anesthesia, the surgical wound was created, in an outpatient surgical suite, with a dermatological punch (circular cutting blade fixed to a plastic rod) measuring 3 mm in diameter on the upper eyelid, removing the skin just above the upper eyelid. groove in the mid-pupillary region (Figure 1a, b).

The 36 eyelids (18 individuals) were divided into two groups: Group A (9 individuals) used a cream based on 5% dexpanthenol, while Group B (9 individuals) used a cream containing 5% of the aqueous extract of *Rhizophora mangle* leaves. The cream was applied by the patient twice a day during 7 days in both groups.

After completing 7 days of treatment using the cream, the patient was submitted to clinical, morphometric and histomorfometric analysis of the wound. The clinical analysis consisted of evaluating the appearance of each wound as the presence of inflammatory signs such as

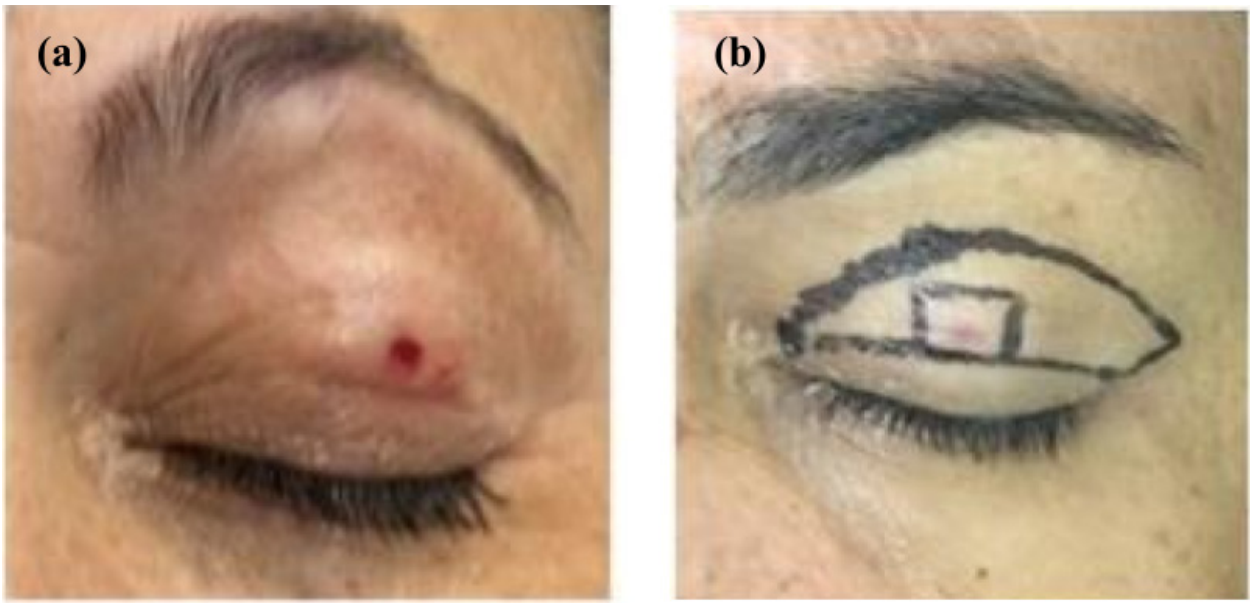

Figure 1. Mid-pupillary region at the upper eyelid: (a) skin incision in the mid-pupillary region and (b) rectangular mark with an overhead projector pen invlolving the skin incision with 2 mm of safety margin.

discharge, infection, bleeding or appearance of crusts, signs of hypertrophic scars and keloids. The morfphometric analysis was realized by using a caliper to measure the scar length and width of the wound and the histomorphometric analysis was realized by concentional histological method to measure the epithelization degree. Before the patient underwent aesthetic plastic surgery of the upper eyelid (blepharoplasty) a rectangular cut of the skin was removed from the scar area (Figure 1) to perform the histomophometric study and the skin sample was fixed in 10% buffered formaldehyde solution and the samples were prepared by the standard conventional histological methodology with preparations in paraffin inclusion, seriated in sections of 5 µm, stained with hematoxylin and eosin (HE) and they were mounted with Entellan and observed under an optical microscope. Selected histological sections were viewed on a slide scanner (3DHISTECH) for image capture. To evaluate epithelialization, the non-epithelialized distances of the wounds were measured with the Pannoramic Viewer program, with 2x magnification, in the samples collected from each patient. Fourscanner fields were acquired per preparation under 40x magnification and quantified using ImageJ 1.48 software.

Statistical analysis

Descriptive statistics were used to analyze the data for mean and standard deviation. In the case of standard deviation, it was higher than the mean value presented: mean, standard error, median and 25th and 75th percentiles. For the comparison between the groups, Student's t-test was used with equal variances, Student's t-test with unequal variances, or Mann–Whitney U test; and in the comparison between the evaluations, the Student's t-test was used. In the comparison between the three groups, F (ANOVA) was used. In the case of a significant difference by the F test (ANOVA), Tukey's multiple comparison tests were used. Student's t-test, F (ANOVA), and paired t-Student test were used in situations where the hypothesis of normality of the data and the Mann–Whitney U test were verified in situations where there was a rejection of the normality hypothesis. The normality of the data was performed using the Shapiro–Wilk test, and the equality of variances was examined using Levene's test. The margin of error used in the statistical test decision was 5%. The program used for entering the data and obtaining the statistical calculations was SPSS IMB version 23.

RESULTS

Preliminary phytochemical characterization

The yield of obtaining the aqueous extract was 8.78%. Through preliminary characterization of the extract by thin layer chromatography (TLC), it was possible to verify only the presence of flavonoids (+) and tannins (+). The results by UV/Vis spectrophotometry allowed the main constituents to be quantified. The extract presented the following levels of total phenolics (352.4 mg GAE/g of extract), flavonoids (149.5 mg QE/g of extract), flavonols (54.75 mg QE/g of extract) and tannins (139.4 mg ATE/g of extract) corroborating the qualitative analysis of the TLC. These results indicate that the aqueous extract of *Rhizophora mangle* has a mainly phenolic phytochemical profile.

Healing trials

The population was characterized according to age, sex and concentration of melanin in the skin, as shown in table I. Clinical characteristics were similar between the study groups (all $p > 0.05$).

After 7 days of use of *Rhizophora mangle* 5% or dexpanthenol 5% on the surgical wound, uniformity of the macroscopic aspects of the

Table I. Patient characteristics.

	Group		
Variable	***R. Mangle* (n = 9)**	**Dexpanthenol (n = 9)**	***P* value**
Gender n (%)			$p^{(1)} = 1.000$
Male	1 (11.1)	-	
Female	8 (88.9)	9 (100.00%)	
Age: mean ± SD*	54.44 ± 8.40	57.89 ± 6.88	$p^{(2)} = 0.355$
Melanin concentration: mean ± SD*	12.18 ± 2.82	11.64 ± 2.93	$p^{(2)} = 0.694$

(1) Using Fisher's exact test
(2) Using Student's t-test with equal variances
*** Standard deviation.**

wounds was observed in all 36 eyelids studied in the treated and intervention groups. The clinical analysis showed dry wound without inflammatory signs, crusts or secretions, and free from infection or bleeding. No signs of hypertrophic scars or keloids were observed. The morphometric analysis after measurement of the wound area showed zero mm^2 in all 36 eyelids studied (18 patients) with 100% wound cicatrization in both groups.

The histomorphometric study showed higher epithelization with lower distance values between the epithelia in the *Rhizophora mangle* cream group (61.27) and higher values between the epithelia in the dexpanthenol cream group (1374.27), with a significant difference between the groups ($p < 0.05$), according to Figure 2.

From the 18 patients treated with *Rhizophora mangle* or dexpanthenol, 6 patients had zero mm2 distance between epithelia (complete re-epithelialization) in the *Rhizophora mangle* group and 1 in the dexpanthenol group. Figure 3 shows skin sections from the cutaneous scar area of the upper eyelid from the dexpanthenol (a) and *Rhizophora mangle* (b) groups stained with HE.

The histological characteristics of wound healing are persistent, with the beginning of the proliferative phase of wound healing. The graphic showing in figure 2 and the histological images shown in figure 3 are data that indicate the reepithelialization and healing of tissues comparing between the groups studied through treatment with the cream of 5% *R.mangle* and the cream of 5% dexpanthenol. It is possible in figure 3 to verify tissue regeneration and complete wound closure area treated in (b), while in the image (a) the wound is in the process of regeneration and early epithelization.

Table II presents the mean and standard deviation (mean ± standard deviation) of the skin hydration value.

In the period before applying the creams, the averages varied from 43.82 to 43.93, and in the post-application period they varied from 62.12 to 67.40. In the post-application period, the *Rhizophora mangle* group did not show a significant difference in relation to the dexpanthenol groups. Regarding the difference between the pre- and post-application periods, there was no significant difference between the *Rhizophora mangle* and dexpanthenol groups.

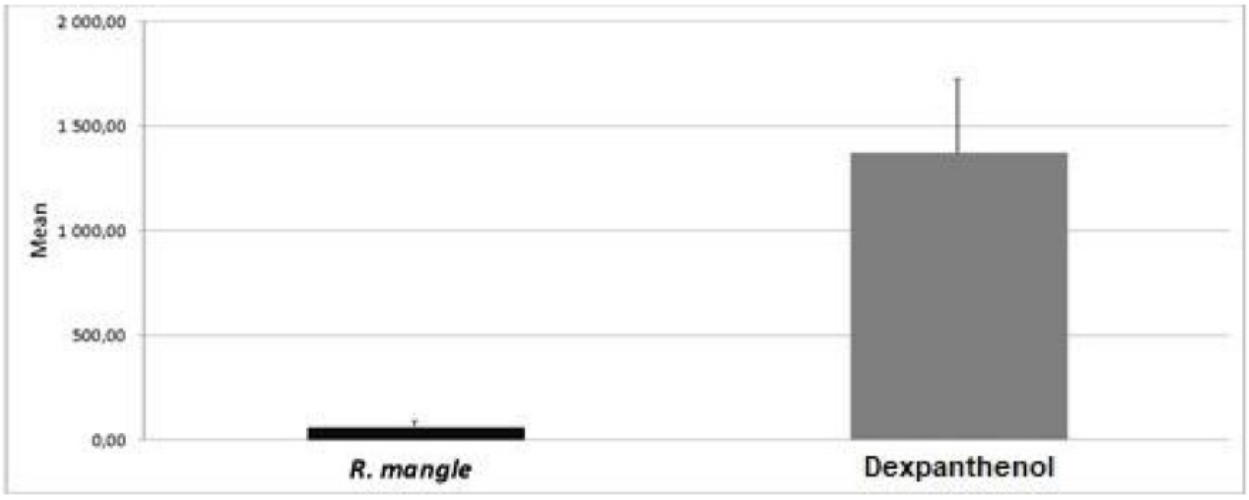

Figure 2. Distances between epithelia after 7 days of use of *R. mangle* 5% and dexpanthenol 5% creams, expressed as mean + standard error.

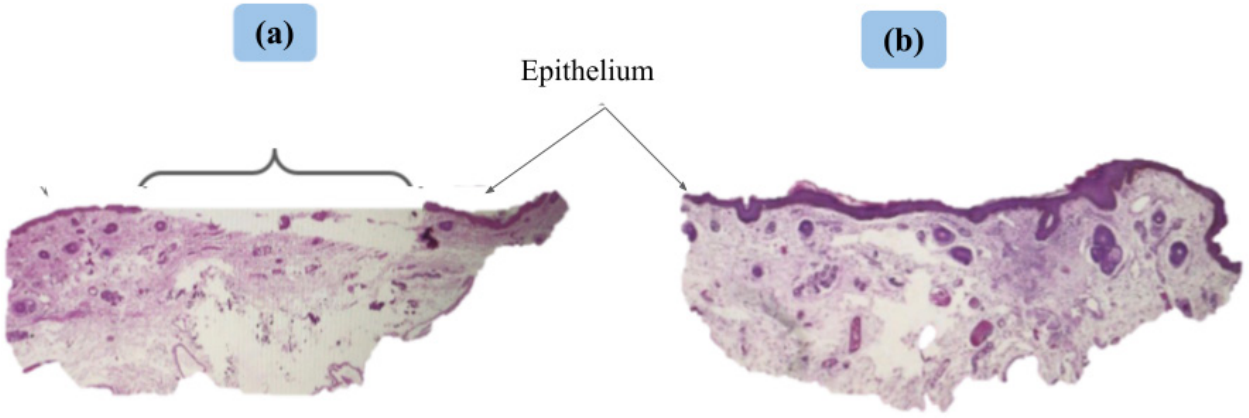

Figure 3. Histological sections of skin of the upper-eyelid wound scar area showing the group using dexpanthenol (a) and the group using *R. mangle* (b). The images show the degree of re-epithelialization after 7 days of treatment: [1] distance between the epithelia and [2] total re-epithelialization; HE coloration; Increase 2x.

DISCUSSION

This is the first randomized controlled clinical trial comparing the effects of wound-healing between creams using *Rhizophora mangle* and dexpanthenol. *Rhizophora mangle* 5% cream proved to be effective in healing upper-eyelid skin wounds in humans with a significant improvement in epithelialization compared to 5% dexpanthenol cream.

Similar results were found by Araújo (2015) for open wounds on rats. Using histomorphometric analysis, these researchers found that, by the 15th day of using the creams, there was a complete re-epithelialization of the wounds (by measuring the distance between the epithelia) of all animals treated with *Rhizophora mangle* 5% cream. However, this was not the case with the other groups treated with dexpanthenol 5% and saline 0.9%, with statistical significance, suggesting that *Rhizophora mangle* is effective in wound re-epithelialization.

Other studies suggest that the extract of this plant has healing effects (Silva et al. 2022, Sudhir et al. 2022). Tannins appear to be responsible for the re-epithelialization

Table II. Pre- and post-application hydration values of *R. mangle* 5%, dexpanthenol 5% and placebo creams.

Variable	*R. mangle* (n = 18)	Dexpanthenol (n = 18)	Placebo (n = 18)	*P* value
	Mean ± SD	Mean ± SD	Mean ± SD	
Pre-application	43.93 ± 10.14	43.82 ± 10.19	45.89 ± 10.44	$p^{(1)} = 0.794$
Post-application	62.12 ± 16.60 (AB)	67.40 ± 9.60 (A)	52.62 ± 14.76 (B)	$p^{(1)} = 0.009$*
Pre-/post-difference	18.19 ± 14.35 (A)	23.57 ± 8.56 (A)	6.73 ± 16.61 (B)	$p^{(2)} = 0.002$*
***P* value**	$p^{(2)} < 0.001$*	$p^{(2)} < 0.001$*	$p^{(2)} = 0.104$	

(*) Significant difference to 5%
(1) Using F (ANOVA) test with Tukey's multiple comparisons
(2) Using paired Student's t-test
Note: The superscript letters point to significant differences between the corresponding applications.

mechanisms of the wound due to the increase in cell proliferation (Wu et al. 2023) and their astringent and antimicrobial effects (Cano et al. 2021). The epithelium is important because of its main function in protecting the skin against environmental hazards and potentially dangerous threats (antimicrobial, innate) and providing immunological, physical, chemical, biochemical, and adaptive barriers (Gushiken et al. 2021).

In the present study, at macroscopy, complete wound-healing in all wounds, without infection or inflammatory signs, was similar to the results obtained by Araújo (2015) in surgical wounds of rats on the 15th day after the use of 5% *Rhizophora mangle* cream compared to 5% dexpanthenol cream. One of the mechanisms that corroborates these results is the protective film effect that *Rhizophora mangle* cream presents due to the presence of tannins and polyphenols in its composition (Kumar & Pola 2023) that interact with peptide structures, forming large agglomerates (Fernandez et al. 2002). The particularly distinctive feature of tannins is their complex capacity with macromolecules (such as proteins and polysaccharides) and with divalent metals, endows them with complex biological activity. (Molino et al. 2023).

Rhizophora mangle showed inhibitory activities against both Gram-positive and Gram-negative strains due to its polyphenol composition (Rodríguez-García et al. 2019), thus, tissue regeneration occur without the interference of those microorganisms. In addition, *Rhizophora mangle* also has antioxidant properties, which removes protease excesses and reactive oxygen species from wounds (Silva et al. 2022).

In the analysis of wound size, complete macroscopic closure draws attention to the potential of wound epithelization of both *Rhizophora mangle* and dexpanthenol creams. These results align with those of Sánchez et al. (2009), who performed pre-clinical studies in rats with open cutaneous wounds using the *Rhizophora mangle* extract and found a reduction in wound size on the 7th post-operative day. Similar results were obtained by Araújo (2015) when evaluating surgical wounds in rats on the 10th day after the use of 5% *Rhizophora mangle* cream, 5% dexpanthenol, and saline 0.9%, which showed a similar reduction in wound size and epithelization in the groups of *Rhizophora mangle* and dexpanthenol but a higher reduction when compared to the group with saline 0.9%. Taheri et al. (2020) suggested

that tannins increase cell proliferation and, thus, also the number of fibroblasts. These, in turn, are responsible for the production of collagen, fibronectin, hyaluronate, glycosaminoglycans, and proteoglycans, which are the major constituents of the extracellular matrix and impart tensile strength to skin (Gushiken et al. 2021). These tannins also appear to be responsible for the epithelization of the wound (Taheri et al. 2020), which depends on cellular regeneration that would be improved by the antimicrobial effect preventing the formation of microbial toxins that would damage the process (Rodríguez-García et al. 2019).

Rhizophora mangle and dexpanthenol creams showed similar skin-moisturizing effects.The increased skin hydration achieved by the topical use of *Rhizophora mangle* cream can be explained by its polyphenols and tannin compounds that lead to antioxidant and free-radical scavenging effects (Cano et al. 2021), as well as by the formation of a film due to the interaction of *Rhizophora mangle* components with local tissue proteins, leading to an isolation of the wound from the environment and consequently to a moist chamber effect (Fernandez et al. 2002). Studies have shown that hydration of the wound site is important for wound healing on the skin, since skin hydration level correlates with vascularity and tissue oxygenation level (Lee et al. 2022).

The study population comprised a mixed Brazilian population with a large variation in the concentration of melanin in the skin, which could lead to changes or complications in the wound due to different healing responses, such as hypertrophic scars and keloids in patients with a high concentration of melanin in the skin (Thomas et al. 2022). However, differences in healing time related to melanin concentration were not expected.

The limitations of this study are those inherent to the small sample size. A convenience sample was carried out due to the limited number of surgeries performed at the service during the study period. Therefore, our findings should be confirmed and expanded with future clinical trials.

CONCLUSIONS

In conclusion, *Rhizophora mangle* 5% cream had a healing effect on upper-eyelid skin wounds in humans with a significant effect on epithelialization evaluated by epithelial distance in histomorphometry compared to dexpanthenol 5% cream. However, the presented hydration power, clinical characteristics, and morphometry of the wounds were similar in regard to the use of both creams. Based on these results, it is suggested that this product can be used as a complementary therapy for the healing of acute or chronic skin wounds, as it is safe and effective in the healing process.

Patents

The product is already patented under the number BR10201801572.

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REFERENCES

ALBUQUERQUE NLL ET AL. 2022. Photoprotective, biological activities and chemical composition of the non-toxic hydroalcoholic extract of Clarisia racemosa with cosmetic and pharmaceutical applications. Ind Crops Prod 180: 114762. https://doi.org/10.1016/j.indcrop.2022.114762

ARAÚJO JG. 2015. Wound healing through topical treatment with Rhizophora mangle L leaf extract cream.

Dissertation, Universidade Federal de Pernambuco. https://repositorio.ufpe.br/handle/123456789/18404.

CANO A, CONTRERAS C, CHIRALT A & GONZÁLEZ-MARTÍNEZ C. 2021. Using tannins as active compounds to develop antioxidant and antimicrobial chitosan and cellulose based films. Carbohydr 73: 100156. https://doi.org/10.1016/j.carpta.2021.100156.

FERNANDEZ O, CAPDEVILA JZ, DALLA G & MELCHOR G. 2002. Efficacy of *Rhizophora mangle* aqueous bark extract in the healing of open surgical wounds. Fitoterapia 73: 564-568. https://doi.org/10.1016/s0367-326x(02)00229-0.

GUSHIKEN LFS, BESERRA FP, BASTOS JK, JACKSON CJ & PELLIZZON CH. 2021. Cutaneous wound healing: An update from physiopathology to current therapies. Life 11: 665. https://doi.org/10.3390/life11070665.

HARBONE JB. 1984. Phytochemical methods. A guide to modern techniques of plant analysis. Londres, Chapman and Hall, 288 p.

KUMAR MK & POLA S. 2023. Mangrove species as a potential source of bioactive compounds for diverse therapeutic applications. In Marine Antioxidants, 1ed, p. 249-263, Elsevier. https://doi.org/10.1016/b978-0-323-95086-2.00020-5.

LEE TY, YOON IJ, HAN SK, NAMGOONG S, JEONG SH, KIM DW & DHONG ES. 2022. Skin Hydration Level Cutoff Value to Predict Wound Healing Potential in Diabetic Foot Ulcers. Diabetes Res Clin Pract 193: 110122. https://doi.org/10.1016/j.diabres.2022.110122.

MARKHAN KR. 1982. Techniques of flavonoid identification. London: Academic Press, p. 52-61.

MITRA S, NASKAR N & CHAUDHURI P. 2021. A review on potential bioactive phytochemicals for novel therapeutic applications with special emphasis on mangrove species. Phytomed Plus 1: 100107. https://doi.org/10.1016/j.phyplu.2021.100107.

MOLINO S, FRANCINO MP & HENARES JAR. 2023. Why is it important to understand the nature and chemistry of tannins to exploit their potential as nutraceuticals. Food Res Int 173: 113329. https://doi.org/10.1016/j.foodres.2023.113329.

MOSES RL, PRESCOTT TAK, MAS-CLARET E, STEADMAN R, MOSELEY R & SLOAN AJ. 2023. Evidence for Natural Products as Alternative Wound-Healing Therapies. Biomolecules 13: 444. https://doi.org/10.3390/biom13030444.

OLIVEIRA AB, FERRISSE TM, ANNUNZIO SR, FRANCA MGA, SILVA MGV, CAVALHEIRO AJ, FONTANA CR & BRIGHENTI FL. 2023. In Vitro Evaluation of Photodynamic Activity of Plant Extracts from Senna Species against Microorganisms of Medical and Dental Interest. Pharmaceutics 15(1): 181. doi: 10.3390/pharmaceutics15010181.

RODRÍGUEZ-GARCÍA CM ET AL. 2019. Antioxidant, antihypertensive, anti-hyperglycemic, and antimicrobial activity of aqueous extracts from twelve native plants of the Yucatan coast. PLoS ONE 14: e0213493. https://doi.org/10.1371/journal.pone.0213493.

SÁNCHEZ J, FAURE R, MARTÍNEZ G, VEGA E & FERNÁNDEZ O. 2009. Propiedades Antioxidantes De Rhizophora mangle (L.) Y Su Relación Con El Proceso De Curación De Heridas En Ratas. Revi Salud Anim 31: 170-175.

SILVA LA, LIRA EC, LEAL LB, DE SANTANA ES, BARBOSA ICF, SILVA YJA, ALVES JUNIOR S & VIEIRA JRC. 2022. Prevention of Necrosis in Ischemic Skin Flaps Using Hydrogel of *Rhizophora mangle*. Injury 53: 2462-2469. https://doi.org/10.1016/j.injury.2022.03.034.

SUDHIR S, ARUNPRASATH A & SANKARA VEL V. 2022. A Critical Review on Adaptations, and Biological Activities of the Mangroves. J Natural Pesticide Research 1: 100006. https://doi.org/10.1016/j.napere.2022.100006.

TAHERI P, JAHANMARDI R, KOOSHA M & ABDI S. 2020. Physical, mechanical and wound healing properties of chitosan/gelatin blend films containing tannic acid and/or bacterial nanocellulose. Int J Biol Macromol 154: 421-432. https://doi.org/10.1016/j.ijbiomac.2020.03.114.

THOMAS A, FARAH K, MILLIS RM & MILLIS R. 2022. Epigenetic Influences on Wound Healing and Hypertrophic-Keloid Scarring: A Review for Basic Scientists and Clinicians. Cureus 14. https://doi.org/10.7759/cureus.23503.

WU K, FU M, ZHAO Y, GERHARD E, LI Y, YANG J & GUO J. 2023. Antioxidant anti-inflammatory and antibacterial tannin-crosslinked citrate-based mussel-inspired bioadhesives facilitate scarless wound healing. Bioactive Materials 20: 93-110. https://doi.org/10.1016/j.bioactmat.2022.05.017.

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