Acta Scientiarum

http://www.periodicos.uem.br/ojs/
ISSN on-line: 1807-863X
Doi: 10.4025/actascibiolsci.v46i1.69794

ZOOLOGY

Evaluation of wound healing activity of *Rhizophora mangle* in cream

Jéssica Guido de Araújo Sá[1], Ivone Antônia de Souza[2], Pedro Paulo Marcelino Neto[2], Eduarda Santos de Santana[1] and Jeymesson Raphael Cardoso Vieira[1*]

[1]Departamento de Histologia e Embriologia, Universidade Federal de Pernambuco, Av. Prof. Moraes Rego, 1235, Cidade Universitária, 50760-420, Recife, Pernambuco, Brazil. [2]Departamento de Antibióticos, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.
*Author for correspondence. E-mail: jeymesson.vieira@ufpe.br

ABSTRACT. Although tissue repair is an evolution of the body itself to resolve the wound, many need special care for proper healing. Medicinal plants, such as *Rhizophora mangle*, have a traditional use for wound healing. This study aimed to evaluate the healing potential of aqueous extract of leaves of *R. mangle* (AELRm) in cream for surgical wounds in rats. Forty-five Wistar rats were subjected to surgical wound care and divided into three groups of 15 animals each: Control group (saline solution at 0.9%), Standard group (dexpanthenol at 5%) and AELRm group (aqueous extract of leaves of *R. mangle* in cream at 5%), undergoing euthanasia on the 5th, 10th, and 15th days. Morphometric and histomorphometric studies of the wounds were performed, as well as macroscopical evaluation of them. The treated group showed uniform wounds and no infection, but the macroscopic analysis showed no difference on the 15th day among the three groups due to the rectangular shape of the initial wound. The microscopic study showed that all animals treated with AELRm in cream showed complete re-epithelialization on the 15th postoperative day ($p = 0.033$) in relation to the standard group (582.21 μm) and Control group (968.89 μm). The present study shows that the topical use of AELRm in cream at 5% has a significant effect on re-epithelialization of surgical wounds in rats.

Keywords: red mangrove; cytotoxicity; wound healing.

Received on November 21, 2023
Accepted on July 18, 2024

Introduction

Wound healing is a dynamic process which includes: initial or inflammatory phase, proliferative or fibroblastic phase, and remodeling or maturation phase (Wang, Huang, Horng, Yeh, & Chen, 2018), characterized by predominant cell population, following a conserved sequence of events that overlap in the time and include tissue inflammation, proliferation, and remodeling (Sorg, Tilkorn, Hager, Hauser, & Mirastschijski, 2017).

In the fibroplasia phase, reepithelialization and angiogenesis occurs in addition to an increase in the number of fibroblasts activated at the site, with a type III collagen production. The formation of the granulation tissue is then started. In addition, in the remodeling phase, the granulation tissue is enriched with collagen I fibers and begins to acquire the fibrotic mass characteristic of a scar and, slowly, maturation and remodeling of the extracellular matrix occurs (Childs & Murthy, 2017). Although tissue repair is an evolution of the body itself to resolve the wound, many of them need special care for proper healing. This may include different time and different drug and surgical alternatives, depending on the etiology and wound characteristics (Liang, He, & Guo, 2021; Markiewicz-Gospodarek et al., 2022). The longer the time to complete the healing, the greater the risk of complications (Guo & Dipietro, 2010).

In order to accelerate healing, several treatments could be applied in the affected region, aiming at higher rate of regeneration of the lesion. It is often necessary to turn local conditions more favorable through appropriate topical therapy to enable the physiological process (Campos, Borges-Branco, & Groth,2007). Considering that the tissue repair process is closely related to the treatment applied, the type of healing and the use of associated therapeutics and drugs, there is a need to research new options to aid wound healing in order to accelerate the repair period and minimize complications related to the lesions (Falcão, Evêncio Neto, & Coelho, 2008).

Medicinal plants are present in several biomes, including the mangrove (Sadeer, Zengin, & Mahomoodally, 2023). *Rhizophora mangle* popularly known as red mangrove has been used in traditional medicine as astringent, anti-diarrheal, anti-hemorrhagic, antiseptic, hemostatic, with antifungal and antiulcerogenic properties (Roig, 1988). In the last years, several authors have described some activities as antioxidant (Sánchez, Faure, Martínez, Vega, & Fernández, 2009; de-Faria et al., 2012), anti-ulcer (de-Faria et al., 2012) and wound healing (Da Silva et al., 2022). Therefore, this study intended to analyze the healing potential of the topical use of aqueous extract of leaves of *R. mangle* (AELRm) in cream at 5%, through morphometric and histomorphometric analysis of surgical wounds in animals.

Material and methods

Animals

Forty-five female *Wistar* rats, aged from 8 to 12 weeks, were randomly divided into 3 groups of 15 animals each according to the treatment proposed for induced wounds: Control group (saline solution at 0.9%), standard group (dexpanthenol at 5%) and AERm group (aqueous extract of *R. mangle* in cream at 5%). Each group was divided into 3 subgroups of 5 animals supervised during 5, 10 and 15 days after the induction of dorsal wound. It was approved in the Bioethics Committee of the Health Sciences Center of the *Universidade Federal de Pernambuco* (UFPE) - Brazil under number 23076.025194/2012-10. The animals were maintained at 27 ± 2 °C, with relative humidity 44 to 56% and light and dark cycles of 10 and 14 hours, respectively, for 1 week before and during the experiments. The animals received standard diet (Labina Purina®, Brazil) and water *ad libitum* (Lopes et al., 2019).

Vegetable materials and preparation of aqueous extract

The leaves of *Rhizophora mangle* were harvested during the flowering period in October 2014 in the mangrove of the city of Itamaracá, Pernambuco State, Brazil, Vila Velha district 7°40'south latitude and 34°50' longitude west, Brazil. An exsiccata was identified by the biologist Marlene Barbosa and is in the UFPE Herbarium under UFP number 69,655. The collection was authorized by the Pernambuco Company for the Control of Environmental Pollution and Resource Administration with the authorization CA DRFB No 120/2014. The extract was prepared by crushing 500 g of the fresh leaves, and was infused with distilled water (40 ºC for 10 minutes) and filtered. Then the solvent was removed in Liobras L101 lyophilizer (McCloud et al., 1988) and the dried residue was stored at 5 ºC and used for making the cream of *Rhizophora mangle*.

Preparation of aqueous extract of leaves of *Rhizophora mangle* (AELRm) in cream at 5%

The aqueous extract of leaves of *Rhizophora mangle* (AELRm) was weighed in a digital analytical balance (Shimadzu trademark ATY 224) using the 3 g of parchment paper and poured into porcelain grains. It was then solubilized with distilled water and homogenized. In a watch glass, the anionic emulsion was weighed to 60 g and poured into the gral containing the previously solubilized *Rhizophora mangle* extract and homogenized until complete solubilization. The pH was measured and maintained between 5.5 and 6.5. Finally, it was packed in a plastic pot composing AELRm in cream at 5%.

Model of wound excision

The animal groups were subdivided into three subgroups with 5 animals each for euthanasia in 5, 10, and 15 postoperative days. The animals were previously anesthetized with intramuscular injection in the dorsal region of the association of ketamine (10 mg kg^{-1} body weight) and xylazine (1 mg kg^{-1} body weight). After the anesthesia, the animals were weighed in an analogue scale and the trichotomy was performed in the dorsal region of approximately 6 cm^2 of area. Then, antisepsis was made with 2% chlorhexidine and a surgical wound of approximately 485 mm^2 was performed with the use of a scalpel with a sterile sheet number 15 until exposure of the dorsal muscular fascia. After hemostasis, by local compression, 1 mL of 0.9% saline was applied to the animals in control group. To the standard and AELRm groups were applying dexpanthenol in cream at 5% and aqueous extract of *R. mangle* in cream at 5% to the wounds respectively. On the following postoperative days, weighing and record of the macroscopic characteristics of the wounds were performed daily, and then the respective solutions or creams were applied once a day, in each group, without applying saline solution and the creams to the wounds until the euthanasia.

Morphometric analysis of surgical wounds

The healing activity was evaluated through the measurement of the size of the surgical wound prior to the use of the substances, initial values of length and width by Digimess universal pachymeter; and the final evaluation of the scar on the 5^{th}, 10^{th}, and 15^{th} postoperative day. A = b x h equation was used to obtain the wound areas. Where: A represents the area in cm^2, b the length, and h the height or width. The degree of contraction expressed as a percentage was measured by the equation proposed by Ramsey, Pope, Wagner-Mann, Berg, and Swain (1995) 100 x (Wo-Wi) / Wo =% contraction. Where: Wo is the initial area of the wound and Wi is the final area of the wound.

Removal of scar and histomorphometric analysis

At the end of 10 and 15 days, a new surgical intervention was performed with removal of the scar with 1 cm margin of skin around the lesion for each group with depth up to the dorsal musculature of the animal. Histomorphometric analysis on day 5 was not performed due to the unfinished healing process. The tissues were placed in 10% formalin buffered solution pH 6.90-7.10. After fixation, the samples were processed in conventional histological technique. The sections of the paraffin blocks had 5 μm and the preparations were stained in hematoxylin-eosin. Each animal was sacrificed through the CO_2 camera at the end of the experiments. Histological sections were microphotographed on Panoramic Midi slide scanner (3DHISTECH). The measurement of the distance between the epithelia in the healing during the reepithelialization process was performed using Panoramic Viewer software version 1.15.4.

Statistical analysis

The data were analyzed through descriptive statistical measures: mean, standard error of the mean or standard deviation and median and inferentially by statistical tests: F (ANOVA) in the comparison between groups, and paired t-Student in the comparison of the initial evaluation with the other evaluations. In the case of significant differences by the test F (ANOVA) Tukey multiple comparisons test was applied. The margin of error used in the statistical test decisions was 5%. The statistical program used to enter the data and obtain the statistical calculations was the SPSS (Statistical Package for the Social Sciences) in version 21.

Results

In the clinical examination of the surgical wounds, different characteristics among the 3 groups were evidenced. After 5 days, the control group showed purulent secretions in two animals with spontaneous resolution during the cicatricial process; after 10 days there was formation of granulation and crust tissue occurred in all animals and at the end of the 15^{th} day a small crust was present in most rats. The wounds of the Standard group after 5 and 10 days showed crusts and after 15 days there was an animal with discrete purulent secretion and granulation tissue. The AELRm group showed a uniform appearance of wounds, with no purulent secretions in surgical wounds and a regular basis but after 15 days the wounds presented a macroscopic scar with a good aspect (Figure 1).

Figure 1. Macroscopic aspects of surgical wounds in the three groups at 0, 5, 10 and 15 postoperative days. Control group (saline solution at 0.9%), standard group (dexpanthenol at 5%) and AERm group (aqueous extract of *R. mangle* in cream at 5%).

In this study, the morphometric analysis of surgical wounds across the areas of the 5th, 10th, and 15th postoperative lesions is shown in Figure 2. On the 5th day, the three groups showed wound contraction (CG-54.7%; SG-50.97%; AELRmG-53.41%) without significant statistical difference between them. On the 10th postoperative day, the wound contraction of the Standard group (93.76%) and the AELRm group (90.65%) were similar when compared to the Control group (80.72%). On the 15th postoperative day, the wound contraction of the Standard group (94.71%) was less than the Control group (96.35%) and the AELRm group (96.21%).

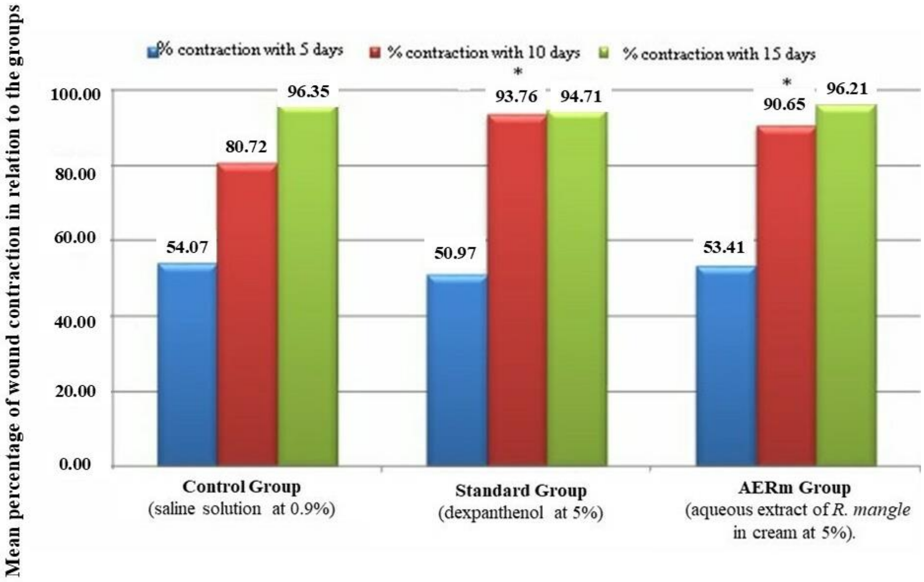

Figure 2. Mean percentage of wound contraction in relation to the groups.

In the histomorphometric evaluation, partial reepithelialization was evidenced in Control group, Standard group and AELRm group on the 10th day with mean values + standard error of 3,498.49 ± 232.40, 706.28 ± 233.73, and 1.759.6 6 ± 613.94, respectively. In statistical analysis, it was verified that Standard and AELRm group were not statistically different from each other, but different from Control group with p = 0.013 (Figure 3).

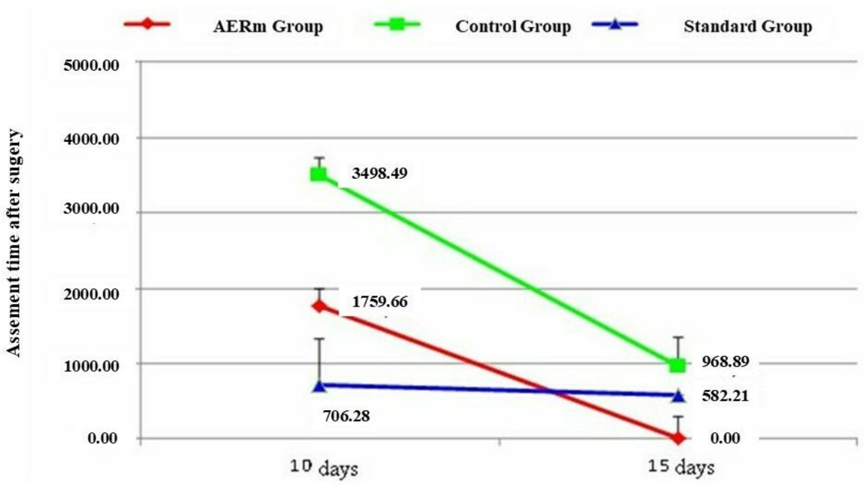

Figure 3. Mean difference of the distance between epithelia of the wound according to time.

Table 1 shows a reduction of the logarithmic means of distances of the epithelia in 10 days and 15 days in the three groups, however the only significant difference ($p < 0.05$) was recorded in the group with *Rhizophora mangle* with p = 0.016. In the comparison between groups, on the 15th day, AELRm group presented better results with p = 0.033 in relation to Control group and Standard group.

Table 1. Statistical evaluation of the distance between the epithelia by decimal logarithm + 1, according to the group and the time of evaluation.

Evaluation time after surgery	Control group (n = 10) Mean ± standard deviation (Median)	Standard group (n = 10) Mean ± standard deviation (Median)	AELRm group (n = 10) Mean ± standard deviation (Median)	p value
10 days	3.54 ± 0.03 (3.55)	2.33 ± 0.59 (2.85)	2.65 ± 0.67 (3.22)	p (1) = 0.264
15 days	2.45 ± 0.62 (B) (2.96)	1.26 ± 0.77 (AB) (0.00)	0.00 ± 0.00 (A) (0.00)	p (1) = 0.033*
P value	p (2) = 0.150	p (2) = 0.301	p (2) = 0.016*	

(*): Significant difference to 5%. (1): Through the F-test (ANOVA) for comparisons between the groups at the 10 and 15-day evaluation with comparisons of the Tamhane test. (2): Through the t-Student test for comparisons between the times of evaluation in each group. Obs.: If the letters between parentheses are different, a significant difference between the corresponding groups is verified.

On the 15th postoperative day, AELRm group did not present distance between the epithelia with 100% of the scars reepithelialized. Standard group presented unexpected value, with a little reduction of the distance between the epithelia (Figure 4).

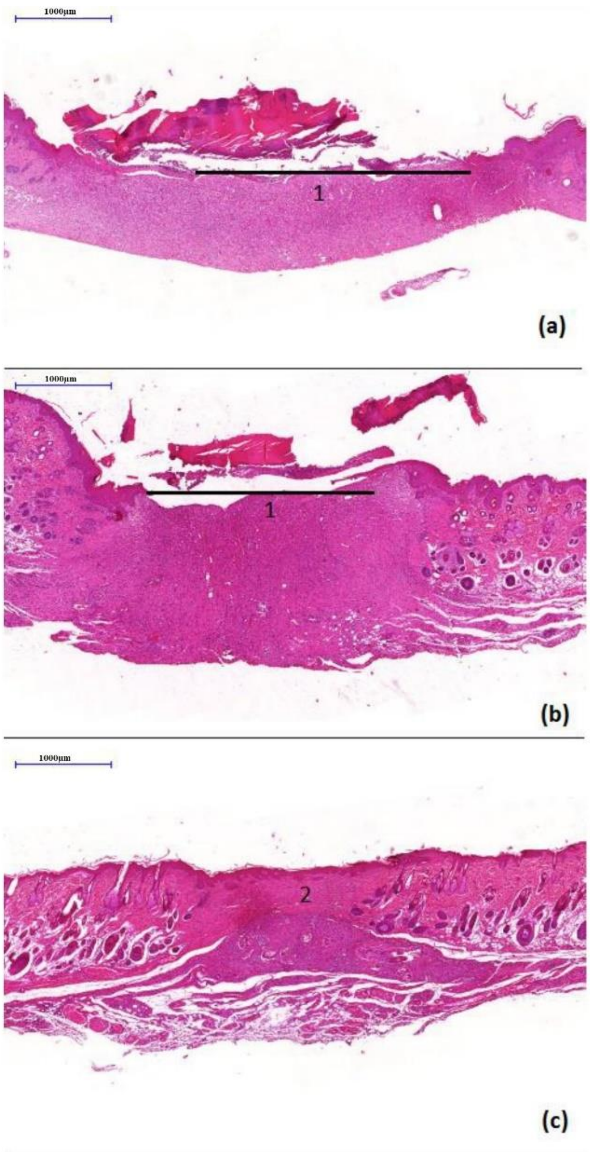

Figure 4. Photographs of the slides on the 15th postoperative day of the animals of Control group, Standard group and AELRm group. Legend: (a) animal of Control group, (b) animal of Standard group and (c) animal of AELRm group. 1: distance between epithelia 2: complete reepithelialization.

Discussion

Inspection of surgical wounds revealed that Control group and Standard group presented crusts and granulation tissue with infectious wound processes during the study period. However, AELRm group presented crusts and scar with no surgical wound infection. These results can be explained by different mechanisms of action of the secondary compounds present in the plant. The *Rhizophora* genus has certain substances present in the extract, such as tannins and polyphenols (Sadeer et al., 2019), which are capable of interacting with peptide structures forming large clusters, which would explain the formation of the protective film (Fernandez, Capdevila, Dalla, & Melchor, 2002; Perera, Escobar, Souccar, Remigio, & Mancebo, 2010).

Chen, Cai, and Phillipson (1994) used a preparation based on tannins in cutaneous wounds. This film must be related to the complex formed by non-hydrolysable tannins with proteins, which can exert a protective action by isolating the wound from the environment. Similar results were found by Fernandez et al. (2002) who observed a dark red film covering the pilonidal cyst wounds in the patients treated with the *R. mangle* stem extract. There were no secondary infections at the site, the wounds were dry throughout the clinical evaluation process. Perera et al. (2010) evaluating the anti-ulcerogenic activity of *R. mangle* extract showed the presence of a thick layer adherent to the gastric mucosa suggesting a physical barrier with gastroprotective properties similar to those observed in cutaneous wounds.

Another hypothesis is that the antibacterial action of the tannins reduces the risk of wound infection, avoiding the delay of the cicatrization process. Melchor, Armenteros, Fernandez, Linares, and Fragas (2001) studied the aqueous extract of the stem of *R. mangle* demonstrating antibacterial properties attributing the action to the polyphenolic constituents present in the extract. Phytochemical studies of *R. mangle* stem extracts showed the presence of tannins (Marrero et al., 2006; Berenguer et al., 2006; de-Faria et al., 2012). Bueno et al. (2014) reinforced that tannins influence the physiology of skin cells through their pharmacological properties, increasing cell proliferation.

The results of the evaluation of the areas of surgical wounds on the 10th postoperative day showed a superior reduction on Standard group and AELRm group when compared to Control group. These results corroborate with the pre-clinical studies of Sánchez et al. (2009), who studied the cicatricial action of extracts of *R. mangle* on open cutaneous wounds of rats with reduction of the areas on the 7th postoperative day.

In all groups on the 15th postoperative day, there was reduction of wound areas but no statistically significant difference among the groups. It is known that the cicatricial process depends on the time of the initial injury, and that the third stage of the healing includes remodeling of the scar with contraction of the wounds or even its hypertrophy (Kirsner, 2008). However, open sores present different clinical problems from incised and sutured wounds. Although the basic morphological and chemical processes, which act on the closed wound, are the same in open wounds that are healing, contraction becomes an important aspect in open wounds, and epithelization plays a prominent role (Coelho, Rezende, & Tenorio, 1999). The two processes seem to be independent (Madden & Arem, 1991). The contraction of the wound is favored in places where the skin is more moveable, such as the skin of the trunk (Ramsey et al., 1995). Skin mobility depends on the direction of the "Langer lines", which is determined by the arrangement of the skin fibrillar system, especially elastic fibers. The maximum distension occurs transverse to the Langer lines, which is why the contraction of the wound occurs in this direction (Coelho, Rezende, & Tenorio, 1999).

Therefore, we suggest that the result of the final areas occurred by the shape of the surgical wound with increased tensile strength in the third stage of healing. For the production of wounds in a square or rectangular form, the skin was incised longitudinally and transversely, resulting in an increase of the area due to the distension caused by the transversal incision to the Langer lines, as pointed out by Coelho, Rezende, & Tenorio (1999). Despite the widespread popular use of *R. mangle*, studies correlating with healing power have always used extracts from the stem, but the general population uses leaf infusions due to the easiness of the harvest (Giraldi & Hanazaki, 2010). Our study used leaf extract with vehicle cream in order to evaluate its potential and corroborate with popular use.

This study, when measuring the distance between the epithelia, showed that on the 10th postoperative day the *R. mangle* 5% EAF in cream was similar to 5% dexpanthenol in cream, and both different from the group in which the 0.9% saline solution was used. This data suggests that *R. mangle* 5% EAF in cream contributes to accelerate reepithelialization. Dexpanthenol is already commercialized and widely used in conventional medicine with good benefits: healing, moisturizing and maintaining mucocutaneous trophism (Stozkowska & Piekos, 2004; Heise et al, 2012). On the 15th postoperative day, all animals treated with 5% *R. mangle* EAF in cream presented complete reepithelialization, with statistical significance when compared to Control group and Standard group, corroborating with the scientific studies that suggest that the extract of this plant possesses healing effects (Perera, Ruedas, & Gómez, 2001; Fernandez et al., 2002).

Perera et al. (2001) evaluated the gastroprotective effect of *R. mangle* stem extract, which was offered prior to the ingestion of hydrochloric acid and ethanol solution in Wistar rats, showing lower ulcer lesions and less lesions in the group receiving the highest concentrations of the extract of *R. mangle* to the detriment of the groups that received cimetidine and distilled water. The authors suggested that the cytoprotective effect should be derived from secondary compounds such as tannin. They also added changes in the composition of the mucus as protection of the gastric mucosa when using the extract in high doses. Studies evaluating the reepithelialization of wounds with extracts of *R. mangle* were not found in literature. This makes it difficult to compare with other studies. However, studies with secondary compounds present in the plant suggest that the healing effect is due to the phenolic compounds.

Study of stem extracts of *Staphodea campanulata* attributed the presence of phytochemicals such as flavonoids and tannins to wound healing ability. These constituents are known to have antimicrobial and antioxidant properties (Ofori-Kwakye, Kwapong, & Bayor, 2011). The antimicrobial effect exhibited by the extract prevents the formation of microbial toxins, which tend to inhibit cell regeneration, whereas its antioxidant action removes the excess of proteases and reactive oxygen species from wounds and protects protease inhibitors from oxidative damage (Houghton, Hylandas, Mensah, Hensel, & Deters, 2005). The flavonoids present in *S. campanulata* extract are known to reduce peroxidation, preventing or delaying the onset of cellular necrosis, as well as improving vascularization. Flavonoids and tannins also promote wound healing, mainly due to its astringent and antimicrobial properties, which appear to be responsible for wound contraction and an increased rate of epithelization (Tsuchyia et al., 1996).

Conclusion

The results of the present study show that topical use of aqueous extract of *R. mangle* leaves at 5% in cream has a significant effect on reepithelialization of surgical wounds in rats. However, the isolation of the plant's component(s) responsible for the positive influence on the tissue repair process should be performed.

Acknowledgments

We wish to express our appreciation to *Universidade Federal de Pernambuco* and the Graduation Program of Health Sciences for providing materials and location to develop this research.

References

Berenguer, B., Sanchez, L. M., Quılez, A., Lopez-Barreiro, M., Haro, O., Galvez, J., & Martın, M. J. (2006). Protective and antioxidant effects of *Rhizophora mangle* L. against NSAID-induced gastric ulcers. *Journal of Ethnopharmacology*, *103*(2), 194-200. DOI: https://doi.org/10.1016/j.jep.2005.08.029

Bueno, F. G., Panizzon, G. P., Mello, E. V. S. L., Lechtenberg, M., Petereit, F., Mello, J. C. P., & Hensel, A. (2014). Hydrolyzable tannins from hydroalcoholic extract from *Poincianella pluviosa* stem bark and its wound-healing properties: Phytochemical investigations and influence on in vitro cell physiology of human keratinocytes and dermal fibroblasts. *Fitoterapia*, 99, 252-260. DOI: https://doi.org/10.1016/j.fitote.2014.10.007

Campos, A. C. L., Borges-Branco, A., & Groth, A. K. (2007). Cicatrização de feridas. *ABCD. Arquivos Brasileiros de Cirurgia Digestiva (são Paulo)*, *20*(1), 51–58. DOI: https://doi.org/10.1590/S0102-67202007000100010

Childs, D. R., & Murthy, A. S. (2017). Overview of wound healing and management. *Surgical Clinics of North America*, *97*(1), 189-207. DOI: https://doi.org/10.1016/j.suc.2016.08.013

Chen, Z. P., Cai, Y., & Phillipson, J. D. (1994). Studies on the anti-tumour, anti-bacterial, and wound-healing properties of dragon's blood. *Planta Medica*, *60*(6), 541-545. DOI: https://doi.org/10.1055/s-2006-959567

Coelho, M. C. O., Rezende, C. M. F., & Tenorio, A. P. M. (1999). Contraction of wound after cover with temporally skin substitutes. *Ciência Rural*, *29*(2), 297-303. DOI: https://doi.org/10.1590/S0103-84781999000200018 de-Faria, F. M., Almeida, A. C. A., Ferreira, A. L., Dunderb, R. J., Takayamab, C., Silva, M. S., … Souza-Brito, A. R. M. (2012). Mechanisms of action underlying the gastric antiulcer activity of the *Rhizophora mangle* L. *Journal of Ethnopharmacology*, 139, 234-243. DOI: https://doi.org/10.1016/j.jep.2011.11.007

Silva, L. A., Lira, E. C., Leal, L. B., Santana, E. S., Barbosa, I. C. F., Silva, Y. J. A., … Vieira, J. R. C. (2022). Prevention of necrosis in ischemic skin flaps using hydrogel of *Rhizophora mangle*. Injury, *53*(7), 2462-2469. DOI: https://doi.org/10.1016/j.injury.2022.03.034

Falcão, S. C., Evêncio Neto, J., & Coelho, A. R. B. (2008). Incorporation by host tissue of two biomaterials used as repair of defects produced in abdominal wall of rats. *Acta Cirúrgica Brasileira*, *23*(1), 78-83. DOI: https://doi.org/10.1590/s0102-86502008000100013

Fernandez, O., Capdevila, J. Z., Dalla, G., & Melchor, G. (2002). Efficacy of *Rhizophora mangle* aqueous bark extract in the healing of open surgical wounds. *Fitoterapia*, *73*(7-8), 564–568. DOI: https://doi.org/10.1016/s0367-326x (02)00229-0

Giraldi, M., & Hanazaki, N. (2010). Uso e conhecimento tradicional de plantas medicinais no Sertão do Ribeirão, Florianópolis, SC, Brasil. *Acta Botanica Brasilica*, *24*(2), 395-406. DOI: https://doi.org/10.1590/S0102-33062010000200010

Guo, S., & Dipietro, L. A. (2010). Factors affecting wound healing. *Journal of Dental Research*, *89*(3), 219-229. DOI: https://doi.org/10.1177/0022034509359125

Heise, R., Skazik, C., Marquardt, Y., Czaja, K., Sebastian, K., Kurschat, P., … Baron, J. M. (2012). Dexpanthenol modulates gene expression in skin wound healing in vivo. *Skin Pharmacology and Physiology*, *25*(5), 241-248. DOI: https://doi.org/10.1159/000341144

Houghton, P. J., Hylandas, P. J., Mensah, A. Y., Hensel, A., & Deters, A. M. (2005). In vitro tests and ethnopharmacological investigations: wound healing as an example. *Journal of Ethnoparmacology*, *100*(1-2), 100-107. DOI: https://doi.org/10.1016/j.jep.2005.07.001

Kirsner, R. S. (2008). Cicatrização de feridas. In R. P. Bolognia, J. L. Jorizzo, & J. L. Rapini (Eds.), *Dermatologia* (p. 2147-2158). Rio de Janeiro, RJ: Elsevier.

Lopes, C. M. I, Baratella-Evêncio, L., Souza, I. A. D., Oliveira, E. B. D., Sá, J. G. A., Santana M. A. N., … Vieira, J. R. C. (2019). Evaluation of cytotoxicity and wound healing activity of *Avicennia schaueriana* in cream. *Anais da Academia Brasileira de Ciências*, *91*(1), 1-13. DOI: https://doi.org/10.1590/0001-3765201920180171

Liang, Y., He, J., & Guo, B. (2001). Functional hydrogels as wound dressing to enhance wound healing. *ACS Nano*, *15*(8), 12687-12722. DOI: https://doi.org/10.1021/acsnano.1c04206

Markiewicz-Gospodarek, A., Kozioł, M., Tobiasz, M., Baj, J., Radzikowska-Büchner, E., & Przekora, A. (2022). Burn wound healing: Clinical complications, medical care, treatment, and dressing types: the current state of knowledge for clinical practice. *International Journal of Environmental Research and Public Health*, *19*(3), 1-25. DOI: https://doi.org/10.3390/ijerph19031338

Marrero, E., Sánchez, J., Armas, E., Escobar, A., Melchor, G., Abad, M. J., … Alcaraz, M. J. (2006). COX-2 and sPLA2 inhibitory activity of aqueous extract and polyphenols of *Rhizophora mangle* (red mangrove). *Fitoterapia*, *77*(4), 313-315. DOI: https://doi.org/10.1016/j.fitote.2006.03.009

Madden, J., & Arem, A. (1991). A cicatrização das feridas. Aspectos biológicos e clínicos. In D. Sabiston (Ed.), *Tratado de cirurgia* (p. 156-168). Rio de Janeiro, RJ: Guanabara Koogan.

McCloud, T. E., Nemec, J., Muschik, G., Sheffield, H. G., Quesenberry, P., Suffness, M., … Thampson, J. (1988). *Extraction of bioactive molecules from plants*. Park City, UT: International Products Research.

Melchor, G., Armenteros, M., Fernandez, O., Linares, E., & Fragas, I. (2001). Antibacterial activity of *Rhizophora mangle* Bark. *Fitoterapia*, *72*(6), 689-691. DOI: https://doi.org/10.1016/s0367-326x(01)00294-5

Sadeer, N. B., Fawzi, M. M., Gokhan, Z., Rajesh, J., Nadeem, N., Kannan, R. R. R. … Pandian, S. K. (2019). Ethnopharmacology, phytochemistry, and global distribution of mangroves-A comprehensive review. *Marine Drugs*, *17*(4), 1-82. DOI: https://doi.org/10.3390/md17040231

Ofori-Kwakye, K., Kwapong, A. A., & Bayor, M. T. (2011). Wound healing potential of methanol extract of *Spathodea campanulatastem* bark formulated into a topical preparation. *African Journal of Traditional, Complementary and Alternative Medicines*, *8*(3), 218-223. DOI: https://doi.org/10.4314/ajtcam. v8i3.65280

Perera, L. M. S., Ruedas, D., & Gómez, B. C. (2001). Gastric antiulcer effect of *Rhizophora mangle* L. *Journal of Ethnopharmacology*, *77*(1), 1-3. DOI: https://doi.org/10.1016/s0378-8741(01)00277-x

Perera, L. M. S., Escobar, A., Souccar, C., Remigio, M. A., & Mancebo, B. (2010). Pharmacological and toxicological evaluation of *Rhizophora mangle* L., as a potential antiulcerogenic drug: Chemical composition of active extract. *Journal of Pharmacognosy and Phytotherapy, 2*(4), 56-63.

Roig y Mesa, J. T. (1988). *Plantas medicinales, aromaticas y venenosas de Cuba*. Habana, CU: Cultural.

Ramsey, D. T., Pope, E. R., Wagner-Mann, C., Berg, J. N., & Swain, S. F. (1995). Effects of three occlusive dressing materials on healing of full thickness skin wounds in dogs. *American Journal of Veterinary Research*, *56*(7), 941-949.

Sadeer, N. B., Zengin, G., & Mahomoodally, M.F. (2023). Biotechnological applications of mangrove plants and their isolated compounds in medicine-a mechanistic overview. *Critical Reviews in Biotechnology*, *43*(3), 393-414. DOI: https://doi.org/10.1080/07388551.2022.2033682

Sánchez, J., Faure, R., Martínez, G., Veja, E., & Fernández, O. (2009). Propriedades antioxidantes de *Rhizophora mangle* (L.) y su relación con el proceso de curación de heridas en ratas. *Revista de Salud Animal*, *31*(3), 170-175.

Sorg, H., Tilkorn, D. J., Hager, S., Hauser, J., & Mirastschijski, U. (2017). Skin wound healing: An update on the current knowledge and concepts. *European Surgical Research*, *58*(1-2), 81-94. DOI: https://doi.org/10.1159/000454919

Stozkowska, W., & Piekos, R. (2004). Investigation of some topical formulations containing dexpanthenol. *Acta Poloniae Pharmaceutica*, *61*(6), 433-437.

Tsuchiya, H., Sato, M., Miyazaki, T., Fujiwara, S., Tanigaki, S., Ohyama, M., … Iinuma, M. (1996). Comparative study on the antibacterial activity of phytochemical flavanones against methicillinresistant *Staphylococcus aureus*. *Journal of Ethnopharmacology*, *50*, 27-34.

Wang, P. H., Huang, B. S., Horng, H. C., Yeh, C. C., & Chen, Y. J. (2018). Wound healing. *Journal of the Chinese Medical Association*, *81*(2), 94-101. DOI: https://doi.org/10.1016/j.jcma.2017.11.002