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EFFECTS OF 3 TOPICAL PLANT EXTRACTS ON WOUND HEALING IN BEEF CATTLE

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Abstract

Eleven heifers of the Purunã cattle breed were used to evaluate wound healing by second intention. An experimental wound excision model in bovines was created by means of a skin punch of diameter 2cm. The animals were topically treated for 17 days with a saline control or decoctions of *Schinus terebinthifolius* Raddi (Aroeira mansa), *Tabebuia avellanedae* Lorentz ex Griseb (Ipê Roxo), and *Casearia sylvestris* Sw.(Guaçatonga) mixed with carboxymethyl cellulose. Centripetal retraction, clinical, and histological aspects of the wounds were observed until complete healing. Decoctions of *T. avellanedae* and *S. terebinthifolius*, but not *C. sylvestris*, had a beneficial effect on wound healing by second intention.

Keywords: wound healing, skin, cattle, phytotherapy.

Introduction

Skin wounds are frequently encountered in cattle as a result of management practices that use bloody interventions, or owing to lesions caused by unsound installations or fights for establishment of herd hierarchy. These lesions, although common, are often neglected, and lead to the development of myiasis (*Cochliomyia hominivorax*) with potential economic losses of up to US$ 150 million in Brazil alone (Grisi et al., 2002), or up to US$ 8 million, if only the annual expenses related to the purchase of repellent and wound healing products is considered (Moya Borja, 2003). Despite the economical impact on the beef cattle industry and human health, negligence prevails in the area of cattle skin healing, in contrast to the situation with horses and pet animals (Martins et al., 2003; Souza et al., 2006). In Brazil, the search for wound-healing phytotherapeutic drugs is based on preclinical and clinical studies in laboratory animals (Leite et al., 2002; Penna et al., 2003; Goes et al., 2005). Although horses have been used in veterinary medicine, (Martins et al., 2003; Souza et al., 2006), bovine species have not been used thus far. Despite the existence of alternative production systems and the abundance of skin lesions in bovine practice, studies showing the effects of phytotherapeutic products on cattle wound healing are rare (Oloumi and Derakhsanfar, 2004; Derakshanfar and Oloumi, 2004).

Notwithstanding the fact that Brazil, the largest country in South America, is a land of diversified flora, research on natural drug development in Brazil is rare, as reported by Desmarchelier (2010). In the present study, 3 native arboreal species (*Casearia sylvestris* "Guaçatonga," *Schinus terebinthifolius* "Aroeira-mansa," and *Tabebuia avellanedae* "Ipê-roxo") were evaluated. *Casearia sylvestris* (Guaçatonga), also known as lizard's herb, belongs to the Flacourtiaceae family, and is found almost throughout the entire Brazilian territory. *Casearia sylvestris* has numerous pharmacological applications in human and dental health. *Casearia sylvestris* extracts exhibit anti-diarrhea, anti-thermal, depurative, anti-rheumatism, cicatrizing, and anti-inflammatory activities, and are also used for the treatment of snake bites (Sassioto et al., 2004; Arantes et al., 2005).

Schinus terebinthifolius (Aroeira-mansa), belongs to the sumac family (Anacardiaceae), and is a native South American plant found in all Brazilian regions. Both popular knowledge and research findings attribute anti-diarrheal, astringent, anti-inflammatory, cicatrizing, antibacterial, and purgative activities to this plant (Lima et al., 2004; Degáspari et al., 2005; Branco Neto et al., 2006; Lucena et al., 2006; Santos et al., 2006). *Schinus molle* (Aroeira-salsa) species have been reported to show histamine, serotonin, and acetylcholine inhibitor activities, similar to those of *Schinus terebinthifolius* (Bello et al., 1998).

Tabebuia avellanedae (Ipê-roxo), which belongs to the Bignoniaceae family, is a South American plant that is found throughout the Brazilian territory. Many medicinal properties, such as anti-ulcerogenic, anti-inflammatory, antibacterial, antimalarial, trypanosomicidal, anti-psoriasis, antiviral, anti-schistosomal, antineoplastic, and immunomodulatory activities, are attributed to its phytocompounds, of which one is lapachol (Fonseca et al., 2003; Souza et al., 2005; Corrêa et al., 2006; Moon et al., 2007).

The purpose of this study was to compare the effects of phytotherapeutics extracted from *Schinus terebinthifolius* bark, *Tabebuia avellanedae* sawdust, and *Casearia sylvestris* leaves and twigs on cicatrization of cattle skin lesions by second intention.

Material and methods

Animals

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Eleven beef cattle heifers from the Purunã breed (average age, 16 months and weight, 240–302 kg) were used in this study conducted in 2007. The experimental animals were confined to individual stalls in a roofed barn at "Fazenda Modelo" Experimental Station of the Instituto Agronômico do Paraná (IAPAR), located in Ponta Grossa, State of Paraná, Brazil. The animals were fed corn silage, mineral mixture, and water on a free-choice basis, in addition to a concentrated ration (2 kg per animal per day) containing 18% crude protein and 70% total digestive nutrients. The animals were confined for 10 days to allow adaptation before initiation of the experiment.

Plant collection/extraction

The *Schinus terebinthifolius* and *Casearia sylvestris* plants (n = 6) used in this study were harvested in spring from Fazenda Rio Grande County, and dried on forced ventilation stove at 37°C for 96 h. *Tabebuia avellanedae* sawdust was obtained from 3 different lumber mills from the city of Curitiba (Paraná, Brazil), and dried as described above. The bark of *Schinus terebinthifolius* and the leaves and twigs of *Casearia sylvestris* were used. For the extractions, a fiber digester with a condenser in a decoction closed system was used as follows: *Schinus terebinthifolius*, *Tabebuia avellanedae* and *Casearia sylvestris* solutions were obtained by boiling 100 g of each material in 1 L of water for 30 min. The forming vapor condenses and was reutilized in the boiling process. The decoction was then filtered (Whatman filter no. 1) and homogenized with 6 g of carboxymethyl cellulose. An isotonic solution of NaCl homogenized with 6 g of carboxymethyl cellulose was used as control therapy. Decoctions were prepared only once, and the phytotherapeutics were stored in amber glass bottles under refrigeration (4–8°C). Exsicattes of the plant materials were deposited[1] in the herbarium of State University of Ponta Grossa / Paraná – UEPG -PR.

Induction of wound

Skin wounds were surgically created after the animals were subjected to a 24-h food withdrawal and a 12-h water withdrawal. Thereafter, the heifers were sedated with chloridrate of xilazyn (0.04 mg/kg, IV – intravenous). Hair was clipped from an area of approximately 40 × 60 cm in the lumbar region. After sedation, chloridrate of lidocaine was applied to the incision areas, and 4 full-thickness lesions were made by excising the skin to the level of loose subcutaneous tissue on each side in the lumbar region, using a punch of diameter 2 cm without antiseptics, thus preserving the resident microbiota. The circular wounds were located at 10 cm from the spinal column, and were separated from each other by the same distance (10 cm).

Treatment regimen and wound evaluation

Clinical treatment was initiated 12 h after the surgical wounds were made, and was administered on a daily basis until complete cicatrization of the lesions. Treatments were completely randomized, so as to avoid performing the same clinical procedure in the craniocaudal direction. The phytotherapeutics (plant decoction condensed with carboxymethyl cellulose) were directly applied on the wounds daily with a syringe. The tails of the animals were tied to their shins with a string throughout the experiment. The lesions on the right side in the lumbar region of each animal were clinically evaluated for local hemorrhage, presence of clots, crusts, granulation tissue, epithelization, and presence of exudate, and were classified as bad (1), regular (2), or good (3) by the same evaluator throughout the study. Macroscopic evaluation was performed on a daily basis until the 17th day after the surgery.

To measure wound retraction, we measured each wound area on days 2, 5, 9, 11, 13, 15, and 17 by placing a transparent plastic sheet on the lesion and marking the surrounding perimeter with a projector pen. Average wound areas were obtained using the formulae for the area of a circle ($\pi \times R^2$, where π is equal to 3.14 and R is the radius) and area of an ellipsis ($\pi \times AB$, where A is the larger radius and B is the smaller radius). The lesions on the left side in the lumbar region of 10 randomly chosen animals were selected for biopsy. Samples were obtained from the geometrical center of the lesions by using a surgical punch of diameter 7 mm on days 6 (5 animals) and 16 (5 animals) after wound establishment. The material was fixed in 10% formaldehyde for histopathological analysis. The fragments were stained with hematoxylin and Harris eosin, and analyzed by a pathologist who was blinded to the experimental methodology. For fragments obtained on day 6, inflammatory reaction was evaluated on the basis of cellularity and edema formation. The presence of young granulation tissue was also evaluated. For cellularity, the following grades were attributed: present (1), moderately infiltrated (2), or severely infiltrated (3). Edema was classified as absent (1), slight (2), or severe (3). The young granulation tissue was classified as traces (1), moderate (2), or abundant (3), by using a semi-quantitative analysis. Treatment averages were obtained from the inflammatory reaction and granulation tissue deposition evaluation grades. The material obtained on day 16 was evaluated for granulation tissue deposition by examining the presence and quantity of young or mature granulation tissue, and was graded as minimum (1), moderate (2), or abundant (3) deposition. Inflammatory reaction was classified as weak (1), strong (2), or severe (3). As on day 6, treatment averages were obtained from the evaluation grades for inflammatory response and granulation tissue deposition.

Statistical analysis

Statistical analysis was performed using the GLM (General Linear Models) procedure from SAS (version 9.1), taking into account the following variables: averages of the macroscopic clinical evaluation grades, i.e., bad (1), regular (2),

[1] Voucher Numbers14.686 for *Tabebuia avellanedae;* 14.687 for *Schinus therebentifolius* ; 14.688 for *Casearia sylvestris*

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or good (3); averages of the lesions areas (cm^2) on days 5, 13, and 17 after the surgery. For microscopic evaluation, the grades of the material obtained on days 6 and 16 were considered. ANOVA was performed with an entirely randomized design of 4 treatments and 11 replications for macroscopic evaluations, and 4 treatments and 5 replications for microscopic evaluations on days 6 and 16. The differences between treatments were evaluated with the *t*-test, and $p < 0.05$ was considered significant. Qualitative parameters from the microscopic analysis were used for defining the healing quality response, as explained above.

Ethical considerations

This study was approved by the Ethical Committee under resolution number 69/06/CEUA-PUCPR (Ethical committee of the Catholic University of Paraná – PUCPR).

Results and discussion

In the first 3 experimental days, wounds treated with *Tabebuia avellanedae* exhibited serous, smooth, and slender crusts, and borders with less edema compared to wounds that were treated by the other extracts. This observation is consistent with the anti-inflammatory properties of *Tabebuia avellanedae* reported previously (Fonseca et al., 2003; Souza et al., 2005; Corrêa et al., 2006). The wounds exhibited significantly better macroscopic characteristics ($p < 0.05$) than the control did, at the beginning and end of the treatment. Although the healing of wound treated with *Tabebuia avellanedae* did not differ from that of the control on days 6 and 12, the average healing rate was still superior to that of the control (Table 1). The wound area averages did not significantly differ from average wound area of the control group at any time. However, the lesion area was slightly smaller in the *Tabebuia avellanedae* group (Table 2). Further studies must be conducted to determine whether changes in lesion area may be easier to evaluate for extensive wounds and in areas of difficult healing.

Table 1: Macroscopic evaluations of cattle skin wounds (n = 88) on days 2, 4, 6, 12, and 17
Data are presented as mean (SD).
Means followed by † in the column do not significantly differ (p >0.05)
‡ p < 0.05 relative to control and treatment *Tabebuia avellanedae*
* p < 0.05 relative to the control and other treatments
** p < 0.05 relative to control only.

	Evaluation grade				
Treatments	D2	D4	D6	D12	D17
Schinus terebinthifolius	1.81‡ (0.87)	2.27† (0.64)	2.36† ± (0.50)	2.45† (0.82)	2.45** (0.82)
Casearia sylvestris	1.81‡ (0.60)	2.18† (0.87)	2.09† ± (0.70)	2.54† (0.82)	2.18† (0.87)
Tabebuia avellanedae	2.72* (0.46)	2.45** (0.68)	2.18† ± (0.87)	2.63† (0.67)	2.63** (0.67)
Control	1.18† (0.40)	1.81† (0.87)	1.81† ± (0.75)	2.27† (0.64)	1.72† (0.90)

Table 2 - Cattle skin wound areas (n = 88) on days 0, 5, 13, and 17

Data are presented as mean (SD) [SE].

	Wound area (cm^2)			
Treatments	D0	D5	D13	D17
Schinus terebinthifolius	3.14† (0) [0]	2.11† (0.63) [0.30]	2.05† (1.13) [0.50]	0.77† (0.58) [0.23]
Casearia sylvestris	3.14† (0) [0]	2.58† (0.85) [0.30]	2.24† (1.75) [0.50]	0.9† (0.78) [0.23]
Tabebuia avellanedae	3.14† (0) [0]	2.27† (0.41) [0.30]	1.89† (0.81) [0.50]	0.62† (0.38) [0.23]
Control	3.14† (0) [0]	2.46† (0.83) [0.30]	2.13† (0.83) [0.50]	0.73† (0.36) [0.23]

† Not significant (p >0.05)

Smaller wound areas were observed on days 2, 5, and 9 in the *Schinus terebinthifolius* group, suggesting that wound retraction is enhanced by the astringent effect of tannins (Panizza et al., 1988).

Interestingly, the day-6 histological evaluation did not reveal significant differences in inflammatory response and granulation tissue deposition between the control and the other treatments (Table 3). The best macroscopic evaluation was

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not associated with quantifiable alterations in microscopic evaluation. The lesions became less exudative, possibly because of the antimicrobial effect of phytocompounds found in *Tabebuia avellanedae* (Fonseca et al., 2003).

Wounds treated with *Casearia sylvestris* presented serous and smooth but slightly edematous and erythematosus crusts, indicating anti-inflammatory activity of the plant (Arantes et al., 2005). This treatment was effective only for the first 2 days (Table 1), and did not differ significantly in macroscopic evaluation from the control treatment. Furthermore, wound retraction was slower than that observed in the other treatments. In microscopic evaluations, *Casearia sylvestris* did not improve the cicatrization process (Table 3). Sassioto et al. (2004) observed that the *Casearia sylvestris* decoction promoted chronological delay in bone reparation in rats, possibly owing to anti-inflammatory activity and reduction in the macrophage, fibroblast, and collagen fiber population at the wound site.

Table 3 - Histological evaluation of cattle skin wounds (n = 88) on days 6 and 16

Data are presented as mean (SD) [SE].
SE, standard error

	Inflammation response		Granulation response	
Treatments	D6	D6	D16	D16
Schinus terebinthifolius	1.8† (0.83) [0.32]	2.2† (0.83) [0.32]	1.8† (1.09) [0.44]	2.4‡ (0.54) [0.20]
Casearia sylvestris	1.6† (0.54) [0.32]	1.8† (0.83) [0.32]	1.6† (0.89) [0.44]	2.0† (0.0) [0.20]
Tabebuia avellanedae	1.4† (0.54) [0.32]	2.0† (0.70) [0.32]	1.6† (0.89) [0.44]	2.2‡ (0.44) [0.20]
Control	1.4† (0.89) [0.32]	2.2† (0.44) [0.32]	1.8† (1.09) [0.44]	1.6† (0.54) [0.20]

† Not significant ($p > 0.05$).
‡ $p < 0.05$ relative to control.

Dry and irregular crusts were observed in the lesions treated with *Schinus terebinthifolius*, an effect attributed to the astringent action of tannins found in the plant (Degáspari et al. 2005). Even with differentiated macroscopic aspects, wounds treated with *Casearia sylvestris* did not significantly differ from those treated with *Schinus terebinthifolius* during the first 3 days. Macroscopic evaluation of *Schinus terebinthifolius*-treated wounds yielded significantly better results than did those treated by the control at the beginning (day 2) and end (day 17) of the treatment (Table 1).

Microscopic analysis on day 16 of the experiment revealed that *Schinus terebinthifolius* was beneficial to the healing process. *Schinus terebinthifolius* treatment resulted in a greater amount of mature conjunctive tissue than the other treatments did. Development of dermal annexes, which may be related to low oxygen tension induced by the tannins, was observed. Fibrin accumulation was also observed in the center of the wound. Fibrin stimulates the multiplication and centripetal migration of fibroblasts through the fibrin net, suggesting that *Schinus terebinthifolius* promoted fibroplasty. Hoffman et al. (2006) have shown that *Schinus terebinthifolius* has a beneficial effect on colon anastomosis cicatrization. Lucena et al. (2006) also found a positive effect of the hydroalcoholic extract of this plant on surgical wounds in mice bladders. Nunes Jr. et al. (2006) obtained positive results for augmentation of the maximum charge rupture and maximum deformation of rat *linea alba* in a tensiometric analysis using *Schinus terebinthifolius*. Santos et al. (2006) concluded that the hydroalcoholic extract of *Schinus terebinthifolius* does not alter stomach cicatrization, as observed by macroscopic, tensiometric, and microhistological evaluations. Branco Neto et al. (2006) tested the hydroalcoholic extract of *Schinus terebinthifolius* on skin wounds of mice and observed a delay in skin re-epithelization.

On days 4, 6, and 12 of our experiment, no significant differences were observed in the visual evaluation of the wounds treated with *Schinus terebinthifolius* and *Casearia sylvestris*, relative to the control wounds. However, *Tabebuia avellanedae* treatment was more effective than the other treatment were, on day 4, possibly because of its anti-inflammatory and antibacterial activities. Fibrin-purulent exudation was more frequently observed in the *Casearia sylvestris* and control groups, suggesting secondary infection, which may be controlled by the antibacterial effect of tannins and essential oils (Lima et al., 2004; Degáspari et al., 2005) present in the *Schinus terebinthifolius* group, and by the antibacterial effect of naphthoquinones present in *Tabebuia avellanedae* (Fonseca et al., 2003; Souza et al., 2005; Corrêa et al., 2006).

During the other days of the reparation phase, there were no significant differences among the groups. However, the *Tabebuia avellanedae* and *Schinus terebinthifolius* groups exhibited better characteristics in the day-17 macroscopic evaluation. Similarly, wounds treated with *Tabebuia avellanedae* and *Schinus terebinthifolius* exhibited better fibroplasia in the microscopic evaluation on day 16 (Table 3). This favorable evaluation is related to the good control of the inflammatory phase and secondary infections, resulting in better cicatrization. Better evolution of lesions treated with *Tabebuia avellanedae* may also be related to the immunomodulatory effects of its phytocomplexes (Corrêa et al., 2006), which may improve phagocytic function, superoxide anion production, and polymorphonuclear and mononuclear leucocyte activity, given that these cells are essential to the cicatrization process owing to their production and liberation of chemical mediators that favor fibroplasia (Balbino et al., 2005).

Microhistological evaluations (Table 3) revealed a positive effect *Tabebuia avellanedae* and *Schinus terebinthifolius* on granulation tissue deposition on day 16. Although an improvement in inflammatory control was expected in the *Tabebuia avellanedae* group, this was not detected in the tissue by microscopy.

The phytotherapeutics obtained from *Tabebuia avellanedae* and *Schinus terebinthifolius* positively affected the cicatrization process in cattle skin wounds by promoting fibroplasty and wound decontamination. Oloumi and Derakhshanfar (2004) examined phytotherapeutic effect of a topical extract from *Glycyrrhiza glabra* on cattle skin cicatrization in Holstein

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heifers, and showed that this extract was effective during the first 7 days. The same researchers also obtained positive results by using *Elaeagnus angustifolia* oil in dermo-epidermic lesions in Holstein female calves. No Brazilian studies showing phytotherapeutic effects on cattle skin cicatrization were found in the literature.

Other papers described substances that interfere with cattle skin cicatrization. Miller et al. (1966) have shown that zinc supplementation in Holstein heifers promotes skin regeneration. Varshney et al. (1997) have shown that saliva has a therapeutic effect on calf skin healing. Marques et al. (1996) used a biological dressing composed of a cellulose microfibril net for treating wounds in the mammary papilla of cows, and reported shortening of the recuperation period, compared to conventional treatments, and in situations where curative substitutes were unavailable.

Statistical analysis revealed significant differences in the macroscopic aspects of the wounds in the comparative study of phytotherapeutics, but the average wounds areas did not significantly differ. Despite these results, daily macroscopic observations and wound area measurement results indicate that centripetal retraction was promoted during the first 10 days of treatment in the *Schinus terebinthifolius* group, and at the end of the experiment in the *Tabebuia avellanedae* group. On the other hand, statistical analysis of the microscopic evaluations revealed only a slight beneficial effect on the fibroplasty process in the *Tabebuia avellanedae* and *Schinus terebinthifolius* groups on day 16 after the surgery.

At the end of the evaluations, the *Tabebuia avellanedae* group exhibited more efficient healing, suggesting that this is attributed to antibacterial and anti-inflammatory activities of the plant (Moon et al., 2007).

Conclusions

The phytotherapeutic agent present in *Tabebuia avellanedae* sawdust improved cicatrization of cutaneous lesions in cattle skin during the first 5 days of treatment. *Tabebuia avellanedae* treatment was beneficial to the reparation process. The phytotherapeutic agent present in *Schinus terebinthifolius* exhibited positive effects in the inflammatory phase and on the reparation process. *Casearia sylvestris* extract exhibited a positive effect on the macroscopic aspect of cutaneous lesions in cattle only during the first 2 treatment days. Both *Schinus terebinthifolius* and *Tabebuia avellanedae* improved fibroplasia. Phytotherapeutic activity of *Tabebuia avellanedae* was the most superior, followed by that of *Schinus terebinthifolius*. *Tabebuia avellanedae* and *Schinus terebinthifolius* may be used in topical treatment of cattle skin wounds.

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