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Research Article
Polysaccharide-Rich Extract of *Caesalpinia ferrea* Stem Barks Modulates Inflammatory and Proliferative Phases Enhancing Diabetic Cutaneous Wound

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Abstract

Background and Objective: Diabetes decreases glucose metabolism, leading to hyperglycemia and delayed wound healing. *Caesalpinia ferrea* or *Libidibia ferrea* (Fabaceae), popularly known as "pau ferro", "jucá" or "jucaína", is widely used in folk medicine for inflammatory conditions. *Caesalpinia ferrea* barks are used in the form of tea and portions to clean injuries and treat wounds and its stem barks infusion to treat enterocolitis, asthma, bruises, chronic cough and wounds. This study aimed to investigate the effect of the polysaccharide-rich extract of *C. ferrea* stem barks (PE-Cf) in the model of excisional cutaneous wounds in diabetic rats. **Materials and Methods:** The PE-Cf was obtained by a combination of NaOH extraction and ethanol precipitation. The analysis of the NMR spectra of PE-Cf revealed a central core composed mostly of 5-linked α-Ara*f* and minority constituents such as α-Rha*p* and α-GalA*p*. For diabetes induction, rats received alloxan (45 mg kg^{-1}) by the intravenous route for pancreatic β cell destruction. One month later, rats that had blood glucose $\geq$200 mg dL^{-1} were selected to be tested in the model of the excisional cutaneous wound. PE-Cf (0.025-0.1%) was topically applied to the wounds twice a day for 14 days for evaluation of hyper-nociception (digital analgesimetry), clinical signs (macroscopy) and histopathology/ histomorphometry. **Results:** 0.1% PE-Cf reduced wound area (2-7th day), hyper-nociception (5-10th day), crust detachment (5-7th day), scar tissue formation (10th day), leukocyte infiltration (5-7th day) and increased fibroblast/myofibroblast (5th and 7th day). **Conclusion:** The PE-Cf accelerates the healing process of diabetic rats, acting both in the inflammatory and proliferative phases. This study validates the popular use of *C. ferrea* barks in the inflammatory process and suggests PE-Cf as an alternative therapy to healing diabetic wounds.

Key words: Alloxan, excisional wound healing, *Caesalpinia ferrea*, plant polysaccharides, anti-inflammatory, keratinocyte, fibroblast migration, macrophage

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Patients with diabetes are affected by the decreased ability of glucose metabolism, resulting in hyperglycemia, which may lead to delayed wound healing[1]. Furthermore, these patients exhibit difficulty in the formation of mature granulation tissue and recovery of tissue integrity[2,3].

The physiological healing process involves 4 overlapping phases: hemostasis, inflammation, proliferation and remodelling, resulting in scar formation[4,5]. Different cell types (neutrophils, macrophages, lymphocytes, mast cells and fibroblasts) are responsible for the reconstruction of the extracellular matrix involving growth factors and inflammatory mediators[6]. It is known that diabetes has important features that include oxidative stress and persistent inflammation[1]. At the early stage occurs persistent oxidative damage caused by reactive oxygen species (ROS), mainly produced by mitochondrial of immune cells[7].

Poor glycemic control can also impair the host immune response, leading to wound healing and difficult recovery from the infection[7,8]. Activities such as impaired angiogenic response and microvascular complications, macrophage and neutrophil function, keratinocyte and fibroblast migration and proliferation, sustained production of pro-inflammatory cytokines and reduced growth factor production has been reported in diabetic animal models[3,9]. In addition, patients can exhibit peripheral neuropathy, diminished perception of pain and increased inflammatory pain due to infected wounds[10,11]. In these cases, dressing techniques that minimize trauma and pain on application/removal should be chosen to avoid wound damage and stress to patients[12].

Plant polysaccharides emerge as an alternative therapy since they are known for their immunomodulatory properties and low toxicity[13,14]. *Caesalpinia ferrea* Mart. ex Tul. or *Libidia ferrea* (Mart. ex Tul.) L. P. Queiroz (IPNI, 1844, 2009) is a leguminous plant belonging to the Fabaceae family, popularly known as "pau ferro", "jucá" or "jucaína", distributed in several Brazil regions and endemic in the North and Northeast[15]. Different parts of this plant (fruits, leaves, seeds, barks) are widely used in folk medicine and for this reason, this species was included in the national list of medicinal plants of interest to the Brazilian Public Health System (Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde-RENISUS)[15]. *Caesalpinia ferrea* barks are used in the form of tea and portions to clean injuries and treat wounds[15] and the stem barks infusion to treat enterocolitis[15], asthma, bruises, chronic cough and wounds[15].

Experimental studies have demonstrated that aqueous extracts obtained from *C. ferrea* barks exhibit pharmacological activities, such as anti-inflammatory, antioxidant, analgesic, hypoglycemic and anti-ulcer[14,16-18]. These extracts are characterized by the presence of polyphenols, terpenes and steroids. Most of the mentioned biological activities are accounted for the polyssacharides[19]. Concerning the polysaccharide extracts and isolated polysaccharides from *C. ferrea* barks it was demonstrated *in vitro* and *in vivo* the activities of anticoagulant and antithrombotic[20], anti-inflammatory and antioxidant[21] and healing effect in the model of excision cutaneous wounds of normoglycemic rats[22].

Moreover, the polysaccharide extract of *C. ferrea* stem barks was characterized revealing arabinose, galactose, rhamnose and uronic acid in its composition. Nuclear magnetic resonance spectra showed a central core composed mainly of 5-linked α-Ara*f*, with non-reducing terminals formed by α-Ara*f* liked to position 2 of the central core, besides other minority components of α-Rha*p* on the central core and α-GalA*p* as terminal units[20].

Based on the recognized low toxicity of plant polysaccharides, the healing effect in normoglycemic rats and the immunomodulator potential of *C. ferrea* stem barks polysaccharides, in this study it was investigated the effect of the polysaccharide-rich extract of *C. ferrea* stem barks in a model of the excisional cutaneous wound in diabetic rats.

MATERIALS AND METHODS

Animals: Female Wistar rats (180-220 g, 6-8 weeks, 6 animals/groups/experimental day/total number of animals used:60, study duration: 08.2018-06.2021) were maintained at 26±1°C under 12/12 hrs light/dark cycle, receiving food and water *ad libitum*. Animals were brought to the laboratory at least 1 hr before the experiments, which were conducted following protocols approved by the Animal Care and Use Committee (UECE n° 12784513-5), following the guidelines of the Brazilian Council of Control in Animal Experimentation (CONCEA). The efforts employed intended to minimize the number of animals used, as well as their suffering.

Plant material: *Caesalpinia ferrea* stem barks were collected in Custódio (Quixadá-CE, Brazil) and a plant sample was deposited in the Herbarium Prisco Bezerra of the Federal University of Ceará - UFC (exsiccate: 46085) and in the Faculty of Education, Science and Letters of Sertão Central (FECLESC). The name of the plant was verified in The Plant List at http://www.worldfloraonline.org.

Obtention of polysaccharide-rich extract from *C. ferrea* barks: Three bark pieces (5 g) were washed with distilled water, dried at 40°C and ground into fine particles. Five grams of powder was added to absolute MetOH (1:50, w/v,76°C) for

depigmentation-the procedure was repeated twice. The polysaccharides were extracted from the extracellular matrix with 0.1 M NaOH at 97°C and the soluble portion was filtered and centrifuged (2496 g, 25°C) (the procedure was repeated three times). The alkaline supernatants, containing the polysaccharides, were pooled, neutralized (1 M HCl), precipitated with 4 volumes of absolute EtOH and re-centrifuged in the same conditions. The precipitate was dialyzed against distilled water under stirring for 72 hrs and re-centrifuged, being the final supernatant lyophilized and named polysaccharide-rich extract of *Caesalpinia ferrea* barks (PE-Cf: 3% yield), adapted from Yoon *et al.*[23].

Alloxan-induced diabetes mellitus: Animals received alloxan (45 mg kg^{-1}) by intravenous (i.v.) route for the destruction of pancreatic β cells and after 48 hours of administration, peripheral blood was collected for blood glucose assessment. Before alloxan administration, the blood glucose levels were also checked for normoglycemia. Rats within one month of induction that had a blood glucose of 200 mg dL^{-1} or higher were selected for experiments. Before performing the glycemic test, animals were maintained fasting for 12 hrs but received water *ad libitum*[3].

Excisional wound model: Animals were anaesthetized by intraperitoneal (i.p.) route with 10% ketamine (100 mg kg^{-1}) and 2% xylazine (10 mg kg^{-1}). After dorsum shaving and antisepsis (ethanol 70%), four circular full-thickness wounds were performed using a biopsy punch of 7 mm diameter (ABC instrumentos cirúrgicos, Brazil), followed by excision of epidermis, dermis and hypodermis to expose the panniculus carnosus[22]. Twenty-four hours after ulceration and recovery to anaesthesia, animals received topical treatment (the route used in traditional medicine) with 0.9% saline as control or PE-Cf (0.025-0.1%, dissolved in saline) for 14 days, twice a day. Wounds were excised using a scalpel and surgical scissors for analysis of inflammatory parameters present in the tissue, such as polymorphonuclear leukocyte infiltrate, fibroblasts and blood vessels[22].

Wound area/closure: The wound area was measured with a 0.5 mm precision digital paquimeter (D = largest diameter, d = smaller diameter) to express the ulcerated area (A = π. D/2.d/2). The wound closure was calculated by the equation:

$$100\times (Ai\text{-}Af)/Ai \text{ (Ai = initial area, Af=final area)}$$

and expressed as a percentage[22].

Inflammatory and scarring clinical signs: Hyperemia, edema, transudate, crust detachment wound scab and scar tissues were classified according to the following scores: (0) absence of edema, hyperemia and transudate, (1) mild edema, hyperemia and transudate, (2) moderate edema, hyperemia and transudate, (3) intense edema, hyperemia and transudate. Crust detachment (fissures, fragility) and scar tissue (rosy, pigmentation absence) were observed for presence or absence[22].

Hyper-nociception was evaluated by a pressure transducer coupled to a digital analgesia meter (Insight, Brazil) that expressed mechanical pressure in grams (g). A mechanical stimulus (polypropylene tip-0.5 mm diameter) was applied to the ulcer edges and the result of the stimulus was interpreted as nociceptive behavior[22].

Histopathology and histomorphometry: Tissues were immediately preserved in 10% neutral buffer formalin for histological analysis. Skin fragments were fixed in 10% formol for 24 hrs, subjected to dehydration in crescent alcoholic series, diaphanized in xylol and impregnated in paraffin (60°C). Fragments were put into paraffin-forming blocks, sectioned in microtome (5 µm thickness) and stained with hematoxylin and eosin (H&E). The histopathological parameters were scored from 0-4 according to Cavalcante *et al.*[24]: (0) absence of ulcer/remodelled connective tissue, (1) absence of ulcer/fibrosis with mild chronic inflammation, (2) presence of ulcer/fibrosis with moderate chronic inflammation, (3) presence of ulcer/chronic inflammation (granulation tissue), (4) presence of ulcer/acute process (dilated vessels, mixed inflammatory infiltrate with neutrophils).

Five fields immediately below the ulcer/reepithelization of each animal were photographed (40× magnification, Nikon Eclipse H550S microscope, Japan) for quantification of polymorphonuclear, mononuclear and fibroblast/myofibroblast cells and blood vessels using the Plugin "Cell Counter" ImageJ's software (National Institutes of Health, EUA). The sample unit for each animal was the sum of the 5 fields per slide[22].

Statistical analysis: Data were expressed as Mean±SEM and analyzed by two-way ANOVA followed by the Bonferroni Test and histopathological data was expressed as Median (maximum and minimum) and analyzed by the Mann-Whitney's followed by the Dunn's Test. Categorical data (absent/present) was expressed as relative frequency (%f) and analyzed by the Chi-Square Test. The $p<0.05$ was considered significant.

RESULTS

PE-Cf reduces the area of the diabetic cutaneous wounds and increases the healing rate: The treatment with PE-Cf (0.05-0.1%) reduced the wound area (Fig. 1a) from the 2nd day (0.05%: 49.80±2.4, 0.1%: 43.33±2.8, saline: 59.76±1.4 mm^2) until the 10th day (0.05%: 5.02±0.4, 0.1%: 6.42±0.5, saline: 19.94±1.6 mm^2). At 0.1% PE-Cf was more effective, reducing the wound area at all stages of the healing process. At 0.05 and 0.1%, PE-Cf increased the healing rate along the entire the time-course (0.05%: 349.9±77.9, 0.1%: 424.8±38.02, saline: 212.4±442.8 AUC), being more efficient at 0.1% and used for the following experiments (Fig. 1b).

1% PE-Cf reduces the inflammatory signs of skin wounds and accelerates diabetic cutaneous wound closure: The intensity of the inflammatory signs of inflammation (hyperemia, edema) of wounds treated with PE-Cf has been significantly reduced (Table 1). On the 5th day after ulceration, there was a reduction in the intensity of hyperemia when compared to the moderate score of the saline-treated animals. In addition, on the 5th day, transudate, when present in the animals treated with PE-Cf was slight. The intensity of edema, was also reduced on the 5th day by 0.1% PE-Cf and PE-Cf increased the nociceptive threshold from the 5th day until the 10th day (Table 1). In the subsequent evaluation days, these parameters did not show any significant difference.

The treatment with PE-Cf reduced the time in which the crust remained on the wounds. On the 5th day, it was observed that PE-Cf caused, partial or total, early crust detachment from the wound edges (48% *vs.* saline: 18%) and increased the frequency of scar tissue (69%), mainly, from the 10th day compared to saline (28%). On the 14th day of treatment 86% of ulcers had scar tissue compared to saline (62%) (Table 1).

1% PE-Cf reduces the inflammatory profile in histopathology and histomorphometry of diabetic cutaneous wound: In Fig. 2a-h, this semi-quantitative analysis of the healing process revealed that PE-Cf had promoted histological improvement in inflammatory parameters at the time course and reduced at 2nd day the inflammatory profile (Table 2, Fig. 2a, e). Diabetes causes a persistent inflammatory phase associated with an impediment in the quantity and quality of the formation of mature granulation tissue. In the present study, the treatment of diabetic animals with PE-CF also reduced the inflammatory histopathological profile on the 2nd day indicating a well-established proliferative phase, that is associated with a resolution of the acute inflammatory phase, as seen in the macroscopic analysis from the 2nd day with an improvement in acute inflammatory clinical signs.

On the 2nd day post-ulceration, the wound tissues treated with PE-Cf demonstrated ulcer with fibrosis and the presence of chronic inflammatory process, while the control animals showed an ulcer and mixed chronic inflammatory process, with granulation tissue and leukocyte infiltrate showing predominance of polymorphonuclear and mononuclear cells. On the 5th day after ulceration, the ulcers presented a similar profile being, fibrosis and moderate chronic inflammatory process still present in the wound (Table 2, Fig. 2b, f).

Non-ulcerated tissue was predominant in both control and PE-Cf treated groups on the 10th day (Fig. 2d, h). The treated tissues displayed discrete fibrosis, granulation tissue and mild chronic inflammatory process, as well as re-epithelialized tissues in some specimens, while control tissues showed persistent chronic inflammatory infiltration with the presence of mononuclear cells. Complete re-epithelization, mild inflammation, fibrosis and remodelled connective tissue, were found in both groups (Table 2, Fig. 2c, g).

Table 1: 0.1% PE-Cf attenuates inflammatory signs in diabetic rats

		Days post-ulceration				
Parameters	Groups	2°	5°	7°	10°	14°
Hyperemia[1]	Saline	3 (3.3)	2 (0.1)	1 (0.1)	-	-
	0.1% PE-Cf	2 (1.2)	1 (1.2)*	0 (0.0)	-	-
Transudate[1]	Saline	2 (1.2)	2 (1.2)	0 (0.0)	-	-
	0.1% PE-Cf	1 (0.2)*	1 (0.1)*	0 (0.0)	-	-
Edema[1]	Saline	3 (3.3)	2 (0.2)	0.5 (0.1)	-	-
	0.1% PE-Cf	2 (1.2)	1 (0.1)*	0 (0.0)	-	-
Detachment of crust (% f)[2]	Saline	-	18	46	-	-
	0.1% PE-Cf	-	48*	62*	-	-
Scar tissue (% f)[2]	Saline	-	-	-	28	62
	0.1% PE-Cf	-	-	-	69*	86*
Hypernocipeption (g)[3]	Saline	54.9±7.95	54.9±14.6	-	51.3±8.3	-
	0.1% PE-Cf	183.53±18.6	285.23±26*	-	266.01±49.31*	-

[1]Median (minimun, maximun), Mann-Whitney/Dunn's post-test, [2]Relative frequency (f%) of animals affected, Chi-Square Test, [3]Mean±E.P.M. (n = 6/group), two-way ANOVA and Bonferroni post-test, PE-Cf: Polysaccharide-rich extract of *C. ferrea* and *p<0.05 vs. saline

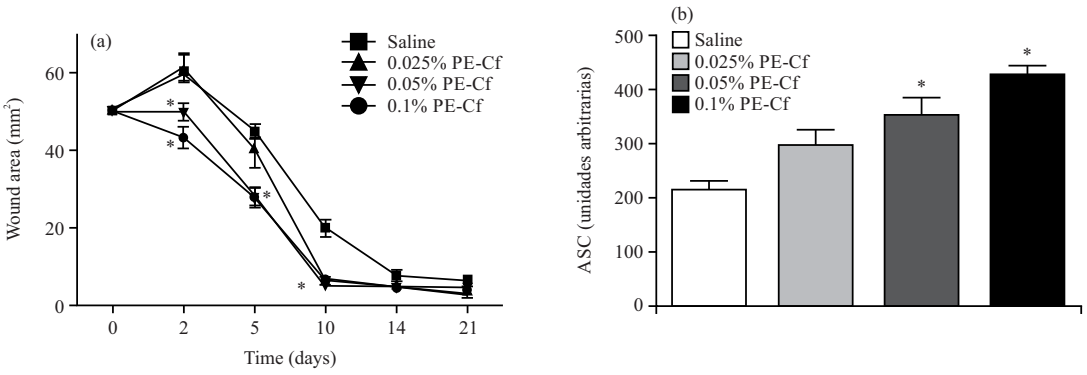

Fig. 1(a-b): 0.1% PE-CF promotes wound closure and increases wound closure index in diabetic rats

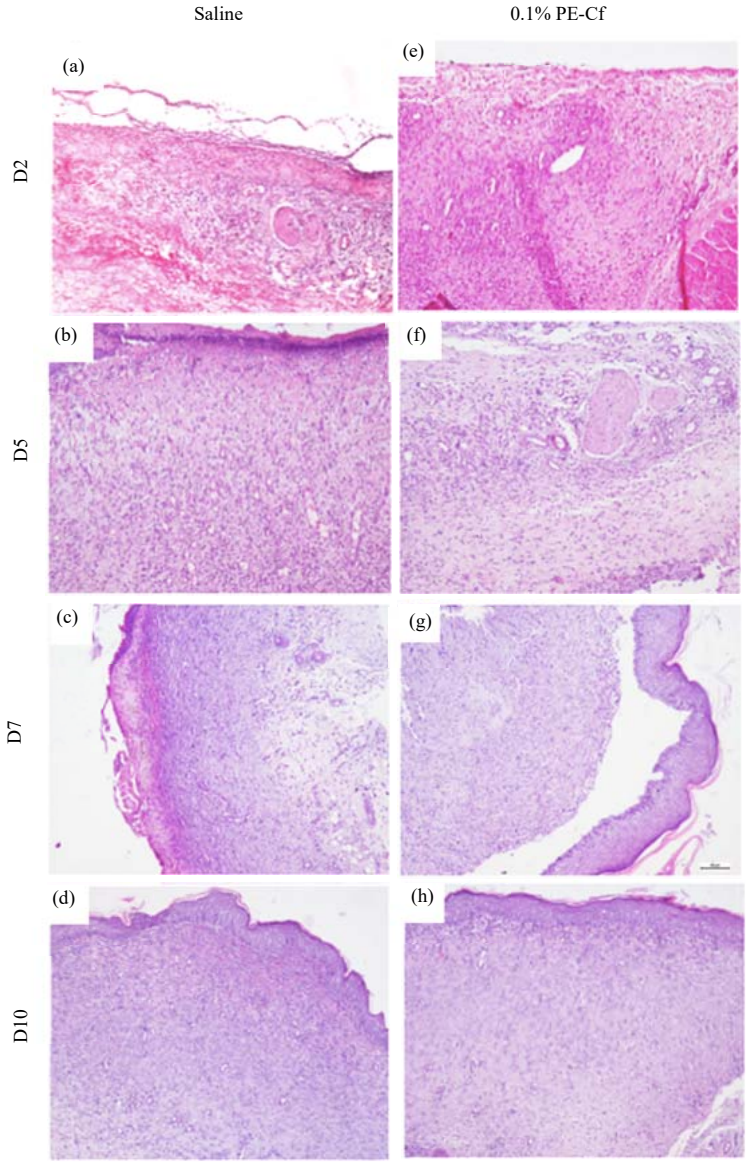

Fig. 2(a-h): Photomicrographs of excisional cutaneous wounds of diabetic rats treated with 0.1% PE-Cf

Table 2: Histopathological profile of diabetic rats with 0.1% PE-Cf treatment

		Days post-ulceration			
Parameters	Groups	2nd	5th	7th	10th
Histological scores[1]	Saline	3 (3-3)	2 (1-2)	2 (2-2)	1 (1-2)
	0.1% PE-Cf	2 (2-3)*	2 (1-2)	1.5 (1-2)	1 (0-2)
Polymorphonuclear[2]	Saline	96±38.84	97.5±44.85	10±5.8	-
	0.1% PE-Cf	59.8±28.36	45.4±43.84	1.25±1.60	-
Mononuclear[2]	Saline	177.4±50.15	233±10.92	163.6±53.77	-
	0.1% PE-Cf	242.4±48.2*	117±27.93*	61.75±12.12*	-
Fibroblast/myofibroblast[2]	Saline	57.2±37.29	210.8±35.9	181.4±35.9	-
	0.1% PE-Cf	141.4±43.85*	317.3±85.8*	232.6±31.79*	-
Blood vessels[2]	Saline	0.2±0.44	5.66±5.85	3±2.7	-
	PE-Cf 0.1%	5±3	5.5±4.5	7.8±4.1	-

[1]Histological scores: Median (minimum, maximum), Mann-Whitney/Dunn's post-test, [2]Mean±E.P.M. (n=6/group), Histomorphometry: Two-way ANOVA and Bonferroni post-test, PE-Cf: Polysaccharide-rich extract of *C. ferrea* and *p<0.05 vs. saline

At any evaluation period was observed polymorphonuclear reduction. However, mononuclear cells were increased by 26% on the 2nd day (242.4±48.2 *vs.* saline: 177.4±50.15) and reduced by 50-63% from the 5th (117±27.93 *vs.* saline: 233±10.92) until the 7th day (61.75±12.12 *vs.* saline: 163.6±53.77), respectively (Table 2, Fig. 2a-g). PE-Cf increased the number of fibroblasts on the 2nd day by 60% (141.4±43.85 *vs.* saline: 57.2±37.9) until the 7th day by 21% (232.6±31.79 *vs.* saline 181.4±35.9). The PE-Cf did not change the number of blood vessels on any day of treatment (Table 2, Fig. 2a-h).

DISCUSSION

The present study demonstrated that the polysaccharide-rich extract obtained from the stem barks of *C. ferrea* (PE-Cf), presented a 3.1% yield, high content of carbohydrate (35.3%, including 5.7% uronic acid), 3.0 mg g^{-1} gallic acid equivalent of polyphenols and low content of protein (3.38%), used topically in the excisional wound in diabetic rats accelerates the healing process via reduction of the inflammatory clinical signs and wound area, an increase of healing rate and recruitment of mononuclear cells and fibroblasts.

In hyperglycemic animals, 0.1% PE-Cf was able to early reduction in transudate from the 2nd-5th day and inhibition of the persistent inflammatory state, seen by the reduction of edema and hyperemia on the 5th day of treatment. Using the same wound model in normoglycemic rats, the treatment with 0.1% PE-Cf reduced the inflammatory clinical signs: edema (5th day), hyperemia (2nd day), transudate (2nd day) and mechanical hyper-nociception (2nd and 5th days)[22]. The inflammatory pain, assessed by analgesimetry was also reversed by PE-Cf on the 5th day. It was demonstrated that PE-Cf (1 mg kg^{-1}) administered in mice by intravenous route inhibited the number of abdominal contortions, peripheral mechanical hyper-nociception, polymorphonuclear migration and the formation of paw edema induced by zymosan[21]. These authors suggested an association of the anti-inflammatory effect of PE-Cf to its anti-oxidant effect since it reduced the formation of pro-oxidants and increased that of anti-oxidants.

Cells have several antioxidant defense mechanisms that prevent ROS formation or neutralize ROS after being generated and when the concentration of ROS overwhelms the capacity of these oxidative stress mechanisms causes damage in biomolecules, such as DNA, proteins, lipids and other cellular components[7]. In diabetes, high oxidative stress plays major role in complications and impairs the healing process. Therefore, it is suggested that the attenuation of the inflammatory phase by PE-Cf could also be related to its anti-oxidant activity, seen by the demonstration of the reduced formation of malondialdehyde (MDA) and the inhibition of the activity of myeloperoxidase (MPO) in the same model of excision cutaneous wounds in normoglycemic animals[22].

Mononuclear assists in the healing process with immune system defense, debridement and regulatory functions. Its unbalanced polarization can be responsible for delayed wound healing[2,3,9]. In diabetes, macrophages show delayed phenotype transition since they can develop inflammatory-oxidative (M1) or anti-inflammatory-healing (M2) phenotypes. Additionally, the histological profile on the 2nd day already pointed to a well-established proliferative phase. PE-Cf may have recruited M2 macrophages attenuating the inflammatory response and stimulating fibroplasia (from the 2nd-7th-day post-wound) via modulation of Transforming Growth Factor beta (TGF-β)[3,22].

Probably due to the persistence of the inflammatory state caused by the condition of acute hyperglycemia, the administration of PE-Cf did not reduce neutrophil migration. In contrast, PE-Cf in normoglycemic rats reduced polymorphonuclear migration from the 2nd-5th day of treatment[22].

It is known that the period of the healing process occurrence is important, since the larger area of the lesion and the higher probability of microorganism's colonization may lead to infection and generate greater loss[25,26]. Because of the data obtained in the present study, which used topical application of PE-Cf in wounds of diabetic animals and the data obtained from normoglycemic rats[22] it was seen that the healing effect obtained after treatment with PE-Cf was accounted for the reduced wound area and the increased rate of healing (2^{nd}-10^{th} day), crust detachment (5^{th} day) and formation of scar tissue (10^{th} day) both in normoglycemic animals and in animals with acute hyperglycemia. It was previously suggested that the early closure of excisional cutaneous wounds was due to the modulation of the expression of the TGF-β on the 5^{th} day[22].

It is known that TGF-β via the Smad pathway is responsible for the proliferation of fibroblasts, synthesis and maturation of extracellular matrix components[27]. In animals with acute hyperglycemia, we can suggest that the migration of fibroblasts from the 5^{th} day and the increase in the healing rate from the 2^{nd} day of treatment may be influenced by the modulation of the inflammatory phase, possibly by TGF-β, released from macrophages, as suggested by de P. Pereira *et al.*[22] using of the same polysaccharide extract.

The state of acute hyperglycemia induced by alloxan had been shown to slow the healing of oral mucosa ulcers and to increase the expression of pro-inflammatory cytokines such as Tumour Necrosis Factor-alpha (TNF-α and leukocyte migration, as it reduces the deposition of total collagen, the expression of fibroblast growth factor and the migration of fibroblasts[3]. The acute hyperglycemia process is also associated to the reduction of neoangiogenesis from the 5^{th} day after the formation of oral mucosa ulcers[3]. In contrast, in cutaneous wounds of normoglycemic animals treated with 0.1% PE-Cf the formation of new vessels was increased from the 5^{th}-7^{th} day of treatment[22]. However, this study following Kazemi-Darabadi *et al.*[28] in which the number of newly formed vessels is lower in diabetics in comparison with normoglycemic animals, is justified by the weakness of the formation of new vessels in the acute hyperglycemia induced by alloxan. Thus, the present study contributes to the suggestion of the use of *C. ferrea* polysaccharide-rich extract as an alternative healing therapy for diabetics, validating the popular use of *C. ferrea* barks in inflammatory processes.

CONCLUSION

In conclusion, PE-Cf accelerates the diabetic healing process acting both in the inflammatory phase by the reduction of clinical signs and leukocyte infiltration and proliferative phase via an increase of fibroblast/myofibroblasts.

SIGNIFICANCE STATEMENT

Based on the healing effect previously demonstrated for the polysaccharide-rich extract of *C. ferrea* stem barks (PE-Cf) in normoglycemic rats, the purpose of this study was to test PE-Cf in the model of excisional cutaneous wounds in diabetic rats. The main findings obtained were the reduction of the wound area, hyper-nociception, crust detachment, scar tissue formation, leukocyte infiltration and increase in fibroblast/myofibroblast, suggesting that PE-Cf accelerates the healing process of diabetic rats, acting both in the inflammatory and proliferative phases. Thus, PE-Cf can be an alternative therapy to healing diabetic wounds.

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