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RANDOMIZED CONTROLLED CLINICAL TRIAL OF THE ANTIMICROBIAL EFFICACY OF GREEN PROPOLIS AGAINST BACTERIA PREVALENT IN PARTICIPANTS WITH CHRONIC WOUNDS, IN THE SERTÃO OF PARAÍBA-NE

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ABSTRACT

Propolis is used to treat a variety of ailments, including ulcer and wound healing. The phytochemical tracking of Brazilian propolis indicates the presence of flavonoids, biologically active ingredients. In the present study, we sought to evaluate the potential antimicrobial effect of Brazilian propolis on chronic wounds in humans, in an experimental study. This is a clinical trial of treatment, randomized, controlled, single-blind, used for 30 days, on an experimental basis in human beings, prospective 40 participants (20 intervention, treated with 5% green propolis ointment, 20 control, treated with AGE- essential fatty acid plus vitamins A and E). epithelialized, with a reduction to 4.8% of lesions with purulent exudate, 90.5% epithelialized the edges, and were clean-contaminated, 23.8% referred pain. In the control group, using AGE, 33.3% had epithelialization, 19% had purulent exudate, 57.1% epithelialized edges, 76.2% were clean-contaminated, 42.9% referred pain. Revealing the antimicrobial effects of Brazilian propolis, with the evolution of granulation tissue, reduction of necrotic tissue and formation of new epithelial tissue. The Brazilian green propolis, with topical application at 5%, promoted an expressive action in the tissue repair process. Thus, considering the relevance of its beneficial effects, propolis is a promising natural product for skin healing.

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INTRODUCTION

Chronic wounds, for purposes of concept, are those that do not evolve in an orderly repair process to produce anatomical and functional integrity within three months. Among them, we highlight pressure injuries, diabetic ulcers and chronic vasculogenic ulcers, as they are more frequent, deserve special attention (Vieira, 2018). In the early stages of chronic wound formation, Gram-positive microorganisms (especially Staphylococcus aureus) dominate. In later stages, gram-negative bacteria, such as E. coli and Pseudomonas aeruginosa, tend to invade deeper layers of the skin, causing severe tissue damage. Furthermore, staphylococci and streptococci were also found in 50% of wounds (Simões, 2018). Bacterial infections from chronic lesions are responsible for high rates of morbidity and mortality, as they are the most common infections and affect approximately 14 million people each year in the United States (Burnham, 2016). A relevant problem for the control and increase of morbidity from infections in skin lesions in hospitalized patients or outpatients is a growing resistance to antibacterial drugs, caused by indiscriminate and empirical use, where in most cases the time is not right (Menezes, 2021). Therefore, it is observed that the treatment of these infections needs to target possible microorganisms and then choose the appropriate antibacterial therapy for the sensitive microorganisms. In this perspective, scientific investigation of the therapeutic efficacy and safety of alternative treatment options for chronic wounds based on natural products with antimicrobial activity is necessary. Thus, the use of Brazilian green propolis, produced by bees, has as its main plant source the shrub Baccharis dracunculifolia (Asteraceae) found in southeastern Brazil (São Paulo and Minas Gerais). This natural product has compounds with important biological activities, such as antitumor and antimicrobial action due to the high content of flavonoids, coumaric acid and ferulic acid (Batista, 2012). Chemical characteristics such as the presence of phenylpropanoids including cinnamic acid, p-coumaric acid, caffeic acid, ferulic acid and its derivatives are found in green propolis. Premethylated cinnamic acids are responsible for the antimicrobial activity of green propolis.

The green propolis extract kept its quality unchanged for the storage condition for a period of 12 months at a constant temperature of 10ºC (Silva, 2006). Thus, a clinical investigation was carried out to assess the presence and identity of sensitive bacteria and antibiotics in chronic wounds, under the hypothesis that Brazilian green propolis is a positive reinforcement in the treatment of chronic infected wounds, in which the object study was a 5% green propolis-based ointment. The research is justified by the estimate that 75% of deaths after chronic ulcers are related to infections (Barud, 2013). Also, because green propolis is a product with low toxicity and low cost, it will contribute to a better prognosis for the person with chronic ulcers, and thus provide the health professional with a therapeutic formula to be dispensed, contributing to the improvement of Brazilian Public Health. In view of the above, this study aimed to evaluate the potential antimicrobial effect of 5% green propolis-based ointment on bacteria prevalent in participants with chronic wounds in the sertão of Paraíba-NE.

MATERIALS AND METHODS

Research Type: This is a randomized, controlled, single-blind clinical trial of treatment, with the purpose of analyzing the antibacterial efficacy of 5% green propolis-based ointment in chronic wounds. Research with experimental development in human beings, to assess the effect of health interventions, using knowledge to produce new materials, descriptive in order to identify possible relationships between variables and accurately provide the facts and phenomena of a reality of participants with chronic wounds, which required from the researcher a series of information about what one wanted to research, such as the population, sample, study objectives, hypotheses, assumptions, clinical characteristics and research questions (Souza, 2009).

Research Location: The research was carried out at the School Clinic of Faculdade Santa Maria, Cajazeiras (06º53'24"S; 38º33'43"W), Paraíba, Brazil. Alto Sertão Paraibano, far west of the state, with an altitude of 298 meters at sea level, 477 km from the capital João Pessoa, with a land area of 562,703 km² [2019], estimated population 62,289 people [2020], population density 103, 28 inhab/km² [2010] being considered the sixth largest city in Paraíba and with a Human Development Index – HDI of 0.679 (IBGE, 2020).

Population and Sample: Forty participants were prospected (20 intervention, treated with 5% green propolis ointment, 20 control, treated with essential fatty acid plus vitamins A and E, standard in the Brazilian Public Service). During the research, there were no losses and/or dropouts by the participants.

Inclusion and Exclusion Criteria: The study included people with chronic wounds of different etiologies, such as: vascular, diabetic and pressure ulcers, of both sexes and age groups, over 18 years old, adults and elderly registered at the School Clinic of Faculdade Santa Maria in Cajazeiras Paraíba. The prospecting was carried out by the researcher in conjunction with the community health agents, in each neighborhood, carrying out previous visits to identify the people who would perhaps participate in the research. Those who did not wish to participate in the research, malnourished people, pregnant women, children under 18 were excluded.

Sample selection: The selection took place at random, through a draw for hidden allocation of the sequence before applying the intervention, through opaque and sealed envelopes, in which the participants chose, containing the form for group A or B and were referred for the respective treatment, evaluated by the observer who followed for 30 days.

Data Collection Procedure and Instrument: Data collection took place in the same treatment environment, individually, through a previously elaborated instrument, completed on days zero, seventh, fourteenth and on the thirtieth day, by the same observer, considering the socio-demographic variables (name, age, profession, housing, sanitation conditions); clinical data (current illnesses, medications in use, alcohol consumption, smoking, topical allergy); participant assessment (blood pressure, pulses, temperature, mobility, lower limb edema, laboratory tests); assessment of the lesion (etiological hypothesis, location, microbial content, appearance of the peri-lesion, aspect and amount of exudate, bed color, pain, odor; written evolution; verification of vertical and horizontal medications, using a disposable ruler, and depth, using a cotton swab, and then measured on the ruler.

Therapeutic Application: During the application of the therapy, daily dressings were performed by the same observer, with the following sequence: the lesion was washed with saline solution at 0.9%, followed by cleaning with gauze from the center of the lesion to the periphery (peri-lesion), and the propolis ointment is applied, followed by a primary covering with gauze, irrigation with saline solution at 0.9% to keep the healing environment moist, and finally, a secondary covering with a band. On the first day of evaluation, the microbiological examination was performed by evaluating the Swab, or secretion culture. The material was collected in the Cytoanalysis Laboratory (CNPJ 12.433.420/0001-40) following the Good Clinical Laboratory Practices, then stored and transported in a cool box to a laboratory for analysis and identification of bacteria. Sample processing follows the microbiology routine already installed in the laboratory. Aerobic organisms were cultured in brain heart infusion broth and brain heart broth for 24 hours, followed by inoculation in blood agar, chocolate agar and macConkey agar.

Material Production

Propolis extract production process: The propolis is collected directly from the hives, through a scraping process; it is washed with distilled water and sanitized in a bath of 150 ppm active chlorine solution for 15 minutes, to reduce the microbial load arising from the collection of crude propolis. Let it dry in a dry heat oven at 45 ºC for 1 hour. This temperature range was chosen to cover the melting point of most propolis: 60 ºC to 70 °C. It is broken into small pieces reviewing the occurrence of possible debris not removed in the washing and is removed with tweezers or manually with sterile gloves. The solvent (cereal alcohol or white wine) is placed at a ratio of 1:10 in a sterilized glass container with a cloth lid for a minimum period of 10 days. Then filtering on sterilized filter paper and microbiological analyses. Once the product has no contamination, it was ready for the preparation of the ointment.

Propolis-based ointment production process: Product produced by the company Baldoni Produtos Naturais, under the responsibility of Mr. Gustavo Delfino Calomeni (according to the donation term). The lanovaselin-based ointment (simple ointment), composed of 30% Lanolin, synthetic antioxidant, 0.02% butyl hydroxytoluene (BHT), solid petroleum jelly q.s.p. 100%, where the propolis extract was added at a concentration of 5% by weight. The components were weighed, then the BHT was solubilized in q.s.p of liquid petroleum jelly, and then all the components were mixed with the propolis extract in a jar and placed in sterile containers to be tested on chronic wounds. Physical, chemical, and microbiological tests were performed, where appearance (25°C), color, density, water content (KF), content, total count of bacteria, molds and yeasts were verified.

Data Processing and Analysis: Data were organized according to CONSORT recommendations. Analyzed in SPSS statistical software (VERSION 24, 2018). Descriptive statistics of absolute and relative frequency, Pearson's chi-square test or Fisher's exact test. $P < 0.05$ was used for statistical significance.

Ethical aspects: The research took place from March to October 2018, after approval by the Research Ethics Committee (CAAE 64526217.9.0000.5180; Opinion No. 2.016.083) to ensure the confidentiality of personal information, complying with the formal requirements of the National Health Council/ Ministry of Health, which provides for research involving human beings pursuant to resolution 466/2012 (BRASIL, 2012).

This study followed the protocols necessary to assist the participant and their families, respecting them as to their autonomy and defending them in their vulnerability, by signing the informed consent form, guaranteeing the freedom to give up their participation in the group whenever they wish. Registration in the Brazilian Registry of Clinical Trials (ReBEC) No. RBR-294d68 (Dotsika, 2012).

RESULTS

Below is a description of the results in which the socio-demographic characterization of the sample, the relationship of bacteria isolated from the wounds, the sensitivity profile of the bacteria and the macroscopic characterization of the wounds can be observed. Regarding the characterization of the sample (Table 01), it was observed in the control group that most were female 13 (65%), elderly 14 (70%), married 10(50%), no education 17 (85%), retired 17 (85%), own residence 18 (90%) and with sanitation 19 (95%). In the intervention group, the male sex prevailed 12(60%), elderly 13(65%), married 11 (55%), without education 14 (70%), retired 14 (70%), own residence 20 (100%) and with sanitation 19 (95%).

Table 1. Socio-demographic characteristics of participants with chronic wounds treated with 5% green propolis or essential fatty acid

	Control group		Intervention group	
	n	%	n	%
Sex				
Male	7	35.0	12	60.0
Female	13	65.0	8	40.0
Age				
Adult (27 to 64 years old)	6	30.0	7	35.0
Elderly (65 to 95 years old)	14	70.0	13	65.0
Civil status				
Married	10	50.0	11	55.0
Widow(er)	6	30.0	6	30.0
Divorced	1	5.0	0	0.0
Not married	3	15.0	3	15.0
Scholarity				
No education	17	85.0	14	70.0
Literate	1	5.0	2	10.0
Incomplete elementary school	0	0.0	1	5.0
Complete primary education	2	10.0	0	0.0
Medium	0	0.0	2	10.0
Higher	0	0.0	1	5.0
Profession				
Retired	17	85.0	14	70.0
Self employed	3	15.0	4	20.0
Attorney	0	0.0	1	5.0
Machine operator	0	0.0	1	5.0
Residence				
Own	18	90.0	20	100.0
Shelter	1	5.0	0	0.0
Settlement	1	5.0	0	0.0
Sanitation				
With sanitation	19	95.0	19	95.0
Without sanitation	1	5.0	1	5.0

Regarding the bacteria isolated from the participants' chronic wounds, the most frequent in the control group was Pseudomonas aeruginosa 7 (35%), for the intervention group it was Pseudomonas aeruginosa 4 (20%), Klebsiella pneumoniae 4 (20%) or Pseudomonas sp. 4 (20%) (Table 2). Regarding the sensitivity profile of the bacteria isolated from the chronic wounds of the participants, for the control group, 12 (60%), as well as for the intervention group, 17 (85%), aminoglycosides were the class of antimicrobials with the highest sensitivity (Table 3). Table 4 shows the macroscopic characteristics of the chronic wounds. Although 20 participants were recruited for both groups, we assessed 21 wounds for each group totaling 42 wounds. The evaluation of the type of tissue in the control group revealed a predominance of necrotic tissue in 8 (38.1%) lesions evaluated on the first day and for the thirtieth day, the presence of granulation tissue prevailed 8 (38.1%) (P=0.021).

Table 2. List of bacteria isolated from chronic wounds of participants treated with 5% green propolis or essential fatty acid

	Control group		Intervention group	
	N	%	n	%
Pseudômonas aeruginosa	7	35.0	4	20.0
Pseudômonas sp	1	5.0	4	20.0
Klebsiella pneumoniae	3	15.0	4	20.0
Escherichia coli	2	10.0	3	15.0
Citrobacter freudii	0	0.0	1	5.0
Proteus sp	4	20.0	0	0.0
Staphylococcus aureus	2	10.0	1	5.0
Acintobacter baumannii	0	0.0	1	5.0
Enterobacter aerogenes	0	0.0	1	5.0
Without bacteria	1	5.0	1	5.0

For the intervention group, there was a higher frequency of necrotic tissue 13 (61.9%) on the first day and granulation tissue 10 (47.6%) on the thirtieth day (P<0.001). As for the type of exudate, in the control group, most lesions had purulent exudate 12 (57.1%) on the first day and serous exudate 10 (47.6%) on the thirtieth day (P=0.011). For the intervention group, purulent exudate 10 (47.6%) or serous exudate 10 (47.6%) on the first day and serous exudate 10 (47.6%) 10 (47.6%) on the thirtieth day (P=0.002) prevailed. Regarding the characteristics of the edge of the lesion, the majority of the control group had an epithelialized edge on the first day 11 (52.4%) and on the thirtieth day 12 (57.1%) (P=0.885).

Table 3. Sensitivity profile of bacteria isolated from chronic wounds of participants treated with 5% green propolis or essential fatty acid

	Control group		Intervention group	
	N	%	n	%
No Antibiotic	1	5.0	1	5.0
Amphenchols	2	10.0	0	0.0
Aminoglycoside	12	60.0	17	85.0
Betalactam	5	25.0	2	10.0

For the intervention group, the epithelialized edge prevailed on the first day 12 (57.1%) and on the thirtieth day (90.5%) (P=0.049). For regularity of the edge, in the control group, irregular edge 12 (57.1%) on the first day and regular edge 13 (61.9%) on the thirtieth day (P=0.217) predominated. For the intervention group, regular border prevailed on the first day 13 (61.9%) and on the thirtieth day 18 (85.7%) (P=0.277). Regarding microbiological characteristics, it was observed that in the control group, most lesions were classified as clean-contaminated lesions on the first day 10 (47.6%) and on the thirtieth day 16 (76.2%) (P=0.012). While in the intervention group, the classification as infected lesion 9 (42.9%) on the first day and clean contaminated on the thirtieth day 19 (90.5%) prevailed (P<0.001). When reporting pain, most of the control group reported the presence of pain 14 (66.7%) on the first day and absence of pain 12 (57.1%) on the thirtieth day (P=0.121). In the intervention group, the report of pain 13 (61.9%) on the first day and absence of pain 16 (76.2%) on the thirtieth day prevailed (P=0.013).

DISCUSSION

In the present study, we sought to evaluate the potential antimicrobial effect of Brazilian propolis on chronic wounds in humans, in an experimental study. Thus, according to the socio-demographic findings, it was observed that the control group was mostly female, and the male gender prevailed for the intervention group. For the other variables, a similar result in both groups, which reveals a homogeneous pattern, which may give security to the findings, since the participants may show similarities in the pattern of illness. In the microbiological findings of chronic wounds in this investigation, most gram-negative bacteria were isolated, with *Pseudomonas aeruginosa* being the most prevalent in the control group or *Pseudomonas aeruginosa, Pseudomonas sp., Klebsiella pneumonae* in the intervention group.

Table 4. Macroscopic characterization of chronic wounds of participants treated with 5% green propolis or essential fatty acid

	Control		Intervention	
	1st day	30th day	1st day	30th day
Kind of tissue				
Necrosis	8 (38.1%)	6 (28.6%)	13 (61.9%)	2 (9.5%)
Slough	2 (9.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Granulation	11 (52.4%)	8 (38.1%)	8 (38.1%)	10 (47.6%)
Epithelialization	0 (0.0%)	7 (33.3%)	0 (0.0%)	9 (42.9%)
p-value	0.021		<0.001	
Type of bed exudate				
None	0 (0.0%)	6 (28.6%)	0 (0.0%)	6 (28.6%)
Serous	9 (42.9%)	10 (47.6%)	10 (47.6%)	10 (47.6%)
Bloody	0 (0.0%)	1 (4.8%)	1 (4.8%)	4 (19.0%)
Purulent	12 (57.1%)	4 (19.0%)	10 (47.6%)	1 (4.8%)
p-valor	0.011		0.002	
Boundary Characteristics				
Epithelialized	11 (52.4%)	12 (57.1%)	12 (57.1%)	19 (90.5%)
Crust	7 (33.3%)	7 (33.3%)	4 (19.0%)	1 (4.8%)
Macerated	3 (14.3%)	2 (9.5%)	5 (23.8%)	1 (4.8%)
p-value	0.885		0.049	
Boundary regularity				
Irregular	12 (57.1%)	8 (38.1%)	14 (66.7%)	18 (85.7%)
Regular	9 (42.9%)	13 (61.9%)	7 (33.3%)	3 (14.3%)
p-value	0.217		0.277	
Microbial Characteristics				
Clean	0 (0.0%)	3 (14.3%)	0 (0.0%)	2 (9.5%)
Clean-contaminated	10 (47.6%)	16 (76.2%)	8 (38.1%)	19 (90.5%)
Infected	8 (38.1%)	2 (9.5%)	9 (42.9%)	0 (0.0%)
Critical colonization	3 (14.3%)	0 (0.0%)	4 (19.0%)	0 (0.0%)
p-value	0.012		<0.001	
Pain				
Absent	7 (33.3%)	12 (57.1%)	8 (38.1%)	16 (76.2%)
Present	14 (66.7%)	9 (42.9%)	13 (61.9%)	5 (23.8%)
p-value	0.121		0.013	
Total	21 (100%)	21 (100%)	21 (100%)	21 (100%)

The presence of gram-negative and gram-positive bacteria in chronic wounds has a great negative influence, delaying the tissue repair process, forming a biofilm barrier. This biofilm barrier protects bacteria from external threats, providing a reservoir of potentially infectious microorganisms that are resistant to antibacterial agents, causing them to fail in the medical devices used to deter them, further favoring inflammatory and chronic conditions (Skrlin, 2016). Corroborating our findings, a survey conducted in swab cultures and biopsy in chronic wounds of different etiologies, gram negative bacteria, specifically Pseudomonas aeruginosa, prevailed (Tolera, 2018). Vasculogenic lesions are usually the foci of gram-negative bacteria, the most prevalent being the bacterium *Pseudomonas aeruginosas*. This can be explained by the need for invasive procedures that these patients have during the healing process for the treatment of vascular involvement. In addition, poorly oxygenated environments create a hostile environment, selecting the most resistant bacteria, which include *Pseudomonas aeruginosa* (SAMAD, 2018).

Thus, the antibacterial activity of propolis must be considered as a therapeutic possibility since, in the first place, it is related to the direct effect on microorganisms, the other is to stimulate the immune system, leading to the activation of the body's natural defenses (Przybyłek, 2019). The analysis of the mechanisms of propolis allows us to infer its influence on membrane permeability and membrane rupture of microbial cells, preventing the production of adenosine tryptophan (ATP) and reducing bacterial mobility (Medeiros, 2019). This mechanism of propolis is understood based on the intervention in the process of cell division, changes in the plasma membrane and also on the possible alteration of cell walls, resulting in bacteriolysis that can generate osmotic imbalances, proving the successful results obtained with the use of propolis (Campos, 2017). As for the sensitivity of bacteria isolated from the chronic wounds of the participants, it was evidenced from our results that, for the control group, as well as for the intervention group, aminoglycosides were the class of antimicrobials with the highest sensitivity. To this end, it is worth noting that the sensitivity of gram negative bacteria to antibiotics of the aminoglycoside class can be explained, due to the fact that this class of antibiotic has bactericidal activity, with the broadest spectrum of action of the class, effective against gram-negative, but it should only be used in the short term in cases of severe infections, given the risk of ototoxicity and nephrotoxicity (BRASIL). Referring to the macroscopic characterization of the chronic wounds of the participants treated with 5% green propolis or with essential fatty acid, it can be inferred that regarding the type of tissue, type of exudate and microbiological characteristics, both treatments, after a period of thirty days, promoted significant change of these parameters in tissue repair. However, on the characteristics of the edge of the lesion and pain report, only the treatment with 5% green propolis showed a significant result. However, for edge regularity, both treatments were ineffective after a period of thirty days. In this perspective, a research using green propolis in wounds found a reduction in the mean diameters of the lesions, reaffirming its healing action by not presenting inflammatory reactions and inducing epithelial formation such as vascular and fibroblastic neoformation of connective tissue (Nogueira, 2018). In another study that sought to investigate the effect of propolis-based ointment on the surface of chronic wounds, where 8.2% of these lesions had necrotic tissue, however after intervention with the use of the ointment, the permanence of necrosis was totally excluded, as well as the reports of pain were reduced, showing that propolis also has an analgesic effect (Freires, 2019).

This healing effect can be attributed to the fact that propolis has positive results in collagen synthesis, mainly by replacing type III collagen with type I collagen, increasing the amount of hydroxyproline (the main component of type I collagen), accelerating healing and wound closure (Hozzein, 2015). Another important factor for wound healing by propolis is its antimycobian activity, as well as reducing biofilms and resulting in accelerated healing processes (Oryan, 2018). In addition, a study conducted with 20 people with chronic wounds, whose purpose was to assess the intensity of pain after treatment with propolis ointment, found that most participants (42.9%) reported the presence of mild pain. Thus, the analgesic effect could be observed during the follow-up with the propolis ointment, as

patients reported pain improvement (Santos, 2007). In this way, confirming the results observed in the present study, where only the intervention group treated with the propolis-based ointment managed to improve the pain of the participants when compared to the use of AGE. Based on the results achieved in this investigation, it can be summarized that gram-negative bacteria were isolated from the chronic wounds of the participants, with *Pseudomonas aeruginosa* being the most prevalent in the control group or Pseudomonas aeruginosa, Pseudomonas sp., *Klebsiella pneumonae* in the intervention group, and *Pseudomonas aeruginosa* in the intervention group and aminoglycosides were the class of antimicrobials with the highest sensitivity. For tertidual repair and evaluation of microbiological characteristics, both treatments were effective, but on the characteristics of the lesion edge and pain report, only the treatment with 5% green propolis was effective. Thus, our investigation showed optimistic results in the parameters evaluated in chronic wounds and from these it can be inferred that 5% green propolis, being a natural product, available at low cost, with good tolerance, ease of handling, presented expressive action in the tissue repair process, significantly improving the quality of life of people with injuries. Thus, considering the relevance of its beneficial effects, propolis is a promising natural product for skin healing.

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