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TOPICAL USE OF GREEN PROPOLIS FOR WOUND HEALING: A SYSTEMATIC REVIEW OF THE LITERATURE

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ABSTRACT

Objective: To systematically identify the effectiveness of the topical use of green propolis in the healing process of surgical wounds. **Methods:** Systematic review of the literature that considered the publications available in the databases: National Library of Medicine (PubMed/MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. The risk of bias of the studies was analyzed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) tool. **Results:** The four studies analyzed used green propolis for the healing of surgically made lesions. All the selected studies were of experimental methodology, performed with animals. Two studies (50%) used the ethanolic extract of green propolis (at concentrations of 2.4% and 20%) and the other two studies (50%) used the hydroalcoholic extract of green propolis at 5.0%. **Conclusion:** The results showed that the topical use of formulated products based on green propolis promoted the healing of skin lesions, since it favored angiogenesis, the proliferation of fibroblasts and, consequently, the synthesis and deposition of collagen, as well as showed antimicrobial activity and showed.

DESCRIPTORS: Propolis. Wounds and injuries. Healing. Pharmacognosy. Enterostomal therapy. Systematic review.

USO TÓPICO DA PRÓPOLIS VERDE PARA A CICATRIZAÇÃO DE FERIDAS: REVISÃO SISTEMÁTICA DA LITERATURA

RESUMO

Objetivo: identificar sistematicamente a efetividade do uso tópico da própolis verde no processo de cicatrização de feridas cirúrgicas. **Método:** revisão sistemática da literatura que considerou as publicações disponíveis nas bases de dados *National Library of Medicine* (PubMed/Medline), *Latin American and Caribbean Health Sciences Literature* (LILACS), *The Cumulative Index to Nursing and Allied Health Literature* (CINAHL) e *Web of Science*. O risco de viés dos estudos foi analisado por meio da ferramenta *Systematic Review Centre for Laboratory animal Experimentation* (SYRCLE). **Resultados:** os quatro estudos analisados utilizaram a própolis verde para a cicatrização de lesões confeccionadas cirurgicamente. Todos os estudos selecionados foram de metodologia experimental, realizados com animais. Dois estudos (50%) utilizaram o extrato etanólico de própolis verde (nas concentrações de 2,4% e 20%) e os outros dois estudos (50%) usaram o extrato hidroalcóolico de própolis verde a 5%. **Conclusão:** os resultados evidenciaram que o uso tópico dos produtos formulados à base de própolis verde promoveu a cicatrização de lesões de pele, uma vez que favoreceu a angiogênese, a proliferação de fibroblastos e, consequentemente, a

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síntese e deposição de colágeno, bem como demonstrou atividade antimicrobiana e não apresentou toxicidade tissular, fatores esses que são considerados importantes para o processo de reparação tecidual.

DESCRITORES: Própolis. Ferimentos e lesões. Cicatrização. Farmacognosia. Estomaterapia. Revisão sistemática.

USO TÓPICO DE LA PROPÓLEO VERDE PARA LA CICATRIZACIÓN DE HERIDAS: REVISIÓN SISTEMÁTICA DE LA LITERATURA

RESUMEN

Objetivo: identificar sistemáticamente la efectividad del uso tópico del propóleo verde en el proceso de cicatrización de heridas quirúrgicas. Método: Revisión Sistemática de la Literatura que consideró las publicaciones disponibles en las bases de datos PubMed/Medline, LILACS (BVS), The Cumulative Index to Nursing and Allied Health Literature (CINAHL) y Web of Science. El riesgo del sesgo de los estudios fue analizado por medio de la herramienta Systematic Review Centre for Laboratory animal Experimentation (SYRCLE). Resultados: los cuatro estudios analizados utilizaron el propóleo verde para la cicatrización de lesiones confeccionadas quirúrgicamente. Todos los estudios seleccionados fueron de metodología experimental, realizados con animales. Dos estudios (50 %) utilizaron el extracto etanólico de propóleo verde (en concentraciones de 2,4 % y 20 %) y los otros dos estudios (50 %) usaron el extracto hidroalcohólico de propóleo verde al 5 %. Conclusión: Los resultados evidenciaron que el uso tópico de los productos formulados a base de propóleo verde promovió la cicatrización de lesiones de piel, debido a que favoreció la angiogénesis, la proliferación de fibroblastos y, en consecuencia la síntesis y deposición de colágeno, así como también demostró actividad antimicrobiana y no presentó toxicidad tisular, factores estos que son considerados importantes para el proceso de reparación de tejidos.

DESCRIPTORES: Propóleo. Heridas y Lesiones. Cicatrización. Farmacognosia. Estomaterapia; Revisión Sistemática.

INTRODUCTION

Propolis is a resin produced by bees and has been used since ancient times as a medicine to treat skin lesions or other ailments. Bees collect exudates from trees, plants, leaves and the pollen of various flowers which, associated with the salivary secretions of these insects, form the resinous material[1,2].

Green propolis can be found in countries such as Uruguay, Argentina, and Brazil. Its botanical origin is mainly the *Baccharis dracunculifolia* DC, also popularly known as "alecrim-do-campo" and "vassourinha". This type of propolis is composed of flavonoids, prenylated derivatives of p-coumaric acid, artepillin C, diterpenes, and triterpenes, among others. It is commercialized *in natura*, in the form of extracts, gels, ointments, oils, shampoos, or associated with other compounds[2-4].

Its antimicrobial, anti-inflammatory, antioxidant, anesthetic, immunomodulatory, and cicatrizing properties, among others, have been described in the literature.[1-6]. Over the years, more than 200 elements have been described in the chemical composition of propolis, among them flavonoids, fatty and phenolic acids, vitamins (C, E, B complex), minerals (iron, zinc, calcium and potassium), proteins, aromatic aldehydes, alcohols and amino acids[6-8].

The flavonoids are the main components of propolis and are considered responsible for its healing effect, acting as an antioxidant and antimicrobial agent, exerting an immunomodulatory and anti-inflammatory function, and favoring the action and absorption of vitamins[6-8].

Tissue healing begins after injury of any nature, and is considered a complex and dynamic process that involves chemical, biological, and physical phenomena. It is composed of the stages of hemostasis, inflammatory, proliferative and remodeling phases, which occur simultaneously and interdependently, depending on the type of injury present (acute or chronic) and its location[9,10]. A recent study describes the stages of the skin healing process and the possible failures that can lead to its delay, enabling the discussion of these issues and the development of strategies by nurses involved in wound care[10].

Acute injuries are those that originate from trauma or surgery and, if no complications occur during the healing process, the time required for tissue repair is shorter than in chronic injuries[11]. Some of the most common complications of acute injuries are infection, seroma, hemorrhage, hematoma, dehiscence, necrosis, and changes related to the tissue repair process, such as hypertrophic scarring or keloid. Age, smoking, immunosuppression, individuals with renal failure, previous infection at the surgical site, location and time of surgery, highly stressed sutures, emergency surgeries, among others, are considered risk factors for these complications[12].

Complex wounds, whether acute or chronic, generate great personal, social and economic impact due to the prolonged healing time and the costs involved in the treatment, since they generate discomfort and pain, besides causing changes related to the well-being and self-image of the affected individuals, since they often limit participation in domestic, social and work activities[13,14].

Pressure, diabetic and venous ulcers stand out as the most prevalent and incident complex chronic wounds in Brazil, especially in the elderly population[15,16]. The treatment of these lesions is challenging and requires specialized care by nurses, since they are associated with comorbidities, such as vasculopathies, malnutrition, diabetes mellitus, autoimmune diseases[13,14].

Since ancient times, natural products derived from plants as well as other substances of plant or animal origin have been used by humans for medicinal purposes, including healing of skin lesions, due to factors such as resource availability, low cost, and different cultures involved[9,17,18].

Several products are currently available in the market for wound treatment, and the technological and scientific advances require constant updating of knowledge by nurses to favor clinical decision making. Products aiming at tissue repair and the prevention of complications, that promote skin protection, control exudate, reduce the microbial load, promote debridement of devitalized tissues, among others, can be found[13,14].

Several countries, including Brazil, are creating laws and regulating the use of natural products for the treatment of wounds or diseases, taking into consideration their effectiveness, the safety criteria that involve their manufacture, and the quality of the material used. The Brazilian Ministry of Health, through the National Policy of Integrative and Complementary Practices (NPICP), defines the responsibilities for implementing these practices[19].

In 2021, the Ordinance No. 702 of 2018 regulated the use of products produced by bees for health promotion and maintenance, also considering apitherapy as a complementary treatment for conditions described since ancient times, such as skin lesions[14]. Such products must have their mechanisms of action and toxicological effects evaluated and scientifically proven, just like other marketed drugs[19].

Considering the complexity involved in the treatment of different skin lesions, the present study aimed to systematically identify the effectiveness of the topical use of green propolis in the healing process of surgical wounds in animals.

METHODS

This is a systematic review of the literature, whose report adopted the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and its protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO), with number CRD42020187904[20,21].

The PICO strategy was used to guide this review: Patient/population/problem of interest (P): rats; (I) Intervention / area of interest: use of green propolis; Comparison (C) - not applicable; and Outcomes (O) - efficacy in surgical wound healing. The present study was conducted based on the guiding question: Is green propolis effective in the healing of surgical wounds in animals?

The sample was selected through an electronic search, from November 2019 to March 2020, in the databases National Library of Medicine (PubMed/MEDLINE), Latin American and Caribbean Health Sciences Literature (LILACS), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science via CAPES portal. Among the selected articles, manual searching of their reference lists was performed, as well as using the gray literature

search through Google Scholar and OpenGrey in order to find any additional studies that might have been missed in the electronic search.

The following descriptors were used in the search strategy for the studies in PubMed/MEDLINE, taken from the Medical Subject Headings (MeSH): ("propolis" OR "green propolis") AND ("wound healing" OR "wound" OR "skin injuries" OR "surgical wound"). For the search of the articles in LILACS the following DeCS descriptors were added to the MeSH descriptors: ("propolis" OR "green propolis" OR "própolis") AND ("wound healing" OR "wound" OR "cicatrização) AND "skin injuries" OR "surgical wound" OR "ferimentos e lesões").

The inclusion criteria established for the selection of articles were: original experimental studies, available in full, written in Portuguese, English, or Spanish that covered the theme of this review. There were no restrictions as to the year of publication of the articles, so that the search would cover as many studies as possible.

Articles that did not meet the inclusion criteria and duplicate articles in the databases were excluded with the aid of the Mendeley tool. Also, those studies that did not specify the type of propolis used or associated green propolis with other compounds (e.g., collagen matrix), or that used propolis to treat other types of lesions (ocular, mucosa or chronic lesions); case reports or series, reviews, letters or texts of personal opinion, book chapters, and abstracts of papers presented at conferences were also excluded.

In the first stage, the Covidence tool was used to facilitate the team's investigation and data extraction. Two reviewers examined the titles and abstracts independently of the previously selected articles that appeared to meet the inclusion criteria set by the researchers.

In the second stage, the same researchers read all the texts that were selected in their entirety, also independently, excluding those that did not meet the research criteria. The disagreements, in both stages, were discussed and resolved between the two reviewers by reaching a consensus, with no need to involve a third reviewer.

The risk of bias of the studies selected for qualitative synthesis was assessed using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) tool, which is an adapted version of the Cochrane Collaboration Risk of Bias Tool, commonly used for evaluation of randomized clinical trials[22].

SYRCLE was adapted and validated for the evaluation of experimental studies involving animals in 2014, including the assessment of group allocation (experimental and control), description of animal characteristics, adequacy of animal allocation and cage distribution/storage, blinding of investigators, randomization of animals for outcome assessment, inclusion of all animals in the outcome assessment of the experiment, protocol recording, primary and secondary outcomes, and identification of other issues that may indicate a high risk of bias[22].

The evaluation of the items proposed by the SYRCLE tool was performed by two reviewers, and again there was no need to involve a third reviewer at this stage. Evaluation was by means of the answers: "yes" to indicate a low risk of bias, "no" to indicate a high risk of bias, and "unclear" to indicate that the topic evaluated presents insufficient data for the evaluation of the risk of bias.

Kappa coefficient was applied to statistically evaluate the interobserver agreement on the items 1, 6, 7, 8, 9 and 10[22]. Values lower than 0.00 were considered as no agreement; 0.00 to 0.20 weak; 0.21 to 0.40 mild; 0.41 to 0.60 moderate; 0.61 to 0.80 good; 0.81 to 1.00 as optimal, considering a 95% confidence interval[23]. The software Statistical Package for the Social Sciences (SPSS), version 23.0 was used for the calculation of this coefficient.

For the descriptive analysis of the selected articles, the data obtained were organized in a table, according to the variables "year of publication and country", "objective", "sample characterization", "intervention in the experimental group", "intervention in the control group", and "main findings".

RESULTS

In the first stage of this review, 325 articles were identified in four databases. After removing the duplicates, 301 articles remained. In the gray literature, 568 studies were found, but 10 were excluded for being duplicates, leaving 558 articles, added to the other 301 in the databases for title and abstract analysis.

After a meticulous review of the titles and abstracts of the articles, only 10 articles were selected for the second stage, 2 of which were from the gray literature (Google Scholar). The manual search for articles through the reference lists of those that were selected did not provide any additional studies.

In the second step, the 10 articles were analyzed in full, and this process led to the exclusion of 6 articles. In total, 4 articles were selected for data extraction and qualitative synthesis, as described in the following flowchart (Fig. 1).

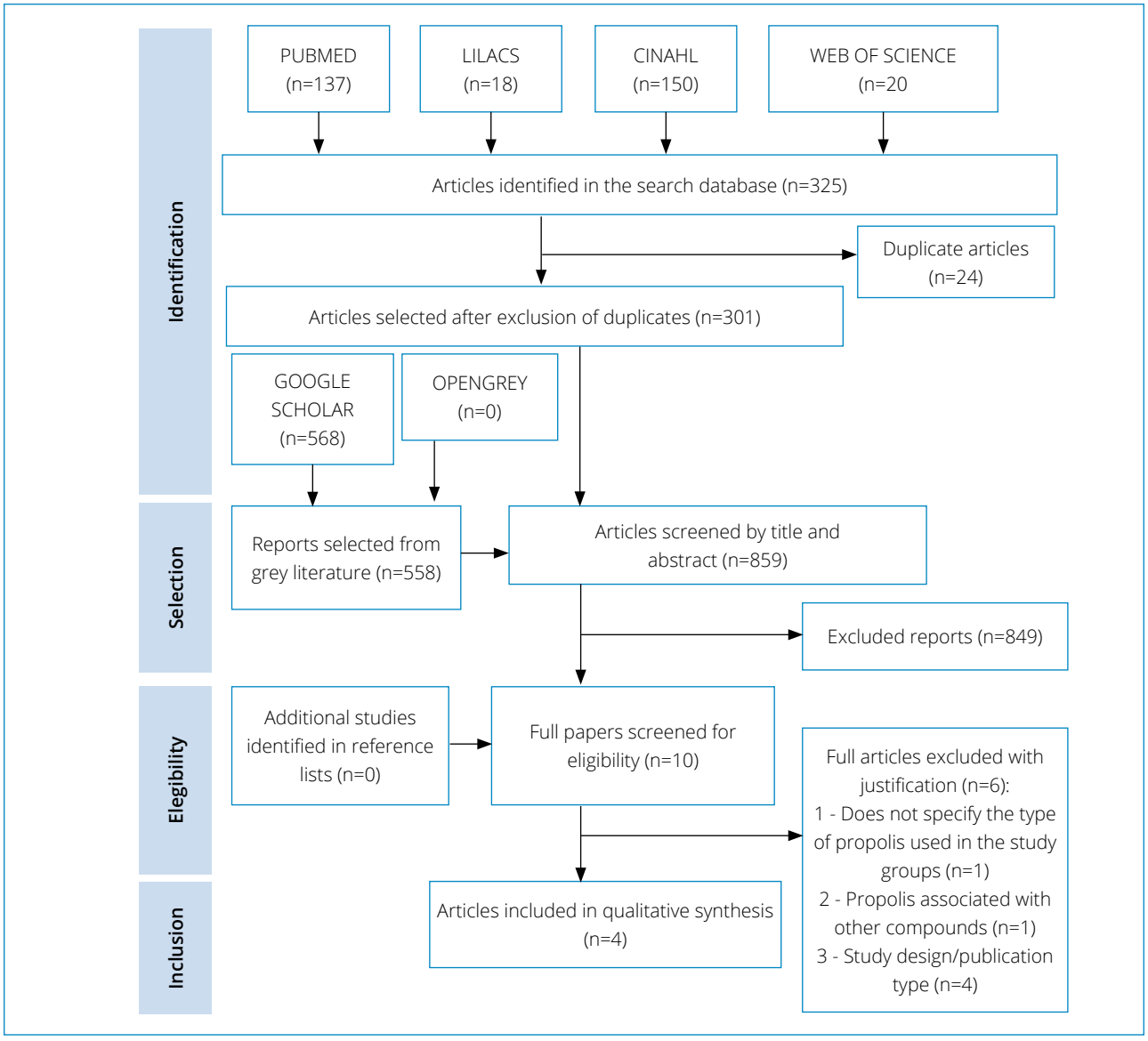

Figure 1. Flowchart of the literature search and selection process. Brasília (DF), Brazil – 2020.

Table 1 summarizes the characteristics of the studies selected for this systematic literature review as assessed by reviewers 1 and 2, according to the methodological quality criteria described in the SYRCLE tool.

Concerning the level of agreement between the reviewers, comparing the dependent variables analyzed in Table 1, the value found for the Kappa coefficient was 0.861 (95%CI [0.127–4.642]; $p < 0.001$), showing an optimal interobserver agreement.

Table 1. Assessment of methodological quality criteria based on the SYRCLE tool by reviewers 1 and 2. Brasília (DF), Brazil – 2020.

Authors	Batista LLV et al, 2012[8]		Barud HS et al, 2013[24]		Mezadri TJ et al, 2009[25]		Staak Junior MC et al, 2011[26]	
Topics	**R1**	**R2**	**R1**	**R2**	**R1**	**R2**	**R1**	**R2**
1- Was the allocation sequence generated and applied properly?	unclear	yes	no	no	no	no	no	no
2- Were the groups similar at the beginning or were they adjusted based on confounding variables in the analysis?	yes	yes	yes	yes	yes	yes	yes	yes
3- Was the allocation of the animals to the different groups adequately concealed during its performance?	unclear	unclear	no	no	no	unclear	no	no
4- Were the animals randomly housed during the experiment?	unclear	unclear	no	no	no	unclear	no	no
5- Were the caregivers and/or researchers blinded to the intervention that each animal received during the experiment?	no	no	no	no	unclear	unclear	no	no
6- Were the animals randomly selected for evaluation of the outcome?	no	no	no	unclear	no	no	no	unclear
7- Was the evaluator of the results blinded?	no	no	yes	yes	no	no	no	no
8- Has data on incomplete results been adequately worked out?	unclear	unclear	unclear	unclear	yes	yes	yes	yes
9- Is the study free of selective outcome registration?	yes	yes	yes	yes	yes	yes	yes	yes
10- Was the study apparently free of other problems that could result in a high risk of bias?	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear

R1 = reviewer 1; R2 = reviewer 2.

Concerning the level of agreement between the reviewers, comparing the dependent variables analyzed in Table 1, the value found for the Kappa coefficient was 0.861 (95%CI [0.127–4.642]; $p < 0.001$), showing an optimal interobserver agreement.

Of the four articles selected, 25% were national studies published in Portuguese (n = 1) and 75% were international studies published in English (n = 3). Regarding the area of publication, 50% correspond to biomedicine (n = 2), 25% to medicine (n = 1) and 25% to pharmacy (n = 1).

As to the use of green propolis, 50% of the researchers (n = 2) used the ethanolic extract of propolis (at concentrations of 2.4% and 20%) associated with other semisolid vehicles such as ointment (lipophilic) and gel (hydrophilic), and the other 50% (n = 2) used the 5% hydroalcoholic extract of propolis, associated with a hydrophilic semisolid vehicle (gel). None of the studies applied pure propolis extract to the lesions.

The healing time of surgical wounds reported in the articles ranged from 3 to 15 days, and the average time was 10.75 days.

By systematically and qualitatively evaluating the selected publications, a synthesis of the studies was prepared according to the year of publication, objective, intervention in the experimental group, intervention in the control group, and main findings (Table 2).

Table 2. Characterization of articles with the application of green propolis for the healing of skin lesions as the object of study. Brasília (DF), Brazil – 2020.

Authors and year of publication	Objective	Sample characterization	Intervention in the experimental group	Intervention in the control group	Main findings
Batista LLV et al, 2012[8]	To compare the healing action of green and red propolis by correlating it to the flavonoid content.	20 healthy adult male rats of the Wistar strain, with a body weight of 200 + 25 g.	Application of ointment based on 20% fluid ethanolic extract of green propolis in one group (n = 5) and ointment based on 20% fluid ethanolic extract of red propolis in another group (n = 5).	Application of ointment base (lanolin + Vaseline in a 3:7 ratio) in the positive control group (n = 5) and saline solution in the negative control group (n = 5).	The total flavonoid content of the ethanolic extract of green and red propolis were high; however, it was observed that green propolis was more effective in the repair process of lesions in rats.
Barud HS et al, 2013[24]	To demonstrate the antimicrobial and wound-healing activity of green propolis.	24 healthy adult male rats of the Holtzman strain, with body weight of approximately 250 g. For antimicrobial activity analysis, the microorganisms (S. aureus and S. epidermidis) were inoculated on plates.	In the experimental group (n = 8) the biocellulose gel plus 2.4% ethanolic fluid extract of green propolis was applied.	In the positive control group (G1) the pure biocellulose gel was used (n = 8). The negative control group (G3) received no treatment (n = 8).	The biocellulose gel plus the ethanolic extract of green propolis showed lesion healing in less time when compared to the other groups, as well as greater antimicrobial activity. Despite this, the macroscopic evaluation of the three groups showed no statistical significance ($p > 0.05$).
Mezadri TJ et al, 2009[25]	To evaluate the topical action of green propolis on wound contraction by means of its macroscopic characteristics and lesion measurement using digital images.	10 healthy adult female rats of the Wistar strain, with body weight between 200–250 g.	The experimental group (lesions 1 and 4) was treated with carboxymethylcellulose gel plus 5% fluid hydroalcoholic extract of propolis.	The control group (lesions 2 and 3) received no treatment.	The groups were followed for 10 days and, at the end of the experiment, all showed complete healing of the lesions (no macroscopic differences were observed). The methodology used did not prove to be a good indicator to assess the process of tissue repair in this case.
Staak Junior MC et al, 2011[26]	To evaluate the topical action of green propolis on wound healing by counting inflammatory cells using light microscopy.	10 healthy adult female rats of the Wistar strain, with body weight between 200–250 g.	The experimental group (n = 5) was treated with carboxymethylcellulose gel plus 5% fluid hydroalcoholic extract of green propolis.	The control group (n = 5) received no treatment.	After 24 hours, the experimental group showed a higher number of macrophages, leukocytes and fibroblasts when compared to the control group ($p < 0.05$). The results showed an increase in the cells present in the inflammatory and proliferative phases of healing, indicating the satisfactory action of the product in the process of tissue repair.

DISCUSSION

In this systematic review, it was observed that all the articles analyzed have descriptive methodology, of the experimental type, carried out with rats. The data analysis revealed that in all experiments propolis extract in different concentrations were used. Studies differ on the concentration of propolis needed to promote healing of skin lesions, as there was a range from 2.4 to 20.0%. Despite this, there were favorable results regarding the healing process of injuries with the use of green propolis in animals[8,24-26].

Fifty percent of the studies used the fluid ethanolic extract of propolis (n = 2) and the other 50% used the fluid hydroalcoholic extract (n = 2), associated with ointments or gels to convey the active compounds present in the resin, without adding other actives that could interfere in the process of tissue repair. By the methodology implemented in the experiments, the use of both types of extracts associated with semisolid vehicles proved to be effective in the healing of skin lesions; however, it was not possible to determine significant differences in healing time when comparing the two forms of presentation of green propolis (ointment or gel).

It is worth highlighting that the use of antiseptic solutions in wounds, such as alcohol, povidone iodine, sodium hypochlorite and chlorhexidine is not recommended, since they interfere in the synthesis of collagen, promote bacterial resistance, cause skin irritation, among other factors that impair the process of tissue repair[27,28]. In the studies analyzed, the presence of alcohol in green propolis extract did not seem to negatively interfere with the surgical wound healing process, since it was used as a resin stabilizer in the formulation and was associated with semisolid vehicles that had water in their composition.

Only two of the selected studies specified the amount of product applied to the lesions. In the study by Batista et al., 1 mL of the ointment containing the ethanolic extract of propolis was used on the lesions[8]. Meanwhile, in the study by Staak Junior et al., 34 mg of the gel containing the hydroalcoholic extract of green propolis was used on the lesions made in the animals[26]. Analyzing all the selected studies, this factor did not seem to influence the healing process of the lesions made in the animals.

The healing time was evaluated in two ways: microscopic analysis by making a histological slide and collecting blood samples from the animals for biochemical analysis (total cholesterol, triglycerides, albumin, glutamic transaminase and glucose); macroscopic analysis of the contraction of the lesions by observing tissue characteristics and signs of inflammation, photographic recording and measuring the lesions with a ruler, and using specific imaging software[8,24,25]. These parameters are commonly used and enable the objective assessment of the lesion, as well as the monitoring of the healing process by the examiner.

It is known that the healing process of acute or chronic skin lesions is complex and involves, among other factors, the cells that make up the immune system, as well as biochemical and inflammatory events, with the intra- and extracellular metabolism being important[8,29-31]. The articles analyzed showed similar results regarding fibroblast proliferation and collagen production and deposition, which are relevant to the tissue repair process.

Regarding the antimicrobial activity of propolis, this was demonstrated in the study by Barud et al.[24], corroborating the data in the literature[5-8,32]. In the mentioned study, the activity of green propolis was evaluated *in vitro* against *Staphylococcus aureus, S. aureus* (MSRA) and *Staphylococcus epidermidis*. After the incubation period of the microorganisms mentioned above, 5.5 mm discs containing propolis were applied and the diameter of the inhibition zones was measured with a specific ruler. The study showed satisfactory results against all tested microorganisms, suggesting that green propolis can also be used in the treatment of infected lesions.

It is worth noting that the antimicrobial action of wound care products is also an essential factor in this process, since infected lesions have a delay in healing due to the prolongation of the inflammatory phase, which directly influences the deposition of collagen for local contraction and epithelialization[33].

The limitation of this study is the small number of publications that refer only to the use of green propolis for the healing of surgical lesions. During the article selection stage, it was observed that many studies associated green propolis

with other products that also favor tissue repair, such as collagen matrices, making it difficult to evaluate the efficacy of the resin produced by bees in wound healing.

The establishment of positive (gold standard) and negative (placebo) control groups for comparison with the treatment being studied is recommended in experimental studies. Another limitation was that only two of the selected articles used a positive control group, but did not establish the use of a treatment considered the gold standard for surgical wound management that could be compared to the topical use of propolis, which is recommended for this type of study.

Thus, it is suggested that experimental studies be conducted using a rigorous methodology that follows, among others, the criteria proposed by the SYRCLE tool, so that the results can be used as a scientific basis for future research on the topical use of propolis for the treatment of wounds in humans.

CONCLUSION

The results of this systematic review showed that the topical use of formulated products based on green propolis, in concentrations from 2.4 to 20%, promoted the healing of surgical lesions in rats, as it favored angiogenesis, fibroblast proliferation and, consequently, the synthesis and deposition of collagen, as well as demonstrating antimicrobial activity and showed no tissue toxicity, factors that are considered important for the process of tissue repair.

However, there are gaps and flaws related to the methodology of the selected studies, mainly related to the comparison between the treatment and control groups, which make the development of more robust evidence necessary to elucidate the aforementioned findings.

AUTHORS' CONTRIBUTION

Conceptualization: Faria TF and Kamada I; **Methodology:** Faria TF, Faria RF and Kamada I; **Investigation:** Faria TF and Faria RF; **Writing - First version:** Faria TF, Faria RF and Barreto LCLS; **Writing - Review & Editing:** Faria TF and Faria RF; **Financing Acquisition:** Faria TF and Barreto LCLS; **Resources:** Faria TF and Barreto LCLS; **Supervision:** Kamada I and Barreto LCLS.

AVAILABILITY OF RESEARCH DATA

All data were generated or analyzed in the present study.

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