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The anti-inflammatory effect of propolis on human tissue: A systematic review

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Abstract

Introduction: The healing process that occurs after a tissue lesion is divided into three distinct phases: inflammation phase, proliferation, and remodeling. Despite the structural similarity of the anatomy of the skin and oral mucosa, the oral mucosa presents a unique healing environment. Treatment options for chronic lesions are still limited, hence efforts in the research of traditional therapies with alternative clinical treatments, such as the use of propolis, have been conducted. Objectives: This systematic review aims to evaluate the anti-inflammatory property of propolis in the tissue repair process. Methods: A database search was performed using the descriptors "Propolis", "Wound Healing" and "Complementary Therapies". Results: Ninety-three publications were found in electronic databases. Of these 93 articles, 84 were excluded for failing to meet the eligibility criteria and only 9 articles were read in full. With regard to design, seven works were considered to be of "fair" methodological quality and two considered to be "poor". Only one study was classified as Level of evidence III-2, three studies as III-3, and five studies as IV, due to the studies having been carried out without specific interventions. Conclusions: The benefits of propolis can be considered to be its proven anti-inflammatory activity, as well as collagen stimulation, rapid promotion of the healing process, and few side effects..

Keywords: Propolis; Wound healing; Complementary therapies; Anti-inflammatory activity.

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Introduction

The healing process that occurs after a tissue injury is divided into three distinct phases: phase of inflammation, proliferation, and remodeling.[1]

The phases of healing are defined as (i) Inflammation Phase: hemostasis is initially achieved by the formation of a platelet buffer followed by a fibrin matrix, which becomes a framework for the infiltration of cells. Thus, inflammation occurs immediately after tissue damage, and the components of the coagulation cascade, inflammatory pathways, and immune system are activated to prevent continuous losses of blood and fluids; (ii) Proliferation Phase: the formation of new tissue occurs 2-10 days after injury, and is characterized by cell proliferation and angiogenesis; (iii) Remodeling Phase: fibroblasts are attracted from the edge of the lesion or bone marrow and myofibroblasts (contractile cells) approach the edges of the injury, and both interact to produce the extracellular matrix (ECM), mainly in the form of collagen.[2]

Any injury trigger this cascade, which can be induced by a surgical procedure, accident, or cases of disease,[3-4] infection, and cases of vesicle-bullous origin.[5] Any alteration of this cycle can generate an abnormal fibroproliferative response in which the tissue grows excessively and invasively beyond the original edge, forming the scar tissue known as keloid.[6] Despite the structural similarity of the anatomy of the skin and oral mucosa,[7] the oral mucosa has a unique and

different healing environment that encourages the fast resolution of the lesion at each stage.[8]

The cutaneous tissue contains three layers: (I) epidermis, composed of dense keratinocytes;[9] (II) dermis, mainly formed by ECM and fibroblasts, of which collagen is the main component;[9] and (III) Subcutaneous tissue, which provides passage to skin nerves, blood vessels, and lymphatic vessels.[9,10]

In human tissues, strength, integrity, and structure are provided by collagen.[5] During the regeneration stages, collagen type I participates as an important component of the extracellular matrix that confers integrity, homeostasis, and epithelialization. The growth transformation factor β (TGF-β) is also important due to the regulation conducted by platelets, which are responsible for the chemotaxis of inflammatory cells. In addition, TGF-β stimulates the deposition of ECM, moderates the substitution of type III collagen by type I collagen and stimulates the proliferation of keratinocytes.[11-14]

Although clinical practices have been tested to reduce delays in healing, the treatment options for chronic lesions remain limited. Therefore, efforts in the research of traditional therapies with alternative clinical treatments have been made.[15] These agents of traditional therapy could provide an efficient and approachable economic alternative among treatment modalities.[16] This research has been focused on seeking healing methods in natural products,[17] such as propolis.[4,16-19]

Propolis has a complex chemical composition, being usually composed of 50% resin, 30% wax, 10% essential oils, 5% pollen, and 5% other substances.[20-22] It is part of a combination of 300 or more chemical components, including flavonoids, phenolic acids, terpenes, and caffeic acids, identified in different proportions according to the seasonality and region of collection.[16]

Propolis has biological effects that accelerate the healing process[16] and shows significant anti-inflammatory properties, which are attributed to caffeic acid, flavonoids, and terpene.[5,15,22,23] Researchers believe that propolis performs a supra-regulation of the TGF-β gene, activates collagen expression, and restores the expression of markers of induction of inflammatory response by cytokines, such as IL-1β, IL-6, and TNF-α.[24] Propolis also performs actions to reduce pain and deterioration of lesions.[4]

Finally, the objective of this systematic review is to evaluate the anti-inflammatory property of propolis in the tissue repair process.

Methodology

Search question, search, and record

This systematic review aimed to answer the following question: Does the use of propolis have benefits in the healing of human tissue? The inclusion criteria of this review were based on the PICO strategy,[25] which refers to "Patients or situation, Intervention, Comparison and Outcome" (where P = human tissue; I = use of propolis; C = anti-inflammatory action or not; O = benefits the acceleration of the healing process).

To achieve the objective of this study, an electronic data search of the BVS, PubMed and SCOPUS databases was performed on October 24, 2020. The search was restricted to articles in the English language. The descriptors used in the research were "Propolis", "Wound Healing" and "Complementary Therapies".

This review had its protocol developed and registered in the Prospero database (CRD42020221681), and was developed in accordance with the PRISMA protocol.[26]

Study selection and data extraction

Two properly calibrated researchers identified studies aligned with the objective of our study that had been published between January 2015 and October 2020. During the identification process, words referring to the outcome of the initial question were included in order to identify the greatest possible number of publications, so each descriptor was accompanied by a series of related words.

From the strategies elaborated with descriptors in English and their respective free terms, 93 publications were found in the electronic databases. Of these 93 articles, 40 were excluded by the establishment of a cut-off date that restricted the articles under consideration to those published within the last five years. From the search result, duplicate articles were removed using the Mendeley program.[27] Then the initial list with 53 articles was submitted to two researchers (PHSBJ, RVP) for analysis (identification), as a result of which 6 duplicates were removed. Inclusion/exclusion criteria (screening) were applied to determine the final sample of articles, which were evaluated at this stage by their title and abstract (eligibility criterion). Next, the same researchers excluded articles that discussed herbal medicines, systematic reviews and other works that did not include the discussion of injuries. Thus, only thirteen articles were selected for purposes of reading under the

inclusion and exclusion criteria pre-established by the two researchers. Gray literature was not seen in the current systematic review.

Of the thirteen articles selected, four raised issues of discrepancy from the point of view of the researchers. To resolve eligibility discrepancies, a third researcher (SCH) was consulted. After reading by the third researcher, these four articles were discarded from consideration, because they did not directly address anti-inflammatory action, but rather antimicrobial actions and other actions that did not fit the objective of the review question. Thus, only nine articles were selected.

Eligibility criteria

The studies included in this review dealt with (i) the healing action of propolis; (ii) tissue regeneration in humans and animals; and (iii) the anti-inflammatory action of propolis. The articles excluded from this review involved: (i) healing of lesions without the action of propolis; (ii) other propolis actions unrelated to healing and anti-inflammatory action; and (iii) herbal medicines. Also excluded were duplicates, comments, letters, conference summaries, books, book chapters, incomplete reviews, systematic reviews, and meta-analyses or narrative reviews.

Methodological quality and level of evidence

The methodological quality of the articles was evaluated using the Physiotherapy Evidence Database (PEDro) scale.[28] Although this test measures the efficacy of physiotherapeutic interventions, the scale has also been used in several other types of interventions. The PEDro scale is divided into eleven criteria, ranging from "consensus of researchers" to "no empirical data". Each criterion is scored based on the satisfaction of the researchers. Publications assigned a score higher than or equal to seven on the PEDro scale are considered to be of "high" methodological quality, those with a score of five to six are considered to be of "regular" quality and a score of four or less is classified as "low" quality"[28]. The methodological quality of this review is presented in Table 1.

The Level of Evidence (LE) of each study was classified according to the National Health and Medical Research Council (NHMRC) 2003-2009 and the hierarchy of evidence[29] classifying the studies included in this systematic review consists of six levels: (i) LE I - Systematic review; (ii) LE II - randomized clinical trial; (iii) LE III-1 - Controlled pseudo-randomized assay; (iv) NE III-2 - Comparative study with concurrent controls: non-randomized experimental trial, cohort study, case-control study, interrupted time series without a parallel control group; (v) NE III-3 - Comparative study without concurrent controls: historical control, study of two or more single arms, interrupted time series without a parallel control group; (vi) NE IV - Series of cases with post-test or pre-test/post-test results. The assigned classifications can be found in Table 1.

Assessment of quality and risk of bias

The evaluation of quality and risk of bias was made in accordance with the Cochrane Collaboration tool, with seven different domains related to the risk of bias being independently evaluated for each selected study (1): (I) random sequence generation, (II) blinding allocation, (III) blinding of participants, (IV) personnel evaluation and results, (V) measures of incomplete results, (VI) selective results reports, (VII) other types of bias. The assessment of quality and risk of bias are presented in Table 2.

Data analysis

Considering the different types of studies with various methods of testing for healing and anti-inflammatory action resulting from the performance of propolis, and nine publications considered to have little scientific base, no meta-analysis was performed. Furthermore, the study aims to analyze whether the action of propolis is effective in anti-inflammatory and healing action, as summarized in a systematic review.

Results

Study design

The search strategy, as seen in Figure 1, presents the PRISMA flowchart with the different stages of the current systematic review, showing the articles selected, as well as the research process as a whole. Ninety-three articles were found in the databases; of which forty were excluded when the search was limited to the last 5 years.

Of the remaining fifty-three articles, seven were excluded because they were reviews (narratives, systematics, or meta-analyses) and six because they were duplicates. Of the remaining forty articles, thirty-one were excluded for failing to address the anti-inflammatory or healing properties of propolis,

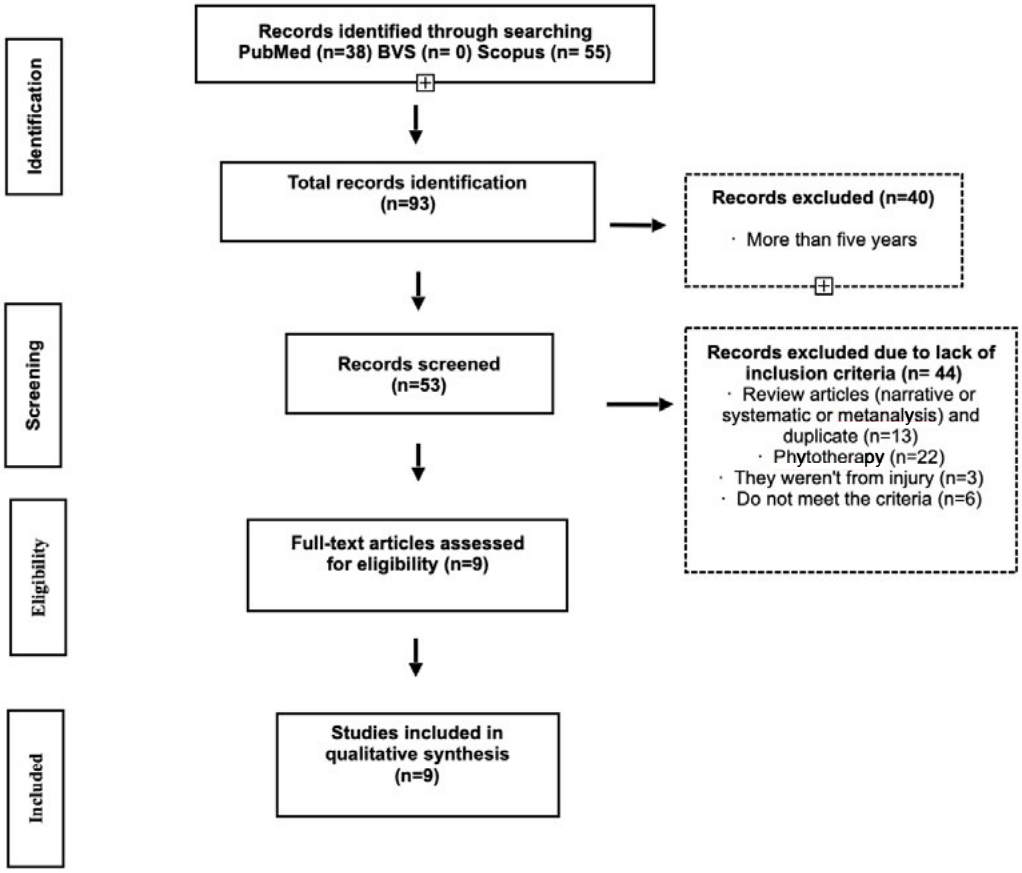

Figure 1. PRISMA flowchart of bibliographic research and its different stages of the systematic review
Source: The authors (2021).

for discussing herbal medicines, antimicrobial activity and other biological activities of propolis, or for not being in English. The full text of the nine articles that met all inclusion criteria was evaluated.

Quality assessment

Considering the eligibility criteria, one study was classified as Level III-2,[16] three as Level III-3,[5,17,19] and five as Level IV.[3,4,18,23,30] With regard to methodological quality (PEDro score), seven works were considered to be of "fair" quality[3,4,17-19,23,30] and two to be "poor".[5,18]

Table 1 shows the risk of bias according to the Cochrane Collaboration tool. All nine selected publications have a "high risk" of bias.

Study result

Table 2 shows the characteristics of the selected study populations. *In vivo* and *in vitro* studies were carried out, of which one article came from Indonesia, two from Iran, one from China, three from Turkey, one from Egypt, and one from Brazil. One hundred and eighty-nine rats, six dogs, and sixty-one human subjects participated in the *in vivo* analyses. The *in vitro* studies used fibroblasts and breast cancer cells. There was an analysis of the healing time according to the affected region when *in vivo* and the incubation period when *in vitro*.

Table 4 presents the methods used for obtaining and isolating the propolis extract, as well as the region of collection. In the groups of each study, a control group was made for the research and the extraction of propolis in different concentrations of ethanol or a certain concentration at a specific application time in a region. Also, the results of all the studies considered propolis to be an effective healing and anti-inflammatory agent.

Table 1. Methodological quality and Level of evidence of the selected publications

Author/year	Items on the PEDro scale											Total Score	Level of Quality	LE*
	1	2	3	4	5	6	7	8	9	10	11			
1. Al-Irayfawee et al (2019) [4]	1	0	1	0	1	1	0	1	0	1	0	5	Fair	IV
2. Altıparmak et al (2019) [16]	1	1	0	0	1	1	0	1	0	1	0	5	Fair	III-2
3. Astrada et al (2019) [3]	1	0	1	0	1	1	0	1	1	1	0	6	Fair	IV
4. Cao et al (2017) [30]	1	0	0	0	1	1	0	1	0	1	1	5	Fair	IV
5. Eslami et al (2017) [5]	1	0	0	0	1	1	0	1	0	1	0	4	Poor	III-3
6. Nani et al (2018) [17]	1	1	0	0	1	1	0	1	0	1	0	5	Fair	III-3
7. Saral et al (2016) [23]	1	1	0	0	1	1	0	1	0	1	0	5	Fair	IV
8. Uçar & Değer (2019) [18]	1	0	0	0	1	1	0	1	0	1	0	4	Poor	IV
9. Zohery et al (2018) [19]	1	1	0	0	1	1	0	1	0	1	1	6	Fair	III-3

Source: The authors (2021).

Table 2. Summary of the risk of bias assessment

Author/year	Bias sources						
	1	2	3	4	5	6	7
Al-Irayfawee et al (2019) [4]							
Altıparmak et al (2019) [16]							
Astrada et al (2019) [3]							
Cao et al (2017) [30]							
Eslami et al (2017) [5]							
Nani et al (2018) [17]							
Saral et al (2016) [23]							
Uçar & Değer (2019) [18]							
Zohery et al (2018) [19]							

High risk	
Uncertain risk	
Low risk	

(1) random sequence generation, (2) allocation concealment, (3) blinding of participants, (4) personnel and outcome assessment, (5) incomplete outcome measures, (6) selective outcome reporting, (7) other types of bias.

Source: The authors (2021).

Table 3. Individual characteristics of the selected studies regarding population size, country, region (tissue)/culture medium, healing time/incubation, and study design

Author/year	Population size/ Country	Region (tissue) / Culture medium	Healing time / Incubation	Study Design
Al-Irayfawee et al (2019) [4]	60 diabetic patients (Iraq)	Foot	-	Experimental control case study
Altıparmak et al (2019) [16]	50 rats (Turkey)	Spine	21 days	Animal study
Astrada et al (2019) [3]	1 hospital patient (Indonesia)	Foot	72 days	Case report
Cao et al (2017) [30]	Fibroblasts (China)	DMEM culture medium, fetal bovine serum	15 hours	In vitro study
Eslami et al (2017) [5]	Human gingival fibroblasts (Iraq)	RPMI culture medium, fetal bovine serum, glutamine, penicillin, streptomycin	24 hours	In vitro study
Nani et al (2018) [17]	90 rats (Brazil)	Dorsal cervical region	14 days	Animal study
Saral et al (2016) [23]	49 rats (Turkey)	Periosteum*	-	Animal study
Uçar & Değer (2019) [18]	Breast cancer cells (Turkey)	DMEM culture medium, l-glutamine, FBS	24 – 72 hours	In vitro study
Zohery et al (2018) [19]	6 dogs (Egypt)	Mouth (periodontal defect - furcation)	30 - 90 days	Animal study

* Body region not cited by the author.

Source: The authors (2021).

Table 4. The Table shows the author, the method used to extract propolis, the sample, and the results of the study

Author/year	Propolis Extraction	Sample Groups	Observed Results
Al-Irayfawee et al (2019) [4]	*Punica granatum* propolis extract	Group I: control group Group II: treated with *Punica granatum* extract Group III: treated with propolis extract	Positive effect of Punica granatum and the Propolis extract on the healing of diabetic foot ulceration. Incidentally, the propolis extract is characterized by an effective cure.
Altıparmak et al (2019) [16]	*Hypericum perforatum* (HP) was collected and mashed with olive oil	Group I: control group Group II: HP + propolis (1: 1) Group III: HP + Liquidambar orientalis (LO) (1: 1) Group IV: LO + propolis (1: 1) Group V: HP + LO + propolis (1: 1: 1)	Propolis has proven to have a positive impact on wound healing.
Astrada et al (2019) [3]	Trigona honey was obtained by independent production	It was applied to 1 patient	The Trigona honey-treated ulcer exhibited re-epithelialization of the wound edge. A shorter inflammatory phase, and had a faster healing time.
Cao et al (2017) [30]	Propolis type *Populus spp.* of Apis mellifera colonies in Shandong province. The propolis samples were extracted with 95% ethanol	It was not reported	The ethanolic extract of propolis efficiently reduced the excessive accumulation of reactive oxygen species. Protecting skin cells from oxidative damage.

* Body region not cited by the author.

Source: The authors (2021).

Table 4. The Table shows the author, the method used to extract propolis, the sample, and the results of the study (cont.)

Author/year	Propolis Extraction	Sample Groups	Observed Results
Eslami et al (2017) [5]	Propolis, harvested manually, was prepared in 10g bottles. It was subjected to 14 days of extraction to obtain the ethanol extract of propolis.	Group I: control group Group II: irradiation of 1.5 J/cm² Group III: irradiation of 0.15 J/cm² Group IV: propolis extract Group V: propolis extract + 1.5 J/cm² irradiation Group VI: propolis extract + 0.15 J/cm² irradiation	The propolis extract or combined laser (0.15 J/cm² or 1.5 J/cm²) with the propolis extract showed a decrease in the expression of the type 1 collagen gene.
Nani et al (2018) [17]	AlpaWash ointment with micronized Brazilian propolis. And *P. ostruthium* leaf extract	Group I: lesions treated with PEG ointment Group II: lesions treated with AlpaWash Group III: lesions treated with Polysporin Group IV: untreated injuries	It provided improvements in the healing process when compared to injuries. The groups of the base of the PEG ointment, AlpaWash and Polysporin were able to close the lesion. However, AlpaWash and Polysporin showed some additional benefits, including anti-inflammatory activity, fibroplasia, and hydroxyproline production. Suggesting that the newly formed skin is of better quality with these two treatments.
Saral et al (2016) [23]	Samples of chestnut honey, pollen, propolis, and royal jelly were obtained by farmers.	Group I: saline solution (control group) Group II: ethanol (control group) Group III: CCL4 only (untreated group) Group IV: honey treatment Group V: pollen treatment Group VI: treatment with propolis Group VII: treatment with royal jelly	Propolis exhibited the highest levels of phenolics and flavonoids and therefore exhibited proposed activity.
Uçar & Değer (2019) [18]	Propolis samples were collected and ground, kept at -20ºC, and centrifuged	Group I: 24-hour incubation Group II: 48-hour incubation Group III: 72-hour incubation	Turkish propolis extract has antiproliferative and cytotoxic effects. Thus, the propolis extract can be a suitable alternative.
Zohery et al (2018) [19]	Biopropolis® propolis capsules were available on the market.	Group I: collagen/propolis group Group II: collagen/nanohydroxyapatite group	The use of propolis as a substitute for a bone graft can be considered in the management of periodontal defects due to its biocompatibility and regenerative potential. It was a viable therapy and good predictability of success.

* Body region not cited by the author.

Source: The authors (2021).

Discussion

The objective of this current systematic review was to assess the anti-inflammatory properties of propolis in the tissue repair process, against the samples selected for each type of study. The samples selected for each type of study are worthy of consideration. Similarities and nuances were observed with regard to studies in rats,[16,17,23] *in vitro*,[5,18,30] in humans,[3,4] and in dogs.[19] It is relevant to note that only one study was classified as Level of Evidence III-2, three studies as III-3, and five studies as IV (NHMRC), since the studies

were carried out without specific interventions. Also, the methodological quality (PEDro score) of seven publications was to be considered "Fair" and two publications as "Poor" (Table 1). In addition, most of the selected studies show a high risk of bias (Table 2).

In contemporary medicine, propolis has been used in clinical contexts for the treatment of a variety of diseases.[3,4] Propolis contains phenols, the most active of which is the phenethyl ester of caffeic acid, which has anti-inflammatory, antioxidant, antibacterial, anti-tumor, anticarcinogenic, and immunomodulatory action.[31-33]

The use of this substance has been studied in several types of tissue lesions, focusing on the evaluation of the anti-inflammatory property of propolis in the tissue repair process in different areas of the body. These include diabetic ulcerations, dental lesions, and liver damage.[17,19,23]

According to research by Zohery and colleagues, 2018,[19] propolis presents proven benefits of accelerating healing in class II furcation defects, being a potential substitute for bone grafts in equivalent to the nanohydroxyapatite. Regarding liver damage, Saral and colleagues, 2016[23] suggest that propolis significantly improves the cure of CCL4- (a highly toxic agent that releases reactive free radicals, which can initiate lipid peroxidation and cell necrosis), reaffirming ¨its effectiveness in anti-inflammatory action.

Eslami and colleagues, 2017[5] and Uçar M and Deger O, 2019,[18] despite obtaining satisfactory results in their in vitro clinical trials on the use of propolis in reference to type 1 collagen gene expression and proliferation, cytotoxicity, lateral motility, and MDA-MB231 cells, corroborate the need for further studies to prove the effectiveness of propolis in these contexts.

Other aspects found in studies of diabetic patients with foot ulcers[3,4] demonstrated that propolis extract facilitates tissue healing. However, the differences in the methodology of study designs are considerable. Al-Irayfawee and colleagues, 2019[4] conducted a study with 60 patients subdivided into small groups, while Astrada and colleagues, 2019[3] evaluated only one patient. This contrast suggests that further studies with significant samples must be performed to clarify results.

Studies with rats[16,17] showed that a combination of propolis with other elements (*hypericum perforatum*, *liquidambar orientalis*, alpawash, and *peucedanum*) engendered a stable response to wounds, suggesting a favorable synergy with these compounds.[16,17]

Another important point was addressed by CAO and colleagues, 2017[31] in his *in vitro* dissertation on the induction of gene expression related to antioxidants. This work found that propolis extract offers significant potential in relieving oxidative stress in wound tissues.

Looking at the tissue/culture medium of the works, great polarization is found. There are reports on bovine sera in populations of fibroblasts,[5,30] feet of diabetic patients,[3,4] intraperiosteum, the cervical region of rats,[16,17,23] oral cavities of dogs,[19] and the DMEM of cells.[18] This wide variety of tissues and culture media makes it impossible to obtain accurate and reliable results related to the tissue repair process. Furthermore, it is worth mentioning that the duration of the studies varied. There are surveys with a duration of 30/90 days[19] and others with a total of 15 hours,[30] highlighting the opposing extremes.

With regard to the limitations of the studies, these included the variety of methodologies proposed. Articles were also limited by: (i) lack of research on better methodologies and systematic reviews/meta-analyses, (ii) inconclusiveness of existing articles, (iii) need for more *in vitro* and *in vivo* studies in order to better ascertain the potential effect of propolis and (iv) need for more comparative studies on healing time. Another limitation of this article may be the limitation to the English language and the restriction to the last 5 years, which may have led to articles with more effective results in other languages and from other regions being disregarded.

In light of the growing amount of scientific production related to propolis, the scientific evidence contained in the material analyzed in this review suggests that propolis has advantages in the healing of tissue injuries. However, evidence is still limited in the field of health, especially in dentistry. The articles found this review have a low level of evidence, a high risk of bias, even regarding the positive results on the use of propolis evaluated in the full texts. Thus, more research with larger study groups is required to better demonstrate that propolis is an effective healing and anti-inflammatory agent.

Conclusion

According to the studies examined in this systematic review, we can consider the benefits of propolis to be its proven anti-inflammatory activity, as well as collagen stimulation, rapid promotion of the healing process, and low number of side effects.

Propolis can be used as a resource in complementary therapies involving phases of inflammation, proliferation, and remodel action. However, more work is required on this question, since few studies can be found in the scientific literature, and these are mostly in vitro experiments, with few cases or experiments reported on humans. More studies are needed to determine which propolis compounds exert anti-inflammatory effects.

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