# Efficacy and safety of propolis in the treatment of periodontal diseases: systematic review and meta-analysis

Eficácia e segurança da própolis no tratamento de doenças periodontais: revisão sistemática e meta-análise

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#### ABSTRACT

Periodontal diseases (PD) have traditionally been associated with the development of certain systemic conditions. The possible treatment of PD with natural agents has been the subject of great interest in recent years, due to the increasing bacterial resistance to antibiotic therapy. Propolis is a natural substance which has proven useful for treating periodontal disease. This systematic review and meta-analysis gather evidence of the efficacy and safety of propolis intervention in PD. CINAHL, Central Register of Controlled Trials (CENTRAL), Embase, LILACS, PubMed, SciELO, Scopus, and Web of Science databases were searched for studies. This systematic review has a protocol registered in PROSPERO (CRD42021273137). 1,884 records were obtained from the searches, of which 12 met the eligibility requirements. The results demonstrated the efficacy and safety for all dental formulations containing propolis. Toothpaste was the most effective in removing biofilm, with improvement in gingival inflammation. However, the most accessible formulation was mouthwash, highlighting its use in patients with motor difficulties. Subgingival irrigation of the hydro-alcoholic solution of propolis is the method of choice in the clinic to reduce inflammation and microorganisms responsible for periodontitis, according to the results observed in the meta-analysis regarding the parameters gingival index (GI), pocket probing depth (PPD), and clinical attachment index (CAL). The different pharmaceutical forms containing propolis showed efficacy and safety in the treatment of PD. In this meta-analysis, it was possible to prove the efficacy of the treatment by subgingival irrigation in the parameters GI, PPD, and CAL. New perspectives for standardizing clinical protocols for the diagnosis of periodontal diseases, for better clinical evidence.

Keywords: Gingivitis, Periodontitis, Biofilms, Bee products, subgingival irrigation.

#### RESUMO

As doenças periodontais (DP) têm sido tradicionalmente associadas ao desenvolvimento de certas condições sistêmicas. O possível tratamento da DP com agentes naturais tem sido objeto de grande interesse nos últimos anos, devido ao aumento da resistência bacteriana à antibioticoterapia. A própolis é uma substância natural que tem se mostrado útil no tratamento da doença periodontal. Esta revisão sistemática e meta-análise reúne evidências da eficácia e segurança da intervenção da própolis na DP. As bases de dados CINAHL, Central Register of Controlled Trials (CENTRAL), Embase, LILACS, PubMed, SciELO, Scopus e Web of Science foram pesquisadas em busca de estudos. Esta revisão sistemática possui protocolo registrado no PROSPERO (CRD42021273137). Foram obtidos 1.884 registros, dos quais 12 atenderam aos requisitos de elegibilidade. Os resultados demonstraram a eficácia e segurança de todas as formulações odontológicas contendo própolis. O creme dental foi o mais eficaz na remoção do biofilme, com melhora da inflamação gengival. Entretanto, a formulação mais acessível foi o colutório, destacando-se seu uso em pacientes com dificuldades motoras. A irrigação subgengival da solução hidroalcóolica de própolis é o método de escolha na clínica para reduzir a inflamação e os micro-organismos responsáveis pela periodontite, de acordo com os resultados observados na meta-análise quanto aos parâmetros índice gengival (GI), profundidade de sondagem de bolsa (PPD) e índice de fixação clínica (CAL). As diferentes formas farmacêuticas contendo própolis mostraram eficácia e segurança no tratamento da DP. Nesta meta-análise foi possível comprovar a eficácia do tratamento por irrigação subgengival nos parâmetros GI, PPD e CAL. Novas perspectivas para padronização de protocolos clínicos para o diagnóstico de doenças periodontais, para melhor evidência clínica.

Palavras-chave: Gengivite, Periodontite, Biofilmes, Produtos apícolas, irrigação subgengival.

## **INTRODUCTION**

Oral health is an important factor in the well-being of the human body, as it summarizes the general health and maintenance of the physical, mental, and social well-being of individuals. However, several problems can affect the oral cavity, such as cancer, glandular dysfunction, caries, trauma and periodontal disease. When diagnosed early, periodontal disease (PD; e.g., gingivitis and periodontitis) can be properly treated and controlled to prevent the disease progression. Otherwise, it is possible that there will be a loss of tissue supporting and supporting the tooth, as well as the alveolar bone, periodontal ligament fibers, mobility and, finally, tooth loss (MIRANDA *et al.*, 2019; PAROLIA *et al.*, 2022; SPARABOMBE *et al.*, 2019).

Focusing on PD etiology, interactions involving microorganisms, host immune system, oral hygiene, heredity and possible systemic changes must be present (ALMEIDA; MATHEUS, 2019). The development of effective strategies for the treatment of periodontitis has been a challenge, considering the increase growing in opportunistic

bacterial infections, deficient oral hygiene, the habit of brushing and systemic diseases. To date, nonsurgical, surgical and plaque control interventions have been the conventional modalities of periodontal treatment (KIM *et al.*, 2021).

Although adjuvant therapies including antibiotics or supplements may be employed, their use has been limited by the resistance of microorganisms, as well as their partial efficacy (KIM *et al.*, 2021). Hence, the use of natural compounds has gained popularity due to their low cost and greater ease of access, especially in communities with inadequate public health conditions. Furthermore, there is a greater patient compliance due to the low incidence of adverse events (HASANI-RANJBAR *et al.*, 2013; LISBONA-GONZÁLEZ *et al.*, 2021; NAKAO *et al.*, 2020; PAROLIA *et al.*, 2022).

Propolis is a natural product, composed of resinous substance produced by bees as a defense against intruders, in addition to being used as a repair, isolation, fixation and microbiological protection material in hives (SILVEIRA *et al.*, 2021; SOBRINHO *et al.*, 2022). Its composition generally includes 50% resin of vegetable origin, 30% wax, 10% aromatic and essential oils, 5% pollen and 5% other compounds (DEHGHANI *et al.*, 2019; PUNDIR *et al.*, 2017).

A great progress and development have been acquired in research with preparations containing propolis, both for the prevention of PD and for the maintenance of oral health (ANAUATE NETTO *et al.*, 2013; DEHGHANI *et al.*, 2019; FURTADO JÚNIOR *et al.*, 2020; LISBONA-GONZÁLEZ *et al.*, 2021; PAROLIA *et al.*, 2022). On the other hand, there is a gap in literature focusing on this quality of publications regarding this subject.

In this context, the present systematic review and meta-analysis evaluated the clinical use of propolis in PD, the products used and their dosage in addition to estimating the quality and the risk of bias of the publications.

# **METHODS**

The protocol for this systematic review was registered in PROSPERO (CRD42021273137) (OLIVEIRA; MANO-SOUSA; DUARTE-ALMEIDA, 2021), following the guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (MOHER *et al.*, 2015). The study was conducted and investigated the following question: *"Is the treatment of periodontal diseases with propolis safe and effective?* 

# Study search and selection strategy

Electronic searches were performed in the following databases: CINAHL, Central Register of Controlled Trials (CENTRAL), Embase, LILACS, PubMed, SciELO, Scopus, and Web of Science, using the descriptors periodontal disease, propolis, gingivitis, and/or periodontitis, without language and date restrictions. The search criteria and date are described in Supplementary Table 1.

Duplicate records were excluded using the reference managers (Mendeley<sup>°</sup> and JabRef). The nonduplicate citations were imported into the Rayyan Systematic Review platform (https://rayyan.qcri. org/) (OUZZANI *et al.*, 2016). The eligibility process was conducted in two distinct phases. First, two researchers independently (BJMS or CFO) screened all non-duplicate articles and excluded non-relevant articles based on title or abstract. Discrepancies were resolved by a third researcher (JMDA). In a second moment, the full texts of the studies selected in the screening were re-evaluated for eligibility criteria by the two researchers. Any discrepancies were also resolved by a third investigator (JMDA).

# Eligibility Criteria

The selection of studies for this review was defined and carried out using the PICOS strategy (Population, Intervention, Comparison, Outcome, and Study Type):

- *Population (P):* Individuals, of any age, of both sexes and with periodontal disease;
- *Intervention (I):* Treatment with propolis in any route of administration and concentration;
- Comparison (C): Values at the start of treatment were compared with values after treatment in the intervention and control groups;
- Outcome (O): Efficacy of propolis in patients with PD (gingivitis and periodontitis) or possible adverse events;
- *Type of study (S):* Clinical studies including values before and after treatment and with the existence of a control group.

Reviews, studies on animals, case reports, summaries in annals of events, editorials, with endodontic, orthodontic, cariostatic purposes, prosthesis,

Table 1						
Data	Base	Descritores de pesquisa				
10/07/2020 26/04/2021	2015	propolis [Palavras] and doença periodontal [Palavras] propolis [Palavras] and Odontologia [Palavras] Propolis gengivites propolis [Palavras] and gengivite [Palavras]				
10/07/2020 26/04/2021	Embase	'propolis'/expAND 'periodontal disease'/exp 'propolis'/expAND 'dentistry'/exp ('propolis'/exp OR propolis) AND ('gingivitis'/expORgingivitis)				
10/07/2020 26/04/2021	CINAHL	propolis AND periodontal disease propolis AND dentistry propolis AND gingivitis				
10/07/2020 26/04/2021	Scopus	(TITLE-ABS-KEY (propolis) AND TITLE-ABS-KEYperiodontal AND disease (TITLE-ABS-KEY (propolis) AND TITLE-ABS-KEY (dentistry) (TITLE-ABS-KEY (propolis) AND TITLE-ABS-KEY (gingivitis)				
10/07/2020 26/04/2021	Web of Science	(propolis) AND TÓPICO: (periodontal disease) (propolis) AND TÓPICO: (dentistry) (propolis) AND TÓPICO: (gingivitis)				
10/07/2020 26/04/2021	PubMed	("Propolis"[Mesh]) AND ("Dentistry"[Mesh] OR "Evidence-Based Dentist- ry"[Mesh]) ("propolis"[MeSH Terms] OR"propolis"[All Fields]) AND ("periodontal diseas- es"[MeSH Terms] OR ("periodontal"[AllFields] AND"diseases"[All Fields]) OR "periodontal diseases"[All Fields] OR ("periodontal"[AllFields] AND"dis- ease"[All Fields]) OR"periodontal disease"[All Fields]) ("propolis"[MeSH Terms] OR"propolis"[All Fields]) AND ("gingivitis"[MeSH Terms] OR"gingivitis"[All Fields])				
13/07/2020 26/04/2021	CENTRAL	propolis in Title Abstract Keyword AND periodontal disease in Title Abstract Keyword - (Word variations have been searched) propolis in Title Abstract Keyword AND gingivitis in TitleAbstract Keyword - (Word variations have been searched) propolis in Title Abstract Keyword AND dentistry in TitleAbstract Keyword - (Word variations have been searched)				
13/07/2020 26/04/2021	SciELO	(propolis) AND (dentistry) (propolis) AND (periodontal disease) (propolis) AND (gingivitis)				

**Table 1.** Characteristics of the studies included in this systematic review and meta-analysis.

periodontal disease of systemic origin or with the use of prostheses, propolis associated with any other herbal medicine, studies *in vitro* and *in silico*, and articles not available in full, even after contacting the authors, were excluded.

## Data extraction

The information collected was described in the form of tables in the Microsoft Excel<sup>®</sup> software (Microsoft Office 2019, Microsoft, California, USA). The following data were collected: author, year of publication, study location, type, and concentration of propolis and pharmaceutical form for dental use. All papers were written in English language. Also was collected the number of participants, parameters evaluated and biological activity, as well as any typification and concentration of propolis and pharmaceutical form.

## Assessment of quality and risk of bias

Study quality was assessed using the Jadad scale (JADAD *et al.*, 1996). In addition, the risk of bias was evaluated using the Cochrane Risk of Bias (RoB) 2.0 tool (HIGGINS, GREEN, 2015). In case of missing information, the answer "no" was given for this criterion. The "not informed", "not likely" and "yes probable" were attributed to possible risk of bias.

# Statistical analysis

Statistical analyses were performed with Comprehensive Meta-analysis software, version 2.0.057 (Biostat, Englewood, NJ, USA). Fixed-effect meta-analyses (MANO-SOUSA *et al.*, 2021) were performed to pool data of two studies according to the outcomes grouped at 4 and 12 weeks. Differences between pre- and post-treatment means in the intervention and control groups were combined to produce the pooled standardized mean differences. The heterogeneity in the primary results was analyzed using the Q test and the l<sup>2</sup> statistic, which describes the percentage of real dispersion in effectsizes which is not due to the random error. In all procedures, the significance level was 5%. Studies not included in the meta-analyses were discussed qualitatively, based on statistical significance and the strength of associations.

# RESULTS

## Search results

The searches found 1,884 documents. After removing duplicates, 1101 studies were analyzed by reading the title and abstract. 998 articles that did not meet the eligibility criteria. 101 articles were selected for full reading. After this step, 12 articles were included, as reported in the PRISMA flow chart detailing the screening process and some reasons for excluding the articles (Figure 1). Finally, only two studies were analyzed in the meta-analysis (PUNDIR *et al.*, 2017; SANGHANI *et al.*, 2014).

# Characteristics of the included studies

The characteristic of our population was a slightly higher proportion of female patients (58%) and aged between 12 and 73 years (ANAUATE-NETTO et al., 2014; BRETZ et al., 2014; COUTINHO, 2012; ERCAN et al., 2015; GEBARA et al., 2003; NAKAO et al., 2020; SANGHANI et al., 2014; SKABA et al., 2013). The older population range was reported by Nakao et al. (2020), while the younger ones were described in the article by Peycheva et al. (2019). Several origins of propolis used in the studies, with a predominance of Brazilian green propolis (ANAUATE-NETTO et al., 2014; BRETZ et al., 2014; GEBARA et al., 2003; NAKAO et al., 2020; SKABA et al., 2013), followed by Indian propolis (COUTINHO, 2012; SANGHANI et al., 2014), and propolis of Bulgaria (PEYCHEVA et al., 2019). Pharmaceutical forms distributed in the following



Figure 1. PRISMA Flowchart reporting the study screening process. Cochrane Central Register of Controlled Trials (CENTRAL).

groups: toothpaste (KUMAR, 2015; PEYCHEVA et al., 2019; SKABA et al., 2013), mouthwash (ANAUATE-NETTO et al., 2014; BRETZ et al., 2014; ERCAN et al., 2015), subgingival application (COUTINHO, 2012; GEBARA et al., 2003; NAKAO et al., 2020; PUNDIR et al., 2017; SANGHANI et al., 2014), and chewable gum (GHAIBIE et al., 2016). Five implemented microbiological evaluation (COUTINHO, 2012; GEBARA et al., 2003; NAKAO et al., 2020; PUNDIR et al., 2017; SANGHANI et al., 2014) and one used interleukin as markers of gingival inflammation (PEYCHEVA et al., 2019). Different clinical parameters: gingival index (GI), plague index (PI), bleeding on probing (BOP), proximal plaque index (PPI), pocket probing depth (PPD), sulcus bleeding index (SBI), papillary bleeding index (PBI), tooth mobility (TM), clinical attachment index (CAL).

## Propolis as toothpaste formulation

This dental group was included in three studies (KUMAR, 2015; PEYCHEVA *et al.*, 2019; SKABA *et al.*, 2013). The dosage of dentifrice containing propolis was described in only two articles. However, they do not adequately describe the amounts of material used. The authors described the addition of ten drops or a peanut-like portion of propolis added to commercial toothpaste.

Microbiological assessment is an auxiliary tool in the prognosis of periodontal pathologies and was used in three studies (KUMAR, 2015; PEYCHEVA *et al.*, 2019; SKABA *et al.*, 2013). Propolis provided significant reduction in microbial load in salivary analyses, in the gingival sulcus, in the subgingival biofilm. Yet, different markers such as interleukin 1-beta (IL-1 $\beta$ ) or polymerase chain reaction (PCR) were used (KUMAR, 2015; PEYCHEVA *et al.*, 2019; SKABA *et al.*, 2013).

The composition of propolis was evaluated qualitatively and quantitatively by different methods. In the qualitative analysis, the chromatographic methods were mentioned, with the use of High Performance Liquid Chromatographic with diode array detector (HPLC-DAD). Flavonoids and cinnamic acids were the most cited active compounds in propolis. In the quantitative evaluation, the Folin-Ciocalteu spectrometry method was used, highlighting the high concentration (58.90 mg/g) of artepillin C in Brazilian green propolis and Caffeic acid (55.16%) in propolin<sup>\*</sup>(PEYCHEVA *et al.*, 2019; SKABA *et al.*, 2013).

## Propolis as mouthwash formulation

Three *in vivo* studies that contained propolis in their formulation as mouthwashes were reviewed (ANAUATE-NETTO *et al.*, 2014; BRETZ *et al.*, 2014; ERCAN *et al.*, 2015). Bretz *et al.* (2014) performed a study of co-twins, which explored the correspondence in many observed and unobserved factors. The stronger the residual phenotypic correlation between the twins (attributable to known factors), the greater the power to detect differences in outcomes.

The concentration of propolis in mouthwashes varied between 2% (ANAUATE-NETTO *et al.*, 2014; BRETZ *et al.*, 2014) and 5% (ERCAN *et al.*, 2015). The dosage of 20 mL, twice daily, for thirty seconds, after oral hygiene was performed by Bretz *et al.* (2014), while Ercan *et al.* (2015) used for one minute, twice a day, resulting in significant inhibition of biofilm and gingival inflammation, demonstrated in the Gl. In conclusion, the mouthwashes were more effective in comparison to the control group of chewable gum containing propolis.The effect of chewing gum containing propolis was significant in improving

the GI, however, its effect on the value of PI was insignificant.

Overall, the results presented by Bretz *et al.* (2014) were promising, which may be related to the antibacterial and anti-inflammatory properties of propolis. The use of propolis-based mouthwash, standardized at 2%, was similar to a positive control in a 21-day induced gingivitis model (BRETZ *et al.*, 2014).

## Propolis as subgingival irrigation solution

The application of subgingival propolis was cited in five articles for use in periodontitis (COUTINHO, 2012; GEBARA *et al.*, 2003; NAKAO *et al.*, 2020; PUNDIR *et al.*, 2017; SANGHANI *et al.* 2014).

The hydro-alcoholic solution with 20% propolis applied to gingival sulcus, demonstrates efficacy of propolis against gram-negative bacteria (COUTINHO, 2012; GEBARA *et al.*, 2003). The *Porphyroms gingivalis*, precursors of periodontal diseases, were reduced with the application of propolis in the subgingival pockets with the help of syringes in the office (COUTINHO, 2012; GEBARA *et al.*, 2003).

The papers that mentioned the use of propolis solution were applied topically with 3 mL, 2-3 times a week (COUTINHO, 2012; GEBARA *et al.*, 2003). After sizing and root planning, one article made a single application, lasting one minute, of the alcohol solution containing propolis (PUNDIR *et al.*, 2017). Nakao *et al.* (2020) used Brazilian green propolis in the form of an ointment with the aid of a syringe. The application was done in periodontal pockets, three times, in an interval of one month.

All articles included in this review showed significant results in the main clinical parameters. Tooth mobility (TM) was assessed only by Nakao *et al.* (2020), demonstrating the effectiveness of propolis as adjunctive therapy in periodontitis.

## Propolis as chewing gum

Chewable gum with propolis was used in only one study. Ghaibie *et al.* (2016) researched the use of five units a day, with at least 20 minutes of use, after main meals, for three consecutive days, with a twoweek interval between use in 20 candidates. The age of the subjects, as well as the origin of the propolis and concentration, were not informed. However, the authors described that the active compounds present in propolis from chewable gum performed antibacterial and antifungal activities. After the consumption of gum with propolis, there was a decrease in the GI (of 0.70 to 0.57) as opposed to the PI (of 0.26 to 0.76). Therefore, an improvement in oral health, but on the other hand there was accumulation of biofilm.

## Side effects events

No side effect events resulting from the insertion of propolis were mentioned in the toothpaste, subgingival application and chewable gum groups. In the mouthwash, Anauate-Netto *et al.* (2014) reported breathing modification, burning sensation, dental yellowing, altered taste, and bitter taste in the intervention and control groups. Skaba *et al.* (2013) used a questionnaire with scores for color, taste, smell, and foam resulting in smell and cleanliness. Although not mentioned in articles, it would also be important to assess the allergy of some people to bee products.

#### Risk of bias and quality of reports

The Risk of Bias of the articles included in this systematic review is shown in Figure 2. Most of them presented low risk. In addition, the articles included in the meta-analysis did not present risk of bias.

The quality of the evidence scores of the 12 articles used in this study is shown in Table 1. The criteria used in the evaluation of these articles were mainly in randomization and double-blind studies using the Jadad scale. Six articles presented low quality due to lack of randomization and blinding. One article included in the meta-analysis was of high quality (SANGHANI *et al.*, 2014), while the other was of low quality (PUNDIR *et al.*, 2017).

#### Meta-analysis

The Meta-analysis was performed with two articles (PUNDIR *et al.*, 2017; SANGHANI *et al.*, 2014). These included individuals in good health, diagnosed with chronic periodontitis, with at least 3 teeth adjacent to the periodontal pocket, aged between 25-55 years, of both sexes, with clinical parameters of GI, PPD above 5 mm and CAL (Figure 3).

The evaluation shows statistically significant changes in GI and CAL (Figures 3A and 3C, respectively). Although the PPD showed heterogeneity in the results, the difference in means between the groups was significant (Figure 3B).



Figure 2. Assessing the risk of bias of controls included.

A	Study name	Statistics for each study					
		Std diff in means	Standard error	Lower limit	Upper limit	p-Value	
	Sanghaniet al.	-0,71	0,33	-1,35	-0,07	0,03	
	Pundir et al.	-0,93	0,38	-1,68	-0,18	0,02	
		-0,80	0,25	-1,29	-0,31	0,00	

Standard

error

0.32

0,40

0.25

Statistics for each study

Lower

limit

-1,61

-2.20

-1,64

Statistics for each study

Lower

limit

-0.91

-2,13

-1.18

Upper

limit

0,34

-0,55

-0.20

Upper

limit

-0,30

-0,60

-0,63

 $I^2 = 0$  *p*-value = 0,6581

Std diff

in means

Std diff

in means

-0,95

-1,40

-1,13

*p*-value = 0,3989

-0,28

-1,34

-0.69

p-value = 4,0298

Standard

error

0,33

0,41

0,26

**B** Study name

Sanghani et al.

 $I^2 = 76.22$ 

Pundiret al.

C Study name

Sanghaniet al.

Pundir et al.

 $I^2 = 0$ 





Favours propolis Favours control





Favours propolis Favours control

#### Std diff in means and 95% CI



**Figure 3.** Results of the meta-analysis of the assessment of the total score of the ABC scale in the treatment of periodontitis with topical application of propolis. **A**: gingival index (04 and 12 weeks); **B**: Pouch Probing Depth (PPD) (04 and 12 weeks); **C**: clinical attachment level (CAL) Confidence interval (04 and 12 weeks); (CI), Heterogeneity (I<sup>2</sup>) and the p-value of heterogeneity (*p*-value).

# DISCUSSION

The articles included in this review presented promising results and a new perspective on the use of propolis in PD. Although there are many articles on this subject, only twelve clinical studies showed the effectiveness of propolis in PD. There was a great diversity of products and their forms of use, dosage, origin, and concentration of propolis, as well as aspects related to microbiological studies. The heterogeneity of gingival and periodontal clinical parameters was also noted. The quantitative analysis with the variables GI, PDD and CAL in both studies showed the efficacy of propolis in chronic periodontitis with subgingival application.

Our review demonstrated the efficacy of Indian propolis (COUTINHO, 2012; PUNDIR *et al.*, 2017; SANGHANI *et al.*, 2014), and Brazilian green propolis in PD (ANAUATE-NETTO *et al.*, 2014; BRETZ *et al.*, 2014; GEBARA *et al.*, 2003; NAKAO *et al.*, 2020; SKABA *et al.*, 2013). It is noteworthy that this type of propolis is found exclusively in the Southeast region of Brazil (NAKAO *et al.*, 2020). Artepillin C is considered the compound responsible for the anti-inflammatory and antimicrobial properties (SKABA *et al.*, 2013).

Adverse events were not observed in studies using toothpaste, subgingival applications, and propolisbased chewable gum. However, in the groups that used mouthwash, there was a report of adverse events indicating color and hypersensitivity changes in the teeth, allergies and dyspepsia, in addition to a bitter taste and burning sensation in the mouth (ANAUATE-NETTO *et al.*, 2014). Xerostomia may have been caused by ethanol; the solvent used in the preparation of the products (ANAUATE-NETTO *et al.*, 2014). The allergy can be attributed to some component of propolis that caused the hypersensitivity (PAROLIA *et al.*, 2022). Reports on adverse events caused by propolis are little documented, or few are known. Zhang and Yan (2020) reported a case of allergic contact stomatitis caused by propolis mints in the throat, a reaction they attributed to caffeic acid phenethyl ester (CAPE). Further research is needed in order to assess the effectiveness of this gum formulation, as an adjunct treatment in the mechanical control of plaque, biofilm and gingivitis.

Toothpaste containing propolis and vegetable oils has a regenerative effect on the gums, significantly reducing gingival bleeding (MACHOROWSKA-PIENIAZEK *et al.*, 2016). As for dosage, it was observed that the routine uses of a small amount associated with the modified Bass technique is necessary to promote the adjuvant action of propolis in gingivitis and in the accumulation of biofilm. Thus, propolis could be an ally in the control of bacterial plaque, demonstrating efficiency in the removal of biofilm, and in the prevention of periodontal diseases (KUMAR, 2015).

Significant reductions in gingival index, with reduced inflammation, were observed in studies with propolis-based mouthwashes and in the treatment of gingivitis when using toothpaste as an adjunct. Possibly, mouthwash is the most used due to its practicality and better control in the management of gingivitis. However, Bretz et al. (2014) recommend that there is a need for a protocol for individuals to keep usual oral hygiene practices. Furthermore, propolis in the pharmaceutical form of mouthwash was also shown to significantly reduce gingival bleeding, according to Anauate-Netto et al. (2014). Groups older than 18 years were more effective. According to the authors, this may be due to the greater number of subgingival restorations, which present a greater risk factor for the increase and accumulation of dental plaque in this age group (ANAUATE-NETTO et al., 2014).

Long-term randomized clinical trials should be carried out to establish the efficacy of propolis and an ideal protocol for concentration, type of solvent, time of use and handling of applications. The disadvantage of subgingival application in periodontal pockets refers to the invasive action, which is performed with the aid of a syringe and needle and by a qualified professional, which makes home-treatment unfeasible. However, there were no reports of adverse events in the subgingival application group (NAKAO *et al.*, 2020).

Subgingival applications of propolis extract showed efficacy on chronic periodontitis. Furthermore, it has been observed that this type of application is seen as an adjunct treatment to conventional therapy, scaling, and root lanning (COUTINHO, 2012; GEBARA et al., 2003; NAKAO et al., 2020; PUNDIR et al., 2017; SANGHANI et al., 2014). Some researchers recognize that more studies are needed to show whether increasing the concentration of propolis extract and the frequency of application can bring even better results (GEBARA et al., 2003; PUNDIR et al., 2017). Based on the results evaluated in our review of topical subgingival application, there are some suggestions for future research, including the need to standardize periodontal indices for evaluating periodontitis, given that index systems are subjective and lack a professional trained and calibrated with research.

In reference to chewable gum containing propolis, the study by Ghaibie *et al.* (2016) reports an improvement in gingival indices. This can be an adjuvant therapy in the prevention of bacterial plaque, and it can be indicated for people with poor oral hygiene. It is a product that requires further research to better assess the formulation's efficacy in the mechanical control of plaque, biofilm/gingivitis and promote greater market acceptance. There are some limitations in this review, such as the evaluation of the effectiveness of chewable gum, as only one article was found, which relates to PD, gingivitis/periodontitis. Also, in other products there is a lack of standardized clinical protocols such as gingival and periodontal indices. This was a limiting factor that hindered meta-analysis of most of the articles, as measures and methods were not equivalent. It was observed that even though no research was carried out on pregnant women and children under 12 years old, generating a limitation in this sense.

Therefore, the results of this meta-analysis indicated the efficacy of using propolis in reducing the level of CAL and PPD. However, despite the significance, it is necessary to establish clinical parameters with standardized methods to enable the comparison of studies. The biggest limitation for performing this meta-analysis was the use of different methodologies for the same clinical parameter.

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## CONCLUSION

In summary, propolis is a natural product and has been added to the active pharmaceutical ingredient used in dentistry for the adjuvant treatment of oral diseases such as chronic gingivitis and periodontitis. In our study, the results demonstrated the efficacy and safety for all dental formulations containing propolis. Toothpaste was the most effective in removing biofilm, with improvement in gingival inflammation. However, the most accessible formulation was mouthwash, highlighting its use in patients with motor difficulties. In this meta-analysis with studies using subgingival irrigation, it was possible to demonstrate the effectiveness of propolis in the parameters GI, PPD and CAL. Therefore, it is concluded that the possibility of using propolis against microorganisms responsible for periodontitis is safe and effective, in addition to the potential in the adjuvant treatment of periodontal diseases. For clinical applications, subgingival irrigation solution is recommended and, if not possible, the use of mouthwash containing propolis by the patient at home is recommended.

More studies are needed with larger populations of propolis concentrations, dosage, time of use and standardization of clinical parameters, for better diagnosis and conduct of clinical research and industrial certification for reproduction of pharmaceutical products containing propolis for dental purposes.

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## **CONFLICT OF INTEREST AND SOURCE**

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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#### **Figure Caption**

**Figure 1.** PRISMA Flowchart reporting the study screening process. Cochrane Central Register of Controlled Trials (CENTRAL).

Figure 2. Assessing the risk of bias of controls included.

**Figure 3.** Results of the meta-analysis of the assessment of the total score of the ABC scale in the treatment of periodontitis with topical application of propolis. **A**: gingival index (04 and 12 weeks); **B**: Pouch Probing Depth (PPD) (04 and 12 weeks); **C**: clinical attachment level (CAL) Confidence interval (04 and 12 weeks); (CI), Heterogeneity (I<sup>2</sup>) and the p-value of heterogeneity (*p*-value).

#### **Table Caption**

**Table 1.** Characteristics of the studies included in thissystematic review and meta-analysis.

**Supplementary Table 1.** Search criteria details.