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Original Article

Evaluation of the Effects of Propolis and Xylitol Chewable Tablets on the Salivary Concentrations of Oral Micro-organisms in Orthodontic Patients: A Pilot Study

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ABSTRACT

Objectives: This study sought to evaluate the effectiveness of red propolis and xylitol chewable tablets in reducing concentrations of micro-organisms such as *Streptococcus mutans* (SM) and gram-negative bacteria (GNB). **Methods:** A total of 12 volunteers of both sexes presenting no caries (ICDAS II 0), users of fixed orthodontic appliances and with visible plaque index were randomly assigned to one of two groups. Was to determine the variations in the concentrations of SM and GNB in the saliva before and after the administration of the chewable tablets. The appearance of adverse reactions and side effects was analyzed. The Mann-Whitney (parametric) test was used for pairwise comparisons of means. The Wilxocon test was also used. **Results:** The study revealed that the propolis and xylitol chewable tablets had antimicrobial activity, reducing the concentration of GNB by -1.39 $\log_{10}$ CFU/mL (p = 0.036) and compared to placebo (p = 0.004698). There was a significant reduction of SM of -0.22 $\log_{10}$ CFU/mL (p = 0.031) and compared to placebo (p = 0.002165). **Conclusion:** Thus, in addition to the good safety profile, with a low rate of adverse effects, red propolis and xylitol tablets proved to be an effective potential low-cost alternative to combat dental caries and other periodontal diseases.

Key words: Propolis, Xylitol, Chewable tablets, *Streptococcus mutans*, Dental decay.

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INTRODUCTION

Dental caries are considered the most prevalent disease in humans, affecting 80%-90% of the world population. In children, dental caries have a higher prevalence than asthma. *Streptococcus mutans* was considered the main causative agent of the disease for decades. However, other bacteria, such as gram-negative bacteria, have been isolated and proved to be related to the process of dental decay and periodontal disease.[1-3]

These species of bacteria are present in the biofilm of the dental plaque and produce acids as metabolic by-products of carbohydrate fermentation, which alter the local pH below the critical value, resulting in demineralization of the dental tissue. Some behaviors and social determinants are associated with a higher incidence of dental caries. Some of them are carbohydrate-rich nutrition, poor or nonexistent oral hygiene and low socioeconomic status.[4,5] It is known that the use of fixed orthodontic appliances facilitates the formation of plaque stagnation areas, increasing the susceptibility to demineralization around the brackets and gingivitis.[6]

Gram-negative cocci of the genus *Branhamella* are also potentially pathogenic to the oral mucosa. They are found singly or as diplococci. The main representative is *Branhamella catarrhalis*, formerly known as *Neisseria catarrhalis*, which mainly colonizes the tongue and oral mucosa.[7]

Treatments for dental caries mostly involve comprehensive strategies that go from tissue revitalization and restoration with synthetic resins to the use of lasers and nanoparticles to recover damaged tissue.[8] The use of natural products is an option that can facilitate the access to a mechanism for preventing caries and periodontal disease. The insertion of these products in the form of pharmaceutical product such as pellets, which are self-administered, expands their use, since this type of pharmaceutical form is widely used by the population to treat conditions such as halitosis and is also used in a recreational way.[9]

In this sense, red propolis can positively modulate the de-remineralization process and can be an important tool in combating caries. Among its advantages are its pharmacological efficacy, easy obtainability and

benefits to the environment. It can be effient in preventing caries because it acts against gram-negative bacteria and *S. Mutans.*[10]

In a previous study, toothpaste with propolis extract from Alagoas, Brazil, were analyzed as to the perceptions of patients undergoing orthodontic treatments in order to assess the sensations and possible adverse effects after using the toothpaste with Brazilian red propolis. After four weeks of use, no adverse effects were observed and there was an excellent acceptance by users. The ease of use practically reached the maximum score in the study. Parameters such as taste, odor and cleanliness, also obtained high scores.[11]

The anti-cariogenic action of xylitol is determined based on its non-fermentability by acidogenic micro-organisms such as those of the genus *Streptococcus*. Xylitol also reduces the amount of insoluble polysaccharides and increases that of soluble polysaccharides. This results in a less adherent bacterial plaque and facilitates its removal through brushing, facilitating the destabilization of the biofilm.[12,13]

This study aimed to evaluate the antimicrobial activity of a propolis and xylitol chewable tablets of in salivary concentrations of oral gram-negative micro-organisms and *S. mutans.*

METHODOLOGY

Administration of chewable tablets

A total of 12 volunteers of both sexes presenting no caries (ICDAS II 0), users of fixed orthodontic appliances and with visible plaque index were randomly assigned to one of two groups. The type of chewable tablet that each volunteer used was unknown by both the professionals involved in the clinical trial and the participants.

The active ingredients xylitol and red propolis were added in the production of the tablets. Brazilian red propolis extract was collected in the city of Marechal Deodoro (9° 44.555' South Latitude and 35º 52.080' West Latitude, 18.1 m above sea level, geographical location provided by the National Institute of Industrial Property, in the state of Alagoas, Brazil).

This study was approved by the Research Ethics Committee of the Quixadá Catholic University Center (Opinion nº 3,935,708) and complied with resolution nº 466/12 on research involving human beings and with the Declaration of Helsinki on ethical principles for medical research involving human beings.

Informed Consent Forms were given to the volunteers, where they received instructions about their cooperation and the posology of the chewable tablet in the study. Adolescents with a history of allergies, asthma, urticaria, rhinitis, sinusitis or intraoral soft tissue injury were excluded from the study. None of the patients had undergone antimicrobial treatment during 3 months before the start of the study, nor during the course of this clinical trial.

Each patient chewed a tablet only once, within 3 to 5 min (swallowing). Samples were collected immediately after they chewed the tablets. In one group, the participants received the placebo (chewable tablet without xylitol and red propolis) and the other the test tablet (chewable tablet containing red propolis and xylitol).

Analysis of adverse reactions

After administration of the chewable tablet formulation, an analysis of adverse reactions was performed. For this, the volunteers were questioned about the appearance of symptoms such as itching, irritation, redness, burning sensation in the oral cavity, nausea, intestinal colic and laryngeal discomfort.

Saliva collection

Two saliva samples were collected in different stages. In the first stage, the patient chewed a piece of Parafilm® (3 cm x 3 cm), to stimulate the salivation and release of bacteria from the dental biofilm. After 60 (sixty) sec, saliva was collected with the aid of a Pasteur pipette (3 mL) from the volunteer's mouth and placed in a sterile flask (Eppendorf®) identified with a number for further analysis.

The second stage of collection was performed after using/swallowing the chewable tablet, where all participants were instructed not to drink or eat, or perform chemical or mechanical methods of biofilm control for at least one hour before collection. To minimize the influence of circadian rhythms on salivary flow, all samples were collected between 9:00 am and 11:00 am.

Microbiological analysis

For isolation and CFU/mL count of *S. mutans* and gram-negative bacteria, dilutions of 1:10 were made in sterile 0.9% saline, homogenized in a tube shaker for 30 sec. A volume of 0.1 mL of each sample was transferred to a sterile test tube, containing 0.9 mL of saline.

A volume corresponding to 10 µL of each saliva sample (dilution) was plated onto *Mitis salivarius* agar supplemented with bacitracin (50 µg/mL) and 1% potassium tellurite. The same dilution of samples was done in MacConkey agar medium.

The plates were incubated at 37°C for 48 hr in Mitis salivarius agar, in bottles under microaerophilic conditions and for 24 hr in MacConkey agar. For microbiological analysis, the saliva was transported to the microbiology laboratory in sterile flasks containing ice (2-8°C), which allows analysis in up to two hours.

After incubation, the number of colonies of *S. mutans* and gram-negative bacteria was estimated by multiplying the number of colonies in a standardized area of 1 cm^2 by the respective dilution factor, the value being expressed in Colony Forming Units (CFU)/mL of saliva.

The concentration values were expressed in $\log_{10}$ CFU/mL.

Methodology for data analysis

The Mann-Whitney (parametric) test was used for pairwise comparisons of means of samples. The Wilxocon test was also used because the samples are small. If by chance the normality was not confirmed, the the non-parametric Wilcoxon test for paired samples was used. In all tests, a 5% significance level was adopted.

RESULTS

During and after administration of red propolis and xylitol chewable tablets, none of the volunteers showed signs or symptoms of adverse reactions.

Table 1 shows the salivary concentrations of gram-negative micro-organisms, in $\log_{10}$ CFU/mL, of the placebo group and the group that received the chewable tablets before and after treatment. It was found that there was a significant reduction in CFU/mL after treatment with the propolis chewable tablet associated with xylitol (p = 0.036), both among the group itself and also when compared with the placebo group

Table 1: Concentrations of in $\log_{10}$ of UFC / mL of Gram-negative bacteria before and after using the chewable tablet based on red propolis and xylitol and placebo.

	Before	After	*p*-value[1]	Variation	*p*-value[2]
Gn	1,72(0,62)	0.33(0,52)	0,036	-1,39 (0,64)	0,004698
Placebo	1.44(0,67)	1,53 (0,24)	0,181	0,09 (0,11)	

(p = 0.004698). However, there was a non-significant increase in CFU/mL in the group treated with the placeblo.

Table 2 shows the salivary concentrations of *S. mutans*, in $\log_{10}$ CFU/mL, of the placebo group and the group that received the chewable tablets before and after treatment. As with the other tested micro-organisms, there was a significant reduction in the CFU/mL of *S. mutans* after treatment with the tested chewable tablet (p = 0.031). There was also an increase in CFU/mL after treatment with placebo (p = 0.002165).

Graph 1 shows the variation of the means of salivary concentration of $\log_{10}$ CFU/mL values of *S. mutans* and gram-negative bacteria before and after using red propolis and xylitol chewable tablets. There was a significant reduction in the salivary concentrations of the tested micro-organisms.

Graph 2 shows the variation of the means of salivary concentration of $\log_{10}$ CFU/mL values of *S. mutans* and gram-negative bacteria before and after using placebo chewable tablets. An increase in the salivary concentrations of the tested micro-organisms was observed.

DISCUSSION

Propolis is a source of several pharmaceutical and cosmetic products, including those intended for use in the oral cavity for therapeutic purposes. In this way, several patents are verified that have been deposited in several intellectual property banks.[14,15] Chewable tablets made with xylitol and other substances such as propolis are an attractive way to make the prevention strategy a reality. Most consumers buy and chew tablets for appreciation of their taste and texture, but also because they are accessible and bring specific benefits for oral health.[16] This pharmaceutical form proves to be a practical, comfortable and versatile alternative as a complement to oral hygiene.

The safety profile of natural products is higher than that of products of synthetic origin, as a rule. Thus, propolis extract has shown a low rate of adverse reactions in its various presentations. Some studies reported side effects of red propolis, including swelling, redness and hives, besides the fact that there are individuals allergic to propolis and, thus, they should not use formulations containing this substance. In addition, it is not suitable for children under one year of age.[17] These data corroborate the present study, since no adverse effects were reported by the participants.

The industry is incorporating bioactive molecules in different formulations on the market, especially mouthrinses for dental plaque removal such as Malvatrikids ®, Anapyon®, Clinexidin®, Malvatricin Plus® Plax® Colgate Fresh Tea, Propolis®, Calendula®, Malvona®, among others. Besides mouthrinses, toothpastes are the most commonly found formulations.[1,6,18]

It is known that orthodontic appliances facilitate the accumulation of biofilm, which can cause microbiota imbalance. Thus, antibacterial substances can be used to destabilize the biofilm in individuals with difficult control of dental plaque. Several studies demonstrate the antimicrobial effect of propolis, with significant results in patients with gingivitis.[11,19]

Propolis is distinguished by the broad gram-positive and gram-negative spectrum against oral biofilm micro-organisms, such as *S. mutans, Lactobacillus, Aggregatibacter actino-mycetemcomitans, Actinomyces naessludii, Porphyromonas gingivalis* and *Prevotella intermediate*.[6,20,21]

A study carried out a clinical and microbiological evaluation of the effectiveness of a new toothpaste incorporating Brazilian red propolis for biofilm control in adolescent patients using orthodontic appliances and who presented signs of gingivitis. The study reported a good activity of the propolis toothpaste against *S. mutans* and gram-negative bacteria and a reduction in marginal bleeding after 4 weeks of treatment.[6] The search for substances with pharmacological properties with less adverse effects has generated a growing interest in natural products. The high demand for propolis and the modernization of analytical devices have contributed to the release of several products on the market.[22,23] These data are similar to those found in this study, in which the decrease in *S. mutans* and salivary gram-negative bacteria was also found.

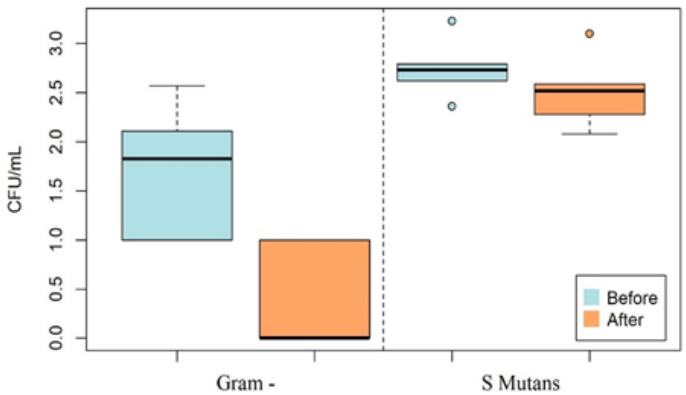
A cross-sectional clinical trial evaluated the action of a Brazilian red propolis dental varnish on the salivary *S. muntas*. It was verified that the concentration of 2.5% of Brazilian red propolis was effective in reducing salivary levels of the tested micro-organism, given that it is similar to the study presented here, in which the same concentration was used.[2]

A crossover study showed a greater efficiency of toothpaste incorporating propolis than commercial toothpaste in reducing plaques. This reinforces the effectiveness in terms of antimicrobial activity of this natural compound.[24]

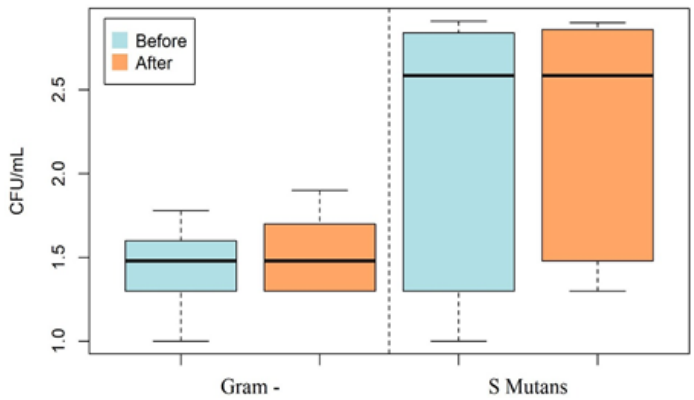
A research showed the effectiveness of preparations containing up to 3% propolis extract. In these experiments, the toothpaste with propolis generated an efficient contribution in the removal of plaques and proved

Table 2: Concentrations of in log10 of UFC / mL of Steptococcus mutans before and after the use of the chewable tablet based on red propolis and xylitol and placebo.

	Before	After	p-value[1]	Variation	p-value [2]
S mutans	2,74 (0,28)	2,52 (0,35)	0,031	-0,22 (0,74)	0,002165
Placebo	2,20 (0,83)	2,29 (0,71)	0,419	0,08 (0,19)	



Graph 1: Variation of the concentrations of salivary micro-organisms before and after the use of chewable tablet containing red propolis and xylitol.



Graph 2: variation of the concentrations of salivary micro-organisms before and after the use of the placebo chewable pastille.

to be able to improve the general marginal periodontal health.[25] As to xylitol, this substance has an anti-cariogenic action determined mainly by the non-fermentability by bacteria of the genus *Streptococcus*. The proliferation of bacteria is limited and this promotes a reduction in insoluble polysaccharides, forming a less adherent biofilm, of easier removal during brushing.[13,26] Furthermore, xylitol can promote enamel remineralization by increasing salivary flow, preventing a drop in the pH of the tooth surface and increasing the buffering capacity and bacteriostatic activity of saliva.[13,27]

The effect of xylitol on the inhibition of the growth of *S. mutans* in human and artificial saliva has been verified, even with the addition of glucose.[26] In study has already been observed that xylitol and L-carbohydrates induced less adhesion and formation of biofilm of the species *Candida albicans* and *S. mutans*.[28] This fact becomes relevant because it may favor the patient's oral health as a complement to adequate oral hygiene.

Removal of dental biofilm, oral hygiene practices and professional intervention are essential to eliminate dental biofilm. Brushing contributes to the maintenance of gingival health, but there is consistent evidence that the use of antimicrobial substances contributes to the control of plaques and prevents most oral pathologies, such as gingivitis in situations of greater risk.[6,9,11,29] It was, therefore, verified that the combination of propolis and xylitol in chewable tablets was beneficial, presenting positive effects on the dental biofilm.

This study is a pilot clinical trial, however it appears that a chewable tablet incorporated with propolis and xylitol shows itself as a promising strategy as an ally in maintaining oral health along with proper hygiene habits and health education. Therefore, further studies are needed to evaluate the long-term performance of this pharmaceutical product.

CONCLUSION

This study showed that chewable tablets containing propolis and xylitol had a remarkable antibiofilm activity against gram-negative micro-organisms and *S. mutans*.

Thus, besides the good safety profile, with absence of adverse effects documented in this study, red propolis and xylitol tablets revealed to have a major potential to be an effective low-cost alternative and yet natural adjuncts in the prevention of dental caries and other periodontal diseases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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