Propolis in Periodontal Disease

Subjects: Nursing

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Propolis is a natural substance produced by bees which has proven useful for treating periodontal disease.

propolis | periodontal disease/periodontitis | gingivitis | oral health | oxidative stress

1. Introduction

Propolis is a non-toxic resinous substance produced by bees that has antimicrobial, antifungal, anti-inflammatory, antioxidant and antitumor properties, among others[1][2], which have attracted the attention of researchers, both in the medical and in the dental field.

It is a mixture of plant extracts mixed with the bees' own saliva, which varies according to its place of origin, with Brazil leading the research on this product. Its composition is based on vegetable resins (50%), waxes (30%), essential and aromatic oils (10%) and pollen and other organic substances (10%). The chemical composition of propolis depends on the geographic location, the botanical origin and the species of bee[3][4]. Nevertheless, its composition is quite complex, its main components being flavonoids and phenolic esters such as caffeic acid phenethyl ester[5][6]. The flavonoids contained in propolis have been found to have antimicrobial, anti-inflammatory and immunomodulating properties, which are extremely useful to treat aphthous ulcers, candidiasis, gingivitis and periodontitis[7][8].

Periodontal disease is likely to be the most common chronic infection in adults[9]. There is evidence that suggests that nearly all forms of periodontal disease are specific chronic bacterial infections that stem from the overgrowth in dental plaque of a limited number of species, mainly anaerobic, such as *Porphyromonas gingivalis*, *Bacteroides forsythus* and *Treponema denticola*[10], considering the induction of inflammatory signaling pathways by pathogenic bacteria to be crucial for the development of inflammatory processes in the periodontium[11].

Periodontal diseases have traditionally been associated with the development of certain systemic conditions, systemic inflammation being one of the main reasons for this association[12].

The presence of inflammatory infiltrate and an increase in the oxidative response of peripheral polymorphonuclear cells, are constant characteristics of periodontal disease, there being greater damage as the disease advances because of the increase in the number of reactive oxygen substances (ROS). The increase in the amount of free radicals, causes oxidative damage to gingival tissue, periodontal ligament and alveolar bone. The deterioration caused by free radicals is regulated by an antioxidant defense system, in such a way that when an imbalance

between the production of free radicals and antioxidant levels takes place, it triggers a condition known as oxidative stress (OS), which is defined as an imbalance between the production of free radicals and the body's capacity to eliminate these reactive species [13][14][15].

Free radicals are extremely unstable organic and inorganic molecules that contain an unpaired electron. They have the capacity to take electrons from other atoms and molecules, causing a release of proinflammatory cytokines such as interleukin-2, 6 and 8 (IL-2, IL-6 and IL-8), interferon-β and tumor necrosis factor α (TNF-α), which play an extremely relevant role in the pathogenesis of periodontal disease[16][17].

It is believed that disturbances in the local and/or general indicators of oxidative stress are one of the mechanisms in the etiopathogenesis of periodontitis, and, in recent years, different basic clinical and experimental studies have provided evidence of a strong association between oxidative stress and periodontal disease[18].

A better understanding of this association could provide deeper insight into the pathology of this disease, shed further light on the relationship between periodontal disease and systemic inflammation, and increase knowledge of therapeutic approaches.

2. Effectiveness of Propolis in the Treatment of Periodontal Disease

Treatments based on natural products are regarded as alternative or complementary in certain oral conditions. Indeed, products from the hive such as honey and royal jelly, are used to treat mucositis and other disorders of the oral mucosa[19][20][21].

Although propolis has been traditionally used in folk medicine to treat certain diseases, its mode of action and the chemicals that are responsible for its therapeutic activity remain unknown. It is generally used as a mouthwash at different concentrations (1%, 2.5%, 5%, 10%), although there are other formulations that include oral capsules, gels or cosmetic creams[22].

The aim of this meta-analysis was to determine the effectiveness of propolis in the treatment of periodontal disease. According to the findings, propolis acts better than standardized treatments for certain therapeutic goals such as reducing dental plaque and microbial activity and stabilizing gingival and periodontal indices. It is significant that none of the results included in this review reported harmful or counterproductive effects in participants treated with propolis.

Two of the studies[23][24] addressed the effect of propolis on dental plaque control; four[25][26][27][28] explored the effects of propolis in relation to the reduction of probing pocket depth, inflammation and gingival bleeding; and two [29][30]analyzed the decrease in *Porphyromonas gingivalis* through the use of propolis mouthwashes.

The antimicrobial effect of propolis against periodontal pathogens has been studied in vivo and in vitro[31][32][33]. Nakao and colleagues[29] reported significant improvements in CAL and PPD alongside a trend towards a reduction of *Porphyromonas gingivalis* (a pathogen that plays a key role in periodontal disease) in gingival crevicular fluid (GCF) in patients treated with propolis solutions. Similarly, Yoshimasu and colleagues[34] proved the effectiveness of isolated propolis products such as artepillin C, baccharin and ursolic acid as antimicrobial compounds against *Porphyromonas gingivalis*; artepillin C and bacchatin are bacteriostatics and ursolic acid is a powerful destructor of the bacterial membrane, probably because of its highly lipophilic nature. In a study based on a sample of 20 patients diagnosed with chronic periodontitis, Sanghani and colleagues[30] reported a statistically significant reduction ($p < 0.05$) of *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum* in periodontal pockets in the group of patients under propolis treatment.

Two of the selected studies analyzed the effect of propolis on dental plaque. Sparabombe and colleagues[23] evaluated its anti-inflammatory effect using a sample of patients with moderate/severe periodontitis who underwent a 3-month treatment with propolis-based mouthwashes, finding a significant improvement in the reduction of plaque buildup and gingival bleeding. Likewise, Piekarz and colleagues[24] reported a significant reduction during the first week of treatment with toothpaste containing ethanolic extract of propolis ($p < 0.006$), and a very significant reduction after 4 weeks of using it ($p < 0.0002$). These results are consistent with those of other studies on the antiplaque and antigingivitic effects of mouthwashes containing other flavonoids and essential oils in individuals with and without periodontal disease[35][36]. Nonetheless, certain studies have shown that certain forms of periodontitis are not associated with plaque and depend exclusively on the individual's systemic condition[37].

Gingival and periodontal indices and salivary markers of oxidative stress were measured in four of the included studies[25][26][27][30]. Giammarinaro and colleagues[25] studied the efficacy of propolis as compared with chlorhexidine in a sample of 40 patients suffering from gingivitis, finding no significant differences between the control and the experimental group in probing pocket depth (PPD), bleeding on probing (BoP) and plaque index (PI); however, the patients treated with propolis achieved better results in terms of oxidative stress markers in the saliva, with considerable improvement in their periodontal health. Different studies have related oxidative stress in the saliva and the progression of periodontal disease. The main enzymatic antioxidants which have been widely studied in the gingival fluid, saliva and blood serum of patients with periodontitis are superoxide dismutase, glutathione peroxidase and catalase. The activity of these enzymes in gum tissue, gum fluid, saliva and blood serum during the different types of periodontitis (chronic or aggressive) is quite uneven. Despite the fact that Toczewska and colleagues reported that activity in gingival tissue is usually high[38], Tartaglia and colleagues[39], in a preliminary study, found that antioxidant levels in the saliva are reduced in patients with periodontal disease.

Likewise, Miricescu and colleagues[40] found high levels of oxidative stress associated with alveolar bone loss in the saliva of patients with periodontal disease. Likewise, other authors have suggested that patients suffering from this condition are more likely to experience oxidative stress imbalance and have reported that such a situation would be a consequence of periodontitis[41][42][43]. A study on test animals conducted by Aghel and colleagues[44] also proved the beneficial effect of propolis on saliva antioxidants.

The study by Sharkawy and colleagues[27] was the only one where propolis was used as a dietary supplement. It provided a comparison of the use of a placebo and the ingestion of 400 mg of propolis in patients with long-standing diabetes mellitus associated with periodontitis, reporting a significant reduction in periodontal parameters. The group treated with propolis showed a greater reduction in pocket depth (PD) and an increase in CAL as compared with the control group, probably because of the anti-inflammatory, antimicrobial and antioxidant activity of propolis. Interestingly, the use of propolis as complementary to oral hygiene revealed similar results in other studies[45][46].

Pérez de Andrade and colleagues, and Anauate-Netto and colleagues[26][28] reported a reduction in gingival inflammation and probing depth in patients treated with propolis solution mouthwashes as compared with those using 0.12% chlorhexidine or saline mouthwashes.

In general, the anti-inflammatory and antimicrobial properties of propolis have been well documented[45] and it will eventually be possible to explain any type of clinical result, either in healthy or diseased individuals, through the analysis of the oral microbiome[47][48][49].

Nevertheless, this study has a series of limitations, especially because of the heterogeneity found in the measurement of periodontal disease parameters such as plaque or bleeding, loss of clinical attachment, patient hygiene or the oxidative stress of the saliva. We only found unanimity among studies in the measurement in millimeters of probing depth, although two of the studies included did not measure this parameter[24][28]. Bleeding was measured using a variety of indices and assessment criteria: two studies did not evaluate gingival bleeding [24][26], two used the Bleeding on Probing (BoP) index[29][25], another used the Papillary Bleeding Score (PBS)[28], another the Eastman Interdental Bleeding Index (EIBI)[27] and others used unspecified bleeding indices[23][30].

In relation to plaque index, four studies used the Plaque Index (PI)[25][24][26][27], one used the Plaque Control Record (PCR)[29] and another[23] used the Plaque Score (PS); another two studies did not measure plaque[28][30]. An additional factor that is relevant to the assessment of periodontal disease is the Gingival Index (GI), which was only assessed in two studies[26][30]. It should also be noted that certain studies used different indices to measure the parameters and did not specify the criteria used for measurement with each of the indices, which hinders the interpretation of results. Others provided the data concerning the assessment of these indices at the beginning of the study but did not provide numerical data in reassessments, only showing graphs or mentioning that the parameters had been measured but providing no data. There were also discrepancies regarding assessment timing, some studies testing after 1 month and others after 3. Regarding oxidative stress, despite this being considered a predictable and measurable value related to a severe inflammatory state and a marker of the risk of periodontal disease[38][39], only the study by Giammarinaro and colleagues[25] dealt with this situation. All these factors hindered data analysis and precluded their inclusion for quantitative analysis.

For all these reasons, the authors recommend that the results be interpreted with caution, mainly due to the small number of selected studies and the small sample sizes used in each of them.

It would be advisable to perform a larger number of randomized clinical trials comparing the use of propolis with a placebo or chlorhexidine, using unified criteria, to assess periodontal parameters (plaque, bleeding, hygiene, dental mobility…) unified research indices and test timing for such parameters and structured, and standardized guidelines and measures in product administration, which could guarantee reliable and predictable results. Likewise, it would be advisable to reduce the bias of selective disclosure of results and for studies to provide the data related to all the assessed parameters, even if as annexed material to the published study.

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