Review Article
Advancements in Life Sciences – International Quarterly Journal of Biological Sciences

ARTICLE INFO

Date Received: 03/05/2023;
Date Revised: 11/09/2023;
Date Published Online: 31/12/2023;

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How to Cite:
Gholamine B, Alwaily ER, Mustafa YF, Habash RT, Naghdi N, et al., (2023). An overview of the uses of propolis for oral health. Adv. Life Sci. 10(4): 515-524.

Keywords:
Propolis; Dentistry; Honeybee; Oral health; Bee glue

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An overview of the uses of propolis for oral health

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Abstract

Propolis is a gummy agent exploited from bees, which has anti-inflammatory, antibacterial, anti-allergic, wound healing, antidiabetic, and antiviral effects against various injuries and diseases. It also produces antifungal, antitumor and local anesthetic effects. The aim of the review was to review research findings on the role of propolis in oral health. This study was conducted by reviewing published articles on the use of propolis in oral health. To this end, Persian electronic databases such as Google, SID and Magiran as well as English databases such as PubMed and WOS were searched for articles published from 1979 onwards, 140 papers were retrieved, 21 articles were excluded, and 119 articles were included in final review. So far, propolis has been studied for the treatment of surgical wounds, intracanal irrigation, inhibition of the decay process, treatment of periodontitis and dentin hypersensitivity, and potential antifungal and antibacterial activities in the canal with a mostly satisfactory efficacy. Propolis has been reported to improve surgical wounds and produce anti-decay, anti-dentin hypersensitivity and anti-aphthous ulcer properties, and to be useful as a tooth-storing medium after tooth extraction, an intracanal irrigant and a mouthwash. substances highly useful properties of propolis, it can be argued that in the future, the substance will play a substantial role in dental science are necessary to isolate its compounds and identify their beneficial effects.

Introduction

Propolis (bee glue) is a sticky composition produced by bees that has long been used in medicine due to its beneficial properties. The word propolis means *in front* (pro) *of the city* (polis), which accentuates the protective role of propolis in bee colonies. Many studies in medicine have shown the potential benefits of propolis and its components, including a wide range of effects, such as antioxidant, wound-healing, antitumor, antidiabetic, protective and anti-inflammatory effects. During the Egyptian and Greek civilizations, propolis was widely used for its therapeutic properties [1]. The use of this substance in dentistry is a relatively new issue, however, thanks to the impacts of propolis on infection, decay and cancer, it may have applications in the prevention of oral diseases as well [1-3]. Humans have been familiar with the medicinal properties of propolis for a long time [4]. There are more than 100 systemic diseases and more than 500 drugs for oral diseases, of which 145 prescribed drugs cause dry mouth, and there is evidence that they can affect oral health [5]. Some of the most common dental diseases are dental caries, bacterial dental plaque, tooth decay, bad breath, swollen gums and cancer. Propolis is composed of plant resins, which are collected by honeybees. Some propolis compounds, bees later add bee secretions and pollen to produce the final product, i.e., propolis [3,5,6]. The important chemical components of propolis are flavonoids, several phenolic and aromatic compounds, minerals and vitamins A, E and B-complex [2, 7]. Caffeic acid reduces the inflammatory response by inhibiting the lipoxygenase and cyclooxygenase enzymes. Propolis also boosts the body's immune system by inducing phagocytic activity and cellular immunity. Various enzyme systems present in propolis are involved in cell metabolism cycles [8]. These attributes of propolis heal wounds. This may be due to the presence of similar active ingredients in different types of the substance [9-11]. Since the past, propolis has been widely used to treat oral diseases and dental problems because oral health is one of the most important aspects of public health and has a profound impact on mental and social health. Oral diseases include dental cavities, gum disease, swollen and bleeding gums, oral infectious diseases, and oral cancer. Dental cavities usually occur and lead to decay when plaque accumulates on the teeth. The bacteria in the plaque produce acids that destroy tooth enamel. People who have oral infections are prone to bacterial, fungal and viral infections that cause ulcers in the lips, under the tongue and soft tissues in the face. These ulcers can be uncomfortable or painful and cause dry mouth, swallowing problems and oral cancer, although various oral cancers often do not cause specific symptoms in the initial stages. Therefore, propolis is used for to prevent and treat caries and other dental diseases, as the temporary growth medium of extracted teeth, and to treat dentin hypersensitivity, cases of using dentures and swollen gums due to its antimicrobial properties. The aim of the present study is to review the research findings on the effects and applications of propolis in improving oral hygiene and its protective effect in oral care and hygiene against dental plaque-induced infections, caries, swollen gums, bad breath and oral cancer. Propolis is also useful to prevent the effects related to the treatment of head and neck cancers, including chemotherapy-induced oral mucositis and dry mouth, and to heal mouth sores.

Methods

Literature Search and Selection Criteria

Since we did our best to conduct a comprehensive and inclusive study, search was done using the keywords *Propolis* combined with *Dentistry*, *Honeybee*, *Oral health* and *Dental treatment* in electronic data banks, Google resources and scientific databases such as: the Scientific Information Database (*SID*), Iranian Food Science and Technology Data Bank (Magiran) and Latin databases *Web of Science* and *PubMed*. Most of the articles were retrieved from PubMed. Articles published from 1979 were included after the search, and a total of 140 articles were retrieved, 20 of which were excluded, and the rest were included in the final review. The title and abstract of each article were studied and then articles published in Persian or English that reported clinical trials and *In-vitro* or *In-vivo* studies on the use of propolis in dentistry were selected based on the inclusion criteria. In order to complete the information from all the searched electronic banks, a checklist was designed that included items such as: type of study, time of study, and study of the use of propolis in dentistry. The inclusion criteria were as follows: 1) Accessing the full text of the article; and, 2) Being published in Persian or English. Publications such as case reports, letters to the editor, and article summaries accepted in conferences were not included for review.

Discussion

Preventive uses in dentistry

Anti-decay agent: In addition to several methods that are currently used to prevent tooth decay (such as fluorides, diet measures, betadine, probiotics) that affect one or more stages of the caries process, propolis can also be considered as an anti-decay agent because it prevents the synthesis of water-insoluble glucans, affects acid production and the resistance threshold of microorganisms to acidity [6, 19, 34, 58] .The mechanisms of action of anti-caries and anti-plaque

properties of propolis include antimicrobial activity against caries-causing bacteria as well as inhibition of glycosyltransferase enzyme activity [59-61]. In a study, the effect of propolis on *S. mutans* and the activity of glucosyltransferase and cavities spread in the teeth of laboratory mice was examined. The results of that research showed that propolis acted satisfactorily as an anti-decay agent and inhibited the activity of this enzyme. The study of Ikeno *et al*. also showed this effect [19, 60]. The multiple activity of propolis causes the synthesized glycan to be insoluble and the activity of glycosyl transferase enzyme, which is an effective enzyme in glucose transfer, is discontinued [61, 62]. Propolis is also used as an adjuvant for vaccination. It may also be used as an anti-caries vaccine in the future, such as fluorides, betadine, casein, phosphopeptide, and non-crystalline calcium phosphate [6, 10, 63-65]. Hidaka *et al*. investigated the inhibitory effect of bee propolis on the rate of conversion of non-crystalline calcium phosphate to hydroxyapatite, which is effective in the formation of dental plaque [20].

Culture medium for storing extracted temporary teeth: If a tooth is traumatized and completely extracted, the time it is out of the bony location of the tooth, as well as the material in which it is kept, is very important in the long-term prognosis of the tooth that is placed back in its place. Pileggi *et al*. used HBSS of milk and salt to keep teeth outside the mouth and the results showed that propolis was better than HBSS solutions of milk and salt because more PDL cells remained viable. It has also been demonstrated that propolis can prevent root resorption up to 2% compared to fluoride solution [13, 14, 39, 66-70]. Alshaher *et al*., comparatively studied viability life of fibroblast cells of periodontal ligament and dental pulp in treatment with propolis and calcium hydroxide powder *in vitro*. The dental pulp and periodontal ligament cells were isolated from extracted human wisdom teeth and exposed to various concentrations of propolis (0-20 mg/mL) and calcium hydroxide (0-250 mg/mL), and then the cells were stained and spectrophotometrically examined. The results showed that if periodontal ligament cells or dental pulp fibroblasts were exposed to propolis at 4 mg/ml or less, 75% of the cells would survive. On the contrary, calcium hydroxide at 4 mg/mL was lethal to cells and less than 25% of cells survived. The findings of that study revealed that propolis was a suitable storage medium for extracted teeth [16].

Gum therapy: Swollen gums is a common disease in the gums that when plaque, which is a kind of adhesive bacteria, forms on the teeth, it gradually leads to inflammation in the gum tissue and, in many cases, bleeding gums. This bacteria and plaque can even damage other parts of the oral cavity such as tooth enamel. Propolis is effective to prevent the development of inflammation and also specifically affects the causes of gum inflammation. Therefore, inflammations can be removed with propolis, and reducing the amount of insoluble polysaccharides by propolis not only reduces the plaque volume, but also affects the possibility of caries development. In laboratory mice, propolis when given systemically, histological morphological evaluations showed a reduction in gingival caries. Propolis extract is known to be much more effective than other conventional treatments to reduce inflammation of the gums and tooth enamel. [20, 22, 33, 71-74].

Root canal therapy is examined in two ways:

Intracanal medication: Calcium hydroxide has been commonly used as an intracanal medication, but it has disadvantages including the need for a long time for activity and the inability to destroy all types of microorganisms. It has been reported that propolis produces a substantial inhibitory effect on *Enterococcus faecalis* in comparison with calcium hydroxide and a combination of three antibiotics, ethanol and saline. By comparing propolis and corticosteroid antibiotics, it is determined that propolis has reduced the inflammation of dogs' teeth over a period of 28 days. Propolis and calcium hydroxide have similar physical properties, however, propolis is 10 times less toxic on the tissues of the tooth covering [16, 27, 36, 75]. In another study, they investigated the effectiveness of three intracanal drugs and propolis against *Enterococcus faecalis*. The results showed that propolis in the root canal could prevent the growth of *Enterococcus faecalis* and its antibacterial activity is suitable [69]. Also, in another study, they compared propolis and calcium hydroxide as intracanal drugs, and their results showed that propolis is a good intracanal medicine and destroys Enterococcus faecalis quickly [27]. In investigations to compare the antimicrobial activity of propolis extract and calcium hydroxide powder mixed with physiological serum in agar culture medium, Ahangari *et al*. reported that propolis was more effective than calcium hydroxide on *Enterococcus faecalis*, *Peptostreptococcus* and *Lactobacillus* [28].

Propolis as an intracanal irritant: In a study in which the antimicrobial efficiency of propolis, sodium hypochlorite and salt were investigated for intracanal irrigation, microbiological samples were collected immediately after opening of the canal, preparation of the access hole and preparation and irrigation of the canal, and the effects of propolis on the number of existing colonies were investigated.

Reference	Years of publication	Type of study	Shortened title
Carvalho&Magro[12]	1990	Randomized clinical trial	The healing of surgical wounds
Pileg&Martin [13]	2004	In vitro	Propolis as a tooth storage medium after tooth extraction
Ozan [14]	2007	In vitro	Propolis as a storage medium for the cells of the pulled tooth ligament
Gopikrishna [15]	2008	In vitro	Propolis as a storage medium compared to other mediums
Al-Shaher [16]	2004	In vitro	The effect of propolis on fibroblasts and periodontal cells
Al-Madi&Qathami [17]	2003	In vitro	Propolis as a canal cleaner
Ozan [18]	2007	Randomized clinical trial	Propolis as a mouthwash
Hayacibara [19]	2005	In vitro	Propolis as an anti-decay agent
Hidaka [20]	2008	Randomized clinical trial	Propolis in the treatment of periodontitis
Toker [21]	2008	In vitro	Propolis effects on the regeneration of alveolar and jaw bones
Murray [22]	1997	Randomized clinical trial	Mouthwash on dental plaque
Martins [23]	2002	Randomized clinical trial	The effect of propolis on *Candida albicans*
Momen [24]	2009	In vitro	Antibacterial effect of propolis on the most common oral pathogens
Santos [25]	2008	Randomized clinical trial	Propolis in the treatment of stomatitis
Oncag [26]	2006	In vitro	Propolis as an intracanal medication
Awawdeh [27]	2009	In vitro	The effect of propolis as a medicine on Enterococcus faecalis
Ahangari [28]	2009	In vitro	The effect of propolis on the pathogenic bacteria *Enterococcus faecalis*, *Peptostreptococcus* and pathogens
Samet [29]	2007	Randomized clinical trial	Propolis in the treatment of recurrent aphthous stomatitis
Mahmoud [30]	1999	Randomized clinical trial	Propolis in dentin hypersensitivity
Parolia [31]	2010	Randomized clinical trial	Propolis as pulp capping
Sales [32]	2011	In vitro	Reducing dentin permeability
Troca [33]	2011	In vitro	Propolis and its combination with dental materials for the improvement and quality of dental hygiene
Bertolini [34]	2012	In vitro	Antimicrobial capacity of propolis in toothpastes
Mattigatti [35]	2012	Randomized clinical trial	Antibacterial effects of drugs compared to propolis in endodontic treatment
Ramos [36]	2012	In vitro	Analysis of propolis paste as intracanal medication after pulpectomy
Altan [37]	2013	In vitro	Study of histomorphology and bone formation under the influence of propolis
Jolly [38]	2013	Randomized clinical trial	Comparison and evaluation of antimicrobial potential
Mahal [39]	2013	In vitro	Propolis as a suitable storage medium for periodontal ligament cells
Tomazevic [40]	2013	Randomized clinical trial	Propolis as a reducer of oral mucositis in children undergoing chemotherapy
AkhavanKarbassi[41]	2016	Randomized clinical trial	Propolis and its effect on oral mucositis in patients undergoing head and neck chemotherapy
Bretz [42]	2014	Randomized clinical trial	The effect of propolis on swollen gums
Tulsani [43]	2014	Randomized clinical trial	Antimicrobial effect of propolis on *Streptococcus mutans* saliva
Zare Jahromi [44]	2014	In vitro	Effects of propolis on dental fibroblasts
El-Sharkawy [45]	2016	Randomized clinical trial	Propolis reduces periodontotis and type 2 diabetes
Niedzielska [46]	2016	Randomized clinical trial	Propolis effect extract on oral microbiota
Sabir [47]	2017	In vitro	Anti-inflammatory and immune system modulating properties in dental pulp tissue
Shabbir [48]	2020	Randomized clinical trial	The effect of propolis as an intracanal medication for the treatment of root pain
Bapat [49]	2021	Randomized clinical trial	Propolis mouthwash on oral microorganisms
Gonzalez [50]	2021	Randomized clinical trial	Gel containing propolis extract and nanovitamin on mucositis around the implant
Machorowska [51]	2021	Randomized clinical trial	Benefits of propolis paste for oral health in cleft lip patients
Papp [52]	2021	In vitro	Antifungal properties of propolis
Park [53]	2021	Randomized clinical trial	Clinical and immunological effectiveness of propolis extract and mangosteen on gingivitis
de Faveri [54]	2022	Randomized clinical trial	The effect of propolis on the microbiota of people with morning breath
Neto [55]	2020	Randomized clinical trial	Propolis extract against *Streptococcus mutans* infection and prevention of tooth decay
Kiani [56]	2022	Randomized clinical trial	Effects of propolis on clinical periodontal parameters in patients with gingivitis
Lotif [57]	2022	Randomized clinical trial	Effects of propolis on teeth orthodontics

Table 1: The shortened titles and characteristics of some studies conducted on the properties of propolis in dentistry.

The results of that study showed that propolis had the same antimicrobial activity as sodium hypochlorite [17]. Intracanal irrigation: The role of propolis as an intracanal irrigant has been reported to be effective in reducing the growth and inhibiting the activity of common bacteria such as *Canada albicans*, *E. coli*, *aureus Streptococcus*, *E. faecalis* [35, 76].

Pulpotomy: Propolis has been used as a protective material of the pulp in permanent teeth and as a material in the pulpotomy of milk teeth. Studies have shown that the reason for this protection by propolis is related to components like flavonoids, which increase hardness. Flavonoids can reduce bacterial growth [31, 87]. In the study of Parolia *et al.*, the outcomes of MAT treatment with propolis were similar to those of calcium hydroxide treatment. The reason for the effectiveness of this substance in reducing the sensitivity of the pulp is its resinous and adhesive properties, which causes blockage of dentin tubules, and also its anti-inflammatory property, which reduces pulpitis [30, 31, 77].

Orthodontics: In a study, it was determined that propolis solution had an optimal effect on the formation of bone tissue in the mouth after suturing, and caused the repair and improvement of bone formation in the damaged sites. In that study an increased number of osteoblasts and rapid bone repair were observed in mice that had received propolis solution in their treatment [37].

Oral oncology: In an investigation of sensitivity to radio waves using propolis in cancer cells of the human head and neck, it was observed that in one third of the cases, propolis increased the sensitivity to radio waves and caused the growth of cancer cells to decrease [78]. Dentin hypersensitivity: Dentin hypersensitivity refers to a short and acute pain in the dentin that appears in

response to tactile, thermal, or chemical stimuli and does not have symptoms similar to other oral and dental diseases. Various substances have been used to reduce this hypersensitivity, one of which is propolis.

The possible mechanism can be associated with the blockage of the root canal infection. Mahmoud *et al*. investigated the effect of propolis on dentin in the clinic. Twenty-six women aged 16 and 40, with an average age of 28, participated in this study. Those whose teeth were hypersensitive applied propolis to their teeth twice a day. Then, after 1 and 4 weeks, the sensitivity of their teeth was scored with a visual ruler that was graded from 0 to 10. Seventy percent of the samples had hypersensitivity at enrollment. In the first examination, 50% of them still suffered from dentin hypersensitivity, in the second examination, 50% had mild sensitivity, 30% had no sensitivity, and only 19% had moderate sensitivity. *In vitro*, scanning electron microscope images showed that propolis blocked dentin tubules [30]. The propolis extract has been found to be much more effective in reducing inflammations of the gum and the enamel than conventional treatment methods [20-22, 72, 73].

Gingivitis: Systemic consumption of propolis at 5 mg per day has been reported to be effective in reducing the prevalence or progression of diseases caused by gingivitis [29].

Antifungal property: Martins *et al*. compared the susceptibility of patients with AIDS and simultaneous acquisition of oral candidiasis to the 20% ethanol extract of propolis in the inhibitory actions of the nystatin, clotrimazole, econazole and fluconazole antifungal agents. Ethanol extract of propolis caused significant differences compared to other antifungal drugs. Propolis extract prevented the growth of *Candida albicans* and it was argued that it could serve as an alternative drug for candidiasis-induced lesions in AIDS patients [23]. Antiviral property: Studies show that in the future, propolis can play a role in preventing or improving and treating infection caused by herpes simplex virus. Both *in vivo* and *in vitro*, propolis does this by preventing viruses from being absorbed into the host's cells [12, 79]. Antibacterial effect of propolis: Momen-Beitolahi *et al*., investigated the antimicrobial properties of Iranian type of propolis on harmful oral microorganisms including *Candida albicans*, and *Streptococcus mutans* and *Actinobacillus*, and the results showed that propolis extract produced substantial antimicrobial effects on oral microorganisms, including *Candida albicans* [24]. Propolis has antibacterial effects, among which the effect of propolis against gram-positive bacteria especially *Staphylococcus aureus* can be mentioned [80]. Researchers have investigated the antibacterial activity of propolis against some anaerobic oral pathogens and the results of their research showed that propolis acted against *L. acidophilus*, *A. naeslundii*, *P. oralis*, and *P. melaninogenica*, *P. gingivalis*, *F. nucleatum* and *P. veillonella* and the reason for this effect was the presence of flavonoids [62]. Kujumgiev *et al*., investigated the antibacterial property of propolis against *S. aureus* and *E. coli*, its antifungal property against *C. albicans*, and the antiviral property of this substance against Avian influenza virus, and their results showed that propolis was effective against them. In addition, the use of propolis with other antibiotics makes their effect 10-100 times more pronounced and therefore propolis seems to produce a synergistic effect in cotreatment with them [81]. Regarding the mechanism of antibacterial action of propolis, research has shown that propolis prevents the cell division of bacteria and causes them to form false multicellular spores. Park *et al*. have shown that propolis prevents the activity of bacterial glucose transferase [59]. It has been demonstrated that propolis inhibits the activity of RNA polymerase enzymes dependent on bacterial DNA and its restriction enzyme [82]. The most important antibacterial compounds of propolis are pinobanksin, pinocembrin, galangin, caffeic acid phenethyl ester, di- and trioxyflavones, sinapic acid, isoferulic acid, diterpenic acid, and syringaldehyde, which produce the effects either alone or synergistically [78-82]. The study of Farajzadeh *et al*., on antibacterial effect of propolis on a number of pathogenic bacteria using various bacterial strains and three ethanolic, methanol and chloroform extracts of the substance, showed an inhibitory effect on gram-positive bacteria but no effect on gram-negative bacteria, although this difference remains to be explained [78-82]. In one *in vitro* study where the extract had no effect on gram-negative bacteria, and on the other hand, stimulation of the immune system by *Klebsiella pneumoniae* bacteria and *Proteus vulgaris in vivo*, it was argued that the immune system was stimulated after propolis extract treatment [6]. The propolis of honeybee is one of the substances that have long been used as a disinfectant [6]. In ancient Egypt, pharaohs used propolis for embalming corpses [19]. In a study on the control of rat tooth decay and the effect of propolis on *Streptococcus mutans* and *Streptococcus sobrinus*, it was determined [11]. Mouth ulcer healing: In a study after tooth extraction, patients' mouths were washed with alcoholic propolis mouthwash to investigate its effect on the healing of oral wounds. The patients were asked to return 7, 14, 30, and 45 days after the surgery for cytological and clinical examinations, and the following results were obtained: 1- The mouthwash accelerated wound healing and had anti-inflammatory and pain-relieving properties; 2- It

had a stimulating effect on accelerating the healing of wounds due to tooth extraction; and 3- Cytological examinations showed that the surgical wounds were epithelialized. The results of that study showed that if the alcoholic propolis solution was applied locally, the epithelium would recover faster after tooth extraction [12]. Hydroalcoholic propolis solution has analgesic and anti-inflammatory effects and also helps to heal wounds caused by oral surgery [81, 82]. Propolis as a culture medium for periodontal ligament (PDL) cells: In a study, PDL cells of extracted teeth were left in propolis to determine the biocompatibility of the cells. The cells were extracted from healthy wisdom teeth and left in Dulbecco's Modified Eagle Medium (DMEM). Then the cells were kept in a solution of 10% and 20% propolis and milk with low fat percentage and Hanks' Balanced Salt Solution for negative control and DMEM for positive control, and to determine PDL cells viability, Trypan blue exclusion test was used [14]. In another study, coconut water preservation medium was compared with propolis to see which solution keeps periodontal ligament cells viable. The teeth were kept dry for 30 minutes and then immersed in one of the two preservation solutions, coconut water and propolis, and then the teeth were removed and treated with dispase grade II and collagenase for 30 minutes, and then the viable PDL cells were counted using a hemocytometer. One interesting finding of their study was that more PDL cells remained viable in coconut water, while fewer cells remained viable in propolis [15]. In a comparative study on the effects of mouthwash solutions containing propolis at different concentrations and chlorhexidine 0.2% mouthwash on oral microorganisms and human gingival fibroblasts. Propolis mouthwash at four concentrations of 1%, 2.5%, 5%, and 10% was used. In addition, chlorhexidine was used in the control group. At these concentrations, chlorhexidine mouthwash was comparably more effective on oral microorganisms. On the other hand, less cytotoxicity was observed in gingival fibroblasts compared to chlorhexidine. Propolis mouthwash is used to maintain oral hygiene and prevent decay due to its antibiotic and anti-plaque effects. Simple mouthwash can be prepared by adding 10-50 drops of propolis liquid to a glass of warm water. Unlike common mouthwashes, the mouthwash liquid can be swallowed to enjoy the advantages of its propolis that can be taken orally [18]. The effect of propolis in treating stomatitis due to dentures: Stomatitis is a chronic disease that affects patients who have dentures, especially in the upper jaw. Despite the availability of many antifungal agents, sometimes the treatment fails. Propolis has antifungal and anti-inflammatory properties. Santos *et al*. [37] studied the clinical effects of a new Brazilian propolis gel on patients with stomatitis. 30 patients with stomatitis were included in the study, 15 patients were treated with miconazole gel and 15 patients used Brazilian propolis gel. All patients consumed the product four times a day for one week. After the treatment, clinical evaluation was done on them again. All patients who were treated with Brazilian propolis gel and miconazole had swelling, inflammation and redness of their mouths healed. The new Brazilian propolis gel is comparable to miconazole and can be used for topical treatment of stomatitis [25]. The effect of propolis on recurrent aphthous stomatitis: Recurrent aphthous stomatitis causes painful ulcers that affect the oral cavity and whose reasons are unknown. There is no specific treatment and the available drugs only reduce the pain of the wounds and are applied superficially and reduce the time of pain recurrence. In this study, the patients did not know what medicine they were taking, and some of them were taking a placebo, and another group of patients were taking one 500 mg propolis capsule per day. The patients using propolis also provided a personal report regarding the recurrence of ulcers, which showed that propolis reduces and improves the number of recurrences of wounds. In aphthous ulcers, this substance forms a sticky coating that prevents wound irritation and also creates an anesthetic and anti-inflammatory effect [29]. On the other hand, it seems that this substance has a positive effect on reducing the recurrence of these pests by stimulating the immune system [29]. In general, propolis is safe and non-toxic. Many people do not feel any irritation when they put it on their skin. However, some people are allergic to propolis [83]. For the first time, a report about the sensitivity of people who used cosmetics containing propolis was reported [83]. Caffeic acid in propolis causes allergy to propolis. If someone is sensitive to propolis, their skin becomes red, itchy, swollen, irritable, or even cracked. In addition, it is possible for the skin to burn at the point of contact, and eczema, psoriasis or oral ulcers may occur. It is argued that people who are allergic to pollen have propolis allergy. The pollen in propolis may originate from any plant and not from the plants around the areas where the person buys the product. If someone has asthma, he/she should avoid propolis because the chemicals and impurities in it may induce an asthma attack. Those who have allergy to bee stings should also avoid propolis. Propolis may cause side effects similar to stinging [8, 83]. Anti-inflammatory property of propolis: Another unique feature of this substance is its anti-inflammatory property, which by inhibiting the production of prostaglandins by inhibiting the lipoxygenase enzyme, creates effective anti-inflammatory and analgesic mechanisms similar to aspirin yet with fewer side effects. Caffeic acid phenethyl ester is the main cause of propolis

properties, which is a derivative of bioflavonoid present in the substance and can be easily isolated. This compound can also prevent the release of inflammatory mediators from the mast cells and thus prevent inflammation and allergic reaction [77-83]. Propolis can increase immune mechanisms by influencing interferons and increasing antibody production and phagocytosis activity [77-83]. Side effects: Propolis is known as a safe medicinal substance, however, like other bee products, it may cause allergic reactions. Therefore, patients suffering from asthma and people who are allergic to bee stings and also allergic to honey products should avoid consuming propolis [77-84].

Although research has been conducted on the use of honey in head and neck cancer patients undergoing chemotherapy, the evidence is still not conclusive enough to use propolis as a standard method in the treatment of these patients. Currently, in Australia and New Zealand, honey and propolis are commercially available as high-level controllers of antibacterial activity and for use in wound healing. Research on the use of propolis with a focus on its anti-inflammatory activities should also be done to increase its use as a therapeutic substance as much as possible. Various cohort studies and clinical trials have recommended propolis as a suitable mouthwash [83] to reduce inflammation [83] and dentin hypersensitivity [19, 32] and produce antifungal effects [25] with respect to its properties. Propolis is not used in its raw form, but its aqueous or ethanolic extract should be obtained. The alcoholic extract is more effective due to the release and better purification of flavonoids, which are the active ingredients of the substance [77]. Propolis is non-toxic and does not usually cause any irritation when applied to the skin. However, some people are allergic to propolis [83]. Based on findings from numerous *in vitro* and *in vivo* investigations and animal studies as well as human clinical trials, the use of propolis is safe and has therapeutic benefits. However, propolis can cause allergic reactions. Cases of contact dermatitis and other allergic reactions related to the use of propolis have been reported [81-83]. To the best of our knowledge, no study has yet been conducted on the effects of propolis on pregnant women and fetuses, so our information in this field is limited and pregnant women should not use it. One study showed that propolis produces a synergistic effect with other antibiotics [83]. Some other studies showed the analgesic effects of propolis on skin wounds. Additionally, the addition of propolis to toothpastes and mouthwashes has been shown to increase their antimicrobial activity and to reduce marginal plaque accumulation. And therefore it will be effective for the treatment of gingivitis. Researchers conducted several cohort studies and clinical trials showed that propolis was suitable for use as a mouthwash [79-82], to reduce inflammation and dentin hypersensitivity [22] and due to its antifungal effects [79-82]. This matter increases in importance when we know that the structure and compounds in the propolis of various regions differ and even the propolis produced in one season in one region is different from that produced in other seasons in the same region [83, 84]. Chronic and non-chronic, infectious and non-infectious diseases are serious health problems and cause pain and suffering to the patient, and finding a treatment solution for them seems essential [85-90]. Due to their presence, propolis and many natural and herbal compounds can be used for various diseases, especially oral and dental diseases [91-95]. The use of propolis in dentistry is at the beginning of the journey and still needs more extensive and comprehensive research.

Conclusion

Given the extremely useful properties and the potential of propolis, it can be argued that in the future, the substance will play a significant role in dental science, which requires further investigations. Meanwhile, clinical trials seem necessary in order to isolate each of its compounds and identify their beneficial effects.

Competing Interest

The authors declare that there is no conflict of interest.

Author Contributions

Babak Gholamine, Enas R. Alwaily, Yasser Fakri Mustafa, Ruqayah Taher Habash: Literature review. Nasrollah Naghdi, Masumeh Jalalvand, Sepideh Papi, Seyedeh Mahsa Khodaei: Preparation of the manuscript. All authors read and approved the article.

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