Review Article

Propolis in Dentistry and Oral Cancer Management

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Abstract

Propolis, known as bee glue, is a wax-cum-resin substance, which is created out of a mix of buds from some trees with the substance secreted from the bee's glands. Its diverse chemical content is responsible for many valuable properties. Multiple applications of propolis have been studied and described in detail for centuries. However, currently available information on propolis is scarce. A literature search in the PubMed database was performed for English language articles, using the search terms propolis, oral health, dentistry, and oral cancer; no restrictions were used for publication dates. The aim of the article was to review propolis and its applications in dentistry including oral cancer.

Keywords: Dentistry, Oral health, Oral cancer, Propolis

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Introduction

Propolis, also known as bee glue, is a natural nontoxic resinous sticky substance produced by honeybees through mixing the secretions of their hypopharyngeal glands with the digested product of resins collected from leaves, flowers of plants, trees, and certain barks, which is used as a sealant and sterilizer in honeybee nests.[1,2] It is dark green or brown in color, and its chemical content depends on the geographic zone from which it comes.[3] The term propolis comes from the Greek "pro", in front, "polis" means town or city and relates to the protective properties of the substance.[4] Bees use it to protect and reinforce their hives, repair their structure, and cover honeycombs. It protects against rain and is a very sticky substance that prevents unwanted guests such as insects, rodents, and robber bees from entering the hive. It helps maintain aseptic conditions and appropriate temperature in the hive. In the hive, propolis acts as a biocide to kill invasive bacteria, fungi, or even larvae. The diversity of plants in the vicinity of the hive is the main factor in determining the chemical composition of propolis.[5,6]

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Not all species of bees produce the same degree of bee glue. The colonies of *Apis dorsata*, called giant honey bee, use propolis to strengthen adhesion of the hive while *Apis cerana* does not use it at all. *Apis mellifera* is the species using propolis in every possible way.[6]

Propolis has been used for anti-inflammatory purpose in folk medicine since early times, especially in Europe and ancient Egypt. It has traditionally been used in curing infections, common cold, throat inflammation, and healing wounds and burns. It is also used for the management of numerous diseases, such as airway disorders and mucocutaneous infections, mainly for bacterial and viral etiologies. In modern times, it has been found to have a wide range of biological activities, including antibacterial, antiviral, fungicidal, anti-inflammatory, antioxidative, hepatoprotective, free-radical scavenging, immunomodulatory, anti-diabetic, local anesthetic, radioprotective, and tumoricidal or anticancer. The anti-inflammatory properties of propolis have been described to act mainly against infections, rheumatism, torsions, and muscular and articular diseases as well as other types of inflammation. In addition to its antibacterial and anti-inflammatory actions, propolis promotes tissue reorganization and is a serious candidate to be added to topical formulations due to its antioxidant properties. In addition, propolis

is still used as a remedy in modern medicine due to a general "back to nature trend".[2,3,7-9]

Propolis is a complex mixture of different naturally-occurring constituents with more than 300 constituents identified to date, which includes phenolic acid, terpenes, cinnamic acid, caffeic acid, aromatic aldehydes, alcohols, amino acids, fatty acids, vitamins (A, B1, B2, B3, and B7), several esters, minerals, essential oils, and flavonoids (flavones, flavonols, and flavanones).[1,2,8,10] The biological activity of propolis is associated mainly with flavonoids and derivatives of hydroxycinnamic acids.[2] Among its biological activities, its antimicrobial activity is outstanding and varies according to its flavonoid contents, depending on the vegetation of the collection area. Flavonoids are phenolic compounds containing a hydroxyl radical directly bound to an aromatic ring and are well-known plant compounds that have antioxidant, antibacterial, antifungal, antiviral, and anti-inflammatory properties.[10,11] As an anti-inflammatory agent, propolis is shown to inhibit synthesis of prostaglandins, activate the thymus gland, aid the immune system by promoting phagocytic activity, stimulate cellular immunity, and augment healing effects on epithelial tissues.[10] Propolis is antibacterial because it can inhibit bacterial RNA-polymerase; it is immunomodulatory, antioxidative, and a healing agent because of the ability to sequester or inhibit free radical formation.[11] Flavonoids (quercetin, galangin, and pinocembrin), caffeic acid, benzoic acid, and cinnamic acid may probably act on the microbial membrane or cell wall, causing functional and structural damages. Additionally, propolis contains elements, such as iron and zinc that are important for the synthesis of collagen.[10] Aromatic compounds, such as caffeic acid, in propolis are known to be antimicrobial and antibacterial, anti-inflammatory, immunomodulatory, and hepatoprotective.[11] In temperate zones, the main constituents are flavonoids while in tropical zones, other classes of bioactive components have been described, such as aromatic acid derivatives, specific terpenoids, and prenylated p-coumaric acids, and acetophenones.[2] Most often propolis is composed of resins (40-55%), bee wax, and fatty acids (20-35%), aromatic oils (about 10%), pollen (about 5%), and other components like minerals and vitamins. Nevertheless, their presence and percentage of these contents in propolis depends on their origin, the type of plant pollen, climate, season, location, year, and the species of bees that produced it. Therefore, the chemical formula of propolis is not stable.[6,10] The composition of chemical compounds is responsible for the properties of propolis. Nowadays, however, since several pathogens are developing resistance to potent antibiotics and the latter are causing side effects in humans, there is an increased need to search or screen for new antimicrobial agents.

The aim of this article was to review and highlight uses of propolis in various branches of dentistry and its possible use in the prevention and management of oral cancer. A literature search was made in the PubMed database for English articles with the search terms-"propolis", "oral health", "dentistry", and "oral cancer". No restrictions were used for publication dates. Articles about effects of propolis on cancer, which have impact on management of oral cancer, were also included.

Uses of Propolis in Dentistry

Dental use of propolis has been emphasized by several studies; in addition to decrease dentinal hypersensitivity and permeability of dentin and occlude dentinal tubules,[12,13] it has been found to be beneficial in many aspects, including prevention of dental caries;[14] reduction of oral mucositis resulted from chemotherapy;[15] oral cancer;[11,16] gingival and periodontal diseases; plaque inhibition and anti-inflammatory;[6] as a constituent of dentrifice to control oral microbiota;[17] as an effective transport medium for increasing periodontal ligament cell viability of avulsed teeth;[18] direct pulp capping;[19,20] and as an analgesic.[2] Moreover, as an antiviral, it delays growth and progression of skin changes in an early stage of infection with Herpes simplex and does not cause cytotoxic effect. A study assessed Brazilian propolis against Herpes virus Type 1 infection in mice. Ethanol extracts of propolis significantly limited development of herpetic skin lesions. It significantly enhanced delayed type hypersensitivity to inactivated virus. Oral ethanol propolis extract administration also significantly increased production of interferon gamma.[21]

A study evaluated the effect of bee propolis on recurrent aphthous stomatitis (RAS), 500 mg of propolis capsule taken daily significantly reduced outbreaks of RAS ulcers. The quality of life of these patients significantly enhanced, and there was decrease in the number of recurrence of these ulcers.[22,23]

Glass-ionomer cement (GIC) containing propolis is antibacterial against *Streptococcus mutans*. A study found the distinct antibacterial and antibiofilm efficacy of propolis containing GIC and concluded that GIC containing propolis would be a promising material for restoration.[9]

Propolis effectively limits the quantity of *Enterococcus faecalis* in root canals and can be used as intracanal medicament.[24] Since propolis has good diffusion abilities and adds to the antimicrobial action of calcium hydroxide, it can be used as a vehicle for calcium hydroxide.[8]

Propolis limits the number of cariogenic microorganisms, slows down synthesis of insoluble glucans, and inhibits

glucosyl transferase enzyme, which is essential for *Streptococcus mutans* to catalyze the formation of soluble and insoluble glycans and provide adherence. Cariostatic effect of propolis is through a high quantity of fatty acids, which slow down the production of acids by *Streptococcus mutans,* and decrease the tolerance of microorganisms to acid pH.[25,26] Propolis is considered to be safe in low doses. Propolis-based solutions have a lower cytotoxic effect on the cells of human gum fibroblasts than chlorhexidine, which predisposes them to be used as ingredient of mouthwashes.[10] The antimicrobial properties of propolis against oral pathogens is attributed to the flavonone pinocembrin, the flavonol galangin, and the caffeic acid phenethyl ester (CAPE); the mechanism of action is probably based on the inhibition of bacterial RNA-polymerase.[9] A study assessed *in vitro* antibacterial effect of Iranian propolis on oral microorganisms and concluded that ethanol extract of propolis is effective in control of oral biofilms and dental caries development.[4]

Propolis-based products have strong antifungal properties in relation to *Candida albicans* and other types of *Candida* species. *Candida albicans* (*C. albicans*) is most sensitive to propolis. Propolis solutions can be also used in form of mouthwash or gel for local application in patients with oral candidiasis using removable dentures.[6]

The flavonoids in propolis, mainly pinocembrin with a high content of aromatic acids and amyrins, have been considered to be responsible for inhibitory effect on *Candida*. Due to the increasing resistance to fluconazole and toxicity of some antifungal drugs, new alternatives in the treatment of denture stomatitis are a novel idea. Propylene glycol Brazilian green propolis has been shown to have an antifungal activity, which is similar to miconazole in the *C. albicans* colonies decrease and in the erythema reduction of patients with *Candida*-associated denture stomatitis. The study recommended propolis to be an alternative therapeutics for this condition.[7]

Skaba *et al*.[3] showed clinical effectiveness of a toothpaste and gel containing 3% ethanolic extract of propolis in a group of patients with a greater risk of gingivitis caused by dental plaque. Preventive effect of propolis on periodontal tissues includes the slowing down of formation of precipitates of calcium phosphates; therefore, it can be used as ingredient of mouthwashes or toothpastes to limit the accumulation of dental plaque. Propolis also reduces halitosis.[6]

The assessment of both clinical and microbiological parameters have showed that additional subgingival irrigations with propolis extract during periodontologic treatment allows to obtain better results than scaling and root planning by themselves.[1] Animal research has shown that propolis prevents the loss of alveolar process bone in the case of periodontitis in rats.[27] The regenerative features of propolis were observed by Stojko *et al*. in animals, which showed that soft tissue and cartilage wounds of dogs granulate quickly if the ethanol extract of propolis (EEP) or a water solution of propolis was applied.[3]

Streptococcus spp. and *C. albicans* are found to be susceptible to low concentrations of propolis, though *Staphylococcus spp*. and *E. coli* are found to be more resistant. The concentration at 10% of propolis solutions showed significant activity on *Candida* strains, and it is useful to prevent candidial infections.[10]

According to Amoros *et al*. and Bonhevi *et al*. the activity against microorganisms is more related to the synergistic effect of flavonoids or other phenolics than to the individual compounds. These findings are in agreement with those of Takaisikikuni and Schilcher, who observed that the antibacterial action against *Streptococcus. Agalactiae* was complex, involving different mechanisms including the formation of pseudomulticellular *Streptococci*, disorganization of the cytoplasm, the cytoplasmatic membrane, and the cell wall, partial bacteriolysis, and inhibition of protein synthesis. Propolis has mucoprotective properties, as described in oral and gastric mucosa.[10]

Propolis is relatively non-toxic, and studies have exhibited a no-effect level in mice at 1400 mg/kg weight/day leading the authors to propose that a safe dose in humans would be 1.4 mg/kg weight/day, or approximately 70 mg/day. Therefore, the administration of propolis at appropriate concentrations will be effective on oral microorganisms and non-cytotoxic to gingival fibroblasts.[10] The presence of quercetin, myricetin, kaempferol, rutine, pinocembrin, coumaric acid, caffeic acid, and CAPE is found in Chilean propolis, which inhibits mutans streptococci growth.[28]

Propolis is used in replantation of avulsed permanent teeth and supports the healing process after a surgery in the oral cavity. Propolis turned out to be a better means for transportation than milk or Hank's Balanced Salt Solution. It not only reduces apoptosis of the periodontium cells but also increases the metabolic activity and proliferation of those cells. Local application of propolis helps to heal wounds following a surgery within the oral cavity reduces inflammation, speeds up creation of granulation tissue and epithelialization, and has an analgesic effect.[6] It can be used in the treatment of dry socket in deep parodontopathies. Propolis accelerates the tissue regeneration process. Ethanol extract of propolis promotes the healing processes in

damaged cartilage and enhances ossification in the artificially induced bone defects.[29]

In malocclusions accompanied by a considerable narrowing of the maxilla, it is necessary to use a device to expand the palatine suture. During the treatment, bone remodeling takes place within the palatine suture. The research carried out by Altan *et al*.[6] on rats showed an increased quantity of osteoblasts in preparations from rats, which received propolis during the treatment. In such cases, the bone remodeling within the palatine suture was quicker.

The regenerative effect of propolis on the tooth pulp has been known for a long time. It not only prevents the inflammatory reaction, infection with microbes and pulp necrosis but also induces the formation of high quality tubular dentin through stimulation of stem cells. The simulative effect on dental pulp is conditioned by presence of flavonoids in propolis extracts. Because of inconsiderable inflammation of periapical tissue and protective effect on the cells of periodontium, propolis is effectively used as a product to disinfect the root canals.[6]

Table 1 provides information on some of the important studies done in the field of dentistry.

Oral Cancer

Oral cancer is the most common among all cancers. It has poor prognosis and survival rate. Various forms of treatment such as surgery, radiotherapy, and chemotherapy have been employed with various degrees of results. However, each of these treatments has their own disadvantages and side effects with resulting morbidity. Therefore, there has been an increasing interest to research natural products available in nature, which can combat cancer and its side effects, and prevent them from occurring and increase the life span and the quality of life of these patients. Propolis is one of the natural agents researched for these purposes. The antitumor action is attributed to its flavonoids. The following are some of the study/research done on the field of cancer/oral cancer which has a bearing for its management.

CAPE is a strong antioxidant bioactive component extracted from honeybee hive propolis with no known

Table 1: Research on propolis in dentistry

Reference	Study	Results
Maryam Zare Jahromi, *et al*.[30]	Root canal disinfection	Propolis is effective against *Enterococcus faecalis* and is an effective antimicrobial intracanal agent
Elizete Maria Rita Pereira *et al*.[31]	As alcohol free mouth wash to control plaque and gingivitis	No side effects in hard and soft tissues of the mouth. Brazilian green propolis 5% showed significant decrease in gingival and plaque index
Tadeusz Morawiec *et al*.[32]	Propolis containing tooth paste for patients suffering from periodontal problems associated with implants usage.	Propolis is a promising local agent against pathogenic oral microflora in individuals with high risk periodontal problems, improves oral health, and reduces gingivitis triggered by gingival plaque
Zohreh Ahangari *et al*.[33]	Biological storage media for avulsed tooth	Propolis showed more viable periodontal ligament cells, as compared to Hank's balanced salt solution, milk, and egg white. Propolis was recommended as a suitable biological storage media for avulsed teeth.
Agnieszka Machorowska-Pienidhek *et al*.[34]	3% ethanol extract propolis tooth paste on hygiene, gingival, and microbiological status of oral cavity in patients with cleft lip and palate treated with fixed orthodontic appliances.	Orthodontic plaque index, Gingival index, and the percentage of the *Actinomyces* spp. and *Capnocytophaga* spp. were significantly decreased. The improvement of oral health confirms antibacterial, anti-inflammatory, and regenerative properties of propolis.
Vidya Dodwad, *et al*.[35]	Propolis containing mouth rinse for plaque inhibition and improvement of gingival health.	The propolis extract possesses anti-plaque activity, improves gingival health, and might be used as an alternative measure to prevent periodontal and gingival problems.
Garima Agarwal *et al*.[36]	Evaluation of Chinese propolis on *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*	Chinese propolis has a potential antimicrobial activity against the two periodontal pathogens and is recommended to use in periodontal therapy.
Kouidhi B, Zmantar T, *et al*.[37]	Tunisian propolis ethanol extract as anticariogenic, anti-biofilms and antiproliferative effects of different cell lines.	Propolis extract can inhibit cancer cell proliferation, cariogenic bacteria and oral biofilms formation, and has a promising role in future medicine.
Zohreh Ahangari *et al*.[38]	Effect of propolis on dentin regeneration and potential role of dental pulp stem cells in guinea pigs.	Propolis produces no pulpal inflammation, infection, or necrosis, and produces a high quality of tubular dentin. It has advantages over calcium hydroxide as a capping agent in vital pulp therapy. Though calcium hydroxide group had more stem cells than propolis, the dentin produced by propolis was of high quality.

toxic effects. The administration of CAPE is a potential adjuvant therapy for patients with oral squamous cell carcinoma (OSCC). CAPE treatment suppresses the cell proliferation and colony formation of TW2.6 human (OSCC) cells via inhibition of Akt signaling dose-dependently. It decreased G1-phase cell population, increased G2/M-phase cell population, and induced apoptosis in TW2.6 cells. Co-treating TW2.6 cells with CAPE and 5-fluorouracil (5-FU), a commonly used chemotherapeutic drug for oral cancers, exhibited additive cell proliferation inhibition, suggesting that these patients receiving chemotherapy will benefit from co-treatment of CAPE. CAPE may enhance the regression of tumors and reduce the required dosage of 5-FU, thereby reducing the side effects of 5-FU.[16]

CAPE is a well-known NF-κB inhibitor at high concentrations of 50-80 μM. CAPE treatment suppresses the proliferation of several human cancer cell lines, including breast, prostate, lung, cervical, and oral cancer cells. CAPE treatment causes G2/M arrest in Japanese squamous cell carcinoma SAS cells and Taiwanese oral epidermoid carcinoma OEC-M1 cells. CAPE treatment does not affect the proliferation of normal human oral fibroblast (NHOF) cells at a concentration lower than 100 μM, suggesting that CAPE exhibits a selective suppressive effect on human oral cancer cells. CAPE treatments have been shown to sensitize cancer cells to chemotherapeutic drugs and radiation treatment by inhibiting pathways that lead to treatment resistance in animal models. In addition, CAPE treatments are also shown to protect tissues and organs from chemotherapy-associated toxicities in animal models. Therefore, the patients with oral cancer on chemotherapies may benefit from the co-treatment of CAPE, which may enhance the regression of tumors, and protect tissues and organs of patients from chemotherapy.[16]

CAPE exerts antioxidative, anti-inflammatory, and anticancer activities, suppresses eicosanoid synthesis, and inhibits the release of arachidonic acid from cell membranes. The anti-inflammatory activity of CAPE is derived from the downregulation of COX-2 expression. It increases tissue inhibitor of metalloproteinase-2 (TIMP-2) expression, and inhibits focal adhesion kinase (FAK) phosphorylation. It also inhibits p38, mitogen-activated protein kinase (MAPK), and c-JUN N-Terminal Kinase (JNK) activation. MMP-2 and MMP-9 are considered as predictors of risk or recurrence of metastasis or cancer prognostic markers.[39]

Various studies have been carried out to research the effect of propolis on cancer. The results of these studies give insights of propolis applications in oral cancer. An *in vivo* study determined the effects of green propolis extracted in *L*-lysine (WSDP) and *L*-lysine for 40 weeks on the induced rat bladder carcinogenesis (BBN), and concluded that WSDP was chemopreventive if administered 30 days prior to BBN, and that *L*-lysine cause's promotion of bladder carcinogenesis. It has showed that the chronic use of propolis at low concentrations in rats is not genotoxic and is capable of protecting against the genotoxicity of BBN. Green propolis is a Brazilian variety of propolis known for its many pharmacological properties. Among the most promising pharmacological properties is the anticarcinogenic action of its constituents. The alcoholic extract of green propolis containing artepillin C and synthetic artepillin C reduces lung carcinogenesis in mice. At a concentration of 1000 ppm, propolis shows an antioxidant activity close to that of the controls vitamin C and Trolox, a synthetic antioxidant similar to vitamin E. *p*-Coumaric acid is one of the compounds identified in lyophilized propolis. The presence of flavonoids and derivates of *p*-coumaric acid correlates with substantial antioxidant activity. Oral administration of propolis in combination with 5-FU reduced the tumor with improvement in the cytopenia induced by the antimetabolite. Pharmacological compounds isolated from propolis, including artepilin C, CAPE, *p*-coumaric acid, caffeic acid, quercetin, chrysin, and naringenin, have been shown to reduce tumors in animals and cytotoxic effects in cultured human tumor cells, and thus, is potential effective for treatment of oral cancer.[5]

A study evaluated the effect of a hydroalcoholic extract of green propolis (EPV) on chemically induced epithelial dysplasias in rat tongues and concluded that EPV seems to play an important protective role in the chemically induced lingual carcinogenesis in rats. Orsolic *et al*. showed that several hydrosoluble compounds of propolis, such as caffeic acid, CAPE, and quercetin, could be extremely useful for the control of tumor growth in experimental models. Luo *et al*. showed a compound isolated from Brazilian propolis PM-3 (3-[2-dimethyl-8-(3-methyl-2-butenyl)benzopyran]-6-propenoic) acid inhibited significantly the growth of cancer MCF-7 cells from human breasts. This evaluation was associated with cell inhibition in the cell cycle and induction of apoptosis. These findings suggested that the administration of hydroalcoholic green propolis extracts decreased the dysplasia induced by chemical carcinogenesis, and that chemoprotection is likely to be related with the dose of propolis. Veronez suggested that CAPE is the main substance with antitumor activity, which is shown to have cytotoxic activity against tumor cells, through inhibiting oxidative processes essential for generating tumors, suppressing the oxidative destruction of polymorphonuclear leukocytes, and inhibiting protein, DNA, and RNA synthesis in tumor cells. The histological findings corroborated the mitosis-suppressing effect of CAFE.[11]

Many of the therapeutic effects can be attributed to the immunomodulatory functions. Two main immunopotent chemicals, CAPE and artepillin C, have been identified. Propolis, CAPE, and artepillin C have been shown to exert a summative immunosuppressive function on T-lymphocyte subsets but paradoxically activate macrophage function. On the other hand, they also have potential antitumor properties through different postulated mechanisms such as suppressing cancer cells proliferation via its anti-inflammatory effects, decreasing the cancer stem cell populations, blocking specific oncogene signaling pathways, exerting anti-angiogenic effects, and modulating the tumor microenvironment. The good bioavailability by the oral route and good historical safety profile makes propolis an ideal adjuvant agent for the future immunomodulatory or anticancer regimens.[40]

A study indicate that a low dose of a super critical extract of propolis may find application as a potent chemopreventor of mammary carcinogenesis.[41]

Water-soluble derivative of propolis, caffeic acid, caffeic acid phenethyl ester could be potential useful tools in the control of tumor growth in experimental tumor models.[42]

A study evaluated honey and a mixture of honey, beeswax, and olive oil-propolis extract in the treatment of chemotherapy-induced oral mucositis for acute lymphoblastic leukemia and oral mucositis grades 2 and 3, and showed that honey produced faster healing in patients with grade 2 and 3 chemotherapy-induced mucositis, and recommended using honey and possibly other bee products and olive oil in future therapeutic trials targeting chemotherapy-induced mucositis.[15]

A study examined the effects of crude, water-soluble propolis (CWSP) on tumor progression, chemotherapeutic efficacy, and hematopoiesis in the peripheral blood using an ICR mouse model bearing a syngeneic Ehrlich ascitis carcinoma and suggested that the subcutaneous injection of CWSP could regulate the development of tumors by possibly stimulating multicellular immunity. In addition, oral administration of CWSP concurrently with 5-FU or mitomycin C (MMC) significantly increased tumor regression as compared with the respective chemotherapy alone, illustrating the adjuvant effect of orally administered CWSP for tumor regression when combined with chemotherapeutic agents. Orally administered CWSP in combination with chemotherapeutic agents significantly increased tumor regression and ameliorated the cytopenia induced by the chemotherapeutic agents alone. These results suggest the benefits of potential clinical trials using CWSP combined with chemotherapeutic agents in order to maximize enhanced immunity while potentially minimizing post chemotherapeutic deteriorated reactions.[43]

A study assessed amelioration of renal carcinogenesis initiated by diethylnitrosamine (DEN) and promoted by ferric nitrilotriacetate (Fe-NTA) by bee propolis in Wistar rats. The study found that bee propolis (BP) was able to down regulate expression of proliferative cell nuclear antigen, cyclooxygenase-2, tumor necrosis factor-alpha, and upregulated p53 along with induction of apoptosis. The study inferred that BP possess potent antioxidant, anti-inflammatory, anti-proliferative, pro-apoptotic, and nephroprotective activities and is a promising chemopreventive agent.[44]

Nymphaeol-A, the major component of Okinawan propolis, suppresses angiogenesis, and that is the reason why it is a useful agent for preventing tumor-induced angiogenesis. The chemopreventive effect of propolis is exerted by multiple molecular mechanisms of the apoptosis signaling pathways in cancer cells. EEP and polyphenols isolated from propolis have been shown to sensitize cancer cells to TNF-related apoptosis-inducing ligand.[45]

Propolis has been sold as a dietary supplement. Propolis is also used in the form of gel and rubbing ointment, 10% ethanol solution for brushing, and a 0.2% ethanol-water solution for mouth washing is used in the treatment of periodontal diseases, ulcerative gingivitis, chronic and recurrent aphthous ulcers, desquamative chelitis and bullous, and ulcerative forms of lichen planus. Treatment can be supported with chewing three times a day for half an hour of a 3-gram lump of propolis while people with dentures can sprinkle them with a powdered form. Propolis extracts prove to be highly effective in soothing post extraction pain and treatment of alveolar osteitis. The repeated intra-alveolar application of a seton soaked with EEP assuages the pain and accelerates wound healing.[3]

In spite of many benefits and possibilities of application of propolis in dentistry, there is a risk of allergy to it. Symptoms of a contact allergy have been observed and documented in beekeepers. The symptoms were mostly itching and rashes.[6]

Allergic reactions may manifest as contact chelitis, contact stomatitis, perioral eczema, labial edema, oral pain, peeling of lips, and dyspnea. Contact stomatitis and allergic contact chelitis in an HIV-positive patient taking propolis solution orally has also been reported. Acute renal failure occurred in patients taking propolis, and renal function improved when propolis was withdrawn. Propolis contains alcohol, which may cause side effects in patients concurrently taking metronidazole. It also

interacts with anti-inflammatory, antifungal antibiotics, anticoagulants, antiretrovirals, and anticancer drugs. Allergens isolated from propolis include methyl cinnammate, ferulic acid, tectochrysin, 3-methyl-2-butenyl caffeate, phenylethylcaffeate, benzyl caffeate, geranyl caffeate, and benzyl alcohol benzyl cinnammate. Routine patch testing should be done in patients before prescribing it to avoid contact sensitizing.[46] Propolis may also cause hypersensitivity and anaphylaxis, and occasionally cause allergic cheilitis, and oral ulceration.[47]

Though most of the studies support the use of propolis in oral cancer, one study identified acute mutagenic potential *in vivo* for Brazilian green propolis. This may be due to lower dose of propolis and lack of artepillin C in the propolis used for the study.[48]

Some of the studies regarding oral cancer are shown in Table 2.

Discussion

Although most findings on propolis published in the dental literature are based on *in vitro* or animal studies, extrapolating the results of these present studies to clinical practice may be too early, as these results may not be necessarily replicated in human trials. Propolis has multiple applications in dentistry. It can be effectively employed as an oral hygiene product and treatment of oral candidiasis, denture stomatitis, viral infections, aphthous stomatitis, oral surgery, endodontics, and orthodontics. These should be thorough evidence-based researched in human trials for its safe use. The optional dose of propolis for its different applications should be determined. Both toxic and safe doses for children, adolescents, adults, elderly people, male, female, and pregnant patients should be formulated. Safety of use of propolis in pregnancy and whether it can cause teratogenic effects should be researched thoroughly. The dose-dependent biological actions, metabolism, excretion, and its various interactions with different drugs and tissues of the human body of both normal and immunocompromised patients should be thoroughly clinically researched and documented. The composition of propolis and process of manufacturing it for the specific uses should be made uniform, generalized, and regulated. The solvent used for propolis extracts is also important. Alcohol content in propolis should be minimized as it is already known that alcohol increases the mucosal permeability and potentiates the actions of various carcinogens, which is a co-carcinogen as seen. Advantages of various modes of administration of propolis via oral, intravenous, intramuscular, or subcutaneous in specific applications should be further explored. Oral CWSP acts as an efficient vehicle for selective delivery of chemotherapeutic agents to tumor sites rather than to tumor cells, whereas when subcutaneously injected, it acts on tumor cells through the enhanced immunity and direct DNA damage induced by apoptotic processing. This shows a distinction of the active products, depending on the route of administration.

Table 2: Research done in the field of oral cancer

Reference	Study	Results
Abdulrhman M *et al.*[15]	Effect of topical application of honey and a mixture of honey, olive oil-propolis extract, and beeswax (HOPE) in the treatment of oral mucositis.	Honey produced faster healing than either the HOPE or controls. Use of honey and possibly other bee products and olive oil are recommended for therapeutic trials targeting chemotherapy-induced mucositis.
Ricardo Lopes-Rocha *et al.*[49]	Effects of propolis on lingual mucosa of hamsters subjected to experimental carcinogenesis.	Ethanol propolis extract (EPE) induces carcinogenesis. Absence of chemoprevention if due to propolis extract containing fewer amounts of polyphenols, flavonoids and also due to ethyl alcohol.
Danielle Rodrigues Ribeiro Cavalcante *et al.*[11]	Effect of green propolis on oral epithelial dysplasia in rats.	Hydroalcoholic extract of green propolis plays an important protective role in the chemically-induced lingual carcinogenesis in rats.
Ying-Yu Kuo *et al.*[16]	Effect of caffeic acid phenethylesther (CAPE) on human oral cancer cells.	CAPE suppressed cell proliferation and colony formation of TW2.6 human oral squamous cell carcinoma (OSCC) cells, via inhibition of Akt signaling. Co-treatment of TW2.6 cells with CAPE and 5-fluorouracil, exhibited an additive cell proliferation inhibition. CAPE is a potential adjuvant therapy for patients with OSCC oral cancer.
Chih-Yu Peng *et al.*[39]	Effect of CAPE on oral cancer cell metastasis	CAPE attenuated SCC-9 cell migration and invasion at noncytotoxic concentrations. CAPE inhibits oral cancer cell metastasis by regulating matrix metalloproteinase-2 and the mitogen-activated protein kinase pathway and could potentially be used as a chemoagent to prevent oral cancer metastasis.

Propolis in the field of regenerative dentistry and in oral cancer is an exciting and rewarding field of research. It can be incorporated into tissue bioscaffolds used for tissue engineering, thereby preventing recurrence of cancer. Thorough studies should be conducted in this field to elevate the quality of life of these patients. As there is risk of allergy on use of propolis, studies should be conducted to modify the composition of propolis to nullify this limiting factor. With advances in biotechnology, biochemistry, biomaterials, bioengineering, nanotechnology, gene therapy, and regenerative medicine should be used with advantage to harness the power of propolis to full degree to get miraculous new exciting results and new modes of management or prevention of various diseases. In future, more definitive roles of propolis will be found in applications in dentistry; however, clinical trials are necessary to isolate the individual components responsible for its beneficial effects.

Conclusions

Propolis-based preparations have a wide range of applications in various specialties of dentistry. Bee glue has antibacterial, antiviral, antifungal, anti-inflammatory, analgesic, and many other applications. The development of new therapies for the treatment of oral cavity diseases is of great importance since the systemic and local administration of antimicrobials brings different concerns. Some of these problems include the selection of multidrug-resistant microorganisms, interbacterial transfer of resistance determinants, and unpleasant side effects. Further steps should be taken to verify if an optional dose for the target microorganisms can be reached in the oral cavity, without causing major local or systemic adverse effects.

Oral cancer is a public health problem. The use of natural substances such as propolis aims to search for chemoprevention with fewer side effects. Desirable effects of propolis on the treatment of oral cancer are regression of tumors by stimulating multicellular immunity, prevention of metastasis, speeding up apoptosis of cancer cells, mitosis-suppressing effect, anti-angiogenesis effect, immunomodulatory effect, and antioxidant effect. Propolis maintains high circulating levels of chemotherapeutic drugs such as 5-FU and MMC, thus reducing the dose of these drugs. When concurrently administered with propolis, the dose and side effects of these chemotherapeutic drugs are reduced; the cytopenia resulting from these drugs is ameliorated by administration of propolis via increasing WBC and RBC counts in peripheral blood. Propolis also has radioprotective effect. Flavonoid quercetin in propolis potentiates the growth-inhibitory activity on tumors.

It is very important to know that propolis composition varies geographically and depends on different factors. Therefore, the absence or decrease in key constituents with antitumor activities or decreased propolis dose may not be useful in the treatment of cancer. Therefore, it is important to know the ranges of chemopreventive dose for the safe use of propolis. Propolis as a natural substance has very few side effects, except of risk of allergy. This side effect can be minimized by removing the constituents responsible for allergy. The extensive clinical human trials should be considered for safe use of propolis.

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