

## Effects of Propolis on Oral Health and Oral Cavity Cancers

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### Abstract

For centuries, people have used apitherapy, the therapeutic use of bee products like propolis, honey, bee venom, wax, pollen, and royal jelly, to prevent and treat various diseases. Propolis is well-known for its antimicrobial, anti-inflammatory, anticancer, and antioxidant properties. It contains over 300 bioactive compounds, including flavonoids, phenolics, and aromatic substances. Recent studies have highlighted its growing application in dentistry, especially in products like toothpaste, mouthwashes, and sprays, which have demonstrated efficacy in preventing dental caries, reducing gum inflammation, and accelerating the healing of oral ulcers. Moreover, due to its antioxidant capacity, propolis may help mitigate oxidative stress, potentially contributing to the prevention of oral cancer. Given its therapeutic potential in both oral health and oncology, propolis emerges as a promising natural treatment option. However, further in-depth studies are required to fully elucidate its clinical potential and verify its efficacy and safety.

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### 1. Introduction

A systematic analysis of the chemical composition and biological properties of propolis is important due to its wide range of applications. Propolis is a complex bee product that contains over 300 constituents, which are beneficial for humans in different ways. The name propolis is derived from the Greek and has two parts “pro”, which means defense, and “polis”, which corresponds to city resulting in the translation of ‘Hive defense’ (1). These insects use propolis as an element that helps to disinfect hives and repel bacteria, viruses, fungi and parasites. It shall do this by sealing the gaps and making the external environment aseptic and characterized by moderate temperatures and humidity. The nature of propolis is a complex one and it has been observed that propolis exhibits differences in chemical composition based on the phytogeographic location, the month of collection, or even the species of bee. As for its

chemical content, propolis, in most cases, contains resins, volatiles,

polyphenols, polysaccharides, and wax. They possess various biological activities comprising of activities against protozoan parasites, fungi, inflammation, viruses, bacteria, and cancer cells. Further, propolis possesses mineral matter, carbohydrates, flavonoids, amino acids, and vitamins B, C and E, and many aromatic matters (2,3). The non-specific biological activity contributes to the use of propolis as a natural remedy and especially for oral health concerns and diseases. As found, there is a strong correlation between oral health and general health. Dysbiosis which refers to the impaired balance of microbe’s paves way for the pathogenic microbes in the mouth due to poor hygiene practices (4). The toxins and inflammatory mediators which are released by these pathogens can enter the bloodstream thus resulting in a compromised systemic health. Therefore, personal oral

hygiene implies practical techniques required to prevent the development of caries, periodontal diseases, and pulpitis. In this regard, propolis has been identified as a natural substance that can be used effectively (5,6).

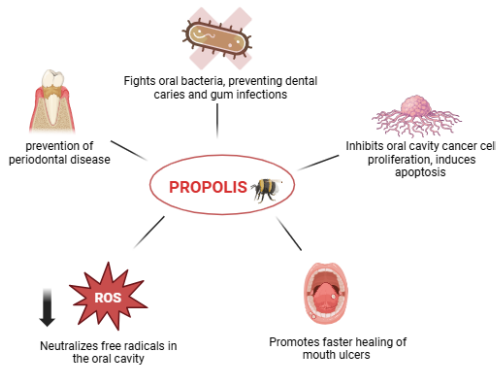
The effects of this compound have been hiked in the recent years because of its incorporation in the production of a number of dental products such as toothpaste, mouthwash, and chewable tablets. Propolis has been used effectively in the treatment of oral diseases including periodontal disease, oral ulcers, candidiasis, acute necrotizing ulcerative gingivitis and pulpitis (7). Some research have provided proofs in support of the antibacterial and anti-inflammatory properties of propolis with particularly good results in the field of odontology and, more recently, in the context of oral cancer (8). Propolis contains a number of bioactive components that are effective against cariogenic bacteria. Flavonoids and phenolic compounds are the most important antimicrobial components of propolis. These components damage the cell wall of bacteria, causing pores to open in the cell membrane, which leads to disruption of the intracellular metabolic processes of bacteria. Flavonoids such as galangin and apigenin inhibit the DNA replication of bacteria, limiting their ability to reproduce. Furthermore, propolis stops the demineralization of tooth enamel by disrupting the acidic metabolic processes of bacteria(1). Propolis also directly affects the formation of cariogenic biofilms. Propolis components inhibit the synthesis of extracellular polysaccharides that allow bacteria to adhere to the tooth surface. This results in reduced plaque accumulation on the tooth surface and decreased acid production by bacteria. Flavonoid components reduce the ability of *Streptococcus mutans* to form biofilms, maintaining balance in the oral microbiome(2). In addition, caffeic acid phenethyl ester (CAPE) inhibits the glucose metabolism of bacteria such as *Streptococcus mutans*, reducing acid production and thereby protecting tooth enamel. CAPE also has antioxidant properties that suppress bacterial growth and biofilm development, which plays an important role in preventing dental caries. Research have confirmed that flavonoids; phenolic acids and CAPE reduces the proliferation rate of oral cancer cells and induces apoptosis (9). Also, it has been suggested that propolis could alleviate some of the side effects of chemotherapeutic agents, and to overcome tumor chemosensitivity leading to improved cancer treatments (10). If the above discussion is to be believed, then propolis may be very effective in regulating the balance

of the bacterial flora. This effect is believed to be suitable for both oral health and other general conditions such as neurodevelopmental disorders. For instance, more study into the connection of the microbiota and autism reveals that microbial homeostasis is an essential aspect of the

disease development of autism (11). Lastly, it is clearly seen that there rising importance of propolis in oral health and cancer research. However, more clinical trial is needed to assess the full therapeutic role of this drug and its relevance impacts on health to enshrine it.

## 2. Biological Properties of Propolis

It is through studying the biological properties that make up propolis that we can comprehend this substance and its uses in different areas. One of the most important uses is in the dental field, where propolis has been investigated for its effectiveness in the prevention and treatment of dental caries and other oral diseases. Because of the chemical structure of polyphenols among its many compounds, it excelled in combating free radicals. The flavonoids Content, which is one of the main compounds of propolis, demonstrate proven antioxidant properties: they shield cell membranes from the damaging action of lipid peroxidation by means of neutralizing free radicals (12). Of all the biological activities of propolis, the antimicrobial activity has been the most investigated. This can be explained either by the direct impact of propolis on microorganisms or by the ability to trigger the body's immune response and enhance the activity of the natural defense system. The ability of propolis to inhibit microbial growth is usually higher towards gram-positive bacteria as compared to gram-negative bacteria because of outer membrane structure of the later and hydrolytic enzymes which can degrade the active compounds of propolis. Further, propolis has been depicted to possess antibacterial, antifungal, antinematodal, antiviral, and antiprotozoal properties. These effects could be attributed to combined interaction of some of the constituents found in propolis. The compounds responsible for its antimicrobial activity are galangin, terpenoids, p-coumaric acid and caffeic acid, apigenin, phenols and esters (13,14). Furthermore, propolis has variety of pharmacological properties such as cytostatic, wound healing, antitumor, antidiabetic, antiallergic, anti-inflammatory and immunomodulatory effects (15,16-18).



**Figure 1:** This figure illustrates the key effects of propolis on oral health, emphasizing its role in inhibiting cancer cell proliferation through the induction of apoptosis in malignant cells. Propolis also exhibits significant anti-inflammatory properties, reducing gum inflammation and preventing periodontal diseases. Additionally, it promotes the healing of oral ulcers and alleviates associated pain, while its antioxidant activity neutralizes free radicals, thereby reducing oxidative stress. Moreover, propolis contributes to improved oral hygiene through its antimicrobial effects, which help prevent dental caries and gum infections.

### 3. Use of Propolis in Dentistry

#### 3.1. Propolis in the Prevention and Treatment of Caries

Dental caries or tooth decay is officially one of the world's most prevalent chronic diseases affecting a large population, and it poses a major problem to health systems across the globe (19). This disease can be described as the gradual loss of minerals in the hard tissues of the teeth, especially the enamel and dentin, through the action of acid-secreting cariogenic bacteria. Demineralization process takes place through enzymatic reactions of the by-products of bacteria metabolism and fermentable carbohydrates from the diet with extra attention to the sugars like sucrose, glucose, and fructose (20-22). These reactive conditions, over time, dissolve the mineralized structure of the tooth to form cavities and, finally, dental caries where the cavitation is left untreated. Some of the key microorganisms that play a role in the growth of carious lesions are *Streptococcus mutans*, *Lactobacillus* and *Actinomyces* spp. Of these, *S. mutans* is known to be the major cause of initiation of

dental caries or the initial process in the development of carious lesion. It is well adapted to colonize on the tooth surfaces and create biofilms or microbial accretions that enhance cariogenic processes. Thus, attachment and biofilm development allow *S. mutans* to utilize fermentable carbohydrates under acidic environments and in the localized production of lactic acid that enhances demineralization (22,23). *Lactobacillus* species are also implicated in caries progression, particularly in advancing the lesion once it has formed. *Actinomyces* species, while less studied, have been associated with root caries and are thought to contribute to the overall microbial diversity of cariogenic biofilms (24). The increasing resistance of cariogenic bacteria to conventional antimicrobial agents has sparked interest in natural products such as propolis, which offers a broad spectrum of biological activities. Propolis, a resinous substance collected by honeybees from plant exudates, has been extensively studied for its antimicrobial properties, particularly its ability to target oral pathogens involved in caries development. Studies have demonstrated that propolis exerts potent inhibitory effects against *S. mutans*, *Lactobacillus*, *Actinomyces*, and other oral microorganisms implicated in caries formation. This antimicrobial activity is attributed to the diverse chemical composition of propolis, including flavonoids, phenolic acids, terpenoids, and other bioactive compounds with strong bacteriostatic and bactericidal properties (25,26). Therefore, the ability to prevent the formation of biofilms is one of the keyways on how propolis has a potential to protect. Biofilms can therefore be described as massive, and highly ordered microbial systems that fix themselves to surfaces such as enamel and are encased in a thick layer of extracellular polymers formed by the microorganisms themselves. This matrix protects the bacteria from various environmental factors, for instance, antimicrobial agents and host's immune system responses thus making biofilms quite difficult in their elimination (27,28). There has also been information suggesting that propolis inhibits biofilm formation and *S. mutans*' capacity to bond to the surface of the teeth along with the capacity to alter the cohesiveness of the matrix of the biofilm. This disruption results in the reducing bacterial load as well as the acicular production which aids in preventing the further demineralization of the tooth surface and or extension of the carious lesions as it is stated in the literature (29). Also, it has proved that propolis has the potential to advance the mineralization of white spot, that

is early caries lesions. Besides the fact that it contains high flavonoids and phenolic compounds which slow the growth of cariogenic bacteria it also increases the adsorption of calcium and phosphate ions on the surface of teeth. These properties that include the ability to prevent demineralization and to allow remineralization also points that propolis can be used as the additional preventive measure in the process of dental caries (7,30). In addition to the antimicrobial effect of propolis it has anti-inflammatory and antioxidant property that assist propolis when used in mouth maintenance. Infection is one of the enemies that a person has to fight, especially when bacteria live in the oral cavity and the inflammation experienced, especially in chronic form, increases the wear of the tissue, including in the development of caries. The anti-inflammatory effects of propolis, mediated through the downregulation of pro-inflammatory cytokines, help to mitigate the inflammatory response, thereby protecting the surrounding tissues from further damage. Given these multifaceted effects, propolis has gained increasing recognition in the development of novel oral hygiene products. Regarding the toothpastes, mouth washes and other dental preparations containing propolis these has relatively appreciable results in preventing and in the curing and controlling of caries (31). Literature also revealed that propolis could be ingested or other products containing propolis help in reduction of dental caries, enhanced on the plaque control in the oral cavity, and improvement of the health of the mouth. On the other hand, all of this research suggested that propolis possess various pharmacological actions and should for formulators to set standardized protocols of propolis in clinical medicine. This means that there are some issues to define the preparations with constant effectiveness of the main chemical compositions of propolis as they vary depending on the geographic location, kind of bees, and plant resources. Therefore, efforts should be made to determine the optimal concentration, preparation and ways of propolis use in the light of its frequent use in dental practice.

### 3.2. Gingivitis

Gingivitis is a not unusual inflammatory circumstance that impacts the gum tissues and is particularly universal among people aged 11 to 13 years (32). It is the second one-maximum not unusual oral ailment global, following dental caries, and impacts over 75% of the global population (33). Poor oral hygiene

ends in the accumulation of dental plaque, which finally outcomes in gingivitis (34). Microbial biofilm performs a crucial function within the pathogenesis of both periodontal illnesses and dental caries (35). Clinical research has validated that toothpastes and mouthwashes containing propolis drastically enhance gingival fitness, reduce plaque and biofilm formation, and enhance standard oral hygiene because of their anti-inflammatory and antibacterial houses (nine,10,36).

### 3.3. Propolis in the Healing of Oral Mucosal Wounds

Studies have established that preparations containing propolis are appreciably extra effective at getting rid of pathogenic and opportunistic microorganisms compared to conventional oral hygiene merchandise. In addition to their strong antimicrobial houses, those arrangements play an important position in keeping the physiological stability of the oral microflora, that's crucial for long-time period oral fitness (37). Propolis promotes collagen synthesis by increasing fibroblast activity during wound healing in the oral mucosa. Fibroblasts are connective tissue cells that play an important role in wound healing and components in propolis such as caffeic acid phenethyl ester (CAPE) stimulate fibroblast proliferation. This process accelerates the reconstruction of damaged tissues. At the same time, the anti-inflammatory properties of propolis suppress the inflammatory response, which accelerates wound(3, 4). The phenolic compounds contained in propolis show an effect that limits tissue damage by suppressing the production of inflammatory mediators (e.g. prostaglandin E2 and TNF- $\alpha$ ). The reduction of prostaglandin E2 is particularly critical in reducing acute and chronic inflammation. At the same time, propolis prevents free radical damage to cell membranes, inhibiting lipid peroxidation and protecting cellular membranes. Thanks to these effects, propolis accelerates wound healing in the oral mucosa and contributes to tissue reconstruction (4). Propolis acts selectively, concentrated on dangerous bacteria even as keeping beneficial microorganisms, thereby contributing to the maintenance of a wholesome oral atmosphere (38). Maintaining right oral hygiene, specifically the powerful removal of dental plaque, is vital throughout the put up-surgical recuperation process. Dental plaque, a biofilm composed of microorganism and their through-products, can substantially obstruct healing by means of promoting contamination and inflammation at the surgical web page

(39). Ensuring the powerful elimination of dental plaque is therefore essential in minimizing postoperative headaches. Propolis, with its effective antibacterial and anti-inflammatory houses, has been proven to decorate wound restoration via decreasing bacterial load and controlling inflammation. Research similarly indicates that the software of propolis following dental approaches, together with extractions or periodontal surgical procedures, positively impacts the oral microflora and speeds up the healing system. This accelerated recovery is likely attributed to propolis' capacity to sell tissue regeneration even as simultaneously inhibiting the boom of harmful microorganisms. Consequently, sufferers revel in faster recuperation times, decreased infection, and a decrease prevalence of postoperative infections, all of which make a contribution to improved remedy outcomes (40-42).

### 3.4. Dentin Sensitivity

Sudden onset of severe nerve pain caused by external factors such as temperature changes, tactile forces, or chemical stimulation of exposed nerves can affect various mechanisms a directly below, causing discomfort or pain (43). Traditionally, vasoconstrictive agents have been advocated to manage dental hypersensitivity by blocking vasoconstriction or reducing vasomotor excitability (44 ) but recent studies in vitro and in vivo have shown propolis to be a promising alternative therapy ( 45,46 ). Propolis has been shown to be effective in reducing tooth sensitivity by creating a barrier that creates exposed teeth, thereby preventing drainage and reducing irritation to the periodontal tissue (47) Furthermore, propolis is recognized as safe, affordable, and biocompatible The use of propolis, which is a viable low-cost alternative, not only reduces early symptoms not only but also provides long-term protection of the tooth surface, thereby reducing the risk of re-sensitivity (48,49).

### 4. Oral Cancers and Anticarcinogenic Properties of Propolis

Propolis shows increasing promise in treating oral malignancies, and its potential extends to mitigating the side effects of cancer therapies, such as aphthous formation (50). Chemotherapy and radiation treatments often result in painful oral mucositis, and the healing properties of propolis offer a natural solution for alleviating these symptoms. The anticarcinogenic effects

of propolis are attributed to its bioactive constituents, such as flavonoids, phenolic acids, terpenoids, and caffeic acid phenethyl ester (CAPE). These compounds inhibit cancer cell growth and proliferation, activate programmed cell death pathways, and reduce tumor formation (51-53). Oral cancers are prevalent globally and have a significant fatality rate. Oral cavity cancers are frequently linked to risk factors such as smoking, excessive alcohol intake, and human papillomavirus (HPV) (54,55). Given the influence of genetic and environmental factors on cancer development, researchers are increasingly investigating the potential impact of natural compounds, such as propolis, on these processes (56). Research on the anticancer properties of propolis has demonstrated its strong inhibitory effects on the growth of cancer cells. Propolis has been shown to effectively suppress cell proliferation and induce programmed cell death pathways in human oral squamous cell carcinoma cell lines (HSC-2, HSC-3) (57). This research demonstrated that propolis could disturb the mitochondrial membrane potential, resulting in an elevation of intracellular reactive oxygen species and ultimately causing the demise of cancer cells (50). Furthermore, the antioxidant properties of propolis may help mitigate oxidative stress, a significant factor in cancer progression. Oxidative stress, caused by an overproduction of free radicals, can damage cellular components such as DNA, proteins, and lipids, promoting carcinogenesis. Propolis, through its rich polyphenol and flavonoid content, can neutralize these free radicals, reducing the risk of DNA mutations and inhibiting tumorigenesis (58). Additionally, propolis has been shown to modulate immune responses, which is critical in the context of cancer progression and therapy. Studies indicate that propolis can enhance the activity of natural killer (NK) cells, which are involved in detecting and destroying abnormal cancer cells. By boosting immune surveillance, propolis contributes to the body's ability to fight off early-stage cancer cells before they proliferate into larger tumors (59).

Moreover, propolis plays a role in the inhibition of angiogenesis, the process by which new blood vessels form to supply nutrients to growing tumors. By inhibiting angiogenesis, propolis can starve cancer cells of the nutrients they require for growth, effectively slowing tumor progression (10). This anti-angiogenic effect, combined with its pro-apoptotic and immune-modulatory properties, makes propolis a multifaceted natural agent with potential in both cancer prevention and therapy. Further studies have highlighted the potential of propolis

in overcoming chemotherapy resistance, a significant challenge in cancer treatment. Cancer cells can develop resistance to chemotherapeutic agents through various mechanisms, such as efflux pumps that remove drugs from cells, mutations in drug targets, and enhanced DNA repair. Propolis, when used in conjunction with chemotherapeutic agents, may sensitize resistant cancer cells to treatment by interfering with these resistance mechanisms. For instance, flavonoids and phenolic compounds in propolis have been shown to inhibit efflux pump activity, allowing chemotherapeutic drugs to accumulate within cancer cells and exert their cytotoxic effects more effectively (10). In summary, the potential of propolis to prevent and treat oral cancers should be considered a promising strategy due to its anticarcinogenic properties. However, more comprehensive research, including clinical trials involving human subjects, is necessary to substantiate this potential. The clinical application of propolis will remain limited until its safety, efficacy, and appropriate dosages are thoroughly established.

## 5. Conclusion and Future Perspectives

Propolis has received a lot of attention as a natural treatment for oral health and oral cancer treatment. Due to its antibacterial, antiviral, and carcinogenic properties, propolis has shown effectiveness in treating tooth decay, gum disease, gum disease, and oral cavities. Used propolis plays a major role in pharmaceuticals such as toothpastes, mouthwashes, and chewable medicines, and is apparently sufficiently capable of maintaining oral health (65). Oxidant activity: Cellular oxidative May help prevent oral cancer by providing protection against stress, and studies showing promise as an ingredient in cancer treatment have also shown effectiveness in cancer in targeting drug-resistant cells. However, further clinical studies are needed to fully understand the potential of propolis, especially its role in the treatment of oropharyngeal abscesses and the prevention of periodontitis in cancer patients. These promising data suggest that propolis may improve treatment compliance during cancer therapy (66,67). Future studies should prioritize the efficacy, safety, and appropriate dosing of propolis to ensure safe and effective clinical use. In addition, ongoing research into the biological effects, molecular mechanisms, and clinical applications of propolis will further expand its therapeutic potential, enhancing its role in oral health and cancer treatment.

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