

Complementary and Alternative Medicine (CAM): A Review of Propolis in Dentistry

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ABSTRACT

Complementary and Alternative Medicine (CAM) is a rapidly evolving area of medicine and dentistry with a prevalence of use of 9 to 65% worldwide. Phytomedicines have come to occupy a place in dentistry and of these; propolis is a medicament that has been widely tested. Propolis has far reaching applications in dentistry, ranging from its use as a pulp capping agent to its role as a medium for avulsed tooth replantation. This review focuses on the characteristics and applications of propolis in dentistry.

Keywords: Propolis, Dentistry, Complementary and alternative medicine.

INTRODUCTION

Complementary and alternative medicine (CAM) is a rapidly evolving field of medicine that consists of medicines/therapy used as an alternatives or adjuncts to conventional medicines/therapy. CAM has been defined by Ernst E¹ as ‘any diagnosis, treatment or prevention that complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual framework of medicine.’ Alternatively, the National Center for Complementary and Alternative Medicine (NCCAM)² defines CAM as ‘a

group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine.’ CAM is developing into a popular approach towards holistic medicine. The prevalence of the use of CAM has been reported as 9 to 65% globally.³

Advocacy of a holistic approach to treatment, cost limitations of conventional therapy and beliefs of ethnic groups are some of the most common reasons cited for the increasing use of CAM worldwide.^{3,4} A vast array of CAM therapies are available for medical and dental diseases. These have

been broadly divided by the NCCAM into: biologically based therapies (e.g. herbs, aromatherapy, dietary supplement use, oxygen therapy), mind-body interventions (e.g. yoga, hypnotherapy, art therapy), energy therapies (e.g. Reiki, Tai Chi), manipulative and body based methods (e.g. chiropractic, reflexology) and alternative medical systems (e.g. homeopathy, Chinese herbal medicine, naturopathy).⁵

The motivating reasons and benefits perceived by the patient for the use of CAM for dental and medical applications include perceived effectiveness, perceived safety, psychologic satisfaction, perceived emotional well being, emphasis on holistic treatment, embracing of natural remedies and perceived active role of patient, dissatisfaction with conventional health care, concern about adverse effects of conventional therapy, poor doctor- patient relationship and rejection of science and technology.^{4,6}

One CAM medicament used in dentistry for a wide variety of applications is propolis. Propolis (bee glue/ royal jelly/ honey comb extract) is a naturally derived honey bee (primarily *Apis mellifera* L. species) extract used by honey bees to coat, repair and strengthen their hives.⁴ Propolis is a term that originates from two Greek words: 'pro' meaning before or entrance and 'polis' meaning city or community. Historically, propolis was used most often in surgery and wound treatment.⁷ The aim of this review is to provide a comprehensive picture of the characteristics and applications of Propolis in dentistry.

Composition and Characteristics of Propolis

Propolis is generated from different geographical areas of the world and is majorly produced by USA, Brazil, China, Australia and Uruguay.⁸ Different varieties of propolis with known therapeutic functions in dentistry and medicine, based

on geographical region of isolation, include Brazilian green, red and brown propolis, Mexican red propolis, Cuban red propolis, and also Greek/Mediterranean, Jordanian, Egyptian, Algerian, Turkish, Iranian, Bulgarian, Polish, New Zealand, Indonesian, Taiwanese, Thai and Indian propolis. In India, propolis has been isolated from Karnataka, West Bengal, Madhya Pradesh, Maharashtra and Gujarat.⁹

Propolis is a yellow to dark brown colored, pleasantly aromatic resin that majorly contains 50-55% resins and vegetable balsams, 30% waxes, 10% aromatic oils, 5% pollen, and 5% different organic compounds in its raw form (Figure 1).⁹ The precise composition includes more than 300 components.⁹ Propolis extracts are generally made using any one of the following: ethanol, water, methanol, glycerol, propylene glycol or oils. Propolis with high balsamic content has a higher content of biologically active components (propolis balsam refers to the ethanolic fraction of propolis).¹⁰ A variety of techniques are used to isolate the compounds in propolis. These include spectrometry, gas or liquid chromatography, atmospheric pressure chemical ionization, Magnetic Nuclear Resonance (MNR), electro-aspiration and chemometric methods.^{11,15}

The composition of propolis varies according to its geographical area of isolation, botanical sources, method of harvest and climatic conditions.^{16,17} Broadly, propolis contains the chemical classes of flavonoids, phenolics and various other aromatic compounds.¹⁸ Specifically, propolis contains flavonoids including flavones, flavonols and flavanones; amino acids; terpene and sesquiterpene alcohols and their derivatives; benzoic acids and their derivatives; caffeic acid phenethyl ester; tetrochrysin; isalpinin pinocembrin chrysin galangin; ferulic acid; caffeic acid; vanillin;

sterols and steroid hydrocarbons; cinnamic acid and cinnamyl alcohol and their derivatives; various minerals and sugars.^{9,19} Additionally, it contains elements such as iron and zinc which are important for the synthesis of collagen.^{20,21}

Therapeutic functions

Propolis has been used in traditional or folk remedies for several decades.²² This phytomedicine has several documented therapeutic and medicinal effects. These documented benefits include anti-inflammatory,²³⁻²⁵ hepatoprotective,²⁶ antibacterial,^{10,27} antiviral,²⁸ antimycotic,^{29,30} antioxidant effects.³¹ Propolis also shows anesthetic,^{24,25} regenerative,^{24,25} anti-oncogenic³² and immunomodulatory activity with augmentation of non-specific antitumour resistance³³ effects. Propolis is available commercially in various forms such as dentifrices, mouth rinses, lozenges, cough syrups and tablets, creams and gels (Figures 2-6).³⁴ The exact mechanism of therapeutic action of propolis is yet unclear.

Propolis in dentistry

Phytomedicine is rapidly gaining a place in dentistry with a large number of plant derived materials being researched. Propolis from different geographical regions shows similar antimicrobial, antiviral and antifungal properties despite compositional differences.¹⁰ These properties confer various therapeutic benefits to propolis, allowing its use in dentistry for a variety of reasons, ranging from pulp therapy to its use as a tooth replantation medium. The therapeutic actions of propolis specific to dentistry are as follows:

Anti-inflammatory action

The anti inflammatory actions of propolis are due to flavonoids and caffeic acid phenyl ester (CAPE) present in propolis.¹⁸ Both of these compounds work

through inhibition of the lipoxygenase pathway of arachidonic acid.^{18,35}

Antimicrobial efficacy of propolis

Propolis shows antimicrobial, antiviral and antifungal properties.³⁶ Concentrations of propolis used to demonstrate antimicrobial actions of propolis range from 11 to 30% (weight to volume).^{10,37-9} Flavonoids in propolis have antimicrobial (antiviral, antifungal, antibacterial) properties.¹⁸

Antibacterial action

Propolis shows antibacterial action against a range of oral microorganisms, both Gram negative and Gram positive.^{36,40} The antibacterial action is targeted more against gram positive (such as *S. aureus spp.*, *Streptococcus spp.*, *Actinomyces naeslundii*) than Gram-negative bacteria (such as *E. coli*, *E. faecalis*, *P. aeruginosa*, *Peptostreptococcus spp.*, *S. enteritidis*).^{10,41} Antibacterial activity is evaluated by either the disc diffusion method (more laborious and less accurate) or the dilution method (more accurate). The mechanism of antimicrobial activity of propolis may be largely due to the flavonoids- pinocembrin, galangin, and pinobanksin.⁴² The efficacy of propolis against the main microorganism implicated in caries etiology, *Streptococcus mutans*, has also been reported.⁴³ Thus, it has been tried in various forms as an anticaries agent.

The antibacterial efficacy of 4% dimethyl sulfoxide (DMSO) extract of propolis has been compared with 2% chlorhexidine in a few studies.⁴⁴⁻⁶ Propolis showed significantly lower levels of *E. faecalis* but this decrease were lesser than that shown by 2% chlorhexidine.⁴⁴⁻⁶ Awawdeh^{38,47} et al. demonstrated that 30% Jordanian propolis can eliminate *Enterococcus faecalis* from infected dentin models. Mirzoeva⁴⁸ et al. suggested that the

effect of propolis on membrane permeability and membrane potential may contribute enormously to its overall antibacterial activity.

Propolis also has antibacterial activity against root canal pathogens of primary teeth as demonstrated *in vitro* by Rezende⁴⁹ *et al.* They found that 11% Brazilian propolis paste combined with calcium hydroxide (ethanolic extract as well as non ethanolic extract) inhibited growth of microorganisms from polymicrobial primary root canal cutures.⁴⁹ The ethanolic extract produced larger inhibition zones as compared to the non ethanolic extract of propolis.⁴⁹ These authors postulated that this could be because ethanol permits diffusion of propolis into the agar.⁴⁹

Antimycotic action

Propolis has been found to have antimicrobial action against several fungal species such as *Candida albicans*, *C. krusei*, *C. glabrata*, *C. tropicalis* and *Trichosporon* spp.⁵⁰⁻² The flavonoid content of propolis confers its antimycotic properties and also prevents fungal cell division, breaks down fungal cell wall and cytoplasm and this action is comparable to the action of some antibiotics.⁵³

Antiviral action

Propolis shows some action against viruses and may be as effective as acyclovir against herpes simplex virus.⁵⁴

Immune Modulation by propolis

Propolis contains flavonoids and caffeic acid phenyl ester that assist the immune system.^{18,35} It also modulates the immune system by promotion of phagocytic activities, stimulating cellular immunity and augmenting healing effects.¹⁸

Antioxidant properties of propolis

Antioxidants in many phyto-medicines, such as propolis, scavenge free radicals which are responsible for the oxidative damage of lipids, proteins and nucleic acids.⁵⁵⁻⁸ The regenerative properties offered by propolis are also attributed to its superoxide and free radical inhibiting properties.⁵⁵ The total polyphenol and flavonoid content account for much of the antioxidant activities in the ethanolic extracts of propolis.⁵⁶ Flavonoids in propolis may inhibit lipid peroxidation as well as platelet aggregation and may influence the lipoxygenase and cyclo-oxygenase pathways.^{57,58} Caffeic acid phenyl ester (CAPE) also plays a role in anti oxidant properties of propolis.³⁵ The antioxidant properties actions involve scavenging of reactive oxygen species, metal ion chelation and synergistic action with other antioxidant compounds.^{59,60} Antioxidant actions also play a role in anti-oncogenic effects of propolis.⁶⁰

Anti-oncogenic properties of propolis

Tumor cells are more sensitive to radiation effects when there is deficiency of glutathione synthesis.⁶¹ Propolis exerts anti-oncogenic properties through production of glutathione in haematopoietic tissue.⁶² Reduction in lipid peroxidation, increased blood cells and hemoglobin are also some of the beneficial radio-protective effects attributed to propolis.⁶³ Caffeic acid phenyl ester (CAPE) in propolis has anti-mitogenic and anti-carcinogenic properties.³⁵ Studies specific for on the effect of propolis in oral cancers were not retrieved despite thorough literature search.

Effect of propolis on the mechanical properties of teeth

Giamalia⁶⁴ *et al* studied the effect of the propolis solutions on the microhardness of enamel. They found a steady increase in

microhardness with increasing percentage of propolis in the solution from 0.4% to 2%.⁶⁴ They were, however, unable to identify the component of propolis responsible for this mineralization effect.⁶⁴

Anticaries action of propolis

Propolis has been shown to have anti-caries activity and studies have focused on its action against *Streptococcus spp.*, considered to be the prime etiologic factor in caries.⁶⁵⁻⁶ Ikeno⁶⁵ *et al* demonstrated early on in 1991 the *in vitro* potential of propolis to decrease dental caries in rats. Propolis showed antimicrobial activity against *Streptococcus mutans*, *crictus* and *sobrinus*.⁶⁵ Further, propolis inhibited water-insoluble glucan synthesis, and glucosyltransferase activity, without any observable untoward effects on the experimental rats.⁶⁵ Propolis also reduces total salivary bacteria and also *Streptococcus mutans* counts *in vivo*.³⁴ Duarte⁶⁶ *et al* further demonstrated the anticaries action of Brazilian (flavonoid free) propolis on *Streptococcus mutans* biofilms in rats. In this study, propolis decreased acid production by the biofilms and also inhibited the activity of F-ATPase which resulted in cariostatic effects.⁶⁶ The propolis tested was rich in fatty acids (oleic, palmitic, linoleic and stearic) and these were attributed to the biological actions of propolis.⁶⁶ Conversely, one study suggested that propolis contains sugars that may render it unsuitable for use as an anticaries agent.⁶⁷

Propolis in plaque and calculus control

Propolis has been tried as a plaque control agent because of its antimicrobial activity in various forms of delivery, such as dentifrices and mouthrinses.⁶⁸⁻⁷² Ozan⁶⁸ *et al* have documented the mucoprotective effect of propolis when used as a mouthrinse. Serial dilutions (20, 10, 5, 3 and 2.5%) of Indian (Chennai) propolis have been tried as

a mouthrinse *in vivo*.⁶⁹ Five percent propolis was found to be the minimal inhibitory concentration and determined to have antimicrobial activity against *Streptococcus mutans* as it resulted in 90% reduction of bacterial load.⁶⁹ Similar results were obtained by Netto⁷⁰ *et al* demonstrating that 2% typified, alcohol-free propolis may have greater efficacy than 0.12% chlorhexidine when used *in vivo* as a mouthrinse as it suppressed the levels of *Mutans streptococcus* and *Lactobacillus* after 28 days of use. Patient acceptability of propolis mouthrinse has also been reported to be better for propolis mouthrinses as compared to the chlorhexidine mouthrinses.^{70,71} Conversely, other investigators have reported that 10% propolis used as a mouthrinse has no significant antiplaque/antimicrobial effect when compared to chlorhexidine.^{67,72}

When used as a dentifrice, Panzeri³⁶ *et al* showed that propolis exhibited antimicrobial activity against Gram-positive cocci (*Staphylococcus aureus*) and weak antibacterial activity against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and yeasts (*Candida albicans*).

Propolis also appears to have anti-calculus activity.⁷³ Hidaka⁷³ *et al* (2008) evaluated the anti calculus effects of 3 types of Brazilian green propolis and one Brazilian brown propolis, *in vitro*. Of these, Green propolis 2 and 3 and brown propolis showed inhibition of amorphous calcium phosphate formation as compared to HEBP (1-hydroxyethylidene-1, 1-bisphosphonate).⁷³ The authors suggested that flavonoids in propolis may be responsible for the inhibition of calcium phosphate formation through direct inhibition of hydroxyapatite formation.⁷³

Propolis in the control of oral malodor

The usual cause of oral malodor is the putrefactive activity of Gram negative

bacteria. Sterer⁷⁴ *et al* evaluated the activity of several herbs and propolis in the control of oral malodor. They determined that propolis reduced oral malodor and Gram negative bacterial population but was less effective than Echinacea and lavender in this respects.⁷⁴

Dentinal hypersensitivity and propolis

Dentinal hypersensitivity is sharp pain arising due to stimulation of dentinal tubules.⁷⁵⁻⁸ Mehta⁷⁵ *et al* compared the actions of propolis with hydroxyapatite, sodium fluoride and potassium nitrate for the treatment of dentinal hypersensitivity *in vivo*. Propolis was determined to reduce dentin hypersensitivity to the maximum extent as compared to the other agents studied over a period of 7 days.⁷⁵ These authors suggested that the anti inflammatory action of propolis and propolis induced dentinal bridge formation may reduce dentin permeability and account for its dentin desensitizing actions.⁷⁵ Similarly, Geiger⁷⁶ *et al* suggested that propolis decreases dentin permeability by 85% through dentinal obstruction and precipitation.

Madhavan⁷⁷ *et al* compared the dentin desensitizing actions of propolis over a longer period of 3 months. They found that propolis performed better than CPP-ACPF (Casein Phospho Protein- Amorphous Calcium Phosphate Fluoride) and sodium fluoride in terms of dentin desensitizing as well as rapidity of action.⁷⁷ Mahmoud⁷⁸ *et al* suggested that the flavanoids in propolis prevent free radical formation through chelation of heavy metal ions which results in dentin desensitization.

Propolis in tooth replantation

Propolis has been tried as a storage media for avulsed teeth prior to replantation.⁷⁹⁻⁸⁶ Commonly used storage media include HBSS (Hank's Balanced Salt Solution), milk, saline, egg white and saliva.

Some investigators have shown propolis to better preserve periodontal cell viability as compared to HBSS.^{79,80} Other investigators have shown that propolis and its combinations (propolis with Dulbecco's modified Eagle's medium) performed better than milk, saliva and egg white, in terms of periodontal cell viability.^{81,82} Similarly, Ahangari⁸³ S *et al* found that 10% and 50% Iranian propolis showed greater number of viable periodontal ligament cells than milk while 10% propolis showed better viability than egg white too after 1 and 3 hours of tooth storage, *in vitro*.

Mori⁸⁴ GG *et al* also studied propolis as storage medium (60 minutes soaking time) for avulsed teeth in rats. Results at 15 and 60 days following replantation showed that the occurrence of inflammatory resorption, dental ankylosis and the formation of the connective tissue parallel to the root surface were similar for 20% Brazilian propolis, milk, avulsed teeth kept dry for 60 min and avulsed teeth that were immediately replanted.⁸⁴ For propolis, better results were obtained for replanted teeth that were stored for 6 hours as compared to those stored for 60 minutes.⁸⁴ Gulinelli⁸⁵ *et al* reported similar results when 15% propolis was used as a root surface treatment media for delayed tooth replantation in rats. Propolis showed similar rates of external root resorption and reduced inflammatory resorption, as compared to acidulated phosphate sodium fluoride, 60 days following replantation.⁸⁵ The authors suggested that the antimicrobial actions of propolis combined with systemic antimicrobial therapy could account for its inhibitory effects on inflammatory root resorption.⁸⁵

Conversely, one study reported that soaking teeth in propolis for 45 minutes did not improve periodontal cell viability following dry storage while soaking in

coconut water resulted in higher percentages of viable cells.⁸⁶

Role of Propolis in dentinal bridge formation and pulp capping

Propolis has been tried as a pulp capping agent as Propolis has the capacity to stimulate mineralization.⁸⁷ Parolia¹⁸ *et al* investigated the response of pulps to Propolis as a pulp capping agent in premolars. Propolis was comparable to MTA and Dycal as a pulp capping agent in terms of hard tissue/ dentinal bridge formation.¹⁸ The stimulation of various enzyme systems, cell metabolism, circulation and collagen formation could contribute to the hard tissue bridge formation by Propolis.⁸⁸ These effects have been shown to be the result of the presence of arginine, vitamin C, provitamin A, B complex and trace minerals such as copper, iron, zinc as well as bioflavonoids.⁸⁸

Sabir⁸⁹ *et al* demonstrated through a histological study on rat dental pulp that use of propolis-derived flavonoids as a pulp capping agent resulted in partial dentinal bridge formation at 4 weeks from capping.

Propolis as an obturating agent in primary teeth

Propolis is effective against endodontic aerobic and anaerobic microbes. Propolis is able to diffuse through dentin and this property may allow its use as a vehicle for calcium hydroxide.⁹⁰ Panzeri H³⁶ *et al* investigated Brazilian Propolis in combination with calcium hydroxide as an obturating paste in primary teeth. They showed that Brazilian Propolis in combination with calcium hydroxide (with or without ethanolic extract) showed larger growth inhibition zones against microorganisms from primary root canal samples than Calcium hydroxide paste *in vitro*.³⁶ Several studies have shown similar

results demonstrating the efficacy of propolis against endodontic pathogens.⁴⁴⁻⁶

Propolis as an endodontic irrigant

Propolis has been tried as an endodontic irrigant because of its antibacterial action, particularly against anaerobes found in the root canal. In an *in vitro* study, it was found that Brazilian propolis was as effective as 3% sodium hypochlorite against *E. faecalis* when used as a root canal irrigant in permanent teeth, but less effective than MTAD (mixture of doxycycline, citric acid and Tween-80).⁹¹ Similar results were obtained in another *in vitro* study on permanent teeth using 30% Brazilian green propolis as an endodontic irrigant.⁹² In this study, propolis was found to be more effective against *E. Faecalis*, but less effective against *C. albicans*, compared to chlorhexidine at the end of 48 hours and 10 days.⁹² Brazilian green propolis used in these studies has lower concentrations of flavonoids but relatively greater amounts of dihydrocinnamic acid, prenylated acetophenones and specific terpenoids which account for its antimicrobial activity.^{24,25} Similar results were obtained by Bolla⁹³ *et al*. Similarly, Bhardwaj⁹⁴ *et al* demonstrated propolis is efficient in removal of *E. faecalis* biofilm from root canal walls *in vitro* when used along with passive ultrasonic irrigation. Its action was superior to other 'natural' or plant derived irrigants-morinda citrifolia juice and aloe vera, but the difference was not statistically significant.⁹³⁻⁴ However, the action of propolis was inferior to 1% sodium hypochlorite.⁹³⁻⁴

Propolis in oral wound healing

Propolis has been reported to hasten wound healing.⁹⁵⁻⁷ The mechanism for this has been suggested through the action of caffeic acid phenyl ester (CAPE) that increases submucosal collagen.⁹⁸ One study

showed increased amounts of immature and mature collagen following propolis application on oral ulcers in rats.⁹⁹

Biocompatibility of Propolis

Propolis is a non toxic material and is generally biocompatible with oral tissues. Garcia¹⁰⁰ *et al* studied the inflammatory response in rats to subcutaneous injection of 2 Brazilian propolis- calcium hydroxide containing pastes. The pastes were prepared with different vehicles, namely non-fractionated Copaiba-oil resin and the volatile fraction of Copaiba-oil resin. At 42 days, slight inflammation only was reported for both pastes.¹⁰⁰

Safety profile of propolis

Phytomedicines such as propolis, though naturally derived from plants and herbs, cannot necessarily always be regarded as safe.¹⁰¹ Propolis is well recognized as causing hypersensitivity and anaphylaxis¹⁰² and as occasionally causing untoward reactions such as allergic cheilitis¹⁰³ and oral ulceration^{104,105}. The key allergenic component of propolis is recognized to be CAPE and in some instances, flavonoids and other ingredients.^{106,107} Despite its allergenic potential, propolis is generally non toxic.¹⁰⁸ In clinical trials involving propolis, generally subjects with a history of allergic reactions to bee stings are excluded to avoid anaphylactic reactions.¹⁰¹⁻⁸

SUMMARY

CAM has become one of the most rapidly evolving spheres in dentistry. Propolis has found a place in dentistry primarily because of its antimicrobial actions. The chief component that is responsible for its biological actions is flavonoids. Although propolis is regarded as biocompatible, it must be used with caution

in individuals with a known allergy to bee stings.

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Figure 1. Propolis in its raw form.¹⁰⁹

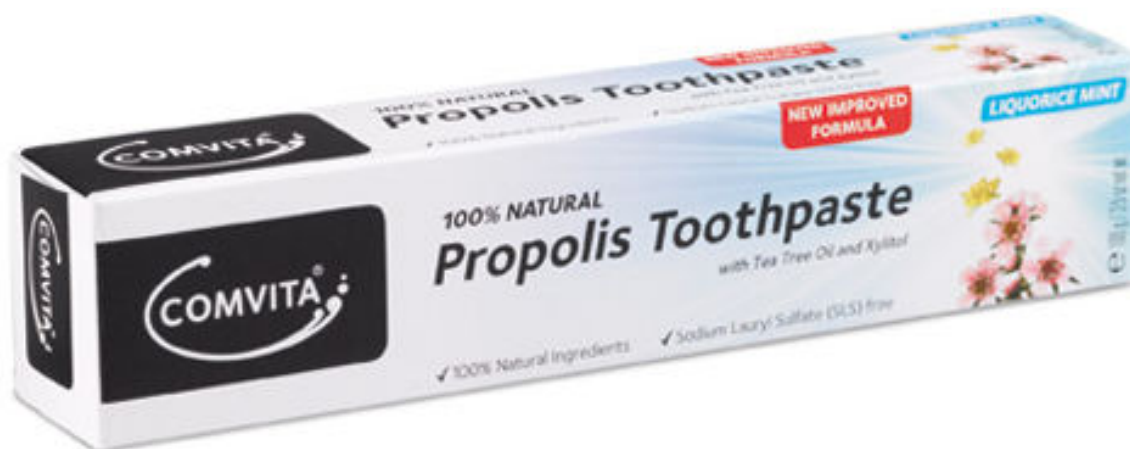


Figure 2. An example of a commercially available Propolis toothpaste/dentifrice.¹¹⁰

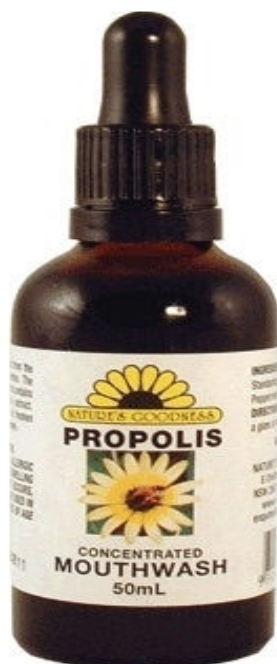


Figure 3. An example of a commercially available Propolis mouthrinse.¹¹¹



Figure 4. An example of commercially available propolis lozenges.¹¹²

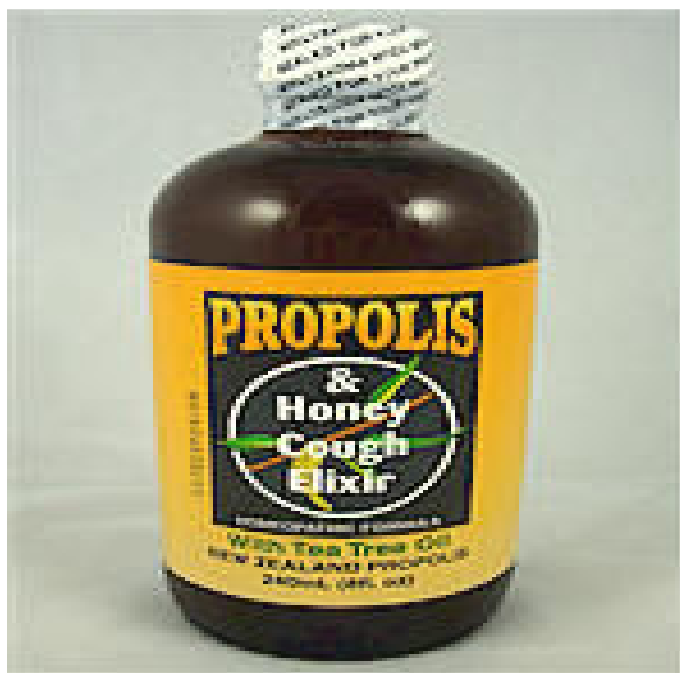


Figure 5. An example of a commercially available propolis cough syrup.¹¹³



Figure 6. An example of a commercially available propolis cream.¹¹⁴