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TYPE OF ARTICLE

Use of Apitherapy as a Novel Practice in the Management of Oral Diseases: A Literature Review

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ABSTRACT

Man has always been ignorant of the plethora of natural products that are available around him. In his search for newer treatment modalities in medicine, he has reached back to the source of several vital materials that are available in nature. These natural products are not only highly bioactive, they also have several interactions that are synergistic in preventing infections, promoting healing and preserving health in total.

Bees have been around much longer than humans and the pinnacle of their evolution has been the development of honey. This multifaceted material is vital to the survival of the species and plays a major role in the physiologic development and maturity of bees. Man has been harvesting this natural resource of infinite applications and has been using it in traditional medicine since time immemorial.

Developments in science have led to us having a better understanding of the ingredients present in bee products and it has generated great interest in its use for medical treatment. This is the field of apitherapy. Its applications in oral diseases are not widely known. It has certainly shown great promise as being the next gold mine of therapeutic medicines that are useful in managing many oral diseases.

Keywords: Apitherapy, Propolis, Bee venom therapy, Oral diseases, Dental use.

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INTRODUCTION

Apitherapy is the use of honey bee products such as honey, bee venom, propolis and royal jelly for medicinal purposes.¹⁻³ According to Dr Stefan Stangaciu, apitherapy, or 'bee therapy' (from the Latin word 'apis' which means bee) is defined as, 'the art and science of treatment and holistic healing through the honey bee and her products for the benefit of mankind and all the animal kingdom'.^{1,2} Therapies involving the honeybee have existed for thousands of years and some may be as old as human medicine itself.¹

Propolis is resinous material/sap that is collected after it oozes out from tree bark and bud.¹ The term Propolis (bee glue) derives from 'pro' (Greek = before), and 'polis' city based on the fact that honeybees use propolis to narrow

the opening to their hives.⁴ It has been characterized as an antibacterial, antiviral, anti-inflammatory, antioxidant and anticarcinogenic agent.² After bees have collected propolis they mix it with wax flakes and their saliva in the hive.¹ Though bees use propolis to reinforce their hive walls and protect the hives from infection, humans use these products to boost their immune system.^{1,2}

Pollen (reproductive spores of seed-bearing plants) is collected by bees from flowers. Benefits of bee pollen extracts include detection and immunization against allergies. Pollen provide relief for bodily weakness, premature aging, constipation and weight loss.^{1,2} For use in apitherapy, practitioners prefer to have pollen that is as fresh as possible.⁵

Royal jelly is a thick, milky mix of nutrients, which is produced from a combination of honey and pollen. All of the bees in a hive consume this substance, but larvae that consume it exclusively and in high doses grow larger than the other bees, thus enabling them to become queens of the hive.^{1,2} Royal jelly is a concentrated source of many nutrients, including all the B vitamins, vitamins A, C, D and E and essential fatty acids.⁵

Bee venom therapy can be administered two ways: Directly from a bee sting or by a prepared injection. Bee venom causes inflammation where it is introduced in the body. The inflammation triggers the body to increase circulation to that point and to create anti-inflammatory hormones to relieve pain. By injecting bee venom directly to the joint that is painful, the body's anti-inflammatory response will treat the arthritic joint.^{1,2}

HISTORICAL REVIEW

- Honey is the most ancient wound dressing known, mentioned by the Greek philosopher Aristoteles⁶ and it has continued to be used throughout the ages. Dioscorides (c 50 AD) wrote of honey being 'good for sunburn' and 'for all rotten and hollow ulcers'.^{1,6,7} More recently, honey has been reported to have an inhibitory effect to around 60 species of bacteria including aerobes and anaerobes, Gram-positives and Gram-negative microorganisms.^{1,6}
- The history of apitherapy can be traced back to the ancient Egyptians¹ the first known prescription using

honey was written on a clay tablet, found in the Euphrates valley and dating from somewhere between 2100 and 2000 BC.⁵

- Hippocrates, the ancient Greek physician and ‘father of medicine’ listed the physical effects of honey: ‘It causes heat, cleans sores and ulcers, softens hard ulcers of the lips, and heals carbuncles and running sores’.^{1,5}
- The use of honey has been documented in several religious texts including the Vedas (a book of Hindu scriptures), the Bible and Quran.^{1,5}
- In 1597, John Gerard wrote about the healing power of propolis in ‘The History of Plant’.^{1,6}
- In the 1989 issue of the Journal of Royal Society Medicine an editorial expressed that ‘the time has come for conventional medicine to lift the blinds off this ‘traditional remedy’ (honey) and to give it due recognition’.¹

COMPOSITION OF HONEY (TABLE 1)¹

Honey is defined as a sweet liquid substance produced by bees from the nectar gathered from flowers and stores by them for food. The color and flavor are determined by the flowers used.¹

COMPOSITION OF PROPOLIS

The composition of propolis varies greatly depending on its geographic and botanical origin.⁶

Propolis is composed of resin and balsams (50-60%), pollen (5-10%) and other constituents which are amino acids, minerals, vitamins A, B complex, bioflavonoid, phenols and aromatic compound. Flavenoids are well known plant compounds which have antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory properties. Cinnamic acid is a white crystalline acid, which is slightly soluble in water and is obtained from oil of cinnamon, or from balsams.⁸

PROPERTIES OF HONEY AND PROPOLIS

Antimicrobial

The antibacterial property of honey was first recognized in 1892 by van Ketel¹ and all examined types of propolis revealed a strong antibacterial activity⁶ (Table 2).

Important factors which influence the antibacterial effectiveness are as follows:

1. *Its hygroscopic properties*: This effect is based on high osmotic properties so it can extract water from bacterial cells and cause them to die. Honey, like other saturated sugar syrups and sugar pastes, has an osmolarity sufficient to inhibit microbial growth.
2. *Its acidic pH*: Honey is characteristically quite acidic, its pH being between 3.2 and 4.5, which is low enough to be inhibitory to many animal pathogens. The optimum pH for growth of these species normally falls between 7.2 and 7.4.
3. *Hydrogen peroxide*: The major antibacterial activity in honey has been found to be due to hydrogen peroxide produced enzymatically in the honey.¹

Antioxidant

Propolis is a powerful antioxidant. This effect is due to the high concentration of phenolics and other antioxidant compounds.⁶ Propolis can prevent tissue damage from oxidative stress by decreasing the overproduction of superoxide anion and by restoring respiratory control ration in mitochondrial tissue. According to an Italian study, propolis extract and its active components showed a dose-dependent free radical scavenging effect, a significant inhibition of xanthine oxidase activity, and an anti-liperoxidative capacity.²

Anti-inflammatory

The anti-inflammatory activity can be explained by the presence of active flavonoids and cinnamic acid derivatives.

Table 1: Composition of honey

Composition	Percentage
Water	22.0
Carbohydrates	79.7
Fiber	0.0
Protein	0.2
Ester Extract	0.0
Ash	0.1
Carbohydrates	Fructose, glucose, sucrose
Enzymes	Invertase, amylase, glucose oxidase, catalase, acid phosphorylase
Free amino acids	Lysine, histidine, arginine, aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, cysteine-valine, methionine-isoleucine, leucine tyrosine, phenylalanine
Minerals	K, Na, Ca, Mg, Fe
Vitamins	Riboflavin, niacin, folic acid, pantothenic acid, vitamin B ₆ , vitamin C
Antioxidants	Flavonoids, vitamin C, catalase, selenium

The former includes acacetin, quercetin, and naringenin the latter includes caffeic acid phenyl ester (CAPE) and caffeic acid (CA).⁶ Ethanolic extract of propolis inhibits hyaluronidase activity. As this enzyme is responsible for several inflammatory processes, propolis holds a great potential as an anti-inflammatory agent.²

Antitumor and Antiradiation Effect

A literature review finds that propolis's pharmacological properties make it safe and effective as an adjunct for patients receiving cancer treatment:

- **Biological therapy:** Biological therapy works hand in hand with the immune system. Propolis's biological activities, such as antitumoral activity, DNA protection, free-radicals scavenging, and immune stimulation act in synergy with each other and with conventional chemotherapy medication.
- **Synergy with chemotherapy:** Antioxidants may boost the effects of anticarcinogenic drugs, thus enabling a decrease in the administered dose and in turn leading to a reduction in side effects. They may also influence the response to chemotherapy.⁹

Immunomodulating Effect

The proliferation of peripheral blood B-lymphocytes and T-lymphocytes in cell culture is stimulated by honey at concentrations as low as 0.1%; and phagocytes are activated by honey at concentrations as low as 0.1%. Honey (at a concentration of 1%) also stimulates monocytes in cell culture to release cytokines, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6, which activate the immune response to infection.¹

Antidiabetic and Antihypertensive

Recent studies have reported that propolis prevented and mitigated diabetes and hypertension, but it remains unclear

whether propolis similarly prevents and mitigates the accumulation of visceral adipose tissues and hyperlipidemia.²

Healing Activity

Propolis has been reported to promote epithelial formation as well as vascular and fibroblastic neoformation of the connective tissue. Thus, the topical application of propolis on surgical wounds may promote faster epithelium and connective tissue healing.²

DENTAL USES

Oral Candidiasis

According to Brazilian researchers, green propolis is effective against oral candidiasis. In this study, all the patients treated with the commercial ethanol propolis extract showed a lesion regression similar to that observed in those patients treated with nystatin.^{2,9,10} Martins et al (2002) assessed the susceptibility of *C. albicans* strains, collected from HIV-positive patients with oral candidiasis, to a commercial 20% ethanol propolis extract (EPE) and compared it with various antifungals used in oral candidiasis. EPE inhibited all the *C. albicans* strains tested. He concluded that commercial EPE could be an alternative medicine in the treatment of candidiasis from HIV-positive patients.¹¹

Oral Lichen Planus

Zyada et al (2012) evaluated the effectiveness of topical mucoadhesive gel-containing propolis in management of patients with atrophic and erosive oral lichen planus and proved that propolis showed to be a promising pharmacological agent for inhibiting epithelial cell proliferation and has anti-inflammatory effect in these oral lichen planus lesions.¹²

Table 2: Spectrum of antimicrobial action of propolis

Gram-positive bacteria	<i>Bacillus cereus</i> , <i>Bacillus mesentericus</i> , <i>Corynebacterium spp</i> , <i>Corynebacterium diphtheriae</i> , <i>Diplococcus pneumoniae</i> , <i>Enterococcus spp</i> , <i>Mycobacteria sp</i> , <i>Mycobacterium tuberculosis</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus: Critecus epidermis faecalis mutans</i> , <i>pyogenes</i> , <i>viridans</i> , <i>sobrinus</i>
Gram negative bacteria	<i>Branhamella catarrhalis</i> , <i>E. coli</i> , <i>Helicobacter pylori</i> , <i>Klebsiella ozaenae</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i> , <i>Salmonella: Choleraesuis</i> , <i>dublin</i> , <i>enteritidis</i> , <i>exneri</i> , <i>gallinarum</i> , <i>pullorum</i> , <i>paratyphi-A</i> , <i>paratyphi-B</i> , <i>typhi-shigella: Dysenteriae</i> , <i>sonnei</i>
Fungi	<i>Aspergillus sp</i> , <i>Candida albicans</i> , <i>guilliermondii</i> , <i>parapsilosis</i> , <i>tropicalis</i> ; <i>Cryptococcus sp</i> , <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Madurella mycetomi</i> , <i>Microsporum: Audouinii</i> , <i>canis</i> , <i>capleoi</i> , <i>distortum</i> , <i>ferrugineum</i> , <i>gypseum</i> ; <i>Piedraia hor</i> , <i>Phialophora jeanselmei</i> , <i>Saccharomyces sp</i> , <i>Trichophyton: sp</i> , <i>mentagrophytes</i> , <i>rubrum</i> , <i>Trichosporon cutaneum</i>
Viruses	<i>Adenovirus</i> , <i>Coronavirus</i> , <i>Herpes simplex</i> , <i>Influenza A and B virus</i> , <i>Newcastle disease virus</i> , <i>Polio virus</i> , <i>Vaccinia</i> , <i>Rotavirus</i> ; <i>Vesicular stomatitis virus</i> , <i>Coronar virus</i>
Parasites	<i>Cholomonas paramecium</i> , <i>Eimeria: Magna</i> , <i>media</i> , <i>perforans</i> ; <i>Giardia lamblia</i> , <i>Trichomonas vaginalis</i> , <i>Trypanosoma cruzi</i> .

Recurrent Aphthous Stomatitis

Samet et al (2007) evaluated the potential of a product to reduce the number of outbreaks of recurrent aphthous stomatitis ulcers and showed that propolis is effective in decreasing the number of recurrences and improve the quality of life in patients who suffer from recurrent aphthous stomatitis.¹¹

Denture Stomatitis

Santos et al (2008) evaluated the clinical efficacy of a new Brazilian propolis gel formulation in patients diagnosed with denture stomatitis. All patients treated with Brazilian propolis gel and Daktarin (miconazole gel) had complete clinical remission of palatal edema and erythema. They concluded that Brazilian propolis gel formulation had efficacy comparable to Daktarin and could be an alternative topical choice for the treatment of denture stomatitis.¹¹

Radiation Mucositis

A study was conducted in Malasiya to evaluate the effect of pure natural honey on radiation mucositis. Forty patients were advised to take 20 ml of pure honey 15 minutes before, 15 minutes after and 6 hours postradiation therapy and were evaluated every week for the development of radiation mucositis using the RTOG grading system. The results showed significant reduction in the symptomatic mucositis among honey-treated patients compared to controls.¹³ The anti-inflammatory action and stimulating effect on tissue repair of honey could possibly be of benefit for the relief of oral conditions resulting from radiotherapy and chemotherapy of cancer.¹

ORAL INFECTIONS, ULCERS AND ORAL SURGICAL WOUND HEALING

A small clinical trial of the placing honey in the socket before closure of the wound after surgical removal of impacted third molars showed less pain, less incidence of postoperative complications and less swelling in the honey treated group than in the untreated control group. In another study, natural honey showed antibacterial action against anaerobic bacteroides present in dental abscess and osteomyelitis.¹

A study conducted by Magro-Filho and Carvalho analyzed the effects of propolis mouthrinse on the repair of surgical wounds after sulcoplasty by the modified Kazanjian technique. It was concluded that: (a) The mouth rinse containing propolis in aqueous alcohol solution aided repair of intrabuccal surgical wounds and exerted an analgesic and anti-inflammatory effect, (b) it had a minor irritant effect

on infrabuccal surgical wounds, (c) exfoliative cytology showed epithelization of infrabuccal surgical wounds. In histological examination, the effects of topical application of propolis hydroalcoholic solution to dental sockets and skin wounds accelerated epithelial repair after tooth extraction.¹¹

A rapid alleviation of pain was observed when the gelled honey was used in a case of erosion of the gum and jaw bone due to infection following surgery with bone grafting to repair damage to the jaw from traumatic injury that had been nonresponsive to any conventional treatment for more than 6 months. The infection cleared and the wound healed up within a month after starting the application of the gelled honey.¹

Another study was done to determine the effects of the topical administration of propolis and dexamethasone on oral surgical wounds. The study showed that ethanolic extract of propolis demonstrated a greater anti-inflammatory effect and shorter healing time in oral surgical wounds in hamsters, in comparison to dexamethasone in orabase gel.¹⁴ The features observed when honey is used in treatment of wounds are the rapid clearance of bacteria from colonized and infected wounds, the rapid removal of malodor from wounds, and the debriding effect, which painlessly lifts off slough and necrotic tissue making surgical debridement unnecessary. The rapid rate of healing achieved and its ability to start the healing process in recalcitrant chronic wounds are also noted. It also promotes tissue regeneration through stimulation of angiogenesis and the growth of fibroblasts and epithelial cells, thereby hastening healing and minimizing the need for skin grafting.⁷

ANTICARIOGENIC

Propolis extracts contains pinocembrin and galangin which inhibit the growth and enzyme activity of *Streptococcus mutans*.³ The production of acid by these bacteria was also inhibited by propolis.¹

Hayacibara et al (2005) suggested that propolis is a potentially novel anticaries agent by evaluating the influence of propolis on mutans streptococci viability, glucosyl transferases (GTFs) activity and caries development in rats.^{8,11}

A study done by Gamal El-Din et al to evaluate and compare the effect of sodium fluoride and bee propolis mouth rinses on salivary *S. mutans* count showed that the mean of the effect of both mouthrinses on the change in salivary *S. mutans* was statistically significant during the follow-up period. This agreed with the results of Kulkarni and Damle (2003) who revealed that sodium fluoride along

with its antimicrobial property has remineralization potential.¹⁵

Simone et al (2006) in his *in vitro* study indicated that at least two pathways by which propolis extracts exert cariostatic effect, first is the reduction of acid production of *S. mutans* and secondly the inhibition of the proton translocating F-ATPase activities which is one of the mechanisms that *S. mutans* have developed to alleviate their influence of acidification.¹⁵

PULP CAPPING AGENT

According to Sabir et al, direct pulp capping with propolis in rats may delay dental pulp inflammation and stimulate reparative dentin.^{2,11}

INTRACANAL IRRIGANT

Al-Qathmi and Al-Madi found that propolis was as effective as NaOCl when used as an antimicrobial irrigant on extracted human teeth.^{8,11,16}

INTRACANAL MEDICAMENT

Oncag et al (2008) compared the antibacterial efficacy of three commonly used intracanal medicaments with propolis against *Enterococcus faecalis*.^{8,11} and Awawdeh et al (2009) evaluated the effectiveness of propolis and calcium hydroxide as a short-term intracanal medicament against *E. faecalis*. They concluded that propolis is very effective in rapidly eliminating *E. faecalis* and can be used as an alternative intracanal medicament.¹¹ As an oily substance, propolis may promote low-speed dissociation and diffusion when used as a component in an endodontic paste for primary teeth.² The association of propolis with calcium hydroxide could aggregate the benefits of each material.^{2,17}

DENTINAL HYPERSENSITIVITY

Mahmoud et al (1999) studied on the effect of propolis on dentinal hypersensitivity *in vivo* and concluded that propolis had a positive effect in the control of dentinal hypersensitivity.^{8,11} In another *in vitro* study (Almas et al 2001) using scanning electron microscopy, it was found that propolis occluded the dentinal tubules.¹¹ Sales-Peres et al (2010) studied on effect of propolis gel on the *in vitro* reduction of dentin permeability and concluded that it can be used for partially obliterating the exposed human dentin as its effects are similar to those of potassium oxalate gel.¹⁸

ANTIPLAQUE

Murray investigated the effectiveness of a propolis mouthrinse in the inhibition of plaque formation concluded that it

was marginally better than negative control.^{8,11} Ozan et al (2007) compared the effects of four different mouthrinse containing propolis solutions and 0.2% chlorhexidine on oral microorganisms and human gingival fibroblasts. The antibacterial effectiveness of mouthrinse containing propolis samples on oral microorganisms were not found as effective as chlorhexidine, but samples found less cytotoxic on human gingival fibroblasts than chlorhexidine.^{8,11} A study by Koo et al to evaluate the effect of a mouthrinse-containing propolis on 3 days plaque accumulation concluded that propolis containing mouthrinse was efficient in reducing supragingival plaque formation.^{2,8,11}

ANTIHALITOSIS

Candy made with honey is useful for preventing halitosis as it rapidly removes malodor from infected wounds by the antibacterial action. The bacteria would use the glucose in honey in preference to amino acids, and thus would produce lactic acid instead of bad-smelling amines and sulfur compounds.¹

PERIODONTITIS TREATMENT

Propolis and honey seems to have *in vitro* activity against a variety of bacteria that cause periodontal diseases³ and the anti-inflammatory activity blocks the direct cause of the erosion of the connective tissues and bone, antioxidants protect the periodontal tissues from the damaging free radicals formed in the inflammatory response and stimulation of the growth of granulation tissue and epithelial cells, aid in repair of the damage done by infecting bacteria and by the free radicals from the inflammatory response to them.¹ Toker et al (2008) analyzed the morphometric and histopathologic changes associated with experimental periodontitis in rats in response to the systemic administration of propolis and concluded that systemically healthy administered propolis significantly reduced the periodontitis related bone loss.^{8,11}

Cairo de Maral et al in a study on periodontitis treatment with Brazilian green propolis gel had found that periodontal diseases are amendable to the treatment by green propolis and had recommend 10% Brazilian green propolis to be used in conjunction with treatment of chronic periodontitis.^{2,9,19} A study by Amita Coutinho to evaluate the clinical and microbiological parameters of the effect of subgingival irrigation with propolis concluded that propolis can be used as an adjuvant to periodontal treatment as it is more effective than scaling and root planning.^{2,20} Another *in vitro* study was conducted by Gebara et al on propolis extract antimicrobial activity against periodontopathic

bacteria. The positive results suggest that the propolis extract should be further tested as an adjuvant to periodontal therapy.²¹ Hidaka et al have suggested that propolis may have potential as anticalculus agents in toothpaste and mouthwashes.⁸

A NEW STORAGE MEDIA FOLLOWING AVULSION

Numerous studies have examined various media in an attempt to determine the ideal material for storage of the avulsed tooth.¹¹ Al-Shaher et al examined the tolerance of fibroblasts of the periodontal ligament and dental pulp to propolis and compared with that of calcium hydroxide *in vitro*. They concluded that propolis can be recommended as a suitable transport medium for avulsed teeth. According to Martin and Pileggi (2004) and Ozan et al (2007) propolis has the ability to serve as a temporary storage medium for the maintenance of periodontal ligament cell viability of avulsed teeth and is more effective storage medium than other groups.^{8,11}

DISPENSIBLE FORMS FOR TREATMENT IN DENTISTRY

Propolis mouthwash (5% aqueous alcohol solution), toothpaste, propolis ointment, propolis intracanal medicament, propolis extract, tablet form, propolis mouth spray.

SAFETY

In general, propolis is safe. It is a nontoxic substance and does not cause irritation when used as supplements or applied to skin.¹¹ Purified bee venom for subcutaneous injection is an FDA-approved product. For Adults and children above 1 year, it is safe when taken orally. But it is possibly unsafe for infants or young children as ingestion of raw honey contaminated with *Clostridium botulinum* spores can cause botulism poisoning.³

In pregnancy and lactation it is possibly safe when apitherapy using bee venom is given as subcutaneous injection by a trained medical professional. But possibly unsafe when apitherapy using bee venom is given by subcutaneous injection in high doses it can increase release of histamine, which can cause uterine contraction.³

FUTURE CHALLENGES

Although many researches have reported the benefits of apitherapy, some disadvantages have also been found. It gets frequently contaminated by yeast, fungi and bacterial spores. The physicochemical characteristics of bee products are directly related to the fact that their properties depend

on various factors, including the plant sources, climate, environment and bee species.¹

Patients allergic to bee and bee products are more likely to experience allergic reaction, such as hypersensitivity, asthma, anaphylaxis, and occasionally allergic cheilitis and oral ulcerations.^{3,4,11}

CONCLUSION

- Apitherapy is one of the few natural remedies that maintained its popularity over a long period of time. Scientific research has revealed its antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory, antitumor and immune-modulating properties and in dentistry it is a recent dental research.
- Further research and studies with more significant patient number are necessary for statistical confirmation of its results and further randomized studies are essential to validate the findings.
- However, apitherapy is a gift from mother nature and serve to be a promising alternative medicament for oral diseases.

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