INNOVARE JOURNAL OF AYURVEDIC SCIENCES

Vol 4, Issue 1, 2016

ISSN- 2321-6824

Review Article

HEALING EFFECT OF PROPOLIS IN MEDICINE AND DENTISTRY: A REVIEW

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Received: 10 December 2015, Revised and Accepted: 23 Febuary 2016

ABSTRACT

Propolis is a natural product derived from plant resins collected by honeybees. Propolis has maintained its popularity over a long period. The pharmacologically active molecules are flavonoids, phenolic acids, and their esters. Propolis has a degree of antimicrobial action against fungi such as *Candida albicans* and some bacteria including a range of oral microorganisms and viruses and may be as effective as acyclovir against herpes simplex virus. In addition, propolis and its components have anti-inflammatory, immunomodulatory activities, and antitumor activity. In dentistry, propolis has been used in dentifrices, as a storage medium for teeth that have avulsed, in periodontal therapy. Its use in canal debridement for endodontic procedures has been explored. Because of its strong, anti-infective activity, propolis has often been called a "natural antibiotic." Many studies show its strong inhibitory effect on a wide variety of pathogenic organisms. Propolis extract used as mouth rinse procure antimicrobial activity against *Streptococcus mutans* present in the oral cavity. Subgingival irrigation with propolis extract as an adjunct to periodontal treatment may also be more effective than scaling and root planning alone. Propolis extract possesses antiplaque activity and improves gingival health. The extract might be used as an alternative measure to prevent periodontal and gingival problems. It has a promising role in future medicine as well as dentistry.

Keywords: Alternative therapy, Dentistry, Propolis.

INTRODUCTION

Name of the medicinal plant: Propolis
Common name: Propolis

Great trend to use natural materials as a cure for a variety of diseases. The health field has also always aimed to use natural products as an alternative to the conventional allopathic formulations. Propolis is one such natural substance which has gone unnoticed in spite of its potential uses in curing a large array of diseases. The word propolis is derived from the Greek word "pro" before, "polis" city or defender of the city [1]. It is a hard resinous substance consisting chiefly of wax and plant extracts. It plays a role in the bee colony as protection against invasion and infection, providing the bees with an "immune system" and is used to seal the hive [2].

Propolis was used at the time of Egyptian and Greek civilizations which recognized its healing qualities. Hippocrates, the founder of modern medicine, used it for healing sores and ulcers internally and externally. This non-toxic resinous substance was classified into 12 types according to physicochemical properties and related to geographic locations; however, the botanical origin of only three types was identified. A new type of propolis named Brazilian red propolis because of its color; it has attracted the attention of international business. Propolis has been used for treating different diseases and inflammatory conditions as both local and systemic applications. In nature, or when in room temperature, it is a sticky substance but becomes hard and brittle at low temperature [3].

CONSTITUENTS

Propolis is composed of resin and balsams (50-60%), pollen (5-10%), and other constituents which are amino acids, minerals, Vitamins A-, B-complex and the highly active biochemical substance known as bioflavonoids (Vitamin P), phenols, and aromatic compounds [4]. It is commonly brown in color, but it varies depending on the botanical source. Flavonoids are well-known plant compounds which have antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory properties. Flavonoids are the most common group of polyphenolic compounds in the human diet and are found ubiquitously in plants. They are divided into four subgroups: Flavones, Flavonol, Flavonones, and Flavonol. Cinnamic acid ($C_6H_5CHCHOOH$) is a white crystalline acid, which is slightly soluble in water and is obtained from oil of cinnamon, or from balsams [5].

COMMERCIALLY AVAILABLE AS

Propolis is available in the world markets in different forms as capsules, lozenges, tincture, and cream and recently added to the list are mouth rinses and toothpaste.

MEDICAL IMPLICATIONS

Antimicrobial activity of propolis

Antibacterial activity

Antibacterial activity of propolis and its extracts against Gram-positive and Gram-negative strains and they found that propolis had antibacterial activity against a wide range of Gram-positive rods but had a limited activity against Gram-negative bacilli.

Ethanolic extract of propolis (EEP) was effective against anaerobic bacteria. EEP showed the greatest effectiveness against strains of bacteroides and peptostreptococcus and was slightly less effective against the Gram-positive rods of Propionibacterium, Arachnia, and Eubacterium. Strains of clostridium were the least sensitive to EEP [6].

Antibacterial activity was observed against a range of commonly encountered cocci and Gram-positive rods, in addition to *Mycobacterium tuberculosis*, but only limited activity against Gram-negative bacilli [7]. Aga *et al*. (1994) [8] isolated three antimicrobial compounds from Brazilian propolis and identified them as 3,5 diprenyl-4- hydroxycinnamic acid, 3-prenyl - 4- dihdrocinnamoloxycinnamic acid, and 2,2- dimethyl -6- carboxyethenyl-2H-1-benzopyran. Their respective antimicrobial activities against *Bacillus cereus*, *Enterobacter erogenous*, and *Arthroderma benhamiae* were investigated; they found the first compound showed the highest activity and were likely to be one of the major antimicrobial compounds in Brazilian propolis.

Antiviral activity

In vitro activity of 3-methyl-but-2-enyl caffeate isolated from poplar buds against *Herpes simplex* virus Type 1 was investigated. They found that this compound, as a minor constituent of propolis, reduces the virus titer and viral DNA synthesis effectively [9]. It was found that isopentyl ferulated (isolated from propolis) inhibited significantly the infectious activity of influenza virus A1 Honey Kong (H3N2) *in vitro* [10].

Antifungal activity

Ota *et al*. (2001) [11] studied the antifungal activity of propolis in sensitivity tests on 80 strains of Candida yeasts: 20 strains of *Candida albicans*, 20 strains of *Candida tropicalis*, 20 strains of *Candida krusei,* and 15 strains of *Candida guilliermondii*. The yeasts showed a clear antifungal activity with the following order of sensitivity: *C. albicans* > *C. tropicalis* > *C. krusei* > *C. guilliermondii*. Patients with full dentures who used a hydroalcoholic propolis extract showed a decrease in the number of Candida.

ANTIPROTOZOAL AND ANTIPARASITIC ACTIVITY

The EEP and dimethyl-sulfoxide extracts of propolis were active against *Trypanosoma cruzi* [12].

ANTI-INFLAMMATORY ACTIVITY

The effects of EEP on chronic inflammation were evaluated using rat adjuvant arthritis. In the chronic inflammatory animal model, the arthritis index was suppressed by EEP treatments (50 mg/kg/day and 100 mg/kg/day, P.O.). Moreover, physical weakness, induced by the chronic disease state, was dose-dependently improved in the EEP-treated groups. Its analgesic effect, assessed using the tail-flick test, was comparable to prednisolone (2.5 mg/kg/day, P.O.) and acetylsalicylic acid (100 mg/kg/day, P.O.). In carrageenan rat hind paw edema, which was conducted to test the effects of subfractions of EEP, the petroleum ether sub-fraction (100 mg/kg, P.O.) showed an inhibitory effect on the paw edema, whereas EEP (200 mg/kg, P.O.) showed a significant anti-inflammatory effect at 3 and 4 hrs after carrageenan injection. From these results, they concluded that the EEP had profound anti-inflammatory effects on both chronic and acute inflammations [13].

ANTITUMOR ACTIVITY

Artepillin C was extracted from Brazilian propolis. Artepillin C (3,5-diprenyl-4-hydroxycinnamic acid) has a molecular weight of 300.40 and possesses antibacterial activity. When artepillin C was applied to human and murine malignant tumor cells *in vitro* and *in vivo*, artepillin C exhibited a cytotoxic effect, and the growth of tumor cells was clearly inhibited. The artepillin C was found to cause significant damage to the solid tumor and leukemic cells by the MTT assay, DNA synthesis assay, and morphological observation *in vitro*. When xenografts of human tumor cells were transplanted into nude mice, the cytotoxic effects of artepillin C were most noticeable in carcinoma and malignant melanoma. Apoptosis, abortive mitosis, and massive necrosis combined were identified by histological observation after intratumor injection of 500 g of artepillin C 3 times a week. In addition to suppression of tumor growth, there was an increase in the ratio of CD4/CD8 T cells, and in the total number of helper T cells. These findings indicate that artepillin C activates the immune system, and possesses direct antitumor [14].

PM-3 (3-[2-dimethyl-8-(3-methyl-2-butenyl) benzopyran]-6-propenoic acid) isolated from Brazilian propolis markedly inhibits the growth of MCF-7 human breast cancer cells. This effect was associated with inhibition of cell cycle progression and induction of apoptosis. Treatment of MCF-7 cells with PM-3 arrested cells in the G1 phase and resulted in a decrease in the protein levels of cyclin D1 and cyclin E. PM-3 also inhibited the expression of cyclin D1 at the transcriptional level when examined in cyclin D1 promoter luciferase assays. Induction of apoptosis by PM-3 occurred within 48 hrs after treatment of MCF-7 cells. The MCF-7-treated cells also displayed a decrease in the level of the estrogen receptor (ER) protein and inhibition of ER element promoter activity [15].

PROTECTIVE EFFECTS ON THE BRAIN

Oxygen-derived free radicals have been implicated in the pathogenesis of cerebral injury after ischemia reperfusion. Caffeic acid phenethyl ester (CAPE), an active component of propolis extract, exhibits antioxidant properties. The effects of ischemia and subsequent reperfusion on rat brain and the effects of two free radical scavengers, CAPE, and alpha-tocopherol, were investigated on the *in vivo* model of cerebral injury. Ischemia was induced by bilateral occlusion of the carotid arteries for 20 minutes, and reperfusion was achieved by releasing the occlusion to restore the circulation for 20 minutes. Control rats underwent a sham operation. CAPE at 10 micromol/kg or alpha-tocopherol at 25 micromol/kg was administered intraperitoneally before reperfusion. Reperfusion led to significant increase in the activity of xanthine oxidase and higher malondialdehyde levels in the brain. Acute administration of both CAPE and alpha-tocopherol suppressed ischemia-reperfusion-induced cerebral lipid peroxidation and injury, but CAPE seems to offer a better therapeutic advantage over alpha-tocopherol [16].

DENTAL IMPLICATIONS

Wound healing

A study conducted by Magro-Filho and Carvalho, 1994 [17] analyzed the effects of propolis mouth rinse on the repair of surgical wounds after sulcoplasty by the modified Kazanjian technique. Patients returned 7, 14, 30, and 45 days after surgery for cytological and clinical evaluation. It was concluded that:

a. The mouth rinses containing propolis in aqueous alcohol solution aided repair of intra-buccal surgical wounds and exerted a small pain killing and anti-inflammatory effect
b. The vehicle employed had a minor irritant effect on infra-buccal surgical wounds
c. Exfoliative cytology showed epithelization of infra-buccal surgical wounds.

They also examined histologically the effects of propolis topical application to dental sockets and skin wounds. It was concluded that topical application of propolis hydroalcoholic solution accelerated epithelial repair after tooth extraction but had no effect on socket wound healing [18].

PROPOLIS: A PROMISING NEW STORAGE MEDIA FOLLOWING AVULSION

Both lengths of extra alveolar time and type of storage media are significant factors that can affect the long-term prognosis of replanted teeth [3]. Gopikrishna *et al*. (2008) [19] the potential of a new storage medium, coconut water, in comparison with propolis, Hank's balanced salt solution (HBSS) and milk in maintaining viable periodontal ligament (PDL) cells on simulated avulsed teeth. A total of 70 freshly extracted human teeth were divided into 4 experimental groups and 2 control groups. The positive and negative controls corresponded to 0 minute and 8 hrs dry times, respectively. The experimental teeth were stored dry for 30 minutes and then immersed in 1 of the 4 media (coconut water, propolis, HBSS, and milk). The teeth were then treated with dispase Grade II and collagenase for 30 minutes. The number of viable PDL cells was counted with a hemocytometer and analyzed. Statistical analysis showed that coconut water kept significantly more PDL cells viable compared with propolis, HBSS, or milk. Coconut water can be used as a superior transport medium for avulsed teeth.

AS A PULP CAPPING AGENT

Propolis has been shown to possess potent antimicrobial and anti-inflammatory properties. The main chemical classes present in propolis are flavonoids, phenolics, and other various aromatic compounds. Flavonoids and caffeic acid present in propolis are known to play an important role in reducing the inflammatory response by inhibiting

lipoxygenase pathway of arachidonic acid. Flavonoids and caffeic acid also aid the immune system by promoting phagocytic activities and stimulates cellular immunity. Propolis also helps in hard tissue bridge formation; this has been attributed to the property of propolis, which has been shown to stimulate various enzyme systems, cell metabolism, circulation, and collagen formation. 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. All these factors of propolis help in good wound healing. In addition to wound healing ability, propolis is a good antimicrobial agent. It prevents bacterial cell division, breaks down bacterial cell wall and cytoplasm [3].

AS AN INTRACANAL IRRIGANT

Al-Qathami and Al-Madi (2003) [20] compared the antimicrobial efficacy of propolis, sodium hypochlorite, and saline as intracanal irrigants. Microbiological samples were taken from the teeth immediately after accessing the canal and after instrumentation and irrigation. The results of this study indicated that the propolis has antimicrobial activity equal to that of sodium hypochlorite.

AS A MOUTH RINSE

Ozan *et al.* (2007) [21] performed a study to compare the effects of four different mouth rinse containing propolis solutions and mouth rinse containing 0.2% chlorhexidine (CHX) on oral microorganisms and human gingival fibroblasts. Mouth rinse containing propolis was prepared at four different concentrations as 10, 5, 2.5, and 1%. Besides, CHX was used as control group. The antibacterial effects of five solutions on oral microorganisms were tested, and their cytotoxic effects on human gingival fibroblasts were evaluated by agar diffusion test. At this concentrations effectiveness of mouth rinse containing propolis samples on oral microorganisms were not found as effective as CHX. On the contrary, samples found less cytotoxic on human gingival fibroblasts than CHX.

AS A CARIOSTATIC AGENT

Hayacibara *et al*. (2005) [22] evaluated the influence of propolis on mutans streptococci viability, glycosyltrans-ferases (GTFs) activity, and caries development in rats. The data suggested that propolis is a potentially novel anticaries agent.

IN DENTINAL HYPERSENSITIVITY

The clinical trial of propolis on female subjects for 4 weeks was conducted. 26 female subjects with age range 16-40 years (mean 28 years) were included in the study. Propolis was applied twice daily on teeth with hypersensitivity. The hypersensitivity was assessed on a visual scale 0-10 and by slight, moderate, and severe classification at baseline, after 1 and 4 weeks. About 70% of the subjects had severe hypersensitivity at the baseline. At first recall, 50% reported moderate hypersensitivity, 50% reported slight hypersensitivity at second recall, and 30% had no hypersensitivity while only 19% had moderate hypersensitivity. It was concluded that propolis had a positive effect in the control of dentinal hypersensitivity. In another *in vitro* study using scanning electron microscopic, it was found that propolis occluded the dentinal tubules in both 60 and 120 s application on human dentin [23].

IN TREATMENT OF PERIODONTITIS

Toker *et al*. (2008) [24] analyzed the morphometric and histopathologic changes associated with experimental periodontitis in rats in response to the systemic administration of propolis. Changes in alveolar bone levels were clinically measured, and tissues were histopathologically examined to assess the differences among the study groups. Propolis significantly reduced the periodontitis-related bone loss, the findings of this study provided morphologic and histologic evidence that propolis, when administered systemically, prevented alveolar bone loss in the rat model.

IN TREATMENT OF DENTURE STOMATITIS

Denture stomatitis presents as a chronic disease in denture-bearing patients, especially under maxillary prosthesis. Despite the existence of a great number of antifungal agents, treatment failure is observed frequently. Propolis, a natural bee product, possesses well - documented antifungal and anti-inflammatory activities [3]. Santos *et al.* (2008) [25] evaluated the clinical efficacy of a new Brazilian propolis gel formulation in patients diagnosed with denture stomatitis. 30 complete - denture wearers with denture stomatitis were enrolled in this pilot study. At baseline, clinical evaluation was performed by a single clinician and instructions for denture hygiene were provided. 15 patients received Daktarin (Miconazole gel) and 15 received Brazilian propolis gel. All patients were recommended to apply the product four times a day during 1 week. Clinical evaluation was repeated by the same clinician after treatment. All patients treated with Brazilian propolis gel and Daktarin had complete clinical remission of palatal edema and erythema. They concluded this new Brazilian propolis gel formulation had efficacy comparable to Daktarin and could be an alternative topical choice for the treatment of denture stomatitis.

AS AN INTRA-CANAL MEDICAMENT

Awawdeh *et al*. (2009) [26] evaluated the effectiveness of propolis and calcium hydroxide as a short-term intracanal medicament against *Enterococcus faecalis*. They concluded that propolis is very effective as an intracanal medicament in rapidly eliminating *E. faecalis ex vivo*.

EFFECT OF PROPOLIS ON RECURRENT APHTHOUS STOMATITIS (RAS)

RAS is a common, painful, and ulcerative disorder of the oral cavity of unknown etiology. No cure exists and medications aim to reduce pain associated with ulcers through topical applications or reduce outbreak frequency with systemic medications, many having serious side effects [3]. Samet *et al*. (2007) [27] evaluated the potential of a product to reduce the number of outbreaks of RAS ulcers. Propolis is a bee product used in some cultures as a treatment for mouth ulcers. In this randomized, double-blind, placebo-controlled study, patients were assigned to take 500 mg of propolis or a placebo capsule daily. Subjects reported a baseline ulcer frequency and were contacted biweekly to record recurrences. Data were analyzed to determine if subjects had a decrease of 50% in outbreak frequency. The data indicated a statistically significant reduction of outbreaks in the propolis group. Patients in the propolis group also self-reported a significant improvement in their quality of life. This study has shown propolis to be effective in decreasing the number of recurrences and improve the quality of life in patients who suffer from RAS.

CONCLUSION

Propolis is one of the few natural remedies that has maintained its popularity over a long period of time. The pharmacologically active molecules are flavonoids, phenolic acids, and their esters. These components have multiple effects on bacteria, fungi, and viruses. In addition, propolis and its components have anti-inflammatory, immunomodulatory activities, and antitumor activity. Now-a-days, propolis can also be used to treat canker sores. Its use in canal debridement for endodontic procedures has been explored. Because of its strong, antiinfective activity, propolis has often been called a "natural antibiotic." Many studies show its strong inhibitory effect on a wide variety of pathogenic organisms. Propolis extract possesses antiplaque activity and improves gingival health. The extract might be used as an alternative measure to prevent periodontal and gingival problems.

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