Journal of Ethnopharmacology 125 (2009) 1–9

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

The potential use of propolis as a cariostatic agent and its actions on mutans group streptococci

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ARTICLE INFO

Article history:
Received 6 March 2009
Received in revised form 24 April 2009
Accepted 26 April 2009
Available online 5 May 2009

Keywords:
Propolis
Streptococcus mutans
Dental caries
Cariostatic agent

ABSTRACT

Propolis is a resinous substance made by bees. It possesses many biological activities, and many studies have reported its potential application in the control of dental caries. However, variability in the chemical composition of propolis is a potential problem in its quality control, especially since propolis has already been incorporated into products for oral use. Therefore, a critical analysis of the available data on propolis is warranted. The present review discusses the *in vitro* and *in vivo* studies published in the period between 1978 and 2008 regarding the effects of propolis on *Streptococcus mutans* growth, bacterial adherence, glucosyltransferase activity, and caries indicators. Several investigations carried out with crude propolis extracts, isolated fractions, and purified compounds showed reductions in *Streptococcus mutans* counts and interference with their adhesion capacity and glucosyltransferase activity, which are considered major properties in the establishment of the cariogenic process. Data from *in vivo* studies have demonstrated reductions in *Streptococcus mutans* counts in saliva, the plaque index, and insoluble polysaccharide formation. These findings indicate that propolis and/or its compounds are promising cariostatic agents. However, the variation in the chemical composition of propolis due to its geographical distribution is a significant drawback to its routine clinical use. Thus, further studies are needed to establish the quality and safety control criteria for propolis in order for it to be used in accordance with its proposed activity.

Contents

Abbreviations: MGS, mutans group streptococci; BHI, brain heart infusion; GTF, glucosyltransferase; EE, ethanolic extract; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; HX, hexane; CHL, chloroform; EA, ethyl acetate; ET, ethanol; BUT, *n*-butanol; EEP, ethanolic extract of propolis; EP, extract of propolis.

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doi:10.1016/j.jep.2009.04.047

1. Introduction

The investigation of natural products with antimicrobial activity has attracted the attention of many researchers, motivated mainly by the increasing bacterial resistance to traditional antimicrobial agents (Cragg et al., 1997; Normark and Normark, 2002; Sheldon, 2003) and the side effects frequently observed after the use of antibiotics (Cunha, 2001; Gleckman and Czachor, 2000).

Among those natural products, propolis has been considered a good candidate for an adjuvant in the treatment or prevention of many infectious diseases. Propolis is relatively non-toxic (Burdock, 1998; Cuesta et al., 2005; Jasprica et al., 2007) and displays a wide range of antimicrobial activity against a variety of bacteria, fungi, parasites, and virus (Grange and Davey, 1990; Dobrowolski et al., 1991; Amoros et al., 1992; Serkedjieva et al., 1992; Higashi and de Castro, 1994; Bankova et al., 1995; Steinberg et al., 1996; Kujumgiev et al., 1999; Sforcin et al., 2000; Ito et al., 2001; Orsi et al., 2005; Freitas et al., 2006). The use of propolis by man dates back to ancient times, when the product was employed in the embalming of bodies in Egypt (Ghisalberti, 1979).

In addition to an antimicrobial activity, other biological and pharmacological properties have also been demonstrated for propolis, including anti-inflammatory, antitumor, cytotoxic, hepatoprotective, antioxidant, hematostimulative, and immunomodulatory properties (Banskota et al., 2000; Ahn et al., 2004; Orsolic and Basic, 2005; Sforcin, 2007).

Dental caries is an infectious disease of worldwide public health concern, especially in developing countries. It is characterized by the colonization and accumulation of oral microorganisms on dental surfaces, resulting in the formation of dental plaque (or bacterial biofilm) and demineralization of the tooth structure (Selwitz et al., 2007). Many bacteria have been described in association with the cariogenic process, especially large populations of acidogenic and aciduric bacteria, such as *Streptococcus mutans*, *Streptococcus sobrinus*, and *Lactobacillus*, which are capable of demineralizing enamel by producing an acidic environment (Loesche, 1986; Leverett et al., 1993; Marsh, 1999; Featherstone, 2000).

Thus, control of the bacterial biofilm on teeth is essential to the maintenance of oral health, and can be achieved by proper oral hygiene, use of fluoride products, and regular check-ups with a dentist (Berkowitz, 2003; Selwitz et al., 2007). An additional approach is the application of chemical agents with antimicrobial activities on dental surfaces to promote a reduction in biofilm formation. Such agents have been frequently prescribed as adjuvants in the prevention or treatment of oral diseases because they can inhibit bacterial colonization, growth, and metabolism, and consequently interrupt the formation of mature biofilm, changing it at biochemical and ecological levels (Featherstone, 2000; Twetman, 2004; Paraskevas, 2005; Zhan et al., 2006; Selwitz et al., 2007).

Of the available antiseptics, chlorhexidine digluconate is the most studied and most recommended agent for use in the oral cavity (Bouwsma, 1996). However, in spite of its significant *in vitro* antimicrobial activity on cariogenic microorganisms (Jarvinen et al., 1993; McDermid et al., 1987), the use of chlorhexidine digluconate in Dentistry is still controversial because of some local side effects. Additionally, data from several studies have shown that its role in caries prevention is inconclusive (Autio-Gold, 2008).

It was previously demonstrated in rats that dental caries can be significantly reduced by propolis, which suggests its potential adjuvant effect in the control of dental caries (Ikeno et al., 1991). Since that study, interest in the use of propolis against a number of oral pathogens has grown significantly (Park et al., 1998; Steinberg et al., 1996; Koo et al., 2000a, 2002b; Duarte et al., 2003; Gebaraa et al., 2003; Hayacibara et al., 2005; Orsolic et al., 2005; Bruschi et al., 2006; Koru et al., 2007). Moreover, significant advances in other areas have contributed to our understanding of the chemical composition and variability of propolis, its pharmacological properties, and its biological activities, all of which are relevant in the treatment of oral diseases (Bankova, 2005a,b; Sforcin, 2007). This review focuses on the therapeutic application of propolis in the control of dental caries, especially on mutans group streptococci (MGS).

The Biological Abstracts, Chemical Abstracts, Medline, Web of Science, PubMed, Highwire and Lilacs databases were searched for articles published in English from 1978 to 2008. The search terms were "*Streptococcus mutans*", "propolis", "dental caries", "natural products", "oral bacteria", and "antimicrobial activity".

2. Chemical composition of propolis

Propolis results from the addition of the mandibular secretions of bees to resins collected by these insects from different parts of plants. It is a structurally complex resinous, gum-like balsamic substance, which contains approximately 50–55% resins and balsams, 30% wax, 10% volatile oils, 5% pollen, and 5% other substances that vary according to the flora of the region and the bee species. Inside the hive, propolis is used by bees to line internal walls and seal possible openings to allow thermal control of the colony and prevent the entry of other insects. In addition, propolis is used to embalm dead insects and to prevent the proliferation of microorganisms in the colony (Ghisalberti, 1979; Burdock, 1998).

The chemical composition of propolis is highly variable and complex, due to the biodiversity of the vegetation of each region visited by bees (Koo et al., 1999; Kujumgiev et al., 1999; Sforcin et al., 2000; Velikova et al., 2000; Bankova, 2005a; Salatino et al., 2005; Katircioglu and Mercan, 2006; Melliou and Chinou, 2004; Mohammadzadeh et al., 2007). Although there are a few exceptions, the main source of propolis in temperate zones is the bud exudate of *Populus* species (Poplar). This has been concluded from studies carried out with propolis from Europe (Nagy et al., 1986; Greenaway et al., 1987; Bankova et al., 1992), North America (Garcia-Viguera et al., 1993), New Zealand (Markham et al., 1996), and Asia (Bankova et al., 1992). However, samples of European propolis that were not of poplar origin have also been described (Bankova et al., 2002).

On the other hand, in tropical regions where there are no poplars, bees find other plant sources for propolis production. In the Sonoran Desert, *Ambrosia deltoidea* has been considered the plant source (Wollenweber and Buchmann, 1997). Some compounds detected in propolis samples from Venezuela were identical to components detected in *Clusia* species (Guttiferae), indicating that they are the source of propolis production in that country (Tomas-Barberan et al., 1993). In southeast Brazil, *Araucaria* spp. (Bankova et al., 1996) and *Baccharis* spp. (Marcucci et al., 1998) were described as the putative plant sources for propolis.

Therefore, the composition of propolis from different phytogeographical areas are expected to vary and as a consequence, the intensity or presence of some biological activities also varies (Katircioglu and Mercan, 2006; Mohammadzadeh et al., 2007). However, even within the same country the propolis composition may be qualitatively and quantitatively different depending on the region and period of its collection (Koo et al., 1999). In Brazil, for instance, some authors have reported that propolis from distinct regions were chemically classified into 12 types (Park et al., 2002).

Among the numerous groups of substances identified in propolis samples from different localities, the most common are aromatic acids and esters, chalcones, flavonoids, terpenoids, and waxy acids. Most of the biological activities of propolis have been attributed to these compounds, especially the flavonoids (Marcucci, 1995; Marcucci et al., 2001; Park et al., 2002; Bankova, 2005b; Salatino et al., 2005; Silva et al., 2006; Trusheva et al., 2006). In this regard, antimicrobial activities have usually been attributed to flavonoids as well. However, other components present in propolis, such as