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Fitoterapia 73 Suppl. 1 (2002) S1–S6

FITOTERAPIA

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Propolis, an old remedy used in modern medicine

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Abstract

Propolis is one of the few natural remedies that has maintained its popularity over a long period of time. The pharmacologically active molecules in the propolis are flavonoids and phenolic acids and their esters. These components have multiple effects on bacteria, fungi and viruses. In addition, propolis and its components have anti-inflammatory and immunomodulatory activities. Moreover, propolis has been shown to lower blood pressure and cholesterol levels. However, clinical studies to substantiate these claims are required.

Keywords: Propolis; Old and modern medicine

1. Introduction

The term propolis derives from the Greek pro (for 'in front of', 'at the entrance to') and polis ('community' or 'city') and means a substance in defense of the hive. Propolis, or bee glue, is a brownish resinous material collected by worker bees from the leaf buds of numerous tree species like birch, poplar, pine, alder, willow and palm. In order to manufacture propolis, bees may also use material actively secreted by plants, or exuded from wounds in plants (lipophylic material on leaves, mucilages, gums, resins, lattices, etc.). Once collected, this material is enriched with salivary and enzymatic secretions [1] and is used by bees to cover hive walls, fill cracks or gaps and embalm killed invader insects. In Venezuela and other tropical countries of South America there exist indigenous bees which collect resinous material from plants and mix it with bees wax and soil to form geopropolis.

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0367-326X/02/$ - see front matter
PII: S0367-326X(02)00185-5

Propolis is a natural remedy that has been employed extensively since ancient times. Egyptians knew very well the anti-putrefactive properties of propolis and used it to embalm cadavers. Propolis was recognized for its medicinal properties by the Greek and Roman physicians, Aristoteles, Dioscorides, Pliny and Galen. The drug was employed as an antiseptic and cicatrizant in wound treatment and as mouth disinfectant, with these uses being perpetuated in the Middle Ages and among Arab physicians. Propolis was also recognized by other peoples unrelated to Old World civilizations: Incas employed propolis as an anti-pyretic agent, and the London pharmacopoeias of the seventeenth century listed propolis as an official drug. Between the seventeenth and twentieth century the drug became very popular in Europe on account of its anti-bacterial activity.

Modern herbalists recommend it for its anti-bacterial, anti-fungal, anti-viral, hepatoprotective and anti-inflammatory properties, to increase the body's natural resistance to infections and to treat gastroduodenal ulcers. Applied externally, propolis relieves various types of dermatitis caused by bacteria and fungi.

Today propolis is currently used as a popular remedy and is available in the form of capsules (either in pure form or combined with aloe gel and rosa canina or pollen), as an extract (hydroalcholic or glycolic), as a mouthwash (combined with melissa, sage, mallow and/or rosemary), in throat lozenges, creams, and in powder form (to be used in gargles or for internal use once dissolved in water). It is also available commercially as purified product in which the wax has been removed. Propolis is also claimed to be useful in cosmetics and as a constituent of health foods.

2. Chemical constituents

Up to now, more than 180 compounds, mainly polyphenols, have been identified as constituents of propolis. The major polyphenols are flavonoids, accompanied by phenolic acids and esters, phenolic aldehydes, ketones, etc. Other compounds in propolis are volatile oils and aromatic acids (5–10%), waxes (30–40%), resins, balms and pollen grains which are a rich source of essential elements such as magnesium, nickel, calcium, iron and zinc [2]. New compounds have also been isolated from Brazilian (3,5- diprenyl-4-hydroxycinnamic acid) and Chinese (octacosanol) samples of propolis. While the chemical composition of propolis has been clarified to some extent in recent years, there still remains one problem which is the striking variability of its chemical composition depending on the site of its collection.

Anti-microbial properties of propolis seem attributable mainly to the flavonoids pinocembrin, galangin and pinobanksin. Pinocembrin also exhibits anti-fungal properties. Other active compounds are ester of coumaric and caffeic acids. Of the other compounds, prenylated *p*-coumaric and diterpenic acids possess anti-bacterial and cytotoxic activities. Caffeoylquinic acid derivatives show immunomodulatory and hepatoprotective actions and furofuran lignans inhibit the growth of some bacteria. Caffeic acid phenethyl ester (CAPE) is also cytotoxic towards tumor cells.

3. Pharmacological properties and toxicity

Propolis preparations show in vitro anti-microbial activity mainly against Gram-positive (*Staphylococci* and *Strepthococci* spp.) and Gram-negative bacteria (*E. coli*, *K. pneumoniae*, *P. vulgaris* and *P. aeruginosa*), *Helicobacter pylori*, protozoa (*T. cruzi*), fungi (*Candida albicans*) and viruses (*HIV*, *Herpes viruses* or *influenza viruses*). A study carried out by Tosi et al. [3] indicates that the solvent employed for the extraction of propolis may influence the potency of its anti-microbial activity. In fact, the oil preparation has a wide range of anti-microbial activities; the glycerine solutions show little inhibition of Gram-positive bacteria, whereas the ethanol and propylene glycol solutions show good activity against yeasts. Studies also demonstrate a marked synergistic effect of propolis on the anti-bacterial activity of streptomycin and cloxacillin, and a moderate synergistic effect on the anti-bacterial activity of chloramphenicol, cefradine and polymyxis B in culture medium containing a fixed amount of a standard strain of *Staphilococcus aureus* [4]. Studies have also been done on 15 bacterial strains of clinical relevance in dentistry: propolis extract showed in vitro anti-bacterial activity, inhibition of cell adherence and inhibition of water-insoluble glucan formation [5]. Arnica extract, compared to propolis extract, was only slightly active in those three conditions.

It is well known that genital HSV infection is to some extent a difficult disease to treat. A recent study by Vynograd et al. [6] showed that an ointment containing propolis was effective in healing genital herpetic lesions and in reducing local symptoms. A topical treatment with extracts or ointments of propolis is useful not only against herpes infections but also in dentistry, dermatology and otorhinolaringology [6].

Propolis also exhibits anti-inflammatory effects against acute and chronic models of inflammation (formaldehyde- and adjuvant-induced arthritis, carrageenan- and PGE_2-induced paw oedema, cotton pallet granuloma). The exact mechanism of the anti-inflammatory actions of propolis is still unclear. Recently, Rossi et al. [7] demonstrated that propolis inhibits in a concentration-dependent manner COX activity from lung homogenates of saline- or LPS-treated rats. Among the compounds tested, only CAPE and galangin contributed to the anti-inflammatory activity of propolis; however, the contribution of CAPE was greater.

Propolis also exhibits immunostimulatory and immunomodulatory effects in vitro on macrophages [8,9], while in vivo it increases the ratio of CD4/CD8T cells in mice [10].

This range of effects could explain the rationale for propolis being used in chronic and acute inflammations in the mouth, periodontis sinusitis, pharingotracheitis or upper and lower airway diseases and cutaneous ulcers [11–13]. Propolis also exhibits hepatoprotective effects in acute liver damage induced in rats by carbon tetrachloride and in mice by paracetamol [14] and allyl alcohol [15]. It is known that hepatic GSH has a protective role against chemically-induced cellular injury. GSH is one of the most important anti-oxidant molecules of the liver and at physiological concentrations contributes to the maintenance of the normal redox

state of cells. Propolis is able to reverse the depletion of GSH induced by paracetamol in mice and thereby prevent cell death.

Propolis may also act as a scavenger against oxygen radicals [16]. Recent studies indicate that propolis is able to inhibit the formation of the superoxide anion, which is produced during autoxidation of β-mercaptoethanol [17]. In these studies CAPE was more active than galangin in inhibiting the formation of the superoxide anion. CAPE also protects against ischemic spinal cord injury after infrarenal aortic occlusion in rabbits. This experimental result suggests a prophylactic use of propolis and its active compound CAPE to avoid this complication during the surgical repair of thoracic or thoracoabdominal aortic aneurysms [18].

Propolis also has an anesthetic effect similar to that of cocaine [19] and shows regenerative effects on biological tissues [20,21] and anti-neoplastic activity against many cancer cells [10,22–24]. Propolis is also able to inhibit cell division and protein synthesis [25]. CAPE has also been identified as one of the major active compounds in propolis with chemopreventive and anti-tumoral properties [24]. However, the exact mechanisms underlying the positive effects of propolis and its component CAPE on cancer treatment is not fully understood and requires further experimental studies.

Propolis is considered safe in low doses: however, adverse effects are common at doses over 15 g/day. The adverse effects most commonly experienced are allergic reactions, as well as skin or mucous membrane irritations. Caution should be used in the treatment of asthmatics and in patients with eczema and nettle-rash.

4. Future perspectives

It has been reported that propolis lowers blood pressure and cholesterol levels, the latter of which may persist for some weeks after drug withdrawal [26]. These unexpected activities make propolis prospectively a very interesting compound for use in the prevention and treatment of atherosclerosis. Atherosclerosis is viewed as a multifactorial disease whose pathogenesis cannot be exhaustively explained by recognized classic risk factors (hypertension, hypercholesterolemia, diet, smoking, etc.). Today there is growing evidence supporting the inflammatory, immunologic pathogenesis of atherosclerosis. On the other hand, some data suggest that monocyte activation could play a role in atherosclerosis progression [27]. The link between inflammation, monocyte activation and atherosclerosis could be a microbial agent such as *Chlamidia pneumonia*, *Helicobacter pylori* or *Cytomegalovirus* (bacterioscleroris). Bacteria could release lipopolysaccharides (LPS) which activate monocytes and endothelial cells. Activated endothelial cells express on their surface vascular endothelial cell adhesion molecules (CAMs) such as selectins and integrins, which promote rolling, sticking and finally extravasation of blood monocytes. On the other hand, LPS promote monocyte activation and release of cytokines, chemokines and prostaglandins, which stimulate smooth muscle cell migration and potentiate CAM expression on the endothelial cell surface. In light of the fact that

propolis is active against bacteria and inflammation, as well as being able to reduce blood pressure and cholesterol and diminish apoptosis [9], it could be proposed as a 'global remedy' for atherosclerosis prevention and cure.

5. Conclusions

The beneficial effects of propolis are mentioned in the writings of ancient Greek and Roman physicians. Propolis has also been used for centuries for a multiplicity of unrelated human ailments; for example to treat tuberculosis, duodenal ulcers and gastric disturbances, and to relieve various types of dermatitis and reduce fever. Two uses, however, have persisted for centuries: the main one being its external use as an antiseptic and cicatrizant; the second being its internal use in the treatment of gastroduodenal ulcers. Apart from these uses, propolis appears also to offer benefits to patients with inflammatory diseases. Clinical studies are now also in progress to verify the effects of propolis in the prevention and treatment of atherosclerosis. Current opinion is that the use of standardized preparations of propolis is safe and less toxic than many synthetic medicines.

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