

## Review article

# Propolis: chemical composition, biological properties and therapeutic activity

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**Summary** — The plant sources and chemical composition of propolis are reviewed. The chemical constituents that may be relevant to its biological and therapeutic activity are discussed. The cytotoxic activity and antimicrobial and pharmacological properties of propolis are presented. Propolis components, which cause allergy and are responsible for anticancer activity, *eg*, caffeic acid derivatives, are reported. The therapeutic efficacy of propolis in treating diseases caused by microorganisms is described. Some recent concepts about propolis and its use in medicine are presented.

**propolis / phenolics / antimicrobial activity / toxicity / therapeutical activity**

## INTRODUCTION

In recent years there has been renewed interest in the composition of propolis, a substance that can be regarded as a potential natural source in folk medicine and in the chemical industry. This article describes the composition, biological and pharmacological properties, therapeutic activity and uses of propolis in pharmaceutical and cosmetic products.

## COMPOSITION OF PROPOLIS

Propolis is a natural resinous substance collected by bees from parts of plants, buds

and exudates (Ghisalberti, 1979). Bees use it as a sealer for their hives (García-Viguera *et al*, 1992) and, more importantly, to prevent the decomposition of creatures which have been killed by bees after an invasion of the hive (Brumfitt *et al*, 1990). Characteristically, it is a lipophilic material, hard and brittle when cold but soft, pliable, and very sticky when warm, hence the name bee-glue (Hausen *et al*, 1987a). It possesses a pleasant aromatic smell, and varies in color, depending on its source and age (Brown, 1989). Among the types of chemical substances found in propolis are waxes, resins, balsams, aromatic and ethereal oils, pollen and other organic matter (Ghisalberti *et al*, 1978). The proportion of these types of substances varies and depends on the place

and time of collection (Ghisalberti *et al*, 1978; Bankova *et al*, 1992b). The compounds identified in propolis resin originate from 3 sources: plant exudate collected by bees; secreted substances from bee metabolism; and materials which are introduced during propolis elaboration (Ghisalberti, 1979; Marcucci *et al*, 1994b).

Simple fractionation of propolis to obtain compounds is difficult due to its complex composition. The usual manner was to extract the fraction soluble in alcohol, called 'propolis balsam', leaving the alcohol-insoluble or wax fraction (Ghisalberti, 1979). Although ethanol extract of propolis (EEP) is the most common, extracts with other solvents have been carried out (Villanueva *et al*, 1964; Cizmárik and Matel, 1970; Hladón *et al*, 1980; Bankova *et al*, 1983, 1988, 1989; Manolova *et al*, 1985; Cortani, 1987, 1991; Grunberger *et al*, 1988; Andrich *et al*, 1987; Neychev *et al*, 1988; Ross, 1990) for identification of many constituents. Many analytical methods have been used for separation and identification of propolis constituents (Bankova *et al* 1982, 1988, 1989, 1992a, 1994; König, 1986; Cortani, 1987; Pápay *et al*, 1987; Grenaway *et al*, 1988, 1989, 1991; Walker and Crane, 1987; Nagy *et al*, 1989a, 1989b; Campos *et al*, 1990; Christov and Bankova, 1992; Tomás-Barberán *et al*, 1993). The known components of propolis resin are listed in table I.

Vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub>, C, E, and mineral elements silver, cesium, mercury, lanthanum, antimony, copper, manganese, iron, calcium, aluminium, vanadium and silicon have all been identified in propolis samples (Deblock-Bostyn, 1982; Debuyser, 1983).

The plant origin of propolis has been studied by many researchers. Bankova *et al* (1992b) showed that propolis composition is very similar to bud exudates. Qualitative composition of many compounds, *eg*, flavonoids aglycones in propolis of different tree species has indicated that propolis has

been collected from *Populus fremontii* (USA), *P x euramericana* (UK), *Dalechampia* spp and *Clusia* spp (Equator) (Greenaway *et al*, 1990); *P nigra*, *P italica*, *P tremula* (Bulgaria) and *P suaveolens* (Mongolia) (Bankova *et al*, 1992b; 1994); *Betula*, *Populus*, *Pinus*, *Prunus*, *Acacia*, *Aesculus hypocastane* (Hungary) (Nagy *et al*, 1985), *Clusia minor* (Venezuela) (Tomás-Barberán *et al*, 1993), *Plumeria acuminata* and *P acutifolia* (Hawaiian Islands) (König, 1985) and *Betula* and *Alnus* (Polish regions) (Warakomska and Maciejewicz, 1992).

## BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES

### *Antibacterial activity*

The *in vitro* activity of propolis against several bacterial strains has been reported (Ghisalberti, 1979; Vanhaelen and Vanhaelen, 1979b; Pepeljnjak *et al*, 1981, 1982; Pápay *et al*, 1985b; Kawai and Konishi, 1987; Toth and Papay, 1987; Okonenko, 1988; Petri *et al*, 1988; Rosenthal *et al*, 1989; Brumfitt *et al*, 1990; Cuéllar *et al*, 1990; Soboleva *et al*, 1990; Dimov *et al*, 1991; Dobrowolski *et al*, 1991; Kujumgiev *et al*, 1993; Ventura Coll *et al*, 1993; Langoni *et al*, 1994; Woisky *et al*, 1994).

Meresta and Meresta (1985) examined the sensitivity of 75 bacterial strains to propolis extracts. Of these, 69 were identified as *Staphylococcus* spp and *Streptococcus* spp. All strains exhibited a high sensitivity to propolis extracts. The antibacterial activity of propolis against *S aureus* 209P had minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of 10 and 120 mg/ml, respectively (Meresta and Meresta, 1980). Valdez Gonzalez *et al* (1985) observed that EEP inhibited the growth of various bacteria including strains of *Streptococcus* and *Bacil-*

lus. Grange and Davey (1990) related that preparations of EEP (3 mg/ml) completely inhibited the growth of *Pseudomonas aeruginosa* and *Escherichia coli*, but had no effect on *Klebsiella pneumoniae*. Fuentes and Hernandez (1990) showed that EEP had a pronounced activity against Gram-positive bacteria, including *S aureus*, *E coli*, *P aeruginosa*, *B subtilis*, *S epidermidis* and *Streptococcus* sp (B hemolytic). The results of Fuentes and Hernandez were confirmed by Marcucci *et al* (1994c) with the same *E coli* strain.

Besides aerobic bacteria, the antimicrobial effects of EEP have been tested against a total number of 267 anaerobic strains. The cultures of bacteria generally showed the highest sensitivity to 1 mg/ml of EEP (Kedzia, 1986, 1990).

Extracts of propolis have been shown to potentiate the effect of certain antibiotics (Ghisalberti, 1979; Kedzia and Holderna, 1986; Hernandez and Bernal, 1990; Krol *et al*, 1993). The antibiotic action against *S aureus* (various strains) and *E coli* was increased by the addition of propolis to nutrient medium. The presence of propolis prevented or reduced any gradual build-up in tolerance of *Staphylococci* to antibiotics (Ibragimova and Pankratova, 1983; Meresta and Meresta, 1985).

The antibacterial activity of propolis is reportedly due to flavonoids and aromatic acids and esters present in resin (Debuyser, 1983; Meresta and Meresta, 1985/1986). Galangin, pinocembrin and pinostrobin have been recognized as the most effective flavonoid agents against bacteria (Dimov *et al*, 1992). Ferulic and caffeic acid also contributes to bactericidal action of propolis (Debuyser, 1983).

Kedzia *et al* (1990) reported that the mechanism of antimicrobial activity is complicated and could be attributed to a synergism between flavonoids, hydroxyacids and sesquiterpenes. Scheller *et al* (1977b) and Krol *et al* (1993) also observed this effect .

### **Antiviral activity**

There are few data from studies of the antiviral effects of propolis (Esanu *et al*, 1981; König, 1986; Bankova *et al*, 1988; Neychev *et al*, 1988; Debiaggi *et al*, 1990; Vachy *et al*, 1990; Amoros *et al* 1994; Serkedjieva *et al*, 1992). In virological studies carried out with extracts obtained with various solvents, some fractions affected the reproduction of influenza viruses A and B, vaccinia virus and Newcastle disease virus in different biological testing systems (Maksimova-Todorova *et al*, 1985; Manolova *et al*, 1985). The action of these active fractions was similar both in strain spectrum and in the degree of antiinfluenza activity of propolis concentrations from 0.2–3.0 mg/ml.

Amoros *et al* (1992a, 1992b) investigated the *in vitro* effect of propolis on several DNA and RNA viruses, including herpes simplex type 1, an acyclovir resistant mutant, herpes simplex type 2, adenovirus type 2, vesicular stomatitis virus and poliovirus type 2. The inhibition of poliovirus propagation was clearly observed. At a concentration of 30 µg/ml, propolis reduced the titer of herpes simplex virus by 1 000, whereas vesicular stomatitis and adenovirus were less susceptible. In addition to its effect on virus multiplication, propolis was found to exert a viricidal action on the enveloped viruses herpes simplex (HSV) and vesicular stomatitis virus (VSV).

Flavonoids and aromatic acid derivatives exhibit antiviral activity (Helbig and Thiel, 1982; Ishitsuka *et al*, 1982; Mucsi, 1984; Mucsi and Pragai, 1985; Kaul *et al*, 1985; Tsuchiya *et al*, 1985; Vanden Berghe *et al*, 1986; Vrijien *et al*, 1988; Wleklík *et al*, 1988; Serkedjieva *et al*, 1992; Amoros *et al*, 1994). König and Dustmann (1985) verified that luteolin was more active than quercetin, but remarkably less than caffeic acid, in the inhibition of Amazon parrot herpes virus (strain KS144/70) at range concentration of 12.5–200.0 mg/ml. Phenolics

**Table I.** Compounds identified in propolis resin.

<i>Basic structure</i>	<i>Compound *</i>
Alcohols	Benzene methanol <sup>rt</sup> ; cinnamyl alcohol <sup>rt</sup> ; glycerol <sup>w</sup> ; $\alpha$ -glycero phosphate <sup>rt</sup> ; hydroquinone <sup>rt</sup> ; isobutenol <sup>l</sup> ; phenethyl alcohol <sup>rt</sup> ; prenyl alcohol <sup>l</sup>
Aldehydes	Benzaldehyde <sup>t</sup> ; caproic aldehyde <sup>t</sup> ; <i>p</i> -hydroxybenzaldehyde <sup>t</sup> ; isovanillin <sup>ghit</sup> ; protocatechualdehyde <sup>rt</sup> ; vanillin <sup>ghit</sup>
Aliphatic acids and aliphatic esters	Acetic acid <sup>t</sup> ; angelic acid <sup>t</sup> ; butyric acid <sup>t</sup> ; crotonic acid <sup>t</sup> ; fumaric acid <sup>t</sup> ; isobutyric acid <sup>t</sup> ; methylbutyric acid <sup>t</sup> ; isobutyl acetate <sup>t</sup> ; isopentyl acetate <sup>t</sup> ; isopentenyl acetate <sup>t</sup>
Amino acids	Alanine <sup>opz</sup> ; $\beta$ -alanine <sup>o</sup> ; $\alpha$ -amino butyric acid <sup>o</sup> ; $\delta$ -amino butyric acid <sup>o</sup> ; arginine <sup>opz</sup> ; asparagine <sup>p</sup> ; aspartic acid <sup>opz</sup> ; cystine <sup>op</sup> ; cystein <sup>z</sup> ; glutamic acid <sup>opz</sup> ; glycine <sup>opz</sup> ; histidine <sup>opz</sup> ; hydroxyproline <sup>o</sup> ; isoleucine <sup>opz</sup> ; leucine <sup>opz</sup> ; lysine <sup>opz</sup> ; methionine <sup>opz</sup> ; ornithine <sup>o</sup> ; phenylalanine <sup>opz</sup> ; proline <sup>opz</sup> ; pyroglutamic acid <sup>ot</sup> ; sarcosine <sup>o</sup> ; serine <sup>oz</sup> ; threonine <sup>opz</sup> ; tryptophan <sup>op</sup> ; tyrosine <sup>opz</sup> ; valine <sup>opz</sup>
Aromatic acids	<i>p</i> -Anisic acid <sup>rt</sup> ; benzoic acid <sup>ghilrtvwx</sup> ; caffeic acid <sup>cghirtv</sup> ; cinnamic <sup>ghirt</sup> ; coumaric(- <i>o</i> , <i>-m</i> , <i>-p</i> ) acid <sup>ghirtv</sup> ; 3,4-dimethoxycinnamic acid <sup>rtvwx</sup> ; ferulic acid <sup>ghilrtvwx</sup> ; gallic acid <sup>ghil</sup> ; gentisic acid <sup>ghl</sup> ; hydroxycinnamic acid <sup>rt</sup> ; <i>p</i> -hydroxy benzoic acid <sup>ghilrt</sup> ; isoferulic acid <sup>ghilrtvwx</sup> ; 4-methoxy cinnamic acid <sup>rtv</sup> ; protocatechuic acid <sup>ghilt</sup> ; salicylic acid <sup>ghl</sup> ; vanillic acid <sup>rtvwx</sup> ; veratric acid <sup>rt</sup>
Aromatic esters	Benzyl acetate <sup>t</sup> ; benzyl benzoate <sup>rt</sup> ; benzyl caffeate <sup>rtvwx</sup> ; benzyl coumarate <sup>lrt</sup> ; benzyl-3,4-dimethoxycinnamate <sup>rt</sup> ; benzyl ferulate <sup>rtv</sup> ; benzyl isoferulate <sup>rt</sup> ; benzyl salicylate <sup>rt</sup> ; butenyl caffeate <sup>rtv</sup> ; butyl caffeate <sup>t</sup> ; cinnamyl benzoate <sup>t</sup> ; cinnamyl caffeate <sup>rtv</sup> ; butyl caffeate <sup>rtvwx</sup> ; cinnamyl coumarate <sup>rt</sup> ; cinnamyl isoferulate <sup>rt</sup> ; ethyl benzoate <sup>t</sup> ; ethyl caffeate <sup>v</sup> ; methyl benzoate <sup>t</sup> ; 2-methyl-2-butenyl caffeate <sup>rt</sup> ; 3-methyl-2-butenylcaffeate <sup>wx</sup> ; 3-methyl-3-butenyl caffeate <sup>lvwx</sup> ; 3-methyl-3-butenyl coumarate <sup>t</sup> ; 3-methyl-2-butenylferulate <sup>lvwx</sup> ; 3-methyl-3-butenyl ferulate <sup>twx</sup> ; 2-methyl-2-butenyl isoferulate <sup>twx</sup> ; 3-methyl-3-butenylisoferulate <sup>twx</sup> ; methyl salicylate <sup>twx</sup> ; phenyl ethyl caffeate <sup>twx</sup> ; phenyl ethylcoumarate <sup>rtvwx</sup> ; phenylethylisoferulate <sup>rtvwx</sup> ; pentyl caffeate <sup>v</sup> ; pentenyl caffeate <sup>rtv</sup> ; pentenyl ferulate <sup>v</sup> ; prenylcaffeate <sup>t</sup> ; prenyl coumarate <sup>t</sup> ; prenyl ferulate <sup>t</sup> ; prenyl isoferulate <sup>t</sup>
Chalcones and dihydrochalcones	Alpinetin chalcone <sup>tw</sup> ; naringenin chalcone <sup>t</sup> ; pinobanksin chalcone <sup>rtw</sup> pinobanksin-3-acetate chalcone <sup>rt</sup> ; pinocembrin chalcone <sup>rtw</sup> ; pinostrobin chalcone <sup>rtvw</sup> ; sakuranetin chalcone <sup>t</sup> ; 2',6', <i>a</i> -trihydroxy-4'-methoxy chalcone <sup>rt</sup> ; 2',6'-dihydroxy-4'-methoxydihydro chalcone <sup>tw</sup> ; 2',4',6'-trihydroxydihydro chalcone <sup>tw</sup>

Basic structure	Compound *
Flavanones	Naringenin <sup>†</sup> ; pinobanksin <sup>hntw</sup> ; pinobanksin-3-acetate <sup>mntw</sup> ; pinobanksin-3-butyrate <sup>†</sup> ; pinobanksin-3-hexanoate <sup>†</sup> ; pinobanksin-3-methyl ether <sup>tw</sup> ; pinobanksin-3-pentanoate <sup>tw</sup> ; pinobanksin-3-pentenoate <sup>†</sup> ; pinobanksin-3-propanoate <sup>tw</sup> ; pinocembrin <sup>bgklrtvw</sup> ; pinostrobin <sup>fgltvw</sup> ; sakuranetin <sup>fgltw</sup> ; 3,7-dihydroxy-5-methoxyflavanone <sup>v</sup> ; 2,5-dihydroxy-7-methoxyflavanone <sup>v</sup>
Flavones and flavonols	Acacetin <sup>ghiklm</sup> ; apigenin <sup>ghiklmt</sup> ; apigenin-7-methyl ether <sup>†</sup> ; chrysin <sup>ghiklm</sup> ; fisetin <sup>†</sup> ; galangin <sup>aghiklmrtw</sup> ; galangin-3-methyl ether <sup>mrtw</sup> ; izalpinin <sup>gmnrw</sup> ; isorhamnetin <sup>klmn</sup> ; kaempferide <sup>ghilnt</sup> ; kaempferol <sup>ghiklmnt</sup> ; kaempferol-3-methyl ether <sup>†</sup> ; kaempferol-7-methyl ether <sup>†</sup> ; kaempferol-7,4'-dimethyl ether <sup>†</sup> ; pectolinarigenin <sup>glm</sup> ; quercetin <sup>ghikt</sup> ; quercetin-3,7-dimethyl ether <sup>nt</sup> ; ramnetin <sup>gkmt</sup> ; ramnocitrin <sup>lm</sup> ; tectocrisin <sup>ghiklnt</sup>
Hydrocarbons esters ethers, hydroxy and keto waxes	Heneicosane <sup>rswy</sup> ; hentriacontane <sup>rswy</sup> ; heptacosane <sup>rswy</sup> ; hexacosane <sup>w</sup> ; nonacosane <sup>rswy</sup> ; pentacosane <sup>rswy</sup> ; tricosane <sup>rswy</sup> ; tripentacontane <sup>y</sup> ; tritriacontane <sup>rswy</sup> ; dotriacontylhexadecanoate <sup>u</sup> ; dotriacontyl-[(Z)-octadec-9-enoate] <sup>u</sup> ; hexacosylhexadecanoate <sup>u</sup> ; hexacosyl-[(Z)-octadec-9-enoate] <sup>u</sup> ; octacosylhexadecanoate <sup>u</sup> ; octacosyl-[(Z)-octadec-9-enoate] <sup>u</sup> ; tetracosylhexadecanoate <sup>u</sup> ; tetracosyl-[(Z)-octadec-9-enoate] <sup>u</sup> ; tetratriacontylhexadecanoate <sup>u</sup> ; tetratriacontyl-[(Z)-octadec-9-enoate] <sup>u</sup> ; triacontylhexadecanoate <sup>u</sup> ; triacontyl-[(Z)-octadec-9-enoate] <sup>u</sup>
Waxy acids	Arachid acid <sup>u</sup> ; behenic acid <sup>u</sup> ; cerotic acid <sup>ru</sup> ; lauric acid <sup>u</sup> ; linoleic acid <sup>†</sup> ; lignoceric acid <sup>ruw</sup> ; montanic acid <sup>rw</sup> ; myristic acid <sup>ruv</sup> ; oleic acid <sup>ru</sup> ; palmitic acids <sup>ruw</sup> ; stearic acid <sup>ruv</sup>
Ketones	Acetophenone <sup>rtv</sup> ; <i>p</i> -acetophenolacetophenone <sup>†</sup> ; dihydroxyacetophenone <sup>v</sup> ; methylacetophenone <sup>v</sup> ; hept-5-en-2-one <sup>†</sup> ; 6-methylketone <sup>†</sup>
Terpenoids and other compounds	$\alpha$ -Acetoxibetulenol <sup>ehi</sup> ; $\beta$ -bisabolol <sup>ehi</sup> ; 1,8-cineole <sup>†</sup> ; $\alpha$ -copaenol <sup>†</sup> ; cymenol <sup>†</sup> ; limonene <sup>†</sup> ; pterostilbene <sup>†</sup> ; styrene <sup>†</sup> ; xanthoreol <sup>†</sup> ; xylitol <sup>†</sup> ; naphthalene <sup>†</sup> ; 4-hexanolactone <sup>†</sup> ; sesquiterpene alcohol <sup>rtw</sup> ; sesquiterpene alcohol <sup>rtw</sup> ; sesquiterpene diol <sup>rtw</sup>
Steroids	Calinasterol acetate <sup>†</sup> ; $\beta$ -dihydrofucosterol acetate <sup>†</sup> ; ucoesterol acetate <sup>†</sup> ; stigmasterol acetate <sup>†</sup>
Sugars	Fructofuranose-1 <sup>rw</sup> x; fructofuranose-2 <sup>rw</sup> x; $\alpha$ -D-glucopyranose <sup>w</sup> x; $\beta$ -D-glucopyranose <sup>w</sup> x

\* Common name. <sup>a</sup> Villanueva *et al*, 1964; <sup>b</sup> Villanueva *et al*, 1970; <sup>c</sup> Cizmárík and Matel, 1970; <sup>d</sup> Cizmárík and Matel, 1973; <sup>e</sup> Ghisalberti, 1979; <sup>f</sup> Ghisalberti *et al*, 1978; <sup>g</sup> Vanhaelen and Vanhaelen, 1979a; <sup>h</sup> Vanhaelen and Vanhaelen, 1979b; <sup>i</sup> Vanhaelen and Vanhaelen, 1980; <sup>j</sup> Maciejewicz *et al*, 1982; <sup>k</sup> Bankova *et al*, 1983; <sup>l</sup> Debuyser, 1983; <sup>m</sup> Nagy *et al*, 1985; <sup>n</sup> Pápay *et al*, 1985a; <sup>o</sup> Gabrys *et al*, 1986; <sup>p</sup> Moreira, 1986; <sup>q</sup> Bankova *et al*, 1987; <sup>r</sup> Greenaway *et al*, 1987; <sup>s</sup> Seifert and Hasslinger, 1989; <sup>t</sup> Greenaway *et al*, 1990; <sup>u</sup> Seifert and Hasslinger, 1991; <sup>v</sup> Bankova *et al*, 1992b; <sup>w</sup> García-Viguera *et al*, 1992; <sup>x</sup> García-Viguera *et al*, 1993; <sup>y</sup> Marcucci *et al*, 1993; <sup>z</sup> Marcucci *et al*, 1994a.

such as caffeic acid were found to have a weak activity against influenza although vaccinia and adenovirus were more sensitive than polio and parainfluenza virus (Vanden Berge *et al*, 1986). Debiaggi *et al* (1990) studied the effect of propolis flavonoids on the infectivity and replication of some herpes virus, adenovirus, coronavirus and rotavirus strains. The cytotoxicity of flavonoids, including chrysin, kaempferol, acacetin, galangin and quercetin was evaluated.

The antiviral activity of constituents of propolis, such as esters of substituted cinnamic acids, have been studied *in vitro*. One of them, isopentyl ferulate, significantly inhibited the infectious activity of influenza virus A (Hong Kong strain) at 50 mg/ml (Serkedjiev *et al*, 1992). Similar results were found by Amoros *et al* (1994) when the *in vitro* activity of 3-methylbut-2-enyl caffeate identified in propolis samples was tested against herpes simplex virus type 1 (HSV-1). The same synthetic compound showed strong inhibition of HSV-1 growth at a concentration of 25 mg/ml. Some authors suggested that the antiviral activity of propolis is due to both the main constituents and the minor components like 3-methylbut-2-enyl caffeate and 3-methylbutyl ferulate (Bankova *et al*, 1987; Amoros *et al*, 1994).

### **Antifungal activity**

Millet-Clerc *et al* (1987) reported that propolis exhibited an important antifungal activity against *Trichophyton* and *Mycrosporium* in the presence of propylene glycol, which interacts synergistically at a 5% concentration. Combinations of some antimycotic drugs with propolis (10%) increased their activity on *Candida albicans* yeasts. The greatest synergistic effect against most strains was obtained when propolis was added to antifungal drugs (Holderna and Kedzia, 1987). Valdés *et al* (1987) tested 30 propolis samples produced in Cuba

against 2 strains of *C. albicans*. Lisa *et al* (1989) verified the antifungal activity of propolis extracts (10% in ethanol) against 17 fungal pathogens. The EEP inhibited *Candida* and all tested dermatophytes. Fernandes Junior *et al* (1994) evaluated the antifungal activity of EEP against *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. guilliermondii*; 98% of fungi samples were sensitive to EEP concentrations of less than 5.0%. Lori (1990) observed that in *in vitro* tests, propolis concentrations of 5 or 10% prevented growth of *Trichophyton verrucosum*. The antifungal activity of propolis was observed in some plant fungi *in vitro* (La Torre *et al*, 1990).

### **Cytotoxic activity**

Extracts of propolis have been examined for *in vitro* cytotoxic activity by different methods of tissue culture in some cell lines. Hladón *et al* (1980) investigated the cytostatic activity of propolis extracts on human KB (nasopharynx carcinoma) and HeLa (human cervical carcinoma) cell lines. The ethereal propolis fraction (DEEP) exhibited the strongest cytostatic activity. The secondary fractions of ethyl acetate and butanol of DEEP presented a good activity. Intermediate activity was verified in the  $\text{CHCl}_3$ /DEEP fraction. The killing action of propolis on HeLa cells was tested by Ban *et al* (1983). A concentration of 10 mg/ml caused 50% inhibition of colony-forming ability. In assessing the killing action of propolis, flavonoids were also tested. HeLa cells were found to be more sensitive to quercetin and rhamnetin, but less sensitive to galangin. Grunberger *et al* (1988) described caffeic acid phenethyl ester (CAPE) as the compound partially responsible for the cytostatic properties of propolis. The effect of CAPE on human cancer cell lines was tested in breast carcinoma (MCF-7) and melanoma (SK-MEL-28 and

SK-MEL-170) cell lines in culture. A dose of 10 µg/ml of CAPE completely inhibited the incorporation of [<sup>3</sup>H]thymidine into the DNA of breast carcinoma. More dramatic effects were observed in the melanoma, colon (HT 29) and renal carcinoma cell lines, but the CAPE effect on normal fibroblasts and melanocytes was significantly less. Because the cytostatic action of CAPE is more effective in transformed cells, it is reasonable to assume that it is responsible for the claimed carcinostatic properties of propolis.

The antitumoral activity of caffeic acid derivatives, *eg.* methyl ferulate, methyl acetyl ferulate, methyl acetyl isoferulate and methyl diacetyl caffeate, was reported by Inayama *et al.*, 1984. The effect of other caffeic acid derivatives has been investigated by König (1988). Ross (1990) reported that the cytotoxic effect of propolis *in vitro* against Chinese hamster ovary cancer cell lines was due to naphthalene derivatives in propolis. *In vitro* tests of extracts of Brazilian propolis from *A mellifera* on human hepatocellular carcinoma, KB and HeLa cell lines showed that the cytotoxic effects were caused by quercetin, caffeic acid and phenyl ester constituents of propolis (Matsuno, 1992). Scheller *et al.* (1989c) reported a cytotoxic activity of propolis in mice bearing Ehrlich carcinoma *in vivo*.

### **Antiprotozoan activity**

Scheller *et al.* (1977b) reported antiprotozoan activity of propolis (EEP) *in vitro* on 3 strains of *Trichomonas vaginalis*. EEP solutions *in vitro* presented a lethal activity on strains at a concentration of 150 mg/ml.

The antiprotozoan activity of propolis was verified in experimental animals infected with *Eimeria magna*, *E media* and *E perforans* treated with 3% EEP and other antiprotozoan drugs. The coccidiostatic effect of propolis was higher than other

drugs (Hollands *et al.*, 1988a). Propolis preparations were classified as a good coccidiostat against *Chilomonas paramecium* (Hollands *et al.*, 1988b). Torres *et al.* (1990) evaluated the effect of EEP on the growth of the protozoan parasite *Giardia lamblia in vitro*. At an EEP concentration of 11.6 mg/ml there was a 98% inhibition effect.

### **Other properties**

Many other biological and pharmacological properties of propolis have been described by various authors, including regeneration of cartilaginous tissue (Scheller *et al.*, 1977a), bone tissue (Stojko *et al.*, 1978) and dental pulp (Scheller *et al.*, 1978; Magro Filho and Perri de Carvalho, 1990), anaesthetic activity (Paintz and Metzner, 1979), hepatoprotective activity (Giurgea *et al.*, 1985, 1987; Hollands *et al.*, 1991; Tushevskii *et al.*, 1991), increasing the number of plaque-forming cells in the spleen of populations of immunized males (Scheller *et al.*, 1988), immunomodulatory action (Benková *et al.*, 1989; Dimov *et al.*, 1991, 1992), immunogenic properties (Scheller *et al.*, 1989d), liver detoxifying action, choleric and antiulcer action *in vitro* (Kedzia *et al.*, 1990), antioxidant activity (Yanishlieva and Marinova, 1986; Krol *et al.*, 1990; Scheller *et al.*, 1990; Dobrowolski *et al.*, 1991; Misic *et al.*, 1991; Olinescu, 1991; Volpert and Elstner, 1993a, 1993b), anticaries in rats (Ikeno *et al.*, 1991), protection agent against gamma irradiation in mice (Scheller *et al.*, 1989b), antileishmaniosis in hamster (Sartori *et al.*, 1994), antitrypanosomal agent (Higashi *et al.*, 1991) and inhibition of dihydrofolate reductase activity (Strehl *et al.*, 1994).

### **Toxicity**

As propolis use increases, its side-effects are observed more frequently (Wanscher,

1976; Petersen, 1977; Monti *et al*, 1983; Ayala *et al*, 1985; Machácková, 1985; Rudzki *et al*, 1985; Tosti *et al*, 1985; Cirasino *et al*, 1987; Hausen *et al*, 1987b; Sartoris *et al*, 1987; Young, 1987; Hay and Greig, 1990). Propolis contains some compounds which cause toxicity. Beekeeper's dermatitis due to propolis is well known and an apparent association between sensitivity to propolis and to poplar resins has been observed (Hausen *et al*, 1987a, b).

Hausen *et al* (1987b) described the incidence of nearly 200 cases of allergic contact dermatitis due to propolis. They identified a substance 1,1-dimethylallyl caffeic acid (LB-1) responsible for the allergy. They also described the sensitizing properties of LB-1 in guinea pigs provoked by several propolis samples, demonstrating that this compound is the main sensitizer in propolis. The flavonoid tectochrysin was considered a second allergen, although Schmalte *et al* (1986) stated that tectochrysin was a very weak sensitizer. Hashimoto *et al* (1988) verified the allergenic properties of phenylethyl and prenyl esters of caffeic acids from propolis.

Observations of propolis used orally suggest that intestinal absorption could play an important role in propolis sensitization. Limiting the extent of oral administration may be useful in preventing propolis allergy (Angelini *et al*, 1987; Hausen *et al*, 1987a, 1988; Kleinhans, 1987; Trevisan and Kokelj, 1987; Machácková, 1988).

### **Therapeutic activity**

Propolis has been used since ancient times in the remedies in folk medicine in many parts of the world (Ghisalberti, 1979). It has a long tradition of medicinal use in many parts of the world. Many European countries are interested in natural products to heal diseases and propolis is an important product used for this purpose. It is found in pharmaceutical and cosmetic products, such

as anti-acne lotion, face creams, ointments, lotions and solutions (Debuyser, 1983; Lejeune *et al*, 1988; Pons and Cueto, 1988, 1989; Goetz, 1990).

### **Propolis in dermatology**

Bolshakova (1975) treated 110 patients infected with *Trichophyton* on the hairy zone of the head with 50% propolis (as an unguent). In 97 patients, it was found to produce excellent results. Other examples of the treatment of dermatological diseases were described when propolis was used as an antiseptic (Bolshakova, 1975; Gafar *et al*, 1986), antimycotic (Holderna and Kedzia, 1987; Millet-Clerc *et al*, 1987), bacteriostatic (Soboleva *et al*, 1990; Dobrowolski *et al*, 1991; Stark and Glinski, 1993; Ventura Coll *et al*, 1993), antiviral (Giurcaneanu *et al*, 1988; Vachy *et al*, 1990) and fungistatic (Millet-Clerc *et al*, 1987) agent. Many other propolis applications in dermatology have been described. It has been used for wound healing, tissue regeneration, treatment of burns, neurodermatitis, microbial eczema, contact dermatitis, leg ulcers, psoriasis, morphea, herpes simplex and genitalis, pruritus ani, dermatophytes, trophic ulcers, pulp gangrene and as an astringent (Bolshakova, 1975; Molnar-Toth, 1975; Scheller *et al*, 1977a, 1978; Ghisalberti, 1979; Korsun, 1983; Gafar *et al*, 1986; Hausen *et al*, 1987a; Giurcaneanu *et al*, 1988; Ponce de Leon and Benitez, 1988; Goetz, 1990; Fierro Morales, 1994).

### **Propolis in otorhinolaryngologic (ORL) diseases**

Matel *et al* (1973) described the treatment of 126 subjects suffering of external otitis, chronic mesotympanic otitis and tympan perforation with propolis solutions (5–10%) which had a positive therapeutic result in



most cases. Propolis effects in other ORL diseases were reported: acute inflammations of the ear (Kachnii, 1975; Palos *et al*, 1989), treatment of mesotympanitis (Popnikolov *et al*, 1973), pharyngitis (Doroshenko, 1975), tuberculosis (Karimova and Rodionova, 1975), chronic bronchitis (Chuhrienko *et al*, 1989; Scheller *et al*, 1989a), rhinopharyngolaryngitis (Isakbaev, 1986), pharyngolaryngitis (Lin *et al*, 1993a) vasomotor catarrh treatment (Zommer-Urbanska *et al*, 1987) and rhinitis (Nuñez *et al*, 1988/1989).

### ***Propolis in gynecological diseases***

Zawadzki and Scheller (1973) investigated 90 cases of therapeutic activity of 3% EEP in cases of vagina and uterus cervix inflammation caused by *S pyogenes*. They observed that more than 50% of the cases responded well to treatment with EEP. The action of propolis to treat inflammatory and dystrophic lesions of the female genital system caused by protozoan and fungi has been studied. Some 137 cases of diffuse inflammations, ulcerations and ex-ulcerations of cervix uteri diseases were investigated by Roman *et al* (1989). After 20–25 d of associated treatment (allopathic and apitherapeutic) very good results were obtained in 53 cases, good results in 24, and satisfactory in 28 cases. The results obtained by Roman *et al* (1989) confirm that propolis potentiates the antiseptic, antifungal and antitrychomonas actions of specific chemical medicines. Stojko and Stojko (1993) also reported the use of propolis preparations for treatment of gynecological disorders.

### ***Propolis in stomatology***

Mirayes *et al* (1988) described a clinical assay with an extract of propolis that showed its efficacy against giardiasis. Some 138

patients were studied, 48 children and 90 adults, and treated with propolis (in children, concentration of 10% and adults 20%). At these concentrations, 52% of the children showed a cure. In adults, the propolis effect was the same as tinidazole, an antiprotozoan drug. When the propolis concentration was elevated to 30%, there was a higher efficacy (60% cure *versus* 40% with tinidazole). Some authors described the use of propolis in the following therapies: acute colitis, chronic colitis, acute gastric ulcers, and acute duodenal ulcers (Gorbatenko, 1971; Makarov 1972; Nikolov *et al*, 1973; Kabanov *et al*, 1989).

### ***Propolis in odontology***

Paintz and Metzner (1979) verified the anaesthetic properties of propolis. Scheller *et al* (1978), Gafar *et al* (1986), Magro Filho and Perri de Carvalho (1990) and Ding *et al* (1993) observed regeneration of dental pulp with gangrene in the presence of propolis. The healing effect of propolis was evaluated in periodontitis (Wang *et al*, 1993), plaque and gingivitis (Neumann *et al*, 1986) and buccal affections (Draganova *et al*, 1989). Neumann *et al* (1986) suggested that a propolis preparation could be a useful subsidiary treatment in oral hygiene.

### ***Other propolis uses in therapy***

The use of propolis has been reported for other diseases (human and veterinary) including osteoarthritis (Lin *et al*, 1993b), eyes diseases (Popescu *et al*, 1993), as an antiinflammatory agent (Mihail *et al*, 1984; Christova, 1985; Busciglio, 1988; Soboleva *et al*, 1990; Olinescu, 1991; Fierro Morales, 1994), angiology (Gonzalez *et al*, 1988/1989) and orthopedic treatment (Quezada and Cueto, 1988/1989). The diverse use of propolis in clinical trials shows that its

therapeutic efficacy lies mainly in diseases caused by microbial contaminations.

## DISCUSSION

Based on the very complex chemical composition of propolis and its pharmacological and therapeutic properties, we conclude that propolis is a very powerful natural product produced by bees. It can be used to treat human and veterinary diseases with great success. Nevertheless, it is evident that propolis cannot be a remedy for all diseases and any who make such claims are guilty of deception and harm the reputation of all hive products (Tóth, 1985). The great problem with propolis, as with some other hive products, is that its composition varies with the flora of a given area, the time of collection and the inclusion of wax contaminants. This further adds to the problem of defining propolis for medicinal use since the product's quality varies so greatly. Although standardization is possible in principle, exact chemical tests have not been applied yet for the purpose of quality control. The problem of quality control is well demonstrated by the propolis products currently marketed in various countries (Tóth, 1985). It is expected that this review will provide some aid to further investigations about propolis, "the purple gold of the beehive" (Asis, 1989).

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**Résumé — Propolis : composition chimique, propriétés biologiques et activité thérapeutique.** On fait le point des connaissances sur la composition chimique de la propolis et ses origines végétales probables

(tableau I). Les principaux constituants chimiques sont discutés par rapport à leurs activités biologiques et thérapeutiques : activité antibactérienne, antivirale, antifongique et cytotoxique. Certains composés, par exemple les dérivés de l'acide caféique, ont une action allergène et carcinogène. On rapporte les nombreuses études cliniques concernant l'utilisation thérapeutique de la propolis, principalement contre les maladies microbiennes, dans divers domaines (dermatologie, ORL, gynécologie, odontologie). En conclusion, on souligne la nécessité de développer des tests chimiques précis pour standardiser le produit.

**propolis / composition chimique / activité antimicrobienne / toxicité / activité thérapeutique**

**Zusammenfassung — Propolis: chemische Zusammensetzung, biologische Eigenschaften und therapeutische Aktivität.** Die chemische Zusammensetzung von Propolis wird beschrieben (Tabelle I). Es wird hauptsächlich auf die in den letzten 14 Jahren identifizierten Komponenten und ihre mögliche pflanzliche Herkunft eingegangen. Die chemischen Bestandteile, die für die biologische und therapeutische Wirksamkeit verantwortlich sind, werden diskutiert. Die antimikrobielle zytotoxische Aktivität und die pharmazeutischen Eigenschaften von Propolis werden vorgestellt. Einige Komponenten von Propolis (zB Kaffeesäurederivate) mit allergenen und anti-karzinogenen Wirkungen werden beschrieben. Zahlreiche klinische Untersuchungen von Propolis werden dargestellt, besonders die Behandlung von durch Mikroorganismen verursachten Krankheiten. Abschließend werden einige neue Konzepte über Propolis und seine Anwendung in der Medizin dargelegt.

**Propolis / Phenole / antimikrobielle Aktivität / Toxizität / therapeutische Aktivität**

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