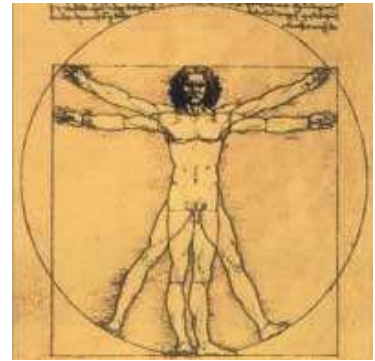




Propolis: biological properties and medical applications

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COMPOSITION AND NUTRITIONAL REQUIREMENTS

The composition of propolis varies greatly depending on its geographic and botanical origin. Approximate figures for the main nutrients estimated from the qualitative data from the literature are:

Proteins: max 1 g/100 g

Carbohydrates: max 1 g/100 g

Fat: max: 1 g/100 g

Considering the low suggested intake of 200 mg per day propolis has an insignificant contribution to the daily requirements regarding the basic nutrients.

HEALTH ENHANCING EFFECTS

Hundreds of publications have appeared in the last 40 years describing the biological and health enhancing properties of propolis. The different biological and health enhancing effects, as tested in cell experiments and animals are summarised on table 1. The effects described here were achieved in cell and animal experiments. A number of reviews have summarised the knowledge on propolis:^{31, 52, 179, 220}. The health enhancing effects are divided into main and secondary. This division has been made taking into consideration the number of publications and the health significance of the effect.

Most studies have been carried out with poplar and Brazilian baccharis propolis, while in some of them the propolis type was not determined. It is astonishing, that while the composition of the different type of propolis differs greatly depending on its botanical origin, the biological effects of the different propolis types are very similar: see Propolis Book One and tables 2 and 3.

The main propolis types on the market are poplar and baccharis propolis. These two types of propolis have similar biological properties but the active ingredients are different (table 3).

The health enhancing effects are found in the ethanol extractable part of propolis is called balsam. The biological activity of ethanol extracts is generally tested with 70 to 100 % ethanol extracts. 60-80 % aqueous ethanol solutions have a higher biological activity than tinctures, prepared with more or less water^{232, 233}

Table 1: **Health enhancing properties of propolis as tested in cell cultures and animal experiments**

Effect	Tested propolis type	Reference
Main functional effects		
<i>Antimicrobial, anti-inflammatory, immunomodulating, wound and ulcer healing</i>		
Antibacterial	All propolis types	31, 52, 95, 161, 179, 278
Antiviral	All propolis types	31, 52, 95, 161, 179, 278
Antifungal	All propolis types	31, 52, 95, 161, 179, 278
Food preservative	Poplar, Baccharis, Argentine, Egypt	1, 8, 18, 153, 175, 202, 261, 287, 311
Against parasites	Poplar, Baccharis, Cuba, Mexico	7, 80, 86, 224, 245, 310
Antiinflammatory	Poplar, Baccharis, Cuba, Egypt	11, 31, 126, 150, 231, 236, 251, 257, 294, 326, 326
Immunostimulating	Poplar, Baccharis, Brazil	31, 95, 220, 248, 277
Immunomodulating (immunosuppressive in autoimmune diseases)	Baccharis	215
Antiulcer (stomach, skin, buccal)	Baccharis, India	32, 60, 78, 79, 127, 228, 242, 278
Wound healing	Different propolis types	9, 41, 186, 242, 275
Improves corneal wound healing and inflammation in rats	Baccharis	183
<i>Antioxidant, antitumor, hepatoprotective, radiation protective</i>		
Hepatoprotective	All propolis types	29-31, 95
Antitumor, antimutagenic	Poplar, Baccharis, Cuba, Taiwan, Marocco, Korea	6, 3, 31, 52, 57, 82, 130, 179, 220, 246, 324
Anti-angiogenic	Poplar, Baccharis,	4, 73, 74, 164, 189, 220
Cyto- and chemopreventive	Poplar, Baccharis	38, 39, 220, 303
Antioxidant	All propolis types	31, 52, 95, 95, 179
Radiation protective	Poplar, Baccharis	38, 39, 99, 220, 298
<i>Anti-aging, brain and nervous system effects</i>		
Antiaging, increases life span of mice (1) reduces oxidative stress in aged mice (2)	1: Poplar: 2: Spain (poplar?)	37, 172
Anti-Alzheimer and anti-Dementia	Poplar, Baccharis	42, 59, 322
Anti-depressant	China, Korea, Turkey (poplar?)	165, 169, 328
Neurotrophic effects in PC12m3 cells	Baccharis	145
Water-soluble propolis derivative relieves scopolamine-induced amnesia in mice	Poplar	58
<i>Others</i>		
Muscle contracting at small concentration	Poplar, Baccharis	16, 67, 88, 147, 237, 299
Muscle relaxant at higher concentration		
Anti-diabetes	Poplar, Baccharis	2, 15, 132, 144, 185, 278, 329, 334
Cardioprotective: antimyocard, antithrombogenic, antihypertensive, antiarrhythmic	Poplar, Bacharis, Asia,	12, 60, 65, 65, 74, 95, 127, 129, 198, 216, 228
Local anaesthetic	Poplar, Bacharis	230, 308, 313, 281
Improves regeneration of cartilagenious and bone tissue, dental pulp, cicatrising	Poplar, Baccharis	111, 271, 272, 301, 308

The Propolis Book, Chapter 2

Secondary effects		
Anti-osteoporose	Poplar, Egypt	14, 89
Against skin aging and for skin protection	Poplar, Baccharis, Algeria , Australia,	53, 69, 274, 312
Against scratching behaviour in mice	Baccharis	281
Against experimental rhinitis in mice	Baccharis	282
Against experimental colitis in rats	Poplar, Turkey, Baccharis	17, 106
Against rat colon anastomosis in rats	Poplar, Turkey	151
Angiostatic in human umbilical vein endothelial cells	Baccharis	63, 139
Anti-allergenic	Poplar, Bacharis	211, 277, 304
No effect on basic blood parameters, protects erythrocytes against radiation, anti-aggregation effect;	Poplar, Baccharis	16, 279
Protects sperm membrane from oxidative attack (1), improves rabbit (2) and rat (3) sperm quality	1: Chile; 2: Egypt 3: Baccharis	55, 119, 259
Improves the health of mother sheep	Brazil (red propolis)	206
Estrogenic	Poplar	293
Enhancement of the hyperthermal tolerance in immune mononuclear cells of competitive cyclists	Poplar	61
Protective against rabbit pasteurellosis	Egypt	212
Anti-atherogenic and anti-angiogenic	Baccharis, Cuba (red) Chile (brown)	75, 189
Treatment of fibrotic diseases and asthma	Taiwan	146
Photoprotective against skin UV radiation	Poplar, Baccharis	43, 209
Against contrast-induced nephropathy	Poplar	36
Lipid bioactive nano-carrier for topical nasal drug delivery	Sardinia (Italy)	252
Laxative effect in mice	Baccharis	143
Inhibits cell growth of higher plants and animals inhibits germination of wheat seedlings	Poplar	16, 295

Table 2 Biological effects of propolis components

Component, propolis type	Biological Activity	Reference
Polyphenols and flavonoids Mostly poplar, but present in most propolis types	Antibacterial, antiviral, antifungal, antioxidant, antiaging, antiulcer, antitumor, antiallergic, antiinflammatory, antiosteoporotic, antitrombogenic, antiatherosclerosis, cardioprotective, immunomodulating, hepatoprotective, sicatrising	11, 31, 52, 103, 117, 120, 176, 179, 213, 238, 251, 277
Caffeic acid phenethyl ester (CAPE) and other caffeates Poplar, Bacharis	Antioxidant, anti-inflammatory, antitumor, antibacterial, antiviral, fungicide, immunomodulatory, cardioprotective, hepatoprotective, antiosteoporosis	22, 25, 14, 95, 273, 284
Caffeic acid (CA) Poplar, Baccharis	Antiviral, Antioxidant, antiulcer, antitumor	95
Polyprenylated benzophenones Cuba, Venezuela and Brazil	Antioxidant, antiinflammatory, antitumor	22, 25
Artepillin C Baccharis	Antioxidant, antiinflammatory, antitumor, apoptosis inducing	22, 25
Prenylated flavanones (propolins) Taiwan	Antioxidant, anticancer, apoptosis inducing,	22, 25
Terpenes Greece, Crete, Croatia, Brazil	Antibacterial, antifungal	23, 24, 46, 187, 187, 247 26
Essential oils Brazil, Poland	Antibacterial, antifungal	26, 27, 77, 335
Furfuran lignans Canary islands	Antibacterial	66

Table 3: **Biologically active ingredients in Poplar and Baccharis propolis**

Biological activity	Propolis type, active ingredient	Ref.
Antibacterial	Poplar: different flavonones, flavons, phenolic acids and their esters Baccharis: prenylated p-coumaric acids, labdane diterpenes	21, 95, 160 21, 24, 180
Antifungal	Poplar: pinocembrin, galangin, benzoic acid, salycilic acid, vanillin Baccharis: mono and sesquiterpenes, Artipellin C	97, 193 97
Antiviral	Poplar: Polyphenols, phenyl- carboxylic acids, and esters of substituted cinnamic acids, caffeic acid, quercetin, luteolin, fisetin, quertecagetin, Baccharis: activity detected but no substances identified	95, 154 51, 161
Antioxidant	Poplar: different flavonoids phenolics and their esters	21, 95, 162
Radiation protective	Baccharis: different prenylated p-coumaric acids and flavonoids	21, 95, 162
Hepatoprotective	Poplar: different flavonoids, CAPE, ferulic acid, caffeic acid Baccharis: different prenylated p-coumaric acids, flavonoids, lignans	21, 95, 162 28, 95
Anticancer and antitumor	Poplar: CAPE, CABE, caffeic acid, caffeic acid phenylethyl ester, apigenin, quercetin, genistein, rutin, p-coumaric acid, and ferulic acid, kampferol, naringenin Baccharis: artipelline C, baccharin, drupanin, cinamic acid derivatives, prenylated p-coumaric acids, clerodane diterpenes, benzofuranes	21, 95, 141, 220, 290, 302 21, 95, 220
Immuno modulating	Poplar: CAPE, chrysin, benzylcaffeate, phenethylferrulate, cinamic acid Baccharis: caffeoylquinic acid derivatives, clerodane diterpenoid, artipelline C	102, 138, 277 277, 305
Anti-inflammatory	Poplar: flavonons, flavons, phenolic acids and their esters Baccharis: artipelline C	21, 95 236
Cardioprotective	Poplar: CAPE, acetin, chrysin, quercetin Baccharis: caffeoylquinic acid	95 198
Anti-ulcer	Poplar: CAPE, caffeic acid, pinocembrin, galangin, chrysin Baccharis: ferulic, p-coumaric and cinnamic acids,	70, 95, 137 95

Propolis against bacteria, fungi, molds and parasites

Table 4 : **Effects of propolis against pathogenic and harmful bacteria funghi, viruses, molds and parasites** after ^{31, 52, 76, 103, 112, 179, 308}

Gram-positive bacteria <i>Bacillus cereus, Bacillus mesentericus, Corynebacterium spp., Corynebacterium diphtheriae, Diplococcus pneumoniae, Enterococcus spp., Mycobacteria sp., Mycobacterium tuberculosis, Staphylococcus aureus, Streptococcus: critecus epidermis faecalis mutans, pyogenes, viridans, sobrinus,</i>
Gram negative bacteria <i>Branhamella catarrhalis, E. coli, Helicobacter pylori, Klebsiella ozaemae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella: choleraesuis, dublin, enteritidis, exneri, gallinarum, pullorum, , paratyphi-A, paratyphi-B, typh;i Shigella: dysinteriae, sonnei</i>
Fungi <i>Aspergillus sp., Candida: albicans, guiliermondi, parapsilosis, tropicalis; Cryptococcus sp., Cryptococcus neoformans, Histoplasma encapsulatum, Madurella mycetomi, Microsporium: audoinini, canis, cepleo, distortum, ferrugeneum, gypseum; Piedra hortae, Phialophora jeanselmei, Saccharomyces sp. , Trichophyton: sp., mentagrophytes, rubrum, Trichosporon cutaneum</i>
Viruses <i>Adenovirus, Coronavirus, Herpes simplex, Influenza A and B virus, Newcastle disease virus, Polio virus, Vaccinia, Rotavirus; Vesicular Stomatitis Virus, Coronar virus</i>
Parasites <i>Cholomonas paramecium, Eimeria: magna, media, perforans; Giardia lambia, Giardia duodenalis, Trichomonas vaginalis, Trypanosoma cruzi, Trypanosoma evansi</i>



Illustration: Don Smith

The antimicrobial activity of propolis is by far the most important biological property of propolis, which has deserved the highest scientific interest, considering the high number of performed studies. Around 700 hundred papers deal with this aspect. In spite of the big compositional differences of the different propolis types, they all have antimicrobial activity. It seems that rather

the sum of the propolis antimicrobial components than individual substances are responsible for the antimicrobial action¹⁶¹.

The results summarised below show that propolis has antibacterial, fungicide, antiviral and antiparasitic effects of against harmful and pathogen organisms. These properties make it a good candidate for its application in therapy (see section apitherapy).

Antibacterial activity

Propolis is the bee product with the highest antimicrobial activity. The antibacterial activity of propolis has been confirmed by numerous scientific studies. Antibacterial activity has been demonstrated against both gram positive and gram-positve, both aerobic and anaerobic types.

Although the composition of propolis differs considerably depending on its botanical origin, all examined types of propolis revealed a strong antibacterial activity^{21, 25}. The antibacterial activity of poplar propolis and other types of propolis of different geographical and botanical origin was similar¹⁶¹.

Poplar propolis gathered by by *Apis mellifera caucasica* had a higher antibacterial activity than the one gathered by *Apis mellifera anatolica* and *Apis mellifera carnica*²⁸⁸

The antibacterial activity of propolis to pathogenic or harmful bacteria is summarised in the table below^{31, 52, 103, 110, 179}. It has been proposed that propolis is more active against gram-positive pathogens¹¹⁰ but many gram negative bacteria are also inhibited (see table).

More recent research has revealed antibacterial activity against *Micrococcus luteus*, *Salmonella typhimurium*³¹⁵ *Klesbsiella pneumoniae*³¹⁶. Although in previous studies¹¹⁰ it was claimed that *Listeria monocytogenes* is not sensitive to propolis, recent works revealed significant antibacterial activity^{227, 327}. In recent study it has been shown that propolis has a stong antibacterial activity against 13 different plant pathogens³⁵.

With the increasing of antibiotic resistance in the last years there is a considerable interest of hospitals in propolis as an antibacterial agent. It has been shown that propolis has synergistic effects with antibiotic action against bacteria^{179, 218, 219, 269, 297, 300}.

The antibacterial effect of propolis is bactericidal, that means bacteria-killing,^{110, 197, 239} by inhibiting their mobility¹⁹⁷. Each propolis type has different antibacterial substances (see table 5). The antibacterial substances of the two main propolis types are given in table 6. It has been shown that the antibacterial activity of poplar propolis is also based on quorum sensing inhibitory (QSI) action, the flavonoid pinocembrin being an important QSI agent²⁶⁷

Generally biological activity decreases with increasing storage. However it was found that propolis solution in ethanol stored for 10-15 years results not in result in a decrease, but in an increase of antibacterial activity¹⁹¹.

Antifungal activity

Poplar propolis is the bee product with the highest antifungal activity as tested with 40 yeast strains of *Candida albicans*, *Candida glabrata*, *Candida krusei*, and *Trichosporon spp.*¹⁵²

Poplar propolis gathered by by *Apis mellifera caucasica* in Turkey had higher antifungal activity than the one gathered by *Apis mellifera anatolica* and *Apis mellifera carnica*²⁸⁶. On the other hand the antifungal and mostly antiviral properties of propolis from different botanical and geographical origin was similar¹⁶¹.

Recent research on the of propolis have shown fungicide effects on juice spoilage fungi *Candida famata*, *C. glabrata*, *C. kefir*, *C. pelliculosa*, *C. parapsilosis* and *Pichia ohmeri*¹⁵³.

Antivirus activity

Propolis kills the funghi and also the viruses, while the growth of the latter is also inhibited¹⁷⁹. Propolis acts against many different viruses (table 4). Most notable is its activity against the influenza virus, found in propolis of different origin¹⁶¹ and in Brazilian green propolis²⁸⁰ CAPE, a poplar propolis constituent is a prominent antiviral substance⁹⁰

Antiparasite activity

Propolis acts against a number of parasites (table 4). Thus, it could act as a protective agent against intestinal parasites, e.g. against *S. mansoni*¹³⁶ and against *Giardia duodenalis trophozoites*¹⁰⁰. Propolis from Portugal has antiparasitic activity against the *Trypanosomas brucei*, the parasite of the African sleeping disease⁹⁴

Antioxidant and hepatoprotective activity

Antioxidant activity



An antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules and so to prevent such changes. The antioxidant effect correlates roughly with the anti-inflammatory and hepatoprotective activity.

Although the phenolic content seems to vary according to the botanical origin, antioxidant effects for most propolis types have been reported.

Compared to pollen and royal jelly, propolis extracts exhibited the highest antioxidant activity²¹⁰.

Antioxidant In a study with propolis of different geographical and botanical origin it was found that the antioxidant activity correlates well with its total concentration of polyphenols^{162, 192}. Poplar propolis with relatively higher polyphenol content has a higher antioxidant activity than Brazilian propolis, which contains less polyphenols^{156, 162, 163}.

The antioxidant activity of Spanish (poplar) and Polish (poplar) propolis correlated significantly to the phenolic content^{45, 292} while in Polish and Argentina propolis it correlated in addition also significantly to the flavonoid content^{50, 292}. The antioxidant activity differs on the type of the polyphenols. CAPE, a typical constituent of poplar propolis, seems to be one of the most powerful antioxidant substances of propolis⁹⁵.

The antioxidant activity is measured in different units. The antioxidant activity of different foods is compared mostly to the so called ORAC (Oxygen Radical Absorbance Capacity) index. According to a 2007 US Patent a 50/50 water/acetone extract of poplar propolis scored 2459 ORAC units, while a hexane/ethylacetate (75:25) scored 7215 ORAC units. Pure propolis resin scored 9674 ORAC units ($\mu\text{mole TE/g}$)¹³¹. The ORAC value of Uruguay poplar propolis was similarly high: 8000 $\mu\text{mol TE/g}$ propolis²⁸⁹. Thus propolis is one of the strongest natural antioxidants.

10 % ethanol poplar propolis extract from Croatia had about 70 % of the FRAP antioxidant activity of known antioxidants as vitamin C and trilox. Propolis modulated antioxidant enzymes (AOE) and significantly decreased lipid peroxidation processes (LPO) in plasma, liver, lungs, and brain of mice. The effect was dose- and tissue-dependent. The highest vulnerability to oxidative stress was observed in lungs where hyperoxia was not associated with augmentation of AOE. Propolis protected lungs from hyperoxia by increased catalase (CAT) activity. This is of special importance for lungs since lungs of adult animals are highly vulnerable to oxidative stress because of their inability to augment AOE activity. The authors conclude that because of its strong antioxidant and scavenging abilities, native propolis might be used as a strong plant-based antioxidant effective not only in physiological conditions but also in cases that require prolonged high concentration of oxygen²⁹¹.

It was found that water soluble propolis extracts of Chinese (poplar) propolis was significant and that it contains more biologically active flavonoids, and also that its antioxidant capacity was similar to that of the ethanol extracts¹¹⁴

Propolis is a powerful antioxidant. This effect is due to the high concentration of phenolics and other antioxidant compounds. The radical theory in human physiology claims that the active free radicals are involved in almost all the cellular degradation process and leads to cell death. Oxidative stress is thought to contribute to the development of chronic and degenerative diseases such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular and neurodegenerative diseases²⁴¹. Propolis can be regarded as a supplement preventing chronic degeneration diseases, e.g. cancer.

Hepatoprotective activity and anti-radiation activity

The liver is perhaps the hardest working organ of the body. It has hundreds of tasks to perform, including detoxification of the blood. A sluggish liver means fatigue and toxemia and a high risk of various chronic diseases. Phenolics are known to have a hepatoprotective function. Hepatoprotective activity for different

types of propolis has been reported, which correlated to the antioxidant activity²⁹⁻³¹. Propolis counteracts hepatotoxic effects of alcohol liver injury in mice^{171, 253} and also of paracetamol induced liver damage of mice¹⁰⁹ and carbon tetrachloride induced liver damages in rats¹⁰⁸.

The anti-radiation effect of propolis have been reviewed by Orsolich in 2010. As an antioxidant propolis has a powerful effect to counteract radiation as tested in tumor cells or animals. Propolis act also in apoptosis of cancer cells thus improving the anti-cancer effect of radiation²²⁰

Propolis supplementation is prophylactic for liver health and for counteracting the damaging effect of tumor irradiation.

Immunomodulating effects

The immunomodulating effect has been reviewed in 2007 by Sforcin²⁷⁷. All propolis types have immunostimulating activity (see table 3). However the active substances of the various types of propolis are different (table 5 and 6).

Action on macrophages

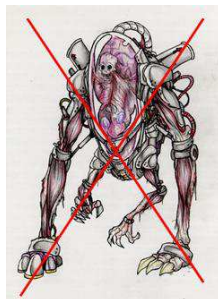
In vitro and in vivo assays demonstrated the modulatory action of propolis on murine peritoneal macrophages, increasing their microbicidal activity and stimulating the lytic activity of natural killer cells against tumor cells by enhancing antibody production. The best immunostimulating results were observed when propolis was administered over a short-term to animals. Both poplar and baccharis propolis increase the macrophage activity²⁷⁷

Action on lymphocytes and antibody production

Both poplar and baccharis propolis can have an immunostimulating effect by increasing antibody production and by activating B and T lymphocytes, an adjuvant like activity of propolis²⁷⁷. The propolis compounds chrysin, quercetin, and galangin have a antiparasitic activity²⁵⁵

Propolis can be regarded as a supplement for the stimulation of the immune system.

Antitumor effects



The antitumor activity of propolis was reviewed by Orsolich in 2010: The chemopreventive activity of propolis in animal models and cell cultures are likely to be the result of their ability to inhibit DNA synthesis in tumour cells, their capability to induce apoptosis (cell death) of tumour cells, and their property to activate macrophages to produce factors capable of regulating the function of B-, T- and NK-cells, respectively. Especially interesting is the synergy between propolis and anticancer agents. Moreover, flavonoids from propolis play a protective role against the toxicity of the chemotherapeutic agents or radiation in mice, giving hope that they may have similar protective action in humans. The combination with an adjuvant antioxidant therapy may

enhance the effectiveness of chemotherapy by ameliorating the side effect on leukocytes, liver and kidneys and consequently enabling dose escalation²²⁰

The cytotoxic effects leading to the anticancer activity have been reviewed in 2011 by Watanabe et al.³²³

Vit et al, 2015, reviews the different properties of propolis which lead to anticancer activity: antioxidant, antiproliferating, cancer cells apoptosis causing, anti-angiogenic (multi-step process to form blood vessels, this process is disturbed in cancer), immuno-suppressive, anti-inflammation, immunomodulatory³¹⁷

Although many polyphenols have a anti-metastatic activity, caffeic acid phenethyl ester (CAPE) from poplar propolis and Artepillin C from baccharis propolis have been identified as the most potent antitumor agents^{5, 22, 25, 221, 222, 277}, but antitumor effects of chrysin (poplar propolis) and both nemorosone and plukenetione A (in Cuban prropolis) have been reported³¹⁷

Consumption of propolis supplement can have a suppressive effect against mutation induced cancer²⁵⁴

Regular consumption of propolis food supplements can have a preventive effect against cancer

Anti-inflammatory activity

Inflammation (inflammatio, to set on fire) is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, irritants and free radicals. Antiinflammatory activity is thus defined as the primary effect of the host defence system.

The antiinflammatory activity of propolis has been reviewed by Almeida and Menezes. Propolis has inhibitory effects on mieloperoxidase activity, NADPH-oxidase ornithine decarboxilase, tirosine-protein-kinase, and hyaluronidase from guinea pig mast cells. This anti-inflammatory activity can be explained by the presence of active flavonoids and cinnamic acid derivatives. The former includes acacetin, quercetin, and naringenin the latter includes caffeic acid phenyl ester (CAPE) and caffeic acid (CA)¹¹

CAPE and galangin, both typical poplar propolis constituents exhibited anti-inflammatory activity and significantly inhibited carrageenan oedema, carrageenan pleurisy and adjuvant arthritis inflammations in rats^{47, 83}.

An ethanol extract of propolis suppressed prostaglandin and leukotriene generation by mouse peritoneal macrophages in vitro and during zymosan-induced acute peritoneal inflammation in vivo. Dietary propolis significantly suppressed the lipoxygenase pathway of arachidonic acid metabolism during inflammation in vivo. CAPE was a more potent modulator of arachidonic acid metabolism than caffeic acid, quercetin and naringenin¹⁹⁶.

Baccharis propolis suppresses the hypoxia-induced neuroinflammatory responses through inhibition of the NF-kappa B activation in microglia. Furthermore, increased generation of ROS from the mitochondria is responsible for the NF-kappa B activation. Therefore, propolis may be beneficial in preventing hypoxia-induced neuroinflammation³²⁶

Propolis can be regarded as food supplement for counteracting body and nerve inflammation

Digestion and the gut

Recent studies indicate that dietary polyphenols are relevant in the modulation of gut microbiota and that these microorganisms convert polyphenols into active and bioavailable metabolites; hence, variations in gut microbiota can affect polyphenol activity³⁰⁹. Also there is a complex interaction between polyphenols and the gut mucus barrier¹⁰⁷

Polyphenol-rich propolis extract strengthens intestinal barrier function by activating AMPK (adenosine monophosphate-activated protein kinase) and ERK (extracellular signal regulated kinase) signaling and provide novel insights into the potential application of propolis for human gut health³²¹.

Green propolis supplementation reduces inflammatory response and endotoxemia by preventing dysbiosis in mice challenged with a high-fat diet by reducing the levels of circulating lipopolysaccharides and the inflammatory cytokine expression in muscle²⁵⁶

Propolis and the Brain

As seen in table one there are numerous publication that show a positive influence of propolis (both poplar and baccharis) on depression, Alzheimers and dementia. Polyphenols generally have a preventive function in dementia due besides to their antioxidant, antiinflammatory and neuroprotective properties also to their modulatory action of the P-glycoproteins²⁶⁸. For following propolis polyphenols anti-Alzheimers effects have been reported: pinocembrin¹⁷³ CAPE and quercetin³²⁰

Parkinson is also a neurodegenerative disease due to oxidative stress and propolis has thus also anti-Parkinson properties³²⁰ Also, propolis extracts decreases neurotrophic factors and protects tyrosine hydroxylase neurons in the brain in rat model Parkinson disease studies¹⁹

APPLICATIONS IN MEDICINETable 5: **Health enhancing effects tested in human cells or in humans**

Study, effect	Propolis type	Reference
Cell and tissue experiments		
Antiproliferative activity in many different human cancer cells	All propolis types	220, 277
Antioxidant and antiproliferative activity in human B (human mouth epidermoid carcinoma cells), Caco-2 (colon adenocarcinoma cells) and DU-145 (androgen-insensitive prostate cancer cells)	Chile (poplar)	258
Propolis has protective action against oxidative modification of lipids in human unfractionated serum	Argentina	135
Propolis may have a role in protection against male infertility	Chile (poplar)	259
Propolis extracts and CAPE have protective action of propolis in cartilage tissue alteration, that appears greater than that elicited by indomethacin, commonly employed in joint diseases	Italy (poplar)	56
Dressing of artificially formed losses of the cartilaginous tissue with the preparation containing ethanol extract of propolis (EEP) caused acceleration of regenerating processes in the lesioned cartilage.	Poland (poplar)	272
10% propolis was a more effective storage medium for human periodontal ligament cells than other tested media and is a suitable transport medium for avulsed teeth	Turkey (poplar)	223
Antiapoptotic effects on human macrophages	?	68
Preclinical Treatment of Candidiasis vulvovaginal infection	Brazil (Baccharis)	40
Clinical studies		
Successfully applied against the different stomatological pathologic conditions: stomatitis, paradontosis, gingivitis and caries	Poplar and Baccharis	13, 122, 155, 174, 174, 184, 217, 263, 308
Use of combined therapy with propolis and antibiotic against Heliobacter pillory in humans, better efficiency than antibiotic alone	Italy, Poland (poplar)	214, 244
Propolis was successfully used in patients operated for goitre, patients with wounds and ulcerations difficult to heal and patients with non-specific rectal inflammation.	Poland (poplar)	118
A total of 260 steel workers suffering from bronchitis were successfully treated for 24 days with an ethanolic extract of propolis (EEP) in a physiological salt solution.	Poland (poplar)	270
CAPE-rich water-miscible extract propolis suppressed completely the growth of a human NF1 cancer and an almost complete regression of human NF2 tumor (Schwannoma), both grafted in nude mice.	New Zealand (poplar)	81
Successful treatment of human giardiasis (intestinal parasitism)	Cuba	199
In vivo effect in healthy (n=49), Effect gender specific (only in men) For the men test group after the initial 15 days of propolis treatment, 23.2% (p = 0.005) decrease in concentration of malondialdehyde was observed.	Croatia (poplar)	140
Clinical study for the treatment of bronchial asthma with 22 patients receiving a propolis supplement and 24 with a placebo control: a substantial improvement of conditions in treatment group, accompanied by drop of proimflammatory cytokinines	Egypt	149
Propolis decreases the erythrocytes membrane fragility of patients with hereditary spherocytosis red blood cells.	Two Braslian propolis types	205
Improves the immunological response of humans		48
Treatment of chronic vaginitis		134
Treatment of asthma	Poplar	149
Treatment of Peyronie's disease		168
Treatment of psoriasis with propolis ointment or propolis intake	Egyptian propolis	123
Treatment of recurrent cervicitis	Baccharis	235
Treatment of mild cognitive impairment at high altitude	Baccharis	333

The main medical application of propolis are based on its antimicrobial, anti-inflammatory and immunomodulating effects: e.g. in stomatology, otorhinolaryngologic diseases, gastroenterology, gynecology, pediatric, urological and surgical diseases. It has also potential in other medical fields such as cancerology, dermatology, endocrinology, where the other biological effects of propolis also play a role.

The medicinal effects of propolis are summarised in table 5, as available in original publications.

Dentistry

The application of propolis in dentistry is probably the most well scientifically documented and now practically applied in many countries, mostly the developing ones. The different applications were reviewed in different publications, the last in 2013^{170, 217, 234, 325}. Propolis is applied in the different dental specialities: oral hygiene; periodontology and oral mucosa pathologies; oral surgery; orthodontics; restorative dentistry; endodontics and prosthetic dentistry

Oral hygiene

Propolis inhibits in the mouth different pathogenic microbes such as bacteria, fungi and viruses^{122, 264, 265, 285} and can be successfully applied against the different stomatological pathologic conditions: plaque formation, mouth wounds and ulcers, denture and aphthous stomatitis, paradontosis, periodontitis, gingivitis, dental hypersensitivity and caries^{13, 122, 155, 170, 174, 184, 217, 234, 240, 263, 308} and against Candida-associated denture stomatitis⁵⁴

Most of the in vivo test carried on rats and also clinical tests on humans showed positive results in reducing bacterial plaque (caries). The clinical application of propolis against caries has been reviewed in 2016, suggesting that propolis can be successfully used¹⁷⁸

The soft and periodontal tissues surrounding dental implants are particularly susceptible to bacteria invasion and inflammatory reactions due to complex histological structures. A study was carried out to investigate the influence of a Baccharis propolis-containing hygienic agent on selected oral health parameters, oral microflora, and the condition of periodontal health. Sixteen subjects who underwent an oral rehabilitation with dental implants were selected and randomly assigned into two groups, which received a newly formulated propolis-containing toothpaste (3%(CA)) or a negative control without an active ingredient (CC). Approximal plaque index (API), oral hygiene index (OHI, debris component), and sulcus bleeding index (SBI) were assessed in three subsequent stages. During the first and last examinations, the swabs were employed for microbiological inoculation. Propolis-containing toothpaste was found to be distinctively effective in improving oral health and hygiene and the occurrence of gingivitis triggered by dental plaque. The qualitative and quantitative changes in oral bacteria spectrum were observed. Antibacterial measures containing propolis might be used as a natural adjuvant to other active substances in individuals with a high risk of periodontal problems against pathogenic oral microflora²⁰⁴.

Halitosis, an unpleasant breath, is also largely related to hygiene of the oral cavity. The byproducts of degradation of microorganisms located in the mouth are one of the reasons of bad breath. Microbes particularly related to the creation of bad breath include the red complex bacteria and: *Prevotella intermedia*, *Porphyromonas endodontalis*, and *Eubacterium*. The measurements of the content of volatile sulfur components in exhaled air with the use of halimeter indicate that propolis reduces halitosis, see original references in³²⁵,

Periodontology (inflammation of the teeth supporting tissue) and oral mucosa pathologies.

The confirmation of the effectiveness of propolis in fighting etiological factors of periodontitis made some authors include these preparations in the periodontologic therapeutic protocol. Mucoadhesive hydrophilic gel containing propolis, when applied to gingival pockets, can be useful in treatment of periodontitis. Additional subgingival irrigations with a propolis extract during periodontologic treatment allowed to obtain better results than scaling and root planning. Not only local, but also oral use of propolis-based preparations turns out to be effective in periodontal treatment, see original publications in³²⁵

In cases of infection of the oral mucosa caused by *Herpes simplex* it was shown that propolis solutions had a high antiviral effectiveness. Propolis delays growth and progression of skin changes in an early stage of

infection with Herpes simplex and does not have cytotoxic effects. Propolis can be used also in the treatment of recurrent aphthoid stomatitis, see original publications in ³²⁵

A 6-month masked, randomized clinical trial comparing propolis (of Chinese origin) with placebo (placebo + SRP group, n = 26) or SRP (scaling and root planning) combined with a 6-month regimen of 400 mg oral propolis once daily (propolis + SRP group, n = 24) was performed in patients with long-standing Diabetes Melitis type 2 (DMt2) and chronic peridontitis (CP). After 3 and 6 months, average HbA1c levels in the propolis group decreased significantly by 0.82% and 0.96% units, respectively (P <0.01); however, there were no significant differences in the placebo group. Likewise, fasting plasma glucose and serum carbamyl-lysine levels were significantly reduced in the propolis group, but not in the placebo group. After therapy, periodontal parameters of CP were significantly improved in both groups. The propolis group showed significantly greater probing depth reduction and clinical attachment level gain than the control group after 3 and 6 months. Conclusion: A 6-month regimen of 400 mg propolis once daily is a potentially viable adjunct to SRP that significantly reduces levels of HbA1c, FPG, and CML, and improves periodontal therapy outcome in people with DMt2 and CP⁸⁷

Oral surgery

Most studies show very good effects of storage of avulsed teeth in propolis. Propolis is extremely effective; it not only reduces apoptosis of periodontium cells but also increases their metabolic activity and proliferation. Local application of propolis after surgery helps wounds to heal, reduces inflammation and has also an analgesic effect, see original publications in ³²⁵

Orthodontics

In malocclusions accompanied by a considerable narrowing of the maxilla, it is necessary to use a device to expand the palatine suture. There is a positive effect of propolis solution on bone forming process during the treatment with the device to expand the palatine suture, there is an increased quantity of osteoblasts in preparations from rats which received propolis during the treatment. In such cases bone remodelling within the palatine suture was quicker, see original publications in ³²⁵

Restorative Dentistry

In restorative dentistry, propolis can be used to decrease permeability of the dentin and to direct pulp capping in order to create restorative dentin. Propolis can reduce dentin permeability. On this basis, it can be concluded that it counteracts tooth sensitivity. The regenerative effect of propolis on the tooth pulp has been known for a long time. Nevertheless, there is no consent on the subject of propolis extracts effectiveness in comparison with calcium hydroxide which is most often used in stimulation of creation a reparative dentin. It seems that there are no important differences in direct capping with propolis and with calcium hydroxidebased products. Both of them offer a similar degree of healing pulp inflammation, reducing quantity of microbes and stimulating creation of dentin bridge. Also propolis, calcium hydroxide, and MTA have similar effectiveness in the induction to create reparative dentin. It seems that there is a higher effectiveness of direct pulp capping with propolis than with calcium hydroxide-based products. Propolis not only stops infammatory reaction, infection with microbes and pulp necrosis but also induces formation of high quality tubular dentin through stimulation of stem cells, see original publications in ³²⁵

Endodontics

One of the aims of endodontic treatment is a complete elimination of microbes in root canals. The effectiveness of medicines used in endodontology is often assessed through a test of *Enterococcus faecalis* growth which is resistant to unfavorable environment and can survive in the root canal system despite application of medicaments. Many studies show that propolis effectively limits the quantity of *E. faecalis* in root canals, but its effectiveness might be lower than that of chlorhexidine see original publications in ³²⁵

For the different purposes propolis is applied in form of sprays, mouthwashes (both with or without alcohol), toothpastes, gels and other specific preparations



Propolis toothpaste



Propolis mouthwash



Propolis oral spray without alcohol

Otorhinolaryngologic and respiration diseases (ear, nose, throat, and head and neck disorders)

This topic has been reviewed by Marcucci¹⁷⁹, Asavova¹⁶, Shkenderov-Ivanov²⁸³ and Tichonov³⁰⁸
 Following diseases have been treated, indicated is also the number of cited studies:



- Chronic and acute inflammation of the inner ear: 10
- Common acute cold, acute and chronic inflammation of the upper respiration path: 13
- Synositis: 3
- Laryngitis (larynx inflammation): 2
- Tonsillitis (infections of the tonsils): 4
- Pulmonary tuberculosis: 5 (sometimes together with antibiotics and together in complex of anti-tuberculosis measures)

- Bronchial asthma: 3

A total of 260 steel workers suffering from bronchitis were treated for 24 days by various methods including local and systemic regulation of the immune system and local treatment with an ethanolic extract of propolis (EEP) in a physiological salt solution. The best results were obtained in patients treated with EEP inhalations²⁷⁰

For the otorhinolaryngologic (ear, nose, throat) treatments following application forms have been used:

- Common acute cold, acute and chronic inflammation of the upper respiration path, synositis, bronchial asthma: *aerosol inhalation combined with EEP intake*
- Inflammation of the inner ear: *tampons and washing with propolis extracts*
- Tonsillitis: *aerosol inhalation, application of propolis ointments*

Application forms

- Propolis inhalation 3 to 5 times a day
- Drops (10-15 drops of 20 % propolis, 3 times a day) or
- Tablets: 4-6 times daily of tablets containing 50 mg propolis
- Cream and ointments containing 5-10 % propolis

Gastroenterology

From the different effects reported in table 5 and 6 the most widely mentioned are the ones concerning the effects of propolis in gastroenterology. Propolis is known as a powerful inhibitor of *Helicobacter pylori*, the causative agent of gastric, duodenal ulcers and gastritis^{29, 84, 137, 332} and it was used alone^{174, 308} or in combination with antibiotics for in the prevention and treatment of gastric ulcers^{29, 84, 332}.

Due to its antiinflammatory and antimicrobial properties propolis supplements can be used for the prevention of bacterial infection and of inflammation of the stomach and duodenum.

Propolis against cancer

This promising area has been reviewed by Galvao et al.¹⁰¹ and in 2010 by Orsolic²²⁰ showing that there are numerous antitumor effects in cell culture and animal tests.

Thus regular propolis consumption could have a preventive anticancer effect²⁵⁴.

On the other hand, there are very few human studies. One major threat for women is the human papilloma virus (HPV) infection which can lead to cervical cancer, which is the most frequent cancer in women, especially in the developing world. But even in Western countries there are many HPV-associated dysplasias which require surgery by means of conisation or even hysterectomy. In a randomised trial, HPV infections were present after three months of treatment in 28% of patients treated with propolis compared to 90% in the control group¹³³. Similarly, another study described an improvement in PAP smears of 76% with the use of propolis¹³⁴. Here, treatment with bee products offers an interesting approach which could avoid invasive surgery.

CAPE-rich water-miscible extract propolis suppressed completely the growth of a human NF1 cancer called MPNST (malignant peripheral nerve sheath tumor) and caused an almost complete regression of human NF2 Schwannoma tumor, both grafted in nude mice. The same preparation is currently tested on patients^{81, 194}

Regular consumption of propolis food supplements can have a preventive effect against mutation linked cancers in humans²⁵⁴

In a controlled clinical trials it was shown that propolis treatment prevented oral mucositis in breast cancer patients²⁴³ and in head and neck patients⁴⁴

Supplementation with propolis capsules (400 mg, 3 times daily) for 10 consecutive days before radiotherapy of breast cancer (BC) patients, during the course of radiation treatment and 10 days after completing the radiotherapy was tested in clinical study (against a control). There was a measurable protection against DNA damage caused by ionizing radiation in BC patients leukocytes and inhibits bonucleotide reductase M2 subunit overexpression. Moreover, propolis has beneficial effects on the serum antioxidant capacity and improves the digestive utilization of iron and the regeneration efficiency of hemoglobin²⁰⁰.

The experience of Ludyanski

Ludyansky, a chief doctor in a big Russian hospital, with life-long practice in apitherapy, has summarised the apitherapy knowledge in his monograph “Apitherapia” (in Russian)¹⁷⁴. He summarises the medical uses of propolis in his hospital in the following table:

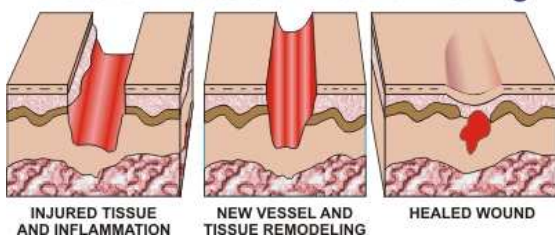
Table 6. Applications of propolis in a big Russian hospital

Treated disease	Very good and good improvement	No improvement
Alopecia	69	10
Geriatrics	22	10
Impotency	20	2
Inflammation of the vagina	26	9
Pediatrics	100	-
Prostatitis	13	5
Radiculitis, polyradiculoneuritis	39	2
Stomach ulcer	23	5
Stomatology	16	3

EXTERNAL APPLICATIONS: SKIN LESIONS, SURGERY, WOUNDS, BURNS, ULCERS, SKIN AND EYE DISEASES, GYNECOLOGY

Skin lesions, surgery, wounds, burns, ulcers

Natural Phases of Wound Healing



Propolis applications in this area are known since ancient times and are based on its antimicrobial and anti-inflammatory properties. This area has been recently reviewed by Barbosa³³, “In this review 4 studies on the successful use of propolis in skin lesions such as ischemic ulcer, stasis ulcer, venous ulcer, iatrogenic lesion and ulcer were reported. Applied was 30 % aqueous propolis extract. After the first week of use already, improvement of wound odor and patient’s sensitivity to pain was observed, as well as a decrease in the number of microorganisms. The authors of this study emphasized that wound healing efficacy is closely associated with the propolis

concentration in the solution. Another study, which used propolis ointment on 22 chronic wounds, of which 11 were venous ulcers, seven pressure ulcers, two diabetic ulcers, and two post-trauma injuries, found that necrotic tissue was present in 14 (8.2%) during tissue assessment process. However, there was no necrotic tissue after therapeutic intervention. Mean healing time was 13.2 weeks. Considering a 20-week follow-up, 74.1% of ulcers healed before this period. In addition, regarding pain felt by people with chronic wounds, all of them reported improvement, even though its level was not assessed by this study. “

The applications, citing Eastern European studies has been reviewed by Asavova¹⁶. The applications can be summarised as follows, together with indication of the number of the successful studies:

Ulcers: 5; Burns: 2; Healing of damages due to cancer radiation treatments:2; badly healing wounds: 1

In humans it has been used for treatment of surgical diseases ¹¹⁸, wounds ⁹⁶ and burns ^{111, 229}. In Cuba a better success was achieved by mixing honey, propolis and thyme oil.

In Poland Sheller has used ethanol extracts of propolis in the clinic to treat patients with burns, crural ulceration, pressure ulcers, osteomyelitis, infections of the wound after trauma/injury and infections of the operative wound¹⁵⁹

In the Russian centre for the treatment of burns 15 % propolis in animal fat or plant oils was used. The propolis ointment had a anaesthetic, bactericidal and wound regeneration effect, improving also blood and lymphatic system²²⁹. More recently the Russian preparation “Propolis Geliant”, based on a propolis containing mixture with sunflower oil and heavy fractions of a dark natural wax is successfully used for the treatment of burns, wounds, skin diseases and in cosmetics⁶².

Hartiwich et al. tested propolis treatments on patients operated for goitre, patients with wounds and ulcerations difficult to heal and patients with non-specific rectal inflammation. They also tested the effectiveness of propolis as supplementary means in eradicating treatment of *Helicobacter pylori*. It was found that the drug was tolerated very well, practically had no side-effects and was highly effective¹¹⁸

In another study, the effect of Brazilian propolis skin cream was compared with that of silver sulfadiazene (SSD) in the treatment of minor burns (superficial second degree) in the ambulatory care setting (less than 20% total body surface area burned). The study was conducted at a burn clinic in Brazil. Patients were admitted to the study only if their initial presentation for burn care was within 48 hours post-injury and if bilateral wounds of similar depth and quality were present. Patients had propolis skin cream applied to one wound and SSD applied to the other selected wound on initial presentation and underwent debridement and dressings change the following morning. Patients subsequently returned to the clinic every 3 days to have the wounds checked and dressings changed. At these check-ups, wounds were cultured for microbial growth and photographed to document inflammation and cicatrisation. Patients were instructed not to disturb their wounds or change their dressings at home, thus propolis skin cream and SSD were applied to the wounds only at the specified 3-day intervals. The results do not show any significant difference in microbial colonization between wounds treated with SSD and propolis skin cream, however, wounds treated with propolis skin cream consistently showed less inflammation and more rapid cicatrisation then those treated with SSD. It is concluded that propolis skin cream appears to have a beneficial effects on the healing of partial thickness burn wounds. More frequent application of propolis should enhance the antimicrobial and wound healing effects of propolis¹¹¹. Antimicrobial Brazilian propolis (EPP-AF) containing Biocellulose Membranes is a promising biomaterial for skin wound healing³⁴

In a study with Bacharis propolis it was found that optimum results for treating wounds can be achieved by propylene glycol containing 3.6 % propolis. At this concentration all tested bacteria could be inhibited⁴¹ Propolis gels for application on wounds or burns have been recently developed²⁰

Application forms: propolis ointments or creams, 10-20 % water or glycol propolis tinctures, no ethanol

Skin diseases

Against epidermophytosis, skin tuberculosis alopecia; psoriasis; different microbial and chronic eczemas, cutaneous conditions of cold regions, pyoderma; Trichophyton skin inflammation¹⁶

Application forms: 10-50 % propolis ointments or creams, 10-20 % propolis water tinctures

Eye diseases

Several successful clinical studies on the treatment of a variety of eye diseases are reported: keratitis, conjunctivitis and blepharitis¹⁶. 0.3 - 1 % aqueous propolis solutions have been applied. Tichonov et al. developed special propolis preparations, bases on specific propolis fractions, especially adapted for eye applications³⁰⁸.

Gynecology and urology

The applications of propolis in gynecology and urology are based on the antibacterial and anti-inflammatory effects of propolis. These applications have been reviewed by Asavova¹⁶. Most successful is the treatment of the inflammation of the vagina and of the female genital area, where 8 successful studies were cited. For this purpose direct application of 20-30 % EEP and EEP-tampons were used. Two studies with successful treatments of vagina erosions were cited, alone or in combination with cortisone creams, with application of 15% propolis in fatty cream or intake of EEP.

Other external applications

Propolis ointments have been successfully used against cold sores, *Herpes simplex* skin lesions and Herpes zoster lesions^{105, 124} and also against genital herpes^{105, 124, 318}. Egyptian propolis was successfully used against different types of warts³³¹. According to Potschinkova propolis-beeswax warming plasters can be used for the treatment of arthritis and arthrosis and against sprains, physical injuries, inflammations of muscles, nerves and filaments²⁴⁹. Propolis ointments are also used for these conditions.

Attention when applying propolis externally: test for propolis contact allergy before application

VETERINARY MEDICINE AND AGRICULTURE

The application of propolis in veterinary medicine is based on its antimicrobial properties. It is reviewed in the monographs of Zakoff³¹⁴ and Teterev (1998)³⁰⁷

Uses of propolis in veterinary medicine

Mastitis: application of propolis linement	85, 148, 190, 195, 307
Gynecological diseases: application of propolis candles	307
Feeding of weak pigs, prophylactics of gastroenterological and respiration diseases of pigs; feeding with 0.5 % propolis in milk	307
Improves weight gain and reduced diarrhoea in mild-fed calves with 5 ml of 20% ethanol extract	113
Prophylactics of calf diarrhoea: at to feeding 0.5 ml/kg of 10 % ethanol extract	307
Prophylactics against paratyphoid fever of ducks: feeding with 50 % propolis aqueous extract	307
Wound healing: application of 5% propolis in fish oil or fat	307
As a local anaesthetic in surgery: 1 to 10 % PEP	314
Against foot-and-mouth disease' induced damages on the utter of cows and pigs	314
Against enzootic pneumonia of pigs	314
Stimulant for the growth of underdeveloped lambs, pigs and calves	314

Teterev describes several preparations for veterinarian use: Biogel 5: containing 0.5 % propolis and 2 % carboxymethylcellulose for intake against gastroenterology diseases, for prophylaxis; Biogel 10, similar to Biogel 5 but contains 1 % propolis.

Agriculture

This use has been reviewed by Teterev³⁰⁷. Intake of propolis increases of weight gain, development rate and productivity of different animals. 1 to 10 % propolis in milk is used, the intake bein about 10 ml/kg.

Following uses have been described.

- ❖ Weight gain, increased rate of development of animals and productivity
- ❖ Improvement of meat quality
- ❖ Increased rates of egg laying of hens

Propolis has been also used:

- ❖ to control the white rot disease of onions⁹³

- ❖ against potato viruses⁹²
- ❖ to inhibit the growth of *A. ochraceus* NRRL 3174 as well as biosynthesis of ochratoxin in Ras cheese ripening²⁰¹
- ❖ as a natural antioxidant for conservation of plant oils and butter^{225, 226} and meat^{115, 116}
- ❖ against soy-bean and sunflower wild diseases²⁶⁰
- ❖ inhibitory effect on germination and cell division in the root tips of wheat seedlings²⁹⁵
- ❖ as potential pre- and post-Harvest fungicide in avocado storage¹⁰⁴
- ❖ better feeding of bulls than conventional additives³³⁰
- ❖ enhancing the ruminal degradability²⁰⁷

PROPOLIS PREPARATIONS

The application forms shown in this section are adapted after Ludyanski¹⁷⁴Pochinkova²⁴⁹, Tichonov et al.³⁰⁸ and in the online publication of [Krell](#)¹⁵⁷, where more recipes can be found.

Tichonov's monograph on propolis preparations

Prof. Tichonov and his team of the Ukrainian Kharkov pharmacy faculty, has produced a detailed propolis monograph describing in detail different propolis preparations (poplar propolis) He compared the extraction of phenolic substances in 40, 70 and 95 % ethanol for 24 to 144 hours extraction time (maceration). Best extraction of the phenolics was achieved by 70 % and 95 % ethanol after 144 hours. About 90-95 % of the maximal extraction was achieved already after 72 hours. He also compared also the dependence of the extraction efficacy on the size of the propolis particles, best extraction was found with 0.5 - 1 mm particles. Tichonov developed a fractional-differential extraction method with better efficacy than the traditional maceration method. The extracted propolis is called Phenolic Hydrophobic Preparation (PHP). The aim was to produce a water soluble PHP containing a maximal concentration of the phenolic active ingredients, using detergents. For that purpose he uses Polysobate 20, 40, 60 and 80 (Tween 20) a polysorbate surfactants whose stability and non-toxicity allows it to be used as detergents and emulsifiers in a number of domestic, scientific and pharmacological applications. The oral toxicity dose for the Tween substances is 25 g/kg. A maximal concentration of the phenolic fraction was achieved by mixing 1 part of PHP, 0.3 p Tween 80 and 0.5 p water, a concentration of 55.5 % PHP. Tichonov tested also solubilisation with different non toxic, synthetic non-ionic surfactants. He chose ethylene oxide / propylene oxide copolymers type surfactants with a MW of 5500. Tichonov determined the bioavailability and the toxicity of water soluble PHP. Based on his studies different propolis preparations are marketed in the Ukraine³⁰⁸.

A topical formulation of Brazilian propolis was developed, containing Polowax as a stabilizer against UV damage¹⁸².

Raw whole propolis

The simplest application of is to grind frozen propolis to powder with the help of a mill. Simple coffee mill does the job. The propolis powder can be mixed to honey food or drinks for intake, can be used as a starter for solutions or can be used for the production of propolis pills. Large pieces of propolis can be chewed, but it should be consumed in small quantities. Powder can be made into capsules or mixed with A special form of raw propolis, the so called water soluble whole propolis has been developed by Glenn Perry, www.glennperry.com

Tinctures

Tinctures are prepared in ethanol, glycol and olive oil. The latter two ones are better for skin and cosmetic applications. Ethanol is the best solvent for extracting the bioactive substances (balsam). Propylenglycol can dissolve less propolis, 20 g per 100 ml glycol can be dissolved²⁷⁶. Glycol tinctures are highly antioxidant and can be used in skin protection¹⁸¹.

Total amount of phenolic compounds in extracts made in polyethylene glycol 400 (PEG) and water mixture or in PEG, olive oil and water mixture at 70 °C was comparable to that of ethanolic extract. Predominantly identified compounds were phenolic acids, which contribute ca. 40 % of total radical scavenging activity. Investigated nonethanolic extracts inhibited the growth and reproduction of all tested microorganisms. Antimicrobial activity of some extracts was equal or exceeded the antimicrobial effect of ethanolic extract. Extracts made in pure water or oil only at room temperature, contained more than 5 - 10-fold lower amount of phenolic compounds, and demonstrated no antimicrobial activity.¹⁵⁸

Ethanol tinctures

Tinctures are prepared in ethanol, glycol and olive oil. The latter two ones are better for skin and cosmetic applications. Ethanol is the best solvent for extracting the bioactive substances (balsam). Propylenglycol can dissolve less propolis, 20 g per 100 ml glycol can be dissolved²⁷⁶. Glycol tinctures are highly antioxidant and can be used in skin protection¹⁸¹.

Ethanol tinctures

The optimal conditions for propolis extraction have been studied in different publications. In practice propolis is generally macerated (extraction in the solvent without stirring) with occasional shaking. Other extraction methods as Soxhlet, ultrasound or microwave or differential extraction are better^{72, 308} but need specific equipment and cannot be used under home conditions. 60-80 % aqueous ethanol solutions have a higher biological activity than tinctures, prepared with more or less water^{232, 233, 266}. In practice many different propolis maceration procedures are given, the maceration time being sometimes as long as one year. The maceration time for best extraction of bioactive materials depends on different factors: e.g. on the extraction time, extraction method, on the solvent composition, on the propolis concentration and on the size of the propolis particles. Higher temperatures increase the extraction power, but due to the volatility of ethanol room temperature between 20 and 25 °C are optimal.

Extraction has been studied for poplar propolis in detail by Tikhonov and coworkers³⁰⁸ who developed a semi-industrial method of differential extraction for optimal and reproducible extraction of propolis. They found that optimum extraction of phenolics is when fine propolis particles (size 0.5-1 mm) are extracted using 95 % ethanol. These particles which already after 3 days optimum extraction of phenolics is achieved under conditions of maceration.

Cunha et al. found out that when using 70 % ethanol the maceration of 20 g/ 100 ml of green propolis is optimal 30 days of extraction time, although there was no statistical difference between the extractions of 10 and 30 days⁷². In another study on extraction of Baccharis propolis a minimum of 5 days was suggested¹⁸⁸. Salonen found that a maceration time of 2 months of Finish propolis will further improve extraction by about 5-10 %, but it was not tested if this effect was significant²⁶²



In Russia and the Ukraine there are many propolis preparations based on the extended research in these countries

Raw propolis

Unprocessed, pure propolis can be frozen and broken down to pieces or ground to fine powder. Large pieces of propolis can be chewed, but it should be consumed in small quantities. Powder can be made into capsules or mixed with food or drinks. A special form of raw propolis, the so called water soluble whole propolis has been developed by Glenn Perry, www.glennperry.com

Whole dry water soluble propolis

A patent described by Sosnowski²⁹⁶, based on the extraction of poplar propolis

“The following examples are set forth in order to fully describe the method for extracting and purifying propolis as well as the resulting dry propolis powder and its uses. About 500 grams of clean raw propolis was placed in an amber glass container and covered with about 1 liter of absolute ethanol. This mixture was allowed to sit for ten days at room temperature with periodic agitation several times each day. At the end of ten days, the mixture was filtered through Whatman No. 1 filter paper. The resulting propolis-containing filtrate was then incubated at about 70 degrees C until a dry propolis powder was obtained”.

Another method patented by Hajime (1999) uses extraction of Brazilian propolis under conditions of pH adjustment, the method is available [online](#)

Glenn Perry www.wholepropolis.com developed a method for the preparation of whole water soluble propolis as a water emulsion.

Ethanol tinctures

Practical considerations



- ❖ *For human use only non-toxic solvents should be used, ethanol of Pharmacopeia quality is the best choice.*
- ❖ *Propolis should be pure, remove coarse debris and excessive wax.*
- ❖ *Place propolis in freezer and break it in small pieces or mill it to powder for a better solubility*
- ❖ *60-80 % aqueous ethanol solutions have a higher biological activity than tinctures, prepared with more or less water^{232, 233}, 70% seems to be optimal*
- ❖ *Prepare a 70 % (v/v) aqueous ethanol by adding 700 ml ethanol to 300 ml of water*
- ❖ *Calculate necessary quantities of propolis and aqueous ethanol. Solutions are expressed in weight per weight. 1 L of ethanol weighs ca. 800 g, 1 L of 70 % eth., ca. 860 g*
- ❖ *5-30 % propolis solutions are used, do not make more than 30 % solutions in order to prevent precipitation of active compounds.*
- ❖ *Ethanaol tincture intake only after a strong dilution with water (10-30 drops in a glass of water)*

Propolis ethanol tincture

- ❖ *Add 100 g propolis to 400 g 70 % ethanol (for 20 % tincture)*
- ❖ *Store vessel in the dark for two weeks, shaking occasionally (the longer the extraction time, the greater the concentration of active ingredients, but 1-2 months will further improve the extraction by 5-10 %^{71, 262})*
- ❖ *Filter through a paper filter (coffee filter will do) and store tincture closed in a clean dark vessel. If vessel is not brown or reddish, store in the dark, or pack vessel in aluminium foil.*

Tincture in 30 % ethanol for uses in dentistry:

- ❖ *26 ml 95 % ethanol, 74 ml distilled water and 33 powdered propolis*
- ❖ *Store vessel in the dark for at least two days, better one or two weeks, shaking occasionally (the longer the extraction time, the greater the concentration of active ingredients, but more than 2 weeks does not bring more benefit)*
- ❖ *Filter through a paper filter (coffee filter will do) and store tincture closed in a clean dark vessel. If vessel is not brown or reddish, store in the dark, or pack vessel in aluminium foil.*

Propolis water extracts

Simple extraction with water

- ❖ *Add 50 g of propolis to 100 ml of water*
- ❖ *Boil for 60 minutes*
- ❖ *Cool down to room temperature and filter*

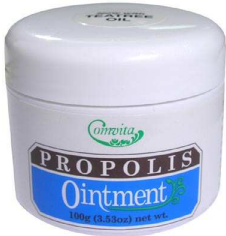
Water extract after Ludyanski¹⁷⁴

- ❖ *300 ml of water is poured in a pan over 30 g propolis, cut in small pieces.*
- ❖ *Close pan and boil gently for 40-45 min.*
- ❖ *Cool down, collect wax from the surface and decant supernatant (1).*

- ❖ Add a new portion of 30 g propolis pieces to remaining precipitate in the pan and 300 ml of cold water.
- ❖ Boil gently for 10-15 minutes
- ❖ Cool down, collect wax from the surface and decant supernatant into vessel with supernatant 1 to give about 500-600 ml of propolis water extract

According to Ludyanski this water extract has an antifungal, antibacterial effect and also other known biological effects. This water is ready for drinking. Keep in a dark place.

Mixtures, emulsions, concentrates, creams, ointments



Ethanol-water mixtures

- ❖ Mix 1 part 30 % propolis ethanol tincture with 5, 10 or 100 parts of water.

Some the propolis constituents will precipitate. The durability of this mixture durability is limited to 7 days. Store in the dark. Shake before use. Used for stomatology and for compress.

Ethanol-oil emulsion:

- ❖ Mix 1 part 30 % prop ethanol tincture with 1 or 2 parts of glycerol or edible oil. Store in the dark. This emulsion has an indefinite shelf life.

Propolis concentrate

There are propolis concentrates with 25 % liquid ("wet" concentrate) and 5 % liquid ("dry" concentrate). The concentrates are prepared by the ethanol of a 30 % propolis ethanol tincture 1 at 60°C in water bath (see above). These concentrates are used for the preparations of creams, pastes and suppositories, or for mixing it to honey.

Propolis creams and ointments for different uses

Creams on the basis of a propolis concentrate

- ❖ Use vaseline or vaselin-sunflower (2:1) oil and lanoline as an emulgator. In practice 1,2 and 5 % propolis are used.
- ❖ 1 and 2 % cream: add 90 g vaseline, 10 g lanoline to 1 or 2 g of a dry propolis concentrate.
- ❖ 5 % cream: add 80 g vaseline, 15 g lanoline to 5 g of a dry propolis concentrate.
- ❖ While mixing lanoline with a spatula add first propolis concentrate until a uniform mass is attained, then add vaseline and mix well.

For the basis of the cream vaseline and lanoline in proportions 9:1 and 8:2 are used. For 100 g of this basis 10-20 ml of 30 % propolis ethanol extract are used:

- ❖ warm up basis in a water bath (at about 40-50°C) and add propolis extract
- ❖ while stirring, warm to boiling to evaporate ethanol
- ❖ While still warm sieve cream, containing 3 or 6 % propolis and pack it in a dark cream box, tightly closed.

Propolis paste

Place propolis in freezer, cut it into small pieces and ground it to a fine powder. Mix it in a vessel with the basis (honey, margarine, butter etc.), so that 5, 10, 15 and 20 % propolis cream is obtained. Also, the dry concentrate can be used (5 g dry propolis concentrate for 100 g basis). The dose to be taken is 3 times a day, take a tea spoonful 0.5-1 hour before meals.

Propolis butter

- ❖ Boil 1kg of butter and cool down to 80°C
- ❖ Add 150 g propolis powder and mix well
- ❖ Cover with lid and wait 20 min. while stirring from time to time, in order to prevent propolis from stirring to pan.
- ❖ Extract propolis into butter by heating mixture at 80-90°C while energetically stirring
- ❖ Filter hot mixture through a gaze and keep closed in a cool dark place until consummation.

The dose to be taken is 3 times a day, take a tea spoonful 0.5-1 hour before meals.

Propolis cream for dentistry, ingredients (in parts by weight) after²⁹⁶

- 10 Lanolin
- 10 Unbleached beeswax
- 10 Petrolatum (or Vaseline, the trade name for a petrolatum)
- 2 Ethyl aminobenzoate
- 3 Clove oil
- 15 Propolis (50% EEP)

COSMETICS



Propolis is used as in cream or in lotions for different cosmetic purposes. The propolis uses for cosmetics have been investigated^{166, 167}. Its use is based on the antibacterial, antifungal, anti-viral anti-acne, anti-inflammatory, antioxidant effects, epithelial, micro-circulation and topical anaesthetic effects. Low toxicity and good skin compatability have been demonstrated, despite the risk for allergic reactions. For skin lotions and creams for cosmetic use 1-2 % propolis seems to be the appropriate amount¹⁴². However, before use a test on a small skin surface should be made, if there is a propolis allergy problem. The possible allergising effects should

be marked on the product.

Different uses of propolis in cosmetics after Krell¹⁵⁷

Function	Application
Anti-bacterial agent	Deodorants and antiperspirants
Anti-dandruff and sebum equalizing agent	Shampoos and hair lotions
Anti-microbial and healing agent	Anti-acnes and after-shave products
Purifying agent	Cleansing creams and lotions
Preservative	In all of the above

Propolis for skin care

Propolis used in skin care is based on its anti-allergy, anti-inflammation, anti-androgen, anti-lipase, an antimicrobial and a promotive action on collagen synthesis³⁰⁶. Thus, the dermatological and cosmetic uses for propolis and its extracts are very common¹⁶⁷. The skin lesion applications of propolis have been reviewed by Barbosa et³³

Propolis can be used in skin and mouth cosmetics for mouth prophylactics and for the preventions of different stomatological pathologic conditions: stomatitis, paradontosis, gingivitis and caries. While use of Baccharis propolis is without problems, people using poplar propolis allergy should make an allergy test.

ALLERGY AND TOXIC EFFECTS

Most allergy studies are conducted with poplar propolis. There are no reporteds on allergy cases of other propolis types.

Contact dermatitis

Poplar propolis can cause contact dermatitis. The responsible contact allergen are 3-methyl-2-butenyl caffeate and phenylethyl caffeate³¹⁹

In a 2010 contact dermatitis test in the UK with 2828 normal human subjects 1.9 % were found to be sensitive to propolis²⁵⁰. In a questionnaire filled out by 1051 German beekeepers 3.6 % declared skin sensitivity to propolis²⁰⁸. Thus it seems that people that regular contact with poplar propolis seems to have a skin allergising effect. In another study 4.1 % of 605 dermatitis allergic patients were allergic to propolis¹⁷⁷.

Walgrave reviewed different contact dermatitis studies and concludes that 1.2 to 6.6 % of the patients undergoing patch testing are sensitive to propolis³¹⁹.

Individual cases of people allergic to ingested propolis (mouthwash, toothpaste) have been described^{49, 98, 121}.

Special hypoallergic propolis preparations have been developed for skin and wound applications^{125, 203}

A simple chemical procedure has been proposed to remove allergic esters from poplar propolis¹⁰

Allergy after ingestion

Propolis allergy upon ingestion seems to be less frequent than contact allergy, due probably to its anti-allergenic and anti-inflammatory properties (see table 4). No data on the allergy frequency of the population is available. Reports on individual cases of people allergic to propolis ingestion have been published^{121, 128}.

On the other effect propolis ingestions has been shown to have an anti-allergenic effects, due to the flavonoids⁶⁴

Toxicology

Burdock reviews many animal toxicological studies in animals. He concludes that an intake until 4000 mg/kg per day there are no measurable effects and establishes a No Effect Level (NOEL) at 1400 mg/kg per day⁷. Generally a safety margin of 100 is assumed for drug and food additives. **This means that a maximum of 14 mg/kg per or 980 mg per day for a human of 70 kg can be the daily acceptable intake.**

HEALTH CLAIMS FOR PROPOLIS

According to the EU Regulation 1924/2006⁹¹ different health claims can be made. According to the evidence presented in this review following health claims can be made:

1. Diet-related cancer

Intake of propolis can reduce the risk for the immergence of cancer

2. Gut health, digestion and immunity

Intake of propolis can improve gut health, digestion and immunity

APPLICATION FORMS, INTAKE, AND DOSAGE

Application forms

Tinctures

The most widely used form as 10 or 20 % tinctures in 70 to 100 % ethanol. The percentage of the propolis tinctures is calculated according to the amount of propolis used. However the actual concentration of the propolis components is only half of that as the alcohol soluble resin is about 50 % of the total propolis.

An intake of 3 times 20 drops of 20 % tincture a day corresponds to about 1 g tincture (from a standard 30 ml eye drop bottle) or about 200 mg of propolis per day, far from the maximum of 1400 mg per day. Children: half dose.

Propolis in honey

In many countries propolis is mixed to honey at about 1 g/100 g ratio. 10 g of honey (one full tea spoon) corresponds to about 100 mg of propolis. An intake of 3 spoons per day is often recommended, corresponding to a total of 300 mg propolis. Children: half dose

Tablets

Tablet contain generally about 50 mg of propolis, 3 to 6 pills per day are recommended, in total 300 mg of propolis, children: half dose.

It is necessary to supply information on the labels of propolis skin and cosmetic products about possible allergy reactions in risk individuals. Ingestion of propolis products is without problems.

LEGAL STATUS OF PROPOLIS: FOOD SUPPLEMENT OR MEDICINE

In most countries of the world the propolis use is not regulated. In some countries, e.g. Austria, France, Spain, Japan, Taiwan, Korea, USA and Brasil propolis is considered as food supplement, together as the bee products bee pollen and royal jelly. In others like Switzerland and Germany it is considered a medicine. Due to its natural variation and varying properties propolis its application in medicine is problematic. It should be rather considered a food supplement with functional properties.

Propolis forms for internal application



Tincture



Propolis in honey



Propolis pills



The health enhancing properties of propolis have much in common with the original function of propolis as a “defendant of the hive”. It is used to defend human health against microbes and to enhance human immunity against microbial intruders and disease.

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