

## *Characteristics and uses of propolis\**

**Keywords:** polyphenolic compounds, diabetes, medicinal food, estimated glomerular filtration rate (eGFR), DPPH, ABTS, ORAC, FRAP, CUPRAC, Folin-Ciocalteu methods, gallic acid equivalent, catechin equivalent

### 1. SUMMARY

Propolis (bee glue) is an extremely valuable “byproduct” of beekeeping. Its ingredients include many bioactive substances that have a beneficial effect on the human body, which is why propolis has been used by mankind for thousands of years, mainly for medicinal and occasionally cosmetic purposes. Many medicinal and cosmetic products are still produced from the substance today. Its composition varies considerably depending on the geographical location and the health of the producing bees. Its most important components are polyphenolic compounds (phenolic acids, flavonoids, flavonoid esters, diterpenes, sesquiterpenes), lignans, aromatic aldehydes, alcohols, amino acids, fatty acids, organic acids, hydrocarbons, vitamins and minerals. Propolis can be considered a medicinal food. Extracts made from it possess antibacterial, antiviral and antifungal effects. Propolis, in limited quantities, is also suitable for human consumption. The safe dose of propolis for healthy people is 70 mg/day.

With our manuscript, we intend to provide a brief review of the literature on the beneficial effects of propolis on human health.

*\* Current European legislation food information shall not attribute to any food the property of preventing, treating or curing a human disease, nor refer to such properties. Results on the effects of propolis on human health are published as scientific information. The Editor.*

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## 2. Introduction

Bees have been around for 125 million years, and their evolutionary success has allowed them to become a perennial species that can utilize virtually every habitat on Earth. This ability to survive is largely due to the chemical composition and application of the special products they produce (honey, beeswax, venom, propolis, pollen and royal jelly). Propolis, the bees' remedy against pathogenic microorganisms, has been used by mankind as a medicine since ancient times [1].

Propolis, known in Hungarian as bee glue, is a sticky, resinous substance, produced by bees (*Apis mellifera* L.) from beeswax, saliva and sap from the bark, buds and leaves of trees [2, 3]. They collect mainly from poplar, but also from birch, willow, horse chestnut, pine, oak, elm and alder [4]. The composition of propolis is mostly made up of plant resins, waxes, essential oils and pollen. In addition to these, it also contains smaller amounts of other substances, such as compounds partially produced by bees [2].

Bees use propolis in the hive many ways, including for disinfection, construction and maintenance of the hive, and for protection [2, 4, 5, 6], as well as to keep the humidity and temperature in the hive stable throughout the year, to seal holes and cracks and the inner wall of the hive. Propolis is also an important element of the so-called social immune system of honeybees, which, thanks to its antipathogenic (antimicrobial) properties, provides a certain general protection to the entire bee family against infections and parasites [8, 9].

## 2. Characteristics of propolis

The physical and chemical components of propolis, its quality and the possibilities of using it for physiological and medicinal purposes depend on the origin of the propolis, i.e., the climate, the botanical source and the species of the bees [4, 10]. The color of the product also depends on the origin, it is usually brown, but at the same time all the shades from yellow to black appear in it, in many cases with a reddish or greenish hue. The smell of propolis is aromatic, with notes of honey, resin, wax and vanilla mixed in it. Its taste is very characteristic [4].

Raw propolis typically consists of 50% plant resin, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% of other organic matter. More than 300 components have been identified in propolis, which differ depending on the source [9].

The compounds found in propolis include polyphenolic compounds (phenolic acids, flavonoids and their esters, e.g., caffeic acid phenyl ester), diterpenes, sesquiterpenes, lignans, aromatic aldehydes, alcohols, amino acids, fatty acids, organic acids, hydrocarbons, vitamins and minerals [9, 11].

The main bioactive components of propolis are flavonoids, which greatly contribute to the pharmacological effects of propolis. The amount of flavonoids is used as a criterion when evaluating the quality of temperate climate propolis. Flavonoids have a wide spectrum of biological properties, such as antibacterial, antiviral and anti-inflammatory effects [9].

Although volatile substances make up only 10% of the components of propolis, they are responsible for the characteristic resinous smell and contribute of the beneficial effects of propolis on health. Volatile substances are dominated by terpenoids, which play an important role in distinguishing good quality propolis from poor quality or counterfeit propolis, and also exhibit antioxidant, antimicrobial and other biological effects [9].

Although different bee species prefer different plants, even the chemical profile of propolis produced by the same species is not always the same. The composition of propolis varies by bee colony, location and season, and this makes it difficult to study it and make consistent health claims [12]. The protective properties of the bioactive substances found in propolis can also provide significant benefits in maintaining human health [5].

In recent years, several studies have confirmed that different propolis samples can be completely different in terms of chemical composition and biological activity [1, 7].

### 3. Propolis-containing products

A significant number of propolis-containing products are available on the market: medical and over-the-counter preparations, foods and drinks that help maintain health [7].

Propolis tincture is an extract of raw propolis made with a solvent (most often a mixture of water and ethanol). According to our knowledge, there are practical and application questions related to propolis tincture that should be answered and uniform regulations should be applied:

- Various preparation recipes are known;
- Soaking raw propolis for different lengths of time results in different tinctures;
- Differences in the extraction solvent (different amount and ethanol concentration) affect the composition of the preparations;
- The relationship between raw propolis and the composition of the tincture is not known.

In addition to tinctures, other propolis-containing foods are also available, such as lozenges, propolis honey, capsules filled with propolis extract [3].

In some countries, standardized propolis products with a constant bioactive substance concentration are already available [13].

### 4. Dose and safety

Clinical studies on mice and humans report that propolis and its constituents are generally well tolerated and non-toxic, except when used in very large amounts [5].

Determining the exact dose of propolis, on the basis of the studied population, the dosage regimen, *compliance* (accurate taking of the substance) and the purity of the product, faces significant difficulties, since the phenolic compounds found in propolis vary according to geographical origin, the bioactivity can also differ significantly, which makes it difficult to determine the correct dosage [14]. According to a particular study, based on previous animal experiments and applying a margin of safety, the safe dose of propolis for healthy humans is 70 mg/day [15].

### 5. Physiological and therapeutic effects of propolis

Propolis has received increasing attention in recent years due to its beneficial effects on the human body. It is increasingly accepted as a preventive and therapeutic agent. However, the bioavailability of the useful substances found in propolis varies, which is also influenced by individual physiological conditions. According to a study, as a result of the consumption of propolis, its active ingredients can also be detected in the blood plasma [16].

#### 5.1. Fighting infections, the immune system

Propolis can be considered as a potential medicinal food (“nutraceuticals”). Propolis extracts have antibacterial, antiviral and antifungal effects [3]. The immunoprotective and antioxidant properties of propolis are explained by its bioactive phytochemical components, regardless of its origin. A 2019 review cited immune system support as a health benefit of propolis [5].

The effect of propolis supplementation has also been studied among patients infected with the COVID-19 virus. In a recent, high quality (double-blind, placebo-controlled) study conducted in 2020, the effect of propolis on clinical symptoms was investigated. Infection was confirmed with a PCR test in participants aged 18 to 75. Members of the intervention group (n=40) received tablets containing 300 mg of Iranian green propolis extract three times a day for 2 weeks, while the control group (n=40) received no such treatment. The main result of the study was that the clinical symptoms of the disease improved faster in the group receiving propolis in terms of the duration and severity of the initial symptoms [17].

#### 5.2. Cancerous diseases

Propolis has an antioxidant effect, which can be beneficial for the body in terms of neutralizing free radicals formed in excess [3], thus it can contribute to the regulation and control of inflammatory processes, tumor formation and aging processes. Its anti-inflammatory properties have been demonstrated in connection with propolis samples of Brazilian, Chinese and Malay origin. Its antitumor effect has been proven not only in *in vitro*, but also in *in vivo* experiments taking place in living organisms) [3].

According to the results of another research, Brazilian red propolis had antioxidant properties and significantly reduced the percentage of survival of human tumor cells under laboratory conditions [10]. Alcoholic extracts of Turkish propolis also exhibited an inhibitory effect on the growth of tumor cells against human tumor cells (liver, colon, breast, cervix, prostate) [18].

The study, the aim of which was to find out whether propolis and the polyphenolic/flavonoid compounds contained in it can have an inhibitory effect on the growth of human bladder tumors in a cell culture, ended with promising results. Based on this, propolis may be suitable for auxiliary treatment of the disease in addition to surgery, to reduce or prevent the chance of tumor recurrence [19].

### **5.3. Diabetes**

In relation to the effect of propolis on the human body, the reduction of blood sugar levels has also been studied [2]. According to the reliable, aggregated, comprehensive analysis of the results of several studies with similar objectives, the use of propolis reduced the fasting blood sugar level by 0.8 mmol/l compared to the subjects who did not receive treatment. In addition, taking propolis also reduced the value of HbA1c (A subunit of hemoglobin. The Ed.), which indicates the evolution of the blood sugar level of the examined person in retrospect over a period of 1 to 3 months. It is interesting to mention that the treatment did not affect the insulin level, so it follows that the drop in blood sugar level was not due to the effect of insulin. Almost 400 diabetic patients took part in the study, who were treated with 226 to 1,500 mg of propolis per day for 56 to 180 days. According to the authors, despite the positive results, further research is still needed regarding the type (composition) and dosage of propolis. This is so because the dose ranges were wide and the places of origin of the propolis samples used were varied [2]. In the studies related to propolis, it was stated that it is important to know the geographical and botanical origin, because they can affect the biological activity of the propolis, its effect and the composition of its organic components [3].

The objective of another study was to investigate the effect of Brazilian green propolis on type 2 diabetes patients through changes in blood test data. 80 people participated in the study, of which 39 received a placebo. The 41 people in the other group received 226.8 mg Brazilian green propolis per day during the 8-week period. The results indicate that Brazilian green propolis used in the aforementioned quantity and frequency can reduce then deterioration of uric acid levels and eGFR (estimated Glomerular Filtration Rate) values, which indicate kidney complications, in patients with type 2 diabetes [20].

In connection with the healing of diabetic leg ulcers, a favorable effect was reported in the study of Australian propolis samples. A favorable wound-healing role was also mentioned in connection with Chinese propolis extracts [3].

### **5.4. Cardiovascular diseases**

In a human study published in 2017, changes in blood lipid levels were investigated as a result of oral application of propolis solutions. In the double-blind, placebo-controlled clinical trial, 35 of the 67 subjects received propolis, while 32 were given a placebo supplement (without propolis). In the propolis group, a significant increase in HDL (High Density Lipoprotein) was observed after 90 days. This effect may contribute to the reduction of the risk of cardiovascular diseases [21].

A 2019 review paper mentions lowering blood pressure as one of the health benefits of propolis. In this literature review, a total of 63 publications were reviewed, the majority of which were reports on animal experiments, but some key human studies were also included. According to the results, propolis can be an effective antioxidant and anti-inflammatory agent. Based on this, it is presumably effective against various chronic diseases, e.g., in preserving the health of the cardiovascular system, reducing atherosclerosis and reducing high blood pressure [5].

### **5.5. The skin and the nervous system**

The components of propolis can be widely used to heal wounds and the human skin itself, and can also contribute to reducing the symptoms of some nervous system diseases (Alzheimer's disease, Parkinson's disease) [5].

In addition to research related to nervous system diseases, the protective effects of propolis on retinal cells have also been reported [22]. Propolis can also be used to prevent various eye diseases, such as macular degeneration in the aging population and myopia in the younger generation, but further studies are needed to prove this [5].

The range of commercially available propolis-containing skin care products is expanding, with creams and body lotions predominating. According to the advertisements, the majority of skin care products have a „soothing, moisture-rich, anti-aging” effect, and are also effective against eczema [23].

## **5.6. Alimentary canal**

When examining the beneficial properties of various propolis, in the case of Brazilian green propolis, the stimulation of the functioning of the intestinal system was mentioned, as well as its beneficial effect in the treatment of gastric ulcers, while the liver protective function of propolis was proven in animal experiments [3].

The polyphenols in propolis can support the development and maintenance of a healthy intestinal flora by limiting the growth of pathogenic bacteria and, in addition, prevent their adhesion to human intestinal cells [24]. The possible therapeutic effect of propolis on inflammatory bowel diseases is still being investigated today, but many experiments still need to be performed before clinical application can begin [5].

## **5.7. Allergizing effect**

In addition to its many beneficial physiological effects, propolis can also trigger allergic reactions (swelling, dermatitis, hives) in susceptible individuals. This is most common among beekeepers, but it also depends on individual sensitivity [3]. Therefore, it is recommended that the therapeutic use of propolis products is always carried out under medical supervision [5].

## **5.8. Summary of physiological and therapeutic effects**

Several studies have proven that the observed beneficial physiological effects are not the result of a single prominent compound, but rather the combined effect of the complex components of propolis [9].

Overall, it can be stated that as a natural substance with good medicinal properties, propolis and its components can be used in a wide range of ways, including wound and skin healing, and in the treatment of some neurological diseases and atherosclerosis. Interest in the health effects of propolis and the number of publications have been continuously increasing in the last 30 years. However, even more human clinical studies are needed to confirm the beneficial effect of propolis for specific population groups. Preclinical studies support the antioxidant and anti-inflammatory effect of propolis, which can prevent or slow the progression of various chronic diseases, including heart disease, diabetes, high blood pressure, tumors and neurodegenerative diseases (e.g., Alzheimer's disease) [5].

## **6. New areas of application of propolis**

One of the areas of use of propolis can be to improve the growth performance and productivity of farm animals. Based on our knowledge so far, it can be said that propolis has a beneficial effect on the normal laboratory values, growth and productivity of the animals included in the studies. In addition, it is considered as a possible alternative to antibiotics in the production of animal feed, because it has the advantage that it does not induce resistance in microorganisms [25].

Another area of intensive research in the last few years have been the application of propolis in food preservation. Food preservatives primarily include antimicrobial and antioxidant agents. Antimicrobial agents added to foods serve two purposes: to stop the natural spoilage of food and to avoid/control contamination by microorganisms, including pathogenic microorganisms. Antioxidants are used to extend shelf life and prevent spoilage. Propolis favorably combines antioxidant and antimicrobial properties. However, its large-scale use as a food preservative has not yet been realized, as this would require proper standardization of the product [7].

## **7. Antioxidant properties of propolis**

The antioxidant properties of propolis are mainly determined by the bioactive components found in it, primarily the phenolic compounds, depending on the botanical and geographical origin. The phenolic compound profile of propolis is slightly different from that of honey. While in the former, the profile is mainly determined by the botanical origin, and the dominant flavonoids are quercetin, myricetin, chrysin, apigenin, luteolin, pinocembrin and pinobanksin, and of phenolic acids, p-hydroxybenzoic acid, p-coumaric acid, cinnamic acid, gallic acid, ferulic acid and caffeic acid, in propolis, which typically comes from poplar and birch in Central Europe, chrysin, kaempferol, apigenin, pinocembrin and pinobanksin are the most characteristic and, in addition to phenolic acids, their esters (e.g., caffeic acid and ferulic acid esters) also occur. Among the latter, the phenylethyl ester of caffeic acid is outstanding in terms of tumor prevention properties (although its effect also depends on the synergistic effect of other accompanying phenolic compounds). The polyphenols in propolis have been proven to inhibit the formation of amino, oxide and peroxide type free radical, as well as the formation of complexes between free radicals and transition metals, and also lipid peroxidation [26].

In addition to the differences depending on the origin of propolis, the literature is not uniform regarding the extraction method of the antioxidant compounds, and the differences can significantly influence the extraction results.

Based on the available data, extraction was mainly carried out with different mixtures of ethanol and water in the experiments, but extraction with methanol and other solvent also occurs. Regarding the methods for determining the antioxidant properties, only the results of experiments based on *in vitro* spectrophotometry have been reported, including the determination of radical scavenging properties (DPPH – 2,2-diphenyl-1-picrylhydrazyl, ABTS – 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ORAC (Oxygen Radical Absorbance Capacity), as well as total polyphenol content (Folin-Ciocalteu method) and total flavonoid content. Although in the case of propolis extracts from different locations, polyphenol contents of the same order of magnitude as in the case of honey were measured (typically in the 18-500 mg gallic acid equivalent/ml range), in the case of a Turkish sample there was also a value above 19,000 mg gallic acid equivalent/ml, and values above 1,000 mg gallic acid equivalent/ml were also measured for Brazilian samples. The situation is similar with regard to the total flavonoid content, where the majority of the samples stayed in the range typical of honey (1-25 mg catechin equivalent/ml), however, there were also extremely high values: nearly 5,000 mg catechin equivalent/ml in the case of an Algerian propolis, and a value over 29,000 mg catechin equivalent/ml in the case of a Turkish propolis. As for the radical scavenging ability, once again, values in the range of honey are reported by researchers (e.g., 50-80% inhibition in the case of DPPH radicals), but extreme values are also typical here (e.g., 90.7–99.34% inhibition in the case of a Malay honey). Similar to honey, numerous studies have confirmed in the case of propolis its effectiveness in the case of tests carried out on various animal and human bodily fluids and cell cultures, in terms of antioxidation properties.

### 8. Synergistic interaction of propolis and honey

Propolises of different origins can show a synergistic interaction not only with each other, but also when mixed with honey. Following the mixing of propolis extracts from Iraq, it was possible to prove a synergistic effect against various pathogens (*E. coli*, *S. aureus*, *C. albicans*) in microbiological tests. Similarly, in animal experiments, the extent of the wound healing effect (reepithelization) was increased in the case of a propolis mixture [27].

Due to the deterioration of sensory characteristics, propolis is typically mixed with honey in a proportion of no more than 1%. Even at this concentration, a four- to fivefold increase in the amount of phenolic compounds, phenolic acids and flavonoids was measured, and the anthocyanin and carotenoid content of the mixture also increased several times. Of the flavonoids, especially the amount of galangin, chrysin, pinocembrin and pinobanksin, while of phenolic acids, the amount of ferulic acid, caffeic acid and p-coumaric acid increased. The radical scavenging (ABTS, DPPH) and metal ion reducing capacity (FRAP – Ferric Reducing Antioxidant Power, CUPRAC – Cupric Reducing Antioxidant Capacity), measured by various *in vitro* methods, also showed multiple increases [26].

The synergistic interaction of propolis and honey was also confirmed in antimicrobial tests. In the research, in the case of antibiotic-resistant strains of *E. coli*, *S. aureus* and *C. albicans*, honey strengthened the effect of propolis both in cultures of individual strains and their mixtures [29].

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### 9. References

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