



# Bee Products and Oxidative Stress: Bioavailability of Their Functional Constituents



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## Introduction

Many times, what we live, what we eat is reflected in our health. Natural foods or natural nutritive supplements must have an important place in human diet. Talking about natural products, implicitly we think in bee products. Main hive products are honey, bee collected pollen, propolis, royal jelly, wax and bee venom. These products have different roles in bee colony and in human health.

For men, honey, royal jelly and bee pollen are foods that may improve the health through their functional properties. Propolis and bee venom are used for their therapeutic properties. All bee products have a high bioavailability due to their chemical composition (simple sugars, minerals, vitamins, enzymes, amino acids etc.). Honey is the most important bee product, both quantitatively and economically. Is also the first bee product used by man since ancient times. History of using honey goes in parallel with human history and it can be found in any culture of the world proofs of using honey as food or simbol in religious and therapeutic ceremonias Alvarez-Suarez et al. [1].

Honey is exclusively produced by the bees and "honey denomination can't be given to any similar product, in the manufacture of which bees do not participate exclusively" [2]. Chemical composition of honey is mainly gucidic (approximately 70%) and water (20%), the rest being a large variety of importnt substances, such as: enzymes, minerals, organic acids, phenolic acids and flavonoids and different substances [3], Mărghitaș et al.[4].

The bioactive compounds in nectar depend on numerous factors, such as botanical origin, climatic conditions and

geographic distribution. Honey also depend on these factors, as bees collect nectar as main source for honey producing. For a better knowledge of honey properties, one must know its botanical origin. Depending on the raw material from which bees produce honey, we can distinguish: nectar honey and honeydew honey. Floral honey comes from the nectar of several plants, and if one is predominant we have monofloral honey, and if a mixture of pollen and nectar is present, without the net dominance of a particular plant, we have multifloral honey. Honeydew honey is produced by the bees from the sweet secretions which they collect from other parts of plants, resulting from the digestions of plant seva sucked by aphides. The chemical composition of these types of honey is quite different, depending on their origin. As a rule, lighter honey has a "simpler" composition, with nutrients and biologically active compounds being present in a lesser amount, whereas darker honey has a more complex nutritional and biological composition, being more valuable from this point of view.

Propolis came from the greek "pro" and "polis", meaning before the citadel. The Greeks called it so, noticing how bees build their bee hives and concluding that this substance plays the role of shield against external aggressors, propolis making the hive a true fortress.

Propolis has been used since antiquity in ancient Egypt, where medicine was practiced by priests, who also monopolized the chemistry or practice of mummifying corpses. The fact that propolis was also known in ancient Greece is demonstrated by its name [5].

Chemical composition of propolis consists of various vegetable resins and balms, essential oils, micro and macroelements, flavonoids, as well as secretions of bees and wax. The chemical composition of propolis varies depending on the predominant plant species from which the bee has collected the resins. Propolis in Romania has as predominant sources poplar buds, beech, pine, fir, plum, willow, elm, oak, chestnut, ash and alder, but probably the bees may visit other species to harvest this precious material. Floral pollen is defined as the male sexual cell of the plant, being present on the stamens of the flower. The bees take this powder in the harvesting process, mix it with nectar and its own secretions, forming the well-known colored grains that we can see on their early spring feet until late autumn when they return to the hive.

Bee uses pollen to prepare bee bread, the lipid and protein part of their food. Floral pollen, due to the chemical composition rich in proteins, carbohydrates, lipids, vitamins, mineral salts and amino acids, to which bees add a mixture of nectar and honey or enzymes, forms the pollen we know and consume [6], Mărghitaş et al. [7]. Pollen sugars are glucose, fructose and sucrose, as well as starch and cellulose. Pollen is very rich in B vitamins and vitamin C, mineral elements (Zn, Ca, Mg, K, Na), or carotenoids, which give colors from yellow, orange and reddish or purple anthocyanins to some types pollen deArruda et al. [8]. An important part of pollen's chemical composition are omega 3 and omega 6 unsaturated fatty acids Yang et al. [9].

Because the bee do not consume raw pollen, knowing that the floral pollen exin is very resistant and the compounds within this cell are harder to assimilate, the pollen is brought into the hive and stored in the honeycomb cells for controlled fermentation, producing beebread. Beebread is a lactofermented pollen, which is the main protein source for the bee family. The chemical composition of beebread does not differ greatly from the pollen from which it originates, but all the chemical components of the pollen become easily assimilable, thus providing the protein source for the bee family.

The miracle that the bee secretes to feed the young larvae (until the 3rd day of life) and the queen throughout her life is called Royal Jelly. Indeed, it is a royal substance because it contains all the components needed for queen survival more than 3 years of life. The water content in the royal jelly is very high (60-70%), and the dry substance consists of carbohydrates, proteins, amino acids and fats. Small amounts of minerals and vitamins are also present. Proteins and peptides are the main ingredients with free amino acids belonging to the L series (mainly proline and lysine). Fatty acids are the most significant fraction of the lipid class, followed by neutral lipids, sterols or hydrocarbons.

Organic acids generally have 8 or 10 carbon atoms, most notably 10-hydroxy-2-decenoic acid, which is of particular importance in determining the authenticity of royal jelly. This compound has a high antibacterial activity [10]. Sugars from royal jelly are fructose, glucose in higher amounts and low

concentrations of sucrose, maltose, trehalose, ribose and erlose Barnutiu et al. [11]. Vitamins present in royal jelly are niacin, pantothenic acid, pyridoxine, thiamine, riboflavin, folic acid and biotin. Royal jelly contains significant amounts of potassium, calcium and magnesium.

The only substance the bees possess to defend itself from anyone or anything trying to attack them, is the venom. The needle and the venom bag are the bees' defense apparatus. Research to date has shown that bee venom has a complex chemical composition, consisting of both organic and inorganic substances, which gave it specific properties. The bee venom contains proteins, peptides, enzymes, phospholipids, biogenic amines, sugars, mineral salts, ethereal oils and other volatile substances [12]. The most important protein fraction of the venom is melitin, being considered the most active component of venom. It can increase capillary permeability, increasing blood circulation and lowering blood pressure.

Another well-represented fractions are phospholipase A and hyaluronidase. These are allergenic components, the first being the strongest allergen in the venom. The third protein fraction of crude venom is represented by aphamine and histamine. In the venom composition, a number of free amino acids, nucleic acids, lipids, volatile acids have also been identified. Bioavailability and Therapeutical properties of bee products- their relation with oxidative stress.

Oxidative stress is not a symptom, a condition, or a syndrome, as is sometimes said, but is a biochemical and physiological process in which the response is often inadequate. Endogenous oxidative stress and free radicals produced by the human body are compatible with life, but due to free radicals that enter the body with food, drugs, generally the conditions of modern life, antioxidant internal mechanisms are often overcome. This is why antioxidants are needed to fight against free radicals that can cause various diseases, leading to the disruption of normal metabolism.

What does antioxidant activity really mean? In the human body, unstable oxygen molecules, or free radicals, can create a state of chaos in the living system. Free radicals, also called Oxygen Reactive Species (ROS), are caused by some leaks of normal metabolism caused by toxins present in the environment, tobacco, aging or other destructive mechanisms. The life span of a free radical in the body is very short (by order of the millionths of seconds). But they can use their biochemical force to stabilize themselves. This can be extremely destructive for molecules that become donors, turning themselves into free radicals by losing these electrons. Examples of free radicals are H<sub>2</sub>O<sub>2</sub> (hydrogen peroxide), CO (carbon monoxide), O (singlet oxygen), O<sub>2</sub><sup>-</sup> (superoxide) and OH (hydroxyl). What can be seen above is that all molecules contain oxygen. These molecules are chemically unstable, and they need antioxidants to turn them into stable molecules.

Antioxidants present in the human body, existing or introduced through food, are fortunately able to neutralize these reactive species before they cause great damage. They eventually interact with other complex antioxidant networks to redo to keep the chain from being interrupted. Due to the fact that researchers have been interested in studying the different classes of nutrients in natural products that have beneficial qualitative effects on living systems, in other words, nutrients that help the human body to optimize its normal functions and promote a state general health, in the following we will try to answer some of the questions that appear implicitly. In recent decades, we are witness to an alarming increase in chronic or degenerative diseases such as diabetes, hypertension, cancer or arteriosclerosis. Recent research reveals the implication of the role of oxidative stress in the pathogenesis and/or complications of these conditions [13].

Honey is a very good source of natural antioxidants, which greatly reduce the risk of heart disease, helps restore immunity, treats gastrointestinal diseases, has an effect on asthma, speeds up healing in various infected wounds or surgical or skin ulcers [14]. It is known that some of these diseases are a consequence of oxidative stress, and it seems that part of the therapeutic properties of honey is due to its antioxidant capacity. In addition, the presence in the honey composition of hydrogen peroxide or various minerals can lead to the generation of highly reactive hydroxyl radicals as part of the antibacterial system Molan et al. [15]. but their formation mechanisms must be able to control both the formation and removal of these reactive oxygen species in honey.

In addition to the above-mentioned molecules, the antioxidant activity of honey is also given by the content and type of polyphenolic compounds [4], Dezmirean et al. [16]. The *in vitro* antioxidant capacity of honey and other bee products can be measured in the form of antiradical activity using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, by measuring oxygen absorption capacity (ORAC method) and antioxidant power by FRAP method Erejuwa et al. [17]. Using these tests, honey samples from different countries of the world have been tested for their antioxidant properties. Pine honey produced by *Marchalina hellenica* has shown high activity by the DPPH method Akbulut et al. [18]. Some types of honey in Saudi Arabia or Peru have demonstrated similar antioxidant activity [19,20]. Honey coming from Australia or Malaysia has demonstrated antiradical and antioxidant activity [21]. Honey from United States van der Berg et al. [22], Croatian oak honey Jerkovic et al. [2010], honey from Spain and Portugal [3, 23], Cuban, Venezuelan and Ecuadorian honey [1,24,10] demonstrated a particularly high antioxidant activity *in vitro*. Different honeys from Romania have been analyzed in terms of antioxidant capacity *in vitro*, and a classification of these types of honey can be made according to this property [4,25,26]. Thus, honeydew honey, multifloral honey, heather honey, raspberry honey, thyme or lime honey are excellent sources of natural antioxidant compounds.

Literature data revealed that honey, as well as other antioxidant agents, mediates the oxidative stress relief in tissues such as the gastrointestinal tract, liver, kidney, pancreas, plasma or erythrocytes, due to its composition chemical. Bee pollen, as mentioned earlier, is not only a calorie-providing nutrient to be consumed just as a fuel, but is a complete and complex supplement that has both nutritional and also therapeutic value.

Most antioxidants found in food are bioflavonoids. Studying the chemical composition of pollen, one can notice that there are appreciable amounts of bioflavonoids, which implicitly make antioxidant pollen activity high. In addition to antioxidant activity, these compounds present in pollen, increase capillary resistance or have beneficial effects on the liver. What does this mean for the human diet? It is important to reach a diet that provides a good balance between all kinds of nutrients. Due to the large spectrum of existing nutrients that bee pollen can provide, it can be an excellent supplement for a balanced diet. Pollen may be the supplement to fill some "gaps" in the nutritional profile when not eating the 5 daily fruit and vegetable meals. Because of this, pollen is a valuable addition, as it brings not only antioxidants, bioflavonoids and polyphenols that can be lost in food, but also a significant amount of vitamins, enzymes and lactoferment.

In complementary medicine, many of the protocols, if not all, require the diet to be both cleansing and detoxifying. This is done by removing processed foods such as refined white bread and pasta, fermented cheese and super-processed dairy products. They can be replaced with high quality whole foods such as fruits, vegetables and pollen. In particular, pollen is an essential component of a high-quality food program because it is a source of nutrients of excellent quality. This means that, fundamentally, diet must be the platform on which optimal health is built, not the obstacle that prevents it from happening. We can talk about optimal health when the body can effectively maintain its own defense and healing resources. This is possible when the body is nutritionally fortified and consolidated in a way that allows the immune system to react, defend and fight, rather than being hindered by a poor and restrictive diet.

Modern science has focused more on propolis after 1960, when the general interest in natural compounds began to appear. In these 50 years since the propolis was studied in detail, its antibacterial, antifungal, antiviral, cytotoxic, antioxidant, antiinflammatory or immunomodulatory properties have been highlighted [27,28,17].

The chemical composition of propolis is crucial to understanding its biological activity. In the temperate areas, the main source of bees' resin for the production of propolis is *Populus nigra*, the main compounds of this type of propolis are also found in the vegetable source: flavonoid aglycons and substituted cinnamic acid and caffeic acid esters. Besides, volatile compounds in propolis have great biological significance and action. Propolis is often used in modern medicine, in various medical formulas to treat skin diseases such as shingles,

various burns, frostbite, acne, eczema and dermatitis, lower limb ulcers or other skin diseases. These would be just some of the external uses of propolis. Besides, the effects of propolis or various formulas in which it is incorporated, are very important for the treatment of various internal conditions. The use of aerosols with propolis is indicated for the treatment of asthma or inflammation of respiratory tract. Gastric and duodenal ulcers are improved with oral propolis treatments, as well as chronic gastritis, enteritis, hyperlipidemia and constipation [29].

The most studied and known activity of propolis is antimicrobial. Propolis has been extensively studied, demonstrating antibacterial, antiviral or antifungal activity [27,30]. The anti-inflammatory activity of alcoholic propolis extracts is well known and studied, as well as that against the *Helicobacter pylori* bacteria, which causes most gastric ulcers [31,32].

All these propolis activities are very important, but the most promising action is the anticancer activity. Modern techniques for chemical composition determination lead to identifying a compound called artemisin C (3,5-diphenyl-4-hydroxycinnamic acid) from Brazilian propolis [33]. This compound was applied to human and murine cancer cells in vitro and in vivo, cytotoxic effects being observed, the growth of cancer cells being clearly inhibited. Other studies on various adenomas have shown that after administration of propolis or artemisin C, they have not progressed into carcinomas. Instead of growing in large cancer cells, the macrophages proliferated and local antioxidant activity was observed after these treatments.

Other propolis-isolated compounds: propoline A and propoline B Chia-Nana et al. [34]. produce apoptosis in human melanoma cells and significantly inhibit xanthine oxidase activity. The same authors isolated a third compound, propoline C, which, following the experiments, showed that it was able to release cytochrome C from the mitochondria into the cytosol. This compound has demonstrated antioxidant activity, with the potential to neutralize free radicals and inhibit xanthine oxidase activity. Caffeic acid phenethyl ester (CAPE), another highly studied compound, after its highlighting in propolis, is today well known for its action on cancer cell DNA, inhibiting the proliferation process (angiogenesis, tumor invasion and metastasis) [35-39].

In conclusion, one can state that propolis is one of the few natural remedies that has maintained its popularity over time. Its pharmacologically active molecules are flavonoids, phenolic acids and their esters, as well as volatile compounds. Propolis has shown that it has an effect on blood pressure or cholesterol levels. Of course, clinical trials must continue to strengthen the claims so far, but until then doctors have to weigh the benefits of propolis as an adjunct in the cancer drug treatment of patients.

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