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Apitherapy – the medical use of bee products

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Abstract

Introduction: Bee products have been used by man for centuries. However, their therapeutic options are not fully understood.

Aim of the study: To review research on the possibilities of using the medicinal properties of bee products.

Material and method: Standard criteria were used to review literature data. Search for articles in the PubMed database was carried out using the following keywords: apitherapy, honey, bee venom, propolis, royal jelly, bee pollen.

Description: Apitherapy is a healing method known to mankind since the oldest times. Due to the diverse composition, substances produced by bees show a number of activities, which include Antioxidant, immunomodulatory, antibacterial and anticancer effect. Thanks to numerous mechanisms, they have a beneficial effect on wound healing, cardiovascular diseases and metabolic disorders.

Summary: Numerous properties and a wide range of activity of each bee product brings the possibility of using them in the therapy of many diseases.

Keywords: bee venom; propolis; royal jelly

1. INTRODUCTION

From the beginning, people have been using the goods that nature gives them. For centuries, we have developed, as a species, the skill of breeding animals and benefiting from the care of them. One of the species whose breeding we managed to master is the honey bee (Apis mellifera). In a form similar to the current one, bees appeared on the earth about 100 million years ago. The area of their occurrence covers all continents except Antarctica. Because of this, the lives of humans and bees have been inseparably connected. In the opinion of many people, the quote, "when bees disappear from the face of the earth, then man will have no more than four years to live," Albert Einstein was to say, but there is no clear evidence. However it is true, that if the honey bee were to die out, humanity would most likely be annihilated. 78% of plant species in a moderate climate zone are pollinated by a honey bee, which contributes to creation of about 1/3 of the food produced. The global population of bees is between 80 and 100 million breeding hives, of which each contains between 10,000 and 60,000 individuals. However, it is increasingly emphasized that their population is decreasing [1, 2]. The number of threats to honey bee is increasing all over the world, which is becoming more and more susceptible to diseases and pathogens [1]. Bees are thought to be threatened by: bacteria, viruses, parasites, pesticides used in agriculture, environmental changes, or genetically modified organisms (GMOs), although sufficient evidence has not yet been found [2]. Also, increasing environmental pollution contributes to the extinction of bee families, which in the future will translate into low yields [1].

Bee products, which include honey, bee glue (called propolis), bee pollen, royal jelly and bee venom have been used by man for centuries not only as food products - honey, royal jelly, but also as natural medical substances [3].

Apitherapy - this is the therapeutic use of bee products is a branch of alternative medicine, folk medicine, which uses their natural healing qualities. It originates in the areas of present-day Russia or ancient China [4]. However, its foundations can already be found in ancient Egypt or Greece, where bee products were used as cosmetics and preparations to facilitate wound healing [3, 5]. It should be emphasized that the use of honey or royal jelly will not cure a patient with e.g. diabetes, but the substances they contain are anti-diabetic and their consumption may contribute to improving the glycemic profile. The medical use of honey included treatment of wounds, insect bites, burns, skin diseases and ulcers. Scientific research confirms its ability to heal wounds and effectiveness as a material with antibacterial properties [6]. Propolis, otherwise bee putty, is a product of proven medical value. Its ingredients support the treatment of cardiovascular, allergic and rheumatic diseases and are

also used to treat furunculus and pressure sores. [7]. Royal jelly and its contained substances inhibit the growth of bacteria, including bacteria responsible for severe nosocomial infections, such as P. aeruginosa and MRSA [8]. In addition to antibacterial properties, substances contained in royal jelly have a beneficial metabolic effect on the human body through their anti-diabetic, cholesterol-lowering, and antioxidant effects, which supports the cardiovascular system and contributes to reducing cardiovascular risk [9]. In natural medicine, bee venom has been attributed properties that reduce the severity of rheumatoid arthritis symptoms. This theory is confirmed by today's scientific research [10]. On the other hand, bee pollen are a valuable dietary supplement with proven biological properties such as antioxidant, antibacterial, antifungal, anti-inflammatory and hepatoprotective effects [11]. Further detailed considerations on the composition and properties of individual bee products will be made in the following chapters of this article.

2. HONEY

Honey is one of the products produced by bees and obtained by man for hundreds of years. For centuries it has been used as a sweetener and because of its medical qualities it has been used as a medicinal product. This is one of the products next to royal jelly and propolis, classified as functional foods, i.e. foods that have a beneficial effect on the physiological and psychological condition of the body [12]. The composition of honey varies and depends on many factors such as: vegetation from which nectar or honeydew is obtained, pollen source, geographical region, climate, as well as atmospheric conditions, processing and storage method [13]. It consists of many different substances, the largest of which are sugars. In addition, it is rich in compounds that affect its properties including water, proteins (enzymes - glucose oxidase and catalase), organic acids (aspartic, butyric, citric, acetic, formic, fumaric, galacturonic, gluconic, glutamic, glutaric, glyoxylic acid), vitamins (especially vitamin B6, thiamine, niacin, riboflavin and pantothenic acid), minerals (including calcium, copper, iron, magnesium, manganese, phosphorus, potassium, sodium and zinc), phenolic acids and flavonoids, carotenoids, α -tocopherol and ascorbic acid with antioxidant properties [14-17].

The main sugars in honey are fructose (38%) and glucose (31%) [18]. In addition to them, we can also find sucrose, maltose, turanose, isomaltose, maltulose, trehalose, nigerose, cojibiosis, maltotriose and melezitosis [20]. Their presence in honey determines its energy value, granulation, hygroscopicity and viscosity, are also responsible for the crystallization of honey [19]. During storage, the percentage composition of sugars can change while having the effect of changing the color and taste of honey.

Honey made from nectar is rich in phenolic, which include: p-coumaric acid, eugenol, ferulic acid, caffeic acid and flavonoids, such as pinobanksin, pinocembrin, chrysin, quercetin, apigenin, naringin [21]. Their percentage content in honey varies depending on the species of plant from which nectar is obtained. These are compounds that have antioxidant effects, acting by eliminating free radicals and inhibiting lipid oxidation [22]. Their ability to have anti-inflammatory, antibacterial, antiviral and cardioprotective effects has also been described [23-27]. Anti-inflammatory potential consists in inhibiting the enzyme cyclooxygenase, which is most strongly associated with the inflammatory process. Flavonoids also affect lipoxygenase by inhibiting it, as well as an inhibitor of the release of arachidonic acid, which is necessary in the inflammatory process [28, 29]. Quercetin and routine - these are substances with anti-viral activity against HSV, syncytial virus, polio and Sindbis virus. This mechanism is based on the inhibition of viral polymerase and the binding of nucleic acids or capsid protein [30].

The honey's antibacterial properties are the result of the complexity of its composition and its specific physical and physicochemical properties, which include: high osmotic pressure due to the presence of sugars, which limits the growth and multiplication of bacteria and consequently, the possibility of biofilm formation [31]. Also, lysozyme contained in honey has an antibacterial effect increased by joint action with ascorbic acid and hydrogen

peroxide [32, 33]. Honey is also characterized by other factors such as: low protein content, high carbon to nitrogen ratio, low redox potential, high viscosity limiting oxygen solubility, which prevents bacterial growth [34]. The antibacterial activity of phenolic compounds is also mentioned. This mechanism is to be based on inhibition of bacterial RNA polymerase or degradation of the bacterial cytoplasmic membrane leading to loss of K + ions and as a consequence cell autolysis [35, 36]. Antibacterial activity is also based on antioxidant activity caused by methylglyoxal and hydrogen peroxide present in honey [37, 38]. In addition, it is used in the treatment of skin wounds and damage to cause leukocyte influx to damaged tissues, fibroblast stimulation and angiogenesis [39, 40]. Another advantage of antimicrobial action is the low honey pH causing unfavorable conditions for bacterial growth, which promotes the healing process [41]. Defensins found in honey disrupt the integrity of the bacterial cell membrane, thereby increasing its permeability, and thus susceptibility to damage [42].

Recent studies have also shown an anti-cancer effect of honey, which causes apoptosis in many types of cancer cells through, among others mitochondrial membrane depolarization [43, 44]. Honey increases caspase 3 activation and cleavage of poly (ADPribose) polymerase (PARP) in human colon cancer cell lines, which is to be responsible for the high phenol content [45]. A significant influence of honey on the prevention of initiation and promotion of the cancer process has been suggested [46]. It is suspected that the compounds contained in it may cause cell cycle arrest, tonization of oxidative stress and immunomodulation. Honey, by stimulating the immune system, triggered by the activation of macrophages, B and T lymphocytes and strong antiproliferative activity, in which apoptotic pathways dependent on caspase 9 are involved, can have beneficial effects such as inhibition of tumor cell proliferation, reduction of tumor size, improvement of survival, as well as alleviating the side effects of chemotherapy, which was demonstrated in a study in mice [47]. In addition, researchers report that honey prevents cell proliferation, induces apoptosis, modifies the cell cycle in several types of cancer: cervical cancer cells, endometrial cancer, liver cancer, kidney cancer, colorectal cancer and prostate cancer and melanoma [48].

Antioxidants present in honey, such as flavonoids, polyphenols, and vitamin C can lead to reduced risk of cardiovascular disease. The protective effect of flavonoids is due to their anticoagulant, vasodilating and antioxidant effects [49]. There is also scientific evidence for the antidiabetic effect of honey [50]. Its beneficial effect in diabetes may be manifested by improving the profile of metabolic disorders associated with diabetes, such as elevated levels of liver transaminases, triglycerides and HbA1c, as well as reduced levels of HDL cholesterol [51, 52]. A study in rats showed that the co-administration of antidiabetic drugs (metformin and glibenclamide) and honey lowers glucose to a greater extent than the use of the drugs alone and long-term administration of honey improves glycemia, lipid profile and prevents obesity occurring in patients [53].

Honey is also a substance known for centuries for use in gastrointestinal disorders. The Roman doctor Celsus was already using honey as a medicine for diarrhea. Sources from Eastern Europe and from Arab countries say that it was used to treat and prevent gastrointestinal ailments such as peptic ulcers, gastroenteritis. Phenolic compounds found in honey are also attributed to anti-ulcer activity, but the mechanism of this action remains unresolved. It is suspected that these substances increase the amount of antioxidant prostaglandins and also protects the stomach. There are reports of the inhibitory effect of honey on the development of H. pyroli, the main causative agent of stomach ulcers [54].

3. BEE VENOM

Bee venom also called apitoxin is produced in bee venom glands serving as a defensive element. Its properties have been known to humanity since ancient times. Venom production begins after two or three days of adult bee life and with age decreases. It is a transparent liquid that can also turn yellow, odorless, but has a sharp, bitter taste. This is a

water-soluble substance, while it is insoluble in alcohol and ammonium sulfate. The venom's pH ranges 4.5-5.5 and its specific weight is 1.13. It dries quickly in contact with air, forming a yellow-brown powder [55, 56].

From all the substances in venom, the largest percentage is water, the amount of which is 88%. In addition to water, its main components are peptides such as melittin, apamin, mast cell deregulating (MCD) peptide, promelittinoraz the enzymes hyaluronidase and phospholipase A2. Other substances included in apitoxin are low-molecular compounds such as histamine, sinkaline, glycerol, noradrenaline, amino acids, carbohydrates, phospholipids, physiologically active amines and volatile compounds. All of the abovementioned substances are responsible for the properties and activity of apitoxin. The diversity of these compounds means that bee venom has the largest range of biological activities among all bee products [56, 57]. One of the main peptides (52% of all apitoxin peptides) contained in bee venom is melitin, which has numerous potential therapeutic properties and relatively low toxicity. It has a strong anti-inflammatory effect by inhibiting phospholipase enzymatic activity and increases cortisol production in the body by stimulating the pituitary gland to produce ACTH [58]. The possibility of its use is also seen in the therapy of HIV infection - it destroys the infectivity of the virus particle. However, its use is limited because of its toxic effect on cell membranes. This problem was solved by using nanoparticles that react only with virus components [59]. Melitin also has antioxidant potential by inhibiting the production of hydrogen peroxide by neutrophils. Along with other substances contained in bee venom, it is antibacterial, particularly strong against Gram-positive bacteria [60, 61].

Research on the mechanism and inhibitory effects of bee venom and melitin on melanoma cells by Lim et al. showed that these substances strongly inhibited the proliferation, migration, invasion of cancer cells and melanin production, as well as increased the activity of the apoptotic pathway dependent on caspases 3 and 9, showing role of melitin as a potential compound used in the treatment of melanoma [62].

Bee venom has long been used as a natural remedy for rheumatoid arthritis. Its healing effect has been quite well understood - components of bee venom inhibit the chronic inflammatory response which rheumatoid arthritis based on. Venom components, among others adolapin are inhibitors of pro-inflammatory substances such as: Tumor Necrosis Factor TNF-2, Prostaglandin E2 PGE-2, enzymes like Cyclooxygenase-2 COX-2 and many other cytokines. In a study by Kocyigit et al. it was shown that administration of honey bee venom to rats suffering from rheumatoid arthritis causes an increase in IFN- γ and a decrease in the level of proinflammatory factors, thus causing a therapeutic effect [63].

Among the peptides included in bee venom we can also find apamine, which blocks K + channels activated by Ca2 + ions. Apamine has a neuroprotective effect, which may have a positive impact on the functioning of the nervous system in Parkinson's disease [64]. In addition, calcium-induced blockade of potassium channels induced by apamine may result in neuronal stimulation, enhance synaptic plasticity and induce long-term potential of the hippocampal area, which may be used in the treatment of Alzheimer's disease [65]. In studies conducted on mice suffering from experimental autoimmune encephalomyelitis EAE, which is the model most similar to human myelodegenerative diseases such as multiple sclerosis MS, administration of bee venom had a beneficial effect stimulating the immune system. Both in vitro and in vivo studies in EAE mice have increased the population of CD4 (+), CD25 (+), Foxp3 (+) T cells, which may result in a reduction of the inflammatory response and make bee venom a potential agent therapeutic [66].

Other uses of apitoxin include skin diseases such as psoriasis, dermatitis, boils, and eye diseases - iritis or optic neuritis. In the treatment of skin diseases, bee venom is used as ointments and creams, while in ophthalmology it is a component of drops. Bee venom is also used as subcutaneous injections [67].

4. PROPOLIS

Propolis is a non-toxic, resinous substance produced by bees from their plant secretions. It consists of resin constituting about 50%, wax (30%), essential oils (10%), pollen (5%) and other organic compounds (5%). The collected resin can come from many species of different plants, it is mixed with saliva and transformed by the bee enzymes it contains to form an adhesive-like substance. By bees, it is used to seal hives, fill cracks, and also helps maintain the temperature in the hive. Due to their properties, bees also use it as an antiseptic, protecting them against microbial diseases. The chemical composition of propolis depends on the geographical region and the time of its collection, therefore the amount and type of compounds contained in it may be subject to high variability. Over 300 substances included in its composition have been identified. Among the basic elements we distinguish phenolic compounds, esters, about 12 different flavonoids, terpenes, beta-steroids, aromatic aldehydes, alcohols and ketones. In addition, we can also find vitamins B1, B2, B6, C and E and minerals (Mg, Ca, K, Na, Cu, Zn, Mn, Fe, Ni, Co, V) in it. Additionally, it contains several enzymes - amber dehydrogenase, glucose-6-phosphatase and acid phosphatases [68, 69, 70].

Due to such a diverse composition, propolis is assigned numerous properties. Król et al. demonstrated its antioxidant activity, for which mainly are responsible flavonoids, capable of scavenging free radicals. In this way, it prevents the development of cardiovascular diseases, diabetes, cancer and neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease. In addition, they are capable of inhibiting certain enzymes and causing actions that resemble the activity of some hormones and neurotransmitters. It has also been found that some flavonoids contained in propolis, such as pinocembrin, have beneficial effects in improving cognitive impairment resulting from hypoperfusion brain damage [71, 72].

Mirzoeva and Calder in a study on mice showed that flavonoids contained in propolis also have anti-inflammatory effects resulting from a decrease in the production of leukotrienes and prostaglandins caused by inhibition of cyclooxygenases and lipoxygenase. This effect is also enhanced by reducing the activity of myeloperoxidase, ornithine decarboxylase, protein tyrosine kinase and NADPH-oxidase. Propolis also delays the expression of the induced nitric oxide synthase gene and blocks TNF- α release. It is also of great importance in the process of wound healing, in which, in addition to its antiinflammatory and antibacterial activity, also uses the antioxidant effect that increases the amount of collagen produced. The presence of many vitamins, minerals and flavonoids in propolis also has a beneficial effect on wound healing, by accelerating some enzymatic reactions, cell metabolism and improving blood circulation [73-75].

Propolis also has an antibacterial effect. Grange and Davey have shown its activity against S. aureus, S. epidermidis, Enterococcus spp. Corynebacterium spp. B. catarrahlis and B. cereus. Koo et al. Also found its inhibitory activity against S. mutans, S. sanguis and A. naeslundaii [76]. It causes an inhibitory effect on bacterial cell division, protein synthesis, and destroys the bacterial wall and cytoplasm, thereby causing bacterial death [77]. A study by Sforcin also showed anti-fungal activity of propolis. Pinocembrin has been found to inhibit the development of mycelium and disrupt the metabolism and function of membranes, thus causing developmental disorders in the fungus Penicillium italicum [78]. In addition, researchers have also proved the antifungal effectiveness of propolis in contact with yeast, fungi of the genus Trichophyton and Fusarium and other fungi causing skin infections [79].

Propolis components such as caffeic acid ethyl ester also have anti-cancer effects. A study by Salomão et al. showed the ability of propolis to inhibit the synthesis of cancer cell DNA, activate apoptosis and regulate leukocyte function. Researchers also proved that by inhibiting matrix metalloproteinases and inhibiting angiogenesis, propolis is able to inhibit tumor growth and its transmission between body tissues. Flavonoids found in propolis also have anti-tumor activity, which are able to inhibit the division of cancer cells. According to Martinotti and Ranzato, they have an effect on inhibiting the development of breast cancer,

lung cancer, oral cancer as well as cancer of the esophagus, stomach, colon, prostate and skin cancer. Due to the selective toxicity to cancer cells and the low toxicity of propolis to normal cells of the body, Chinese researchers point to its potential role in the treatment of breast cancer [80,81].

5. ROYAL JELLY (RJ)

Royal jelly is a yellowish-white, creamy liquid with a sour taste secreted by the glands of worker bees, used to feed larvae and the queen mother. It consists of numerous organic and inorganic substances with known medical properties. Among these substances we find proteins, lipids, sugars, free amino acids, vitamins such as riboflavin, thiamin, niacin, folic acid, biotin and pyridoxine, smaller amounts of vitamins C, D, A and E as well as elements calcium, sodium, potassium, copper, iron , zinc and manganese. Royal jelly is a cosmetic known to people for centuries. It stops the skin aging process thanks to its strengthening, regenerating and rejuvenating properties. Numerous studies have been carried out to assess the biological properties [82].

One of the main activities that royal jelly has is antibacterial activity. The first research on this issue appeared as early as in the 1940s McCleskey and Melampy. Among the substances that make up royal jelly, several have been identified that showed such properties. These are: royalactin, royalisina, 10-hydroxy-2-decenoic acid (10H-2DEA), Trans-2-decenoic acid (2DEA), royal jelly peptides (RJPS), 24-methylenecholesterol (24MET). Its antibacterial potential has been the subject of numerous scientific studies. Fujiwara et al. studied pure RJ and isolated and purified royalisin. At that time, extensive royalisin activity against Grampositive bacteria with negligible activity against Gram-negative bacteria was demonstrated. However, in relation to whole royal jelly, sensitivity to its effects was revealed, both for Gram-positive and Gram-negative bacteria. This difference was due to the presence of other active substances in full RJ, such as 10-hydroxy-2-decenoic acid, which inhibits, among others: Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus MS, Staphylococcus aureus MR, Escherichia coli [8]. Another of the substances contained in RJ royalactin in vitro studies is active against numerous Gram-positive and Gram-negative bacteria and additionally two independent research teams have shown its antifungal activity. The antifungal activity of royal jelly components includes such species of pathogenic fungi as Aspergillus fumigants, Aspergillus niger, Candida albicans, and Syncephalastrum racemosum [83].

A study in rats treated with cisplatin showed that ingested RJ increases the individual body's natural enzyme-reducing, i.e. superoxide dismutase, catalase and glutathione peroxidase. Watanabe et al., demonstrated in their research the ability of royal jelly to capture free radicals such as superoxide and hydroxyl radicals [85]. The authors of these studies see the possibility of using RJ and its components in preventing the undesirable effects of anti-cancer treatment through protective effects on organs such as kidneys and liver, as well as a positive effect on protective enzymes produced there, glutathione reductase, glutathione peroxidase, superoxide dismutase and reduction of genotoxic production malonic aldehyde [86].

There have also been reports of anti-cancer effects of royal jelly ingredients shown in a mouse and human study [87, 88]. Researchers show the inhibitory effect of RJ on the proliferation of human breast cancer cells induced by bisphenol A and vascular endothelial growth factor (VEGF) as one of the proangiogenic proteins - an inducer of cancer neovascularization [89].

There is also scientific evidence for the anti-diabetic effects of royal jelly. It has been shown that 8 weeks of 1g RJ administration to patients with type 2 diabetes reduces fasting glucose and increases serum insulin. A similar effect was observed in healthy volunteers [90, 91].

A lot of other activities are attributed to royal jelly. In their works, Fujii et al. point to its anti-inflammatory and immunomodulatory effects. The body's lipid-lowering properties have also been studied. They have proven the effect of reducing cholesterol and total lipid levels in blood serum in patients with atherosclerosis. In addition, RJ may act as a cholesterol-lowering agent and thus reduce the risk of cardiovascular disease. Research carried out by Tokunage also shows the hypotensive activity of substances contained in royal jelly [92].

6. BEE POLLEN

Bee pollen is another product of bees and available on the market as a natural supplement with valuable medicinal properties. For example, bee pollen is a product widely used and recommended in many disease states in clinical management in the People's Republic of China, while in Germany it is officially recognized as a medicine [93]. Bee pollen is produced as a result of lactic fermentation of pollen collected by bees, which is then mixed with salivary gland secretion and nectar or honey, tightly stuffed in the cells of the patch to ferment there without air at around 30 degrees Celsius, which protects it from deterioration [94]. Among the substances forming it we find: proteins and amino acids (10-40%); carbohydrates (13-55%) mainly are fructose and glucose; fats (1-20%) such as saturated and unsaturated fatty acids, phospholipids, phytosterols; polyphenols constituting about 1.6% of flavonoids, leukotrienes, catechins and phenolic acids; vitamins: C, A, E, B1, B2, B6, nicotinic acid, pantothenic acid, folic acid, biotin, routine; micro- and macroelements: K, Mg, Ca, Na, Cu, Zn, Cr, Mn, Mo, Kb, Si, Se, Fe; oleanic acid, b-ursolic acid, betulin [94]. As a bioactive substance, bee pollen is attributed to a number of therapeutic activities: antibacterial, antiviral, antifungal, anti-inflammatory, immunostimulatory, hepatoprotective, anti-cancer, it is also supposed to act as an antioxidant [11].

The antioxidant potential of bee pollen results from the substances it contains carotenoids, flavonoids, vitamins A and E. Flavonoids such as quercetin, caffeic acid, caffeic acid phenethyl ester (CAPE), rutin, pinocembrin, apigenin, chrysin, galangin, kaempferol and isorhamnetin contained in bee pollen are able to remove free radicals, reactive oxygen species, and inactivation of electrophiles, thus protecting against their mutagenic effects [95]. Flavonoids also have anti-inflammatory properties, inhibiting the metabolism of arachidonic acid and additionally have a positive effect on the cells of the immune system: macrophages, NK, T, B lymphocytes, and granulocytes, which are the body's natural defenses [96]. Fatrcová-Šramková et al. conducted a study in which it showed that an ethanolic extract of pollen collected from specific flower species showed antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Klebsiella sp. and Pseudomonas aeruginosa [97]. Another of the biological activities is the hepatoprotective effect that has been shown in animal studies. Pollen extract reduced the activity of enzymes such as alanine, aspartate transaminase, acid phosphatase and bilirubin pathologically elevated as a result of poisoning with organic substances or drugs [11]. Pollen is recommended in acute and chronic liver inflammation, in liver diseases as well as in its toxic and traumatic injury [97].

In addition, a number of other bee pollen properties were detected. The total lipid and triacylglycerol lowering effect was demonstrated in a study in rats and rabbits and in addition the level of hormones responsible for the body's metabolism correlated with the decrease in lipid concentration [11]. Bee pollen used in patients with hyperlipidemia and atherosclerosis of arteries not responding to fenofibratum, reduced lipid and cholesterol levels by 20 to 30 percent [96]. The presence of unsaturated fatty acids, phospholipids and phytosterols means that bee pollen also has hypoglycemic properties, as well as reducing the aggregation ability of platelets and increasing fibrinolytic activity. Adding these actions are antiatherogenic and preventive in relation to heart disease and stroke. Recent studies also point to the antiallergic effect of bee pollen, it protects mast cells against degranulation by preventing the release of histamine one of the main substances responsible for allergic reactions. Histamine release by anti-IgE antibodies contained in the serum, was inhibited by bee pollen up to 62%.

7. CONCLUSIONS

This review provides information indicating a wide range of therapeutic properties of bee products. Numerous substances found in products coming from the hive, through various mechanisms, have a beneficial effect on the human body. This suggests their possible use in many medical specialties.

A significant role is attributed to honey and its ingredients, which when taken by man exert many desirable effects, strengthening his health and preventing the occurrence of many diseases. An important substance produced by bees is also venom, which, despite its toxic effects, also has a positive effect on the functioning of the body, which can inhibit the development of joint diseases. Propolis, royal jelly and bee pollen can also be used in medicine due to their properties. However, more research is needed on the composition of bee products, because the mechanism of their action has not yet been fully understood.

References:

- 1. Oleksa A., Burczyk J., Markery DNA w hodowli zachowawczej rodzimych linii pszczoły miodnej. Wiad Zoot 2010, XLVIII (1), 55–67.
- Komunikat Komisji do Parlamentu Europejskiego i Rady: W sprawie zdrowia pszczół miodnych. Komisja Europejska. Bruksela, dn. 06.12.2010. online [21.07.2012]. Dostępne na:

http://ec.europa.eu/food/animal/liveanimals/bees/docs/honeybee_health_communicati on_pl.pdf

- Grassberger M., Biotherapy History, principles and practice: a practical guide to the diagnosis and treatment of disease using living organisms. Dordrecht: Springer, 2013. ISBN 978-94-007-6585-6.
- Ong i wsp., WHO global atlas of traditional, complementary and alternative medicine. Japan: World Health Organization, Centre for Health Development, 2005. ISBN 978-92-4-156286-7.
- 5. Wilcox Ch., Venomous: how earth's deadliest creatures mastered biochemistry, First edition, New York, ISBN 978-0-374-28337-7.
- 6. Molan P., The evidence supporting the use of honey as a wound dressing, The International Journal of Lower Extremity Wounds, vol. 5, no. 1, 2006, 40–54.
- 7. Vijay D., Propolis: A Wonder Bees Product and Its Pharmacological Potentials, "Advances in Pharmacological Sciences", 2013, DOI: 10.1155/2013/308249.
- 8. Garcia M., Finola M., Marioli J., Bioassay directed identification of Royal Jelly's active compounds against the growth of bacteria capable of infecting cutaneous wounds. Adv. Microbiol. 3, 2013, 138–144.
- 9. Chiu HF, Chen BK, Lu YY et al. Hypocholesterolemic efficacy of royal jelly in healthy mild hypercholesterolemic adults. PharmBiol, 2017, 55: 497–502.
- 10. Kocyigit A, Guler E, Kaleli S, Anti-inflammatory and antioxidative properties of honey bee venom on Freund's Complete Adjuvant-induced arthritis model in rats. Toxicon, 2019; 161: 4-11.
- 11. Denisow B, Denisow-Pietrzyk M. Biological and therapeutic properties of bee pollen: a review. Journal of the Science of Food and Agriculture. 96 (13): 4303–4309.
- 12. Viuda-Martos M, Ruiz-Navajas Y, Fernández-López J, Pérez-Álvarez J. Functional properties of honey, propolis, and royal jelly. J. Food Sci. 2008, 73, R117–R124.
- Escuredo O, Dobre I, Fernández-González M, Seijo M. Contribution of botanical origin and sugar composition of honeys on the crystallization phenomenon. Food Chemistry, 2014; 149: 84–90

- 14. Ferreres F, Garciaviguera C, Tomaslorente F, et al. Hesperetin C a marker of the floral origin of citrus honey. J Sci Food Agric 1993; 61:121–3.
- Alqarni A, Owayss A, Mahmoud A. Mineral content and physical properties of local and imported honeys in Saudi Arabia. Journal of Saudi Chemical Society, 2012; 5: 618–625.
- 16. Ciulu M, Solinas S, Floris I, et al. RPHPLC determination of water-soluble vitamins in honey. Talanta, 2011; 83: 924–929.
- 17. Pontes M, Marques J, Câmara J. Screening of volatile composition from Portuguese multifloral honeys using headspace solid-phase microextraction-gas chromatography–quadrupole mass spectrometry. Talanta, 2007; 74: 91–103.
- Gheldof N, Wang XH, Engeseth NJ. Identification and quantification of antioxidant components of honeys from various floral sources. J Agric Food Chem. 2002; 50:5870–5877.
- 19. Kamal M, Klein P. Determination of sugars in honey by liquid chromatography. Saudi Journal of Biological Sciences. 2011; 18: 17–21.
- 20. Fuente E, Ruiz-Matute A, Valencia-Barrera R, et al. Carbohydrate composition of Spanish unifloral honeys. Food Chemistry. 2011; 129, 1483–1489.
- 21. Rybak-Chmielewska H. Changes in the carbohydrate composition of honey undergoing during storage. Journal of Apicultural Science. 2007; 51: 39–48.
- 22. F. Ferreres F, Tomás-Barberán C, Soler C, et al. A simple extractive technique for honey flavonoid HPLC analysis. Apidologie 1994; 25: 21-30.
- 23. Alvarez-Suarez J, Giampieri F, González-Paramás A, et al. Phenolics from monofloral honeys protect human erythrocyte membranes against oxidative damage. Food and Chemical Toxicology. 2012; 50: 1508–1516.
- 24. Kerem Z, Chetrit D, Shoseyov O, Regev-Shoshani G. Protection of lipids from oxidation by epicatechin, trans-resveratrol, and gallic and caffeic acids in intestinal model systems. J Agric Food Chem. 2006; 54(26):10288–10293.
- 25. Huang WZ, Dai XJ, Liu YQ, et al. Studies on antibacterial activity of flavonoids and diarylheptanoids from Alpinia katsumadai. J Plant Resour Environ. 2006; 15(1):37–40
- Evers DL, Chao CF, Wang X, et al. Human cytomegalovirus-inhibitory flavonoids: studies on antiviral activity and mechanism of action. Antiviral Res. 2005; 68(3):124– 34.
- 27. Moon S, Cho G, Jung S, et al. Quercetin exerts multiple inhibitory effects on vascular smooth muscle cells: role of ERK1/2, cell-cycle regulation, and matrix metalloproteinase-9. Biochem Biophys Res Commun. 2003; 301:1069–1078.
- Rossi A, Ligresti A, Longo R, et al. The inhibitory effect of propolis and caffeic acid phenethyl ester on cyclooxygenase activity in J774 macrophages. Phytomedicine. 2002; 9(6):530–5.
- 29. Raso GM, Meli R, Carlo G, et al. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. Life Sci. 2001; 68(8):921–31.
- 30. Selway J, Plant flavonoids in biology and medicine: biochemical, pharmacological and structure activity relationships. 1986. New York: Alan R. Liss, Inc. p 75–125.
- 31. Molan P. The antibacterial properties of honey. Bee World. 1992; 73: 59-76.
- 32. Bogdanov S. Nature and origin of the antibacterial substances in honey. LWT Food Sci Technol. 1997; 30: 748–753.
- 33. Al-Waili N, Salom K, Butler G, Al Ghamdi A. Honey and microbial infections: a review supporting the use of honey for microbial control. J Med Food 2011; 14(10): 1079-1096.
- Patton T, Barrett J, Brennan J, Moran N. Use of a spectrophotometric bioassay for determination of microbial sensitivity to manuka honey. J Microbiol Methods. 2006; 64: 84–95.

- 35. Takaisi N, Scjoncjer H. Electron microscopy and microcalorimetric investigations of the possible mechanism of the antibacterial action of a defined propole provenance. Planta Med. 1994; 60: 222–227.
- Cushnie T, Lamb A. Detection of galangin-induced cytoplasmic membrane damage in Staphylococcus aureus by measuring potassium loss. J Ethnopharmacol. 2005; 101: 243–248.
- 37. Atrott J, Henle T. Methylglyoxal in Manuka honey Correlation with antibacterial properties, Czech J. Food Sci. 2009; 27: 163-165.
- 38. Al Somall N, Coley K, Molan P, Hancock B. Susceptibility of Helicobacter Pylori to the antibacterial activity of manuka honey. J. Royal Soc. Med. 1994; 87: 9-12.
- 39. Rossiter K, Cooper A, Voegeli D, Lwaleed B. Honey promotes angiogenic activity in the rat aortic ring assay. J Wound Care. 2010; 19(10): 440-446.
- 40. Sell S, Wolfe P, Spence A, et al. A preliminary study on the potential of manuka honey and platelet-rich plasma in wound healing. Int J Biomater. 2012; 2012:313781.
- 41. Molan P. Re-introducing honey in the management of wounds and ulcers theory and practice. Ostomy Wound Manage. 2002; 48(11): 28-40.
- 42. McDermott A. Defensins and other antimicrobial peptides at the ocular surface. Ocul Surf. 2004; 2(4): 229-247.
- 43. Nicholson D. From bench to clinic with apoptosis-based therapeutic agents. Nature. 2000; 407: 810–816.
- 44. Earnshaw W. Nuclear changes in apoptosis. Curr Opin Cell Biol. 1995; 7: 337–343.
- 45. Fauzi A, Norazmi M, Yaacob N. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. Food Chem Toxicol. 2011; 49: 871–878.
- 46. Kuppusamy P, Yusoff M, Maniam G, et al. Nutraceuticals as potential therapy for colon cancer: a review. Acta Pharm. 2014; 4: 173-181.
- 47. Fernandez-Cabezudo M, El-Kharrag R, Torab F, et al. Intravenous Administration of Manuka Honey Inhibits Tumor Growth and Improves Host Survival When Used in Combination with Chemotherapy in a Melanoma Mouse Model, PLoS One 8 (2013)
- 48. Samarghandian S, Farkhondeh T, Samini F. Honey and health: a review of recent clinical research. Pharmacogn. Res. 2017; 9: 121–127.
- 49. Khalil M, Sulaiman S. The potential role of honey and its polyphenols in preventing heart diseases: A review. Afr J Tradit Complement Altern Med. 2010; 7: 315–321.
- 50. Erejuwa O. Effect of honey in diabetes mellitus: Matters arising. J Diabetes Metab Disord. 2014; 13: 23.
- 51. Erejuwa O, Sulaiman S, Wahab M, et al. Hepatoprotective effect of tualang honey supplementation in streptozotocin-induced diabetic rats. Int J Appl Res Nat Prod. 2011; 4: 37-41.
- 52. Chepulis L, Starkey N. The long-term effects of feeding honey compared with sucrose and a sugar-free diet on weight gain, lipid profiles, and DEXA measurements in rats. J Food Sci. 2008; 73: 1–7.
- 53. Abdulrhman M, El-Hefnawy M, Aly R, et al. Metabolic effects of honey in type 1 diabetes mellitus: a randomized crossover pilot study. J Med Food. 2013; 16: 66–72.
- 54. Bogdanov S, Jurendic T, Sieber R, Gallmann P. Honey for nutrition and health: A review. J. Am. Coll. Nutr. 2008; 27: 677–689.
- 55. Tomas-Lorente F, Garciagrau MM, Nieto J, Tomas-Barberan F. Flavonoids from Cistus-Ladanifer bee pollen. Phytochemistry. 1992; 31: 2027–2029.
- 56. Ishikawa Y, Tokura T, Nakano N, et al. Inhibitory effect of honeybee-collected pollen on mast cell degranulation in vivo and in vitro. Journal of Medicinal Food. 2008; vol. 11, no. 1: 14–20.
- 57. Hundstad S, Gjersoe J, Venoms: Sources, toxicity and therapeutic uses. Nova Science Publishers, 2010.

- 58. Saini S, Peterson J, Chopra A, "Melittin binds to secretary phospholipase A2 and inhibits its enzymatic activity". Biochemical and Biophysical Research Communication. 1997; 238: 436- 442.
- 59. Hood J, Jallouk A, Ratner L, Wickline S. Cytolytic nanoparticles attenuate HIV-1 infectivity. Antiviral Therapy 2013; 18: 95-103.
- 60. Fennell F, Shipman W, Cole L. Antibacterial action of melittin, a polypeptide from bee venom. Proc. Soc. Exp. Biol. Med. 1968; 127(3): 707-710.
- 61. Mihelich E, Schevitz R. "Structure-based design of a new class of anti-inflammatory drugs: secretory phospholipase A(2) inhibitors, SPI". Biochim. Biophys. Acta . 1999; 1441: 223-228.
- 62. Lim H, Baek S, Jung H. Bee Venom and Its Peptide Component Melittin Suppress Growth and Migration of Melanoma Cells via Inhibition of PI3K/AKT/mTOR and MAPK Pathways. Molecules. 2019; 24(5): 929
- 63. Kocyigit A, Guler E, Kaleli S. Anti-inflammatory and antioxidative properties of honey bee venom on Freund's Complete Adjuvant-induced arthritis model in rats. Toxicon. 2019; 161: 4-11
- 64. Kim J, Yang E, Lee M, ET AL. Bee Venom Reduces Neuroinflammation in the MPTP-Induced Model of Parkinson's Disease. International Journal of Neuroscience 2011; 121(4): 209-217.
- 65. Romero-Curiel A, Lopez-Carpinteyro D, Gamboa C, et al. Apamin induces plastic changes in hippocampal neurons in senile Sprague–Dawley rats. Synapse 2011 DOI: 10.1002/syn.20938
- 66. Lee G, Lee H, Park S, et al. Venom Attenuates Experimental Autoimmune Encephalomyelitis Through Direct Effets on Cd4(+)Cd25(+)Foxp3(+) T Cells. European Journal of Inflammation 2013; 11(1): 111-121.
- 67. Bogdanov S. Bee Venom: Composition, Health Medicine: A Review. Bee Product Science. 2014; 1-20.
- 68. Gómez-Caravaca A, Gómez-Romero M, Arráez-Román D, et al. Advances in the analysis of phenolic compounds in products derived from bees. Journal of Pharmaceutical and Biomedical Analysis. 2006; 41(4): 1220–1234.
- 69. Silva B, Rosalen P, Cury J, et al. Chemical composition and botanical origin of red propolis, a new type of brazilian propolis. Evid Based Complement Alternat Med. 2008; 5(3): 313-316.
- 70. Bankova V, De Castro S, Marcucci M. Propolis: recent advances in chemistry and plant origin. Apidologie. 2000; 31: 3–15
- 71. Lotfy M. Biological activity of bee propolis in health and disease. Asian Pacific Journal of Cancer Prevention. 2006; 7(1): 22–31.
- 72. Havsteen B. The biochemistry and medical significance of the flavonoids. Pharmacol Ther. 2002; 96: 67-202.
- 73. Ramos A, Miranda J. Propolis: a review of its anti-inflammatory and healing actions. J. Venomous Anim. Toxins Incl. Trop. Dis. 2007; 13: 697–710.
- 74. Mirzoeva O, Calder P. The effect of propolis and its components on eicosanoid production during the inflammatory response. Prostaglandins Leukot Essent Fatty Acids. 1996; 55: 441-449.
- 75. Król W, Bankova V, Sforcin J, et al. Propolis: properties, application, and its potential. Evidence-Based Complement. Alternat. Med. 2013
- 76. Grange J, Davey R. Anti-Bacterial Properties of Propolis. Journal of the Royal Society of Medicine. 1990; Vol. 83, No. 3, 159-160.
- 77. Lotfy M. Biological activity of bee propolis in health and disease. Asian Pac. J. Cancer Prev. 2006; 7: 22–31.
- 78. Sforcin J, Biological properties and therapeutic applications of propolis. Phytother. Res. 2016; 30: 894–905.

- 79. Fokt H, Pereira A, Ferreira A, et al. How do bees prevent hive infections? The antimicrobial properties of propolis. Curr. Res. Technol. Educ. Top. Appl. Microbiol. Microbial. Biotechnol. 2010; 1: 481–493.
- 80. Salomão K, De Souza E, Henriques-Pons A, Barbosa S, et al. Brazilian green propolis: effects in vitro and in vivo on Trypanosoma cruzi. Evidence-Based Complement. Alternat. Med. 2011
- 81. Martinotti S, Ranzato E. Propolis: a new frontier for wound healing? Burns Trauma 2015; 3: 9.
- 82. Ramadan M, Al-Ghamdi A. Bioactive compounds and health promotingproperties of Royal Jelly: a review. J. Funct. Foods. 2012; 4: 39–52.
- 83. Fratini F, Cilia G, Mancini S, Felicioli A. Royal Jelly: An ancient remedy with remarkable antibacterial properties. Microbiol. Res. 2016; 192: 130–141.
- 84. Silici S, Ekmekcioglu O, Eraslan G, Demirtas A. Antioxidative effect of royal jelly in cisplatin-induced testes damage. Urology. 2009; 74: 545–551.
- 85. Watanabe S, Suemaru K, Takechi K, et al. Oral mucosal adhesive films containing royal jelly accelerate recovery from 5-fluorouracil–induced oralmucositis. J Pharmacol Sci. 2013; 121: 110–118.
- 86. Karadeniz A, Simsek N, Karakus E, et al. Royal jelly modulates oxidative stress and apoptosis in liver and kidneys of rats treated with cisplatin. Oxid Med Cell Longev. 2011; 2011:981793.
- 87. Kimura Y. Antitumor and antimetastatic actions of various natural products. Stud Nat Prod Chem. 2008; 34: 35–76.
- 88. Shirzad M, Kordyazdi R, Shahinfard N, Nikokar M. Does royal jelly affect tumor cells. JHerbMedPharmacol. 2013; 2: 45–48.
- Nakaya M, Sasaki K, Yukiyoshi A, et al. Effect of royal jelly on bisphenol A-induced proliferation of human breast cancer cells. Biosci Biotechnol Biochem. 2007; 71: 253– 255.
- 90. Pourmoradian S, Mahdavi R, Mobasseri M, et al. Effects of royal jelly supplementation glycemic control and oxidative stress factors in type 2 diabetic female: a randomized clinical trial. Chin J Integr Med. 2014; 20: 347–352.
- 91. Münstedt K, Bargello M, Hauenschild A. Royal jelly reduces the serum glucose levels in healthy subjects. J Med Food. 2009; 12: 1170–1172.
- 92. Khazaei M, Ansarian A, Ghanbari E. New findings on biological actions and clinical applications of royal jelly: A review. J. Diet. Suppl. 2018; 15: 757–775.
- 93. Bogdanov S. Pollen: Production, Nutrition and Health: A Review. Bee Product Science. 2014; Available: http://www.bee-hexagon.net/ [10 September 2015].
- 94. Bartosiuk E, Borawska M. Skład chemiczny i właściwości antybakteryjne oraz przeciwnowotworowe pierzgi. Pszczelarz. 2014; 5.
- 95. Pascoal A, Rodrigues S, Teixeira A, et al. Biological activities of commercial bee pollens: antimicrobial, antimutagenic, antioxidant and anti-inflammatory. Food Chem Toxicol. 2014; 63: 233–239.
- 96. Polanski M, Okoń M, Przybyło R, Frasik W. Cardioprotective properties of hydrophilic pollen extract (HPE). Polish Journal of Pathology. 1998; vol. 49, no. 2: 109–112.
- 97. Pascoal A, Rodrigues S, Teixeira A. Biological activities of commercial bee pollens: antimicrobial, antimutagenic, antioxidant and anti-inflammatory," Food and Chemical Toxicology, 2014; vol. 63: 233–239.