Antiviral properties of the bee products: a review

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INTRODUCTION

Bees produce six different products, each of them having a specific origin and unique properties. While honey is world renown for its healing properties, the other products are much less known to the public. You can read my reviews on the health promoting properties of all bee products properties on this website.

In the times of the Covid-19 corona virus pandemy there is a wide need for natural antivirals. Most people have heard of the healing effects of honey in times of colds and flu. But the bees offer far more. It is the purpose of this review to show the scientific and clinical evidence of the antiviral activity of all bee products.

There are two types of antiviral effects: direct and indirect. The direct comes from the direct interaction of the product with the virus during its action. The indirect ones fight viruses by increasing the immunity of the host. The immunity of the host can be increased directly by stimulating its defence, or indirectly, e.g. by stimulating the growth of gut bacteria, which on their side, increase the immune response of the host.

In this review the immuno-activating properties and the antiviral effects of the bee products will be discussed.

HONEY

Honey, the main bee product, is the energy source of bees.

Honey bees gather their honey from two sources: nectar and honeydew. There are no official statistics as to the relative importance of these two honey sources. In some European countries like Greece, Switzerland, Turkey, Slovenia and Austria honeydew seems to be at least as important as nectar.

For a long time in human history it was an important carbohydrate source and the only largely available sweetener until industrial sugar production began to replace it after 1800. At present the annual world honey production is about 1.2 million tons, which is less than 1% of the total sugar production.

It is the main natural food-sweetener with many with biological and functional properties, used in medicine, mainly as a wound dressing[14, 15, 17]

Composition and biologically active components

Besides its main components, sugars, honey has many other components[17] especially phenolics. 56 to 500 mg/kg total polyphenols were found in different honey types, depending on the honey type [2, 35]. Polyphenols in honey are mainly flavonoids (e.g. quercetin, luteolin, kaempferol, apigenin, chrysin, galangin), phenolic acids and phenolic acid derivatives [91]. The flavonoid content can vary between 2 and 46 mg/kg of honey and was higher in samples produced during dry season with high temperatures [43]. The polyphenols are responsible for the antioxidant and also antimicrobial and immuno-activating, and other properties of honey. The main antimicrobial activity is towards bacteria, and to a smaller extent to funghi, parasites and viruses.

Antiviral activity

Honey was reported to inhibit in vitro the *Rubella* virus [105] and *Herpes* virus[5, 37]. Both clover and manuca honey had the same antiviral activity against Varicella Zoster Virus (Shingles)[80]

P. sativum, N. sativa, Z. multiflora and Z. mauritiana honeys from Iran have anti- HIV-1 activity as tested by PCR, due to methylglyoxal[12]

High inhibitory activity against the influenza virus of various sources was reported for Manuka honey[98] due to methylglyoxal[21]

Immuno-activating properties

The effect of honey on the antibody production against thymus-dependent antigen sheep red blood cells and thymus-independent antigen (*Escherichia coli*) in mice was studied [6]. According to this study oral honey stimulates antibody production during primary and secondary immune responses against thymus-dependent and thymus-independent antigens.

It has been reported that honey stimulates T-lymphocytes in cell culture to multiply, and activates neutrophils [1]

In a study with humans receiving a diet supplemented with a daily honey consumption for two weeks of 1.2 g/kg body weight ingestion of honey following effects were observed: Increase of serum iron by 20% and decrease of plasma ferritin by 11%, an 50 % increase of monocytes and slight increases of lymphocyte and eosinophil percentages, reduction in serum of immunoglobulin E (34%) aspartate transaminase (22%) and alanine transaminase (18%), lactic acid dehydrogenase (41%), fasting sugar (5%) and creatine kinase and finally an increase in blood of copper (33%) and slight elevations of zinc and magnesium, hemoglobin and packed cell volume [4]

Honey increase proliferation of B- and T-lymphocytes and neutrophils in vitro[1].

Nigerose, a sugar present in honey [26, 84], has immuno-protective activity[57].

In another study with rats, feeding of honey caused an increase of lymphocytes in comparison with the sucrose fed controls[24].

Apalbumine 1, the dominant royal jelly in honey with immuno-stimulating properties, is present in honey. It is present in unifloforal honeys in different quantities. The quantity of apalbumine decreases in the following order: Chestnut > dandelion > Rape, Linden, Acacia [13]

Indirect immuno-stmulating effects

Prebiotic and probiotic effects can induce indirect immuno-stimulating effects[31, 33]

Prebiotic effects

Important honey effects on human digestion have been linked to honey oligosaccharides. These honey constituents has a prebiotic effect, similar to that of fructooligosaccharides [77, 104]. The oligosaccharide panose was the most active oligosaccharide. These compounds exert the prebiotic effect in a synergistic mode of action, rather to one of individual components, leading to an increase of bifidobacteria and lactobacilli [94]. According to an in vitro study on five bifidobacteria strains honey has a growth promoting effect similar to that of fructose and glucose oligosaccharides[42]. Unifloral honeys of sour-wood, alfalfa and sage origin honey stimulated also the growth of five human intestinal bifidobacteria [83]. In another study honey increases both in vivo (small and large intestines of rats) and in vitro the building of *Lactobacillus acidophilus* and *Lactobacillus plantarum*, while sucrose failed to produce any effect[81].

Honey showed prebiotic activity towards 3 Lactobacillus species isolated from human faeces[90]

It is not clear whether all types of honey exibit prebiotic effects and whether some honeys have a stronger prebiotic effect. Sour-wood, alfalfa and sage[42] and also clover honey[42] have been shown to have prebiotic activity.

The prebiotic activity of chestnut honey was found to be higher than that of acacia honey[49].

Oligosaccharides from honeydew honey have prebiotic activity[77].

Theoretically honeydew honeys, containing more oligosaccharides should have a stronger prebiotic activity than blossom honeys. There is need of more research on prebiotic activity of unifloral honeys.

When added to yoghurt honey improves the viability of *Probiotic* bifidus[7] and *Lactobacillus* bacteria[9]

Honey was successfully used to improve the probiotic properties of the Indian yoghurt product lassi[82]

However the influence of the oligosaccharide content is questioned. Sage, alfalfa and sourwood honey, which vary in their oligosaccharide contents, were compared with sucrose, high fructose corn syrup and inulin in their ability to support growth, activity and viability of lactic acid bacteria and bifidobacteria typically used in yoghurt manufacturing. Growth and the end products of fermentation (lactic and acetic acids) were determined. Growth and acid production by organisms studied in the presence of different sweeteners were dependent on the specific organism investigated; however, it was not influenced by sweetener type, oligosaccharide content or the floral source of the honeys. All the sweeteners studied supported the growth, activity and viability of the organisms studied[67]

Lactic acid bacteria (LAB) isolated from honey can restore commensal microbiomes and prevent infections, it does not have a detrimental effect when applied in a single dose on humans[55]

Probiotic effects

It has been shown in a study by a Swedish research group that fresh honey has probiotic *Bifidus* and *Lactobacilus* bacteria. However these bacteria are viable only in fresh honey, about 2-3 months old [62]

In a 2014 study this research was continued. A unique lactic acid bacterial (LAB) microbiota was discovered which is in symbiosis with honeybees and present in large amounts in fresh honey across the world. The LAB symbionts are the source to the unknown factors contributing to many of honey's properties. The LAB was very active against severe wound pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa and vancomycin-resistant Enterococcus (VRE) among others. The mechanisms of action are partly shown by elucidating the production of active compounds such as proteins, fatty acids, anaesthetics, organic acids, volatiles and hydrogen peroxide. This and other symbionts produce a myriad of active compounds that remain in variable amounts in mature honey[63]

Gluconobacter oxydans isolated from Indian honey was found to possess probiotic properties with siderophorogenic potential[11]

Honey in influenza and common cold

An Iranian study claims that intake of 50 g of honey daily reduces the length of the common cold by two days [70].

The Ukranian doctors Frolov and Peresadin reported on a unique long term honey intake experiment. Frolov is the chair of the department of infectious diseases in the medical university of Luganska. All members of the department took 3 times a day, a total of 40-45 g of honey added to lukewarm tea. In the whole experiment 26 people took part in this unique experiment (n and number of years): n 5 for 20 y; n 6 for 15 y; n 8 for 10 y; n 5 for 5 to 10 y. During the whole experiment no other prophylactic was used. During the last 8 years of the experiment the department was in close contact with 40-60 patients with influenza and inflammation of the upper respiratory organs or with other infectious diseases like virus hepatitis, dysentery and even cholera. During the 20 year duration of the experiment no department member had any of the described diseases. In the immunological blood test it was found that the skin and the blood had an increased bactericidal activity, combined with very low microbial counts on the skin, while there were no pathogens in the whole area of the upper respiratory organs. And there was a control group to this experiment: a medical department, which was in close proximity of Frolov's test group, which had influenza or sore throat 3 to 4 times a year. This shows that a long term honey intake increases the anti-infectious immunity[32].

Honey and Covid 19

Based upon the proven antiviral activity of honey the NIH, USA has commissioned a randomised clinical trial with 1000 Covid 19 patients to see if honey has a positive effect on the disease outcome, citation: *"The National Institute for Health and Care Excellence (NICE) and the Public Health England (PHE) guidelines recommended honey as a first line of treatment for acute cough caused by upper respiratory tract infection which is currently a cornerstone symptom in COVID-19 infectious disease. Moreover, natural honey should no longer be used as "alternative" and deserves to gain more attention by scientists and researchers. The aim of this trial is to study the efficacy of natural honey in treatment of patients infected with COVID-19 in comparison with current standard care ».* ***Trial name*** *: The Efficacy of Natural Honey in Patients Infected With Novel Coronavirus (COVID-19) : A Randomized, Controlled ,Single Masked , Investigator Initiated, Multi-center Trial » Trial start : 15.4.2020, End :15.12. (https://clinicaltrials.gov/ct2/show/NCT04323345)*

In another trial in Egypt honey is included in a ingestion mixture for treatment of COVID 19:

„we introduce TaibUVID therapy as a novel medicinal nutrition formulation. TaibUVID stands for Taibah University anti-COVID-19 treatment as a novel evidence-based approach (using natural products) for treating COVID-19 patients. A single TaibUVID dose includes: 1 large spoonful of nigella sativa oil (or 2 gram nigella sativa seeds) mixed with 1 gram of grinded anthemis hyaline and 1 large spoonful of natural honey. This mixture is to be chewed in the mouth and swallowed orally for both COVID-19 contacts and patients. We adjusted dosing regimen and period of treatment into three clinical levels including contacts or prophylaxis, mild cases and severecase. We also introduce novel nigella sativa oil (or nigella sativa decoction) nebulization for local treatment of pneumonia or bronchopneumonia that is faced in severe COVID-19 cases. The wonderful report by Ulasli et al. (Ulasli et al. Mol Biol Rep. 2014;41:1703-11) deserves a lot of interest where nigella sativa and Anthemis hyalina (chamomile) were confirmed to inhibit corona virus replication maximally. In addition, nigella sativa enhances immunity, exerts tissue protective effects and effectively treats co-morbidities. Oral honey exerts potent antiviral effects, enhances immunity and exerts tissue protective effects. Our suggested TaibUVID is a promising evidencebased approach to rescue lives, decrease fatalities and put a rapid end to COVID-19 pandemic.[78]

POLLEN

The old Egyptians describe it as "a life-giving dust." In ancient Greece the pollen pellets, carried on the bee's legs were considered to be made of wax. Aristotle in his Historia animalism observes, that they resemble wax in hardness but are in reality sandarace or bee-bread. Later it was called farina.The name bee bread persisted until many centuries. Pollen (a Latin word for fine flour or dust) was used for the first time by John Ray in Historia plantarum (1686). The first works on the mechanism of pollen foraging were carried out by Meehan in 1873.

Bees gather pollen as food and protein source to raise their brood.

It is a food supplement with functional properties.

Biologically active components in pollen

Its main biological components are polyphenols, but they contain also significant amounts of vitamins, mainly B3, A and E, minerals and sterols. The polyphenolics flavonoids are responsible for the colour of pollen and are either colourless or yellow, red and purple. The flavonoids are also responsible for the bitter taste of pollen. Most flavonoids exist as glycosides, called aglycones, i.e. sugar derivatives. In one study their amount varied between 1293 and 8243 mg/100 g, in another, between 530 and 3258 mg/100 g, the variation been due to variation of the flavonoid content of the different pollen types. Rutin seems to be the main flavonoid. There are no official daily allowances for flavonoids, suggestions lie between 200 to 1000 mg a day[16]

Humans use bee pollen as a functional food with many biological properties, the main ones being : in sport performance, antioxidant and anti-microbial[16]

Antiviral activity

Antiviral activity was mentioned in few studies : in unspecified pollen [46] for the pollen flavonoid kaempferol[40] ;for mixture of pollen/manuka honey 1:1 [89]. Antiviral activity against influenza virus has been reported for quercetin, a flavonoid found in pollen[100]

Immuno-stimulating effects

Bee pollen is an immuno-stimulator. It stimulates humoral immune response and changed the reaction of delayed-type hypersensitivity in rabbits[27]. In a Chinese study in mice it was shown that ethanol and acetone extracts, as well as whole Brassica bee pollen has an immunoactivating activity[72, 73].

In a study with bee pollen from Brazil it was found that supplementation of broilers food with up to 1.5 % BP resulted in increase of the bird immunity[25]

Pre- and probiotic effects

Probiotic

Recently a probiotic effect of fresh (deep frozen pollen) but not of dry pollen was announced. The probiotic lactic bacteria were not found in dry pollen, because they are not viable[65, 66]. Probiotic bacteria are found in bee bread[95]

Prebiotic

Bee pollen ethanol extract supplementation in broiler chicken significantly increases the number of Lactobacillus spp. and Enterococcus spp. in the caecum of chickens. Bee pollen could be therefore used as a potential feed additive with prebiotic activity to the poultry diet[41].

ROYAL JELLY

Until the end of the 19[th] century royal jelly (RJ) was not known as a bee product. RJ is produced by the hypopharyngeal gland of young worker bees. In 1888 the German von Planta found, that the food of workers, drones and the queen was different.

In the sixties and seventies an intensive research by Rembold and coworkers to identify of the key queen substance was carried out. It became clear, that the main components of the queen and the worker feedings , i.e. proteins, carbohydrates and lipids are the same, while royal jelly contains more amino acids, nucleotides and vitamines [74-76, 96].

Royal jelly is the special food that bees use to feed the special larvae for raising a queen. It is used as a food supplement with functional properties.

Antiviral effects

Antiviral effects against Herpes viruses[37] , against Coxsackie viruses[88]

Immuno-activating properties

Immuno-stimulating activity in animals or in cell cultures, increase of leucocytes count has been found in many studies: [3, 28, 34, 47, 48, 52, 58-61, 86, 97, 99, 101, 102]

RJ seems to improve the immune response to HIV-1 multivaccine [50]. It seems that the main acid of RJ, 10-Hydroxydecenoic acid[29] , but also its main protein apalbumin1[51] and other proteins and peptides have immune-stimulating (monocyte-proliferation stimulating) activity [45, 61].

PROPOLIS

Propolis was known to the ancient Greeks

The word propolis originates from Greek: «pro» = in front, «polis» = city. The meaning „ in front of the city„ suits well the protecting role of propolis for the bee colony. The Greek world propolis means also to glue and describes also the role of propolis to cement openings of the bee hive. Another name of propolis is bee glue.

The Russian researcher Popravko proved that propolis originates in the buds resin of trees [68, 69] (poplar, birch).

Now it is known that bees gather propolis from different plants, in the temperate climate zone mainly from poplar. In Brazil, a major propolis producer, the main propolis type is the green propolis from Baccharis.

Composition

The composition of propolis varies a lot, depending on its botanical origin. The two main commercial types originate in poplar (temperate climate zone) and Baccharis (Brazil). Appart from beeswax, propolis is composed from organic substances, minerals and carbohydrates. The main organic substances of poplar propolis are the polyphenol. Green Baccharis propolis contains mainly cinnamic acid and derivatives, coumaric acid, prenylated coumpounds, artepillin C and minor quantities of phenolics.

Antiviral activity

Table 1 : Antiviral activity of the different propolis constituents, adapted from[85]

Origin	Propolis type/plant source	Type of extract/isolated compound(s)	Species/cells/viruses	Effect
Purchased: Sigma Aldrich Co.	Characteristic of European type propolis	Caffeic acid, *p*-coumaric acid, benzoic acid, galangin, pinocembrin, and chrysin	RC-37 cells, herpes simplex virus type 1 (HSV-1) strain KOS	High anti-HSV-1 activity for both extracts when cells were treated prior to viral infection
Czech Republic	European propolis/*Populus nigra*	PEE and PWE	RC-37 cells, herpes simplex virus type 2 (HSV-2)	High antiherpetic activity for both extracts when viruses were pretreated prior to infection
Brazil	Brown propolis/*B. dracunculifolia*	HPE	HSV-2 strain propagated in Vero cells, female BALB/c mice	Effective against HSV-2 infection and in reducing extravaginal lesions by acting on inflammatory and oxidative processes; reducing reactive species, tyrosine nitration, ascorbic acid levels, and myeloperoxidase activity and protecting against inhibition of catalase activity
	Characteristic of Brazilian propolis	Isopentyl ferulate (isolated from an PEE)	Influenza viruses A/PR/8/34 (H1N1), A/Krasnodar/101/59 (H2N2), and A/Hong Kong/1/68 (H3N2)	Suppression of influenza virus A/Hong Kong reproduction *in vitro*
	Green propolis/*B. dracunculifolia, B. erioclada, Myrceugenia euosma*	PEE	Influenza A/PR/8/34 (H1N1) virus propagated Madin-Darby canine kidney (MDCK) cells, female DBA/2 Cr mice	Reduction of body weight loss of infected mice and virus yields in the bronchoalveolar lavage fluids of lungs
	European	PEE	RC-37 cells, HSV-1 strain	Reduction of titre of herpes

Origin	Propolis type/plant source	Type of extract/isolated compound(s)	Species/cells/viruses	Effect
France	propolis/*Populus nigra*		H29S, acyclovir resistant mutant HSV1-R strain H29R, HSV-2, adenovirus type 2, poliovirus type 2, and vesicular stomatitis virus (VSV)	virus, being vesicular stomatitis virus and adenovirus less susceptible; virucidal action on the enveloped viruses HSV and VSV
Brazil	Geopropolis from the stingless bee *Scaptotrigona postica*	Hydromethanolic extract	African green monkey kidney cells (ATCC CCL-81); herpes simplex virus strain (McIntyre)	Inhibition of HSV replication and entry into cells
Synthesized	Characteristic of Brazilian red and green propolis	Homoisoflavonoids, specially 3-benzyl-4-chromones	BGM (Buffalo Green Monkey) cells, coxsackie viruses B3, B4, and A9 and echovirus 30	Good antiviral activity against the coxsackie viruses B3, B4, and A9 and echovirus 30
Canada	European propolis/*P. trichocarpa* and *P. tremuloides*	PEE	HSV-1 and HSV-2 virus replicated in MDBK (monolayer cultures of Madin-Darby bovine kidney) cells	Impairing the ability of the virus to adsorb or to penetrate the host cells
Brazil	Green propolis/*Baccharis dracunculifolia*	Water extracts	Female BALB/c mice, Influenza A virus strain A/WSN/33 (H1N1)	Extension of the lifetime of mice. 3,4-dicaffeoylquinic acid which increases mRNA levels of tumor necrosis factor-related apoptosis-inducing and decreases H1N1 hemagglutinin mRNA
	Characteristic of Brazilian green propolis	3,4-Dicaffeoylquinic acid (Isolated from Brazilian propolis)		
Brazil	Characteristic of Brazilian green propolis	Melliferone, moronic acid, anwuweizonic acid, and betulonic acid (isolated from Brazilian propolis)	H9 lymphocytes, HIV-1	Moronic acid inhibiting anti-HIV replication
Israel	Mediterranean propolis/*Populus* spp., *Eucalyptus* spp., and *Castanea sativa*	PWE	Jurkat, uninfected human T-cell lines, and MT2 (HTLV-1 infected human T cells) cells	Inhibition of the activation of NF-κB-dependent promoter by Tax and prevention of Tax binding to IκBα and its degradation
Purchased: Sigma Aldrich Co.	Characteristic of European propolis	CAPE		
Provided by Binzhou Animal Science and Veterinary Medicine Academy of Shandong Province		Nanometer propolis Flavone	Kidney cells (PK-15) Porcine parvovirus (PPV) Britain White guinea pigs	Inhibition of PPV infecting porcine kidney- (PK-) 15 cells Restraining of PPV copy in lung, gonad, and blood, decrease of the impact of PPV on weight of guinea pigs, and increase of hemagglutination inhibition of PPV in serum as well as improving the contents of IL-2, IL-6, and γ-IFN
USA and China	European propolis/*Populus nigra*	PEE	Peripheral blood mononuclear cells obtained from blood of healthy donors, microglial cells isolated from human fetal brain tissue, HIV-1_{AT}, HIV-1_{SF162}	Inhibition of HIV-1 variants expression

Effects of propolis different pathogenic viruses

Effects of both poplar and baccharis propolis was found against the following pathogenic viruses [10, 20, 36, 54, 85]: *Adenovirus, Coronavirus,* Coxsackie viruses *Herpes simplex (HSV-1, HSV-2, Human T-Lymphozyte Virus-(*HTLV-1), *Influenca A and B virus, Newcastle disease virus, PPV, Polio virus, Vaccinia, Rotavirus;, Vesicular Stomatitis Virus (VSV)*

Anti - Corona Virus

Coronavirus is the common name for Coronaviridae and Orthocoronavirinae, also called Coronavirinae. Coronaviruses cause diseases in mammals and birds. In humans, the viruses cause respiratory infections, including the common cold, which are typically mild, though rarer forms such as SARS, including the one causing COVID-19 and MERS can be lethal.

Quercetin and luteolin, (components of poplar propolis) have antiviral activity against SARS-CoV virus, the pathogen of SARS.

Propolis has anti- Corona virus of the SARS type (see table 2). Corona inhibits also PAK1, a protein kinase, an enzyme. PAK1 is the major "pathogenic" kinase whose abnormal activation is responsible for a wide variety of diseases such as cancers, inflammation, viral infection, malaria, immuno-suppression. All propolis types are natural PAK1 blockers [56]. Thus, propolis might be useful for blocking coronavirus-induced fibrosis of lungs and stimulating the immune system.

Immuno-stimulating effects in cell and animal experiments

The immuno-modulating effect has been reviewed in 2007 by Sforcin[79]. All propolis types have immuno-stimulating activity. However the active substances of the various types of propolis are different [16]. The immuno-modulating properties of propolis have been reviewed by Silva-Carvalho et al.[85]

Table 2 Immunomodulatory activity of propolis and its chemical constituents adapted from[85]

Origin	Propolis type/plant source	Type of extract/isolated compound(s)	Species/cells	Effect
Brazil	Green propolis/*B. dracunculifolia*	PEE	Male BALB/c mice	Upregulation of toll-like receptor-2 and receptor-4 expression and increases in interleukin-1 and interleukin-6 production
				Upregulation of toll-like receptor-2 and receptor-4 mRNA expression
			Male C57BL/6 mice, B16F10 cell line	Stimulation of the expression and production of interleukin-2 and interleukin-10 and Th1 cytokine (interleukin-2 and IFN-γ) production
			Male BALB/c mice	Inhibition of Th1 cells generation; reduction of the frequency of IFN-γ-producing $CD4^+$ T cells under Th1-polarizing conditions
			Male BALB/c mice	Increase of H_2O_2 generation and decreases in the NO generation in peritoneal macrophages
			Male BALB/c mice	Increase in the interiorization and killing of the parasites *Leishmania (Viannia) braziliensis* by macrophages; increase in TNF-α production and decrease in interleukin-12 production
			Monocytes from human blood	TLR-4 and CD80 expression in human monocytes as well as TNF- α and IL-10 production
			Melanoma cells (B16F10); male C57BL/6 mice	Reduction of IL-1β and IL-6 in LPS-stressed mice; induction of IL-1β and IL-6 and Th1 cytokines in melanoma-bearing mice submitted or not to chronic stress

Origin	Propolis type/plant source	Type of extract/isolated compound(s)	Species/cells	Effect
Brazil Purchased: Acros Organics	Green propolis/*B. dracunculifolia* Characteristic of European, Brazilian, Russian, Mediterranean, and Australian type propolis	PEE, cinnamic and coumaric acids	Male BALB/c mice	Stimulation of interleukin-1β production and inhibition of interleukin-6 and interleukin-10 productions
Purchased: Acros Organics	Characteristic of European, Brazilian, and Mediterranean propolis	Caffeic acid	Monocytes from human blood	Stimulation of monocytes activity against *C. albicans*; downregulation of TLR-2 and HLA-DR expression and inhibition of cytokine production
Purchased: Acros Organics	Characteristic of European, Brazilian, Russian, Mediterranean, and Australian type propolis	Cinnamic acid	Monocytes from human blood	Downregulation of toll-like receptor-2, HLA-DR molecules from human antigen-presenting cells, and CD80; upregulation of toll-like receptor-4, inhibition of TNF-α and interleukin-10 production
Purchased: Sigma Aldrich Co.		Cinnamic acid	Female IRC mice	Increase of lymphocyte proliferation and release of cytokines interleukin-1 and interleukin-2
Brazil	Green propolis/*Baccharis dracunculifolia*	Hydroalcoholic (HPE) solution	Male BALB/c mice	Increase of H_2O_2 generation and decrease of NO generation
			Male BALB/c mice	Decrease of splenocyte proliferation and increase of IFN-γ production by spleen cells
Indonesia	The Pacific region propolis/*Macaranga tanarius* and *M. indica*	HPE	Male BALB/c mice	Increase of IgG generation and macrophage phagocytosis activity and capacity
Turkey	Mediterranean propolis/*Populus* spp., *Eucalyptus* spp., and *Castanea sativa*	PEE	Peripheral blood mononuclear cells from healthy humans	Suppression of neopterin release and tryptophan degradation, downregulation of the enzyme indoleamine 2,3-dioxygenase (IDO) and decrease of IFN-γ and TNF-α levels
Purchased: Sigma Aldrich Co.	Characteristic of European type propolis	CAPE	Human monocyte-derived dendritic cells (MoDCs) generated from peripheral monocytes	Inhibition of IL-12 p40, IL-12 p70, IL-10, IFN-γ-inducible protein- (IP-) 10 levels; inhibition of IκBα phosphorylation and NF-κB activation
			Female BALB/c mice	Increase of IgM antibody production, T lymphocyte proliferation, interleukin-4 and interleukin-2 production by splenocytes, and IFN-γ production
			Human peripheral blood mononuclear cells, jurkat cells	Inhibition of transcription factors NF-κB and NFAT; inhibition of interleukin-2 gene transcription, interleukin-2 receptor expre

Immuno-stimulating effects: application in medicine

In a clinical trial in an Austrian hospital propolis ingestion induced an immuno-stimulating effect in humans, by increasing cytokine secretion [18]

In traditional medicine propolis is used against common colds, which are induced by different viruses [16].

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

BEE VENOM

Whether the humans began keeping bees because of the healing effects of their stings or to get honey, or for both reasons, we do not know. Already in the early ancient civilizations know about the healing found virtues in the painful bee stings. Bee stings are probably one of the first natural cure for arthritis. In the ancient civilization of China, India, Egypt, Babylon and Greece bee venom was used for apitherapy[93].

In Huandi Neijing, an ancient Chinese medical book, around 500 BC, bee sting therapy was mentioned [23].

The ancient Greek doctor Hippocrates used bee venom for therapeutic purposes. He described it as *Arcanum*, a mysterious substance whose curative properties he did not quite understand

Antiviral activity

The main component of bee venom (BV) melittin has many biological properties, and is also antiviral[8, 92]. Phospholipase A2 has also antiviral activity against many viruses[22, 39]

BV has antiviral activities against many viruses inactivation of Adenovirus, Enterovirus, Herpes Virus (HPV16, 18), HIV, Picornavirus, Influenza A (PR8), Leukaemia Virus Vesicular Stomatitis (VSV), Respiratory Syncytial (RSV), Enterovirus-71 (EV-71) and Coxsackie (H3)- viruses[8, 30, 38, 44, 53, 92, 103]

Immuno-activating activity

It is known that BV has an immunostimulating effect. The weakened immune system of cancer patients was activated by BV[71]. The immuno-stimulating effect of BV is due to Phospholipase A2[64]

It has been proposed that by increasing the immune response BV can help the body to fight the pandemic swine influenza A (H1N1) [87] (PSI) Russian apitherapists claim that by 5-6 BV prophylactic treatminents the risk for getting PSI is significantly decreased (www.apiterapia.ru)

BEESWAX

Beeswax has shown in one study only weak antiviral activity[38]

CONCLUSIONS

Honey bees must protect themselves against viruses and have developed an immune system capable of fighting viruses by a variety of different mechanisms[19]. However, they produce products with antiviral activity adding compounds which are different from the ones they use for their own defence.

Bees specifically provide antivirals to

- royal jelly: the protein defensin and 10-HAD
- bee venom: melittin and phospholipase A2.
- probiotic bacteria, which they pass to honey and pollen.

The review shows that bee products have a considerable antiviral activity. If we establish an order of the antiviral activity of the bee products decreases in the following order:

Propolis > bee venom > honey > royal jelly > pollen>>beeswax

The vast rest of the antivirals found in the bee products originates from plants. The majority of the antiviral compounds have plant origin. The antiviral molecules found in the products have often also antimicrobial activity and thus their addition has a hygienic purpose.

In conclusion, this review shows that regular intake of the bee products propolis, honey and royal jelly is a good preventive measure against the flu and also against the corona-flu.

A big “THANK YOU” to the bees!

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