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Protective effects of honeybee products against COVID-19: a review

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Abstract. According to the World Health Organization, coronavirus disease (COVID-19-global pandemic) is defined as highly contagious viral infection that causes severe acute respiratory syndrome-coronavirus-2 (SARS-CoV2). This disease is very rapidly transmitted among humans. To date, 30 May 2021, at least 170,689,920 confirmed cases of COVID-19 have been reported while global deaths reached 3,550,093 (<https://www.worldometers.info/coronavirus/>). In Serbia (to date 30 May 2021) at least 712,046 confirmed cases of COVID-19 have been reported, while deaths reached 6,844 and recovered 694,492. Also, Serbia is at the top of the list of country vaccination rates against COVID-19. New concerns regarding vaccine safety and efficacy are coming with the mutated strains of SARS-CoV-2 virus. Natural products of known antiviral activity can be used for various therapeutic purposes. Honey, propolis, pollen, bee bread, bee venom and royal jelly might potentiate the immune system of patients and reduce their susceptibility to COVID-19 infection.

1. Introduction

In December 2019, COVID-19 infection firstly manifested in Wuhan, China, where a number of patients shared similar symptoms to respiratory syndrome [1-4]. According to Kandeel and Al-Nazawi [5] and Harrison [6], scientists started to massively investigate drugs and vaccines for COVID-19 treatment.

Recent years have seen wide application of apitherapy and bee products in medicine. Many studies have investigated health benefits (Figure 1) of different bee products, especially bee bread and pollen, as a means to increase the chemical and nutritional value of food or create functional food [7]. Also, many studies investigated honeys as food, in terms of contaminants, chemical composition and risk for consumer health [8-11]. In addition, the benefits of honey bee products to the immune system are remarkable (induction of antibody production, maturation of immune cells, and stimulation of the innate and adaptive immune responses [12]. Honey might have beneficial effects as an antioxidant, antiviral, antimicrobial, anti-inflammatory, antidiabetic, and cardiovascular and nervous system protective agent (Table 1) [13]. Similar to honey, propolis (*bee glue*) has high antiseptic, antibacterial, anticancer, antioxidant and immunomodulatory effects [13]. The major compounds for these effects are caffeic acid phenethyl ester and artemillin C.





Figure 1. Schematic presentation of the main effects of bee products

Pollen and bee bread are produced by flowering plants and collected by bees. This food is composed of protein (5%-60%), essential amino acids, reducing sugars, lipids, vitamins (provitamin A [β -carotene], vitamin, flavonoids and organic carotenoid pigments [7,14]. Bee venom is composed of several active components, including phospholipase A2 and hyaluronidase, peptides, amino acids, phospholipids, biogenic amines, volatile compounds and pheromones [15,16]. Nowadays, bee venom is use in apitherapy worldwide [13,17,18]. Royal jelly is an acid colloid composed of water sugar, proteins, lipids and low amounts of vitamins [16,19]. Šver et al. [20] showed the high therapeutic and prophylactic potential of royal jelly and its components against human respiratory syndromes, similar to SARS-CoV-2.

Table 1. Antimicrobial activity of honeybee products

Honeybee products	Effect	References
Honey	Antioxidant, chemopreventive, antiproliferative	[13,21,22]
Propolis	Antifungal, antitumor, antimicrobial	[21,22,23]
Bee venom	Antiviral, anti-inflammatory, nociceptive, antimicrobial, antitumoral	[13,16]
Royal jelly	Antiviral, immunomodulatory	[21]
Bee bread	Antibacterial, antiviral	[16,24,25,26,27]

In this review we present current understanding of honey bee products (honey, propolis, pollen, bee bread, bee venom and royal jelly) as antiviral defence mechanisms against COVID-19 infection.

2. Potential protective role of honey

Honey is composed of several bioactive chemicals, phenols, polyphenols, vitamins, bioflavonoids and sugars [28, 29, 30]. This honeybee product is used in traditional medicine to treat viral respiratory diseases [30]. Many studies showed different types of honey (manuka, acacia, multi-floral and mono-floral honey) inhibited viral replication [31]. According to [32], honey antiviral activity is explained by

hydrogen peroxide and the peptide, defensin-1. Similarly, flavonoids from honey have some antiviral activity [33, 34]. Hashem [35] showed the potential action of honey against SARS-CoV-2. According to Lima et al. [16], clinical trials and preclinical studies will indicate the benefit of honey in the therapy of COVID-19.

According to Al Nagggar et al. [13], the physical properties of honey might help to disinfect COVID-19 before passing to the lungs. Beside protective effects on lungs, honey promotes health by supporting the growth of positive intestinal microflora [36, 37]. These effects are explained to its low pH [38], high content of prebiotics [39, 40] and major species of beneficial lactic acid bacteria (*Bifidobacterium*, *Fructobacillus* and *Lactobacillaceae*) [41,42].

3. Potential protective role of propolis

According to Berretta [43] propolis has been widely studied and is already extensively consumed (as sprays or extracts) in many countries. Also, propolis, with high antibacterial, antifungal, antiviral, and immunomodulatory activities, is used in veterinary medicine [44]. Propolis is composed of several bioactive chemicals: limonin, quercetin, kaempferol, myricetin, caffeic acid phenethyl ester, hesperetin and pinocembrin [43].

Effect of propolis against SARS-CoV-2 infection [43]:

- Inhibitory potential with high binding energy to viral components from -9 to -7.1 kcal/mol (*in silico*)
- Blocks the 3a channel that is encoded by ORF 3a of SARS-CoV (*in vitro*)
- Inhibitory potential with high binding energy to ACE2 (*in silico*)
- Inhibitory potential with high binding energy to ACE2 (*in silico*)
- Inhibits PAK-1 directly or up-stream, blocking coronavirus infection
- Regulates IFN- γ , IL-6, and IL-10 cytokines in an experimental asthma model

4. Potential protective role of pollen and bee bread

Many of the bioactive compounds (polyphenols) present in pollen and bee bread have promising activity against SARS-CoV [26,27]. Beside polyphenols, flavonoids and isoflavones have high antiviral activity. According to Yi et al. [27] quercetin inhibited the entry of SARS-CoV into cells (*in vitro*).

5. Potential protective role of bee venom

Bee venom is well known to have antimicrobial activity [45]. The potential protective role of bee venom has been studied [46]. Yang et al., [46] showed that bee venom might potentiate the immune system and reduce the susceptibility to SARS-CoV infection. Also, bee venom induced immunity through substantial upregulation of Th1 cytokines (IFN- γ and IL-12) and several forms of immune cells, which could be very significant for SARS-CoV-2 related pneumonia [16].

6. Conclusion

Honeybee products (honey, propolis, pollen, bee bread, bee venom and royal jelly) are well known for their several medicinal and nutritional values, which have been long explored for different therapeutic effects. Honeybee products have antiviral effects and the ability to stimulate the immune system, so could be used in the therapy of severe viral respiratory infections, such as COVID-19. Also, many studies suggest potential antiviral effects of honeybee products by direct effects of different bioactive components (peroxide, flavonoids and phenolics). The immunomodulatory and antiviral effects of different honeybee products can be useful in preventive treatment, and even symptomatic treatment, of COVID-19.

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