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REVIEW ARTICLE

COVID-19 pandemic: impacts on bees, beekeeping, and potential role of bee products as antiviral agents and immune enhancers

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Abstract
COVID-19 pandemic has passed to the front all the contradictions of the beekeeping sector: the valuable role of bee products as immune enhancers and antiviral agents and the impact that unsustainability of human activities has on bees' health and survival. The COVID-19 emergency led several countries to adopt severe restriction measures to contrast the infection. The lowering of industrial and commercial activities, transports, and the general lockdown had immediate consequences on the air quality, significantly improving environmental conditions. This had a positive impact on honeybees' life's quality. On the other hand, the bee and beehive transportation limitations threaten to hit food production by affecting the pollinator service, and this is particularly true in large, food-exporting countries like the USA and China where due to the few numbers of local bees, beekeepers import them by other countries and convey by truck hives for thousands of kilometers to pollinate crops. Furthermore, honeybee products, focusing on their natural pharmacological properties, can play an essential role as a potential natural contrast to the virus by enhancing the immunity defenses of both humans and animals, and their demand by consumers is expected to increase. Several researchers in the last months focused their attention on bee products to evaluate their effect in the cure of COVID-19 patients to ameliorate the symptoms or to contrast the coronavirus directly. This review reports these preliminary results.

Keywords COVID-19 pandemic · Honeybees · Beekeeping · Bee products · Immune enhancer · Antiviral activity

Introduction

Globally, it is estimated that animals are able to pollinate most of the flowering plants (around 87.5%) (Ollerton et al. 2011), and the western honey bee *Apis mellifera* L. (Hymenoptera: Apidae) is the main animal pollinator (Hung et al. 2018), playing a vital role in not only maintaining plant biodiversity but also sustaining the most critical agricultural productions. This crucial role of *A. mellifera* is also because the anthropic activities and climate change significantly reduced the number of other animal pollinators (Goulson et al. 2015; Potts et al. 2010; Winfree et al. 2009), while *A. mellifera* is predominantly farmed worldwide, and according to FAO data (FAO/STAT 2020), the numbers of beehives in the world increased by 13.6% in the last decade (Fig. 1). According to Aizen and Harder (2009), the world-farmed honeybees' population, however, rises slower than the global demand for pollination.

In recent decades, farmed bee colonies also showed high mortality of honeybees across the USA (Lee et al. 2015; Steinhauer et al. 2014), Asia (Li et al. 2012), and Europe (Zee et al. 2014), and this condition has been named as colony collapse disorder (CCD). The CCD posed several concerns about the pollination of the different cultures (Garratt et al. 2014). Today, the significant factors protecting honeybee colonies from mortality are beekeeper background and practices (Jacques and Laurent 2017). The importance of bees not only for the agriculture but also as food producer has come to the attention of everyone, powerfully, at the beginning of 2020.

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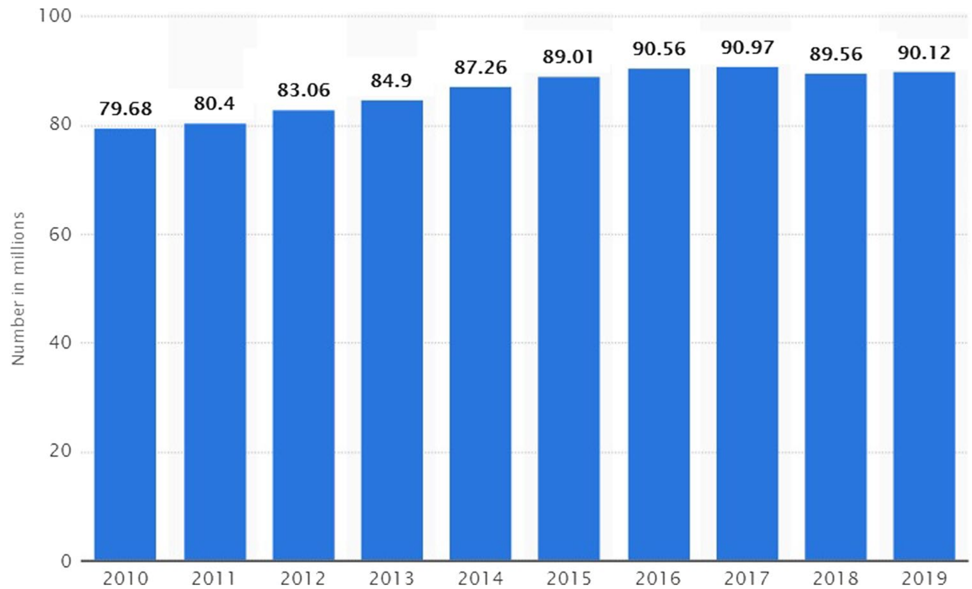

Fig. 1 Number of beehives in the world from 2010 to 2019 in millions

The recent world crisis due to the spread of SARS-CoV-2 and the relative human illness (COVID-19) induced several countries to adopt severe restriction measures to contrast the infection. The consequent lockdown had, immediately, a significant influence on the daily life of people, and a lot of habits have been changed. People stayed for a longer time at home and tried to preserve their health by using natural foods. In this regard, the COVID-19 greatly influenced the food sector (Galanakis 2020), as the domestic consumption increased but all the HO.RE.CA. (Hotellerie, restaurant, cafe) chain suffered a lot from the forced stop.

In the next future, another possible hazard for the food sector is the situation of food security and safety. Even if there is no scientific proof that SARS-CoV-2 can infect humans through foods, most concerns are toward some animal products. Firstly, because COVID-19 is a zoonosis, the fear on intensive animal production has increased because the high animal density could amplify the risks of new pathogens' appearance (Tomley and Shirley 2009). In addition, food contamination is possible if an infected man or woman touches a food and another man or woman, in a short time, touches the same food and thus his/her eyes or mouth (Collins 2008). Again, the perseverance of the virus to frozen temperatures is not well clarified (Chakraborty and Maity 2020).

This review aims to state the situation of bees and beekeeping during the lockdown, underlining the potential role of bee products as antiviral agents and/or enhancers of immune defense of humans and animals under intensive production.

Lockdown and its positive impact on the environment and honeybees' life quality

The lockdown due to worldwide transmission of SARS-CoV-2 had a severe consequence on different areas of animal production, due to changes of lifestyle of consumers, the closure of restaurants, the shortage of feed resources (in particular corn and soybean meal), and the crisis of market trade.

From a particular point of view, beekeeping is relatively safe. First, the sector did not suffer due to feeding shortage as the bee nutrition is nature-based on nectar or honeydew and pollen collected within an average area of 3 km around the hive. In addition, during the lockdown, there was an improved quality of the air, with a significant reduction of the pollution: in New York and China, air pollution and emissions decreased by 50% and 25%, respectively; in Europe, NO_2 emissions decreased over the UK, Spain, and Italy (Ficetola and Rubolini 2020). Other positive effects could be a clear sky, wild animals moving the streets, clear water, and decreasing contamination, particularly in urban areas. The reduction of fumes from cars due to the lockdown could increase the foraging activity of bees considering that air pollution reduces the longevity of floral scents (Fuentes et al. 2016).

Fewer circulating cars have other benefits for honeybees: Baxter-Gilbert et al. (2015) estimated that every year, 24 billion of bees are killed by impacts with vehicles in North America.

Lockdown and its negative impact on pollinator activity

In China, like in the USA, there are a low number of bees concerning territorial extension, so beekeepers move the hives for many kilometers to pollinate fields. The general lockdown adopted to contain the pandemic reduced the beekeepers' movements. This was particularly true for the great distances, with double damage: on agriculture and beekeepers' earnings, considering the critical economic values of insects for pollinator activity (Hein 2009). The pollinator service uses a high number of honeybees. The number of hives necessary for a good pollination is affected by several factors and among these are the strength of the hives, the size and "palatability" of the field, and the "background" pollination provided by wild bees, and, in general 2.5 to 5 hives/ha are suggested (Sagili and Burgett 2011). In addition, the management of pollination service provides that orphaned nuclei were moved to the crops and then left in place at the end of the service. Thus, many bees are "used" and lost by beekeepers, which usually import queens and other bees each spring to replenish their colonies. These honeybees' imports are vital for pollination because some crops need pollinating before home-grown colonies have had an opportunity to breed to a sufficiently large size: this happens in the USA and Canada who import queens from Australia and New Zealand and in the UK who imports queens from Southern Europe (like Italy). Lockdowns, quarantine, and other restrictions strongly impacted this system. The swarm market in Italy, despite an increase in production, suffered a lowering of the requests, and this influenced the swarm price, that downward trend that could continue in the coming months (Prospects 2020). However, the increase in swarm production in Italy is mainly tied to the general decrease of honey production and the research of alternative sources of income by beekeepers. The queen bee market has also been affected during COVID-19 emergency due to the lowering of requests from the main importers: the UK for Italy and the USA for Australia. However, standing the first data of 2020, there is no significant change in the queen bee price.

Impact on bee production amount and market

As for its name, the honeybee is mainly farmed for honey production, but the other "minor" productions such as royal jelly, pollen, propolis, venom, and wax are also to be considered, in general, as "added" income to the honey production because consumers appreciate their characteristics. Honey is well known worldwide due to its high nutritive value and its positive influences on human well-being (Pasupuleti et al. 2017). In the past, honey was appreciated by the most evolved civilizations as Chinese, Greeks, Egyptians, and Romans, due to its properties to heal gut illnesses (Pasupuleti et al. 2017). Furthermore, it is well establish for the therapy of cough, sore throat, and earaches (Rao et al. 2016). Honey is also a functional food (Fratellone et al. 2016; Ajibola 2015) due to its rich inactive compounds such as fructose, glucose, polyphenols, flavonoids, and organic acids (Alvarez-Suarez et al. 2010).

At the date, several vaccines have been developed, but no specific cure is for COVID-19 disease, and this is a vital point considering that also vaccinated people can be infected by SARS-CoV-2, even if in a less severe form. Muscogiuri et al. (2020) recommended the intake of functional foods, suppliers of immuno-supportive nutrients to contrast the stress effect of the quarantine, suggesting that carbohydrate-plentiful diets can be considered self-medicating antistress, improving immune state conditions.

Due to its well-known properties, during COVID-19 emergency, there was an increase in honey consumption as a potential enhancer of immunity defenses and thus a likely natural contrast to the virus activities in the body. The increased request for honey is accompanied by a decrease in its production due to climatic changes, as before discussed: Vercelli et al. (2021) estimate a reduction of 80% of honey production in some regions of Italy. This can further increase the amount of imported honey in Italy: in 2019, Italy imported around 25 million of kg of honey (40% from Hungary and 10% from China). The imported honey has a lower cost than the national one (Pippinato et al. 2019), which negatively affects the market of the national product of the beekeepers. To avoid selling honey at a meager price, we prefer to stock the product, awaiting better times. As no restriction of movements is considering for proven working needs, among that the caring for animals, the small-medium beekeepers can follow their hives and harvest the honey in time. More problematic factor was for big beekeepers, which suffered from the reduced migrant workers (Stojko et al. 2012). The impact of the COVID-19 pandemic on bees is displayed in Fig. 2.

So far, there are no available data on the production and consumption of the other bee products during the COVID-19 emergency. However, it is easy to suppose that, like honey, the other most popular bee products (propolis, royal jelly, bee pollen) showed an increase in consumption. This could be particularly true for those products associated with well-known anti-inflammatory effects on the first respiratory tracts. In addition, due to all the above-descripted properties, during COVID-19 emergency, several researchers

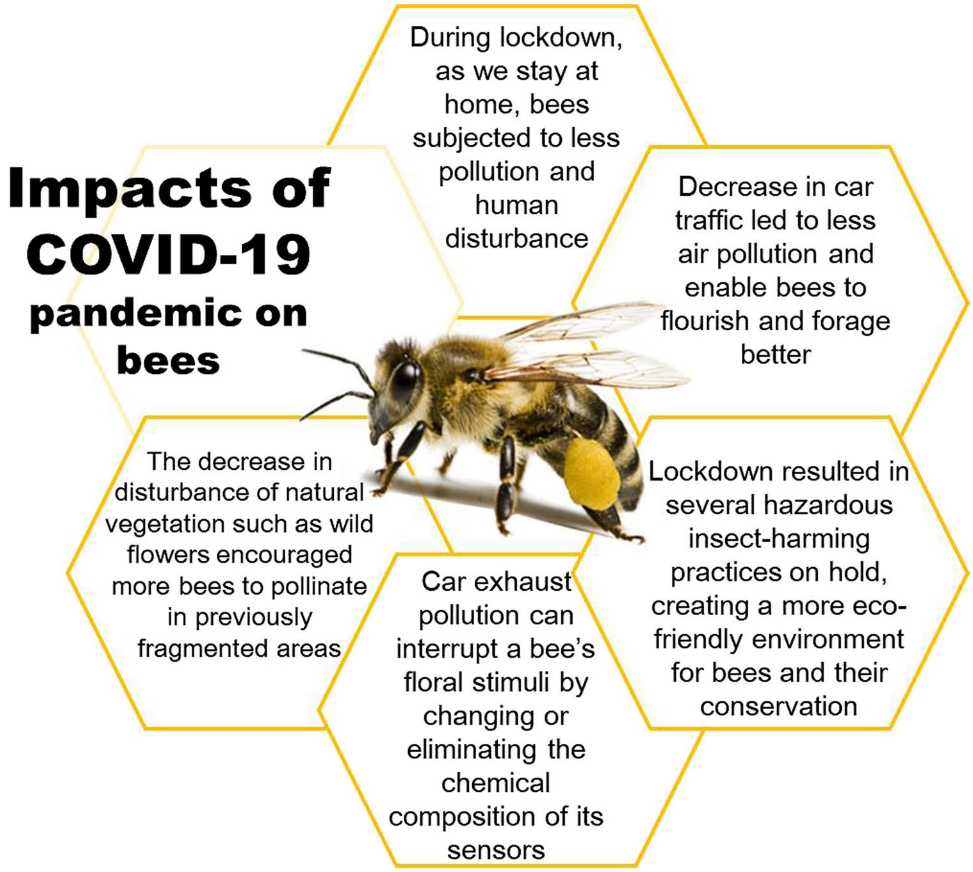

Fig. 2 Schematic illustration for the impacts of COVID-19 pandemic on bees

concentrated their attention on the possible use of honeybees' products mainly for the treatment of the symptoms of the disease, but not only, as described in the next section.

Bee products as immunity enhancers and apitherapy

All bee products (royal jelly, honey, pollen, propolis, venom, and wax) have some biological activities in function of the active compounds in their composition. Table 1 reviews the main potential substances in the bee products and the activity intensity. Figure 3 illustrates the main impacts of bee products against the novel coronavirus (SARS-CoV-2).

Improvement of human health

Standing these properties, several researchers focused their attention on bee products to evaluate their effectiveness in alleviating the symptoms during COVID-19 or to contrast the coronavirus directly. A summary of the latest available evidence regarding the antiviral impact of bee substances, with emphasis on anti-SARS-CoV-2 activity, as modified from Lima et al. (2021) is shown in Table 2.

Table 1 Pharmacological properties of bee products determined by Stojko et al. (2012) and modified by Kadhim et al. (2018)

Pharmacological activity	Pollen	Propolis	Royal jelly	Honey	Venom	Wax
Antibacterial	AA	AAA	A	AA	A	AAA
Stimulating processes of regeneration	A	AAA	AA	AA	AAA	AA
Detoxification activity	AAA	A	AAA	AA	A	A
Metabolic reactivation	AAA	AA	A	AA	A	A
Immune system booster	AA	AAA	AA	AA	A	A

AAA: highly active, AA active, A weakly active

Fig. 3 The potential impacts of bee products against the novel coronavirus (SARS-CoV-2)

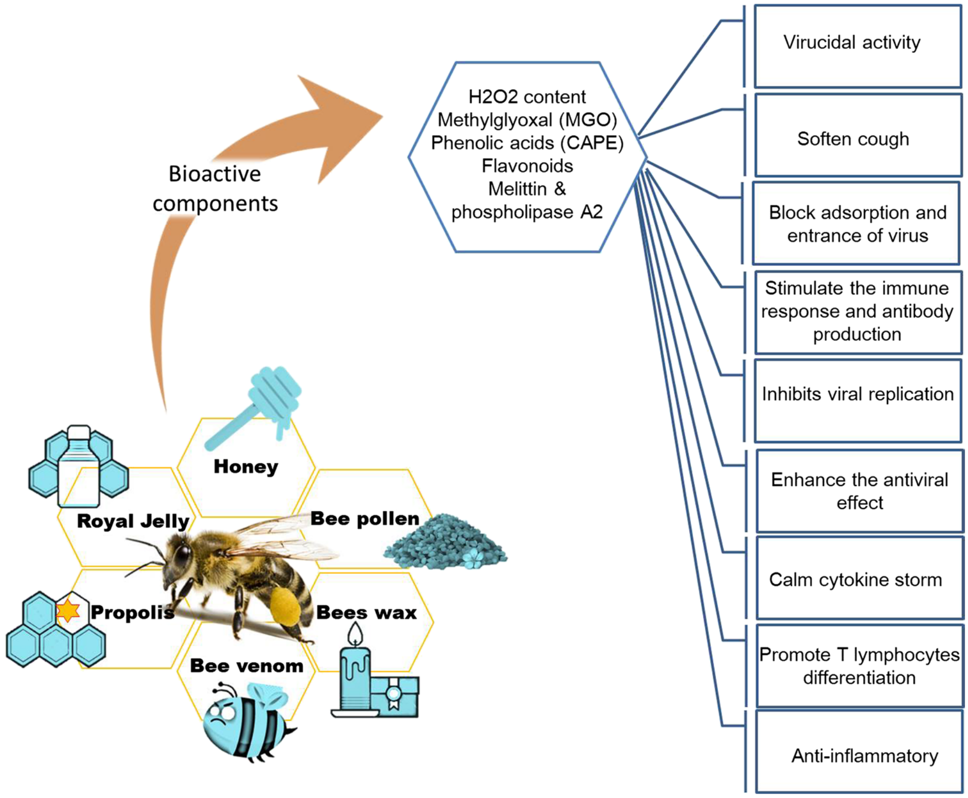

Table 2 Summary of the latest available evidences regarding the antiviral impact of bee substances, with emphasis on anti-SARS-CoV-2 activity, as modified from Lima et al. (2021)

The latest available evidence	Propolis	Honey	Beeswax	Royal jelly	Bee venom	Pollen
Clinical proof of SARS-CoV-2 activity						
In vitro or in vivo (pre-clinical) proof of SARS-CoV-2 activity						
The trial against SARS-CoV-2 was currently conducted	✘	✘				
Pre-clinical antiviral confirmation (excluding SARS-CoV-2) (in vitro or in vivo)	✘	✘	✘	✘	✘	
Clinical proof of antiviral prophylactic properties (exception to SARS-CoV-2)	✘	✘		✘		✘
Clinical proof of curable antiviral properties (exception to SARS-CoV-2)	✘	✘				

Honey

The chemical composition of the most common honeys includes about 16.9–18% water, 65–73% carbohydrates which contain less maltose (1.8–2.7%), and sucrose (0.23–1.21%) than glucose (26–28%), and fructose (36–42%). The proteins, vitamins, amino acids, and minerals are 0.50–1% (Pasupuleti et al. 2017). The wide range of variability of chemical parameters in honeys is due to the different botanical origin, bee species, and climate (Rao et al. 2016).

The most critical medical ability of honeys has tied the presence of antioxidant phenolic compounds (Pasupuleti et al. 2017) with different chemical structures among that an important role is of polyphenols (e.g., flavonoids) and phenolic acids. Apigenin, luteolin, pinocembrin, quercetin, galangin, kaempferol, chrysin, pinobanksin, and genistein are the main flavonoids. Among the phenolic acids, the most representative are gallic acid, syringic acid, chlorogenic acid, p-coumaric acid, vanillic acid, p-hydroxybenzoic acid, and caffeic acid (Pasupuleti et al. 2017). Hashem (2020) observed the 6 compounds (galangin, 3-phenyllactic acid, chrysin, caffeic acid phenethyl ester, lumichrome, and caffeic acid) in honeybee and propolis that could act against the SARS-CoV-2 main protease. In addition, 4 compounds (caffeic acid phenethyl ester (CAPE), caffeic acid, chrysin, galangin) inhibit the main protease and the replication of SASRS-CoV-2.

Al-Motawa et al. (2020) revealed a sensitivity of SARS-CoV-2 to methylglyoxal (MG). Honey obtained from Manuka has high amounts of MG (up to 760 mg/kg), as reported by Mavric et al. (2008). Methylglyoxal is an arginine-modifying reactive metabolite also produced by infected cells (Al-Motawa et al. 2020). Several reactive arginine residues were reported in the 4 most significant proteins of the SARS-CoV-2, suggesting that the SARS-CoV-2 is susceptible to alteration induced by MG (Al-Motawa et al. 2020). In addition, Manuka honey has an ascertained antiviral activity anti alphaherpes and influenza virus in vitro (Shahzad and Cohrs 2012; Watanabe et al. 2014). However, the effects of Manuka honey as a viricidal activity against SARS-Cov-2 are not well established so far.

Experiments by Diehl et al. (2013) and Laird et al. (2009) observed that the stimulation of TLR4 (toll-like receptor 4), generally implicated in the activation of the immune response, can increase RNA virus replication, including SARS-CoV, or suppress the factors able to limit the antiviral response of an organism. Levan (β-2,6-fructan) is produced by *Bacillus subtilis* and can activate the TLR4 pathway (Xu et al. 2006). Esawy et al. (2011) observed that the levan produced by *B. subtilis* isolated from honey has antiviral activity against avian flu virus (H5N1) and adenovirus type 40, an RNA and DNA virus, respectively. The action of levan has not yet been tested against CODIV-19 but it could be noteworthy to assess the TLR4-mediated impacts from honey levan in patients infected by SARS-CoV-2 (Hatmal et al. 2020).

Similarly, to propolis, also honey can alleviate the severity of complications during COVI-19 due to its antimicrobial activity. This effect is tied to the high amount of sugar (glucose), which is oxidized to produce hydrogen peroxide, a molecule with a potent bactericidal activity (Zahra et al. 2020). Hydrogen peroxide production is minimal in Manuka honey, produced by *A. mellifera* foraging on Manuka trees (*Leptospermum scoparium*), one of the most studied honeys for its beneficial effects on wellness and health (Chepulis and Francis 2012). Manuka honey had a higher amount of glucose (from 31.8 to 35.2%, 58) and the low levels of produced H_2O_2 might be further reduced by the catalase-producing organisms, but the microbial inhibitory action seems to resist (Adams et al. 2008; Shahzad and Cohrs 2012).

El Sayed et al. (2020) proposed a treatment protocol based on Nigella sativa, *Anthemis hyalina*, natural honey, and *Citrus sinensis* for COVID-19, with encouraging results based on rapid sero-negativization, decreased mortality, fast recovery, immune enhancers (raised WBCs, CD4 lymphocytes, CD8 lymphocytes, and interferon gamma), reduced anemia and leukocytosis, declined tissue-damage markers, and oxidative stress (lowered malondialdehyde, raised glutathione peroxidase, elevated catalase, and raised total antioxidant capacity). Currently, few ongoing clinical studies of the preventive and prophylactic utilization of bee products for patients suffering from COVID-19 have been conducted (Lima et al. 2021) (Table 3).

In recent work, Mustafa et al. (2020) described that the honey produced by stingless bees reduced the severity of pulmonary complications during COVID-19 due to its antibacterial and anti-inflammatory characteristics; in fact, it is known that secondary bacterial infections occur in around half of COVID-19 patients (Zhou et al. 2020). According to Mustafa et al. (2020), the crucial role of honey is tied to its ability to modulate the interleuchine-6 cascade, limiting the worsening of the COVID-19. The stingless bees live in the subtropical and tropical areas, and the properties of their honey are tied to the visited botanical essences rich in bioactive compounds, mainly phenolic compounds (Hashem 2020) that can change according to the botanical origin. Therefore, it is crucial to standardize the quality of stingless bee honey production and apply strict protocols to clinical trials involving honey.

Table 3 The ongoing clinical studies of the preventive and prophylactic use of bee substances for patients suffering from COVID-19

	NCT04323345	NCT04347382	NCT04480593
Country	Egypt	Pakistan	Brazil
Studies	1000	30	120
Bee product	Honey	Honey	Brazilian green propolis extract
Protocol	1 mg/kg/day divided into 2–3 doses for 14 days + standard care **	30 mL per os twice a day for 14 days + Nigella sativa seed powder (1 mg) twice a day for a maximum of 14 days + standard care **	400 or 800 mg/day orally or via nasoenteral tube with standard care **
Phase of study	III	III	II
Status of study	Recruiting	Recruiting	Recruiting
Category/setting	Treatment/multicenter	Treatment/single center	

*NTC: national clinical trial

**Standard treatment includes routine symptomatic attention and antibacterial or antiviral treatment (if advised by a pulmonologist or infectious disease specialist)

Propolis

Propolis (bee glue) is collected by specialized honeybees from resins and exudates of plant, mixed with bee salivary secretions, and used to "isolate" the hive or to propolize intruders killed and not removed from the hive. Propolis is well identified for its positive influences: recently, several studies evaluated the influences of propolis on bees' immune systems, parasites, and pathogens (Drescher et al. 2017; Simone-Finstrom and Spivak 2010). It seems that propolis antioxidants and immunomodulatory properties can also directly interfere with SARS-CoV-2 metabolism. The antioxidant molecules (mainly flavonoids) contained in propolis have a great role as immunomodulators (Cuesta et al. 2005; Wang et al. 2013). Propolis boosts the levels of interferon-γ and cytokines (Fischer et al. 2007), stimulating host immune defense. All kinds of propolis have antioxidant properties for their contents of flavonoids and total phenols (Osman and Taha 2008). They also have anti-inflammatory properties, due to inhibitory effects on myeloperoxidase, tyrosine-protein kinase, and hyaluronidase (Du Toit et al. 2009). Propolis is also considered an immune booster (Al-Hariri 2019).

It is well known that propolis has an antiviral effect due to its flavonoids, caffeic acid, and esters of aromatic acids (Pobiega et al. 2017). The procedure of antiviral action looks like the block of the transmission of viruses to other cells through the destruction of the virus envelope (Marcucci 1995). The antiviral impacts of propolis have been established against influenza A and B viruses, polio, and retroviruses, and vaccinia virus (Gekker et al. 2005; Shimizu et al. 2008) as well as against herpes simplex viruses (HSV) (Schnitzler et al. 2010; Simoni et al. 2018; Yildirim et al. 2016). The anti HSV-1 activity has been attributed to galangin and chrysin, two substances found in propolis (Schnitzler et al. 2010). Gekker et al. (2005) observed that melittin contained in bee saliva could inactivate HIV, destroying its external envelope. For these properties, during the COVID-19 pandemic, propolis has been largely investigated not only as possible ameliorative of symptoms, but also for its direct effect on SARS-CoV-2. Mohamed (2020) observed that propolis shows an antiviral activity against SARS-CoV-2, reducing its replication. Güler et al. (2020) demonstrated that flavonoids in ethanolic propolis extracts have high activity in binding, and thus blocking the angiotensin-converting enzyme 2 (ACE-2) receptors; this activity indicates that natural bee propolis can have a strong potential for COVID-19 therapy. SARS-CoV-2 utilizes ACE-2 receptors to enter into the cells (Hoffmann et al. 2020; Zhou et al. 2020).

As reviewed by Berretta et al. (2020), propolis contains some compounds that can potentially interact with SARS-CoV-2. In particular, galangin, CAPE, and chrysin are noticed in several kinds of propolis and are able to inhibit the enzyme 3-chymotrypsin-like cysteine of SARS-CoV-2 (Hashem 2020), essential for protein metabolism and thus for the virus, life cycle. Bachevski et al. (2020) underlined that CAPE could downregulate Rac (a signaling protein presented in human cells), playing as a blocker of p21 gene, also known as Rac/CDC42 (cell division control protein 42 homolog)-activated kinase 1 (PAK1). Because pulmonary fibrosis has been recently associated with an increased p21 expression, the findings of Bachevski et al. (2020) confirmed that CAPE could be beneficial to reduce coronavirus-caused fibrosis in the lungs (Maruta and He 2020). The positive effects of CAPE in preventing the SARS-CoV-2 attachment to the stressed cells have been retrieved by Elfiky (2020).

Confirming the interest of research on bee products, other clinical investigations continue to validate the influence of propolis on medical signs in COVID-19 patients (Maruta and He 2020). The PAK1 inhibitory influence of propolis would favor the activity of vitamin D_3 because the elevated activity of PAK1 boosts the expression of the enzyme cytochrome P450C24 (CYP24), generating a consequent greater inactivation of vitamin D_3 (Maruta and He 2020). Low concentrations of vitamin D were correlated with increasing severity of COVID-19 symptoms (Grant et al. 2020). However, vitamin D_3 cure in COVID-19 is under investigation. It has already been thought that the failures in the clinical utilization of vitamin D_3 can be partly ascribed to the inactivating effect of CYP24 (Maruta and He 2020). For this purpose, the use of vitamin D_3 with propolis, at "PAK-1 inhibitory doses," offers a beneficial effect. The combined cure of vitamin C and quercetin has already been used as a prospective cure of SARS-CoV-2 infection due to a synergistic influence that favors the maintenance of serum levels of quercetin (Colunga Biancatelli et al. 2020). Quercetin has already been considered a treatment for SARS-CoV-2, and its visible means of action would have an inhibitory influence on the viral polymerase, an impact already observed in other RNA viruses (Colunga Biancatelli et al. 2020).

Bacterial infections are common complications during COVID-19 (Wang et al. 2020). Bee products could be valuable instruments considering that these products do not carry the risk of increased antibiotic resistance. Campos et al. (2019) observed that propolis could induce the lysis of bacterial cells. In this sense, in addition to direct action on COVID-19, propolis is a critically in combating opportunistic bacterial infections. Block (2020) proposed that azithromycin, Brazilian green propolis, or a combination can be considered for prophylaxis in people with a high risk for severe complications during COVID-19.

Propolis was evaluated as a vaccine adjuvant, and its addition stimulates the immune response providing a prolonged protection period (Fan et al. 2015). The flavonoids present in propolis have been beneficial as adjuvants, potentiating IgG, IL-4, and interferon-γ (IFN-γ) in serum, which are elements that trigger immune responses against pathogens.

Despite all the previous considerations, the use of propolis as a health-enhancing substance in human medicine is restricted in several countries because it is not a standardized product (Lobo-Galo et al. 2021). In the propolis, more than 180 substances have been classified (Mărghitaş et al. 2009) as follows: 50% resin, 30% wax, 10% essential oils, 5% pollen, and 5% other constituents, containing cinnamic acid, the products of phenolic acids, replaced benzoic acids, flavonoids, and amino acids (Abu-Mellal et al. 2012; Bankova et al. 2000). The effects and chemical contents of propolis depend on the kind and amount of each class of compounds, tied to the geographic origin, vegetable sources, year, and collection time (Devequi-Nunes et al. 2018; Salatino et al. 2005). According to these considerations, it would be interesting to test different kinds of propolis, selected among those with the highest content of active compounds, to evaluate the effects against SARS-CoV-2. In this context, a great interest could have the red varieties of propolis which showed the largest beneficial effects due to the high level of antioxidant agents (Devequi-Nunes et al. 2018). In addition, a minimum standardization is mandatory to guarantee the effectiveness of propolis. In this context, Berretta et al. (2020) developed a standardized propolis extract, called EPP-AF®.

Royal jelly

The royal jelly (RJ) is secreted by the mandibular and hypopharyngeal glands of 5–14-day-old bees (Chauvin 1968; Fujita et al. 2013). Bee workers utilize RJ to feed queen and all the larvae of the beehives along with all the life and during the first 3 days of life, respectively (Fratini et al. 2016). The RJ is a "superfood" for its richness of Ca, Fe, Zn, Na, K, Mn, Mg, and Cu, indispensable amino acids (Val, Leu, Ile, Thr, Met, Phe, Lys, and Trp), water-soluble vitamins (B complex, and C) and fat-soluble vitamins (A, and E), enzymes, hormones, nucleotides, polyphenols, and minor heterocyclic substances (Fratini et al. 2016; Melliou and Chinou 2014; Sabatini et al. 2009; Xue et al. 2017). These compounds give to RJ immunomodulatory, antimicrobial, anti-aging, antioxidant, and neurotrophic properties (Ahmad et al. 2020).

Habashy and Abu-Serie (2020) demonstrated that two proteins in RJ (MRJP2—majority royal jelly protein 2—and its isoform X1) interfere with the proteins of SARS-CoV-2, limiting its attachment to the cells. These RJ proteins attach to the active site on the viral envelope nsp3, nsp5, nsp9, nsp12, and nsp16, preventing their activities. Besides, these proteins may inhibit lung difficulties as they can bind the oxy- and deoxyhemoglobin attaching sites of the viral nsps. Consequently, MRJP2 and its X1 form show a powerful way to control virus spreading. Some peptides isolated from RJ, the jelleines (Jelleine I–IV), act as antifungal and antibacterial means and can lower co-infections in patients with COVID-19 (Hashemipour et al. 2014). The most infections associated with COVID-19 are not only from *Pseudomonas aeruginosa*, *Mycoplasma pneumoniae*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*, but also from fungi such as *Aspergillus flavus*, *Candida albicans*, *Candida glabrata*, and *Aspergillus fumigatus* (Lansbury et al. 2020). The antibacterial Jelleines showed high action against *C. albicans* (Jelleine-I: 2.5 μg/mL; Jelleine-II: 2.5 μg/mL) in vitro (Fontana et al. 2007), *P. aeruginosa* (Jelleine-I: 10 μg/mL; Jelleine-II: 15 μg/mL; Jelleine-II: 30 μg/mL), and *K. pneumoniae* (Jelleine-I: 10 μg/mL; Jelleine-II: 15 μg/mL).

Bee venom

Among the other bee products, bee venom is commonly used as a drug in Asian countries for the cure of several illnesses (Billingham et al. 1973; Son et al. 2007). It showed antibacterial, antiviral, and anti-inflammatory effects (Billingham et al. 1973; Habermann 1972; Hwang et al. 2015; Son et al. 2007). Uddin et al. (2016) observed that bee venom has a viricidal activity against influenza A virus, respiratory syncytial virus, vesicular stomatitis virus, enterovirus-71, herpes simplex virus, and coxsackie virus.

Yang et al. (2020) conducted a survey on 5115 beekeepers in the Hubei Province (China) and observed that none of the beekeepers created signs linked with COVID-19. The survey also shows that 121 patients subjected to apitherapy treatments with bee venom did not exhibit COVID-19 signs. Yang et al. (2020) supposed that bee venom potentiates the immune system by enhancing the differentiation of human regulatory T cells, which have a crucial role in the prevention of SARS-CoV-2. Block (2020) considered that the antimicrobial and anti-inflammatory capacities of bee venom could be beneficial in the control of prolonged fibrotic damage of the lung. However, in another survey conducted to support the conclusions of Yang et al. (2020), Männle et al. (2020) interviewed 234 German beekeepers: in disparity to the Chinese study, Männle et al. (2020) observed that two beekeepers died for COVID-19 and 45 were infected.

Bee pollen

Bee pollen (mostly collected in Western countries by traps) and beebread (collected in Asiatic countries) are abundant in flavonoids and polyphenols (Männle et al. 2020), have a high antioxidants power (Mayda et al. 2020), and show therapeutic activities, including antitumoral, anti-inflammatory, antimicrobial (Fatrcová-Šramková et al. 2013; Meda et al. 2005), and immunomodulatory (Komosinska-Vassev et al. 2015). In literature, there are several studies on the application of bee pollen for COVID-19 therapy. Güler et al. (2020) tested the active compounds of the bee pollen obtained from Cistus L. (Cisteceae). They observed that caffeic acid phenethyl ester compounds, pinocembrin, and chrysin effectively inhibit the SARS-CoV-2 spike glycoprotein-human ACE-2 complex. Consequently, high beneficial effect of flavonoids in extracts of Cistus bee pollen to interact with CoV-2 spike RBD/ACE-2 complex suggests that this natural substance has great beneficial for COVID-19 cure.

Beeswax

Beeswax is secreted in liquid form by wax glands located in the abdomen of younger worker bees who are aged between 12 and 18 days (Kim et al. 2018). Beeswax is used to construct honeycomb and contains more than 300 compounds and among that are hydrocarbons, esters of fatty acids, fatty alcohol, free fatty acids, exogenous materials, and diesters (Chauvin 1968; Tulloch 1980). Beeswax is mainly known for its antibacterial activity against a considerable strain of bacteria (Sabatini et al. 2009). However, Hassan et al. (2015) observed an interesting antiviral activity of acetone beeswax extract against Adeno-7 as DNA model and RVFV as RNA virus models.

In the perspective of the COVID-19 pandemic, beeswax showed a great alternative use. Masen et al. (2020) observed that butter-beeswax substances provide long-lasting lubrication able to protect the skin from the injuries of a long-term use of personal protective equipment (PPE) such as respiratory protective equipment, visors, and goggles particularly important for medical staff.

Improvement of livestock immunity as a mean to increase food security and safety

Bee products can also be used to improve the health and immunity status of farmed animals, especially those farmed under intensive conditions. Sustainable food security is an essential goal to give. Most concerns are emerging or reinforcing during the COVID-19 pandemic about the intensive animal farming that could augment the risks of diseases emerging and spreading. COVID-19 is a zoonosis, and it is known that the probability of outbreaks of serious animal diseases is raised by the confinement of increasing animals' housing density (Hafez et al. 2021), so it is very vital to keep the animals under high welfare conditions that often means good health. To reach this objective is preferable to limit the use of antibiotics, considering another emerging problem, that of antibiotic-resistant bacteria. Bee products can represent a valuable alternative due to their characteristics and properties. However, not always breeders know the possibility to use bee products, and a suitable demonstration of this subject matter among animal keepers could inspire them to use these products in the daily routine in farm animal feeding. Bee products can be used for several purposes (increase growth performance, improve the quality of the products): In this review, we focused our attention on the immune status enhancer properties.

The species in which the bee products have been widely investigated are poultry, rabbits, and fish. Several researchers (Attia et al. 2011a, b, 2015, 2019a, b) showed a positive effect of bee pollen and propolis, either alone or in combination, on reproductive performance, health, and immune status of rabbits. Similar results have been obtained in broilers (Attia et al. 2017, 2014; De Oliveira et al. 2013). In addition, Babaei et al. (2016) observed that honey, bee pollen, and propolis supplementation increased lymphoid organ weight, antibody titer vs. avian flu, and New-Castle disease, as well as anti-sheep red blood cell titer in Japanese quails when used at 5 g/kg (pollen and propolis) or 22 g/L (honey); royal jelly at 100 mg/kg increased only the antibody titer vs. avian influenza. Beneficial influences of bee pollen on poultry health are sustained by different studies that proofed an early growth of thymus and bursa of Fabricius, the decrease in the cloacal bursa deterioration and the preferment of splenic immune reply, and the enrichment of development of the broiler chicks' gut (Hosseini et al. 2016; Wang et al. 2007).

Messina et al. (2020) observed that a supercritical fluid extract of honeybee pollen improved immune response and antibacterial activities of gilthead sea bream (*Sparus aurata*). Honeybee pollen significantly improved the blood immunological and hematological profile of Nile tilapia (El-Asely et al. 2014). Gunathilaka (2015) indicated that non-specific immune reactions of olive flounder (*Paralichthys olivaceus*) can be improved by liquid forms and dietary powder of propolis and that the optimal concentration would be 1% in powder form or 0.5% in a liquid substance. The oral administration of ethanolic extract of Brazilian red propolis to Santa Inês ewes (3 g/ewe/day) during the flushing period increased total leukocytes (WBC), total protein, and globulin levels while reduced glutamate pyruvate transaminase, glutamate oxaloacetate transaminase, and triglycerides (Morsy et al. 2013). Hashem et al. (2013) found that the dietary ethanolic extract of the Egyptian propolis improved hematopoiesis, including red blood cell number, hemoglobin levels, and hematocrite values in rabbit bucks. Also, blood plasma cholesterol and triglycerides were decreased while high-density lipoprotein (HDL), glucose, and total antioxidant capacity were enhanced by propolis supplementation. Sarker and Yang (2010) compared the effect of propolis as a natural feed additive (as 0.05% diet) with the antibiotic Naomycine (110 ppm) to the pre-weaned Hanwoo Korean calves (birth until 90 days), although they found an enhancement of the immunoglobulin (IgG, IgA, and IgM) concentrations of propolis group without the potential for the growth and feed intake blood biochemical parameters and the authors attributed these results to the low level of the supplementation of propolis. In this study, the authors mentioned the propolis supplementation as a powder but without any indication of the propolis type, color, method of extraction, or chemical composition.

It is worth mentioning that in animal nutrition, the bee products mainly used are bee pollen and propolis. Very few studies are the research on honey or royal jelly due to their use as human food and thus their high economic value. However, the application of royal jelly in poultry nutrition at 200 mg/kg diet significantly increased total leukocyte and erythrocyte counts compared to a diet containing 100 mg/kg or control without supplementation. Nonetheless, the heterophil percent and heterophil/lymphocyte ratio were decreased in RJ-supplemented chickens (Saeed et al. 2018). Despite all the described positive effects, bee products show two problems limiting their use: the high cost and the small quantity available. In addition, further work is necessary to clean, sterilize, and modify the "crude" products into their final usable form.

Conclusions

The COVID-19 crisis has strongly highlighted the role of honeybees for the food and feed chain and the problems of the beekeeping sector in the world: environmental pollution and climate changes. The beekeepers are the keepers of the world honeybee heritage. More research is mandatory in beekeeper training to support good beekeeping practices and achieve early recognition of diseases' clinical signs and symptoms. The role of honeybees during the COVID-19 emergency is also that of contributing to sustaining human and animal health through their products which can act not only as enhancers of the immunity system but also as natural antiviral agents.

Protecting biodiversity, healthy and good eating will be the basis for restarting after this health emergency. Bees never go on vacation or lockdown, continue their precious work, and without the work of pollinating insects, even agriculture would not be possible, and that is why man has learned to breed them. Their role is fundamental to the balance of terrestrial ecosystems, the diversity of botanical varieties, and their distribution. About 2500 years ago, Hippocrates said: "Let food be your medicine, and medicine is your food". Therefore, international efforts are necessary and required to preserve honeybees for their role as pollinators and all the products that bees can give to humans. The bees' natural products are rich in active compounds able to improve the immune status of both humans and animals and thus, applied on a larger scale, able to ensure a more sustainable animal production and food safety.

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Declarations

Ethics statement As a review, this section may not be applicable.

Conflict of interest The authors declare no competing interests.

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