REVIEW ARTICLE

Therapeutic Potentials of Bee Products for Treatment of COVID-19

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ABSTRACT

Pandemic COVID 19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected millions of people and led to a public health crisis. Thus various aspects including the economy and daily routine of life have been severely affected. For the time being, treatment using previously FDA-approved antiviral such as hydroxychloroquine and remdesivir, as well as using convalescent plasma does not guarantee full recovery of COVID-19 infection. Thus, the search for effective treatment against COVID-19 is actively on-going including using natural products. Bee products such as honey (with trehalulose sugar), propolis, royal jelly, bee pollen, and bee bread, are among the natural products that hold promises in attenuating COVID-19, either as an alternative source of the antiviral activity or to enhance the activity of current standard ward treatments. Besides being used in the human diet since ancient times, numerous pre-clinical and clinical studies have shown their pharmacological activities in improving general well-being as well as reducing the risk of developing various diseases. This review will consider a range of honey bee and stingless bee products and evaluate the evidence available for their therapeutic potential against COVID-19 infection and in reducing the risk of contracting the disease.

Keywords
Bee products; honey bee; stingless bee; COVID-19; antiviral

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INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or mostly known as COVID-19, was first detected in the city of Wuhan (Hubei province, China).[1] Due to its easily transmissible nature via respiratory droplets and aerosols, COVID-19 has spread rapidly around the world and has been declared as a pandemic in March 2020 by the WHO, making it the first pandemic caused by a coronavirus.[2] To date, the number of COVID-19 infection cases is still progressively growing and several variants including B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma) with evidence of an increase in transmissibility, more severe disease and life-threatening, have been reported across the globe.[3]

The clinical symptoms at the onset of COVID-19 illness resemble influenza-like which includes fever, dry cough, sore throat, and loss of taste and smell.[1,4] High-risk mortality was recorded among older (over 60 years of age) and people with underlying comorbidities.[5,6] Quarantine, physical distancing, hand washing, and the use of face masks or covering are some recommended preventive measures to reduce the infection rate and in order to avoid overburdening the healthcare systems.[7]

In general, certain treatments need to undergo clinical trials and obtain convincing results before it can be used widely as standard treatment. The first COVID-19 vaccine that has been issued emergency use authorization by the U.S. Food and Drug Administration (FDA) and WHO is Pfizer-Biontech Covid-19 Vaccine (Pfizer), an mRNA-based vaccine that has been developed by Professor Ugur Sahin under the collaboration of BioNTech and Pfizer.[8,9]

Preliminary analysis on 43, 000 participants showed the efficacy of the Pfizer vaccine is about 95% in preventing COVID-19 infection[10]. Beside Pfizer, other COVID-19 vaccines that have been issued the same approval by the WHO include AstraZeneca/AZD1222 vaccines (developed by AstraZeneca and University of Oxford), Janssen/Ad26.COV 2.S (developed by Johnson & Johnson) and Moderna COVID-19 vaccine/mRNA 1273 (developed by ModernaTX), Sinopharm COVID-19 vaccine (developed by Beijing Bio-Institute of Biological Products), and Sinovac-CoronaVac (developed by Sinovac Biotech).[11] All the WHO-approved COVID-19 vaccines have a high efficacy rate of 50% or above. However, vaccines provide protection against COVID-19, not a cure of the COVID-19 infection. Thus, the search for effective treatment against COVID-19 is still actively undergoing.

Research on the potential treatment for COVID-19 treatment is not limited to conventional medicine but also involves natural products including bee products (Table I).[12] As of 15th November 2020, as many as 2,932 researches on natural products have been completed and several ongoing clinical studies have been listed on the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP).[13] The clinical trials include the use of natural products such as honey and propolis as an alternative treatment of COVID-19 (Table II).

Bee products are popular as nutraceuticals, functional foods, and dietary supplements. Several scientific studies have reported on the potential of bee products in treating COVID-19 infection. Among them, *in silico* testing shown methylglyoxal (MGO) in Manuka honey can inhibit the COVID-19 virus protease enzyme, SARS-CoV-2.[14] The results also revealed that four main active compounds from honey bee and propolis namely caffeic acid, caffeic acid phenethyl ester (CAPE), chrysin, and galangin possessed high binding affinity with COVID-19 main protease.

The immune system is part of the body's defense against pathogens and foreign materials. It involves innate immunity and adaptive immunity which play an important role in fighting COVID-19 infection. The innate immune system varies from physical barriers such as pulmonary, skin, and guts epithelial cells, to highly selective immune cells, including dendritic cells, macrophages, and neutrophils.[15] At the early stages of viral infection, the macrophages and dendritic cells which are also known as antigen-presenting cells (APS), induced the activation of adaptive immunity by the priming and release of B- and T-cells through human leukocyte antigen (HLA). This further activates multiple downstream signaling cascade proteins such as cytokines, chemokines, and the production of reactive protein C which has antiviral activity.[15]

Table I: List of natural products clinical trials for the treatment of COVID-19 Source: Nu-traingredients-asia.com

Research Material	Country	Sponsors and Collaborators
Natural honey	Egypt	Misr University for Science and Technology
Omega-3-riched micronutrients; eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA)	Saudi Arabia	King Saud University
Resistant potato starch and intake of Vitamins (Vitamin C and D)	USA and Europe	Collaboration of Yale University, University of Michigan and University of Minnesota
Traditional Chinese Medicine; Jinhua Qinggan granule, Lianhuan Qingwen capsule and Xuebijing injection	China	Jiangsu Famous Medical Technology
Intravenous injection of high concentration of Zinc	Australia	Austin Health Hospital

In the framework of our review, we aim to present the literature review on the composition and biological properties of each of the bee products such as honey, royal jelly, propolis, bee pollen, and bee bread and elucidate their potential role as COVID-19 treatment in the light of their reported biological and pharmacological properties. This will bring benefits to the researchers and clinical scientists in optimizing the use of bee products as potential therapeutic or adjuvant treatment for COVID-19 infection.

Table II: List of Clinical Trials Using Bee Products for the treatment of COVID-19. Source: https://clinicaltrials.gov/

Bee Product	Study Title	Primary Purpose	Investigator	ClinicalTrials.gov Identifier
Brazilian Green Propolis Extract	The Use of Brazilian Green Propolis Extract in Patients Affected by COVID-19	Treatment	Marcelo Silveira, D'Or Institute for Research and Education	NCT04480593
Natural honey	Efficacy of Natural Honey Treatment in Patients with Novel Coronavirus	Treatment	Mahmoud Ahmed Tantawy, Misr University for Science and Technology	NCT04323345
Honey	The Role of Honey and Nigella Sativa in the Management of COVID-19; A Randomized, Controlled, Open-label, Add-on Trial in Pakistan	Treatment	Sohaib Ashraf and Sheikh Zayed, Federal Postgraduate Medical Institute	NCT04347382

Biological Properties and Therapeutic Potentials of Bee Products for Treatment of COVID-19

Honey

Honey is a natural product generated by honey bees of the genera Apis (honey bee) and Meliponini (stingless bee) that gathered, modified, and stored the nectar and sweet deposited from plants in their honeycombs. Honey has been consumed as traditional medicine as well as an alternative treatment for various health diseases ranging from cough, pneumonia to cancer treatment.[17,16]

It was reported that honey is composed of at least 300 components where fructose and glucose are the most important constituents (38% and 31%, respectively).[17,18] Also, honey is rich in minerals, proteins, vitamins, amino acids, organic acids, flavonoids, phenolic acids, enzymes, and other phytochemicals. Due to its rich biological and chemical content, honey exhibits multiple beneficial activities such as antioxidant, anticancer, antidiabetic, antifungal, antimicrobial, and antiviral (Figure 1).[19] These activities help with the protection of the cardiovascular, nervous, respiratory, and gastrointestinal systems. For instance, polyphenols found in honey have an antioxidant effect that protects the cardiovascular system by improving coronary vasodilatation and preventing low-density lipoprotein cholesterol (LDL-C) from oxidizing.[20,21]

Tualang honey, one of the most well-known Malaysian honeys, was reported to possess numerous therapeutic properties including antibacterial, antifungal, wound healing, anti-inflammatory, and anti-cancer activities.[22–24] The broad spectrum of biological activities displayed by Tualang honey was attributed to its antioxidant properties including a high content of phenolics, flavonoids, and 2,2 -diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging activities.[25,26] Significant anti-cancer activity was also reported in Tualang honey against multiple cancerous cells including cervical, breast, and osteosarcoma.[22–24,27] Interestingly, recent evidence has shown that Tualang honey showed virucidal activity against Chikungunya virus (CHIK).[28] In the *in vitro* studies conducted by Barkhadle et al (2021), pre- and post-treatment of Tualang honey at 5-20 mg/mL led to significant virucidal activity with up to 95% inhibition in CHIKV-infected Vero cells.[28]

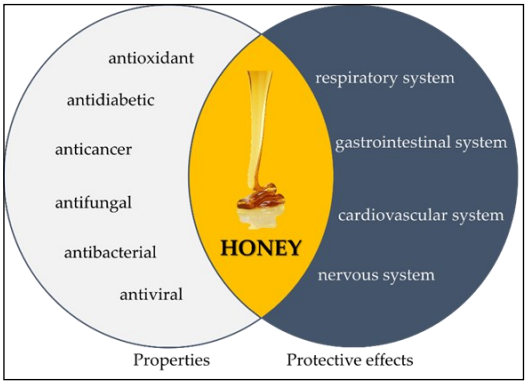

Figure 1: Therapeutic effect of honey

It was reported that the antiviral potential of honey against COVID-19 could be via activation of MD-2/ TLR4 and nitric oxide (NO) pathways as part of innate immune response.[29] A study from Kassim et al. shown that Malaysia's Gelam honey could potentially scavenge peroxynitrite during an innate immune response.[30] Peroxynitrite is a reaction product of NO and superoxide

and is known as a tissue-damaging oxidant. Besides, a clinical study using honey on COVID-19 patients is currently in phase three, led by Mahmoud Ahmed Tantawy from Misr University for Science and Technology.[31] It is a randomized, multicenter, and controlled trial that compares the effectiveness of natural honey in curing COVID-19 infection with current standard ward treatment such as lopinavir tablets, chloroquine phosphate, and hydroxychloroquine.

The content of ascorbic acid, flavonoid antioxidants, nitric acid, and hydrogen peroxide that can be found in most natural honey was reported to inhibit the process of viral replication and subsequently destroy the virus.[32] The antioxidant properties of honey such as quercetin have been reported to induce the cells that have been infected with SARS-Cov-2 to self-destroy themselves through autophagy which is a process of breaking down and recycling abnormal or infected body cells.[32]

Apart from its potential direct effect as an antiviral and stimulating the autophagy process, honey has also been reported to boost the immune system and have anti-inflammatory effects.[33] Interestingly, honey has been found to stimulate the production of B cells, T cells, and the chemicals cytokines, chemokine, and neutrophils.[34] Studies by Tonks et al. found that incubation of monocytic cell line, MonoMac-6 (MM6) with Manuka honey at a concentration of 1% (w/v) for 0–24 hours stimulates the monocytes to produce anti-inflammatory cytokines including interleukin-1 (IL-1) and IL-6 as well as different types of cytokines through a toll-like receptor 4 (TLR4)-dependent pathway.[35] However, it should be noted that the increase in the immune activities through the production of many of the above chemicals could cause uncontrolled or chronic inflammation in the body.[36] Further study on the anti-inflammatory effects of honey through *in vitro* tests (cell culture), *in vivo* (animal studies) and clinical trials may be able to reduce the side effects of the immune system.

Cytokines are small secreted proteins that mediate and regulate immune and inflammatory responses.[37] Hypercytokinemic immune-dysregulation in COVID-19 has been associated with cytokine storm particularly an increase in IL-6 that has led to disease severity of COVID -19.[1,38,39] Cytokine storms are caused by the high and continuous production of immune cells and chemicals including cytokines.[40] There is a growing body of literature that indicates honey could help to reduce the risk of the cytokine storms. Previous work by Hussein et al. showed that Gelam honey possesses anti-inflammatory effects in the acute paw edema rat model. In the study, supplementation with Gelam honey at 2 g/kg of body weight, twice-weekly could decrease and suppress pro-inflammatory cytokines including IL-6, with similar effects to indomethacin which is a non-steroidal anti-inflammatory drug (NSAID).[41] Similarly, an *in vitro* study using human leukemia cell line (HL-60) by Minden-Birkenmaier et al. showed that Manuka honey could inhibit the production of inflammatory cytokines in a dose-dependent manner (0.5% and 3% v/v) observed at 3 and 24-hour time points.[33]

One of the symptoms at the onset of COVID-19 infection is cough due to the inflammation of the respiratory tract.[1] Interestingly, honey is being recommended for the treatment and management of cough in the guidelines by the National Institute for Health and Care Excellence (NICE) and the Public Health England (PHE) for people infected with COVID-19. Moreover, it has been shown before that honey could effectively reduce acute respiratory symptoms due to viral infections.[42] This further call attention to the potential of honey as one of the treatment regime for COVID-19 infection.

Most of the deaths recorded among COVID-19 patients have underlying chronic diseases including diabetes mellitus.[43] Thus, the discovery of trehalulose sugar found only in stingless bee honey can reduce blood sugar, is a significant finding that could further highlight honey as a potential treatment for COVID-19.[44] This unusual trehalulose sugar has a low glycemic index (GI) of only 32 as well as a highly active antioxidant.[44] Apart from that, stingless bee honey has been found to have higher antioxidant content compared to the honey bee.[45] These findings, together with the increase of the stingless bee industry especially in tropical countries, may lead to many potential therapeutic evidence outcomes.

A retrospective study using the combination of honey with other natural products, *Nigella sativa*, and *Anthemis hyaline*, was associated with a fast improvement of lymphopenia on COVID-19 patients and contacts of COVID-19 patients.[46] The use of honey and these herbs improves the lymphocyte profile and earlier symptom, and lower incidence of SARS-CoV-2 infection in contacts. However, because the participant used a nebulizer containing a water extract of *N. sativa, A. hyaline*, and different types of Egyptian honey (the quality of herbs and honey varies according to storage and other conditions), this retrospective design is incapable to confirm the efficacy of honey under such conditions. Another study using the combination of honey (1 gm/kg body weight per day) with *N. sativa* (80 mg/kg body weight per day) orally to Pakistani patients with moderate and severe COVID-19 for 13 days.[47] The treatment was associated with a decreased time of symptom recovery and faster viral clearance in moderate and severe patients.[47]

Concerning the use of honey in SARS-Cov-2-infected patients, only authentic natural bee honey and stingless bee honey should be used to evaluate their true potential in treating COVID-19 infection. Additionally, honey, like other natural ingredients, including herbs, takes a long time to show the expected effects compared to the faster COVID-19 infection. Consumption of honey at the stage of chronic infection may not have an optimal effect. Thus, the consistent practice of honey as nutraceutical food seems to be the most appropriate strategy for the time being.

Royal jelly

Royal jelly is a viscous substance that is produced in the mandibular and hypopharyngeal glands of worker honeybees and stingless bees.[48] It provides both nutrition and protection for the young larvae of less than three days and also as exclusive food for the growth of queen bee throughout her life (from larvae to adult). Royal jelly is a combination of water, sugars, proteins, and lipids. According to Petelin et al., about 90% of royal jelly lipids are free fatty acids, containing 8–12 carbon atoms that are usually in either hydroxyl or dicarboxylic form.[49]

Fresh royal jelly largely constitutes of water (50%) and a complex mixture of proteins (9-18%), carbohydrates (7-18%), fatty acids and lipids (3-8%), and a small amount of sugar, salt, polyphenols, and vitamins.[50] It has been reviewed to possess several pharmacological activities, including anti-inflammatory, immunomodulatory, and rich with antioxidant properties.[50] However, most of the studies did not directly used fresh royal jelly but instead the chemical extraction of it in which the method of extraction determined the bioactive compound that will be obtained from the raw royal jelly.

In vitro studies by Gasic et al. showed that water extract and dry product of royal jelly stimulated T-cell proliferation in a dose-dependent manner.[51] The stimulation later led to an increase in the production of IL -2 which is an important modulator of T-regulatory cells. The water extract of royal jelly contains proteins with immunostimulatory activity (apalbumin-1 and -2) that could stimulate the release of TNF-α from macrophages.[51] Also, major royal jelly protein 3 (MRJP 3), a glycoprotein isolated from water extract of royal jelly was suggested to have both anti-inflammatory and immunosuppressive effects in mouse peritoneal macrophages and T-cells.[52]

To the extent of our knowledge, no study has yet looked into the effect of royal jelly in treating coronavirus. However, the water and alkaline extract of royal jelly was reported to be an effective scavenger against superoxide radical hydroxyl radical.[53] Similarly, Dzopalic et al. reported that royal jelly could stimulate and modulate the immune response.[54] The effect of 3,10-DDA, a fatty acid that was isolated from royal jelly was shown to stimulate the maturation of human monocyte-derived dendritic cells (MoDCs) and polarized the T-cells which is vital for an effective antiviral immune response.[54] Thus, the antioxidant and immunomodulatory properties possess by the biological active ingredients could be beneficial to be investigated as one of COVID-19 treatments.

Propolis

Propolis is a complex resinous mixture produced by the bees (honey bee and stingless bee) by mixing and digested

exudate collected from the buds and the bark of trees, the β-glycosidase enzyme of the honey bee saliva, and beeswax to form the final product.[55] The term propolis comes from the ancient Greek words; "pro" meaning before or in defense and "polis" which means city. Thus, this symbolizes the main purpose of propolis that is used to seal holes and gaps in the beehive as a way to protect it from microbes, fungi, and molds as well as a waterproof resin.[55]

Propolis is made of resin (50%), wax (30%), essential oils (10%), pollen (5%), and various organic compounds which include flavonoids, phenolic compounds, terpenes, ester, and other antioxidant compounds (5%).[55,56] Interestingly, analysis of Lithuanian bee products harvested from different regions showed that propolis was found to have the highest total phenolic content as well as radical scavenging activity in comparison to honey, bee bread, and bee pollen.[55] Just like other bee products, the composition of propolis was dependent on the source of the exudates, botanical, and geographical origins.[56]

The immunity provided by propolis prompted the researchers to investigate deeper on its biological constituent. However, most of the studies did not use raw propolis but instead purified propolis via extraction using aqueous or alcoholic solvents to remove the inert material and preserve the polyphenolic fraction.

A study using Brazilian green propolis extract against one confirmed COVID-19 patients aged 52 years old had improved the patient's condition considerably and shown negative nasopharyngeal swab after consuming the extract three times daily for two weeks.[57] The finding was supported by another bigger study where 82 COVID-19 patients were associated with significant reductions in duration of hospital stay, and renal injury after consuming a single oral dose of the same extracts.[58]

Propolis serves as an excellent antiviral with reported activities against different strains of viruses including Adenovirus, Influenza A and B viruses, Herpes Simplex viruses, and Coronavirus.[59,60] The antiviral effects were mostly associated with the presence of a different range of flavonoids found therein such as apigenin, chrysin, galangin, kaempferol, luteolin, and quercetin.[59] It was reported that a higher number of hydroxyl groups in the molecule presence in flavonols made it more active than flavones, thus an enhanced antiviral activity was observed in galangin compared to kaempferol and quercetin.[56,61] In addition, CAPE present in propolis was reported to be a biologically active ingredient with diverse therapeutic effects including as anti-inflammatory, antiviral, and immunomodulatory agent.[62]

Propolis has been recognized as the natural blocker of oncogenic P21 Activated Kinase 1 (PAK1) in several *in vivo* and *in vitro* cancer studies.[62–64] For example, a study using propolis harvested from Okinawa, Japan inhibited the PAK1 activity with IC_{50} values of 6 μg/mL in human lung cancer cell (A549). The PAK1 is considered as the most "pathogenic" of mammalian family kinases and overexpression of PAK1 has been implicated in various medical diseases including SARS/coronavirus, influenza A virus as well as inflammatory and immune-related diseases.[62,65,66] It was believed that coronavirus could induce a PAK1-dependent signaling pathway which later led to lung inflammation, fibrosis, and suppression of adaptive immune response.[62,67] Thus, blocking PAK1 possibly via bioactive ingredients found in propolis including caffeic acid, CAPE, apigenin, and artepellin C might be beneficial in reducing the effect of COVID-19 infection.[67]

Pollen and bee bread

Bee pollen contains a mixture of the collected plant with nectar and bee salivary secretions.[68] Bees carried pollen onto hairs in the corbiculae on the tibia of the hind legs which later will be consumed and used to feed the larvae.[59,69] The bee pollen mixed with the secretory saliva in the hive will be further fragmented by the flightless bee by covering with a thin layer of honey, wax, and various enzymes which led to fermentation and produced bee bread.[68] Bee bread serves as a nutritional food for the bee colony and the fermentation that it underwent provides unlimited storability and prevents deterioration of nutritional values compared to the dry bee pollen.[71,72]

Bee pollen and bee bread are rich in phenolic compounds including flavonol glycosides such as kaempferol, quercetin, isorhamnetin as well as hydroxycinnamic acid derivatives which may have broad therapeutic potentials.[59] Other biological constituents present in bee pollen and bee bread includes sugars, proteins, essential amino acid, lipids, vitamins, and digestible carbohydrates.[71] The protein elements present in bee pollen are considered life essential in which the organism cannot synthesize them by itself.

Multiple studies have highlighted the potential pharmacological activities for bee pollen and bee bread, including anti-microbial, anti-fungal, immunomodulatory, antioxidant, anti-inflammatory.[68,70,73] Currently, there is a lack of studies that look at the anti-viral effect of bee pollen and bee bread. However, some active biological constituents present in bee pollen and bee bread such as quercetin and kaempferol, as well as their glycosides derivates could potentially inhibit severe acute respiratory syndrome coronavirus.[68,74]

COVID-19- virus could enter the cell through binding with angiotensin-converting enzyme 2 (ACE2) receptor on the cellular membrane.[75] A recent study using molecular modeling has shown that chrysin had affinity binding with ACE2 that led to the conformational changes in the spike protein of COVID-19.[76] Since chrysin is one of the flavonoids found in bee pollen, this further highlights the potential for the treatment of COVID-19.

CONCLUSION

Taken altogether, it is undeniable that bee products are promising resources for therapy and treatment against COVID-19. Bee products could act synergistically as an anti-viral, stimulating autophagic activity, boosting the immune system, induce anti-inflammatory effect, and providing energy, minerals, and a source of nutrients so that cells continue to gain energy to act and respond effectively against the SARS-CoV-2 virus. However, thorough research and experimental studies are needed to clinically prove the therapeutic properties of bee products against COVID-19. If proven, the bee products could offer a low-cost treatment against COVID-19.

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CONFLICT OF INTEREST

The authors certify that there is no actual or potential conflict of interest in relation to this article.

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