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Some Characteristics of Honey and Propolis and Their Effects on Covid-19

Bal ve Propolisin Bazı Özellikleri ve Covid-19 Üzerine Etkileri

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Abstract

The new type of coronavirus disease (COVID-19) caused by coronavirus-2 (SARS-CoV-2) has recently led to a global pandemic due to severe acute respiratory syndrome. The novel coronavirus (COVID-19) is the part of the coronavirus family that contaminates individuals after SARS coronavirus and MERS. Currently, there is no specific medicine, treatment, or vaccine for coronavirus disease. In addition, studies on the use of foods that can be defined as alternative medicine continue in this process. In this context, the consumption of honey bee products in the treatment process, which is called apitherapy, has attracted great interest. Even though the antimicrobial property and immune-strengthen effect of honey are clear, there are limited studies available on its effectiveness against coronavirus outbreaks. In vivo and in vitro studies have been conducted on the potential effects of honey against COVID-19 based on previously investigated antiviral effects and phytochemical components. Despite some bioactive compounds in honey (such as methylglyoxal, chrysin, caffeic acid,

Özet

Koronavirüs - 2'nin (SARS - CoV - 2) neden olduğu yeni koronavirüs hastalığı (COVID - 19), şiddetli akut solunum sendromu sebebiyle son zamanlarda küresel pandemiye neden olmuştur. Yeni tip koronavirüs (COVID-19) SARS koronavirüsü ve MERS sonrası insanları enfekte eden koronavirüs ailesinin üyesidir. Halen koronavirüs hastalığı için belirlenmiş kesin bir ilaç, tedavi veya aşı bulunmamaktadır. Bunun yanısıra bu süreçte alternatif ilaç olarak tanımlanabilen gıdaların kullanımı üzerine araştırmalar devam etmektedir. Bu kapsamda apiterapi adı verilen ve bal arısı ürünlerinin tedavi sürecinde kullanılması büyük ilgi çekmiştir. Bal için tanımlanan antimikrobiyal özellik ve bağışıklığı kuvvetlendirici etkisine rağmen, bugüne kadar koronavirüs salgınlarındaki etkinliğiyle ilgili mevcut sınırlı çalışmalar bulunmaktadır. Balın daha önce araştırılan antiviral etkilerine ve fitokimyasal bileşenlerine dayanarak COVID-19'a karşı potansiyel etkisi üzerine in vivo ve in vitro çalışmalar yapılmıştır. Baldaki bazı biyoaktif bileşikler (metilglioksal, krisin, kafeik asit, galangin ve galangin, and hesperidin) have shown potential antiviral effects and strengthened the immune system, more studies are needed to understand the mechanism of action of these compounds. Propolis, a material produced by honey bees from disparate resinous substances collected from plants, has been utilized as a traditional herbal source for a long time. It is also commonly consumed as an immune system booster. In this case, with the COVID-19 outbreak, the interest in propolis products has increased even more in the world. Various aspects of the SARS-CoV-2 infection mechanism are potential targets for propolis compounds. SARS-CoV-2 entry into host cells is characterized by viral spike protein interaction with cellular ACE-2 and TMPRSS2. This mechanism involves high expression of PAK1, a kinase that mediates coronavirus-induced pneumonia, fibrosis and immune system suppression. There are various in vitro and in vivo antiviral activity studies investigating the inhibitory effects of propolis components on ACE-2, TMPRSS2 and PAK1 signaling pathways. The purpose of this research is to bring together the studies on COVID-19 with the health effects of honey and propolis, to contribute to the in vivo and clinical studies that are still required.

Keyword: Apitherapy, Honey, Propolis, Antiviral effect, COVID-19, Antimicrobial effect

hesperidin gibi) potansiyel antiviral etki göstermiş veya bağışıklık sistemini kuvvetlendirmiş olsa da, bu bileşiklerin etki mekanizmaları için yeni çalışmalara ihtiyaç duyulmaktadır. Arıların bitkilerden topladıkları farklı reçineli maddelerden ürettiği bir materyal olan propolis, geleneksel şifalı bitkisel kaynak olarak uzun süredir kullanılmaktadır. Aynı zamanda bağışıklık sistemi güçlendiricisi olarakta tüketilmektedir. Bu durumda, COVID-19 salgını ile beraber, dünya çapında propolis ürünlerine olan ilgi daha da artmıştır. SARS-CoV-2 enfeksiyon mekanizmasının çeşitli yönleri propolis bileşikleri için potansiyel hedef olmaktadır. Konakçı hücrelere SARS-CoV-2 girişi, ACE-2 ve TMPRSS2 ile viral spike protein etkileşimi karakterize edilmektedir. Bu mekanizma, koronavirüsün neden olduğu pnömoni, fibroza ve bağışıklık sistemi baskılanmasına aracılık eden, bir kinaz olan PAK1 yüksek ekspresyonunu içermektedir. Propolis bileşenlerinin ACE-2, TMPRSS2 ve PAK1 sinyal yolakları üzerinde önleyici etkisinin araştırıldığı çeşitli in vitro ve in vivo antiviral aktivite çalışmaları mevcuttur. Bu araştırma kapsamının amacı bal ve propolisin sağlık üzerine etkileri ile beraber COVID-19 üzerine yapılan çalışmalarını bir araya getirerek hala ihtiyaç duyulan in vivo ve klinik çalışmalara bir katkı sağlamaktır.

Anahtar Kelimeler: Apiterapi, Bal, Propolis, Antiviral etki, COVID-19, Antimikrobiyal etki

Abbreviations: Coronavirus-2 (SARS-CoV-2); Severe Acute Respiratory Syndrome (SARS); Middle East Respiratory Syndrome (MERS); Angiotensin-converting enzyme 2 (ACE-2); Transmembrane protease serine 2 (TMPRSS2); RAC/CDC42-activated kinase (PAK1); transmembrane protease serine 2 (TMPRSS2)

1. INTRODUCTION

Coronaviruses are RNA viruses with broad-enveloped that cause a wide variety of respiratory disorders in humans, such as upper respiratory tract infections and severe pneumonia. Seven forms of coronavirus, known as a human coronavirus (CoVh), have been identified that infect humans. Two are alpha coronaviruses (229E and NL63), whereas the other five are beta coronaviruses (OC43, HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2) (Anonymous, 2020 (a); Lim et al., 2016). It has been reported that coronavirus, which mainly targets the lungs, can be transmitted through droplets, aerosol microparticles and as well as asymptomatic infection (Yoshikawa et al., 2009).

Three outbreaks caused by this human coronavirus have been reported. One of them began in China in 2002 with acute and severe respiratory syndrome (SARS-CoV). The second one began in Saudi Arabia in 2012 with the respiratory tract syndrome (MERS-CoV) in the Middle East, and the third one was the COVID-19 pandemic (SARS-CoV2), which was reported in December 2019 in China. The most recent outbreak was the novel type of coronavirus (2019-nCov) in Wuhan city (Hubei province, China), which was found to be associated with a beta coronavirus and started with the same symptoms as the case of pneumonia. Afterward, the International Virus Taxonomy Committee named 2019-nCov as SARS-CoV2 because the 2019-nCov genome sequence indicated 89% resemblance to SARS-CoV (Lima et al., 2021). SARS-CoV-2 is spread through saliva droplets or nasal discharge when infected people cough or sneeze (UNICEF, 2020).

The recent coronavirus disease (COVID-19) maintains to spread around the world and becomes an emergency of concern on a global level. However, it is known that even after a decade of research on the coronavirus that has already emerged, licensed vaccines or therapeutic agents to heal coronavirus infection still have not been discovered (Lima et al., 2021).

At the stage of this review, it is seen that the COVID-19 pandemic has spread rapidly, vaccine and drug studies for COVID-19 are ongoing, and a definitive treatment method has not yet been developed for the treatment of the disease. People are searching the alternative prevention and treatment methods as well as medical treatment. One of these methods is the consumption of honey bee (*Apis mellifera*) products and the increase in demand for these products. The reason for this is that bee products have been used in the treatment of many illnesses in alternative medicine and the production of some drugs in pharmacology in recent years, moreover these products are the subject of many studies.

Until today, various biological therapeutic, nutraceutical and pharmaceutical properties of honey bee products have been determined and studies have been conducted on their use as cosmetic components (Viuda-Martos et al., 2008). Honey, as a complementary and alternative medicine product, has long attracted the attention of researchers (Al-Hatamleh et al., 2020).

Apitherapy is a type of complementary and alternative medicine that involves the therapeutic use of various bee products, including apilarnil (atomized drone larvae) to prevent and treat diseases (Nitecka-Buchta et al., 2014).

Apitherapy is also defined as the science and art of using products obtained from the honey bee hive to sustain health (Fratellone et al., 2016). Apitherapy, which offers treatments that depend on honey and other bee products against many diseases, has been developed as an alternative medicine branch. Apitherapy (using products produced by honey bees for treatment and pharmacological purposes like pollen, honey, royal jelly, bee venom and propolis) usage by Egyptians has been documented. Recently, some countries in the world, like New Zealand and Australia, have accepted the use of honey and honey products in wound treatment. Researchers conducting both in vivo and clinical studies on the healing of illnesses with honey have determined that honey is beneficial as a wound dressing through different mechanisms such as an antibacterial agent, a debriding agent, and an anti-inflammatory agent (Salcido, 2008).

Apitherapy is also said to be promising for the healing and prophylaxis of COVID-19 as an alternative medicine product combining the field of pharmacology with nutraceutical agents (Lima et al., 2021). In the earlier studies, various bee products such as honey, pollen, propolis, royal jelly and beeswax have been reported to show high antiviral activity against pathogens such as CoVh that cause severe respiratory syndromes (Brown et al., 2016). The benefits of these natural products to the immune system are striking, and it is said that most of them play a key role in the induction of antibody production, maturation of immune cells, and stimulation of innate and adaptive immune responses (Lima et al., 2021) (Figure 1).

Figure 1. Schematic representation of the main effects of bee products that can be utilized against the new coronavirus (SARS-CoV-2) (Lima et al., 2021)

This review, it is aimed to bring together in vivo, in vitro and clinical studies about some physicochemical properties of honey and propolis, which are bee products, and various use of these products as an alternative to the coronavirus pandemic (COVID-19), which continues to be a major and widespread threat to the world, causing various respiratory diseases and even deaths.

1.1. Honey and Covid-19

Honey is stated as "the natural sweet material produced by honey bees from the nectar of plants or the secretions of living parts of plants" (Codex Alimentarius Commission, 2001). Honey, which is naturally produced by bees and is the most common honey bee product, is obtained by digesting the nectar taken from flowers and stored in honeycomb cells. In other words, honey is a supersaturated aqueous solution that is produced at the acidic pH of the stomach of honey bees with the activities of invertase, diastase and amylase enzymes and contains mainly fructose and glucose, small amounts of sucrose, maltose and other sugars. Honey is often marketed for its nutritional benefits, but it has also been utilized as a folk cure since ancient times and recently has been used in pharmaceutical clinical applications (Cornara et al., 2017).

The use of honey, which is stated to date back to the Stone Age and has existed since the beginning of human history, was widely utilized as the only sweetening material until it started to be replaced by refined sugar with industrial sugar production after the 1800s (Bogdanov et al., 2008). Ancient societies such as the Romans, Greeks, and Egyptians have been reported to use honey as a type of sugar or to protect seeds, fruits and stems of plants (Chaven, 2014). In addition, it has been stated that throughout history, honey was used not only as food but also as a medicine (Jones, 2001).

With the increase of the human population, honey production also increases. According to FAO, (2019) data, it has been reported that the biggest honey production in the last ten years was in the Asian continent with approximately one thousand tons, followed by Europe and America. In addition, there are data that the amount of honey consumed per person is mostly in the Central African Republic, followed by New Zealand and Slovenia.

More than 200 substances have been found in honey, and among these components, carbohydrates (fructose, glucose, maltose, sucrose) are the most. Minerals, vitamins, organic acids, flavonoids, phenolic acids, enzymes, proteins and other phytochemicals are also among the key components of honey (Gomes et al., 2011; Iglesias et al., 2012). The color, minerals, vitamins and taste of honey are based on the types of flowers whose nectar is collected (Yaghoobi et al., 2008), geographical origin and seasonal differences, additionally harvest, processing and storage conditions (Gomes et al., 2011; Iglesias et al., 2012). For this reason, it is reported that honey collected from different honey sources has beneficial effects on health in different aspects (Iglesias et al., 2012). Naturally derived honey contains 82.4% carbohydrates, (38.5% fructose, 31% glucose, 12.9% other types of sugars), 17.1% water, 0.5% protein, organic acids, multi-minerals, amino acids, vitamins, phenolic substances, many other compounds and phytochemicals. Honey, which is known as a supersaturated sugar product, also consists of small amounts of bioactive components such as phenolic acid, flavonoid, and α-tocopherol (Shapla et al., 2018). Adaškevičiūtė et al. (2019) determined various mineral amounts of honey and other bee products, and it was reported that these products contain the most potassium. It has been reported that the ingredients of honey, which have positive benefits on health, containing ascorbic acid, carotenoids, as well as certain enzymes like glucose oxidase and catalase (Moniruzzaman et al., 2012). Many of honey's therapeutic characteristics, including anti-oxidant, anti-bacterial, anti-fungicidal, anti-inflammatory, hypotensive, anti-proliferative, anti-mutagenic, anti-diabetic, anti-tumoral (Khan et al., 2018; Terzo et al., 2020). It has been reported that the antioxidant capacity of honey is strongly correlated not only with the concentration of total phenolic components but also with color. The color of honey changes from light brown to dark, and it is stated that dark honey has high total phenolic content and hence high antioxidant capacity (Terzo et al., 2020).

Honey has an antiviral effect due to its contained components (Bogdanov, 2020; Hashemipour et al., 2014; Shahzad & Cohrs, 2012; Zeina et al., 1996). Zeina et al. (1996) investigated the antiviral properties of honey solutions at varying concentrations in their study in vitro and it was determined that honey has antiviral activity. Hashemipour et al. (2014) investigated the antiviral effects of honey and its different products on Herpes simplex virus type 1 (HSV-1), in a study of honey samples used at different concentrations (5, 10, 50, 100, 250, 500, and 800 μg/mL). It has been reported that the highest antiviral effect is seen at 500 μg/mL concentration. Shahzad and Cohrs (2012), determined that honey has an important antiviral effect in vitro. Honey can be effective in chronic inflammatory processes, as it contains significant amounts of compounds such as flavonoids and other polyphenols that can act as anti-inflammatory agents (Terzo et al., 2020). Miryan et al. (2020) reported that honey significantly reduced neutrophil uptake and inflammatory behavior at the wound site in a dose-dependent manner below the cytotoxic limit. Owoyele et al. (2014) investigated the anti-inflammatory properties of honey in vivo. In the research conducted with the application of tamsulosin, propranolol, atropine and hexamethonium as autonomic blockers, it was reported that honey reduced the perception of pain, especially inflammatory pain, and the application of tamsulosin and propranolol preserved the effect of honey. Hexamethonium also preserved the effects of honey in the early and late stages of the test, while atropine only inhibited the early stage of the test. However, atropine and hexamethonium retained the anti-inflammatory effects of honey, but tamsulosin abolished the effects, while propranolol only abolished anti-inflammatory effects at the peak of inflammation. The study determined that autonomic receptors are involved in the anti-nociceptive and anti-inflammatory effects of honey, depending on the receptor types with different participation levels.

Escuredo et al. (2013) found that a hundred and eighty-seven different honey obtained from a certain region on the Atlantic side of Europe, heather, blackberry, polyfloral and eucalyptus honey had the highest content of carbohydrate, while honey extract and chestnut honey had the lowest content of carbohydrate, as well as they determined that there are crucial differences between honey types depending on their presence of some components. They noted that the contents of protein and mineral were significantly higher in honey extract and chestnut honey, and in conjunction with the presence of various antioxidant compounds, heather honey had the highest content of phenolic, while honey extract and chestnut honey had the highest content of flavonoid. In addition, by using the multivariate analysis method, they found that minerals, flavonoids, proteins and phenols were fundamentally correlated with antioxidant activity.

So far, a few studies have been handled observing the effects of honey on SARS-CoV-2. Likewise, there are recently very limited clinical studies on the effectiveness of honey and its active components in COVID-19 patients (Ashraf et al., 2020b; Mustafa et al., 2020; Shaldam et al., 2021). Ashraf et al. (2020a) In a clinical study conducted on COVID-19 patients with different severity of the disease in Pakistan, they reported that the combination of honey and black seed is a healing, safe and effective treatment. In addition, according to this study, it was stated that honey and black seed, as a nutraceutical that does not require much cost, can be used alone or in combination with other drugs to have an additional effect.

Shaldam et al. (2021), in a study investigating the benefits of honey and propolis on COVID-19, among the bioactive components investigated in honey and propolis, ellagic acid, p-coumaric acid, kWaempferol and quercetin have been stated to have the ability to affect the active sites (RdRb and Mpro) of COVID-19. However, they stated that more in vivo study is required to evaluate the predicted affinity of chosen components against target enzymes of the novel coronavirus (COVID-19).

Ashraf et al. (2020a) studied the placebo effect of honey and black seed in randomly selected COVID-19 patients and found a significant reduction in the severity of clinical symptoms. They also reported that honey and black seed can be used alone or in combination with other treatments to achieve treatment-enhancing effects.

Mustafa et al. (2020), reported that honey can be considered as a functional food to complement the treatment of a patient infected with COVID-19. In another study, it was stated that a comprehensive clinical study was initiated that examined the efficacy of natural honey on many patients compared to current standard care in the healing of patients infected with COVID-19 (Anonymous, 2020b).

Hashem (2020) used the molecular modeling method that can estimate the activity of various active compounds from honey bee and propolis to hinder the main protease of SARS-COV2 (COVID-19) from honey, they determined that in which the binding energy of six compounds to the active site of the receptor in the main protease of COVID-19 was high. The study reported that caffeic acid phenethyl ester (CAPE), galangine, chymotrypsin-like and caffeic acid substances can inhibit the enzyme cysteine protease (3CLpro or 3C-Like Protease), so honey may have the potential to inhibit viral replication.

Wu et al. (2020) stated that hesperidin, a flavonoid derived from plant extracts, and rosmarinic acid, which is also reported to be discovered in honey, can inhibit SARS-CoV2 3CLpro (3C-Like Protease). In the research, they reported that hesperidin is the only natural substance that may bind to the S protein receptor binding site (RBD) and therefore can neutralize ACE-2 and increase RBD binding. Al-Hatamleh et al. (2020) noted that honey containing hesperidin can have an important effect in preventing the virus from adhering to target cells.

In addition to the studies completed so far, more laboratory and clinical studies are required to fully determine the therapeutic effects of honey against COVID-19.

1.2. Propolis and Covid-19

Propolis is the general name of the mixture of different resinous materials obtained by bees from plants, used to cover the interior walls of the beehive, defend the entrance against intruders, and inhibit the growth of mold and bacteria (Burdock, 1998) (Figure 2). Propolis is reported to be one of the methods honey bee colonies preserve their immunity, forming an envelope that acts as a crucial antimicrobial layer in the nest (Simone-Finstrom et al., 2017).

(A) **(B)**

Figure 2. (A). Propolis (**B).** Propolis was collected from the hive and brought into pellets (Anonymous, 2020c)

Propolis, one of the most important honey bee products, contains mainly resin (50%), wax (30%), essential oils (10%), pollen (5%) and other organic compounds (5%) (Gómez-Caravaca et al., 2006). Propolis consists of important vitamins (B_1, B_2, B_6, C and E vitamins), minerals (potassium, magnesium, calcium, sodium, copper, zinc, manganese and iron). Various enzymes have been found in propolis like glucose-6-phosphatase, succinic dehydrogenase, adenosine triphosphatase and acid phosphatase (Lotfy, 2006). The essential oil, which is the main active compound of propolis, is also responsible for the specific smell of propolis (Ribeiro et al., 2021).

To date, more than 300 various components have been found in propolis. The chemical content of propolis can be affected by its botanical origin, geographical conditions, collection season and bee species (Chi et al., 2020). Phenolic compounds, esters, flavonoids, amino acids, fatty acids, terpenes, diterpenes, lignans, beta steroids, aromatic aldehydes and alcohols are significant organic components discovered in propolis (Braakhuis, 2019). According to the study, twelve flavonoids, containing acacetin, pinosembrine, seizin, rutin, luteolin, kaempferol, myricetin, apigenin, catechin, galangin, naringenin and quercetin, two phenolic acids, cinnamic acid and caffeic acid, a stilbene derivative, resveratrol, were found in the extracts of propolis (Volpi, 2004). Woźniak et al. (2019) analyzed the chemical content of propolis extracts obtained in three seasons of the year. In this study, which is known that Polish propolis extracts, obtained in three seasons throughout the year, are rich sources of phenolic compounds, it was stated that chrysin, pinocembrin, galangin and coumaric acid are the fundamental phenols found in all extracts of propolis. When the concentrations of the compounds studied in all propolis samples were compared, just seven (Apigenin, Chrysin, Myricetin, Galangin, Kaempferol, Pinocembrin, Vanillic acid) of the fifteen components determined were found to be significantly different ($p < 0.05$).

The protective effect of propolis on the immune system, its pharmaceutical functions such as antioxidant, antibacterial, antiviral, anti-inflammatory, local anesthetic, antioxidant and anticancer properties, is due to its rich bioactive phytochemical components (Braakhuis, 2019; Chi et al., 2020).

Many studies have been conducted on the antiviral activity of propolis in particular (Kujumgiev et al., 1999; Lemos et al., 2020; Liao et al., 2021). Kujumgiev et al. (1999), investigated the antibacterial (against *Staphylococcus aureus* and *Escherichia coli*), antifungal (against *Candida albicans*) and antiviral (against *Avian flu virus*) activities of propolis samples taken from different geographical origins. It was stated that all the samples studied were active against mold and gram-positive bacteria strains and most of them showed antiviral activity. In addition, they found that the samples showed similar antiviral properties, although their chemical contents were different. Liao et al. (2021), investigated the antiviral properties of propolis water extracts (PWE) and propolis ethanol extracts (PEE) against noroviruses and their application in fresh-cut products. As a result of the research, they reported that PEE, which is a polyphenol-rich extract, showed better antiviral activities than PWE.

To date, the antithrombotic property of propolis has not been clinically studied. However, in the study of Ohkura et al. (2020) on the antithrombotic property of propolis, it was stated that the concentrations compiled from different studies will contribute to future clinical studies. In addition, it has been stated that antithrombotic properties of propolis, similar to other biological properties, should be directly related to its chemical configuration and will vary according to regional vegetation, pollen collection season, collection techniques and bee species. It has also been stated that the active components of propolis and their effects on blood coagulation factors, platelets and the fibrinolytic system will require further research before propolis can be applied clinically.

Propolis samples collected from Turkey to determine the phenolic profile and origin of the plant have been analyzed using the High-Performance Thin Layer Chromatography method (HPTLC). In their study, Degirmencioglu et al. (2019), *Populus nigra L*. from the botanical origin O-type as specified propolis has revealed that the most abundant propolis species in Turkey. In addition, they defined 3MQ (3-O-methyl quercetin) rich propolis as a new type of propolis for the first time. Principal component analysis (PCA) showed that 3MQ-type propolis is different from O-type, and antioxidant activity studies have reported that O-type propolis has a higher antioxidant effect than other forms of propolis studied. They also determined that among others, caffeic acid, quercetin, CAPE, and galangin contributed significantly to the antioxidant capacity of O-type propolis. In their study, Chan et al. (2013), stated that the two main immunopotent chemical compounds of propolis, CAPE and artepilin C, exert a summative immunosuppressive function on T lymphocyte subsets, but paradoxically activate macrophage function. On the other hand, it has been reported to have potential antitumor properties with different putative mechanisms, such as suppressing the proliferation of cancer cells through its anti-inflammatory effects. In addition, it was emphasized that propolis could be an ideal adjuvant agent for future immunomodulatory or anticancer regimens, in the form of good bioavailability when taken orally.

It is known that propolis has been utilized in the healing of many illnesses and also in the production of food products and cosmetics since ancient times (Burdock, 1998). However, it has been reported that the activity of propolis as a scientifically therapeutic agent can be proven in the last century. The Egyptians are known to use propolis to embalm the dead after realizing its anti-rotting properties. In Greece and Rome, propolis is known to be used as a natural antiseptic and treatment agent in the healing of wounds and as an oral disinfectant, in the same way, that the Incas used propolis as an antipyretic agent. It is also known that propolis was included in the British pharmacopeia official medicines list in the 17^{th} century (Cauich-Kumul & Campos, 2019).

There is intense research on propolis among natural medicine alternatives and it is currently consumed widely in many countries (Chan et al., 2013; Kuropatnicki et al., 2013). Studies in China, Japan, Russia and Korea show that propolis has an important place in alternative medicine. These important studies are reflected in the number of patents registered for propolis-containing products by 2013, about 1200 by China and about 300-400 each for Japan, Russia and Korea (Toreti et al., 2013). Propolis has a wide range of pharmacological activities and is a dietary supplement generally used by healthy people both as a preventative measure and to treat patients (Furtado Júnior et al., 2020; Gajek et al., 2020). Furthermore, propolis is also used in veterinary studies due to its anti-bacterial, anti-fungal, anti-viral, anti-parasitic, hepatoprotective and immunomodulatory activities (Chan et al., 2013; Santos et al., 2020; Scorza et al., 2020).

To date, many large-scale scientific studies have been conducted on the bioactivity and beneficial effects of propolis on health (Lan et al., 2016; Almuhayawi, 2020). It has been determined in studies that different types of propolis exhibit various biological properties containing anti-bacterial, anti-fungal, anti-protozoal, anti-oxidant, anti-tumor, anti-inflammatory, anesthetic, wound healing, immunomodulatory, anti-proliferative and anti-cariogenic activities (Chan et al., 2013; Cauich-Kumul & Campos, 2019; Jalali et al., 2020). While positive effects of propolis on reducing inflammation in diabetic people were observed in some studies (Afsharpour et al., 2017; Fukuda et al., 2015; Zakerkish et al., 2019; Zhao et al., 2016). To combat SARS-CoV-2, studies on drug and vaccine development are carried out intensively worldwide. At this stage, it is stated that natural molecules isolated from medicinal and other plants show significant inhibitory antiviral activity against SARS-CoV-2 (Orhan and Deniz, 2020). Based on this clinical reason, the use of propolis as an available complementary therapy in infected people with SARS-CoV-2 has been proposed (Scorza et al., 2020).

Alcohol or water-derived propolis extracts have been presented in studies to have a strong and broad-spectrum antiviral property against a diverse panel of viruses such as Influenza virus type A and B, HSV-1, HSV-2, Parainfluenza virus Adenovirus, HIV and avian rheovirus, bovine rotavirus, pseudorabilia virus, feline calicivirus, Newcastle virus disease, canine adenovirus type 2 and bovine viral diarrhea virus (Anjum et al., 2019).

While there are in vitro researches on the effect of propolis flavonoids on various DNA and RNA viruses, including the previous coronavirus (Bachevski et al., 2020; Pagani, 1990), insufficient studies are evaluating the effect on the new form of coronavirus (COVID-19). (Bachevski et al., 2020; Berretta et al., 2020; Burger, 2020; Guler et al., 2021; Khayrani et al., 2021; Miryan et al., 2020; Refaat et al., 2021; Sahlan et al., 2021; Silveira et al., 2021; Scorza et al., 2020; Tort and Acartürk, 2020). Debbiaggı (1990) studied the in vitro effect of five propolis flavonoids on various RNA and DNA viruses, containing coronavirus, using the viral plaque reduction technique. They reported that acacetin and galangin did not have any effect on the infectiousness or spread of any of the viruses studied, and chrysine and kaempferol were quite active in hindering replications.

Refaat et al. (2021), in their study on the development of an optimized liposomal formulation to increase the antiviral activity of propolis against COVID-19, are used as standard antivirals against both COVID-19 3CL-protease and S1 spike protein for certain components of propolis. They performed placement studies using Avigan, Hydroxychloroquine and Remdesivir. As a result of the study, they found that the optimized liposome formula of propolis had a significant inhibitory effect against COVID-3CL protease (IC50 =1.183 ±0.06) when compared with propolis extract (IC50 =2.452 ±0.11).

Sahlan et al. (2021) investigated whether Sulawesi propolis components produced by Tetragonula sapiens prevent the enzymatic activity of the primary protease SARS-CoV-2, as targeting the SARS-CoV-2 main protease to inhibit the COVID-19 virus is thought to be a promising treatment. As a result of the study, it was determined that two compounds (glycerine A and broussoflavonol F) are suitable for use as a potential drug for COVID-19. Both compounds were reported to show the desired effect profiles on the SARS-CoV-2 major protease with 63% and 75% similarities, respectively, compared to the positive control.

Guler et al. (2021) found the potential inhibitory properties of ethanol-extracted propolis against ACE-2 receptors in the treatment of COVID-19. In the study, the binding potential of some flavonoids in propolis to ACE-2 receptors was calculated. The binding constants of ten flavonoid compounds such as caffeic acid, chrysin, pinocembrin, galangin, rutin, caffeic acid phenethyl ester, myricetin, hesperetin, luteolin and quercetin were measured. As a result, it was reported that myricetin, caffeic acid phenethyl ester, hesperidin and pinocembrin, respectively, had the best inhibition potential and high binding energy among the molecules studied. It has been stated that the flavonoids found in extracts of propolis have a high potential to bind to ACE-2 receptors, this natural bee product has a high potential for the treatment of COVID-19, yet this should be supported by experimental studies.

Khayrani et al. (2021) studied the effect of Sulawesi propolis components, a natural medicinal product produced by Tetragonula sapiens, which hinders ACE-2, which is the SARS-CoV2 receptor, in the human body. In the study, the interaction profiles of binding affinity and propolis compounds with ACE-2 were analyzed by representative molecular insertion. As a result, they determined that broussoflavonol F, glisperin A, sulabiroins A, (2S)-5,7-dihydroxy-40-methoxy-8-prenylflavanone and isorhamnetine, which are propolis compounds, may have binding properties. They reported that glycerine A and izorhamnetin compounds can have the highest effect with 85% and 77% binding properties.

In a large-scale study conducted by Burger (2020), the promising effects of propolis, which has a strong physical and electrostatic mechanism of action (detergent-like), to understand the presence of cationic antimicrobial peptide and the use of propolis extract through inhalation in the treatment of COVID-19 were examined. As a result of the research, it was stated that the compounds found in propolis can combine the expected effects of various therapeutic agents and are a potentially viable and promising alternative healing for COVID-19, especially compared to conventional therapy.

Silveira et al. (2021) studied the effectiveness of propolis as an additional therapy for COVID-19 patients who were hospitalized. In the study of adult hospitalized COVID-19 patients, a standardized propolis product (EPP-AF) was used and a randomized, controlled and single-center trial was conducted. They gave patients an oral dose of standard maintenance plus 400 mg/day (n=40) or 800 mg/day (n=42) propolis for seven days and standard care (n=42) alone as a control group. They found that the duration of hospital stay, which was stated as the recovery period of the patients, was shorter in the patients who were given propolis plus. Compared to the control, it was stated that the patients given 400 mg/day propolis stayed in the hospital for 7 days, those given 800 mg/day stayed in the hospital for 6 days, and the controls stayed in the hospital for 12 days. Briefly, they found that propolis given in different doses and for different durations could have a positive effect on patients.

Tort and Acartürk (2020) investigated disinfectants containing propolis and boron against COVID-19 and compared them with previous formulations. Tissue profile analysis, spreadability and bioadhesion tests of the formulations were evaluated. The disinfectant gel formulation containing propolis and boric acid has been reported to contain lower alcohol than the World Health Organization (WHO) recommended formulation, but its effects on bacteria and mold are similar to the formulation recommended by the WHO. As a result, they stated that disinfectant gel formulations containing propolis and boric acid were successfully produced.

Interest in quercetin, which is a flavonol found in propolis, increased after researchers who researched SARS determined that quercetin along with vitamin C was an aminopeptidase inhibitor. Quercetin and its derivatives have been determined to hinder SARS-CoV and MERS-CoV major protease in vitro. In addition, quercetin is known to modulate the cellular UPR (unfolded protein response). In this case, coronaviruses can use UPR to complete all replication cycles, and quercetin can have an anti coronavirus effect because it can modulate this pathway (Polansky & Lori, 2020).

Propolis has proven antiinflammatory and immunoregulatory effects, also inhibition of active kinase (PAK-1). It is also reported that the host cell binding of the SARS-CoV-2 virus to ACE-2, which is the main target, is inhibited by propolis. Propolis components like quercetin, CAPE, rutin, kaempferol and myricetin show a strong interaction with ACE-2 in silico. For instance, kaempferol is reported to have decreased expression of TMPRSS2, also propolis does not interact with main liver enzymes or other key enzymes. The World Health Organization reported that propolis can be used as a supplementary food concurrently with medications without the risk of fortifying or inactivation (Berretta et al., 2020).

Although propolis is one of the safest natural remedy, it is expected propolis or its components may have adverse effects in rare cases, especially an allergic reaction. Therefore, more caution should be exercised in individuals with hypersensitivity when used in the prevention or healing of COVID-19 (Kurek-Górecka et al., 2020).

2. CONCLUSION

In the COVID-19 pandemic, which has affected the whole world, bee products help treatment in this period when the definitive treatment method has not yet been found. This review was made to bring together the studies investigating the physicochemical properties of honey and propolis and their effects on COVID-19. In the literature review conducted within the scope of the review, it has been reported that honey and propolis have a mechanism that can provide an inhibitory effect on the COVID-19 virus and these products provide a healing effect on patients, although in a limited number of clinical studies. Therefore, more experimental and clinical studies are needed to determine the therapeutic effects of both honey and propolis for COVID-19.

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