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Review

Effectiveness of Propolis in the Treatment of Covid-19

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ABSTRACT:
Propolis is one of the ways to protect the colony health and immunity of honey bees, and it is now known that honey bees can protect the colony from many microorganisms by forming a propolis layer inside the nest. This antimicrobial property of propolis and the fact that honey bees use propolis in their nests to kill bacteria and viruses have led scientists to investigate whether it can be used in the treatment of COVID-19. In this review, studies investigating the effectiveness of propolis in the treatment of COVID-19 in the literature were compiled by scanning the PubMed internet database with the terms of propolis, COVID-19, SARS-CoV-2 and novel coronavirus. As a result of the search, nine reviews, five research articles, one case report, two preliminary studies and one randomized controlled study were found. From these studies, a study found that it can be used as a promising treatment method by developing a liposomal formulation against COVID-19 using corn propolis. Another study showed that the propolis prevents and inhibits the adhesion of the COVID-19 virus to the ACE2 protein, which was its main target to infect the host cell. They explained that this was due to the fact that the components of caffeic acid, quercetin, kaempferol and myricetin in propolis had a strong interaction with the ACE2 protein. In a study on the enzymatic inhibition of the SARS-CoV-2, it was determined that molecular compounds of propolis showed therapeutic efficacy. As a conclusion, studies have shown that propolis has promising therapeutic efficacy and can be used in the treatment of COVID-19. However, since most of the studies were experimental, non-clinical studies and reviews, there is a need for clinical studies with a high level of evidence.

Keywords*:* Bee product, COVID-19, propolis, review, treatment effectiveness

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1. INTRODUCTION

The novel coronavirus disease (COVID-19) which was first detected in Wuhan, China in December 2019 and then spread all over the world, is a respiratory disease that is transmitted from person to person through air droplets [1]. The coronavirus (SARS-CoV-2) uses the ACE2 (Angiotensin-converting enzyme-2) receptor to enter cells, similar to the other coronaviruses associated with the severe acute respiratory syndrome [2]. Therefore, it is important to prevent the connection of coronaviruses to the ACE2 receptor or targeting to reduce the binding potential to

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prevent the infection and accelerate the healing process. For this purpose, propolis, one of the popular bee products, has been the subject of researches in different studies in the treatment of COVID-19, due to its antiviral and antioxidant effects. In these propolis studies, it was targeted that propolis may have promising efficacy in the treatment of the COVID-19. In this review, we aimed to investigate these studies in the literature to identify the effectiveness of propolis in the treatment of the COVID-19.

2. METHOD

Different studies examining the effectiveness of propolis in the treatment of COVID-19 are available in the literature. In order to search the studies on this topic, the PubMed internet database was scanned with the term of propolis, COVID-19, SARS-CoV-2 and novel coronavirus. In the literature review, within the scope of the effectiveness of propolis in the treatment of COVID-19; one study examining by in-vitro and in-silico molecular method, one liposomal formulation development study, one enzymatic inhibition study, one host cell entry receptor (ACE2) inhibition study, one clinical study and one case report were included and compiled.

3. STUDIES INVESTIGATING THE EFFECTIVENESS OF PROPOLIS

In a study in Turkey, ethanol extracts of propolis were obtained from different cities in Turkey, from Van, Rize, Zonguldak, Muğla, Antalya, Diyarbakır and Giresun, and a commercial propolis extract sample was included in the study [3]. In the laboratory analyses of the propolis samples; they found that propolis was rich in caffeic acid, p-coumaric acid, ferulic acid, t-cinnamic acid, hesperetin, chrysin, pinocembrin and caffeic acid phenethyl ester (CAPE). The binding energies of these polyphenols to both the spike protein in COVID-19 and the ACE2 receptor in our cells were separately calculated by a molecular docking study. Based on the in-silico modeling and absorption, distribution, metabolism and excretion behavior of polyphenols, the propolis compounds were found to exhibit the potential to act effectively as new drugs. This study suggests that propolis has a high inhibitory potential against the COVID-19 virus, so it can be used as a natural food supplement to protect from COVID-19 and accelerate the treatment process.

Another study in Egypt showed that some components of Egyptian propolis had a higher binding affinity to the 3-chymotrypsin-like protease enzyme (3-CLpro) and spike protein of COVID-19 virus, compared to favipiravir, hydroxychloroquine and remdesivir [4]. An optimized liposomal formulation was also created in that study to increase the anti-viral effect of propolis against COVID-19, and this resulted in better delivery of propolis to both target cells and facilitated the entry of encapsulated propolis into cells.

In a study conducted in Indonesia, the effect of propolis on the enzymatic inhibition of the new coronavirus was investigated [5]. Compounds in Sulawesi propolis, produced by Tetragonula sapiens, a stingless bee genus, was found to

have the potential to inhibit SARS-CoV-2 key protease activity. It was determined that two compounds called broussoflavonol and gliasperin A, which are among the active ingredients in Sulawesi propolis, interact with the main protease catalytic sites of COVID-19 and have the ability to bind with the main protease.

According to a study in Brazil, it was determined that propolis inhibits the binding of COVID-19 to the ACE2 receptor, which is the main target for host cell invasion [6]. It was stated that propolis components, especially CAPE, rutin, quercetin, kaempferol and myricetin, have a strong in-silico interaction with ACE2. It was found that propolis reveals a decrease in interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) levels, thus supporting the immunoregulation of pro-inflammatory cytokines. This immunoregulation includes monocytes and macrophages, as well as Janus kinase 2/signal transduction and activator of transcription 3 (Jak2/STAT3), Nuclear Factor kappa B (NF-kB) and inflammatory pathways, and reduces the risk of cytokine storm syndrome, which is an important death factor in advanced COVID-19 disease. In addition to these positive effects, it was stated that propolis does not interact with major liver enzymes or other key enzymes. It has also been reported that propolis can be used together with main drugs without the risk of potentiation or inactivation according to the criteria accepted by the World Health Organization (WHO).

In a randomized controlled clinical study conducted in Brazil, the efficacy of propolis in the treatment of COVID-19 was investigated by giving Brazilian green propolis as an adjunct treatment to 124 hospitalized COVID-19 patients [7]. In this single-center study, hospitalized adult COVID-19 patients were given a standard green propolis extract supplement as adjunctive therapy. In the study, a control group that received standard treatment and two separate propolis treatment groups that were treated with different doses of propolis treatment in addition to the standard treatment were formed. In the first group consisting of 40 patients from the propolis treatment groups, 400 mg of green propolis orally every day for seven days; the second group consisting of 42 patients was given 800 mg of green propolis orally. Standard treatment was applied to the control group consisting of 42 patients. After admission, the patients were followed-up for 28 days by applying group-specific treatment. It was observed that the length of hospital stay was shorter in both propolis groups than in the control group. The recovery period of the first group receiving 400 mg propolis supplement was seven days; The recovery time of the second group who received 800 mg propolis supplement was measured as six days, whereas, it was measured as 12 days in the control group who received standard treatment. It was determined that the use of propolis did not significantly affect the need for oxygen supplementation of the patients. However, it was observed that both propolis groups had much lower rates of acute kidney injury than the control group; and particularly, it was noted that the rate of acute kidney injury decreased significantly in patients who received high-dose

(800mg/day) propolis. In addition, propolis treatment was not discontinued in any of the patients during the treatment due to any side effects related to propolis. All the results showed that the use of propolis during the treatment of COVID-19 would accelerate the healing process and have positive effects in preventing acute kidney damage that may occur during the disease.

In a case report from Turkey, a 38-year-old male patient was admitted to the hospital with a complaint of tickling in his throat and the reverse transcription polymerase chain reaction (RT-PCR) test was positive [8]. It was stated that the routine blood values and Thorax computed tomography (CT) results when the patient was admitted to the hospital were normal. The patient, whose COVID-19 test was positive, developed a cough complaint 3 days after starting the medical treatment recommended in the Ministry of Health guidelines, and on the 5th day, this complaint became more severe. A repeat control thorax CT showed that bilateral large areas of ground glass were formed. After this stage, moxifloxacin was added to the patient's treatment. However, after 72 hours, it was decided to follow up the patient in the intensive care unit, whose general condition deteriorated and respiratory failure started in addition to the increasing complaints. Continuous positive airway pressure (CPAP) support was started by adding tocilizumab to his treatment. Although 2 days passed in the intensive care treatment, the patient's oxygenation and clinical condition did not improve. When a positive response to the treatment is not obtained despite the complete implementation of standard treatments; it was added Anatolian Propolis as a natural supplement to support the treatment, and Anatolian Propolis extract was started to be given to the patient as a 30% ethanol extract as 80 drops every day. At the end of the third day of propolis supplementation, a remarkable improvement was observed in the patient's oxygenation, blood parameters and radiological findings. The patient was discharged on the 10th day of hospitalization.

As a result of these reviewed studies, it was considered that it would not be correct to attribute the remarkable acceleration of the recovery processes of patients receiving COVID-19 treatment after starting regular propolis supplementation to propolis alone, but we suggest that propolis can be used as a strong natural supplement in addition to treatment in the light of these studies.

4. CONCLUSION

As natural support to the healing process, people who do not have a special allergy to bee products can be supplemented with propolis. We think that propolis, which has proven antioxidant and antiviral effects, will contribute positively to the treatment process of patients receiving COVID-19 treatment. But still further studies are required in this regard.

Conflict of Interest

Author has no personal financial or non-financial interests.

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