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The efficacy of propolis extracts as a food supplement in patients with COVID-19

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Abstract

Propolis is a natural immunomodulator with anticancer, antiviral, and anti-inflammatory effects. Propolis may be considered an agent in the supportive treatment of COVID-19. Propolis is known for its wide range of pharmacological properties, with many studies finding it effective in both the prevention and treatment of a variety of conditions. Forty-five patients who were hospitalized in our hospital and did not need intensive care were divided into groups of 15. The patients were receiving the standard COVID-19 treatment protocol. In the randomized, controlled study, one group of patients received 2 ml of water extract of propolis (WEP) (50 mg/ml) orally three times a day for one week, while another group received 1 ml of olive oily extract of propolis (64 mg/ml) plus 1 ml of olive oily Perga extract (120 mg/ml) (OEP). Hospital discharge times and changes in biochemical parameters were used as indicators of recovery. The WEP and OEP groups were found to have statistically significantly better D-dimer, CRP, and WBC results than the control group when the improvement in parameters between the groups were compared. Significantly different hospital discharge times in groups 1 and 2 were found compared to the control group. The addition of propolis to the treatment as a food supplement has a positive effect on the recovery of patients with COVID-19 and may shorten the treatment time. The use of propolis as a food supplement has been shown to have a range of health benefits, and the addition of it to the treatment regimen for COVID-19 may help to reduce the severity and duration of symptoms.

Keywords: caffeic acid, coronavirus, COVID-19, propolis

1. Introduction

Coronaviruses are a major human and animal pathogen that caused the pandemic that began in Wuhan, China's Hubei Province, at the end of 2019 and spread throughout the world (1). The virus, which is transmitted from person to person through the mucous membranes of the mouth, eyes, and nose, is highly contagious and infective (2). The coronavirus that causes COVID-19 is an envelope-positive-stranded RNA virus in the same subgenus as the severe acute respiratory syndrome virus (3). Over 200 million confirmed cases of COVID-19 have been reported worldwide since the first case reports at the end of 2019 (4). The coronavirus pandemic has caused immense global disruption, including to economies, societies, and individual lives.

Most patients develop serum antibodies against the receptor binding site of the viral spike protein and the associated neutralizing activity (5). The antibody response may be related to the severity of the disease, and the antibody may not be detected in those with mild disease (6).

It recommended various pharmacological agents for the prophylaxis of venous thromboembolism for hospitalized COVID-19 patients (7). Concerns about NSAIDs at the beginning of the pandemic do not seem significant when viewed with the new findings (8, 9). It advised using dexamethasone in patients with severe COVID-19 (10). Remdesivir is used as an approved treatment in some countries (11). Baricitinib, a Janus kinase (JAK) inhibitor used in the treatment of rheumatoid arthritis, is thought to prevent the virus from entering the cell with its immunomodulatory activity (12). Vitamin D, fluvoxamine, famotidine, zinc, and colchicine are some other agents tried in treatment (13–16).

Propolis is a product found in resins and plant exudates produced by plants to protect themselves, and these are collected by bees (17). Quercetin, myricetin, and caffeic acid, which are components of propolis, are thought to play a role in the treatment of COVID-19 (18). Bees show stronger immune properties with propolis (19). Berretta et al. evaluate propolis

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as an immunomodulator used in the treatment of microbial, inflammatory, oxidative stress, and cancer (20). The composition of propolis varies between regions (21).

The components in propolis have effects on the replication, virion integrity, endocytosis, and transcription of viruses (22–25). It forms a protective mechanism against COVID-19 by playing a role in the prevention of thrombosis (26,27), immunomodulation (28), inflammatory response (29), 3C-like protease inhibition (30), PAK-1 inhibition (31), TMPRSS2 down-regulation (32), ACE2 inhibition (33), 3a Channel Protein inhibition (34).

We aimed to investigate the contribution of propolis to the healing process of patients with COVID-19 with the current clinical study.

2. Materials and Methods

We conducted a pilot study with 3 participants to evaluate the required number of participants at a significance level of 0.05, using version 3.01 of the G* Power software (Franz Foul, Kiel, Germany), and found at least 12 participants for each group. In the current study, cases of COVID-19, who were treated at Trabzon Kanuni Training and Research Hospital and continued to take their medications according to the protocol of the Ministry of Health (favipiravir and paracetamol orally, corticosteroids intravenously), were divided into 3 groups of 15 subjects. All the patients were on oxygen therapy.

1st group: patients were given 2 ml of water extract of propolis (WEP) (50mg/ml) orally 3 times a day for 1 week. WEP was provided by Fanus Food Co. (Trabzon, Turkey) (manufacturer code: TR-OT-006-1364).

2nd group: Patients were given 1 ml olive oily extract of propolis (OEP) (64 mg/ml) + 1 ml olive oily extract of Perga (bee bread) (120 mg/ml) orally 3 times a day for 1 week. Olive oil extracts were provided by the same firm (Biopropolis, olive oil extract (25.36%), manufacturer code: TR-OT-006-1364, Bioperga, olive oil extract (12%), manufacturer code: TR-OT-006-1364). In the present study, two types of propolis extract were used: water extract of propolis and olive oily extract of propolis including perga which contributes to its antioxidant potential.

3rd group (control group): patients given only medications for COVID-19 and not given any investigational product.

Our inclusion criteria were patients over the age of 18 who did not need a ventilator while staying in the Covid ward. Exclusion criteria were patients with no oral intake, patients with high temperature (<37° C), patients whose informed consent form was not approved, patients in need of ventilators, and pregnant women. In addition, we did not include patients using warfarin in the study to prevent a possible liver interaction. If an allergic reaction developed in each patient, we planned to complete the trial for that patient or to complete the trial when the 7-day investigational product administration period was completed.

The age, gender, lung computed tomography findings, complete blood count (CBC), C-reactive protein (CRP), D-Dimer, Troponin, and oxygen saturation (sO_2) levels of the patient were all recorded. We analyzed the collected blood samples using the Abbott® chemiluminescence immunoassay method. Lung evaluation was performed by GE Revolution EVO 128-Slice Computed Tomography®. Lung tomography scoring normal=1, patchy atelectasis and/or hyperinflation and/or bronchial wall thickening=2, focal alveolar consolidation involving only one segment or one lobe=3, multifocal consolidation=4, and diffuse alveolar consolidation=5 (35). We recorded the length of the hospital stay in days. We made statistics in terms of compliance with the normal distribution between the groups.

Patient selection was randomized according to administration time, first patient was included in Group 1, second patient in Group 2, third patient in Group 3, and so on, until each group was completed with 15 patients.

After obtaining the approval number T140938 of the Ministry of Health of the Republic of Turkey for the current study, ethical approval was obtained from the Istanbul Medipol University Clinical Research Ethics Committee.

All data obtained were analyzed with IBM Version 23.0 SPSS Statistics for Windows. We examined the conformity to the normal distribution by calculating the mean and standard error of the initial and follow-up routine parameters. After finding out whether there was a difference among the groups for each parameter with ANOVA or the Kruskal-Wallis test (nonparametric), if there was a significant difference, the Mann-Whitney U test or posthoc Tukey test was applied between groups. The comparisons between the groups (before/after) were made with the Wilcoxon Signed Rank test. For the level of significance, $p<0.05$ was used.

3. Results

There were 45 participants in our study, 22 of whom were male and 23 of whom were female. Their ages ranged from 26 to 82. Each group showed a normal distribution according to age and gender. No patient was excluded from the study due to side effects or the need for intensive care. The demographic characteristics and medical histories of the patients are presented in Table 1. Table 2 shows the biochemical parameter results of the patients before and after treatment, as well as the one-week follow-up. During hospitalization, lung tomography scoring was performed on 1 in 10 patients, 2 in 16 patients, 3 in 14 patients, and 4 in 5 patients.

When CRP, D-dimer, Troponin, WBC, and sO_2 levels were compared before and after treatment, each group showed statistically significant improvement ($p<0.001$). When the improvement in parameters between the groups was compared, the WEP and OEP groups had statistically significantly better D-dimer, CRP, sO_2, and hospital discharge results than the control group.

Table 1. Demographic properties of the COVID-19 patients

	Group 1 (WEP) (n=15)	Group 2 (OOP) (n=15)	Group 3 (Control) (n=15)
Age(years) (mean±SD)	56.8±13.4	60.1±15.1	60.4±16.9
Female(n)	7	8	8
Male(n)	8	7	7
Coexisting Conditions (n)			
Diabetes	4	5	4
Hypertension	7	6	5
COPD/Asthma	1	2	1
Obesity	3	2	2
Oxygen therapy (n)			
Nasal canula	3	4	5
High flow nasal canula	12	11	13

COPD: Chronic obstructive pulmonary disease

Table 2. The arithmetic mean±standard error of the mean of study parameters of COVID-19 patients

	Group 1 (WEP) (n=15)	Group 2 (OOP) (n=15)	Group 3 (Control) (n=15)
CRP (before) mg/L	70.4±14.4	79.2±19.2	67.8±14 .0
CRP (after) mg/L*	15.1±8.5[a]	41.9±11.9	42.9±8.7
D-DIMER (before) ng/ml*	1475.3±1153.3[b]	2289.7±795.3	1806.3±822.2
D-DIMER (after) ng/ml*	798.6±643.1[a]	1442.6±501.0	1535.5±698.9
Troponin(before) ng/mL*	29.9±17.2[c]	11.3±1.1	7.7±1.4
Troponin(after) ng/mL	4.4±0.9	3.5±0.5	6.8±1.2
WBC (before) mcL	13.6±1.4	13.8±1.6	13.0±1.3
WBC (after) mcL	8.5±0.8	8.3±0.9	10.5±1.0
sO_2 (before) %	84.3±0.7	86.0±0.5	85.2±0.5
sO_2 (after) %*	92.1±0.8[d]	89.9±0.7	87.8±0.5
Hospital discharge time (day)**	5.5±0.2	5.7±0.2	9.5±0.4[e]

*Significant difference among groups by Kruskal-Wallis test

**Significant difference among groups by ANOVA test

[a]Significantly different from groups 2 and 3 ($p<0.003$), [b]significantly different from group 2 ($p<0.002$), [c]significantly different from group 3 ($p<0.01$), [d]significantly different from group 3 ($p<0.001$) by Mann-Whitney U test, [e]significantly different from groups 1and 2 ($p<0.001$) by post-hoc Tukey test

4. Discussion

In the current study, WEP and OEP were used/employed in addition to the standard COVID-19 treatment recommended by the Ministry of Health. There was no patient whose treatment was discontinued due to side effects during the treatment. When determining the doses, previous studies with propolis were considered (36, 37). We observed both rapid improvement in biochemical parameters and reduced hospital stays in the propolis groups. In another study with Brazilian propolis conducted in 2021, the ethanolic extract was used (400-800 mg/day) and a reduction in the length of hospital stay was reported (38). All of these studies support the use of propolis as an adjunctive treatment in hospitalized patients with COVID-19.

It was valuable for the study that there was no difference between the groups in age and gender. Because age and gender were parameters that could affect the course of the disease (39). Being elderly and having a coexisting disease increase the likelihood of requiring intensive care (40). However, there was no patient in need of intensive care among the patients included in the current study. The mean age of the patients in the present study was 59.1±15.2 years which could be attributed to the exclusion of patients who needed intensive care on admission.

The study's weakness is that it didn't include people who needed intensive care or who were living alone at home with the disease. However, it is not possible to apply oral treatment for those patients in need of intensive care and to follow-up patients at home who are already in relatively good condition. Therefore, this study may not be generalizable to a broader population that includes people who require intensive care or those living alone with the disease.

The propolis extracts used for the current study were prepared from samples obtained from plants native to Turkey and were obtained by completely dissolving in only water or olive oil. It should be considered that propolis components vary with climate and region (41). Both propolis extracts (WEP and OEP) used in the present study include phenolic acids, especially caffeic acid (approximately 200 µg/ml) (42) and flavonoids such as galangin, pinocembrin, and chrysin.

Using propolis not only in the treatment of COVID-19 but also in various cancers and inflammatory diseases has been studied (43, 44). It also has anti-ulcer activity (45). Combining current therapy with propolis in COVID-19 patients has been associated with earlier hospital discharge and lower mortality (46). Despite the promising results in laboratory tests and clinical trials, large-scale studies are needed to definitively establish the efficacy of propolis in the treatment of these diseases.

Limitation of the study: The patient numbers in each group were not sufficient because the study period of the present study was close to the end of the first wave of COVID-19 in Turkey.

As a result, the addition of propolis to the treatment as a food supplement has a positive effect on the recovery of patients with COVID-19. It should also be kept in mind that propolis, which is also used to treat many diseases, may be used as a preventive medicine application. While the evidence of propolis's effectiveness as a treatment for COVID-19 is still being studied, it appears to be an effective treatment in terms of increasing a patient's rate of recovery.

Ethical Statement

The current study obtained ethical approval from the Istanbul Medipol University Clinical Research Ethics Committee with the approval number T140938 issued by the Ministry of Health of the Republic of Türkiye.

Conflict of interest
The authors declared none.

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Authors' contributions
Concept: B.D.K., Design: B.D.K., Data Collection or Processing: B.D.K., E.S., D.K., Analysis or Interpretation: O.D., A.T.A., Literature Search: B.D.K., A.T.A., E.S., O.D., D.K., Writing: B.D.K., D.K.

References

1. Rello J, Belliato M, Dimopoulos MA, Giamarellos-Bourboulis EJ, Jaksic V, Martin-Loeches I, et al. Update in COVID-19 in the intensive care unit from the 2020 HELLENIC Athens International symposium. Anaesth Crit Care Pain Med. 2020 Dec;39(6):723–30.
2. Docea A, Tsatsakis A, Albulescu D, Cristea O, Zlatian O, Vinceti M, et al. A new threat from an old enemy: Re emergence of coronavirus (Review). Int J Mol Med. 2020 Mar 27;
3. Coronaviridae Study Group. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Apr 2;5(4):536–44.
4. D'Souza R, Ashraf R, Rowe H, Zipursky J, Clarfield L, Maxwell C, et al. Pregnancy and <scp>COVID</scp> -19: pharmacologic considerations. Ultrasound in Obstetrics & Gynecology. 2021 Feb;57(2):195–203.
5. To KKW, Tsang OTY, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020 May;20(5):565–74.
6. Rijkers G, Murk JL, Wintermans B, van Looy B, van den Berge M, Veenemans J, et al. Differences in Antibody Kinetics and Functionality Between Severe and Mild Severe Acute Respiratory Syndrome Coronavirus 2 Infections. J Infect Dis. 2020 Sep 14;222(8):1265–9.
7. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. Journal of Thrombosis and Haemostasis. 2020 May 27;18(5):1023–6.
8. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. Clinical Microbiology and Infection. 2020 Sep;26(9):1259.e5-1259.e7.
9. Wong AY, MacKenna B, Morton CE, Schultze A, Walker AJ, Bhaskaran K, et al. Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts. Ann Rheum Dis. 2021 Jul;80(7):943–51.
10. Sterne JAC, Murthy S, Diaz J V., Slutsky AS, Villar J, Angus DC, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. JAMA. 2020 Oct 6;324(13):1330.
11. Kmietowicz Z. Covid-19: Selected NHS patients will be treated with remdesivir. BMJ. 2020 May 26;m2097.
12. Marconi VC, Ramanan A V, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021 Sep;
13. Abbaspour Kasgari H, Moradi S, Shabani AM, Babamahmoodi F, Davoudi Badabi AR, Davoudi L, et al. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. Journal of Antimicrobial Chemotherapy. 2020 Nov 1;75(11):3373–8.
14. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19. JAMA. 2020 Dec 8;324(22):2292.
15. Freedberg DE, Conigliaro J, Wang TC, Tracey KJ, Callahan M V., Abrams JA, et al. Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study. Gastroenterology. 2020 Sep;159(3):1129-1131.e3.
16. Mather JF, Seip RL, McKay RG. Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients With COVID-19. American Journal of Gastroenterology. 2020 Oct;115(10):1617–23.
17. Balandrin MF, Klocke JA, Wurtele ES, Bollinger WmH. Natural Plant Chemicals: Sources of Industrial and Medicinal Materials. Science (1979). 1985 Jun 7;228(4704):1154–60.
18. Mani JS, Johnson JB, Steel JC, Broszczak DA, Neilsen PM, Walsh KB, et al. Natural product-derived phytochemicals as potential agents against coronaviruses: A review. Virus Res. 2020 Jul;284:197989.
19. Turcatto AP, Lourenço AP, De Jong D. Propolis consumption ramps up the immune response in honey bees infected with bacteria. Apidologie. 2018;49(3):287–96.
20. Berretta AA, Nascimento AP, Bueno PCP, de Oliveira Lima Leite Vaz MM, Marchetti JM. Propolis Standardized Extract (EPP-AF®), an Innovative Chemically and Biologically Reproducible Pharmaceutical Compound for Treating Wounds. Int J Biol Sci. 2012;8(4):512–21.
21. Miguel MG, Nunes S, Dandlen SA, Cavaco AM, Antunes MD. Phenols, flavonoids and antioxidant activity of aqueous and methanolic extracts of propolis (Apis mellifera L.) from Algarve, South Portugal. Food Science and Technology. 2014;34(1):16–23.
22. Xie Y, Huang B, Yu K, Shi F, Liu T, Xu W. Caffeic acid derivatives: A new type of influenza neuraminidase inhibitors. Bioorg Med Chem Lett. 2013;23(12):3556–60.
23. Utsunomiya H, Ichinose M, Ikeda K, Uozaki M, Morishita J, Kuwahara T, et al. Inhibition by caffeic acid of the influenza a virus multiplication in vitro. Int J Mol Med. 2014;34(4):1020–4.
24. Wang GF, Shi LP, Ren YD, Liu QF, Liu HF, Zhang RJ, et al. Anti-hepatitis B virus activity of chlorogenic acid, quinic acid and caffeic acid in vivo and in vitro. Antiviral Res. 2009;83(2):186–90.
25. Cheng Z, Sun G, Guo W, Huang Y, Sun W, Zhao F, et al. Inhibition of hepatitis B virus replication by quercetin in human hepatoma cell lines. Virol Sin. 2015;30(4):261–8.
26. Shi ZH, Li NG, Tang YP, Wei-Li, Lian-Yin, Yang JP, et al. Metabolism-based synthesis, biologic evaluation and SARs analysis of O-methylated analogs of quercetin as thrombin inhibitors. Eur J Med Chem. 2012 Aug;54:210–22.
27. Tsai FJ, Lin CW, Lai CC, Lan YC, Lai CH, Hung CH, et al.

Kaempferol inhibits enterovirus 71 replication and internal ribosome entry site (IRES) activity through FUBP and HNRP proteins. Food Chem. 2011 Sep;128(2):312–22.

28. Okamoto Y, Tanaka M, Fukui T, Masuzawa T. Brazilian propolis inhibits the differentiation of Th17 cells by inhibition of interleukin-6-induced phosphorylation of signal transducer and activator of transcription 3. Immunopharmacol Immunotoxicol. 2012;34(5):803–9.

29. Szliszka E, Kucharska AZ, Sokół-Łętowska A, Mertas A, Czuba ZP, Król W. Chemical Composition and Anti-Inflammatory Effect of Ethanolic Extract of Brazilian Green Propolis on Activated J774A.1 Macrophages. Evidence-Based Complementary and Alternative Medicine. 2013;2013:1–13.

30. Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, et al. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res. 2005 Oct;68(1):36–42.

31. Maruta H, He H. PAK1-blockers: Potential Therapeutics against COVID-19. Med Drug Discov. 2020 Jun;6:100039.

32. Da J, Xu M, Wang Y, Li W, Lu M, Wang Z. Kaempferol Promotes Apoptosis While Inhibiting Cell Proliferation via Androgen-Dependent Pathway and Suppressing Vasculogenic Mimicry and Invasion in Prostate Cancer. Analytical Cellular Pathology. 2019 Dec 1;2019:1–10.

33. Sekiou O, Bouziane I, Bouslama Z, Djemel A. In-Silico Identification of Potent Inhibitors of COVID-19 Main Protease (Mpro) and Angiotensin Converting Enzyme 2 (ACE2) from Natural Products: Quercetin, Hispidulin, and Cirsimaritin Exhibited Better Potential Inhibition than Hydroxy-Chloroquine against. ChemRxiv. 2020;2.

34. Schwarz S, Sauter D, Wang K, Zhang R, Sun B, Karioti A, et al. Kaempferol Derivatives as Antiviral Drugs against the 3a Channel Protein of Coronavirus. Planta Med. 2014 Jan 23;80(02/03):177–82.

35. Yoon SH, Lee KH, Kim JY, Lee YK. Pneumonia in Korea. Korean J Radiol. 2020;21(4):494–500.

36. Sahin A, Turkmen S, Guzel N, Mentese A, Turedi S, Karahan SC, et al. A Comparison of the Effects of Grayanotoxin-Containing Honey (Mad Honey), Normal Honey, and Propolis on Fracture Healing. Medical Principles and Practice. 2018;27(2):99–106.

37. Silveira MAD, Teles F, Berretta AA, Sanches TR, Rodrigues CE, Seguro AC, et al. Effects of Brazilian green propolis on proteinuria and renal function in patients with chronic kidney disease: a randomized, double-blind, placebo-controlled trial. BMC Nephrol. 2019 Dec 25;20(1):140.

38. Silveira MAD, De Jong D, Berretta AA, Galvão EB dos S, Ribeiro JC, Cerqueira-Silva T, et al. Efficacy of Brazilian green propolis (EPP-AF®) as an adjunct treatment for hospitalized COVID-19 patients: A randomized, controlled clinical trial. Biomedicine & Pharmacotherapy. 2021 Jun;138:111526.

39. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of <scp>COVID</scp> -19 severity: A literature review. Rev Med Virol. 2021 Jan 30;31(1):1–10.

40. Jain V, Yuan JM. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020 Jun 25;65(5):533–46.

41. Osés SM, Marcos P, Azofra P, de Pablo A, Fernández-Muíño MÁ, Sancho MT. Phenolic Profile, Antioxidant Capacities and Enzymatic Inhibitory Activities of Propolis from Different Geographical Areas: Needs for Analytical Harmonization. Antioxidants. 2020 Jan 15;9(1):75.

42. Bozkuş TN, Değer O, Yaşar A. Chemical characterization of water and ethanolic extracts of Turkish propolis by HPLC-DAD and GC-MS. J Liq Chromatogr Relat Technol. 2021 Jan 20;44(1–2):77–86.

43. Demir S, Aliyazicioglu Y, Turan I, Misir S, Mentese A, Yaman SO, et al. Antiproliferative and proapoptotic activity of Turkish propolis on human lung cancer cell line. Nutr Cancer. 2016 Jan 2;68(1):165–72.

44. Barlak Y, Değer O, Çolak M, Karataylı S, Bozdayı A, Yücesan F. Effect of Turkish propolis extracts on proteome of prostate cancer cell line. Proteome Sci. 2011;9(1):74.

45. de Barros MP, Sousa JPB, Bastos JK, de Andrade SF. Effect of Brazilian green propolis on experimental gastric ulcers in rats. J Ethnopharmacol. 2007 Apr;110(3):567–71.

46. Ali AM, Kunugi H. Propolis, Bee Honey, and Their Components Protect against Coronavirus Disease 2019 (COVID-19): A Review of In Silico, In Vitro, and Clinical Studies. Molecules. 2021 Feb 25;26(5):1232.