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Some Bioactive Properties of Honey

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Abstract
Honey is a functional food that is easy to digest, nutritious and has protective and therapeutic properties against many diseases due to its vitamins, minerals, organic acids, flavonoids, phenolic acids, amino acids and enzymes content. It has been utilized for medical purposes since ancient times. Thanks to the active components, it has antioxidant, anti-cancer, antimicrobial, dermatological, anti-inflammatory and prebiotic effects. Owing to its mighty antimicrobial property, clinical studies has been also proceeded, including the effectiveness of honey in reducing the symptoms of coronavirus (COVID-19). This review aimed to highlight the antioxidant, anticancer, antimicrobial and anti-COVID-19 features of honey.

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Özet
Bal, içerdiği vitaminler, mineraller, organik asitler, flavonoidler, fenolik asitler, aminoasitler ve enzimler nedeniyle sindirimi kolay, besleyici ve pek çok hastalığa karşı koruyucu ve tedavi edici özellik gösteren fonksiyonel bir gıdadır. Antik çağlardan günümüze kadar medikal amaçlarla kullanımı devam etmektir. İçeriğindeki aktif bileşenler sayesinde antioksidan, anti-kanser, antimikrobiyal, dermatolojik, antiinflamatuar ve prebiyotik etkiye sahiptir. Güçlü antimikrobiyal özelliği nedeniyle balın koronavirüs (COVID-19) septomlarını azaltmadaki etkinliğini içeren klinik çalışmalar da devam etmektedir. Bu derleme, balın antioksidan, antikanser, antimikrobiyal ve anti- COVID-19 özelliklerini vurgulamayı amaçlamıştır.

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Introduction

Honey, a natural food produced by Apis mellifera, has higher awareness, availability and consumption compared to other beekeeping products such as propolis, royal jelly, bee venom, beeswax and pollen [1]. It is produced by bees by collecting nectar (blossom honey) from flowers, combining it with bee secretion and drying and storing it for maturation in honeycombs, or the secretions of living parts of plants and/or the secretions of plant-sucking insects (honeydew honey) [2]. Fructose and glucose, the amount of which varies between 55-75 g in 100 g honey, are the main monosaccharide compounds in honey. While the water ratio generally varies from

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15-25 g to 100 g-1 honey, it also contains essential components such as phenolic and volatile compounds, vitamins, proteins, minerals, enzymes, organic acids, amino acids [3-5].

Pyhsicochemical properties of honey

Approximately 181 compounds have been detected in various honey species, change according to different factors such as geographical and botanical origin [6]. Natural honey is called honey with high viscosity, hygroscopic structure, high surface tension and foaming properties due to its colloid content [7]. The chemical composition of honey alters with respect to its botanical source however basically honey consists of approximately 82% carbohydrates, 17% water, 0.7% minerals, 0.3% protein, macro and micro components.

In addition to monosaccharides such as fructose and glucose, the main sugars in honey, disaccharides which are sucrose, maltose, isomaltose, lactose, galactobiose, gentiobiose, nigerose and other oligosaccharides cover the sugar content of honey, for instance, some tetrasaccharides, pentasaccharides and hexasaccharides have been found in New Zealand and Spanish honeys [8,9] or fructo-oligosaccharides such cetose, nystose and inulobiose is isolated from Malaysian Tualang honey [10]. Owing to high carbohydrate content, it has a low water activity content varying in the range of 0.59-0.63. Moisture content is related to percentage of glazed comb, harvest time, climatic conditions at harvest and storage conditions [11,12]. According to Codex Alimentarius Commission Honey Standard (Codex Alimentarius Commission-CAC) and European Union's 2001/110/EC directives, water rate in honey should be less than 20 %. At 24 °C containing 18.9% moisture, honey has a viscosity of 9.9 Pa*s [13]. The moisture content, which is a key factor for microbial growth, affects the properties of honey such as quality, crystallization, viscosity and taste is considered as a criterion point in defining the parameters such as shelf life and maturity level of honey. It has been reported that low moisture content prevents fermentation in honey by osmotolerant yeasts [14].

Honey has different colors from light to dark, depending on suspended particles, botanical source, and storage time. It is usually amber or yellow in color, although less common, bright yellowish (sunflower), grayish (eucalyptus), reddish (chestnut) and greenish (sweet honey) varieties are also available. [7].

Honey is an acidic food because of organic acids of animal and vegetable origin as malic, gluconic (70.0-80.0% of all free acids), acetic, butyric, citric, formic, lactic, oxalic, succinic, fumaric, α-ketoglutaric, pyroglutamic and maleic acid. Acidity is one of the significant criteria for determining the quality of honey. While honey fermentation increases the acidity of honey, the acidity value varies according to the type of honey because of natural variations [15-17].

Honey contains polyphenol subgroups such as hydroxybenzoic acids, hydroxycinnamic acids and hydroxyphenylacetic acids [18]. It contains flavonoids (apigenin, pinobanksin, pinosembrin, kaempferol, galangin, luteolin, hesperetin, catechin, quercetin, rutin, naringin, neringenin), phenolic acids (caffeic, ferulic, ellagic, gallic, syringic, p-coumaric, trans-cinnamic, vanillic, 4-(Dimethylamino)benzoic, chlorogenic acids and pyrogallol) and their derivatives. These types of polyphenols are effective on the appearance (color) and functional properties of honey. Some flavonoids have been identified as markers for various types of honey; e.g quercetin, sunflower honey; kaempferol, rosemary honey; ferulic acid (hydroxycinnamates), p-coumaric acid and caffeic acid are indicators of chestnut honey. It has been noted that pinocembrin, pinobanksin and chrysin normally present in propolis, were also obtained from several European honeys. While the amount of phenolic component of honey varies by the source of nectar and geographical and ecological conditions, it was reported that phenolic content of light-colored honey samples is generally lower than that of dark-colored honey [5,19]. Compared to other flower honeys, Manuka honey has been found to contain more phenolic compounds [20].

Amount of protein in honey is quite low, this value varies due to the nectar source of the bee. Studies have demostrated that proteins such as albumin and globulin are present in honey. Even though the amount of protein in honey is low, it is a food rich in amino acids with 11 to 21 different amino acids in its composition [9]. Proline, phenylalanine, γ-amino butyric acid (GABA), lysine, β-alanine, glutamine, glutamic, arginine, serine and aspartic acid are examples of amino acids exist in honey. Proline amino acid with the highest amount in honey is the precursor of hydroxyproline in the structure of collagen and elastin [21]. Proline, which is found in different amounts in plants (e.g. 222 mg/kg in acacia, 956 mg/kg in thyme) is used as a criterion to distinguish between fake and nectar honey. It has been determined by studies that 80-90% of the amino acid composition is the proline amino acid found in the liquid secreted by the bee when converting the nectar into honey and in collected nectars. For this reason, proline content is one of the main criteria used to evaluate the quality of honey and forgery in honey [22,23].

Honey contains natural enzymes such as glucose oxidase, catalase, peroxidase, invertase (sucrose), diastase (amylase), acid phosphatase in its composition. Invertase responsible for converting nectar into honey, converts sucrose to glucose and fructose; diastase enzyme reduces starch into small sugars, β-glucosidase turns into glycogen to glucose and maltose [24]; glucose are decomposed to gluconic acid and hydrogen peroxide by glucose oxidase enzyme and catalase converts hydrogen peroxide to oxygen and water [25]. Another significant enzyme diastase, an enzyme originating from nectar and bees, is used as a criterion for the evaluation of honey's freshness. Diastase enzyme is inactivated as a result of heat treatment and storage in proper conditions. Inactivation of enzyme is determined by diastase number analysis. Diastase number refers to the amount of starch that amylase enzymes in 100 g honey degrades in 1 hour at 38-40°C [26]. It has been reported that the diastase contained in honey is irreversibly inactivated at temperatures between 90°C and 100°C, therefore diastase number is also a quality parameter of between natural and heat treated honey [27].

The ash value of honey, which ranges from 0.02 to 1.03% (w/w), is related to the mineral content [28]. While the mineral content of honey varies greatly affected by environmental conditions, botanical sources, geographical regions, mineral composition in honey has also been an major marker of the environmental cases (emissions, trace pollutants, etc.) of the region from which it is obtained. For instance, in a research about mineral content of Polish honeys, between 0.38% (dark honeydew honey) and 0.02% (pale rape honey) were recorded [29,30]. In another study, Yaşar and Söğütlü (2020) measured the mineral content of honey samples from the 8 different regions of Bingöl in the range of 0.39-0.54% [31]. Potassium (45-85%) is the predominantly mineral found in honey. Also honey contains small amounts of zinc, calcium, iron, magnesium, manganese copper, and trace metals (<1μgg-1) [8].

There are more than 400 volatile organic compounds that contribute to the aroma, bioactive and apitherapeutic properties of honey. Some volatile compounds have been identified as markers in certain single-flowered honeys, for example heptanal and hexanal for lavender honey; alkanes, diketones, sulfur compounds for eucalyptus honey; cis-rose for lemon honey. Other volatile compounds are also present in low concentrations, such as fatty acids, terpenes (mono- and sesquiterpenes), aldehydes, benzene derivatives, ketones, esters and alcohols. The volatile components of honey change considerably during storage because of secondary reactions such as the Maillard reaction [28]. Dadalı (2021) defined some physical, chemical properties, volatile components and sensory properties of chaste (Vitex agnus-castus L.) honey produced in Aydın, Çanakkale, İzmir and Muğla. A total of 16 volatile compounds, including 1 alkane, 4 aldehyde, 2 alcohol, 2 terpenes, 2 sulphurous compound, 3 furans, 1 benzene compound and 1 ketone groups, were detected in chasteberry honey. Benzeneacetaldehyde, nonanal, 2-furancarboxaldehyde, 1-(2-furanyl)-ethanone, 2-ethyl-1-hexanol, benzaldehyde, 5-methyl-2-furancarboxaldehyde, octane and dimethyl sulfide were determined as common volatile components in all analyzed honeys [32].

Bioactivity of honey

Antioxidant effect

The medicinal use of honey dates back to 8000 years in ancient times. The application of honey in a great number of diseases is mentioned in Egyptian papyruses 1900-1250 BC, in Sumerian tablets dating back to 6200 BC, in the Vedas older than 5000 years, in education of Hippocrates (460-357 BC) and in many religious books [33].

Phenolic compounds or polyphenols are one of the most substantial groups of compounds commonly found in plants. Polyphenols are also products of the secondary metabolism of plants. Flavonoids and phenolic acids (benzoic and cinnamic acid derivatives) form the most essential groups of polyphenols, identified by more than 5000 compounds. Since honey is a natural rich source of polyphenols, all types of flavonoids it reacts as a antioxidant reagent and the antioxidant properties of honey depend on the plant source from that the nectar is collected, seasonal and environmental factors [19].

Reactive oxygen species, most of which are formed by free radicals, are oxygen forms with higher chemical reactivity compared to normal oxygen molecules. Free radicals are high-energy, unstable compounds that contain one or more unpaired electrons in their outer atomic orbitals and this unpaired electron gives free radicals great reactivity, causing them to damage many biological materials such as proteins, lipids, DNA and nucleotide coenzymes. Studies are addressed that this damage promotes cardiovascular diseases, various types of cancer, cataracts, weakening of the immune system, nervous system degenerative diseases and aging [34]. The flavonoids apigenin, pinobanksin, pinocembrin, kaempferol, galangin, luteolin, hesperetin, catechin, quercetin, rutin, naringin, naringenin, luteolin present in several honey types have cytotoxic, apoptotic, and anti-proliferative effect to various cancer cell lines [35]. It has been stated that the antioxidant property of honey, which naturally has antioxidant properties, is related to the total phenolic substance content, and the antioxidant properties of honey increase with the increase in the total phenolic substance content [36]. Main fenolic compounds identified in almost honey are caffeic, trans-cinnamic, ferulic, ellagic, gallic, 4-Dimethylaminobenzoic, syringic, p-coumaric, chlorogenic, vanillic acids and pyrogallol. Thiamine, riboflavin, α-tocopherol, ascorbic acid, salicylic acid as vitamins are also pointed that responsible for high antioxidant effects of raw and fresh honey. It has been found that the increase in vascular permeability created by using ethanol in the stomach of rats can be prevented with Anzer honey [37]. The obtained results were associated with the high ascorbic acid content of Anzer honey. It includes 62.67 mg/g ascorbate that meets the daily vitamin C requirement of 60-100 mg of a 70 kg person. However, this value has been reported as 2-2.5 mg/g in other honeys. In addition to against organic acids found in honey, polyphenols, sulfhydryl groups, carotenoid derivatives and glucose oxidase, catalase, peroxidase, invertase (sucrose), diastase (amylase), catalase, acid phosphatase enzymes content contributes to its role as a precious antioxidant [38,39].

Anti-cancer effect

Honey is a natural food with the effects of inhibiting growth of cancer cells and tumors because of including natural metabolites of nectar and bee secretions collected from different regions. It has been statemented that the inhibitory effect of honey in cancer cells is by virtue of bioactive components such as phenolic acid and flavonoids in its structure, and these compounds prevent the formation of free radicals and oxidative stress that give rise to cancer. Due to these properties, many studies have found that honey consumption has positive effects in the treatment of stomach, colon and liver cancer [40,41].

The main factors that provide anticancer properties to honey are gene regulation, apoptosis and antioxidant activity. The anticancer activity is supported by supports some biochemicals such as chrysin (apoptosis, down-regulation of genesacacetin), quercetin (inhibition of leukemia cells, decreased expression of oncogenes), caffeic acid (inhibition of NF-κB, apoptosis), pinocembrin (increased caspase-3) and p-coumaric acid, acacetin is eugenol (apoptosis) [42]. A study examined the anticancer activity of Manuka, honeydew, and thyme honey against prostate cancer cell lines. Besides the isolated phenolic components of honey, decreasing the metastatic properties, especially migration and adhesion were observed. Even though the sugars found in honey do not show an independent anti-metastatic activity, the phenolic compounds have much less effect in their absence [43] and also induced apoptosis and affected cell-renewal in human colorectal cancer cell lines was recorded [44].

Another structure that confers anticancer activity to honey is 3,4,5-trihydroxybenzoic acid (gallic acid) that is an intermediate of secondary plant metabolism in higher plants. Gallic acid, commonly found in honey, is known to have strong anti-cancer, antioxidant, anti-inflammatory, anti-mutagenic and cardioprotective activities and some pharmacological effects In addition to gallic acid, caffeic acid, which is found in foods such as fruits, vegetables, honey, and medicinal plants, has many biological activities such as antioxidant, anti-cancer, and also has HIV-inhibiting properties. Moreover cinnamic acid in honey is an effective food flavoring agent with anticancer effects [16].

Antimicrobial effect

It is known that the antimicrobial effect of honey is due to its low water activity and high acidity values, as well as the fact that it contains compounds such as hydrogen peroxide, flavonoids and phenolic acids. Thanks to these properties, honey creates an environment that inhibits the growth of pathogenic bacteria that cause disease in humans. In the literature, there are studies reporting the inhibitory properties of honey not only against bacteria, but also against viruses, fungi and parasites [9]. In a study conducted for this purpose, it was determined that 10% honey concentration applied to Ecinococccus granulosus parasite, which causes hydatid cyst (echinococcosis), has a lethal effect from the third minute [45]. In a research for to determine the antimicrobial effects of honey samples collected from Bingöl region, it was reported that 0.1 mL honey sample inhibited the growth of bacterial species including Escherichia coli, Pseudomonas aeroginosa, Klebsiella pneumoniae, Bacillus brevis, Staphylococcus aureusm and fungal species such as Candida albicans and Rhodotorula rubra [46]. In addition, in vitro study with Manuka honey showed that it inhibited the replication of influenza virus and synergized the effects of known anti-viral drugs [47].

Characteristics of honey such as high osmolarity, low water activity, low pH, hydrogen peroxide production due to sugar concentration are effective on its antibacterial activity. Hydrogen peroxide, also defined as inhibition factor, is the most important antibacterial compound formed as a result of the glucose oxidase enzyme produced in the hypopharyngeal glands of bees, oxidizing the glucose in honey. In a last in vitro study, it was noted that the addition of catalase to honey caused a partial decrease (30-50%) in its antibacterial activity due to the decomposition of hydrogen peroxide into water and oxygen. Due to the reduction of hydrogen peroxide, flavonoids such as rutin, chlorogenic acid, quercetin and caffeic acid showed antioxidant and antibacterial effects ($p < 0.05$) [48].

Associated with color, aroma and taste, 1,2-dicarbonyls are extremely reactive products resulting from non-enzymatic glucose metabolism. While the ideal temperature for the formation of Methylglyoxal (CH_3–CO–CHO) produced from dihydroxyacetone in honey is 37 °C, both methylglyoxal and dihydroxyacetone are lost at 50 °C [49]. Methylglyoxal supports the non-peroxide antibacterial activity of honey against gram positive and negative bacteria. Lately, an anti-HIV activity has also been demonstrated by blocking virion assembly at the final stage of infection [50].

The higher content of phenolic compounds in dark colored honeys caused antibacterial activity to be more effective than light colored honeys. Among the bacteria that honey has antibacterial effect, Staphylococcus aureus, Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Enterobacter cloaca, Micrococcus luteus, Klebsiella pneumoniae and Helicobacter pylori;among the fungi, Candida albicans, Candida xerosis, Candida tropicalis and Rhodotorula rubra were reported [26].

Honey is preferred in medicine including on account of its antimicrobial effect, as a results of the high carbohydrate content, high osmotic pressure and high acidity [51]. The high sugar content of honey inhibits the growth of microorganisms, however sugar content alone does not conduce to antibacterial properties of honey. The gastrointestinal tract (GIT) of honey bee contains essential and beneficial bacteria, especially Bifidobacteria, for maintaining health. Bifidobacteria population in GIT can be increased by consuming foods with a rich source of prebiotics such as natural honey [16].

It is awared of from the records of Dioscorides that honey has been used in the treatment of infected wounds for at least 2000 years [26]. Today, there is an increasing interest to apply of honey for therapeutic purposes. Honey is an apitherapeutic agent in the topical wound treatment thanks to its bacteria-inhibiting property. It reduces wound pH by penetrating the bacterial biofilm, reduces pain and inflammation, has a positive effect on wound healing by regulating the epithelial mesenchymal transition process (EMT), promotes fibroblast migration and keratinocyte closure, increases the amount of collagen. Therefore, honey has a potential role in tissue engineering and regeneration [52].

Anti- COVID-19 effect

SARS-CoV-2 causes severe acute pneumonia-associated respiratory syndrome in the human body through the respiratory tract and it is rapidly transmitted by direct and droplet contact. Despite the high virulence and lethal consequences of the 2019 coronavirus epidemic (COVID-19), no specific antiviral treatment is available so far [53]. Therefore corticosteroids, some antiviral drugs, interferons and antibiotics have been used to treat COVID-19 without any evidence in humans [54,55]. Antibiotics have various side effects in terms of liver damage, malnutrition and hypoproteinemia in COVID-19 patients. Therefore, the potential of natural products with multiple bioactivity to strengthen the immune system and cure the disease in COVID-19 is being investigated [56]. Although clinical studies on the oral antimicrobial effect of honey are not many, some positive results have also been obtained. Honey has been clinically shown to increase the activity of interferons and the formation of cytokines since it is assumed to have antiviral activity against a variety of viruses, including SARS-CoV-2, it has antioxidant and anti-inflammatory effects as well as mitosis in T and B lymphocytes [57].

In many parts of the world folk medicine recommends natural honey as first-line treatment for acute cough caused by upper respiratory tract infection, which is a major symptom of COVID-19. It has been reported that flavonoids have possible positive effect of honey against COVID-19 symptoms. Methylglyoxal present in honey interacts with microbial metabolites of different pathogens, resulting in the activation of mucosal-associated invariant T cells that maintain the barrier integrity of the nasal mucosa, which is the key access of SARS-CoV-2 to the human body [58]. Another clinical study examined the effect of a natural honey and black seed mixture against COVID-19 symptoms. As a result of the research conducted on COVID-19 patients, 313 adult patients were found, including moderate (210) and severe (103). According to the results, a 59% reduction in the recovery time of symptoms in the experimental group and earlier virus clearance were noted in the experimental group. When comparing to the control group, it was observed decreasing mortality by 4-folds. Additionally, severe patients in experimental group had a mean oxygen saturation of over 90% six days ago [59]. Table 1 shows that researches based on the possible effects of flavonoids present in propolis and honey against COVID-19 [53].

Table 1: Possible effects of flavonoids against COVID-19

Bee-Related Compounds	**SARS-CoV-2 Proteins**	**Possible Anti-COVID-19 Effects**	**References**
caffeic acid phenethyl ester	transmembrane protease serine 2	inhibiting S protein cleavage	**[60]**
rutin, luteolin, caffeic acid phenethyl ester	angiotensin-converting enzyme-related carboxypeptidase II	inhibiting viral binding to host cell receptor	**[61,62,63]**
naringin, rutin, quercetin	S protein	inhibiting viral fusion in host cell membrane	**[62,64]**
rutin, nicotiflorin, luteolin and caffeic acid phenethyl ester	chymotrypsin-like protease/main protease, RNA-dependent RNA polymerase and papain-like protease	inhibiting viral replication and inflammatory reaction	**[62,65,66,67]**

Conclusion

Honey is a natural bee product that comprises approximately 200 different components in its structure. Although the chemical composition of honey varies considerably according to its floral and geographical origin, it has been proven in the light of previous studies that it has a very rich chemical composition, especially phenolic compounds, and high antioxidant, antimicrobial, anti-diabetic, hepato- and nephroprotective activity, anti-aging effect, wound healing effect, antidote effect and anticancer effect. In addition to these features of honey, the number of studies conducted to optimize its use for the effects of COVID-19 has been gradually increased. Based on studies that resulted in improvement of COVID-19 symptoms and earlier discharge of infected patients with either honey or with its herbal combinations, future studies comparing the effects of bee products alone or in combination are needed.

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