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Natural bioactive compounds of honey and their antimicrobial activity

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Abstract: Honey is a complex and variable mixture that contains more than 180 biochemical compounds from various molecule families. This mixture is obtained after processing the nectar out of plant food sources at the level of the bee abdomen. The bioactive components found in this natural product are in charge of its antimicrobial properties. Honey is used for its antibacterial actions against Gram-positive (Gram+) and Gram-negative (Gram–) bacteria, its anti-fungal and antimycotic actions against moulds and yeasts, along with its protozoal and antiviral activities. This literature review outlines the natural antimicrobial potential of honey; it explains the factors responsible for this potential and spells out their mechanisms of action. Osmotic pressure, water activity, the acid content of honey, presence of bioactive compounds like hydrogen peroxide (H_2O_2), phenolic acids, flavonoids, methylglyoxal (MGO), defensin-1, lysozyme, volatile compounds as well as antibacterial products secreted from the lactic bacteria that are behind this antimicrobial activity. This potential basically depends on the biological activities of the initially harvested floral source, its geographical origin, season, storage conditions, honey age, health of bee colonies and suitable beekeeping practices.

Keywords: bioactive components; antibacterial activity; honey; floral source; biological activities

Honey is a natural product that has been with man since the most ancient times (Gupta et al. 2014), using it for nutritional and medicinal purposes dates back to around 5 500 years (Samarghandian et al. 2017). Honey is a bee product that has a wide range of properties and applications (Kurek-Górecka et al. 2020). This product is a complex and variable mixture of molecules having structures and multiple functions that originate from nectar from plants, pollen, and the bee itself (Brudzynski et al. 2017). This natural product contains around 180 biochemical compounds (El Sohaimy et al. 2015; Bucekova et al. 2019) of which: sugar, water, proteins, vitamins, free amino acids, enzymes, organic acids, phenolics and volatile compounds (Da Silva et al. 2016; Danila et al. 2020). These compounds are predominantly fitted with biological properties (Rafael et al. 2021). Several studies disclosed that honey has numerous activities like wound-healing (Couquet et al. 2013), antioxidants, antimicrobics, nematicides, anti-cancer and anti-inflammatory (Rafael et al. 2021). Nowadays, scientists are looking for new antimicrobial arms within natural products as a result of the alarming advent of antibiotic-resistant bacteria (Donia et al. 2011; Udwary et al. 2011). Honey currently represents a branch of alternative medicine, called apitherapy (Mandal and Mandal 2011; Bourlioux 2013). Many researchers have recently expressed their interest in the mechanisms of honey action as a natural antimicrobial agent (Mc Loone et al. 2016). Maddocks

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and Jenkins (2013) reported that none of the microorganisms has developed a resistance to honey. This natural product has been around for a very long time in treating skin infections (Moody et al. 2011). Russians made use of it during World War I to prevent wound infections and speed up their healing, whereas Germans combined it with cod-liver oil to treat burns, fistulae, and furuncles (Bansal et al. 2005). Honey is mainly used to treat infected wounds (Hegazi et al. 2017) and chronic wounds (Eteraf-Oskouei and Najafi 2013), infected burns (Hananeh et al. 2015), infected postsurgical wounds (Cavanagh et al. 1970), bedsores (Ahmed et al. 2003) and infant respiratory tract infections (Oluwapelumi et al. 2017). This literature review aims to bring together the main studies conducted on the antimicrobial activity of honey, the biochemical compounds involved in these activities together with the mechanisms of action of these high-potential antimicrobial molecules.

PROPERTIES OF HONEY

Several *in vitro* and *in vivo* studies and researches have been conducted on the properties of honey: antibacterial, antifungal, antiviral and antiprotozoal (Mohammed et al. 2017; Rani et al. 2017; Semprini et al. 2018; Guttentag et al. 2021). The antimicrobial potential of honey varies considerably, it mostly depends on the botanical origin of the flowers, geographic source, season, harvest, storage conditions (Irish et al. 2011; Anthimidou and Mossialos 2013), age and the health of bee colonies (Ibarguren et al. 2010; Aween et al. 2012a; Mathialagan et al. 2018). Honey composition and physicochemical properties differ according to the floral source (Table 1) used by the bees (Castro-Vázquez et al. 2009; Chang et al. 2011; Feknous et al. 2021).

Antibacterial activity. A number of studies have found a relationship between the floral origin of some honeys and their microbial activities (Haderbache et al. 2020) because according to Molan (1992) the botanical origin plays a key role in the various activities of honey. The antibacterial activity might differ within the same floral source. This relates as per Basualdo et al. (2007) to soil composition, climate, honey processing and propolis concentration. Honeys of various geographical and floral origins can have different antibacterial properties, according to their chemical composition (Irish et al. 2011; Moussa et al. 2012). According to Lusby et al. (2002), these honeys are named after the geographical location where they have been produced, the floral source or according to trees where the beehives are located. It has been pointed out by Molan (1992) that honey is active on over 60 bacterial species with positive and negative Gram (aerobic or anaerobic). Gram-positive (Gram+) bacteria are more vulnerable to honey's antibacterial activity (including Manuka honey) than Gram-negative (Gram–) bacteria (Mandal and Mandal 2011). The latter have an outer membrane in their wall structure that protects the peptidoglycan of the bacterial cell by preventing antimicrobial agents from entering (Madigan et al. 2015). According to Shenoy et al. (2012) and Ahmadi-Motamayel et al. (2013), honey has a broad spectrum of activities against Gram+ bacteria such as *Streptococcus pyogenes* (Maddocks et al. 2012) and *Mycobacterium* (Asadi-Pooya et al. 2003; Eteraf-Oskouei and Najafi 2013) as well as against Gram– bacteria like *Escherichia coli* (Adebolu 2005; Voidarou et al. 2011; Hegazi et al. 2017), *Pseudomonas aeruginosa* (Shenoy et al. 2012), *Salmonella typhi, Salmonella paratyphi*, *Salmonella enterocolitis, Shigella dysenteriae* (Cortopassi-Laurino and Gelli 1991; Adebolu 2005; Voidarou et al. 2011) and *Helicobacter pylori* (Atrott and Henle 2009; Lyudmila et al. 2015). Several reviews on honey have shown a significant antibacterial and antibiofilm potential against methicillin-resistant *Staphylococcus aureus* (Sherlock et al. 2010; Huttunen et al. 2013; Lu et al. 2014; Jantakee and Tragoolpua 2015; Ng and Lim 2015; Dimitrios et al. 2018; Proaño et al. 2021), against multiresistant *Mycobacterium tuberculosis* (Hannan et al. 2014), multiresistant *S. typhi* (Hussain et al. 2015) and against carbapenem-resistant *P. aeruginosa* (Cooper et al. 2014; Dimitrios et al. 2018). Honey is an alternative remedy in treating udder infections in veterinary medicine. Ahmed and Othman (2013) have proven the effectiveness of honey against pathogens that cause mastitis in cows by inhibiting *Streptococcus agalactiae, S. aureus* and *Klebsiella pneumoniae* (Table 1). Its use thereof as a natural sweetener in probiotic products like fermented dairy products stimulates the growth of lactic bacteria like *Streptococcus thermophilus, Bifidobacterium bifidum, Lactobacillus acidophilus* and *Lactobacillus delbrueckii* (Bansal et al. 2005; Sanz et al. 2005); it also impedes the development of pathogenic bacteria like *Shigella, Listeria monocytogenes* and *S. aureus*, thereby aiding in food preservation and consumer protection (Chen et al. 2000; Bansal et al. 2005; Feknous et al. 2021).

Antiviral activity of honey. Since the 19^{th} century, honey has also been recognised worldwide for its antiviral properties (Küçük et al. 2007). Honey produces actions against influenza (Watanabe et al. 2014), dengue virus (Soroy et al. 2014), viral hepatitis (Abdulrh-

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Table 1. Floral sources of honeys with antimicrobial activities

Honey origin	Plant	Assessed microorganism	References
Danish	*Mentha aquatica* *Tilia cordata* *Crataegus monogyna* *Erica tetralix* *Trifolium repens* *Hudsonia tomentosa* *Calluna vulgaris* *Rubus odoratus* *Brassica napus*	*Staphylococcus aureus* (CCUG 1800), *Staphylococcus aureus* (1094-7), *Staphylococcus epidermidis* (CCUG 39508), *Pseudomonas aeruginosa* (SKN 1317), *Escherichia coli* (K-12)	Matzen et al. 2018
Pakistani	*Ziziphus jujuba* *Acacia modesta* *Eucalyptus* spp. *Carissa opaca* *Helianthus annuus* *Trifolium alexandrium* *Plectranthus rugosus* Wall. *Prosopis* spp. *Nigella sativa*	*Salmonella typhi* (MDR)	Hussain et al. 2015
Polish	*Melilotus albus* *Melilotus officinalis*	*Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 700600), *Salmonella* spp.	Sowa et al. 2017
Saudi Arabia	**monofloral honeys** *Ziziphus nummularia* *Ziziphus spina-christi* *Blepharis ciliaris* *Thymus serpyllum* **polyfloral honeys** *Acacia asak* *Acacia origena* *Acacia negrii* *Acacia senegal* *Anisotes trisulcus* *Ziziphus spina-christi*	*Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 35218), *Proteus vulgaris* (ATCC 13315), *Citrobacter diversus* (ATCC 13315), *Salmonella enterica* (ATCC 700931)	Hegazi et al. 2020
Algerian	*Ziziphus lotus* *Euphorbia bupleuroides*	*Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 9027)	Haderbache et al. 2020
South African	*Eucalyptus cladocalyx* *Myrica cordifoliafynbos*	*Candida albicans* (strain 3118)	Frans et al. 2001
Portuguese	*Castanea sativa* Mill. *Eucalytus globulus* *Citrus sinensis* *Lavandula stoechas* *Erica cinerea*	*Candida tropicalis*, *Candida* biofilms, *Staphylococcus aureus*, *Pseudomonas aeruginosa*	Fernandes et al. 2020

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Table 1. To be continued

Honey origin	Plant	Assessed microorganism	References
Portuguese	*Erica* sp.	*Candida albicans*, *Candida krusei*, *Cryptococcus neoformans*	Feás and Estevinho 2011
North Portuguese	*Lavandula stoechas*	*Candida albicans* (CECT 1394), *Candida krusei* (ESA 11), *Cryptococcus neoformans* (ESA 3)	Maria et al. 2011
Brazilian	*Eucalyptus* sp.	*Staphylococcus aureus (*methicilline resistant S21), *Pseudomonas aerugin*osa (P28)	Proaño et al. 2021
Iranian	*Petroselinum sativum*, *Nigella sativa*, *Citrus sinensis*, *Zataria multiflora*, *Citrus aurantium*, *Zizyphus mauritiana*	anti-HIV-1 activity	Behbahani 2014
Australian jarrah	*Eucalyptus marginata*	*Trichophyton rubrum*	Guttentag et al. 2021
Egyptian	*Cassia javanica* *Citrus reticulata*	*Epidermophyton, Microsporum* *Tricophyton* sp.	El-Gendy 2010
Chilean	*Eucryphia cordifolia*	*Escherichia coli (*ATCC 35218), *Pseudomonas aeruginosa (*ATCC 27853), *Staphylococcus aureus* (methicilline resistant ATCC 43300)	Sherlock et al. 2010
Ukrainian	*Helianthus* spp.	*Staphylococcus aureus* (CCM 4223), *Listeria monocytogenes* (ATCC 7644), *Salmonella enterica* (serovar Typhimurium CCM 3807), *Escherichia coli* (ATCC 25922)	Giovanni et al. 2020
Ukrainian	*Robinia* spp.	*Staphylococcus aureus* (CCM 4223), *Listeria monocytogenes* (ATCC 7644), *Salmonella enterica* (serovar Typhimurium CCM 3807), *Escherichia coli* (ATCC 25922)	Giovanni et al. 2020
Malaysian tualang	*Koompassia excelsa* (tualang tree)	Acinetobacter bauma*nnii* *Stenotrophomonas maltophilia*	Hern et al. 2009
New Zealand	*Leptospermum scoparium*	*Enterococcus* sp., *Streptococcus mutans, Streptococcus sobrinus, Streptococcus pyogenes, Streptococcus agalactiae, Staphylococcus aureus, Staphylococcus* sp., *Staphylococcus* methicilline resistant, *Actinomyces viscosus, Enterobacter cloaceae, Shigella sonnei, Salmonella typhi, Klebsiella pneumoniae, Burkholderia capacia, Helicobacter pylori, Campylobacter* spp., *Porphyromonas gingivalis, Stenotrophomonas matophili, Acinetobacter baumannii, Pseudomonas aeruginosa, Proteus mirabilis, Shigella flexneri, Escherichia coli, Salmonella enterica serovar typhi*	Ahmed and Othman 2013

MDR – multidrug-resistant; ATTC – American Type Culture Collection; CCUG – Culture Collection University of Gothenburg; HIV – human immunodeficiency virus; CECT – Spanish Type Culture Collection; ESA – European Space Agency; CCM – Czech Collection of Microorganisms

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man et al. 2016), rabies (Igado et al. 2010), poliovirus type 1 (Búfalo et al. 2009), gingivostomatitis (Abdel-Naby Awad and Hamad 2018), herpes simplex virus type 1 (HSV-1) (Hashemipour et al. 2014; Semprini et al. 2018), and against human immunodeficiency virus (HIV) (Behbahani 2014). Behbahani (2014) provided evidence that methylglyoxal (MGO) present at high concentrations in Iranian honey was a powerful anti-HIV agent.

Antifungal activity of honey. Furthermore, some honeys are known for their antifungal actions against the species of the genera *Aspergillus* and *Penicillium* (Sampath Kumar et al. 2010) and against some yeasts of the *Candida* genus like *Candida albicans, Candida glabrata, Candida dubliniensis, Candida tropicalis, Candida krusei,* and *Candida parapsilosis* (Obaseiki-Ebor and Afonya 1984; Bansal et al. 2005; Irish et al. 2006; Bulgasem et al. 2016; Fernandes et al. 2020). According to Al-Waili and Haq (2004), honey inhibits fungal growth and diluted honey can inhibit toxin production. Mulu et al. (2010) stated that Ethiopian honey treated the resistant strains of *C. albicans* in HIV-positive patients. Guttentag et al. (2021) disclosed in their *in vitro* assays that Australian honey (Table 1) inhibits conidial germination and damages the structure of hyphae in *Trichophyton rubrum*. Some Egyptian single-flower honeys (Table 1) have shown some antifungal and antimycotic properties against *Epidermophyton* species, *Trichosporon* and *Microsporum* (El-Gendy 2010).

Antiparasitic activity of honey. Other authors described the antiparasitic properties of some honeys. Mohammed et al. (2017) have illustrated in their assays the antiprotozoal activity of some honeys against *Entamoeba histolytica* and *Giardia lamblia* (Table 1). Following some laboratory tests, Aksoy et al. (2020) reported that honey contained an antileishmanial activity after 48 h of incubation on promastigote forms in *Leishmania tropica* and they believed this natural product can be used as an alternative treatment of cutaneous leishmaniasis.

FACTORS OF HONEY ANTIBACTERIAL ACTIVITY AND THEIR MODE OF ACTION

Several antibacterial properties of honey are related to hydrogen peroxide (H_2O_2), naturally low pH, high osmolarity (Rani et al. 2017) and to bioactive compounds such as defensin-1, MGO, lysozymes, flavonoids, aromatic and volatile substances (Martinotti and Ranzato 2018). These factors act synergistically or individually to produce this effect (Alvarez--Suarez et al. 2010).

Acid pH. All types of honey are acid. This acidity results from the presence of thirty-one organic acids (Amenu 2013), the main one is gluconic acid which gives honey its low pH value (Bansal et al. 2005; Bogdanov et al. 2008). Honeys derived from nectar have a pH between 3.5 and 4.5, whereas those produced from honeydew range from 5.0 to 5.5 (Mbogning 2011). This inhibits the growth of pathogenic bacteria (Abdulrhman et al. 2013); the optimal pH ranges between 7.2 and 7.4 (Osmojasola 2002).

Osmotic pressure and water activity. Honey has a water activity (a_w) ranging from 0.56 and 0.62 as well as a high osmolarity related to its high sugar concentration (Belhadj et al. 2015). It is thus a hypertonic solution that leaves very little free water required for the growth of microorganisms (Bogdanov and Blumer 2001; Olaitan et al. 2007).

Hydrogen peroxide (H_2O_2). Hydrogen peroxide or oxygenated water (H_2O_2) is a powerful antiseptic (Goetz 2009). H_2O_2 is present in all types of honey with varying concentrations (Di Girolamo et al. 2012; Chua et al. 2015). The first correlation between the content of H_2O_2 and its antibacterial properties was linked in 1962 by Adcock (1962). H_2O_2 is produced by glucose oxidase (Figure 1) during the enzymatic oxidation of glucose (Kus et al. 2016). This antibacterial factor is the main inhibin found in most honeys (Nolan et al. 2019). We should point out that this inhibin occurs only in unripe honey (Bogdanov and Blumer 2001). In ripe honey, the process is stalled. If honey is diluted, it can be reactivated, though ripe honey contains only small quantities of H_2O_2 impending just slightly the bacterial growth (Bogdanov and Blumer 2001). Oxygenated water thus synthesised has a dual origin: vegetal as long as glucose comes from the foraged nectar and animal given that glucose oxidase is secreted through the hypopharyngeal glands of the worker bee during the conversion of nectar into honey (Desmouliere et al. 2013). Furthermore, the formed gluconic acid (Figure 1) increases honey acidity, thus limiting the growth of pathogenic bacteria (Olaitan et al. 2007; Mandal and Mandal 2011; Kwakman and Zaat 2012). The antibacterial properties result from the action of the free radicals regarded as very powerful cytotoxic oxidants able to break down bacterial deoxyribonucleic acid (DNA) strands (Brudzynski and Lannigan 2012). Most of the antibacterial activity of honey reported in the research in Table 1 is due to H_2O_2 (Temaru et al. 2007). These honeys have a wide range of therapeutic activities (Irish et al. 2006). To reach an optimal antibacterial activity, honey must be placed in a cool dark area and consumed

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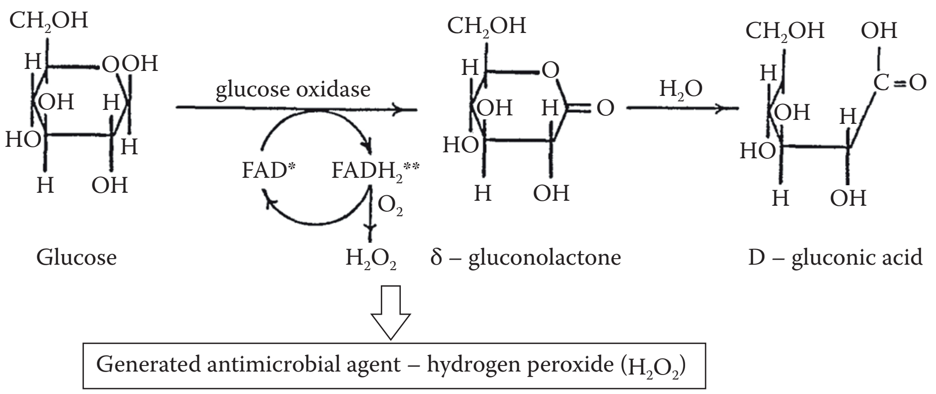

Figure 1. Glucose oxidase reaction and hydrogen peroxide (H_2O_2) generation

FAD – flavinadenindinukleotid (oxidised form); FADH – flavinadenindinukleotid (reduced forms)

Source: Piotr (2017)

fresh (Al-Waili et al. 2011). The process of heating honey will reduce the activity of H_2O_2 (Matzen et al. 2018). Storage at 4 °C and at 25 °C entails a loss of peroxide activity with a greater loss observed at 25 °C (Knight 2013). Some honeys are endowed with an activity labelled 'non-peroxidasic', in other words, they preserve a strong antibacterial power even when their peroxidasic activity is neutralised by catalase or by heating.

Methylglyoxal (MGO). MGO (CH_3-CO-CH=O or $C_3H_4O_2$) is a natural protein glycation agent found in medical honey. MGO is the most predominant antimicrobial component in Manuka monofloral honey derived from *Leptospermum scoparium* tree in New Zealand (Daniels et al. 2016). Manuka honey is known for its powerful 'non-peroxide' antibacterial properties (Daniels et al. 2016), also called non-peroxide activity (NPA) (Lusby et al. 2005; Mavric et al. 2008) which is strongly correlated with its MGO content (Figure 2), molecule identified by Atrott and Henle (2009) as being the active compound of this honey.

MGO concentration is there up to one hundred times higher compared to other honeys (Atrott and Henle 2009) ranging from 38 mg kg^{-1} to 1 541 mg kg^{-1}. It was reported by Kwakman and Zaat (2012) that MGO is also present in other honeys but the concentration did not exceed 24 mg kg^{-1}. The collected nectar on *Leptospermum* sp. contains variable dihydroxyacetone (DHA) levels but no measurable MGO (Adams et al. 2009). MGO occurs with time, during the ripening and storage of honey (Adams et al. 2009) by converting DHA, a compound naturally found in high quantities in the nectar

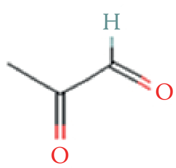

Figure 2. Chemical structure of methylglyoxal (MGO)

Source: Alvarez-Suarez et al. (2014)

of Manuka flowers. MGO is a bacteria-killing substance which induces the alteration of bacterial flagella thus impeding adhesion to the surfaces and accordingly suppressing the formation of bacterial biofilms (Goetz 2009; Rabie et al. 2016). Kilty et al. (2011) demonstrated *in vitro* the effectiveness of Manuka honey against biofilms of methicillin-resistant *S. aureus* along with those of *Pseudomonas* sp. MGO shows also an antiviral activity against influenza (flu) like treatment with neuraminidase inhibitors (Charyasriwong et al. 2015).

Defensin-1 or royalisin. Defensin-1 is one of the four antimicrobial peptides (apidaecin, abaecin, hymenoptaecin, and defensin) secreted by the bee (Ilyasov et al. 2012). It was portrayed by Kwakman et al. (2010) as royalisin and it was isolated for the first time in the royal jelly then turned up in honey. It is a peptide secreted from the hypopharingeal and mandibular glands of bees, consisting of 51 amino acids (Figure 3) hav-

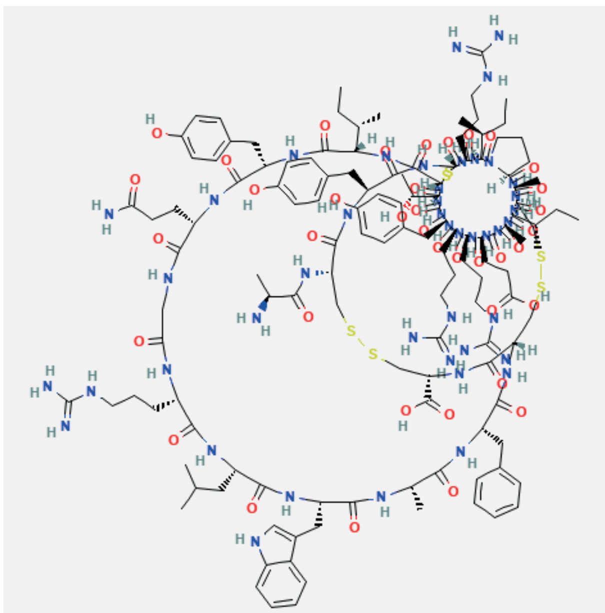

Figure 3. Chemical structure of defensin

Source: PubChem (2022)

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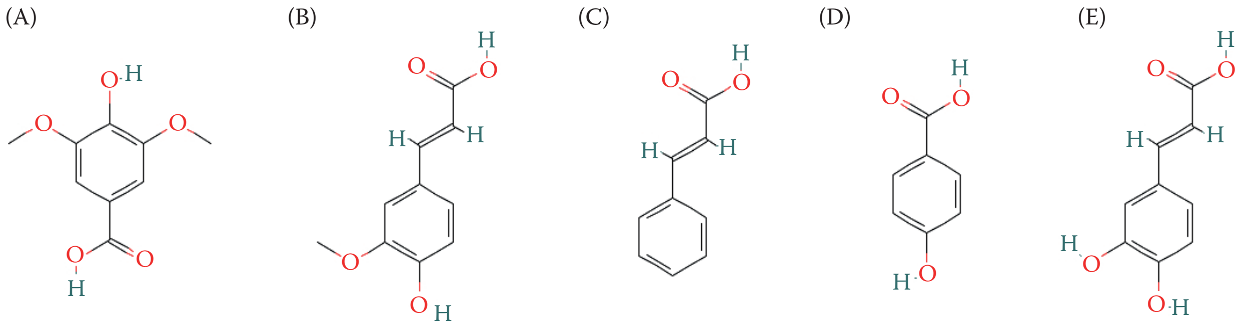

Figure 4. Chemical structures of (A) syringic acid, (B) ferulic acid, (C) cinnamic acid, (D) *p*-hydroxybenzoic acid, and (E) caffeic acid

Source: Chemspider (2022)

ing a molecular weight of 5.52 kDa (Bulet and Stocklin 2005). The antibacterial activity of defensin-1 was highlighted after consecutive neutralisations of bacteria-killing factors already known in honey (Kwakman et al. 2010). Bees secrete this protein in order to protect the brood by exerting a bacteria-killing action against Gram+ bacteria such as *Bacillus subtilis*, *S. aureus*, and *Paenibacillus larvae* (Kwakman and Zaat 2012).

Defensin-1 has cytotoxic activity against Gram+ bacteria (Bulet and Stocklin 2005), Gram– bacteria (Mandrioli et al. 2003) and against species of the genus *Aspergillus* (*flavus* and *niger*), *C. albicans*, and *Aurobasidium pullulans* (Aronstein et al. 2010). According to Majtan et al. (2014) and Sojka et al. (2016), defensin-1 and honey MGO destroy the bacterial biofilms as well.

Polyphenols. Honey is a source of several bioactive compounds among which the phenolic compounds (Liu et al. 2013). The main source of phenols supplied by the bee comes from nectar and vegetal secretions (Cimpoiu et al. 2013). These compounds are involved in pathogenic defence in plants (Dai and Mumper 2010). It was reported by Isla et al. (2011) and Montenegro and Mejıas (2013) that polyphenols found in nectar from flowers inhibit a broad range of Gram– and Gram+ bacteria. These compounds have high therapeutic values (Djossou et al. 2013). This is a diverse group of chemical products distinguished by phenolic structures and containing flavonoids and phenolic acids. Honey comprises a lot of phenolic acids: gallic acid, *p*-hydroxybenzoic acid, caffeic acid, syringic acid,

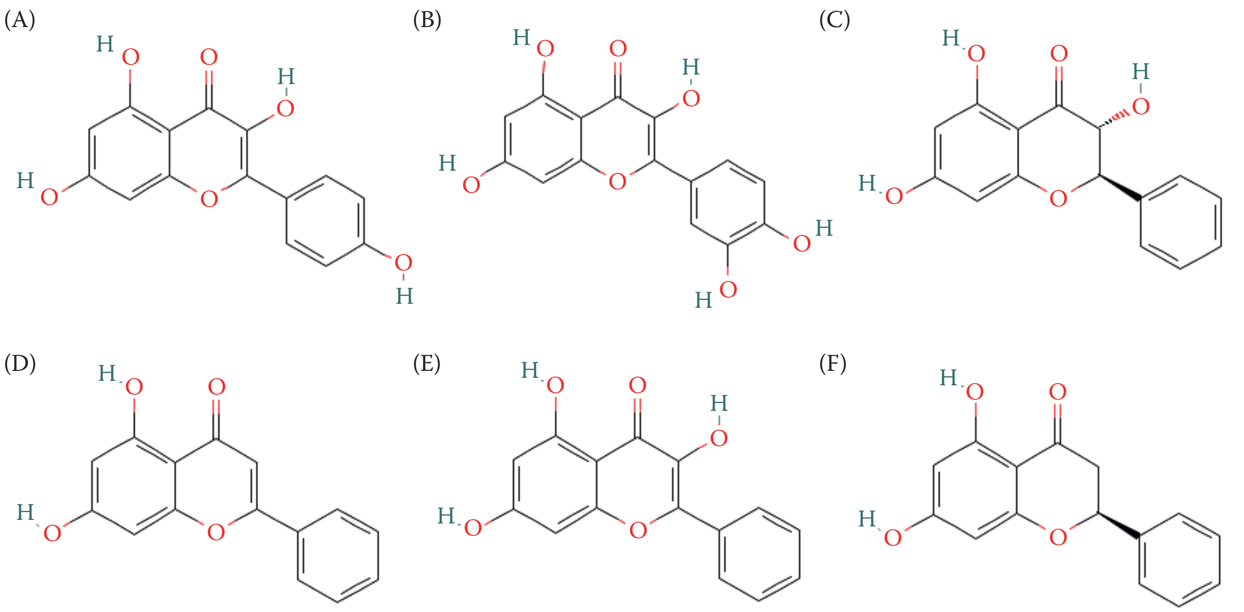

Figure 5. Chemical structures of (A) kaempferol, (B) quercétine, (C) pinobanksin, (D) chrysin, (E) galangin, and (F) pinocembrin

Source: Chemspider (2022)

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cinnamic acid, ferulic acid, vanillic acid, *p*-coumaric acid, chlorogenic acid, rosmarinic acid, and their derivatives (Khan et al. 2017; Waheed et al. 2018). Among the identified structures in honey (Figure 4), that have an antibacterial activity, are syringic, ferulic, cinnamic, benzoic and caffeic acid (Kwakman and Zaat 2012; Cooke et al. 2015; Gradvol et al. 2015; Brudzynski et al. 2017; Kıvrak and Kıvrak 2017).

The amount of phenolic acids in honey depends on the geographic location and the botanical source of the nectar. Moreover, it is obvious that the total content of phenolic acid is also significantly impacted by the season (Almasaudi 2021). Flavonoids in honey are ranked into 4 groups (Khan et al. 2017; Waheed et al. 2018): flavonols (kaempferol, fisetin, quercetin, galangin, and myricetin), flavanones (hesperidin, pinobanksin, nar-

Table 2. Actions of lactic bacteria isolated from different types of achieved honey

Isolated lactic bacteria	Sensitive microorganism	References
Lactobacillus brevis	*Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*	Hasali et al. (2015)
Lactobacillus genus	*Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853)	Homrani et al. (2019)
Lactobacillus curvatus, *Pediococcuspentosaceus*	*Candida glabrata* (ATCC 2001)	Bulgasem et al. (2016)
Lactobacillus plantarum	*Candida albicans*	Bulgasem et al. (2016)
Lactobacillus helsingborgensis (Bma5), *Lactobacillus kimbladii* (Hma2), *Lactobacillus mellis* (Hon2), *Lactobacillus mellifer* (Bin4), *Lactobacillus melliventris* (Hma8), *Lactobacillus apis* (Hma11), *Lactobacillus kullabergensis* (Biut2), *Lactobacillus apinorum* (Fhon13), *Lactobacillus kunkeei* (Fhon2), *Bifidobacterium coryneforme* (Bma6) *Bifidobacterium* (Bin2, Hma3, Bin7)	methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococcus* (VRE)	Olofsson et al. (2016)
Lactobacillus plantarum, *Lactobacillus paracasei*	*Staphylococcus aureus*	Lashani et al. (2018)
Lactobacillus acidophilus	*Staphylococcus aureus*	Aween et al. (2012b)
Lactobacillus rhamnosus (H3), *Lactobacillus paracasei* (H13, H14)	*Listeria monocytogenes* (PTCC 1295), *Shigella flexneri* (ATCC 12022), *Staphylococcus aureus* (ATCC 25923), *Salmonella enteritidis* (F17), enteropathogenic *Escherichia coli* (EPEC) (E2348/69), *Escherichia col*i (O157 H7 EDL 933), *Bacillus cereus* (D14)	Lashani et al. (2020)
Lactobacillus plantarum (H46, H47, H59)	*Shigella flexneri* (ATCC 12022), *Staphylococcus aureus* (ATCC 25923), *Salmonella enteritidi*s (F17), enteropathogenic *Escherichia coli* (EPEC) E2348/69), *Escherichia co*li (O157 H7 EDL 933), *Bacillus cereu*s (D14)	Lashani et al. (2020)

ATTC – American Type Culture Collection; PTCC – Persian Type Culture Collection

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ingin, pinocembrin, and naringenin), flavones (luteolin, genkwanin, apigenin, wogonin, tricetin, and acacetin) and tannins (ellagic acid). Flavonoids spotted in honey are usually derived from propolis (Šedík et al. 2019). These antimicrobial molecules are (Figure 5) kaempferol, quercetin, pinobanksin, chrysin, galangin, and pinocembrin (Couquet et al. 2013).

A Manuka honey extract was separated chromatographically into six fractions (M1–M6); El-Malek et al. (2017) discovered four phenolic compounds in M6 fraction: luteolin, isoferulic acid, kaempferol and chrysin. This fraction was the most active against *S. aureus*, *S. pyogenes*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Proteus mirabilis*. Candiracci et al. (2011) gathered evidence that flavonoids like quercetin, kaempferol, chrysin, galantin and apigenin may be involved in the activity of honey against *C. albicans*.

Lysozyme. The lysozyme, an enzyme produced by the bees, is endowed with bacteriostatic activity (Bruneau 2006). The lysozyme hydrolyses the β-1.4 bond between acid residues of *N*-acetylmuramic acid and *N*-acetyl-D-glucosamine in the peptidoglycan of the bacterial cell wall (Molan 1992). Its presence is optional as some authors underscored the lack of this enzyme in some honey samples (Bogdanov et al. 2008).

Volatile compounds of honey. In the volatile compounds of honey, like terpenes and their derivatives, Peña et al. (2004) and Castro-Vázquez et al. (2006) identified in several honey samples the following monoterpenes and monoterpenoids: linalool and its derivatives, β-terpineol, dihydrocitronellol, β-citronellol, citronellal, geranyl acetone, limonene, β-pinene, tetrahydrogeraniol, carvacrol, *p*-cymene, 1,8-cineol, camphor, isoborneol, and *p*-cymenol. According to Abd El-Moaty (2010), these compounds are notorious for being active against a broad range of microorganisms, including Gram– and Gram+ bacteria, viruses as well as fungi.

Lactic bacteria. Lactic acid bacteria are a highly heterogeneous group; this group is present in the indigenous microflora of animals, in fermented dairy products, on vegetal surfaces, pollen grains and in the nectar of flowers. Lactic bacteria produce various metabolites with antimicrobial properties such as organic acids, H_2O_2, carbon dioxide, reuterin, diacetyl and bacteriocins (Dortu and Thonart 2009). Bahiru et al. (2006), Forsgren et al. (2010), and Hosny et al. (2009) mentioned the presence of lactic bacteria in many types of honeys. It was confirmed by Olofsson and Vásquez (2008) and Vásquez et al. (2012) that lactic bacteria are present in the microbiota of all bees, though their quantity fluctuates depending on the nectar source and the bees' health. These bacteria are known for their antimicrobial activity, particularly the genus *Lactobacillus*. According to Klaenhammer et al. (2002) and De Vuyst and Leroy (2007), lactic bacteria do not exhibit the same antibacterial properties and do not make the same antibacterial substances. Some lactic bacteria in both genera (*Lactobacillus* and *Bifidobacterium*) have been isolated from a microbiota (Olofsson and Vásquez 2008) living in symbiosis in the stomach of honey bee (*Apis mellifera).* These bacteria produce different bioactive metabolites such as organic acids, lactic acids, formic acid and acetic acid, H_2O_2. Volatile compounds like benzene, toluene, *n*-octane, xylene, ethylbenzene, and *n*-nonane contribute to some antimicrobial actions (Table 2) against antibiotic-resistant bacteria (Olofsson et al. 2016).

CONCLUSION

Honey is a natural food that should be free of any addition of exogenous foreign substances. The natural antimicrobial potential of honey comes from the floral source and its biological activities on the one hand and the biochemical quality such as osmotic pressure, water activity, acidity, viscosity and the presence of bioactive compounds containing H_2O_2, MGO, defensin-1, flavonoids (kaempferol, quercetin, pinobanksin, chrysin, galangin, pinocembrin), phenolic acids (syringic acid, ferulic acid, cinnamic acid, benzoic acid, and caffeic acids), lysozyme and lactic bacteria living in symbiosis with the intestinal microbiota of bees producing in their turn antibacterial metabolites like organic acids, H_2O_2, carbon dioxide, reutirin, diacetyl, antimicrobial peptides called bacteriocins along with volatile compounds like monoterpenes and monoterpenoids.

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