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Antimicrobial Properties of Honey

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Honey has been widely accepted as food and medicine by all generations, traditions, and civilizations, both ancient and modern. For at least 2700 years, honey has been used by humans to treat a variety of ailments through topical application, but only recently have the antiseptic and antimicrobial properties of honey been discovered. Honey has been reported to be effective in a number of human pathologies. Clinical studies have demonstrated that application of honey to severely infected cutaneous wounds rapidly clears infection from the wound and improves tissue healing. A large number of in vitro and limited clinical studies have confirmed the broad-spectrum antimicrobial (antibacterial, antifungal, antiviral, and antimycobacterial) properties of honey, which may be attributed to the acidity (low pH), osmotic effect, high sugar concentration, presence of bacteriostatic and bactericidal factors (hydrogen peroxide, antioxidants, lysozyme, polyphenols, phenolic acids, flavonoids, methylglyoxal, and bee peptides), and increase in cytokine release, and to immune modulating and anti-inflammatory properties of honey; the antimicrobial action involves several mechanisms. Despite a large amount of data confirming the antimicrobial activity of honey, there are no studies that support the systemic use of honey as an antibacterial agent.

Keywords: honey, honeybee, antimicrobial, antifungal, antiviral, antimycobacterial

INTRODUCTION

Honey has a very long history of human consumption—as the oldest sweetener and health food. As far back as 5500 BC, honey was mentioned in the writings of Egypt, India, and China. The importance of honey for human use is described in several classical texts of ancient Greece, such as Homer's Iliad and the Odyssey, and in the philosophical texts of Plato, Aristotle, and others. The use of honey in therapy is described in 5000-old Egyptian writings: Papyrus Ebers is full of praises of the curative properties of honey. Honey has been used in Ayurvedic medicine in India for at least 4000 years. The therapeutic use of honey in wound healing is recorded on a Sumerian clay tablet (c. 2500 BC), and it can also be traced to the Chinese Xin dynasty (c. 2000 BC). Physicians of ancient times, such as Aristotle (384–322 BC), Aristoxenus (320 BC), Hippocrates (c.460–c. 370 BC), Cornelius Celsus (early first century AD), Dioscorides (c. 50 AD), Galen (c. 129–200), Porphyry (c. 234–c. 305), and Arab physicians El Mad Joussy and El Basry, have referred to the healing qualities of honey. In India, Persia, Arabia, Assyria, Greece, and in the Roman Empire, honey was much in demand as a remedial agent for internal and external use.[1–4] The nutritional and medicinal qualities of honey have been documented in the Hindu, Greek, Roman, Jewish, Christian, Islamic, and other faiths and cultures. In the Bible, the word "honey" appears 61 times in the various books (eg, Exodus 33, 3; Judges 14, 8: Proverb 24, 13; Mathew 3, 4), giving importance to honey, but mostly in the context of nutritional food and indirectly as a healing substance ("Gracious words are like a honeycomb, sweetness to the soul and health to the body." Proverbs **16**:24).[5] However, the Talmud mentions the use of honey in nutrition and treatment of wounds and several pathologies.[6] In Islam, honey has a special significance[4] because Muhammad strongly recommended honey for healing

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("Honey is a remedy for every illness …;" Bukhari), and the Qur'an promotes honey as a nutritious and healing food:

> And thy Lord inspired the (female) Bee to build its cells in hills, on trees, and in (men's) habitations (and in the trellises) which they build; then to eat of all the produce of the earth, and find with skill the spacious paths of its Lord: there issues (secreted) from within their bodies a drink (fluid) of varying colors, wherein is healing for mankind: verily in this is a Sign for those who give thought (ponder or reflect). (The Holy Qur'an, **16**:68–69).

PRODUCTS OF HONEYBEE

A number of substances are secreted from various glands of the body of the honeybee (Figure 1); these include honey, royal jelly, bee pollen, propolis, beeswax, bee venom (apitoxin), and pheromones. All of these substances have been reported to possess medicinal properties.

PROPERTIES AND COMPOSITION OF HONEY

Honeybees (female) suck flower nectar (via proboscis = tubelike tongue), mix it with saliva and enzymes, and store it in a honey sack; the mixture is then regurgitated into cells and dried to about 16% moisture and stored as a primary food source for the bees. Interestingly, the honeybee is the only insect that produces food eaten by humans. Although honey for human consumption is produced mainly by *Apis mellifera* (and subspecies, such as *A. mellifera caucasica*, *A. m. carnica*, *A. m. anatolica*, *A. m.ssp.sicula*, etc), other species such as *A. andreniformis*, *A. caucasica*, *A. cerana*, *A. dorsata*, *A. florea*, *A. indica*, and *A. ligustica*; *Plebeia wittmanni*, *Tetragonisca angustula fiebrigi*, and *Trigona carbonaria* also make honey.

The composition, physicochemical properties, and flavor of honey vary with the floral source used by the honeybees (such as acacia, almond, apple, aster, avocado, basswood, black seed, blueberry, bluegum, buckwheat, cassia, chestnut, citrus, clover, codonopsis, cotton, cranberry, dandelion, eucalyptus, fireweed, gelam, goldenrod, gossypium, grapefruit, heather, honeysuckle, jujube, lavender, lemon, lime, linden, longan, loquat, lychee, mango, manuka, medlar, milkvetch olive, orange, pincushion, pine, poplar, prickly pear, rape, sage, sourwood, sunflower, thistle, thyme, tualang, tupelo, ulmo, vetch, willow, wolfberry ziziphus, etc), as well as regional and climatic environment (such as temperature, rainfall, etc) and storage conditions.[7–11] According to the National Honey Board, "there are more than 300 unique types of honey available in the United States, each originating from a different floral source."

Various honeys differ in physicochemical parameters, such as moisture (15.6%; range, 15.0%–17.3%), pH (3.9; range, 3.2–4.5), total acidity (29.12 meq/kg; range, 8.68–59.49 meq/kg), density, dynamic viscosity,

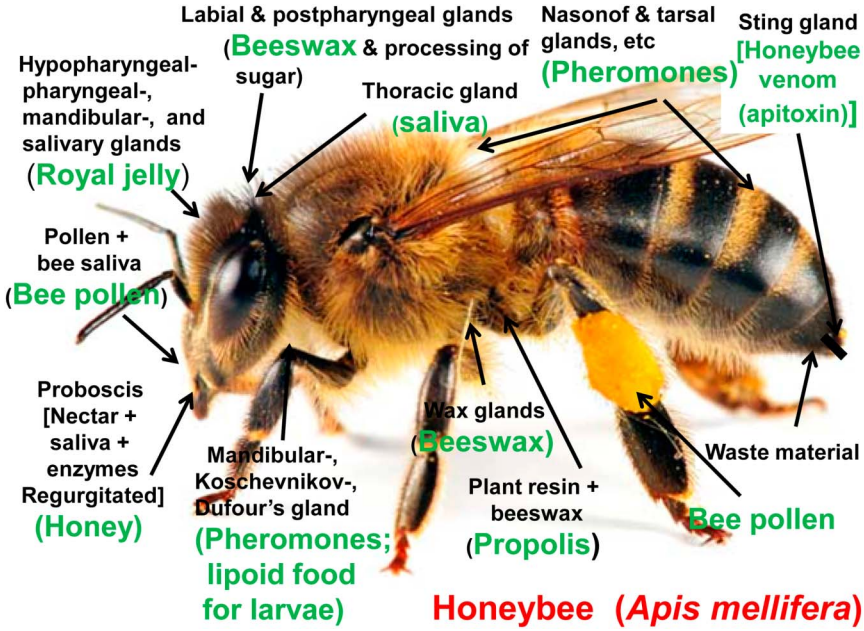

FIGURE 1. Secretions of the honeybee.

refractive index, electrical conductivity, and color, as well as relative amounts of reducing and nonreducing sugars, total sugars, water insoluble solids, mineral composition, 5-hydroxymethylfurfural content, and diastase value, etc.[12–16] Honey, called the most energy-dense food in nature, has a low glycemic index (40, range, 31–78).[12]

Honey has been reported to contain about 600 compounds,[17] including a number of carbohydrates [the sweetness is contributed mainly by fructose (about 38.5%) and glucose (about 31.0%); other carbohydrates include erlose, gentiobiose, isomaltose, isomaltotriose, 1-kestose, 6-kestose, kojibiose, maltose, maltotetraose, maltotriose, maltulose, melibiose, melizitose, nigerose, palatinose, panose, raffinose, sucrose, theanderose, trehalose, and turanose], proteins, arabinogalactan proteins, lipids, and minerals (boron, calcium, chloride, fluoride, iron, magnesium, phosphate, potassium, sodium, and sulfur), as well as trace elements (aluminum, boron, bromine, cadmium, chromium, cobalt, copper, iodine, manganese, molybdenum, nickel, selenium, silicon, vanadium, and zinc). It also contains vitamins [A, B_1 (thiamine), B_2 (riboflavin), C (ascorbic acid), B_3 (niacin), B_5 (pantothenic acid), and B_6 (pyridoxine), D, E, H (biotin), K, and folic acid], choline, acetylcholine, 18 free amino acids (including α-alanine, β-alanine, asparagine, gamma-aminobutyric acid, glutamine, glycine, histidine, leucine, lysine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, valine, etc), β-carotene, lycopene, hormones, enzymes (acid phosphorylase, amylase, catalase, diastase, glucose oxidase, α-glucosidase, glycogenase, inulase, invertase, lipase, myeloperoxidase, peroxidase, phophatase, polyphenol oxidase, sucrase, and superoxide dismutase), antioxidants [polyphenols, pinobanksin, coumarin, and flavonoids (acacetin, apigenin, biochanin, caffeic acid, caffeic acid phenethyl ester, catechin, chrysin, galangin, genistein, hesperetin, kaempferol, luteolin, myricetin, naringenin, pinocembrin, pinostrobin, and quercetin)], organic acids (acetic, butyric, caproic, citric, ferulic, formic, gluconic, lactic, maleic, malic, 2-methylheptanoic, nonanoic, octanoic, oxalic, palmitic, phthalic, propionic, pyroglutamic, succinic, and valeric acid), phenolic acids and phenolic acid derivatives (benzoic, p-hydroxybenzoic, caffeic, chlorogenic, trans-cinnamic, p-coumaric, ellagic, gallic, and syringic acid), acetophenone, benzaldehyde, p-cymene derivatives, a large number of pheromones [such as isopentyl acetate, butyl acetate, 1-hexanol, *n*-butanol, 1-octanol, hexyl acetate, octyl acetate, *n*-pentyl acetate, and 2-nonanol ethyl oleate (E)-9-oxodec-2-enoic acid, (R,E)-(-)-9-hydroxy-2-enoic acid, methyl-p-hydroxybenzoate, 4-hydroxy-3-methoxy phenylethanol, methyl oleate, coniferyl alcohol, linolenic acid, etc], 2-heptanone (an anesthetic), hydroxyketones, methylsalicylate, methyl syringate, reduced glutathione, terpenoid glycosides, volatile compounds [p-anisaldehyde, benzaldehyde, 5-hydroxymethylfurfural, 3-furaldehyde, hexanal, hydroxymethyfurfural, limonyl alcohol, linalool, (E)-β-ocimene, octen-3-ol, and 4-propylanisol], aroma compounds (odorants) [eg, (E)-β-damascenone, 3-phenylpropanoic acid, phenylacetic acid, dimethyl trisulfide, kynurenic acid (an NMDA receptor antagonist), and phenylacetaldehyde, etc], nitric oxide and its metabolites, probiotic bacteria (6 species of lactobacilli and 4 species of bifidobacteria), and antibiotic peptides (abaecin, defensin-1, apidaecin, and hymenoptaecin).[7,18–62] Because honey also contains some propolis, bee pollen and wax, compounds contained in these substances (such as aromatic acids including benzylcinnamate, caffeic acid, cinnamylcinnamate, cinnamoylglycine, methycinnamate, terpenoids, flavonoids, etc), may also be found in honey.[55,63]

Honey ("mad honey") produced from flowers of oleander, rhododendron, mountain laurel, sheep laurel, and azaleas contains grayanotoxin—diterpenoids and pyrrazolidine alkaloids; its consumption may cause serious adverse effects.[64–66] Monofloral honey from almond blossoms is bitter as it contains amygdalin. Some environmental contaminants (heavy metals, pesticides, antibiotics) and microorganisms may also be present in honey[57,67,68] and may pose safety concerns.

MEDICINAL USES OF HONEY

Honey has been shown to have antiarrhythmic, antiatherogenic, antibacterial, anticancer, antidiabetic, antifungal, anti-ischemic, anti-inflammatory, antileishmanial, antimicrobial, antimutagenic, antioxidant, antiparasitic, antiplatelet, antiproliferative, antithrombotic, antitumor, antiviral, and immunostimulant and vasorelaxant activity; it also has antihypertensive, cardioprotective, diuretic, gastroprotective, hepatoprotective, hypocholesterolemic, hypoglycemic, neuroprotective, and metal-chelating effect.[11,14,27,31–33,39,42,43,56,69–125]

Honey has been reported to be of benefit in a large number of human pathologies including allergy, asthma, bronchitis, common cold, flu, hay fever, nasal congestion, rhinitis, sinusitis, upper respiratory infections, sore throat, cough, fatigue, anxiety, migraine (stress related), cuts, lacerations, burns, wounds (venous, arterial, diabetic, malignant), pressure ulcers, malignant ulcers, perianal and gluteofemoral fistulas, bed sores, adult and neonatal postoperative infections, necrotizing fasciitis, pilonidal sinus, insect bites, infections (bacterial including antibiotic-resistant strains and fungal), septicemia, conjunctivitis and other eye

diseases, endophthalmitis, acne, chronic seborrheic dermatitis, dandruff, eczema, psoriasis, inflammation, gingivitis, stomach ache, stomach ulcers, digestive disorders, constipation, vomiting, diarrhea, colitis, dehydration, diabetes, osteoporosis, insomnia, chronic fatigue syndrome, anemia, hypertension, immune disorders, multiple sclerosis, cardiovascular disease, hepatitis, tumors, cancer, and radiation/chemotherapy-induced oral mucositis.[2,81,87,91,93,94,96,104,106,108,114,126–161] Honey is also used in skin moisturizers and hair conditioners.[162]

MODE OF ADMINISTRATION OF HONEY IN HUMANS

Honey, as a therapeutic agent, has been administered by the following routes:

Oral (selected studies): (1) honey ingestion decreased the symptoms of hepatitis A[133] and hepatitis B[122]; (2) controlled increased gastric acidity[133]; (3) improved hematological parameters[101]; (4) at a dose 1.2 g/kg in 250 mL of water for 15 days, honey decreased serum prostaglandin levels (thromboxane B_2, prostaglandin E_2, and prostaglandin F_{2a}) in 12 healthy volunteers[163]; (5) increased antioxidants, serum iron and blood indices, and trace elements and decreased immunoglobulin E, liver and muscle enzymes, and fasting blood sugar in 12 healthy subjects[138]; (6) 75 g of honey ingestion decreased blood pressure in hypertensive patients[137]; (7) ingestion of honey (75 g in 250 mL of water) for 2 weeks decreased plasma glucose levels in 7 patients with type 2 diabetes[81] and reduced cardiovascular risk factors [reduced total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, homocysteine, and slightly increased high-density lipoprotein (HDL) cholesterol in 6 patients with hypercholesterolemia and 5 patients with hypertriglyceridemia] and also reduced levels of C-reactive protein, a marker of systemic inflammation; (8) honey (80 g in 250 mL of water) given at night to healthy volunteers (n = 12) increased total excretion of nitrite, decreased prostaglandin E_2, $F_{2\alpha}$, and thromboxane B_2 in urine[164] and increased nitrite in saliva and plasma[143]; (9) sucking on honey-based products (for 10 minutes, 3 times a day for 21 days) decreased dental plaque and gum bleeding in 30 volunteers[144]; (10) administration of medical honey (in 30 patients with cancer receiving chemotherapy with grade 4 neutropenia) decreased the risk of pancytopenia and the need for treatment with colony-stimulating factors in 5 of 12 patients[165]; (11) 8 weeks of honey ingestion decreased blood pressure, body weight, LDL-cholesterol, triglycerides, and increased HDL-cholesterol in patients with type 2 diabetes (n = 48)[91]; (12) ingestion of 70 grams of honey per day for 30 days improved cardiovascular risk factors (decrease in total cholesterol, LDL-cholesterol, triglycerides, C-reactive protein, and fasting blood glucose, and a small increase in HDL-cholesterol) in overweight obese individuals (n = 38), with no effect on body weight[165]; (13) when ingested, honey promotes healing and shows antibacterial action by decreasing prostaglandin levels, elevating nitric oxide levels, and exerting prebiotic effects[163,164]; (14) administration of several types of honeys (20 g/d for 4 weeks) to healthy volunteers (n = 20) did not result in adverse side effects (no change in serum IgG levels, advanced glycation end products, or gut microbial profile)[166]; (15) 1 teaspoonful of honey with 2 g of *Nigella sativa* seeds daily for 3 months improved pulmonary, hepatic, and renal functions in 5 asthmatics and 22 nonasthmatics, with no adverse effects[148]; (16) in 30 patients with common cold, honey (50 g) administration, along with classic therapeutic regimen (acetaminophen, naproxen, and chlorpheniramine), decreased the duration of signs and symptoms than in the control group[146]; (17) children with acute diarrhea (n = 200) recovered quickly when given honey[150]; (18) honey (20 g/d) given for 16 weeks improved immediate memory in healthy postmenopausal women (n = 40)[112]; (19) in a randomized, partially double-blind clinical trial in 105 children, aged 2–18 years, who suffered from upper respiratory infections receiving no treatment, honey or honey-flavored over-the-counter cough suppressant, those treated with honey had fewer symptoms, including bothersome cough frequency, throat irritation, and child and parent sleep quality.[167] This study was deemed significant,[168] and a recommendation was made to use honey in pediatric patients with cough due to upper respiratory infection because of the low cost, relatively low adverse effect profile, and potential benefit[168]; (20) a single 2.5 mL dose of honey before sleep in children (n = 38) with upper respiratory infection–induced cough improved cough frequency score, and sleep quality better than dextromethorphan or diphenhydramine[147]; (21) in 300 children (1–5 years of age) with upper respiratory infection and nocturnal cough, a single dose of honey (10 g) given 30 minutes before bedtime produced symptomatic relief from cough and sleep difficulty.[157]

Topical (selected reports): (1) Honey has been applied topically to wounds, burns, etc (see below); (2) application of honey in the mouth (10 volunteers) decreased total bacterial count and *Streptococcus mutans* in saliva[169]; (3) topical application of honey was equivalent to or better than acyclovir for providing symptomatic relief in the treatment of recurrent herpes simplex lesions (labial and genital) in 16 patients,[139,170] as well

as various dermal fungal infections[141]; (5) rubbing on the gums suppressed gingivitis and reduced dental plaques[144,171]; (6) topical application of honey (90% in water) twice a week for 4 weeks in patients (n = 30) with chronic seborrheic dermatitis resulted in reduced itching, scaling, and hair loss and reduced relapse[172]; (7) application of a mixture of honey, olive oil, and beeswax was effective for treatment of diaper dermatitis, psoriasis, eczema, skin fungal infection, hemorrhoids, and anal fissure[173,174]; (8) topical application of honey in children (n = 50) with *Tinea capitis* and *T. versicolor* markedly improved erythema, desquamation, and pruritus[175]; (9) application in the mouth was effective in the treatment of chemotherapy-induced oral mucositis (n = 30 children with leukemia)[176]; (10) in a meta-analysis of controlled trials (n = 120 patient), honey had protective effects against radiation-induced oral mucositis (an overall relative risk reduction of 80% in the honey treatment group compared with the control)[177]; (11) a cream containing honey was more effective in preventing radiation-induced dermatitis in patients with breast cancer (n = 43) compared with standard aqueous cream (n = 38)[178]; (12) application at the exit site prevented catheter-associated infections in patients undergoing peritoneal dialysis[179] or hemodialysis.[180]

Intranasal: Of 34 patients with allergic fungal sinusitis, resistant to conventional medical treatment, who sprayed 1 nostril with 2 mL of a 50/50 mixture of honey saline solution once a day at night for 30 days, 9 showed symptomatic benefits.[181]

Intraocular: Direct application of honey in the eye cured some of the ocular diseases[128] and acted as a prophylactic agent in the prevention of endophthalmitis (n = 49 patients) before ophthalmic surgery[156]; application in the infected eyes of patients with conjunctivitis reduced redness, swelling, pus discharge, and time for eradication of bacterial infections because of all the isolates tested.[140]

Intravaginal: (1) Application of honey to the vagina and cervix in women (n = 108) with precancerous lesions of the uterine cervix for 3 months resulted in 95% of the patients with normal pap smears[182] and (2) honey alone (n = 15) or with clotrimazole (n = 30) for 7 days resulted in complete alleviations of symptoms and signs of vulvovaginitis.[183,184] Pregnant women with vulvovaginal candidiasis (n = 82) who received a mixture of honey and yogurt vaginally had a high clinical cure rate and a reasonable mycological cure rate, suggesting that the mixture can be used as complementary or an alternative to antifungal agents, especially during pregnancy.[185]

Intrapulmonary administration (by inhalation): 60% honey solution (24 healthy subjects, 16 patients with type 2 diabetes, and 6 patients with hypertension) deceased fasting and postprandial blood glucose levels, increased plasma insulin and C-peptide, reduced systolic and diastolic blood pressure, and increased peaked expiratory flow rate, with no adverse effects.[137]

Intravenous injection: (1) Intravenous administration of honey solution did not cause serious adverse effects[138] and (2) a total of 1300 injections of honey solution (2%–40% in water) administered to 90 adults (10 healthy individuals and 80 patients with type 2 diabetes, hepatitis C, or allergic disorders, 16–67 years of age) resulted in improvement of symptoms without serious adverse effects (AbdulRhman MAM—presented at the First International Conference on Api—Phytotherapy, Fez, Morocco, May 18–20, 2012).

Intraarticular injection: a case report of a 56-year-old patient with osteoarthritis resistant to pharmacological management received 35 injections (5 mL of 5%–30% honey solution) over a period of 2 years; the symptoms resolved without serious adverse effects (AbdulRhman MAM—presented at the First International Conference on Api—Phytotherapy, Fez, Morocco, May 18–20, 2012).

Nebulization: administration of honey solution (2.5%–5% in water) to 340 infants and children (mean age, 2.5 years) with mild–severe asthma improved symptoms, without severe adverse effects (AbdulRhman MAM—presented at the First International Conference on Api—Phytotherapy, Fez, Morocco, May 18–20, 2012).

THE USE OF HONEY IN WOUND HEALING

Since ancient times, honey has been used successfully for treatment of infected wounds; this practice was rooted primarily in tradition and folklore. Honey (raw honey, AgroMas, Algivon, API-MED, Comvita, Gelam honey, Manuka honey, Medihoney, Melladerm Plus, L-Mesitran, Revamil, Tualang honey, etc) has recently been introduced into clinical practice and clinically proven to be efficacious in healing wounds (infected and nonhealing), arterial-, venous-, chronic pressure-, lower-extremity-, surgical-, traumatic-, diabetic foot ulcers, boils, burns, glutofemoral fistulas, pilonidal sinus, necrotizing fasciitis, Fournier gangrene, *Pyoderma gangrenosum*, gynecological wounds, neonatal postoperative infected wounds, etc. Application of honey causes rapid clearance of infection, debridement of wound, suppression of inflammation while minimizing scarring and stimulating angiogenesis, tissue granulation, and epithelial growth.[2,4,151–153,161,186–217]

A review of human and animal data (17 randomized controlled trials involving a total of 1965 participants,

5 clinical trials of other forms involving 97 participants, and 16 trials on a total of 533 wounds on experimental animals) provides the evidence for the effectiveness of honey in assisting wound healing.[197]

The healing effect of honey in postoperative infection, gynecological procedures (caesarian sections, hysterectomies, etc), burns, necrotizing fasciitis, infected and nonhealing wounds, and ulcers, boils, and diabetic foot ulcers are ascribed to honey's broad-spectrum antibacterial action.[4,140,141,202,217–227] Other explanations for the wound-healing activity of honey include high acidity, high sugar content, high viscosity, immunomodulatory action, stimulation of inflammatory cytokines from monocytic cells, antioxidant and anti-inflammatory properties of honey, and presence of kynurenic acid with its antinociceptive action.[4,223–232]

HONEY IN VETERINARY MEDICINE

Honey is also used in veterinary medicine, mainly in wound care, but also in mastitis, gastrointestinal disorders, otitis, dermal care, and foot and mouth disease[233–236] (Boukraá L—presented at the First International Conference on Api—Phytotherapy, Fez, Morocco, May 18–20, 2012; López-Pazos MA—presented at the First International Conference on Api—Phytotherapy, Fez, Morocco, May 18–20, 2012).

ANTIMICROBIAL ACTIVITY OF HONEY AND ITS MECHANISM(S) OF ACTION

The antimicrobial activity of honey has been known since the 19th century. A large number of in vitro and limited clinical studies have confirmed the broad-spectrum antimicrobial (antibacterial, antifungal, antimycobacterial, and antiviral) activity of honey, which may be because of the acidity (low pH), osmotic effect, high sugar concentration, presence of bacteriostatic and bactericidal factors [hydrogen peroxide (generated by endogenous glucose oxidase), catalase, antioxidants,[27,28,75,79,231,237–242] lysozyme, polyphenols, phenolic acids and flavonoids, methylglyoxal (formed by conversion of dihydroxyacetone during honey maturation), bee peptides (the natural antibacterial agents, abaecin, defensin-1, apidaecin, and hymenoptaecin[41,241]]; increase in cytokine release (tumor necrosis factor-alpha,[204,229,230]) as well as to immune modulating and anti-inflammatory properties of honey.[9,102,149,226,242–247] In addition, because honey contains some propolis and bee pollen, part of the antimicrobial activity of honey may be because of the presence of antimicrobial substances present in these components.[89,248]

ANTIBACTERIAL ACTIVITY OF HONEY AND HONEY COMPONENTS

The antibacterial activity of honey has been known since the 19th century. Various types of honeys have been shown to have antibacterial activity, in vitro, against the following bacterial species: *Acinetobacter baumannii*, *Alcaligenes faecalis*, *Aeromonas hydrophila*, *Bacillus cereus*, *B. subtilis*, *Burkholderia cepacia*, *Campylobacter* spp, *Citrobacter freundii*, *Erwinia carotovora*, *Enterobacter aerogenes*, *Enterobacter cloacae*, vancomycin-resistant *Enterococcus faecium*, *Escherichia coli*, cotrimoxasole-resistant *E. coli*, extended-spectrum β-lactamase–producing *E. coli*, *E. coli* O157:H7; *Haemophilus influenzae*, *Helicobacter pylori*, *Klebsiella oxytoca*, *K. pneumoniae*, *Klebsiella* sp, *Listeria monocytogenes*, *Micrococcus luteus*, *Mycobacterium phlei*, *Proteus* sp (*P. mirabilis* and *P. vulgaris*), *Pseudomonas aeruginosa*, ciprofloxacin-resistant *P. aeruginosa*, *Salmonella california*, *Salmonella enteritidis*, *Salmonella typhimurium*, *Serratia marcescens*, *Shigella dysenteriae*, *Shigella sonnei*, coagulase-negative staphylococci, *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *S. aureus*, *S. epidermidis*, *Stenotrophomonas maltophilia*, *Streptococcus hemolyticus* group B, *Streptococcus mutans*, *Streptococcus pyogenes*, *Yersinia enterocolitica*, and several multidrug-resistant bacterial isolates.[4,11,80,94,102,117,188,195,221,224,226,227,241,243,246,247,249–276]

Some monofloral honeys are more potent than others in terms of antibacterial activity,[44,117,226,261,274–276] and some pathogens are more sensitive than others to a certain monofloral honey.[140,224–226,261] Storage of honey for 5 years decreased its antimicrobial activity, whereas ultraviolet light exposure increased its activity against some microorganisms.[140]

Honey (or its components) acts synergistically when used with other antibiotics, and in many instances, it reverses the resistance of bacteria to that antibiotic. For example: (1) honey and oxacillin acted synergistically to inhibit oxacillin-resistant Gram-negative MRSA and reversed the resistance of MRSA and made it sensitive to oxacillin[277]; (2) honey and gentamicin acted synergically[254]; (3) honey had synergic action with gentamicin, amikacin, and ceftazidime against *Pseudomonas* spp[278]; (4) a synergism was observed in the antibacterial effect of methylglyoxal and pipercillin, carbenicillin or amikacin, against MRSA isolated (n = 12) from hospitals[60,279]; and (5) honey reversed the resistance of MRSA and vancomycin-resistant Enterococcus and made them sensitive to antibiotics.[260,262] In addition,

addition of synthetic peptide "Bactericidal Peptide 2" potentiated and broadened the antibiotic spectrum of honey against antibiotic-resistant isolates of *P. aeruginosa*, *S. epidermidis*, *Enterococcus faecium*, and *Burkholderia cepacia*, and MRSA and β-lactamase–producing *E. coli*.[244] Furthermore, the antibacterial activity of honey was enhanced against drug-resistant bacteria by the addition of starch [*S. aureus*, *E. coli*,[280,281] and *P. aeruginosa*[280] in correlation with diastase number]; royal jelly (*S. aureus*,[282] *P. aeruginosa*,[283] or thyme (*Thymus ciliatus*) powder (*S. aureus*, *E. coli*, and *P. aeruginosa*).[284]

MECHANISM(S) OF ANTIBACTERIAL ACTION OF HONEY AND HONEY COMPONENTS

A number of mechanisms have been proposed for the antibacterial action of honey or its components. Some examples are as follows:

1. Activity against Gram-positive and Gram-negative bacteria was shown to be due to antioxidant polyphenols (and other chemicals) in honey.[11,94,285]
2. The total phenolic content (and radical scavenging ability) in honey was proportional to the cidal activity against various bacteria.[102,285]
3. The antibacterial activity of honey was related to hydrogen peroxide levels[2,237]
4. The antibacterial activity of honey from various floral origins against *E. coli* O157:H7, *Salmonella typhimurium*, *Shigella sonnei*, *L. monocytogenes*, and *S. aureus* was both hydrogen peroxide–dependent and independent.[2] Similarly, in several other studies, both hydrogen peroxide–dependent and –independent antibacterial activity of honey was shown against various bacteria, including MRSA[100,103,106,245,267,268,276]; the inhibition of bacterial growth depended on the type and concentration of honey, as well as on the test pathogen.[252]
5. The antibacterial action of several varieties of honey was found to be related to their DNA degrading activity, which was mediated by coupling of the action of hydrogen peroxide and phenolics with radical scavenging activity.[245]
6. The majority of antibacterial activity against *E. coli* and *S. aureus* was attributed to the amount of methylglyoxal in honey.[286]
7. The bactericidal activity of honey against MRSA was, in addition to the presence of methylglyoxal and hydrogen peroxide, due to the presence of defensin-1 (a bactericidal and cytotoxic peptide).[247]
8. The bacteriostatic action of honey was shown to be due to interruption of cell division, not related to methylglyoxal.[270]
9. The bactericidal activity of monofloral honey against *S. aureus* was due to interruption of cell division and prevention of cell separation, thus leading to the accumulation of cells with fully formed cross-walls, thus, inhibiting the normal progression of cells through the cell cycle.[287]
10. The bactericidal effect of monofloral honey was related to extensive cell disruption (loss of structural integrity), lysis, and marked changes in cell shape and surface of *P. aeruginosa*.[288]
11. Monofloral honey was found to block the attachment of bacteria to tissues (an essential step in the initiation of acute infection) and inhibited the formation of biofilms (which protect bacteria from antibiotics) by reducing the expression of 2 fibronectin-binding proteins (located on the bacterial surface)—thus, making the existing antibiotics more effective against drug-resistant infections.[226,277,289,290]
12. Honey inhibited the growth of oral bacteria, *Streptococcus mutans*, by blocking biofilm formation.[291]
13. Methylglyoxal was effective in inhibiting the formation of biofilms in *P. aeruginosa* and MRSA.[292]
14. Honey at low concentrations reduced biofilm formation, quorum sensing (essential for the synchronization of virulence factors), and virulence in *E. coli* O157:H7k[4]; honey inhibited bacterial growth and viability of *Streptococcus mutans*, by reducing biofilm formation[293]; quorum sensing inhibitory activity of 29 unifloral honeys was responsible for antibacterial activity, independent of hydrogen peroxide.[63,264]
15. Honey downregulated 2 specific proteins in the proteome of *S. aureus* necessary for growth and upregulated a stress-related protein (cold-shock protein C).[294]
16. Monofloral honey treatment downregulated universal stress protein A in MRSA, which compromised its ability to overcome environmental insults, leading to reversal of antibiotic resistance.[271,295]
17. Region-specific and flower-specific honey[249,251,296,297] showed strong anti-*H. pylori* activity, which was attributed to the osmotic effect.[296]
18. A chloroform extract of honey showed strong anti-*H. pylori* activity in vitro.[297]

ANTIFUNGAL ACTIVITY OF HONEY

Honey was found to be an effective topical treatment for ringworms, athlete's foot, jock itch, nail fungus, and yeast infections and reported to be comparable to many over-the-counter antifungal preparations. The antifungal effect of some honeys, especially from darker honeycombs, which contain propolis, may be due to the presence of a number aromatic acids, including benzyl cinnamate, methyl cinnamate, caffeic acid, cinnamyl cinnamate, cinnamoylglcine, and terpenoids (commonly found in propolis). In addition, there may be special proteins in honey that have antifungal activity.

1. Acacia honey significantly improved erythema and desquamation and relieved pruritus nearly and miconazole in children (n = 242) with *T. mycosis* (*T. capitis* and *T. versicolor*).[175]
2. Monofloral honeys were shown to exhibit antifungal activity against a variety of mycotic infections, including several yeasts [*Candida* sp (*C. albicans*, *C. krusei*, *C. glabrata*, etc) and *Trichosoporon* spp, including fluconazole- and miconazole-resistant varieties, *Rhizoctonia solani*] and moulds (*Fusarium oxysporum*, *Cladosporium herbarum*, *Botrytis cinerea*, *Aspergillus flavus*).[96,107,141,255,298–307]
3. Seventy-two isolates of *C. albicans* (from patients), including some resistant to nystatin, miconazole nitrate, and clotrimazole, were found to be susceptible to an extract of honey.[303]
4. The efficacy of various honeys as antifungal agents was demonstrated against clinical isolates of *C. albicans*, *C. glabrata*, and *C. dubliniensis*.[299]
5. 5.Antifingal activity of honey was shown against *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. glabrata*, and *C. dubliniensis*.[304]
6. The antifungal action of 3 South African honeys was demonstrated against *C. albicans*.[305]
7. Four honeys of different types from Algeria exhibited antifungal activity against pathogenic yeast (*Candida* and *Rhodotorula* sp).[306]
8. In 89 samples of *C. albicans*, *C. krusei*, and *C. neoformans*, monofloral heather honey was effective as antifungal agent.[107]
9. In 37 patients with *Pityriasis versicolor*, *T. cruris*, *T. corporis*, and *T. faciei*, honey mixed with olive oil and beeswax was effective as antifungal agent.[141]
10. Antifungal activity of multifloral honey was demonstrated against fluconazole-resistant *C. albicans* isolated (n = 25) from the oral cavity of patients with AIDS.[301]
11. A flavonoid extract of honey was shown to have antifungal acticivity against *C. albicans*.[302]
12. In a single-blind study, manuka honey (50:50 in saline, sprayed in the nostril for 30 days) provided symptomatic relief in allergic fungal rhinosinusitis.[181]
13. The use of honey with other substances increased the activity against a number of fungal infections. For example:

- Honey with yogurt or fluconazole was effective in vulvovaginal candidiasis (n = 129 patients).[183,185]
- Addition of ginger starch to honey increased the activity against resistant *C. albicans*.[307]
- Addition of starch potentiated the antifungal activity of honey against *C. albicans* and *Aspergillus niger*.[308,309]
- Honey with or without miconazole was effective against *T. capitis* or *T. versicolor* infection in children.[175]
- Honey with clotrimazole was effective in the treatment of vaginitis.[184]
- Honey combined with olive oil and beeswax inhibited the growth of *C. albicans*.[255]

ANTIVIRAL ACTION OF HONEY

Honey is an effective antiviral agent as shown by several studies: For example,

1. Topical application of honey on recurrent herpes lesions in 16 adult patients (8 labial and 8 genital) was compared with acyclovir cream; honey was better (28%–43%) than acyclovir in terms of mean duration of attacks and pain, occurrence of crusting, and mean healing time; no adverse effects were noted with honey.[139,170]
2. In a study in monkey kidney cell cultures infected with Rubella virus, honey showed significant antiviral activity.[70]
3. Honey (5% or higher concentration) completely inhibited type 1 herpes simplex virus isolated from the lip lesions of patients and grown in culture in vero cells.[310]
4. In rabbit eyes with viral infection, application of honey significantly increased acyclovir concentration and bioavailability, extended the duration of action, and increased the retention capacity of antiviral drug in the target tissue, thereby improving treatment success.[311]
5. An in vitro study showed that both manuka and clover honey had significant antiviral activity (EC50 = 4.5% wt/vol) against varicella zoster virus isolated from patients, suggesting that honey may be used topically to treat zoster rash.[312]

6. Honey given to children with upper respiratory tract infection (viral?) was found to be superior to dextromethorphan or no treatment in suppressing nighttime coughing.[168,313]
7. Honey was found to have antiviral activity against respiratory syncytial virus (Zareie PP. Masters of Science degree Thesis, University of Waikato, New Zealand, 2011).
8. Adenovirus and herpes simplex virus was sensitive to honey (Littlejohn ESV. Masters of Science degree Thesis, University of Waikato, New Zealand, 2009).

ANTIMYCOBACTERIAL ACTIVITY OF HONEY

Avicenna (Ibn Sīnā; c. 980–1037) recommended honey in the treatment of tuberculosis.[314]

1. In a study in Russia, honey was found to be beneficial in the treatment of tuberculosis.[315]
2. It was demonstrated that the growth of mycobacteria (smears taken from patients) was inhibited by adding 10% honey to the medium. Mycobacteria did not grow in culture media containing 10% and 20% honey, whereas it grew in culture media containing 5%, 2.5%, and 1% honey. The antimycobacterial effect, sterility, low cost, and easy availability of honey may make it an ideal antimycobacterial agent (or as an adjunct).[316]
3. It has been suggested that honey as a dietary supplement may prevent tuberculosis infection/treatment.[51]
4. Honey exhibited antibacterial action against different types of Mycobacterium.[317]

ADVERSE EFFECTS OF HONEY

The adverse effects of honey may be associated with the natural components or contaminants in honey. Honey anaphylaxis is not as rare it was previously thought; individuals with allergic rhinitis, bee venom hypersensitivity, and food allergies are more susceptible. A number of cases of anaphylaxis (urticaria, angioedema, bronchitis, cough, and wheezing), pruritic cheilitis, bronchial asthma, and dysphagia have been reported in both adults and young subjects consuming honey[318–322]; in many of these cases, hypersensitivity was associated with the floral source of honey.[319,323] The allergy to honey could be because of pollen and glandular secretions of the bees.

Honey can also become contaminated with microbes (such as *Clostridium botulinuma*) and environmental chemicals (antibiotics, pesticides, heavy metals, materials in air pollution),[57,67,68] from the floral source(s), bees, or during collection and processing of honey.[154] Some honeys have toxins acquired from the nectar of flowers, which when ingested cause poisoning.[64–66] For example, grayanotoxin intoxication, which is mostly reported from the eastern Black Sea region of Turkey (as well as Japan, Nepal, Brazil, and some parts of Europe), stems from consumption of "mad honey" made by bees feeding on rhododendron (mainly *Rhododendron panticum* and *R. luteum*) flowers.[65,66] In low doses, consumption of mad honey causes dizziness, vertigo, hypotension, sinus bradycardia, chest pain, and respiratory distress, and in high doses, impaired consciousness, syncope, seizures, atrioventricular block, and asystole; patients usually recover 2–6 hours after ingestion.[324–326] Some patients may develop gastritis and peptic ulcer after chronic use. Mad honey is intentionally used to "improve sexual performance."[325] In traditional medicine, mad honey is used to treat gastric pain, bowel disorders, and hypertension.[327]

A large number of cases of botulism, some with severe neurological manifestations, have been reported, especially in infants (younger than 12 months) given raw honey by mouth; the cause could also be environmental exposure to soils and dust contaminated with *Clostridium botulinum*.[328–330] Spores of *C. botulinum* can proliferate in infant intestines and release neurotoxins that block acetylcholine release and cause botulism poisoning (cramps, muscle weakness, hypotonia, oculomotor symptoms, temporary muscle paralysis, apnea, bradycardia, diarrhea, nausea, and vomiting). Management includes supportive intensive care that may include mechanical ventilation and administration of human-derived botulinum immunoglobulin.

(BabyBIG, botulinum antitoxin, specific for infant botulism types A and B, which inactivates neurotoxins); the latter is most effective if given at an early stage of the disease.[328,331] The Center for Disease Control and Prevention (USA) has recommended that honey not be given to infants younger than 12 months. The impact of other organisms (*C. Perfringrs*, *C. tetani*, and *B. subtilis*), which may be present in honey, on human health is unknown. However, honey can be rendered safe by irradiation with high-intensity electrons or gamma radiations, which inactivates the spores of *C. botulinum*;[332–334] the neutraceutical value of honey is not altered.[332–334]

Because there is no safe or effective medicinal dose of honey in adults, consuming too much honey can cause hyperglycemia and gastrointestinal problems (due to high fructose levels).

PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTION OF HONEY WITH PHARMACEUTICALS

There is a risk of pharmacokinetic and pharmacodynamic interaction between co-administered drugs with honey (ingestion). For example, honey may interact with calcium channel blockers in different ways: it may decrease the plasma concentration of diltiazem[335] or it may induce complete heart block when used together with verapamil.[336] Co-administration of honey with licorice was shown to suppress the conversion of liquiritin to its active metabolite, liquiritigenin.[337] Several studies show that honey affects the activities of cytochrome P450 enzymes, for example, honey ingestion inhibited the activity of CYP2C8, with no effect on CYP2C19 and CYP2D2.[338] Thus, honey ingestion may inhibit the metabolism of endogenous (retinol, all-trans-retinoic acid and arachidonic acid) and exogenous substrates (benzphetamine, amiodarone, cerivastatin, paclitaxel, and rosiglitazone) of CYP2D8[338]; this may have significant therapeutic implications.

END NOTES

Honey has been shown to have significant antimicrobial activity. The antimicrobial- and wound-healing efficacy of honey is very much flower, region, and season specific.[44,226] Not all honeys have the same antimicrobial potency due to the variation in the pH, sugar content, concentration of the active principles (hydrogen peroxide, antioxidants, phenolics, methylglyoxal, defensin-1, etc), storage conditions, and different susceptibility of the various strains of bacteria[44,100,117,226,241,246,252,260]; some batches of honey may not have any significant antimicrobial activity. Unlike most conventional local chemotherapeutics, honey does not lead to the development of antibiotic-resistant bacteria, and it may be used continuously.

Among the challenging problems of using honey for medical purposes are variation in the quality and potency, and hence, the dosage and formulation cannot be ascertained. There are no regulations regarding standardization of honey to be used in a clinical setting. At present, there are no standards for quantitative measurement of antimicrobial activity of honey because of large variation in the composition of honey, method of honey processing (eg, filtration, heating, etc), storage conditions, and adulteration.

To date, there are no placebo-controlled, randomized clinical trials of honey to answer the question if honey can be used systemically as an alternative to conventional antimicrobials. Because various honeys may vary greatly in their antibacterial potency,[274] the doses of honey to be used as an antibacterial agent cannot be ascertained with confidence.

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