Honey: A Sweet Way to Health

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Abstract

Honey is one of the most nutritional natural products that not only provides us healthy nutrition but also has a potential to be an alternative treatment option for different pathologies from microbial infection to metabolic disease. Honey is a byproduct of flower syrup produced by honeybees and possesses an intricate chemical composition that varies with botanical sources and geographical locations. This chapter is aimed to provide readers an understanding of complex composition, biological activities, adverse effect, and therapeutic benefits of honey. Honey possesses many biological activities, such as antioxidant, antimicrobial, anti-inflammatory, anti-proliferative, anti-cancer, and anti-metastatic effects, suggesting potential therapeutic roles in many human pathologies. Flavonoids and polyphenols in honey are the two active ingredients, which are of therapeutic importance in many diseases. In conclusion, honey may be developed as a natural therapeutic agent for many pathologies, and extensive studies are therefore recommended.

Keywords

Honey · Composition · Biological activity · Health · Flavonoids · Polyphenols · Natural therapeutic agent · Antimicrobial · Wound healing · Antioxidant · Immunomodulatory · Prebiotic · Preservative

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M. U. Rehman, S. Majid (eds.), *Therapeutic Applications of Honey and its Phytochemicals*, https://doi.org/10.1007/978-981-15-6799-5_4

4.1 Introduction

Honey is a nutritional natural product obtained by honey bees from flower nectars (Dashora et al. 2011) and is known for its cosmetic, therapeutic, and industrial values (James 1906; Bansal et al. 2005; Samarghandian et al. 2017). Since ancient times, Indians, Greeks, Romans, Egyptian, Babylonians, Chinese, and Mayans were cognizant of the nutritional and medicinal properties of honey (Adebolu 2005; Ashrafi et al. 2005; Samarghandian et al. 2017). Honey, which possess a long shelf life, is regarded as a balanced diet for all ages (Babacan and Rand 2007; Hassapidou et al. 2006; Bell 2007). Honey contains high content of sucrose and is used as sweetener since ancient time (Babacan and Rand 2007; Pataca et al. 2007). Besides fructose, other ingredients of honey are glucose, sucrose, oligosaccharides, proteins, vitamins, and minerals (Chow 2002; White and Crane 1975). Honey varies in overall composition depending on the surroundings flora on which bees feed. Natural honey also contains potent bioactive compounds such as antioxidants which include flavonoids (e.g., apigenin, pinocembrin, kaempferol, quercetin, and galangin), polyphenolics (e.g., ellagic acid, caffeic acid, and ferulic acids), vitamins (e.g., ascorbic acid and tocopherols), and antioxidant enzymes (e.g., glucose oxidase, catalase, superoxide dismutase, and peptides like glutathione) (Alvarez-Suarez et al. 2010; Johnston et al. 2005; Turkmen et al. 2006; Rakha et al. 2008; Al-Mamary et al. 2002).

Honey provided a natural cure for many human diseases (Inglett 1976; Samarghandian et al. 2017), in traditional medicine for centuries (Zumla and Lulat 1989; Chowdhury 1999; Ali et al. 1991), due to documented health-beneficial effects including antioxidant (Ahmed and Othman 2013), anti-inflammatory (Khalil et al. 2012), antibacterial (Attia et al. 2008), antidiabetic (Estevinho et al. 2008), anticancer (Swellam et al. 2003), and for the treatment of respiratory, gastrointestinal, cardiovascular, and neurological diseases (Ghosh and Playford 2003; Abdulrhman et al. 2011; Ezz El-Arab et al. 2006). Ancient people from Egypt, China, Greece, and Rome also utilized honey for wound healing and gastrointestinal diseases (Al-Jabri 2005). The most outstanding finding was potent anti-microbial property of natural honey (Al-Waili and Haq 2004a; Emsen 2007), against many microorganisms including *Salmonella* species, *Shigella* species, *Escherichia coli (E. coli)* (Alvarez-Suarez et al. 2010; Jeffrey and Echazarreta 1996), and *Helicobacter pylori (H. pylori)* (Chowdhury 1999). In addition to antimicrobial activity, honey may also possess immune-modulatory activity (Al-Waili and Boni 2003a) and thus helps in the recovery of wound (Medhi et al. 2008; Tonks et al. 2003) and colitis (Bilsel et al. 2002a). Honey, interestingly, may protect cardiovascular system as it could readily attenuate reactive oxygen species (ROS)-mediated lipid oxidation in vitro (Ahmad et al. 2009; Hegazi and Abd El-Hady 2009). Though honey has a vast history of its benefits in traditional medicine, a lack of documented scientific support has limited more widespread utility in modern medicine. This chapter provides a review of current literature and will highlight the therapeutic abilities of honey in various diseases.

4.2 Physicochemical Properties of Honey

Approximately 300 types of honey are currently recognized (Lay-flurrie 2008). These varieties differ widely in the composition, taste, and physical attributes. Freshly isolated honey is a hygroscopic viscous liquid that exhibits a yellow or amber color. The viscosity of honey varies by composition and particularly, by water content. Presence of colloidal substances in honey imparts its characteristic surface tension and, along with viscosity, creates foaming in honey (Olaitan et al. 2007). Color and clarity of honey differ with variations in surroundings, flora, age of beehives, storage conditions, and the amount of colloidal substances and pollens (Olaitan et al. 2007). Once crystallized, glucose present in honey crystallizes into monohydrate white crystals and turns honey lighter in color. This crystallization rate is faster with lower water content, but higher glucose amount (Olaitan et al. 2007).

Natural honey is composed of approximately 200 substances, including carbohydrates, proteins, amino acids, vitamins, minerals, organic acid, and enzymes. However, honey from different geographical locations vary with difference in honeybee species, climatic conditions, and availability of floral nectar. The components of honey are illustrated given in Tables 4.1 and 4.2 and Figs. 4.1, 4.2 and 4.3. Carbohydrate is a central component of honey and accounts for approximately

Table 4.1 Components and nutrients of honey

Components and nutrients	Amount (in g 100 g^{-1})
Carbohydrate	80–85
Fructose	36.2–47.11
Glucose (dextrose)	30.31–40.56
Maltose	0–3
Galactose	0–3.1
Fructooligisaccharides	4–5
Sucrose	0–2.4
Other sugars	11.9–12.9
Water	15–17.1
Protein	0.3–0.5
Ashes	0.2– <0.6
Dietary fibers	0–0.2
Polyphenols	0.04–0.103
Vitamins	0.0008–0.027
Elements	0.06864–0.126015
Other essential nutrients	0.23

Honey contains a wide number of nutrients that vary greatly with geographical location, climate, flora, and honeybee species. Below is the summary of nutrients and their compositions provided on the basis of published literature (Pasupuleti et al. 2017; Samarghandian et al. 2017; Eteraf-Oskouei and Najafi 2013; Khan et al. 2018) and USDA database (FDC 2019)

Table 4.2 Variation in trace elements in honey

Elements	Range (mg 100 g^{-1})
Potassium, K	9.092–195.57
Calcium, Ca	1.86–13.614
Phosphorus, P	0.117–10.07
Sodium, Na	0.61–8.998
Magnesium, Mg	0.601–4.657
Aluminum, Al	0.002–1.304
Iron, Fe	0.113–1.032
Zinc, Zn	0.014–0.387
Lead, Pb	0.0007–0.121
Manganese, Mn	0.007–0.068
Copper, Cu	0.005–0.068
Chromium, Cr	0–0.05
Fluoride, F	0.007
Selenium, Se	0.0008

Honey contains several trace elements that are essential for human health that vary greatly with geographical location, climate, flora, and honeybee species. Below is the summary of various elements present in the honey globally as cited in published literature (Eteraf-Oskouei and Najafi 2013; Khan et al. 2018) and USDA database (FDC 2019)

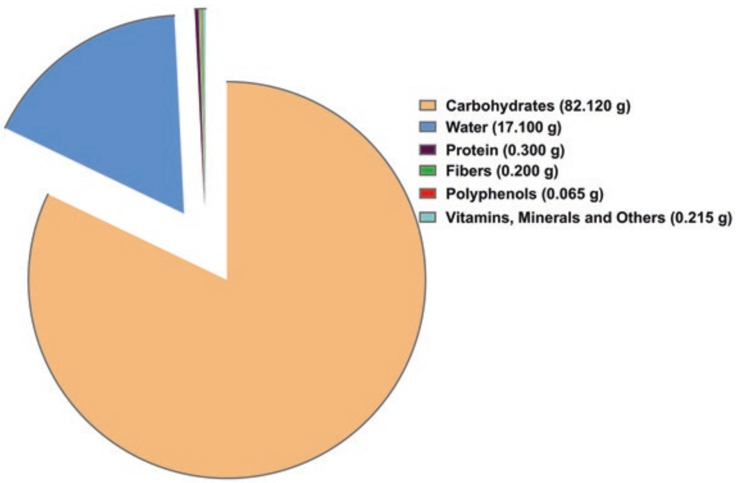

Fig. 4.1 Average compositions of honey. Honey contains many bioactive compounds from carbohydrate to essential elements and vitamins. The above pie chart depicts the average concentration of major group of components in honey (FDC 2019). The components are shown as amount in g 100 g^{-1} honey

95–97% of dry weight of honey. The principal carbohydrates in honey are monosaccharides, such as fructose (32.6 to 38.2%) and glucose (28.5 to 31.3%), which represent 85–95% of total sugars in honey (Ezz El-Arab et al. 2006; Moundoi et al. 2001; Betts 2008; El-Soud 2012; Clarke and Ndip 2011). In addition, smaller

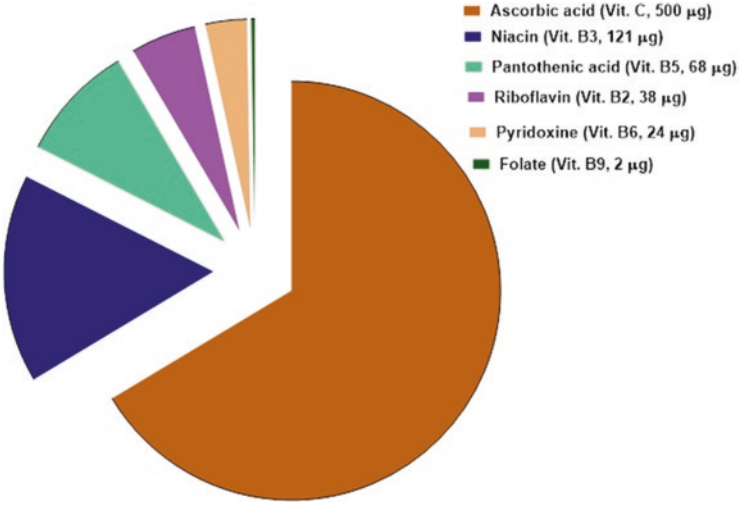

Fig. 4.2 Major vitamins present in honey. Honey contains most water-soluble vitamins, with vitamin C being the abundant one. The pie chart depicts the average concentration of major group of vitamins in honey (FDC 2019; Khan et al. 2007). The components are shown as µg 100 g^{-1} honey

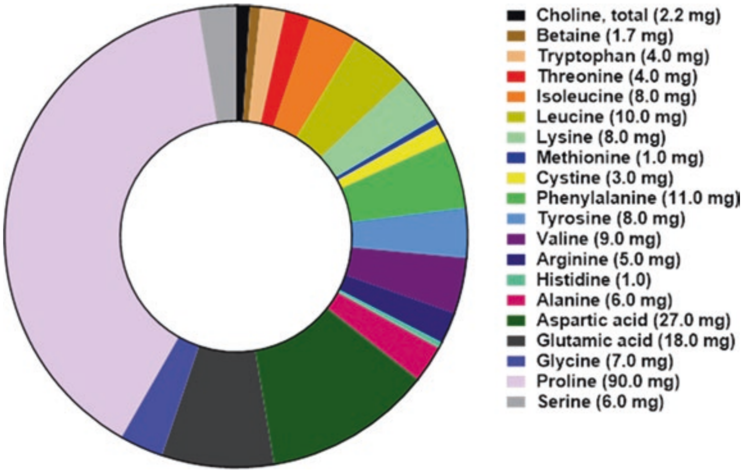

Fig. 4.3 Composition of essential nutrients and amino acids in honey. Honey provides essential nutrients to human in addition to carbohydrates, proteins, vitamins, and minerals. The above pie chart depicts the average concentration of reported nutrients in honey (FDC 2019). The components are shown as amount present in honey (mg 100 g^{-1})

quantities of disaccharides (such as maltose, sucrose, and galactose), trisaccharides (such as melezitose, maltotriose, and 1-ketose), and oligosaccharides are also observed in honey (Sato and Miyata 2000; Siddiqui and Furgala 1967; Ezz El-Arab et al. 2006; Chow 2002). Another type of oligosaccharides, fructo-oligosaccharides, comprises 4–5% of carbohydrates and may serve as probiotic agents (Ezz El-Arab et al. 2006; Chow 2002). Thus, being a natural source of carbohydrates, honey works as an effective nutritional supplements for athletes after strength exercise (Bansal et al. 2005).

Water constitutes about 15–17.1% of honey and essential for viscosity of honey (Bogdanov et al. 2008; Khan et al. 2007; Khan et al. 2018). Organic acids comprise of approximately 0.57% of honey and are responsible for its acidic nature (pH = 3.2–4.5) (Olaitan et al. 2007; Mato et al. 2003; Siddiqui and Furgala 1967). These acids are gluconic acid, acetic acid, formic acid, and citric acid. Gluconic acid is a main organic acid in honey and is derived from enzymatic oxidation of glucose (Siddiqui and Furgala 1967; Olaitan et al. 2007). Other acids found in honey are benzene derivatives and are present in minimum amount. To name few are syringic acid, 2-hydroxy-3-phenylpropionic acid, 2-hydroxybenzoic acid, 3,4,5-trimethoxybenzoic acid, and 1,4-dihydroxybenzene (Obi et al. 1994).

Protein content of honey is approximately 0.1–0.5% and mostly comprises enzymes (Lee et al. 1998; Jagdish and Joseph 2004; Won et al. 2009; French et al. 2005; Iglesias et al. 2004; Bansal et al. 2005; Olaitan et al. 2007). Diastase, invertase, and glucose oxidase are three prominent enzymes in honey. While, amylase and invertase provide fructose and glucose from complex starch, glucose oxidase oxidizes glucose to produce hydrogen peroxide and gluconic acid. Hydrogen peroxide provides antimicrobial properties, while gluconic acid facilitates absorption of calcium. Excessive hydrogen peroxide is neutralized by the activity of catalase and produces oxygen and water. (Bansal et al. 2005; Olaitan et al. 2007). Honey also contains all amino acids except asparagine and glutamine. Among these, proline, lysine, phenylalanine, aspartic acid, and glutamic acid are the most abundant amino acids found in honey (Khan et al. 2018; Samarghandian et al. 2017).

Approximately 600 volatile compounds were reported in honey (Ajibola et al. 2012). The volatile compounds of honey are low in abundance and include aldehydes, alcohols, hydrocarbons, ketones, acid esters, benzene, furan, pyran, terpene, isoprenoids, as well as other cyclic compounds (Manyi-Loh et al. 2011; Barra et al. 2010). Other bioactive compounds in honey are flavonoids, polyphenols, alkaloids, glycosides, and anthraquinone (White 1962, 1980; Islam et al. 2012). Flavonoids and polyphenols are particularly important molecules, which impart bioactive properties of honey (Nurul Syazana et al. 2012; Carlos et al. 2011). Honey has been found to have nearly 30 types of polyphenols (Nurul Syazana et al. 2012; Carlos et al. 2011). In general, the most frequent polyphenolics are gallic acid, ellagic acid, benzoic acid, cinnamic acid, chlorogenic acid, caffeic acid, isorhamnetin, ferulic acids, myricetin, coumaric acid, and flavonoids like chrysin, naringenin, luteolin, quercetin, and apigenin (Nurul Syazana et al. 2012; Carlos et al. 2011).

Flavonoids are active natural polyphenolic compounds with a 15-carbon structure, comprising two benzene rings joined by a heterocyclic pyran ring (Petrus et al. 2011). They are generally classified into four categories: flavonols (quercetin, kaempferol, and pinobanksin), flavones (luteolin, apigenin, and chrysin), flavanones (naringenin, pinocembrin, and hesperetin), isoflavones (genistein), and anthocyanidins (Zand et al. 2000; Nurul Syazana et al. 2012; Carlos et al. 2011). Common flavonoids galangin, luteolin, quercetin, isorhamnetin, and kaempferol are commonly found in honey, whereas naringenin and hesperetin are occasionally present in few varieties (Khalil et al. 2011; Khalil et al. 2012). Few flavonoids like genistein, chrysin, luteolin, and naringenin mimic estrogenic activity and are also known as phytoestrogens (Kyselova 2011).

Honey encompasses approximately 31 variable minerals, collectively comprises 0.1–1.0% of honey dry weight. Potassium is the major element in honey, followed by calcium, magnesium, sodium, sulfur, and phosphorus. Honey also contains essential trace elements like, iron, copper, zinc and manganese, and minor amount of trace elements like silicon, rubidium, vanadium, zirconium, lithium, and strontium (Kumar et al. 2010; Rashed and Soltan 2004; Lachman et al. 2007; Khan et al. 2018). However, it includes few heavy metals like lead (Pb), cadmium (Cd), and arsenic (As) as pollutants (Vorlova and Pridal 2002; Khan et al. 2018). Honey from countries like Nigeria, Bangladesh, Argentina, Spain, and Turkey were also reported to have ash content less than 0.6 g 100 g^{-1} (Khan et al. 2018; Gheldof et al. 2002; Gheldof and Engeseth 2002).

The vitamin level in honey is lower than recommended daily intake. Among all, vitamin C is present in higher amount. Other vitamins are B1 (thiamine), riboflavin, nicotinic acid, B6, and panthothenic acid (Olaitan et al. 2007).

4.3 Biological Activities of Honey

Natural honey possesses several bioactive compounds that provide many nutritional and medicinal properties. In the following section, we discuss different bioactivities of honey from antioxidant to prebiotic use (Fig. 4.4).

Fig. 4.4 Biological properties of honey. Honey provides polyphenols, vitamins, and flavonoids to exert different activities. The above pictorial presentation summarizes the different reported bioactivities of honey which are also utilized to cure different ailments

4.3.1 Antioxidant Activity

Natural honey contains many flavonoids, polyphenols, vitamins, and antioxidant enzymes which make it a potent natural antioxidant (Johnston et al. 2005; Turkmen et al. 2006; Rakha et al. 2008).

The phenolic compounds of honey, flavonoids and polyphenolics, are the major antioxidants (Bravo 1998; Estevinho et al. 2008; Gheldof et al. 2003; Yao et al. 2003; Al-Mamary et al. 2002). Polyphenolics scavenge free radicals, chelate metal ions (Küçük et al. 2007; Vinson et al. 1998; Estevinho et al. 2008), and may easily be distributed into body compartments to exert physiological effects (Blasa et al. 2007). Thus, honey either itself or in combination with other antioxidants might be utilized to reduce oxidative stress (Gheldof et al. 2003).

The antioxidant activity of honey differs greatly with variation in the surrounding flora, while extraction or storage affects honey minutely (Al-Mamary et al. 2002; Frankel et al. 1998; Gheldof and Engeseth 2002; Gheldof et al. 2002; Beretta et al. 2005). As floral variations affects polyphenolics content of honey, dark honey having higher content of total phenolics consequently has a higher antioxidant capacity (Frankel et al. 1998; Beretta et al. 2005; Beretta et al. 2007; Bertoncelj et al. 2007).

4.3.2 Antimicrobial Activity

Honey is known as antimicrobial in wound healing since 2100–2000 BC when Sumerian were using it as an ointment (Mandal and Mandal 2011). Honey works as a physical barrier to the wound when applied on it and maintains the moisture (Lusby et al. 2005). In modern era, honey was first recognized as antimicrobial by van Ketel and was rediscovered as antibacterial in 1892 (Dustmann 1979). Various results confirmed its activity against approximately 60 bacterial species, to name few important ones, are *Bacillus anthracis, Staphylococcus aureus, Corynebacterium diptheriae, Haemophilus influenzae, Klebsiella pneumoniae, Shigella dysentery, Mycobacterium tuberculosis, Yersinia enterocolitica, Salmonella diarrhoea, Salmonella typhi, Streptococcus pneumoniae,* and *Vibrio cholerae* (Jeffrey and Echazarreta 1996; Bansal et al. 2005; Asadi-Pooya et al. 2003; Olaitan et al. 2007; Al-Waili 2004b). Further, natural honey was also found effective against the methicillin-resistant *Staphylococcus aureus* (MRSA) (Natarajan et al. 2001; Chambers 2006; Maeda et al. 2008).

Honey has lower minimum inhibitory concentration (MIC= 1.8–10.8% v/v), which means that it can provide enough inhibition on bacteria if diluted nine times. It has also been implied that honey sufficiently inhibited most common wound pathogen, *Staphylococcus aureus* even if diluted by 56 times (Molan 2001c; English et al. 2004). Further, high dilution pasture (4–8% v/v) and manuka (5–11% v/v) honey inhibited the bacterial growth, while lower dilutions of same [pasture (5–10%) and manuka (8–15%) honey] killed bacteria when applied (Bansal et al. 2005).

Further, 20% (v/v) solution of honey inhibited *H. pylori* in gastric isolates in vitro (Ali et al. 1991; Jeffrey and Echazarreta 1996). Unlike most conventional antibiotics, chronic use of honey may not yield to treatment-resistant bacteria (Emsen 2007).

The anti-bacterial activity of honey is credited to four properties of honey. First, high amount of sugar in honey inhibits microbial growths and dehydrates bacteria; second, the acidic pH of honey restricts growth of many microorganisms; third and most important, hydrogen peroxide formed due to glucose oxidation acts as potent antibacterial factor, although nonperoxide activity (e.g., catalase) of honey might also be attributed to its antimicrobial property and lastly several other components like lysozyme, beeswax, nectar, pollen, propolis, polyphenols, terpenes, organic acid, and redox enzymes were also reported to add into antibacterial activity of honey (Emsen 2007; Al-Waili and Haq 2004b; Beretta et al. 2007; Cushnie and Lamb 2005; Simon et al. 2009; Olaitan et al. 2007; Bansal et al. 2005; Küçük et al. 2007; Estevinho et al. 2008). Other factors such as high osmotic pressure, low protein, high antioxidants, moderate viscosity, and low dissolved oxygen do not allow the growth of microorganisms like bacteria, yeast, and fungi (Patton et al. 2006; Badawy et al. 2004; Wilkinson and Cavanagh 2005). Thus, unique physiochemical properties of honey therefore enable it to be used as wound dressing to suppress infection (Basualdo et al. 2007; Molan 2002).

Antibacterial activities of honey vary in accordance to different amounts of compounds and enzymes present. Among all natural honey, manuka honey showed the highest efficiency against *E. coli* and *S. aureus* (Cushnie and Lamb 2005; Snowdon and Cliver 1996; Molan 2001a). Varied antibacterial activity of honey might be attributed to different components of flower and nectar available to bees (Küçük et al. 2007). In agreement to this, sugar contents in different types of honey were found to be correlated to their inhibition efficiency on growth of various intestinal bacteria (Shin and Ustunol 2005; Basualdo et al. 2007).

4.3.3 Apoptotic Activity

Honey induces intrinsic (mitochondrial) apoptotic events in cancerous cells which include mitochondrial membrane depolarization and rupture (Nicholson 2000; Earnshaw 1995), downregulation of antiapoptotic protein Bcl-2 (Jaganathan and Mandal 2009; Tomasin and Gomes-Marcondes 2011), activation, and cleavage of caspase-3 and poly (ADP-ribose) polymerase (Fauzi et al. 2011). In addition, honey also upregulated p53 and pro-apoptotic protein Bax in colon cancer cell lines in vitro (Fauzi et al. 2011). Similarly, oral gavage of honey inhibited tumor growth by upregulating Bax, activating caspase-9/3 and initiating DNA fragmentation in tumor tissue of Wistar rats (Jaganathan and Mandal 2009; Tomasin and Gomes-Marcondes 2011). According to a report by Fauzi et al., high phenolic contents of honey attribute to its anticarcinogenic activity (Fauzi et al. 2011). However, in view of lack of robust experimental findings, more experimental results are needed to ascertain therapeutic ability of honey in treating cancer.

4.3.4 Immunomodulation by Honey

Honey has shown anti-inflammatory activities in preclinical and in vitro experiments (Fernandez-Cabezudo et al. 2013; Candiracci et al. 2012; Bilsel et al. 2002b), and in clinical trials as well (Leong et al. 2012). Honey or its constituents have shown to regulate cytokines (Cho et al. 2004; Araujo et al. 2011; Hussein et al. 2012) and to activate myeloid/lymphoid immune cells (Timm et al. 2008a). Honey inhibited COX-1 and 2 activities, (Markelov and Trushin 2006), and reduced prostaglandins such as PGE2, PGF2α, and thromboxane B2 in normal human plasma (Al-Waili and Boni 2003b). The immunomodulation property of honey might be attributed to polyphenolic and flavonoid compounds which have shown to inhibit cyclooxygenase-2 and inducible nitric oxide synthase (Viuda-Martos et al. 2008; Al-Waili and Boni 2003b; Al-Waili and Haq 2004b; Cho et al. 2004; Araujo et al. 2011; Hussein et al. 2012).

Anti-inflammatory steroidal drugs, e.g., corticosteroids, dampen tissue regeneration and immune response, while non-steroidal drugs harm stomach linings. Honey is a good anti-inflammatory devoid of adverse side effects (Molan 2001c) and is as effective as other steroidal/non-steroidal drugs. For example, honey showed equivalent efficiency to treat experimental colitis as compared to prednisolone, a glucocorticoid drug (Bilsel et al. 2002b). Honey efficiently treated eczema, psoriasis, and dandruff, and efficiently reduced scar formation and exudation to promote wound repair and tissue regeneration (Al-Waili and Boni 2003b; Al-Waili 2003). Earlier, honey-stimulated release of cytokines from monocytes was believed to be partly associated with wound healing ability (Tonks et al. 2001b, 2003). Later, it was reported that honey's endotoxin contents (>30 kDa) might be responsible for wound healing (Timm et al. 2008b; Gannabathula et al. 2012). Evidently, Kanuka flowers' honey contains substantial amount of high molecular weight (>30 kDa) endotoxins, e.g., lipopolysaccharides, apalbumins, and arabinogalactan proteins, and thus, effectively stimulated the release of TNFα from monocytic cell lines. Similarly, deproteinized natural acacia honey which lacked high molecular weight molecules did not stimulate release of TNF-α. Therefore, high molecular weight components of honey might be argued to be responsible for immunomodulatory effects (Majtán et al. 2006). However, natural protein and peptide can cause nonspecific immune response (Dutta 2002); therefore, a cautious approach is always needed when applying natural products like honey to stimulate immune response.

4.3.5 Honey in Food Preservation

Hydrogen peroxide and non-peroxide components, e.g., antioxidants inhibit microorganisms, provide preservative ability to honey. As a result, honey has been shown to prevent *Shigella species, Listeria monocytogenes,* and *S. aureus* in food, in addition, honey being potent antioxidant, prevented polyphenol oxidation and thus reduced browning of fruits and vegetables during processing and storage (Bansal et al. 2005; Chen et al. 2000).

4.3.6 Honey as Prebiotic

Honey suppresses potentially harmful intestinal bacteria, while promotes the growth of beneficial gut flora (Bansal et al. 2005; Chow 2002; Ezz El-Arab et al. 2006). Honey supported the growth of microbiota like *S. thermophilus*, *Lactobacillus acidophilus*, *Lactobacillus delbruekii*, and *Bifidobacterium bifidum* (Bansal et al. 2005; Sanz et al. 2005). Being rich in oligosaccharides, honey can be added as a dietary supplement to improve gut microflora health.

4.4 Honey in Traditional Medicinal History

Honey is known to mankind as natural food and medicines since stone age (approximately 8000 years ago). Other civilizations later also recognized the benefits of honey and were documented in various ancient scrolls, books, and tablets, e.g., Sumerian clay tablets (6200 BC), Veda (Hindu scripture) [5000 years ago] Egyptian papyri (1900–1250 BC), Hippocrates (460–357 BC), Koran, and Bible (Molan 2001b; Bergman et al. 1983; Mijanur Rahman et al. 2014; Newman 1983; Bansal et al. 2005; Samarghandian et al. 2017; Eteraf-Oskouei and Najafi 2013). These ancient civilizations (Egyptian, Roman, Greek, and Chinese) were fully aware of honey efficacy in treating wounds and diseases of the gut (Al-Jabri 2005; Eteraf-Oskouei and Najafi 2013; Zumla and Lulat 1989). The ancient *Vedic* people regarded honey the most valuable product of nature and emphasized its role in digestion, oral health, and eyesight. In addition, Ayurvedic medicine uses honey to treat herpes, cough, cold, insomnia, skin wounds/burns, lung disease, anemia, and cardiac disease (Bansal et al. 2005; Telles et al. 2007; Eteraf-Oskouei and Najafi 2013). Honey was also popular for embalming of dead (Bansal et al. 2005). “Oenomel,” an ancient Greek beverage, made up of honey and grape juice, was used to treat gout and neuro-disorders (Zumla and Lulat 1989; Eteraf-Oskouei and Najafi 2013). Hippocrates recognized the healing and nutritional properties of honey and prescribed different honey mixtures for different ailments such as oxymel (honey with vinegar) for pain, hydromel (honey mixed in water) for thirst, and a hydromel with antipyretic for fever (Zumla and Lulat 1989; Eteraf-Oskouei and Najafi 2013). In addition, he favored honey for conditions like wound, scar, baldness, cough, sore throat, and eye diseases (Bansal et al. 2005). Ancient Muslims treated diarrhea patients with honey (Molan 1999; Molan 2001c; Eteraf-Oskouei and Najafi 2013), while the Iranian physician, Avicenna (almost 1000 years ago), suggested honey for the treatment of tuberculosis (Asadi-Pooya et al. 2003).

4.4.1 Medicinal properties

Natural honey is being used for its medicinal properties since ancient times (Ahmed et al. 2003) and found to be useful in different disease conditions.

4.4.1.1 Honey in Wound Therapy

Honey has been known for its antibacterial, antiviral, anti-inflammatory, and antioxidant properties and therefore is regarded as the oldest wound-healing agent by us (Snowdon and Cliver 1996; Murosak et al. 2002; Medhi et al. 2008). The Germans and Russians utilized honey in combination with cod oil or alone for treating burns, boils, fistula, or battle wounds (Bansal et al. 2005). Wound pads permeated with honey act as non-sticky dressing and promotes wound healing faster (Bansal et al. 2005; Efem 1988; Al-Waili 2005).

Honey reduced ulcerations and inhibit bacterial infection after surgery of breast carcinoma, vulva and varicose veins, and in cesarean section or hysterectomies successfully. Therefore, it minimized the prolonged use of antibiotics, resulted in minimum scar formations, and thus minimized the hospital care (Cavanagh et al. 1970; Al-Waili 2005). Similarly, honey was effective in reducing bed eruptions, ulcers, or sores (van der Weyden 2003, 2005; Meda et al. 2004). Interestingly, sterilized manuka honey permeated dressing pads led to complete healing of conventional treatment-resistant amputated knee wound, which was also heavily infected with *P.* and *S. aureus* (Dunford et al. 2000). Honey showed expedited recovery in radiation-induced mucus inflammation and in Fournier's gangrene with rapid regeneration of tissue and minimal scar (Motallebnejad et al. 2008; Gürdal et al. 2003).

Honey acts as a good histological preservative for skin grafts (Subrahmanyam 1993) and has also been implemented as a cure for superficial to moderate burns (Simon et al. 2009). Initially, honey provides comforting effect, reduces pain, prevents infection, and later accelerates the healing of wound with less scar and contracture (Subrahmanyam 1991, 1993). Clinical trials showcased the higher efficacy of honey dressing pads in burn patients as compared to other commercially available dressings, for example, amniotic membrane, silver sulfadiazine, or potato peel dressings (Bansal et al. 2005; Meda et al. 2004). Thus, honey dressing provides an economical option to manage wounds by minimizing medical and hospital costs to patients (Zumla and Lulat 1989). However, honey dressing provides non-sticky and pain-free pads which are easy to change, the acidity of honey may cause discomfort in patients with naked nerve endings (Bansal et al. 2005).

Honey is remarkably effective in wound healing as a result of its three important properties: the osmosis gradient, generation of hydrogen peroxide, and immune-modulation. Osmotic outflow of fluid assists in removing debris from bed of the wound, thus provides space and nutrient supply for tissue regeneration (Bansal et al. 2005). Honey contains large amount of glucose which can be utilized by internal glucose oxidase or by leukocytes in respiration to yield hydrogen peroxide, a major antibacterial compound in honey (Efem 1988; Wilkinson and Cavanagh 2005; Dustmann 1979; Basualdo et al. 2007; Al-Waili 2001; Bansal et al. 2005). Further, honey has shown to stimulate phagocytic cells and to regulate the production of cytokines; therefore, its wound healing property might partially be attributed to its immune modulation property (Olaitan et al. 2007; Abuharfeil et al. 1999; Tonks et al. 2001a, 2003; Kumar et al. 2010).

4.4.1.2 Honey in Diabetes

Low glycemic index of honey was found effective in controlling blood sugar level diabetes as well as normal subjects as compared to sucrose and glucose (Erejuwa 2014; Samanta et al. 1985). However, either honey or glucose/sucrose did not show difference in blood sugar level in type 2 diabetes patients (Erejuwa 2014). In addition, management of metabolic complications is another advantage of honey administration (Yapucu Güneş and Eşer 2007) as it improved blood C-reactive protein (CRP) level, homocysteine contents, and lipid profile (Al-Waili 2004b; Bansal et al. 2005) and minimized the rise of plasma glucose in diabetic patients (Bogdanov et al. 2008; Cianciosi et al. 2018; Kamaruzaman et al. 2014; Khalil et al. 2011, 2012; Khalil and Sulaiman 2010). It was argued that honey stimulated insulin secretion that regulated blood glucose level and also improved hemoglobin concentration and lipid profile (Al-Waili and Haq 2004a). Therefore, honey may be utilized as supplement with standard antidiabetic drugs for different types of diabetes. However, in view of small experimental proof and lack of clinical trials, several questions about efficacy and mechanism remained unanswered and warrant further investigation.

4.4.1.3 Honey in Cancer

Honey possesses antiproliferative, apoptotic, mitochondrial membrane depolarization, anti-mutagenic, and immunomodulatory properties that might be attributed to its anticarcinogenic effect (Bansal et al. 2005; Sela et al. 1998; Molan 2001a, b; Eddy et al. 2008). Several reports stated its effectiveness in treating many tumors, e.g., hepatocellular, colorectal, renal, prostate, cervical, uterine cancers, and leukemia (Erejuwa et al. 2014; Fauzi et al. 2011; Yaacob et al. 2013; Samarghandian et al. 2010, 2011a, b, 2014a, b; Baiomy et al. 2009; Swellam et al. 2003; Aliyu et al. 2013). Exploration of honey in therapeutic treatment in cancer is relatively in infancy stage; therefore, more studies are warranted to investigate its mechanistic role as anticancerous mixture.

4.4.1.4 Honey in Asthma

Honey is very effective to treat cough and fever and has been recorded as common cough and fever medicines in folk medicines (Bâcvarov 1970; Ghashm et al. 2010). Honey showed the ability to prevent induction of asthma and reduced chronic asthma-related symptoms in experimental animal models (Ghashm et al. 2010). The beneficial effect of honey is related to its ability to curb inflammation and remodel the airway (Kamaruzaman et al. 2014).

4.4.1.5 Honey in Cardiovascular Diseases

Previously, honey is an excellent antioxidant, reduced cardiovascular risk by lowering hyperlipidemia and oxidative stress (Yaghoobi et al. 2008; Bahrami et al. 2008; Chepulis 2007; Schramm et al. 2003). Honey has shown these three distinct properties which might be attributed to its cardiovascular protection in various diseases: (a) Honey is a good vasodilator, (b) it inhibits platelet aggregation to make a clot, and (c) it prevents oxidation of low-density lipoproteins (LDL) (Kamaruzaman et al. 2014; Cianciosi et al. 2018; Bravo 1998; Khalil and Sulaiman 2010).

Ingestion of 70 g honey daily for a month in 38 overweight individuals significantly reduced total cholesterol, LDL-cholesterol (LDL-C), triacylglycerol (TG), and C-reactive proteins (CRP), without increasing the body weight (Yaghoobi et al. 2008). Similarly, natural honey improved blood lipid profile in hypertriglyceridemia and hyperlipidemia patients, while the exact amount of artificial honey aggravated LDL-C and CRP (Bogdanov et al. 2008; Cianciosi et al. 2018; Kamaruzaman et al. 2014; Khalil et al. 2011, 2012; Khalil and Sulaiman 2010). Abundance of nitric oxide (NO) and its metabolite in honey might be attributed to its cardiovascular activity (Bogdanov et al. 2008) and thus helped to clear venous congestion and to reduce cardiac burden (Rakha et al. 2008).

Several reports depicted protective effect in ischemia/reperfusion-induced injuries (Najafi et al. 2008, 2011; Eteraf-Oskouei and Najafi 2013). Langendorff's heart was protected from ischemia/reperfusion injury either by treating rats with natural honey for 45 days prior to isolation of heart or by perfusing isolated heart by honey-enriched Kreb's solution ex vivo (Najafi et al. 2008, 2011; Eteraf-Oskouei and Najafi 2013). In addition, honey attenuated oxidative stress and thus protected neurons from ischemia-induced cell death (Shimazawa et al. 2005). Thus, antioxidants in honey may serve as potential natural nutrients for improving cardiovascular health directly (Zalibera et al. 2008; Rakha et al. 2008). In addition, cardiovascular ability of natural honey might also be attributed to vitamin C-influenced release of NO from endothelium as administration of honey 1 h prior to adrenaline test in rats reduced vasomotor and cardiac function (Rakha et al. 2008).

4.4.1.6 Honey in Neurological Diseases

Several studies have proposed nootropic and neuroprotective properties of honey-derived polyphenols. Honey has shown anxiolytic, antidepressant, anticonvulsant, antinociceptive, and antioxidative effects (Khalil and Sulaiman 2010; Ghosh and Playford 2003). Honey polyphenols were effective in quenching ROS, inhibited pathological deposition of misfolded proteins and amyloid beta, prevented apoptosis, reduced oxidative stress, and excitotoxicity (Akanmu et al. 2011; Schmitt-Schillig et al. 2005; Shimazawa et al. 2005; Zalibera et al. 2008).

Raw honey as well as honey polyphenols inhibited microgliosis and thus attenuated neurotoxin or ischemia-induced neuroinflammation (Li et al. 2008). Most significantly, honey polyphenols prevented cognitive and memory impairment possibly through suppressing of hippocampal inflammation (Akanmu et al. 2011; Samarghandian et al. 2017) and via modifications of neural connections and synapses (Ghosh and Playford 2003).

4.4.1.7 Honey in Gastrointestinal Diseases

Ingestion of honey was reported to inhibit gastrointestinal diseases, e.g., gastritis, duodenitis, and gastric ulceration caused by *Helicobacter pylori* (Tallett et al. 1977; Haffejee and Moosa 1985; al Somal et al. 1994; Topham 2002; Alnaqdy et al. 2005; Oyefuga et al. 2012). Honey not only prevented gastrointestinal bacterial growth (Alnaqdy et al. 2005), it also limits the bacterial attachment to host intestinal epithelia by altering electrostatic charge and hydrophobicity of bacterial wall (Alnaqdy et al. 2005; Edebo et al. 1980; Sakai 1987). Although manuka honey-based therapy failed to indicate a beneficial treatment against *H. pylori* in earlier clinical trial (al Somal et al. 1994), honey solution with lower peroxide (20%) activity was found to be effective in vitro (Bansal et al. 2005; al Somal et al. 1994). It can be argued that in vitro study is more controlled study and is very different from complex in vivo system with many confounding factors. Further, gastrointestinal discomforts get resolved quickly with honey ingestion. Though, honey did not exert any effect in viral gastroenteritis (Bansal et al. 2005; Haffejee and Moosa 1985; Obi et al. 1994) but was effective in the management of peptic and antral ulcer (Ali 1995). Honey being rich in potassium and water worked as better rehydration fluid and did not increase sodium uptake (McGovern et al. 1999; Haffejee and Moosa 1985). It also helped to reduce inflammation and to repair the inner mucosa layer (Bansal et al. 2005). Further, in indomethacin-induced experimental gastric lesion, oral gavage of honey (2 g/kg) prevented microvascular permeability and myeloperoxidase activity in the stomach (Nasuti et al. 2006). Similarly, perfusion with isotonic solution of honey reduced ethanol-induced lesions in stomach significantly (Gharzouli et al. 2002).

4.4.1.8 Honey in Infectious Diseases

Besides the aforementioned antimicrobial activity (Brady et al. 1996; Kumar et al. 2010; Dunford et al. 2000; English et al. 2004; Molan 2001b; Patton et al. 2006; Al-Waili 2004a), honey also inhibits the fungal (including Aspergillus, Penicillium, as well as all the common *dermatophytes)* and yeast infections (Brady et al. 1996; Kumar et al. 2010). The pure honey was reported to be fungicidal, while its dilution abolished production of toxin (Al-Waili and Haq 2004a; Bansal et al. 2005; Obaseiki-Ebor and Afonya 1984). Honey effectively treated several skin diseases such as candidiasis, athlete foot, ringworm, and dermatitis (Bansal et al. 2005; Obaseiki-Ebor and Afonya 1984; Al-Waili 2001, 2005).

Honey prevented recurrent genital and labial lesions from herpes infection effectively as compared to conventional acyclovir application (Al-Waili 2004a) and inhibited rubella-induced rash (Al-Waili and Haq 2004a). Honey was found effective in various ophthalmological infections such as blepharitis and conjunctivitis and also helped in recovery from corneal injuries (Shenoy et al. 2009; Meda et al. 2004). Topical honey improved eye conditions in more than 85 patients while stopped disease progression in remaining patients in a study in 102 patients with nonresponsive eye disorders (Bansal et al. 2005; Obaseiki-Ebor and Afonya 1984; Al-Waili 2004a). Honey also ameliorated gingivitis and periodontitis (Khan et al. 2007) and prevented leishmaniasis in vitro (Al-Waili and Haq 2004b).

4.4.2 Nonmedicinal Uses of Honey

4.4.2.1 Nanoparticles Synthesis

Nanoparticles showed promises in various processes such as biomedical, optical, biosensor, catalytic, and energy application (Salata 2004). One of the important application of nanoparticle is in drug delivery and molecular doping (Wang et al.

2015). Copper nanoparticles (Cu-NPs) are being good antibacterial and are much advantageous over others in drug delivery (Grass et al. 2011). However, process of making Cu-NPs demands high cost and release toxic byproducts (Cerchier et al. 2017; Kumar et al. 2015). Moreover, copper is a highly unstable metal, and therefore, a stabilizing agent is always incorporated during Cu-NP formation (Sierra-Ávila et al. 2015). Owing to the viscosity and protein and carbohydrate constituents of honey, it provides green and nontoxic alternative to stabilizing agent in the nanoparticles synthesis (Oskuee et al. 2016). In addition, being potent antioxidant, honey could also regulate redox reactions in production of platinum nanoparticles (Venu et al. 2011).

4.4.2.2 Cryoprotective Agent

Saccharides being low toxic and having ability to interact with lipid bilayer and inhibiting crystal formations during freezing phase are increasingly used as stabilizers in cryo-preservative media (Leekumjorn and Sum 2008; Herrick et al. 2016). Honey provides multiple monosaccharides, mostly glucose and fructose, two most frequently utilized sugars in cryopreservation (Lazarević et al. 2012). Considering its antioxidant ability and abundance of monosaccharides, it was found to be effective in semen cryopreservation as alone/in combination with other natural cryopreservative agents (Fakhrildin and Alsaadi 2014; Jerez-Ebensperger et al. 2015) and acted as non-penetrating cryoprotective agent for mammalian embryo more effective than conventional sucrose (Sarmadi et al. 2019).

4.4.2.3 Other Effects of Honey

Natural honey contains high nutritional components and thus provides immediate calories to exhausted tissue in case of fatigue and starvation (Meda et al. 2004). Honey is also capable of immunomodulation (Al-Waili and Haq 2004b) and therefore has been a very effective agent for fixation of skin graft (Emsen 2007). Daily intake of honey improved hematological indices and endocrine system (Al-Waili 2003). Honey further reduced obesity, uterine atrophy, and loss of bone density in menopausal rats. The benefits of honey could be attributed to its influence on endocrine system. (Zaid et al. 2010). Honey was also reported to be beneficial in measles, period pain, toothache, dry mouth, male impotency, and pharyngitis (Meda et al. 2004; Bansal et al. 2005; Sela et al. 1998; Molan 2001a, b). Honey being excellent antioxidant prevented DNA damage (Guerrini et al. 2009) and apoptosis in animal model of obstructive jaundice (Kilicoglu et al. 2008) and augmented glutathione-based redox system to attenuate N-ethylmaleimide-induced hepatic injury (Korkmaz and Kolankaya 2009).

4.4.2.4 Undesirable Effects of Honey

Sometimes, a person having naked nerve endings in skin may experience a stinging sensation after applying honey topically. Honey rarely gives hypersensitive reactions, which is probably arisen due to presence of allergens, such as, pollen or bee proteins. Excess honey on wound or skin may dehydrate the applied region and may need saline treatment to restore hydration. Ingestion of honey infected with clostridia, can pose serious risk of botulism. However, honey irradiated with gamma radiation does not show any clostridia spores without losing its other biological activity (Bansal et al. 2005; Molan and Allen 1996). It is a known fact that not only pesticides have the capacity to eliminate target organism, they also affect the contamination of non-target species. One of the disadvantages of high pesticide use is contamination of food (Souza Tette et al. 2016). According to a global survey, 75% of all honey samples have nicotinoid contamination (Mitchell et al. 2017). More than 95 pesticides and their metabolites were observed in bee pollen, and the level was alarmingly high up to 214 ppm (Mullin et al. 2010). Therefore, pesticides in honey poses a great risk to health of human and bee as well and urge to take serious measures to reduce environmental contamination (Souza Tette et al. 2016).

4.5 Future Direction and Concluding Remarks

To date, with growing interest and notion, alternative medicines are receiving increased interest from the general public, fueling research into natural products as safe and efficacious alternatives to pharmaceuticals and drugs. Honey, an age-old natural medicine and nutritional product, is known for wound healing, as an antimicrobial and as a remedy for cough and throat infection. Honey contains number of compounds including antioxidants, phenolics, dextrose, and enzymes, which can be therapeutically useful in different diseases. However, like other natural mixture, honey varies in composition according to geographical locations, climatic conditions, floral species and bee populations, and thus, complicating the design and interpretation of experimental studies between different centers. Future research focused on identifying the bioactive ingredients and pharmacological components in honey may overcome this potential obstacle. Another problem is decline of bee population due to environmental change and pollution, which has declined the production of natural honey. Moreover, pollutants and pesticides present in floral nectar are accumulating in honey, posing a health threat to both beehives and humans. In conclusion, preservation of the environment is paramount to ensuring a supply of pure honey, a potentially safe and efficacious natural remedy with widespread application.

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