Honey and Its Derivatives: A New Perspective on Its Antimicrobial Activities

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Abstract

Honey is a well-known and historically important sweet food which possesses immense antimicrobial properties. Numerous varieties of honey are present in nature, and all of these honey varieties contain certain key ingredients, which confer upon them various antimicrobial properties. These antimicrobial key ingredients include polyphenolic compounds, hydrogen peroxide, methylglyoxal, and bee-defensin among several others. Honey is nowadays used extensively in modern medicine as potent antibiotic for the treatment of surface wounds and burns. It is also used in combination with other antibiotics to treat antibiotic resistance. As an antifungal agent, honey is used to treat the athlete's foot (tinea pedis), jock itch (tinea cruris), and ringworm of face, scalp, nail, and hand (tinea corporus). In this chapter, we aim to provide a brief overview of various types of honey and their composition and describe extensively its various antimicrobial properties and how these properties are exploited in modern medicine as an alternative to popular therapeutics or in conjunction with it.

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Keywords

Honey · Honeybee · Antioxidant · Antimicrobial · Antifungal · Antiviral

Abbreviations

AT	Agastache honey
CAT	Catalase
G6PD	Glucose 6 phosphate dehydrogenase
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
LOOH	Lipid hydroperoxide
MAPKs	Mitogen-activated protein kinases
MK	Manuka honey
NO	Nitric oxide
O_2^-	Superoxide
OH^-	Hydroxyl
$ONOO^-$	Peroxynitrite
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PKB	Protein kinase B
PKC	Protein kinase C
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RO	Alkoxy
ROO	Peroxyl
SOD	Superoxide dismutase

7.1 Introduction

7.1.1 Honey

Honey is perhaps the oldest consumed food in human history and is still used as natural sweetener and health supplement. The consumption of honey dates back to 5500 BC and is duly mentioned in the manuscripts of various civilizations of Egypt, China, and India. Most of the ancient civilizations, including the Greeks, Romans, Egyptians, Babylonians, Persians, Mayans, Indians, and Chinese utilized honey and its derivatives for nutritional and medicinal reasons (Israili, 2014; Samarghandian et al. 2017; Ahmed et al. 2018). Interestingly, honey is the sole biological commodity of insect origin that is consumed so widely by humans for its nutritional, cosmetic, and therapeutic benefits (Simon et al. 2009; Ahmed and Othman 2013a; Othman 2012a, b).

The syrupy product which humans consume is derived by various species of bees (Apis mellifera; Family: Apidae) from flower nectars. During collection, this nectar gets mixed with the enzymes of saliva present in the honey sack, gets digested/processed and is then finally regurgitated back into the cells of the hive to store it for future use (Michener 2013; Abd Jalil et al. 2017). The most common source of honey consumed by humans is produced by Apis mellifera (and numerous other subspecies like *A. m. anatolica*, *A. m. carnica*, *A. m. caucasica*, and *A. m. ssp. sicula*); however, there are other species like A. andreniformis, A. caucasica, A. cerana, A. dorsata, A. florea, A. indica, and A. ligustica; Plebeia wittmanni, Tetragonisca angustula fiebrigi, and Trigona carbonaria which are known to produce quality honey also (Israili 2014). Honey is one of the most common foods used widely across all ages and gender, all over the world. Honey does not need any special methods of preservation and can be transported and stored at around 25 °C–37 °C in a dark and dry place (Israili 2014; Samarghandian et al. 2017; Othman 2012b; Bell 2007).

The nutritional and therapeutic properties of honey and its concomitant uses have been well described in almost all religious scriptures encompassing all faiths and cultures. Among the three most followed religions of world—Christianity, Islam, and Judaism—honey is mentioned in all the Holy books—Bible, Quran, and Talmud, respectively. In all, honey is regarded as the important food having both nutritional and healing properties (Israili 2014; Rosner 2000; Purbafrani et al. 2014).

7.1.2 Composition

The composition, physical and chemical properties, flavor, color, and consistency of honey varies with floral source, geographical areas, climate, storage conditions, and the type of bees (Samarghandian et al. 2017; Castro-Vázquez et al. 2009; Manyi-Loh et al. 2011; Chang et al. 2011; Brudzynski and Kim 2011). Usually honey is named based either upon various geographic locations where it is produced/harvested or the floral sources or trees on which the hives are found. There are around 300 or more unique types of honey available, of which some 35 types are most used (Lusby et al. 2002). A few different types of honey available around the world are presented in Table 7.1.

It is reported that honey usually contains about 600 different compounds of which carbohydrates contribute about 95–97% of its dry weight and primarily consist of two main sugars—glucose (31%) and fructose (38%). They are derived from the digestion of floral nectar disaccharides by bee salivary enzymes. Sugar content in honey in turn is responsible for crystallization, viscosity, thermal, and rheological properties (Nguyen et al. 2018). Sugars are also responsible for provision of energy equivalent to 300 kcal/100 g of honey, which constitutes about 15% of the recommended daily allowance (Samarghandian et al. 2017). Honey has a moisture content of 15.6% and total solid content of >82.0% (Israili 2014; Samarghandian et al. 2017; Lusby et al. 2002; Rahman 2013; Masalha et al. 2018). Honey is one of the few energy-dense foods in nature with a low glycemic index (40; range, 31–78), pH

Table 7.1 Various honeys and their floral and chemical markers

Honey type	Floral marker	Chemical markers
Acacia honey	Cis-linalool oxide and heptanal	Kaempferol–rhamnosides and rhamnosyl–glucosides
Agastashe honey	Bicyclo undec-4-ene, 4,11,11-trimethyl-8-methylene	Phenol, 2,4-bis(1,1-dimethylethyl) and Estragole
Chestnut honey	2-Aminoacetophenone, 1-phenylethanol	p-Coumaric and ferulic acids
Manuka and tea tree honey	Estragole, Apigenin	Acetanisole and methyl 3,5-dimethoxybenzoate
Tualang honey	5-Methyl furfural, 2-furylmethylketone	Catechin, 2-hydroxycinnamic acid
Eucalyptus honey	2-Hydroxy-5-methyl-3-hexanone, 3-hydroxy-5-methyl-2-hexanone	Myricetin, tricetin, and luteolin
Lime tree honey	Carvacrol and *p*-cymene	
Citrus honey	Limonyl alcohol, sinensal isomers, and α-4-dimethyl-3-cyclohexene-1-acetaldehyde	
Ulmo honey	4-Vinylanisole, benzylaldehyde, ethyl benzoate, ethyl anisate, lyrame, linalool, and damascenone	
Heather honey		Myricetin, myricetin-3-methyl ether, tricetin
Jelly bush		Linalool and nonanal
Turkish honey		3-Carene
Sage honeys		p-Coumaric, p-hydroxybenzoic, and ferulic acid

Nolan et al. (2019), Cianciosi et al. (2018), Ahmed et al. (2018), Samarghandian et al. (2017), Kaškonienė and Venskutonis (2010) and Ahmed and Othman (2013a)

(3.9; range, 3.2–4.5), and total acidity (29.12 meq/kg; range, 8.68–59.49 meq/kg) (Masalha et al. 2018; Feas et al. 2010; Islam et al. 2012; Escuredo et al. 2013). Table 7.2 enlists the average content of constituents generally present in honey.

Apart from carbohydrates, which constitute 95–97% of the solid fraction, honey contains almost all amino acids (except asparagine and glutamine) (Iglesias et al. 2004), various proteinaceous enzymes (like acid-phosphatase, catalase, diastase, glucose oxidase, and invertases) (Wilkins and Lu 1995), minerals (31 of them including phosphorus, sodium, calcium, potassium, sulfur, magnesium, chlorine) (Zhou et al. 2013), vitamins, vitamin C being the most abundant; however, it also contains small amounts of thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), and pyridoxine (B6) (Ajibola et al. 2012) and other organic acids (Daniele et al. 2012), such as flavonoids, polyphenols, alkaloids, glycosides, anthraquinone, and volatile compounds (Jerkovic et al. 2010a, b; Zhou et al. 2002). There are around 26 amino acids present in honey, of them proline constitutes about 50–85% of the total amino acid content, which is primarily produced by the bees' salivary

Table 7.2 Chemical composition of the most consumed types of honey

Amount in 100 g of honey					
Component	g	Vitamins	mg	Minerals	mg
Water	16.9–18	Ascorbic acid	2.2–2.5	Calcium	3–31
Carbohydrates (total)	64.9–73.1	Thamin	0.0–0.01	Potassium	40–3500
Fructose	35.6–41.8	Riboflavin	0.01–0.02	Copper	0.02–0.6
Glucose	25.4–28.1	Niacin	0.1–0.2	Iron	0.03–4.0
Maltose	1.8–2.7	Pantothenic acid	0.02–0.11	Magnesium	0.7–13.0
Sucrose	0.23–1.21	Pyridoxine	0.01–0.32	Manganese	0.02–2.0
Organic acids	0.5–0.7			Phosphorus	2.0–15.0
Proteins and amino acid	0.50–1			Sodium	1.6–17.0
				Zinc	0.05–2.0
				Selenium	0.001–0.003

Nolan et al. (2019), Nguyen et al. (2019), Cianciosi et al. (2018), Ahmed et al. (2018), Samarghandian et al. (2017) and Escuredo et al. (2013)

secretions. Proline content is therefore often used as a parameter to evaluate the maturation degree of honey. Other amino acids include alanine, glutamic acid, isoleucine, leucine, phenylalanine, and tyrosine (Masalha et al. 2018; Hermosín et al. 2003; Perez et al. 2007). Gluconic acid, an oxidative product of glucose is the main organic acid constituent of honey. In addition, small amounts of acetic acid, citric acid, and formic acid are also present; all of which provide the acidic (pH) property to the honey (Mato et al. 2003).

Numerous studies have demonstrated that there are approximately 600 important volatile compounds present in honey which are responsible for most of its potential therapeutic effects. These include acid esters, alcohols, aldehydes, hydrocarbons, ketones, benzene and its derivatives, pyran, terpene and its derivatives, isoprenoids, and lesser amounts of sulfur, furan, and other cyclic compounds (Ajibola et al. 2012). Among them the two main bioactive volatile molecules present in honey are flavonoids and phenolic acids (and its derivatives) (Ahmed et al. 2018; Ahmed and Othman 2013a, b; Manyi-Loh et al. 2011; Cook and Samman 1996; Erejuwa et al. 2012).

The main flavonoids present in honey are apigenin, chrysin, galangin, hesperetin, kaempferol, pinocembrin, and quercetin, and the most important phenolic acids are ascorbic, benzoic, caffeic, chlorogenic, p-coumaric, ellagic, ferulic, gallic, 3-hydroxybenzoic, rosmarinic, and vanillic acids (Masalha et al. 2018; Erejuwa et al. 2012; Kenjerić et al. 2008; Kassim et al. 2010; Khalil et al. 2011; Petrus et al. 2011). Most of these two classes of chemicals perform their activities by having synergistic interaction with each other to yield a variety of antioxidant, antifungal, anti-inflammatory, antimicrobial, antiviral, antiproliferative, antimetastatic, hypotensive, hypocholesterolemic, immune-modulating, vasodilative, anti-mutagenic, and antitumor activities (Israili 2014; Samarghandian et al. 2017; Lusby et al. 2002; Masalha

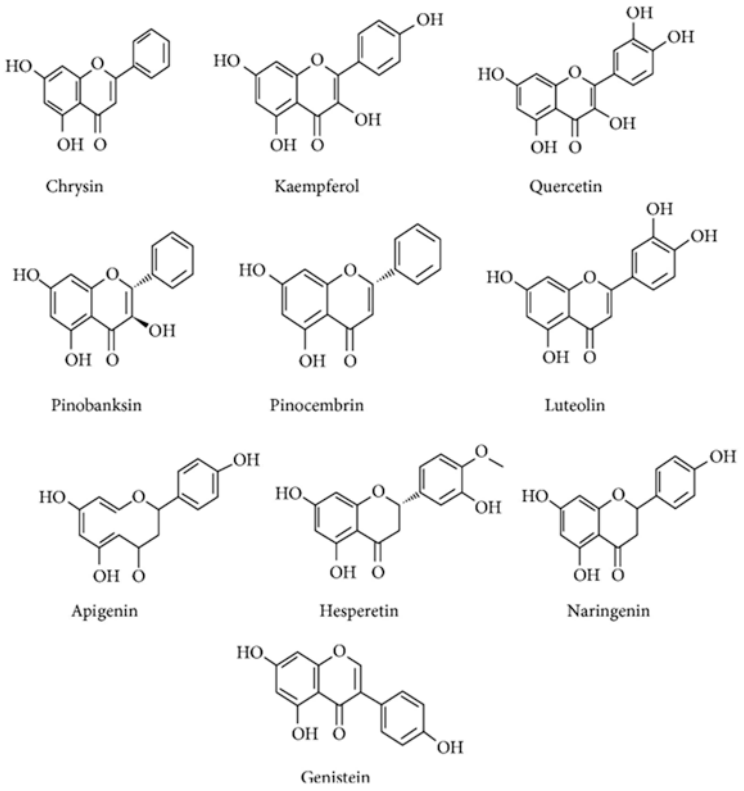

Fig. 7.1 Chemical structures of flavonoids in honey

et al. 2018; Ahmed and Othman 2013b; Cook and Samman 1996; Erejuwa et al. 2012; Kenjerić et al. 2008; Kassim et al. 2009, 2010; Al-Mamary et al. 2002; Gomes et al. 2010; Irish et al. 2006; Rakha et al. 2008; Ferreira et al. 2009; Gannabathula et al. 2012; Frankel et al. 1998; Mckibben and Engeseth 2002; Wang et al. 2002; Gribel and Pashinskii 1990; Al-Waili 2004a; Miguel et al. 2017; Cianciosi et al. 2018). The various flavonoids and phenolic acids present in honey are depicted in the Figs. 7.1 and 7.2 (Table 7.3).

7.2 Biological and Medicinal Effects of Honey

The biological and medicinal effects of honey depend heavily upon the bioavailability of its various constituents especially the phytochemical compounds, as well as their mode of absorption and metabolism (Israili 2014; Samarghandian et al. 2017; Ajibola et al. 2012). Since there is a huge diversity of secondary metabolites in plants which are usually used as food by bees, this variance concomitantly affects the phytochemical profiles in honey as well (Nicolson et al. 2007). Because of its varied constituents being actually accumulated by honeybees from various plant

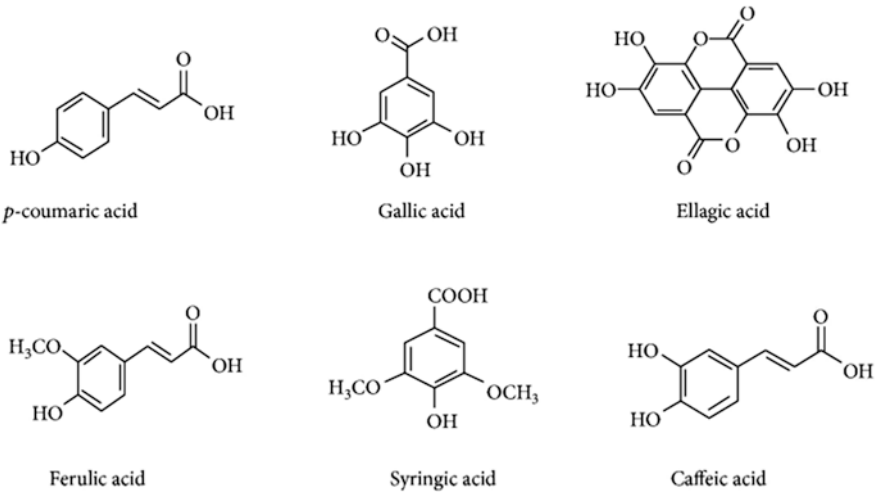

Fig. 7.2 Chemical structures of phenolic acids in honey

Table 7.3 Common phenolic acids and flavonoids in different honeys

Phenolic acids	Formula	Flavonoids	Formula
2-*cis*,4-*trans* Abscisic acid	$C_{15}H_{20}O_4$	Apigenin	$C_{15}H_{10}O_5$
2-Hydroxycinnamic acid	$C_9H_8O_3$	Catechin	$C_{15}H_{14}O_6$
Caffeic acid	$C_9H_8O_4$	Chrysin	$C_{15}H_{10}O_4$
Chlorogenic acid	$C_{16}H_{18}O_9$	Galangin	$C_{15}H_{10}O_5$
Cinnamic acid	$C_9H_8O_2$	Genistein	$C_{15}H_{10}O_5$
Ellagic acid	$C_{14}H_6O_8$	Isorhamnetin	$C_{16}H_{12}O_7$
Ferulic acid	$C_{10}H_{10}O_4$	Kaempferol	$C_{15}H_{10}O_6$
Gallic acid	$C_7H_6O_5$	Luteolin	$C_{15}H_{10}O_6$
p-Coumaric acid	$C_9H_8O_3$	Myricetin	$C_{15}H_{10}O_8$
p-Hydroxybenzoic acid	$C_7H_6O_3$	Pinobanksin	$C_{15}H_{12}O_5$
Protocatechuic acid	$C_7H_6O_4$	Pinocembrin	$C_{15}H_{12}O_4$
Sinapic acid	$C_{11}H_{12}O_5$	Quercetin	$C_{15}H_{10}O_7$
Syringic acid	$C_9H_{10}O_5$	Rutin	$C_{27}H_{30}O_{16}$
Vanillic acid	$C_8H_8O_4$		

Cianciosi et al. (2018), Samarghandian et al. (2017), Escuredo et al. (2013) and Erejuwa et al. (2012)

sources, honey has been referred to as the rediscovered remedy and identified by many researchers as one of the best source of dietary antioxidants (Ahmed et al. 2018; Erejuwa et al. 2012, Khalil et al. 2011; Nicolson et al. 2007).

7.2.1 Antioxidant Effects

Antioxidants are identified as the agents which neutralize the deleterious effects of the oxidative substances/chemicals. Free radical species are derived either directly from oxygen called as reactive oxygen species (ROS) like superoxide (O_2^-),

hydroxyl (OH^-), hydrogen peroxide (H_2O_2), or nitrogen called as reactive nitrogen species (RNS) like nitric oxide (NO), peroxynitrite ($ONOO^-$) or from lipids like alkoxy (RO), peroxyl (ROO), lipid hydroperoxide (LOOH) radical. Usually these substances cause oxidative stress due to excessive generation of free radical species beyond the capacity of the antioxidant defense system to sequester them and hence result in the oxidative damage (Lobo et al. 2010).

Generally, the generated free radicals are highly reactive and unstable. They contain an unpaired electron, therefore behave as oxidants or reductants (Pisoschi and Pop 2015). Free radicals can damage almost all biological molecules like carbohydrates, lipids, proteins, and nucleic acids (DNA) (Lobo et al. 2010). Oxidative stress has been reported to make a significant impact on the etiology of all inflammatory diseases (arthritis, adult respiratory diseases syndrome, glomerulonephritis, lupus erythematous, vasculitis), atherosclerosis, alcoholism, aging, asthma, acquired immunodeficiency syndrome, cancers, diabetes, emphysema, gastric ulcers, hemochromatosis, hypertension and preeclampsia, ischemic diseases (heart diseases, intestinal ischemia, stroke), organ transplantation, neurological disorder (Alzheimer's disease, Parkinson's disease, muscular dystrophy), nephritis, smoking-related diseases, rheumatoid arthritis and osteoarthritis, and many other diseases (Finkel and Holbrook 2000; Lobo et al. 2010; Rahal et al. 2014; Nguyen et al. 2019).

Nature has bestowed every organism with some well-developed self-defense mechanisms to counteract the deleterious impact of free radicals constituting a direct repairing, physical defense, and antioxidant systems (Rahal et al. 2014; Nguyen et al. 2019). An antioxidant system within an individual is of two categories: enzymatic and non-enzymatic. Enzymatic antioxidants are represented by an interacting network of three main enzymes: superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). This detoxification system operates primarily with SOD catalyzing the initial step and then various peroxidases removing hydrogen peroxide in conjunction with catalases (Sies 1997). Nonenzymatic antioxidants include all chemicals having capacity to quench the radicals by directly interacting with them by donating an electron or hydrogen and include ascorbic acid (vitamin C), α-tocopherol (vitamin E), glutathione (GSH), carotenoids, ubiquinol, flavonoids, and other antioxidants (Lobo et al. 2010). (Table 7.4 shows various free radicals and the antioxidants which act upon them and Fig. 7.3 shows various antioxidant preset in nature.)

Table 7.4 Various radical species and the antioxidants that act upon them for quenching

Radical species		Antioxidants
$^1O_2$	Singlet oxygen	Vitamin A, β-carotene, vitamin E
$O_2^{\cdot-}$	Superoxide	Superoxide dismutase, β-carotene, vitamin E
$OH^{\cdot}$	Hydroxyl	
$RO^{\cdot}$	Alkoxyl	
$ROO^{\cdot}$	Peroxyl	Vitamin C, vitamin E
H_2O_2	Hydrogen peroxide	Catalase, glutathione peroxidase
LOOH	Lipid peroxides	Glutathione peroxidase
NO	Nitric oxide	Glutathione peroxidase

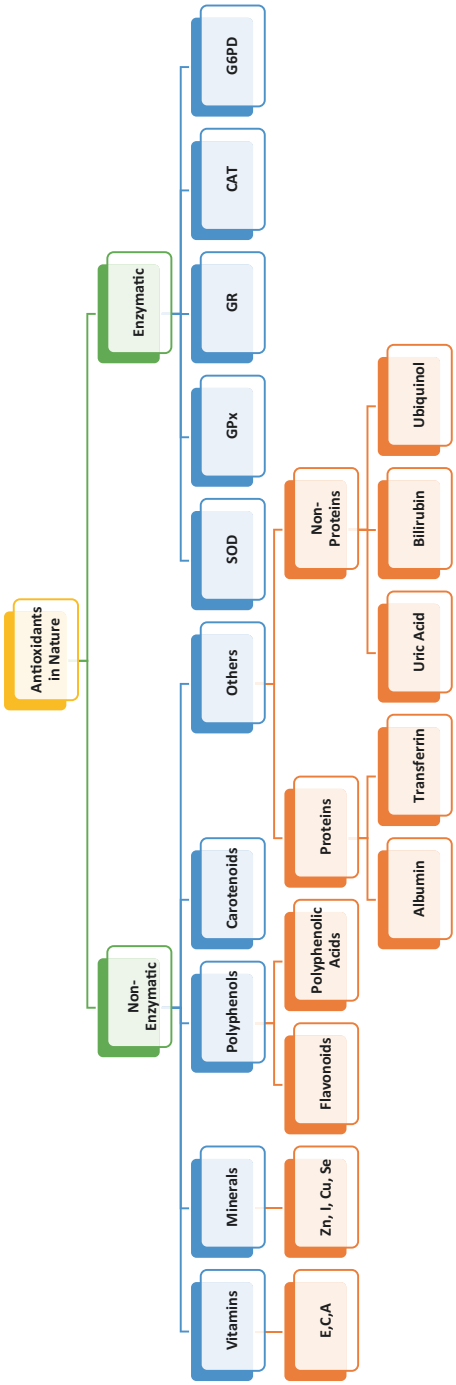

Fig. 7.3 Various antioxidants found in nature

As already mentioned, honey is a balanced concoction of a wide range of active organic molecules—vitamins and phytochemicals, and these have been recognized to be mainly responsible for its antioxidant capacity (AOC) (Ahmed and Othman 2013a; Rice-Evans and Miller 1996). Usually, these molecules act in a synergistic manner to scavenge the free radicals by forming more stable and less toxic molecules (Gheldof and Engeseth 2002; Musa Özcan and Al Juhaimi 2015). Furthermore, phenolic compounds within honey are responsible for the radiation absorbance and hence its color and brightness and in this regard it has been reported that darker honey has higher antioxidant value/concentration (Gheldof and Engeseth 2002; Musa Özcan and Al Juhaimi 2015; Samarghandian et al. 2017).

Numerous studies have been reported on the protective effects honey plays during oxidative stress. The two important mechanisms, reported by researchers, through which honey exerts its protective effect against free radical damage is via (1) antioxidant enzymes (such as SOD, catalase) and (2) numerous phenolic compounds which scavenge or trap free radical species and thereby induce cellular antioxidant systems, both enzymatic and nonenzymatic (Ahmed et al. 2018; Alvarez-Suarez et al. 2014; Erejuwa et al. 2014; Musa Özcan and Al Juhaimi 2015).

Considerable literature is available on the AOC for a wide variety of honeys available from different geographical and botanical origins (Afroz et al. 2016; Escuredo et al. 2013; Estevinho et al. 2012; Pontis et al. 2014; Alvarez-Suarez et al. 2018; Bertoncelj et al. 2007; Socha et al. 2009; Ulloa et al. 2015).

Phenolic acids (carboxylic acid derivatives of phenol) consist of two main parts—a phenolic ring and one functional group, at least, of organic carboxylic acid. They are further categorized depending upon the structure as: C6-C1 structure (e.g., syringic, vanillic, and gallic acids), C6-C2 (e.g., acetophenones and phenylacetic acids), and C6-C3 (e.g., p-coumaric, ferulic, and caffeic acids). Mostly, phenolic compounds are attached to the structural constituents/molecules of the plant (cellulose, lignin) and to other forms of organic molecules like glucose, other sugars, and/or flavonoids (Padayachee et al. 2012) (Fig. 7.1).

The second class of active antioxidant molecules in honey are flavonoids, which are natural low molecular weight and water-soluble chemical compounds. They contain two benzene rings, alternated by a three-carbon linear chain (C6-C3-C6). This structure is often arranged in the form of three rings with 15 carbon atoms called A, B, and C (Fig. 7.2). Generally, flavonoids have at least two phenolic groups (OH) and are often linked with sugars to exist as glycosides, which make flavonoids water soluble. The sugars involved in glycoside formation include mainly glucose and also arabinose, galactose, glucorhamnose, rhamnose, rutinose and xylose. If they are not associated with sugars, they are referred to as aglycones and are therefore further classified as per the degree of oxidation of the C ring as anthocyanins, anthocyanidins, flavones, flavanols, flavonols, flavanonols, flavanones, and isoflavones. The amplest flavonoids found in honey are flavones, flavanols, and flavonols (Moniruzzaman et al. 2014) (Fig. 7.2).

Although the exact antioxidant mechanism possessed by honey is not fully known, researchers have demonstrated that consumption of honey (1.2 g/kg)

elevated both amount and activity of the constituting antioxidant agents like β-carotene, vitamin C, vitamin E, and glutathione reductase in healthy individuals (Al-Waili 2003). A number of different possibilities for the antioxidant effects of honey have been proposed which include sequestration of free radicals, donation of hydrogen, metallic ion chelation, hydroxyl ion capture by flavonoids, and superoxide dismutase activity (Al-Mamary et al. 2002; van Acker et al. 1996; Ahmed et al. 2018). The AOC of honey can be measured as antiradical activity using number of standardized assays like oxygen radical absorbance capacity (ORAC), 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging, and ferric reducing antioxidant power (FRAP) (Erejuwa et al. 2012).

Additionally, both enzymatic and nonenzymatic antioxidant constituents of the honey have been reported to act at distinct cellular levels to prevent oxidation of the essential macromolecules and/or activating gene expressions, which is otherwise known to provoke an antioxidant response (Ahmed et al. 2018; Musa Özcan and Al Juhaimi 2015). Also, phytochemicals present in honey, especially polyphenols, can activate intracellular signaling producing a wide range of second messengers and activated enzymes like mitogen-activated protein kinases (MAPKs), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), tyrosine kinases, protein kinase B (PKB)/Akt, and protein kinase C (PKC) which have a protective effect in the cells (Torre 2017). Figure 7.4 shows various identified mechanisms for the antioxidant effects of honey.

Fig. 7.4 Identified mechanisms for the antioxidant effects of honey

7.2.2 Antibacterial Effects

Antibacterial effect of honey is accredited to the existence of numerous inert antibiotic factors in it. These include both physical aspects and chemical constituents (Cushnie and Lamb 2005). The physical factors are its low water activity (Aw), acidic/low pH, high osmotic pressure (because of sugars), low protein content, high carbon to nitrogen ratio, low redox potential due to high content of reducing sugars, and viscosity that limit dissolved oxygen and all of these prevent bacterial growth (Tan et al. 2009;). In addition to these physical properties, the glucose oxidase enzyme system, presence of flavonoids, phenolic acids like pinocembrin, syringic acid, terpenes, and lysozyme (Agbaje et al. 2006; Cianciosi et al. 2018) also contribute towards antibacterial properties of honey. A substantial antibiotic role in honey is because of bee defensin-1 (antimicrobial peptide), peroxidases which produce hydrogen peroxide (H_2O_2), methylglyoxal (phytochemical), and glucose oxidase and catalase enzymes (Mandal and Mandal 2011). Defensin-1 is one of the antimicrobial peptides (AMP) among others like apidaecin, abaecin, and hymenoptaecin, all of which are present in bee hemolymph and hypopharyngeal glands (6). Its bactericidal properties are due to its ability to disrupt bacterial cell membrane by creating holes in it and via stimulation of MMP-9 secretions from keratinocytes (Ganz 2003; Bucekova et al. 2017). Table 7.5 lists some of the common polyphenolic compounds present in honey together with their mechanism of action.

Interestingly, it has been observed that the dilution of honey increases its antibiotic effect by H_2O_2 because of direct effect on the ability of glucose oxidase enzyme to effectively bind to the glucose and produce a steady source of H_2O_2 (Brudzynski 2006). The levels of H_2O_2 in any form of honey is dependent upon the source of the nectar on which bees feed to produce honey which in turn affects the two critical factors—the content of catalase and the extent of glucose oxidase (Brudzynski et al. 2011, 2017). There are numerous other mechanisms which have been identified for the role played by H_2O_2 as antimicrobial agent. It has been shown that H_2O_2 also mediates its effect via stimulating insulin receptor (IR) which is essential for the uptake of glucose and amino acids required for the cellular growth and proliferation especially of monocytes and lymphocytes. As honey can serve as the best source of essential biomolecules, it provides critical energy for phagocytes to engulf the bacteria (Abuharfeil et al. 1999). Figure 7.5 shows the various identified mechanisms for the antibacterial effects of honey.

Furthermore, honey which is devoid of H_2O_2 (after its removal) still possesses the significant antimicrobial activity referred to as the nonperoxide activity, which is attributed to the presence of numerous other active substances. One of these nonperoxide and highly reactive class of compounds is 1,2-dicarbonyls, which are generated through caramelization or Maillard reactions in the carbohydrate-rich foods (Arena et al. 2011; Degen et al. 2012). These compounds are produced as intermediates of nonenzymatic reaction between glucose and free amino groups which form advanced glycation end products (AGEs). Those produced from hexoses are 3-deoxyglucosone (3-DG) and glucoson while those derived from disaccharides and oligosaccharides are 3-deoxypentosone (3-DP) (Schalkwijk et al. 1999; Arena et al. 2011; Degen et al. 2012).

Table 7.5 Common polyphenolic compounds found within honey and their antimicrobial mechanism of action

Phenolic acids	Mechanism	Flavonoids	Mechanism
Caffeic acid	Oxidative stress	Apigenin	Inhibits DNA gyrase
Chlorogenic acid	Increase in membrane permeability resulting in cytoplasmic and nucleotide leakage	Catechin	Hydrogen peroxide generation
Ferulic acid	Cell membrane dysfunction and changes in cell morphology	Chrysin	Inhibits DNA gyrase
Gallic acid	Cell membrane disruption resulting in pore formation and intracellular leakage	Galangin	Inhibition of peptidoglycan and ribosome synthesis
p-Coumaric acid	Cell membrane disruption and binding to bacterial DNA	Genistein	Disruption to topoisomerase-II DNA cleavage complex
Syringic acid	Cell membrane dysfunction	Isorhamnetin	Unknown
2-*cis*, A-*trans* Abscisic acid	Unknown	Kaempferol	Inhibits DNA gyrase
2-Hydroxycinnamic acid	Unknown	Luteolin	Inhibits FAS-I in mycobacteria and inhibits DNA helicase DnaB and RecBCD
Cinnamic acid	Unknown	Myricetin	Inhibits DNA B helicase
Ellagic acid	Unknown	Pinocembrin	Induces cell lysis
p-Hydroxybenzoic acid	Unknown	Quercetin	Disrupts membranes, transport, and motility
Protocatechuic acid	Unknown	Rutin	Induces topoisomerase IV–mediated DNA cleavage
Sinapic acid	Unknown	Naringenin	Unknown
Vannilic acid	Unknown	Pinobanksin	Unknown

Nolan et al. (2019), Cianciosi et al. (2018), Samarghandian et al. (2017), Erejuwa et al. (2012) and Escuredo et al. (2013)

Methylglyoxal (MGO) and its synthesis precursor dihydroxyacetone (DHA) are both active bacterial growth inhibitors working via urease inhibition, which otherwise facilitates bacteria to acclimatize and grow swiftly by ammonia production in low pH environment (Rückriemen et al. 2017). MGO is the chief antimicrobial constituent in manuka honey and is clinically used to rate honey as "Unique Manuka Factor" (UMF) directly related to its percentage in honey (Roberts et al. 2015). MGO is produced from dihydroxyacetone by either nonenzymatic or enzymatic (by methylglyoxal synthase) conversion (Adams et al. 2009). It has been demonstrated that the amino acid additions (of arginine and lysine) can enhance the production of MGO within honey, so does heating it to 37 °C (Adams et al. 2009; Johnston et al. 2018). MGO works by altering the structure of bacterial motility proteins in fimbriae and flagella, thereby limiting them (Rabie et al. 2016).

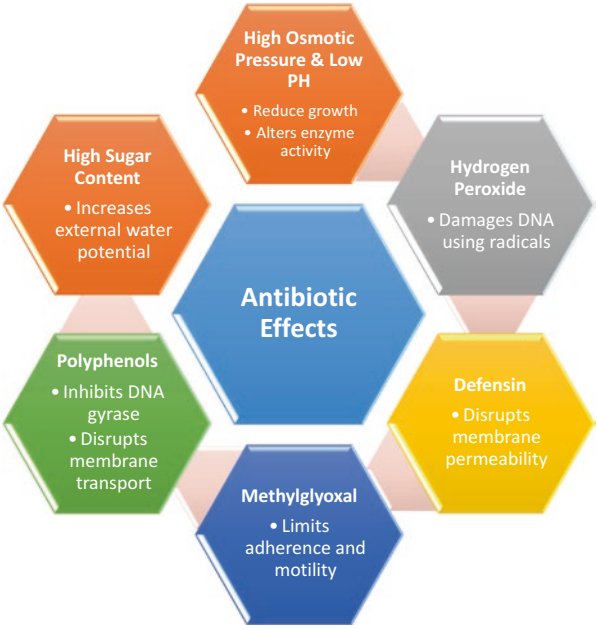

Fig. 7.5 Identified mechanisms for the antibiotic effects of honey

Furthermore, a recent report revealed that honey utilizes two main mechanisms to fight bacterial infections: first by inhibiting the bacterial quorum sensing (QS) system which hinders the expression of various gene regulons like las, MvfR, and rhl, and its associated virulence factors and second by its bactericidal constituents which aggressively kill bacterial cells (Wang et al. 2012). Since honey also contains some quantities of propolis and pollen, a part of its antibacterial activity can also be attributed to these antimicrobial constituents (Viuda-Martos et al. 2008; Redzic et al. 2011).

For any drug to be antibiotic, a minimum inhibitory concentration (MIC) is necessary to be possessed which is tolerant to the cells as well. It is defined as the lowest concentration of an antimicrobial (like an antifungal, antibiotic, or bacteriostatic) drug that inhibits the observable growth of any microorganism after an overnight incubation (Israili 2014). Numerous researchers have reported that the antibacterial activity of honey is equivalent to the minimum inhibitory concentration (MIC), and hence, for the complete growth inhibition of microorganisms, only minimum concentration is required (Samarghandian et al. 2017).

Honey exhibits both bacteriostatic and bactericidal capacities against a wide range of Gram-positive and Gram-negative bacteria (Tan et al. 2009; Alvarez-Suarez et al. 2010; Chang et al. 2011; Israili 2014). Furthermore, honey having a monofloral origin is found to possess potent antibacterial activity than others, and some pathogens are more susceptible than others to a certain type of monofloral honey (Al-Waili 2004b; Lee et al. 2008; Tan et al. 2009; Kumar et al. 2010; Sherlock et al.

Table 7.6 List of microorganisms that have been found to be sensitive to honey

Gram-positive strains	Gram-negative strains
Streptococcus pyogenes	*Stenotrophomonas maltophilia*
Coagulase negative staphylococci	*Acinetobacter baumannii*
Methicillin-resistant Staphylococcus aureus (MRSA)	*Salmonella enterica Serovar typhi*
Streptococcus agalactiae	*Pseudomonas aeruginosa*
Staphylococcus aureus	*Proteus mirabilis*
Coagulase-negative Staphylococcus aureus (CONS)	*Shigella flexneri*
Hemolytic streptococci	*Escherichia coli*
Enterococcus	*Enterobacter cloacae*
Streptococcus mutans	*Shigella sonnei*
Streptococcus sobrinus	*Salmonella typhi*
Actinomyces viscosus	*Klebsiella pneumonia*
	Stenotrophomonas maltophilia
	Burkholderia cepacia
	Helicobacter pylori
	Campylobacter spp.
	Porphyromonas gingivalis

Alvarez-Suarez et al. (2010), Chang et al. (2011) and Israili (2014)

2010; Voidarou et al. 2011; Kwakman et al. 2011; Mandal and Mandal 2011; Cooper and Jenkins 2012). Table 7.6 lists various bacterial strains which are limited by honey.

Bactericidal activities of monofloral origin honeys against many pathogens like S. aureus, P. aeruginosa, *Streptococcus mutans*, and MRSA are demonstrated to be because of numerous mechanisms, a few of which are extensive cellular disruption affecting structural integrity, prevention of cell separation, producing cells with cross-walls, thereby preventing the normal growth and progression, enhanced lysis of cells, affecting normal cell shapes, blocking the attachment of bacteria to tissues, inhibiting formation of biofilms, downregulation of stress protein A of MRSA, and reducing expression of fibronectin-binding proteins (Alnaqdy et al. 2005; Henriques et al. 2010, 2011; Kwakman et al. 2011; Jenkins et al. 2010; Jenkins and Cooper 2012; Maddocks et al. 2012; Nassar et al. 2012).

In addition to using honey alone, it is also used synergistically with numerous antibiotics like gentamicin, amikacin, ceftazidime, methylglyoxal pipercillin, carbenicillin, or amikacin (Karayil et al. 1998; Al-Jabri et al. 2005; Mukherjee et al. 2011), especially to reverse the bacterial resistance, e.g., oxacillin-resistant Gram-negative MRSA, vancomycin-resistant Enterococcus (Jenkins and Cooper 2012; Boukraâ and Sulaiman 2009; Mandal and Mandal 2011; Israili 2014). Also, it has been reported that honey's antibiotic spectrum against various resistant isolates of Burkholderia cepacia, E. coli, Enterococcus faecium, P. aeruginosa, S. epidermidis, S. aureus, MRSA, and β-lactamase-producing E. coli gets enhanced and broadened by the addition of some compounds like synthetic peptide "Bactericidal Peptide 2" (Kwakman et al. 2011), starch (Boukraâ and Sulaiman 2009), royal jelly (Boukraâ 2008), or thyme (*Thymus ciliatus*) powder (Abdellah et al. 2012).

One of the important medical areas where honey's antibacterial activity is extensively utilized is in the management of wounds. Honey is among one of the ancient medicines used in treating infected wounds, and nowadays, it is used in medical field especially in conditions where conventional therapeutic medicine fails (Minden-Birkenmaier and Bowlin 2018). Historically, honey's use find mention in a Sumerian tablet of 2100–2000 BC where it is referred to as an ointment. Aristotle (384–322 BC) reported honey as "*good as a salve for sore eyes and wounds*" (Mandal and Mandal 2011). Topical application of honey has been demonstrated to rapidly clear and heal deep surgical wound infections to facilitate the healing process. For highly infected wounds that are resistant to the conventional therapy of antibiotics and antiseptics, honey has been shown to promote quick healing (Ahmed et al. 2003).

Normal wound healing is a multistep process which includes several events taking place concomitantly with each other like coagulation, cell proliferation, inflammation, tissue remodeling, and replacement of injured tissue (Falanga 2005). Honey has been extensively and effectively used in clinical practice to manage simple wounds, burns, various ulcers, necrotic tissues, diabetic foot, and postoperative split skin wounds (Visavadia et al. 2008; Cianciosi et al. 2018; Ahmed et al. 2018). Honey can sterilize the wounds, stimulates tissue re-growth, rapidly clears infection, enhances debridement, suppresses inflammation, stimulates angiogenesis, tissue granulation, and epithelial growth while reducing edema and scar formation (Falanga 2005; Visavadia et al. 2008; Lee et al. 2011a; Lund-Nielsen et al. 2011a; Orey 2011; Efem et al. 1992; Vardi et al. 1998; Molan 1999, 2001, 2006; Moore et al. 2001; Lusby et al. 2002; Ingle et al. 2006; Boukraâ and Sulaiman 2010; Al-Waili et al. 2011a; Kegels 2011; Sioma-Markowska 2011; Smaropoulos et al. 2011; Jull et al. 2013; Biglari et al. 2013; Mohamed et al. 2015).

Honey helps in eliminating necrotic tissues of the wound, improves its remodeling, and furthermore prevents bacterial growth within it which is critical for healing process (Koenig and Roh 2016). Honey-coated dressing has been reported to be effective in reducing morbidity linked with first- and second-degree burns as well as in aiding to reduce the rehabilitation time (Baghel et al. 2009; Wijesinghe et al. 2009). Also, bandages coated with manuka honey were reported to be as effective as the silver-coated bandages in decreasing and limiting the size of malignant wounds (Lund-Nielsen et al. 2011b).

Recently, honey has been found to cause enhanced activation and production of monocytes, lymphocytes, phagocytes, and/or macrophages which affect the secretion of numerous cytokines like IL-1β, IL-6, and TNF-α, thereby expediting the healing process (Lin et al. 2003;). It has also been found to activate expression and secretion of IL-6 and TNF-α in IL-6-deficient mice at the injury site which enhances the healing process (Tonks et al. 2007; Molan and Rhodes 2015). Honey's high sugar composition and osmolarity play a pivotal role in healing process, as osmotic effect pulls out the water from the wound bed through the outflow of lymph, enhanced by the effective blood circulation at the wound site. Honey is also directly involved in the ameliorative effects during the oxidative stress by activating 5′- adenosine monophosphate-activated protein kinase (AMPK) and antioxidant enzymes like

superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). These enzymatic antioxidants are known to initiate proliferation and exodus of dermal fibroblasts as well as to enhance the mitochondrial function to assist in wound healing (Molan and Rhodes 2015; Alvarez-Suarez et al. 2018).

One of the pivotal factors in antibiotic resistance is the ability of microbes to make biofilms (a layer of extracellular matrix after adhesion to surface), which protect them from killing and static effects of antibiotics (Stewart and Costerton 2001). The antibiofilm capability is because of honey's ability to disrupt the quorum sensing in the biofilm itself (Minden-Birkenmaier and Bowlin 2018). Honey has been demonstrated to be able to penetrate the biofilms and in turn recover the aggressive infection by eradicating bacterial colonies. Numerous biofilms of pathogenic strains like extended-spectrum beta-lactamases (ESBL), Clostridium difficile, *Klebsiella pneumonia*, methicillin-resistant Staphylococcus epidermidis (MRSE), Pseudomonas aeruginosa, Proteus mirabilis, Pseudomonas aeruginosa (PA), Staphylococcus aureus (SA), and enterohemorrhagic E. coli have been demonstrated to be limited or eradicated by the application of honey (Merckoll et al. 2009; Halstead et al. 2017). Honey acts to prevent the attachment of bacterial strains with the fibronectin of the tissue in the wound, thereby halting biofilm growth and in addition limiting the expression of fibronectin binding surface proteins like Sfb1 and Sof, both of which are key requirements for binding of bacteria to the fibronectin (Maddocks et al. 2012). It has also been shown to suppress the expression of three critical proteins: curli genes (csgBAC), quorum sensing genes (AI-2 importer and indole biosynthesis), and virulence genes (LEE genes) in E. coli to limit its virulence. High sugar content of honey has also been shown to play critical role in repressing biofilm formation (Lee et al. 2011b).

7.2.3 Antifungal Properties

Honey has been reported to exhibit wide spectrum of antifungal activity which is equivalent to numerous pharmaceutical antifungal preparations (Israili 2014). Maria et al. reported in vitro antifungal activity of honey after observing the limitation of growth of *Candida albicans*, *Candida krusei*, and *Cryptococcus neoformans* by the application of honey (Maria et al. 2011). It was also reported that honey distillate inhibited the resistant strains of *C. albicans* (Obaseiki-Ebor and Afonya 1984). Honey has antifungal activity against *Aspergillus flavus, Aspergillus niger, Candida albicans, Microsporum gypseum, Malassezia species*, *Penicillium chrysogenum*, and *Saccharomyces* (Anyanwu 2012). The potential antifungal effect of honey is due to the presence of three active systems: glucose oxidase and H_2O_2 production, high sugar contents and osmotic pressure, and methylglyoxal (Cushnie and Lamb 2005; Kwakman et al. 2010; Al-Waili et al. 2011b). Al-Waili et al. (2011b) have reported that honey in concentrations of 30%–50% is inhibiting the growth of C. albicans. Similarly, Irish et al. (2006) found that various honeys had antifungal activity against *C. albicans*, *Candida glabrata*, and *Candida dubliniensis*. Also, Khosravi et al. (2008) found that honey has antifungal activity

Fig. 7.6 Identified mechanisms for the antifungal effects of honey

against C. albicans, C. dubliniensis. C. glabrata, C. kefyr, C. parapsilosis, and C. tropicalis. Figure 7.6 lists various identified mechanisms for the antifungal effects of honey.

Although the actual mechanism of how honey limits the fungal growth is not well known, several theories have been proposed. Some of the important theories of which include as, by preventing formation of biofilm, disrupting the established biofilms, changing exopolysaccharide structure, distorting integrity of cell membranes, shrinking cellular surface, retarding growth, and enhancing apoptotic pathways (Ahmed et al. 2018; Ahmed and Othman 2013a; Moussa et al. 2012; Cancliracci et al. 2012; Khosravi et al. 2008). Many reports have demonstrated that flavonoid constituents of honey negatively affect the fungal growth, by inhibiting critical cellular processes essential for the growth of germ tube as well as affecting external cellular membrane morphology and integrity. Additionally, flavonoid extract affects the hyphal transition by arresting the viable cells in the G_o/G_1 phase and/or G_2/M phase (Canonico et al. 2014).

Even though numerous honeys derived from various resources have demonstrated potent antibacterial activities, this however does not necessarily mean that they do possess antifungal activity as well. Manuka honey although possessing a potent antibacterial activity has a weak activity against fungus like *C. albicans* and *dermatophytes* (Brady et al. 1996; Anand et al. 2019a). *C. albicans* is known to cause candidiasis while most fungal skin infection in humans are caused by *dermatophytes* like T. mentagrophytes and T. rubrum. Also, athletes' foot (*tinea pedis*), jock itch (*tinea cruris*), ringworm of scalp, nail, face, and hand (*tinea corporis*) are

also results of dermatophyte infections (Havlickova et al. 2008; Anand et al. 2019b). Recently, various honey varieties including Agastache, tea tree honey, and manuka honey were demonstrated to be effective in countering dermatophytes (*T. mentagrophytes* and *T. rubrum*) and C. albicans.

Agastache honey was most effective against *dermatophytes* (zone diameter, 19.5–20 mm) and *C. albicans* at 40% concentration while tea tree and manuka honey were effective at 80% (Anand et al. 2019b). Furthermore, Moussa et al. (2012) reported the antifungal action of various honey's against *C. albicans* and Rhodototorula sp. Generally, *C. albicans* was more susceptible to get inhibited by all varieties of honeys than the dermatophytes (Anand et al. 2019b). However, it was reported that fluconazole-resistant *C. albicans* was inhibited by Turkish honey (Rhododendron, Orange and Eucalyptus) in a concentration range of about 40–80% (MIC values) (Koc et al. 2009). Also, jujube honey (*Zizyphus spina-christi*) has potent antifungal properties against *C. albicans* at 40% (w/v) (MIC) and could effectively impede the formation of *C. albicans* biofilms and lead to disruption of established biofilms (Ansari et al. 2013).

The antifungal activity of Agstache honey is attributed to numerous volatile organic compounds in it. Some of the major compounds reported are as: benzaldehyde, estragole (12.31%), ethyl ester (5.68%), hexadecanoic acid, phenol, 2,4-bis(1,1-dimethylethyl) (12.77%), nonanoic acid, ethyl ester (7.22%), 2-propenoic acid, 3-phenyl-, ethyl ester (6.32%), 4 methoxy (5.17%), β-Caryophyllene (4.67%), nonanal (3.19%), and 2H-benzimidazol-2-one, 1,3-dihydro-5-methyl- (2.34%). In addition, Agstache honey was reported to contain limonene at a concertation of 0.11% and trace amounts of menthone, pulegone, methyl eugenol (Yamani et al. 2014).

7.2.4 Anti-Viral Properties

In literature, a limited number of studies are present who have reported the antiviral activity of honey. The earliest and important study on the antiviral effects of honey were on varicella zoster virus (HZV) infected human malignant melanoma (MeWo) cells, which reported the reduction of viral plaques by treatment with manuka and clover honey (Shahzad and Cohrs 2012). Similarly, experiments on influenza virus (H1N1)–infected Madin–Darby canine kidney (MDCK) cells also demonstrated the inhibitory effects of various types of honey especially for manuka honey which exhibited higher antiviral activity synergistically in combination with numerous antiviral compounds (Watanabe et al. 2014). Furthermore, manuka honeys have been found to be successful against rubella virus and herpes simplex virus (HSV-1) in vitro (Zeina et al. 1996; Ghapanchi et al. 2011; Hashemipour et al. 2014). Additionally, honey has been reported to heal herpetic lesions effectively especially occurring in labial and genital sites owing to its ability of inhibiting prostaglandins at the affected site (Al-Waili 2004c). A recent research report has extensively described honey's antiviral activity against respiratory syncytial virus (Feás and Estevinho 2011). Figure 7.7 lists various identified mechanisms for the antiviral effects of honey.

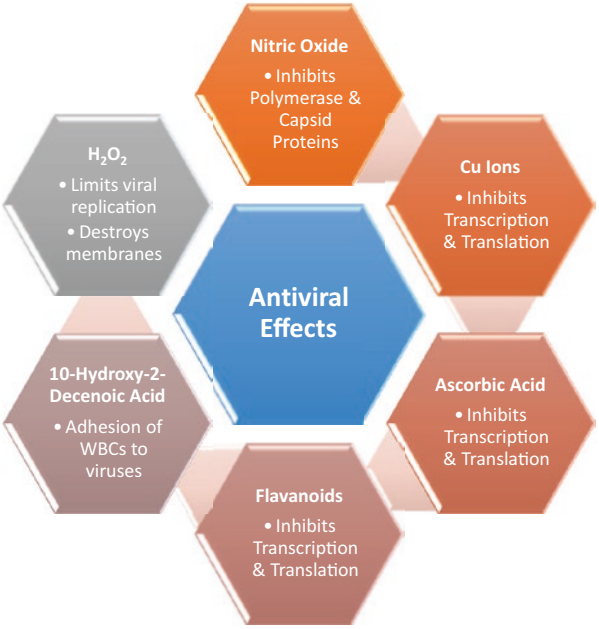

Fig. 7.7 Identified mechanisms for the antiviral effects of honey

Since honey does contain various secretions from honeybee's salivary and pharyngeal glands, it has been found to contain high concentrations of nitric oxide (NO) metabolites, nitrite, and nitrate (Al-Waili 2003). NO is reported to be responsible for the provision of host defense against both DNA- and RNA-based viruses, by preventing their replication. Thus, NO can slow down the development of viral lesions especially in the genital regions (Al-Waili 2003; Al-Waili and Boni 2003). In its identified mechanism of action, NO not only represses replication by interfering with viral polymerase but also inhibits the translation and assembly of viral capsid proteins. The flavonoid, copper, H_2O_2, and ascorbic acid present in honey have also been reported to prevent viral transcription and replication, thereby inhibiting their life cycle (Miguel et al. 2017; Ahmed et al. 2018; Khan et al. 2018). For royal jelly honey, antiviral activity has been credited to the activity of 10-hydroxy-2-decenoic acid (10-HAD), which is known to stimulate white blood cells (WBCs), resulting in their adhesion to viruses culminating in their destruction (Shahzad and Cohrs 2012).

7.3 Conclusion

As discussed extensively, honey can be described as the miracle food which besides being a power-packed diet also has an extensive medicinal property. It is extensively used as a kind of panacea since ages for a wide variety of diseases, and its antioxidant, antibacterial, antifungal, and antiviral properties have been well established in literature. However, there are some adverse effects of using honey also, which are

overshadowed in literature, which may be specifically associated with the contaminants present in it (Israili 2014). These contaminants are usually from floral source, environment, or microbes. This is beyond the scope of this chapter to discuss them in detail. Also, as there is no prescribed or effective therapeutic dose of honey for adults, due care and diligence are required when honey is consumed for treating chronic ailments especially in diabetes, gastrointestinal problems, or treating wounds. This is one of the challenging aspects in using honey. The quality, efficacy, dosage, and formulations are major challenges in standardizing its medical and clinical usage.

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