Honey and Its Phyto-Constituents: From Chemistry to Medicine

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Abstract

Honeybees depend upon plants for everything they want to maintain the colony running; nectar and pollen that is their only carbohydrate and protein essential nutrients. In order to achieve their necessary nutritional requirement, honey bees eventually collect essential plant metabolites when component of nectar and pollen. In addition, several molecules exhibit biological activity which may become significant in the battle against pests and pathogens in the hive. Flavonoids, ter-

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penoids, and polyphenols are essential biologically active ingredients found in honey and also have antioxidant properties. Nonetheless, for reasons of room, it is practically impossible to give a detailed overview of the phytochemical characteristics of honey and pollen in a literature review of this scope. In addition, the therapeutic ability of biologically active ingredients and their use in value-added food products are also at the core of this chapter.

Keywords

Honey · Apis mellifera · Flavonoids · Terpenoids · Polyphenols

3.1 Introduction

Honey is a natural organic material produced by a particular species of bees of the genus Apis from flower nectars (Alvarez-Suarez et al. 2014). It is a sweet, viscous, and flavorful liquid that is high in nutritious content (Havsteen 2002). The transfer of nectar to honey is a process of spewing and evaporation. This is then preserved in honeycomb wax as the primary source of food for honey bee (Adebiyi et al. 2004). The honeycomb consists of hexagonal waxy cells manufactured by the bees to shelter their larvae and store the honey. Beekeepers will take the entire honeycomb out for the honey harvest. The chemical composition of the honey varies depending on the nature of the flora from which the nectar was collected, geographic origin, seasonal and environmental conditions. There are raw honey and pasteurized honey. Raw honey is extracted right out of the hive. It can contain traces of wax and pollen since it is not purified. Pasteurized honey is stored without any impurities. Consumption of fresh honey increases immunity to seasonal allergies. Raw honey is rich in nutrients (Olaitan et al. 2007).

Pollen and nectar are the primary food sources for honey bees. And they are the primary source of proteins and carbohydrates.

Three types of bees are present in the bee hive: the bees of the workers, the bees of the drone, and the bees of the queen. Females that do not breed bees are referred to as worker bees. Queen bee and drone bees develop eggs, and these eggs live in bee hives and form larvae after 3–4 days. The female worker bees are produced from the larva. Mainly sterile female worker bees are found in a typical hive colony. The queen bee will live for up to 3–4 years (Bishop 2005).

3.2 Physical Properties of Raw Honey

Freshly extracted raw honey is very viscous in nature. Depending on the composition and water content, the viscosity of honey varies. It can absorb moisture from the environment. Presence of colloidal particles are responsible for the difference in the surface tension. The surface tension as well as viscosity are accountable for the frothing nature of raw honey (Rueppell et al. 2007).

Liquid honey has different colors from colorless to amber color. The variation in the color depends on the botanical origin, age, and storage. If suspended particles like pollens are present, then the clarity varies. Crystallized form of honey has a light color because of the glucose crystals present in it. Presence of fructose and glucose makes the honey sweet. It has almost same sweetness as that of sucrose. Since the microorganisms do not grow in honey, it can be stored for many years.

3.2.1 Types of Honey Based on the Production Procedures

Based on the production procedures, honey can be classified as extracted honey (made by centrifuging the broodless honey combs), pressed honey (made by pressing the honey combs), drained honey (made by slow draining of the broodless honey combs), and organic honey (made by organic beekeeping). Extracted honey is the most widely marketed honey. Organic honey and natural honey have the same composition. The difference between organic honey and natural honey is that the latter contains no traces of beekeeping pesticides.

3.2.2 Types of Honey Based on the Processing Procedure

On the basis of processing procedures, honey may be classified as normal honey, comb honey, and cut comb honey. Normal honey appears as crystalline form or as liquid form or as a mixture of both. Comb honey usually retailed in the broodless combs itself. Cut comb honey contains small pieces of honey comb in it.

3.2.3 Types of Honey Based on the Origin

According to the Codex Alimenterius

1. Based on the topographical region of the honey production, it can be named, if it is produced within the area.
2. Honey may be named based on the plant or floral source if it is produced mainly from that specific source. It will have the organoleptic, physicochemical, and microscopical characteristics equivalent to that origin.
3. Honey may be named based on the geographical or botanical origin (Bogdanov 2011a).

3.2.4 Types of Honey According to the Botanical Source

Depending on the botanical source, honey may be divided as blossom and honey dew. Each honey type is different from another because of the different sources and different proportions. It can be unifloral or multifloral honey. If the pollen grain is initiated from only one particular plant, it is known as unifloral honey. If there is no dominant pollen type, it is known as multifloral honey. Unifloral honey is more valuable.

3.3 Different Species of Honey Bees

Honey bees are known as one of the primogenital forms of animal life. Honey bees are eusocial, flying creature from the genus *Apis* of the bee clade. They construct colonial nests using wax for their colonies. In these waxy nests, they produce and store honey. The practice of collecting honey from the wild bee colonies is called beekeeping or apiculture. Seven species of honey bees and 44 subspecies of this were identified in the early twenty-first century. Western honey bee is the best known among these and had been used for the honey making and crop pollination. The bee wax has been used for candle making, soap making, lip balms, and other crafts. The scientific study of honey bees is called as melittology.

The main two species of honey bees have been named as *Apis mellifera* and *Apis cerana.*

The *Apis mellifera* or the European honeybee species are the most widely spread all around the world and utmost commonly collected and sold in the world.

In tropical Asia*, Apis cerana* is used for making honey most commonly. This honey is almost similar to the *mellifera* honey in composition and taste. Other common species are *Apis dorsata* and *Apis florea*. These honeys are marketed locally not worldwide.

Small honey bees like *Apis florea* and *Apis andreniformis* can be seen in southern and southeastern Asia. They make their hives in trees and shrubs, and they are relatively small. Their stings are usually unable to penetrate through the human skin. Therefore, these hives and swarms can be picked up with marginal protection (Arias and Sheppard 2005). *Apis florea* is completely yellow in color (Wongsiri 1997).

The subgenus *Megapis* can be very dangerous. They build their hives on tall tree branches, on cliffs, and sometimes on buildings. Honey hunters sometimes robbed their honey and may get stinging from it, and it can be fatal (Nathan et al. 2009).

Africanized bees or killer bees are the crosses of European stock and the subspecies *A. m. scutellata* which is East African lowland species. These bees do not produce excess honey and are more violent than European bees. These honey bees are known to be more resistant to disease and are very good hunters (Wongsiri 1997).

3.4 Folklore Uses

Honey has long been recognized to possess various medicinal properties, and it is used as a wound dressing and as an antiseptic since ancient times. Honey is being used in the traditional medicine since stone age (Needham 2008). Honey is considered as the oldest traditional medicine which has been used for various human diseases worldwide (Fig. 3.1). Some are listed below.

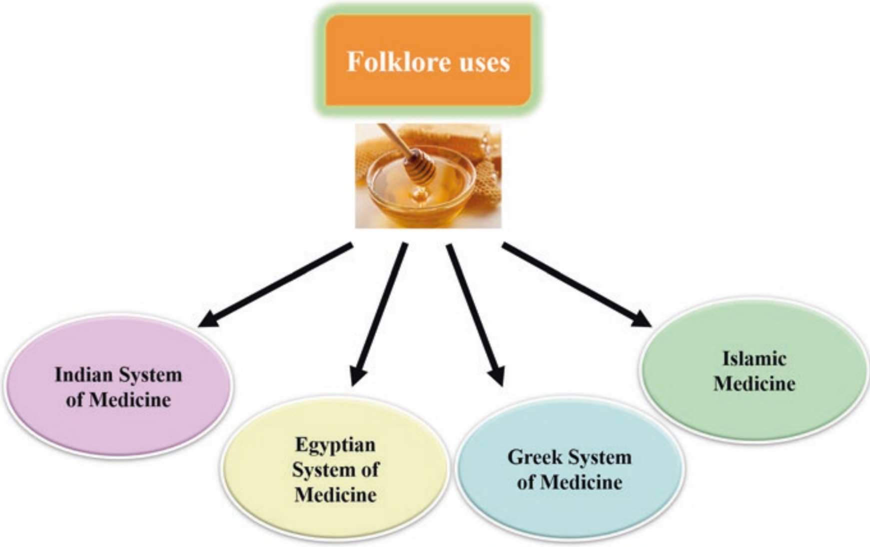

Fig. 3.1 Folklore use of honey used in different medicine systems

3.4.1 Honey in Indian System

According to *Ayurveda,* the ancient system of Indian medicine, honey, without changing its own properties, stimulates the activities of the substances to which it binds. In Ayurveda, honey was used both internally and externally for nutritional and therapeutic uses since hundreds of years. Externally honey was applied for ophthalmic ailments and for wound healing. Internally it was used mainly for cough and asthmatic problems. Honey was used as a base for these cough preparations along with other herbs. It is being used to treat sleep disorders since it has hypnotic action (Murty 2001). Honey has been used in Ayurveda to improve the oral hygiene and to keep the gums healthy (Vaidya et al. 2002). Alvarez-Suarez et al. reported that the consumption of newly formed and collected honey may increase the body weight and stored or old honey can decrease the fat of the body and therefore reduces the body weight (Alvarez-Suarez et al. 2012). In Ayurveda, honey is used as a medicine for the eyes and for the vision, and it reduces thirst, poises hemostasis, and decreases the toxicity. It is used for urinary tract disorders and also for diabetes. Honey is used to stop hiccups, worm infestations, skin disorders, diarrhea, nausea, and vomiting and also for bleeding complaints. Honey speeds up the healing process, and it has been used for the wound healing since long and also for cleaning the wounds (Eteraf-Oskouei and Najafi 2013). According to this system, hot honey can cause toxic effect so it should not be heated or consumed when it is warm (Megan Ware 2015). In Ayurvedic preparations, honey is used as a vehicle or as a preservative (Zumla and Lulat 1989).

3.4.2 Honey in Egyptian System

Ancient Egyptian medicines utilized the medicinal properties of honey. They combined honey with wine and milk and used for many ailments. They offered honey as a sacrifice to their deities in older times (Dash 1972). For embalming the dead bodies, they used honey. Honey was used to heal the infected wounds because of its antibacterial properties. For the topical application, they used honey (Molan 1999).

3.4.3 Honey in Greek System

Ancient Greek people used honey in a drink called Oenomel along with unfermented grape juice. It has been used to treat gout and certain nervous disorders (Dash 1972). Also they used honey for topical antisepsis, contraception, eye diseases, wound healing, cough and sore throat, laxative action, baldness, prevention, and management of blemishes (Molan 1999).

3.4.4 Honey in Islamic Medicine

According to Islamic medicine, honey is used as a healthy drink. The holy Qur'an intensely demonstrates the possible therapeutic values of honey. They used honey for a variety of medical problems, including stomach ailments. They used the beeswax to prevent from cold during winter (Molan 1999).

According to Unani Medicine, honey is used as a natural food supplement, as a nutritive agent, and as antibacterial and anti-inflammatory agent, and it also has wound healing properties (Molan 1999).

3.5 Phyto-Constituents

Pure honey is one of the most essential classes of composites found in plants, containing different identified varieties of primary and secondary metabolites (Fig. 3.2). Some of them are described below.

3.5.1 Carbohydrates

The general chemical formula of simple sugars is $C_nH_{2n}O_n$. It is the fundamental source of energy for cells and among the four major classes of biomolecules (Dilworth et al. 2017; Lee 2007). Carbohydrates are expressed as monosacharaides, disaccharides, polysaccharides, oligosaccharides, as well as glycoconjugates (Wong and Bryan 2003). Honey carries an array of carbohydrates including monosaccharides which makes up 75% of the carbohydrate content, like glucose and fructose, disaccharides such as maltose,

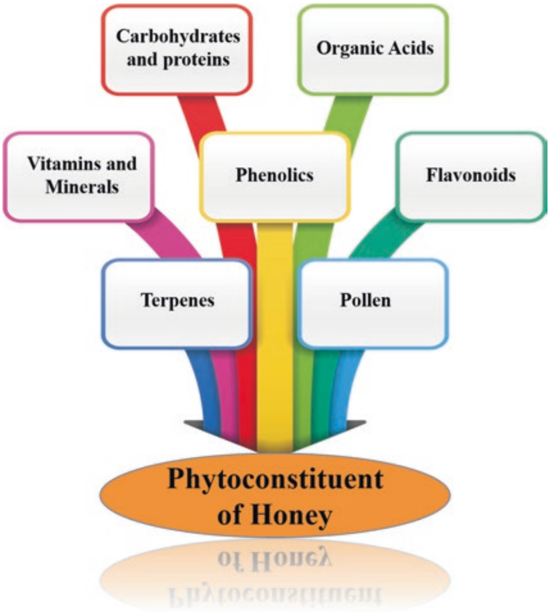

Fig. 3.2 Phyto-constituent profile of honey

sucrose, and palatinose making up 10–15%. Honey owes it sweet flavor to the high concentration of carbohydrates present, and there are nearly 30 complex sugars, taking up 80–83%, therefore making honey an excellent energy source (304 Kcal/100 g) (Sarfraz et al. 2018; Celestino Santos and González-Paramás 2017). Fructose is the superior sugar constituent in the majority of honeys although some exceptions are present in which glucose is the dominant monosaccharide, such as in uniflower honey like rape honey and dandelion honey. About 8–10% of disaccharides present constitute maltose, isomaltose, kojibiose, and turanose. Due to invertase enzyme action, sucrose is present in less than 30% of the total sugar content. Melezitose, erlose, and raffinose are trisaccharides that are present in relatively high amounts in honeydew honey, nevertheless origin/botanical sources of honey can influence its sugar content (Celestino Santos and González-Paramás 2017).

Fructose being the major constituent contains many benefits including evidence in aiding in diabetes, reducing hyperglycemia in rodents, diabetic patients, and healthy subjects (Vaisman et al. 2006; Kwon et al. 2008). Fructose was found to slow down gastric emptying time and absorption; furthermore, studies show that fructose decreases food ingestion which in turn causes the gastric emptying delay (Kashimura and Nagai 2007; Lina et al. 2002; Thibault et al. 1997). Decreased food intake due to fructose has further shown an impact on the selection of macronutrients for absorption (Gregory et al. 1989; Henry et al. 1991). With decreased food intake comes the suggestion that fructose aids in weight loss; a recent study shows that administering supplements of fructose in low or moderate concentrations to obese subjects shows effective weight loss (Madero et al. 2011). Albeit some studies suggest that fructose intake causes an increase in weight hence the results are inconclusive (Bocarsly et al. 2010; Meirelles et al. 2011; Lavin et al. 1998; Anderson and Woodend 2003).

The second major constituent after fructose is glucose. Although it does not have as many effects as fructose, it aids in the absorption of fructose, and the best results were found when equal amounts of glucose and fructose are given as glucose has a synergistic effect however fructose does not enhance the absorption of glucose (Jones et al. 2011; Fujisawa et al. 1991).

Several studies reported that high-fat-fed rats exhibited a decrease in the amount of intestinal bifidobacteria, and those treated with oligofructose present in honey showed an increase in bifidobacteria with enhanced glucose tolerance in addition to glucose-induced insulin secretions (Cani et al. 2007). Monosaccharides join together to form oligosaccharides (Bogdanov 2008; Erejuwa et al. 2012). Several research studies on honey have revealed that it can multiply the amount of Lactobacillus, *Bifidobacterium bifidum*, and *Streptococcus thermophilus*. Evidence has shown that large amounts of fructose and glucose present in honey can increase the development of gastric microflora (Shamala et al. 2000; Chick et al. 2001). Finally, honey varieties that are fructose-rich are considered as a beneficial alternative to high GI sweeteners in the management of diabetes as well as cardiovascular ailments (Bogdanov 2011a; Deibert et al. 2010;). The chemical structure of these compounds are summarized in Fig. 3.3 (Celestino Santos and González-Paramás 2017).

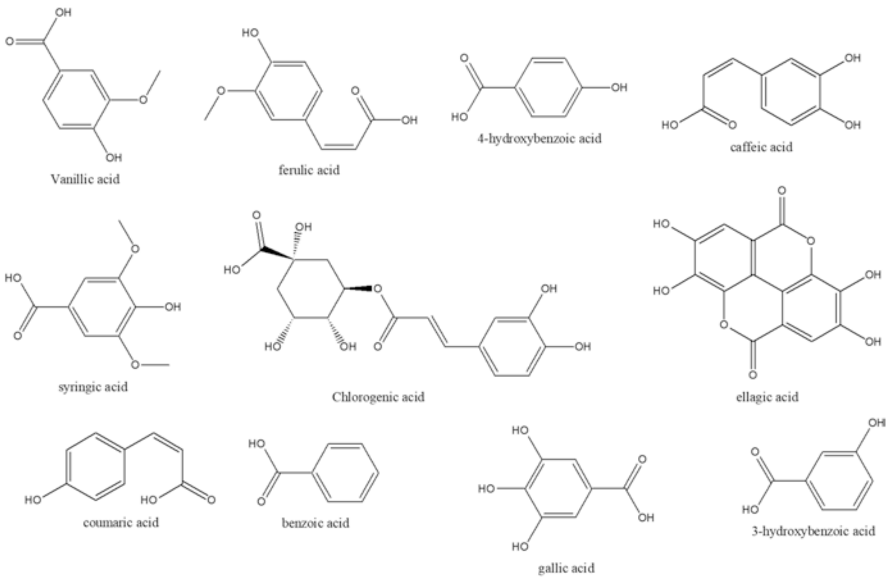

Fig. 3.3 Chemical structures of few carbohydrate derivatives present in different types of honey

3.5.2 Proteins

Honey contains 20 non-enzymatic proteins (0.1–0.5%), comprising albumins, globulins, proteases, and nucleoproteins common to all honey forms. The amino acid content is one fifth of the total content (Gonzalez-Paramas et al. 2006; Sajid and Azim 2012; Hermosın et al. 2003). A free amino acid namely proline is found in honey very commonly (50–85%) (Belitz et al. 2009; Hermosın et al. 2003). Proline is an indicator for botanical origin of honey, and it originates from the salivary secretions of honey bee (Biino 1971). Proline shows a significant role in regulating the nectar enzymatic transfer, in the process of converting the flower nectar into honey (Ortiz-Valbuena and Silva-Losada 1991). Furthermore, a few researchers analyze proline as an indicator for the adulteration of honey with sugar (Bogdanov et al. 1999). Table 3.1 shows the summary of various amino acids present in honey (Doner 2003).

The enzymes such as glucose-oxidase, diastase, and invertase are mostly found in honey along with other enzymes like β-glucosidase (White Jr 1979). Invertase causes honey to be a high energetic food (Crane 1980; Sancho et al. 1991). It hydrolyzes sucrose into fructose and glucose, and it also produces some oligosaccharides in an intermediate step therefore making it an important enzyme which keeps its activity after extraction and during storage (White Jr and Maher 1953).

Diastase value is regulated by many legislations as it is utilized as an indicator for the freshness of honey as it is resistant to heat and provide accurate results. Moreover, diastase produces smaller carbohydrates by hydrolyzing starch and dextrin (Crane 1980; White Jr 1978). The presence of an enzyme glucose oxidase causes increased acidity of honey. Conversion of glucose to gluconolactone also

Table 3.1 List of various chemical components present in various types of honey

S. no.	Amino acids (proteins)	Non-aromatic organic acids	Vitamins
1.	Proline	Butyric	Vitamin B1 (thiamine),
2.	Glutamic acid	Citric	Vitamin C
3.	Alanine	Acetic	Vitamin B6
4.	Phenylalanine	Formic	Vitamin B3 (niacin)
5.	Tyrosine	Fumaric	Vitamin B2 (riboflavin)
6.	Leucine	Galacturonic	Pantothenic acid
7.	Isoleucine	Gluconic	Nicotinic acid
8.	Lysine	Lactic	Folic acid
9.	Histidine	Isocitric	–
10.	Arginine	Methylmalonic	–
11.	Aspartic acid	2-Oxopentanoic	–
12.	Tryptophan	Tartaric	–
13.	Serine	Oxalic	–
14.	Valine	Quinic	–
15.	Methionine	Pyruvic	–
16.	Trypsin	Propionic	–
17.	Threonine	Malonic	–

facilitate by this enzyme, which results in the formation of gluconic acid along with minor quantity of hydrogen peroxide which accounts for honey's microbial resistance (White Jr et al. 1963). Glucose oxidase is inactivated at 60 °C and light sensitive (425–525 nm) (Gonzalez 2002; Ortiz-Valbuena and Silva-Losada 1991).

Some other enzymes found in honey though at lower concentrations include B-glucosidase, an enzyme added by bee secretions that hydrolyzes glycosidic toxins ingested by honey bee and transforms β-glucans into oligosaccharides and glucose (Labropoulos and Anestis 2012). In addition to B-glycosides catalase and phosphates and proteases are present. Catalase produces water and oxygen by converting the hydrogen peroxide produced (Huidobro et al. 2005); acid phosphatase can also be used as an indicator, it produces inorganic phosphate from organic phosphate although phosphatase is used as an indicator for fermentation, the optimum pH for its action is between 4.5 and 6.5 (Alonso-Torre et al. 2006). Finally, there are proteases that yield peptides of lower molecular weight by hydrolyzing polypeptides and proteins as well as esterases that breakdown esters (Labropoulos and Anestis 2012).

3.5.3 Organic Acids

These are essential for the preservation of honey, odor, color, and taste, making it difficult for microorganisms to grow therefore preserving it. Organic acid constitutes less than 0.5% of total solids although they also contribute in electric conductivity and honey acidity (Ananias et al. 2013; Bogdanov 2011b). Organic acid is in equilibrium along with the respective lactone (Gomes et al. 2010; White Jr 1979), and it represents 70–90% of the total organic acid. These lactones are produced with the help of an enzyme called glucose-oxidase from glucose (Bogdanov 2011b; Mato et al. 2003). Various organic acids present in honey are listed in Table 3.1 (Bogdanov 2011c).

The value of citric acid compared to gluconic acid indicates if the honey is from floral or honeydew sources (Selvaraj et al. 2006). The malic, gluconic, and citric acids present in honey can chelate with metal ions and strengthen the antioxidant activity of flavonoids (Aazza et al. 2013). A study directed by Cavie et al. tested the free acidity of 35 Spanish honeys for 30 months with no heat and analyzed every 5 months. During the first 5 months, the free acidity remained the same with a very slight increase. The sample started to show a constant increase in free acid after 20 months although it may vary widely. Increased acidity of honey shows the fermentation due to the conversion of alcohol and sugars by honey yeast into acids (Hemadi et al. 2013).

3.5.4 Vitamins

Trace the amount of vitamins found in honey, and it comprises more water-soluble vitamins than fat-soluble vitamins as well as contains very small amounts of lipid substances (Hemadi et al. 2013; Rahman et al. 2014). The various vitamins present in honey are listed in Table 3.1 (Hemadi et al. 2013). Vitamins C and E are known to have antioxidant activity (Bogdanov et al. 2008). Vitamin E, also known as an antioxidant, is reported to increase antioxidant activity and decrease protein oxidation and lipid peroxidation throughout the small intestine (Shirpoor et al. 2007) and reduces glycosylated hemoglobin and fructosamine (Selvaraj et al. 2006; Ceriello et al. 1991; Vinson and Howard 1996). For the regeneration into their antioxidant form as they are pro-oxidants, these vitamins need anti-oxidants (Halliwell 1996; Bowry et al. 1992). It was reported that pure natural honey may cause healing effects and an induction in its cardio protective (Rakha et al. 2008; Khalil and Sulaiman 2010). All the complex B vitamins and vitamin C are mainly derived from pollen; these vitamins can be influenced by filtration as well as by oxidation reactions carried out by glucose oxidase (Ciulu et al. 2011; Rahman et al. 2014). High-performance liquid chromatography-reverse phase (HPLC-RP) is used for the determination of five water-soluble vitamins in honey (Hemadi et al. 2013). Vitamin E has been reported to be successful in reducing programmed cell death and necrosis in noise-affected cells (Leon-Ruiz et al. 2013).

3.5.5 Phenolic

Phenolics are the groups of compounds that are present in plants. Over 8000 diverse structures of phenolics have been found (Estevinho et al. 2008; Bravo 1998). Phenolic compounds found in plants have been reported to be responsible for various therapeutic activities such as anti-inflammatory and anti-atherogenic (Vinson et al. 1998). Phenolic compounds can indeed be divided into flavonoids and phenolic acids, and honey is rich in both flavonoids and phenolic acids (Fig. 3.4), serving as a reference to the biological source of honey (Yao et al. 2003). Honey possesses strong antioxidant activity due to the presence of phenolic compounds or polyphenols generated as secondary metabolic components, which may differ with floral source (Kucuk et al. 2007; Pandey and Rizvi 2009). For instance, specific phytochemicals such as hesperetin and quercetin have already been discovered in citrus and sunflower honey (Anklam 1998; Ferreres et al. 1993; Tomás-Barberán et al. 2001; Aljadi and Kamaruddin 2004). The total phenolic content could be measured as gallic acid equivalent, and the total phenolic content in Indian honey is approximately 65.06 GAE/100 g and in Rhododendron honey is between 0.24 and 141.83 mg GAE/100 g (Bertoncelj et al. 2007; Jaganathan et al. 2010; Silici et al. 2010; Pontis et al. 2014). Different studies indicate that somehow the phenolic compounds found in honey are accountable for different beneficial effects (Turkmen et al. 2005), and techniques such as TLC, HPLC, GC, CE, and colorimetric assays were also used to evaluate polyphenols in honey and propolis and are separated according to environmental conditions (Alvarez-Suarez et al. 2009; Alvarez-Suarez et al. 2012; Trautvetter et al. 2009). Phenolic compounds which are present in Spanish honey for industrialized thermal processing as well as further liquefaction change to caffeic acid and for liquefaction, and further pasteurization contribute to β-coumaric acids (Escriche et al. 2014). Depending on molecular properties,

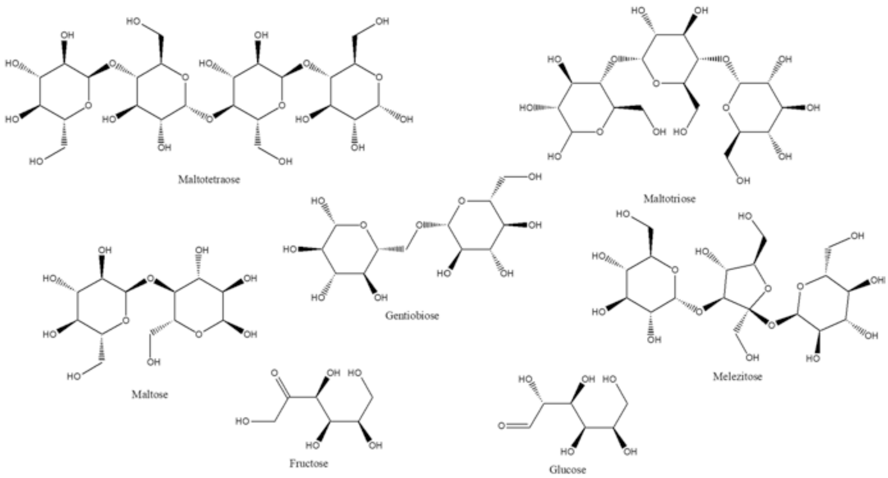

Fig. 3.4 Chemical structures of few phenolic compounds present in various types of honey

polyphenols can be classified into different categories (Grassi et al. 2010; Tomás-Barberán et al. 2001), phenolic acids comprise only one phenolic ring in their molecules and are also known as non-flavonoid polyphenolic compounds (Grassi et al. 2010; Amiot et al. 1989; Ciulu et al. 2016). Phenolic compounds acquire several safe and effective actions like those of antioxidant, antibacterial and antiviral activities, etc. (Zhang et al. 2016; Lampe 1999; Liu 2013). Many various studies also investigated the phenolic profiles in honey and reported a high correlation of phenolic content with antioxidant (Anand et al. 2018; Saxena et al. 2010).

3.5.6 Flavonoids

Flavonoids are present in honey in high amounts and constitute a few thousand compounds making up to 50% of the total phenolic compounds, with a prevalent C6-C3-C6 phenylchromane skeleton, and are known for their antioxidant effect. Various categories of flavonoids are present in honey, such as flavanes, flavonols, and dihydroflavonols, based on oxidation levels; the components of flavonoids differ among honeys from different parts of the world or botanical origins (Tomás-Barberán et al. 2001). Table 3.2 summarizes some of the phenolic and flavonoid compounds present in different types of honey (Kassim et al. 2010; Hussein et al. 2011; Eraslan et al. 2010; Petrus et al. 2011). In most of those varieties of honey, hesperetin and naringenin have been identified. However, flavonoids, such as isorhamnetin, alangin, kaempferol, quercetin, and luteolin, have been reported in most honey varieties (Petrus et al. 2011), and catechin has been identified as a prevalent flavonoid in some of Malaysia's honey that has already been explored (Khalil et al. 2011). Several findings have documented that honey inhibits cellular damage and prevents cell oxidation of cell membrane (Beretta et al. 2007). Antioxidant activity

Table 3.2 Various flavonoids present in different types of honey

Name of the compound	Subclasses	Molecular formula	Molecular weight, g/mol
Apigenin	Flavone	$C_{15}H_{10}O_5$	270.02
Catechin	Flavanol	$C_{15}H_{14}O_6$	290.26
Chrysin	Flavone	$C_{15}H_{10}O_4$	254.20
Galangin	Flavonol	$C_{15}H_{10}O_5$	270.24
Genistein	Isoflavone	$C_{15}H_{10}O_5$	270.24
Isorhamnetin	Flavonol	$C_{16}H_{12}O_7$	316.26
Kaempferol	Flavonol	$C_{15}H_{10}O_6$	286.23
Luteolin	Flavone	$C_{15}H_{10}O_6$	286.24
Myricetin	Flavonol	$C_{15}H_{10}O_8$	318.23
Pinobanksin	Flavonol	$C_{15}H_{12}O_5$	272.25
Pinocembrin	Flavanone	$C_{15}H_{12}O_4$	256.25
Quercetin	Flavonol	$C_{15}H_{10}O_7$	302.23
Rutin	Flavonols	$C_{27}H_{30}O_{16}$	610.52
Naringenin	Flavanone	$C_{15}H_{12}O_5$	272.25
Hesperetin	Flavanone	$C_{16}H_{14}O_6$	302.27

might also be linked to certain other actions, such as increased lipid metabolism and weight loss in human or rat subjects treated with honey (Busserolles et al. 2002; Razquin et al. 2009). The number and orientation of the hydroxyl group and perhaps even the substituents and glycosylation of that same compound determine the antioxidant function of the flavonoid. Glycolysation reduces antioxidant activity particularly in comparison to aglycones.

Quercetin and kaempferol are flavonoids that have a statistically significant effect on heart disease and those whose amount relies on its geographic origin (Alvarez-Suarez et al. 2013). Flavonoids are suggested to minimize the risk of cardiovascular disease through three main mechanisms of action: enhancing vasodilatation, the ability of blood platelets to coagulate, and preventing low-density lipoprotein oxidation (Khalil et al. 2011).

According to a study done by Viuda-Martos et al., it has been shown that galangin is effective against herpes simplex virus and coxsackie B virus, while quercetin and rutin show antiviral activity against herpes simplex virus, syncytial virus, poliovirus, and sindbis virus. Never before has the less unambiguous relation among honey and its chemical compounds been formally reported for its antiviral properties (Viuda-Martos et al. 2008). Studies have shown that certain flavonoids are effective of suppressing sodium-dependent, stimulated migration of monosaccharides into intestinal epithelial cells (Kimmich and Randles 1978). Flavonoids, such as quercetin, chrysin, and galangin, have been shown to minimize the activity of pro-inflammatory enzymes such as cyclooxygenase-2 and prostaglandin, and inducible nitric oxide synthase (Murtaza et al. 2014). Flavonoid content in honey has been shown to reduce matrix metallopeptidase-9, which is an inflammatory mediator leading to chronic inflammation (Candiracci et al. 2012). The first and most important activities of flavonoids are their cytotoxic activity. Standard flavonoid Chrysin has been shown to induce apoptosis (Kasala et al. 2015) in rectal and hepatocellular cancer cell lines used levels ranging from 40 to 100 μm (Ronnekleiv-Kelly et al. 2016; Zhang et al. 2016; Li et al. 2011).

In breast, prostate, and lung cancer cell lines, low levels (10 μm) were successful (Samarghandian et al. 2011; Huang et al. 2016), Chrysin induces apoptosis by caspase activation and Akt inactivation in U937 leukemia cells (Woo et al. 2004). Quercetin is reported to generate apoptosis in cancer cell lines including such human bladder, cervical, ovarian, and breast (Su et al. 2016; Ranganathan et al. 2015). Ellagic acid, another flavonoid observed in honey, generates apoptosis in cancer cells (Ranganathan et al. 2015; Mishra and Vinayak 2014). A mouse study found that Kaempferol had a significant effect on apoptosis in bladder cancer (Umesalma et al. 2015; Dang et al. 2015), colon cancer, ovarian cancer, human cervical cancer, and breast cancer cells (Xie et al. 2013; Lee et al. 2014).

3.5.7 Terpenes

Terpenes are organic and volatile compounds naturally synthesized by honey. Very small amount of terpenes are reported from honey (Kaskoniene and Venskutonis 2010). The characterization of botanical sources of honey has been done by terpenes present in it (Kaskoniene and Venskutonis 2010; Bogdanov et al. 2004). These compounds are aromatic and reported to be active against a wide range of microorganisms such as Gram-negative and Gram-positive bacteria, fungi, and viruses. Different terpenes and their derivatives such as linalool, a-pinene, b-pinene, limonene, camphene, myrtenol, trans-anethol, p-cymene, nerol, and cumene are present in honey (Mato et al. 2003). The flavor, odor, and biomedical properties in honey vary due to the presence of terpenes and their derivatives (Labropoulos and Anestis 2012; Ananias et al. 2013). Norisoprenoids are products of carotenoids (White Jr 1979; Bogdanov 2011b), which influence honey odor (Bogdanov 2011b), and they are known to be anticarcinogenic (Gomes et al. 2010). Terpenes can be identified by gas chromatography quadrupole mass spectrometry which provides qualitative and quantitative data for the identification (Anklam 1998; Cuevas-Glory et al. 2007). These terpenes are found to possess antimicrobial, anti-oxidant, and anti-cancer effects (Manyi-Loh et al. 2011). Several techniques are used for the isolation of terpenes like static headspace extraction, solvent extraction, ultrasound-assisted solvent extraction, etc. (Anklam 1998; Cuevas-Glory et al. 2007; Piasenzotto et al. 2003; Alissandrakis et al. 2003). The oxygenated terpenes can be water-soluble; therefore, heat should not be applied to honey during the isolation technique (Jerkovic et al. 2007). All terpenes are produced from the dimethyl allyl pyrophosphate and its isomer 3-isopentenyl pyro phosphate (Maffei et al. 2011; Dewick 2009). The mostly found terpenes in honey are monoterpenes which are derived from geranyl pyrophosphate (GPP) (Alissandrakis et al. 2007; Jerkovic et al. 2009, 2013).

3.5.8 Pollen

The clearness of honey lies on the level of suspended components like pollens (Busserolles et al. 2002). The pollen and the flower nectar are the key sources of carbohydrate and protein of the honeybees. They also contain fat, vitamins, micro-elements, etc. (Razquin et al. 2009). Hypersensitive responses from nectar are very uncommon, it could be because of pollen (Petrus et al. 2011). Pollen delivers anti-bacterial and antimicrobial properties to the honey (Khalil et al. 2011; Beretta et al. 2007). It is easy to describe the environmental conditions and the flora around the beehive using the pollen analysis. The flora of the origin reflects the pollen content (Alvarez-Suarez et al. 2013). Honey can be classified as monofloral or multifloral with the dominating pollen grain arising from one particular plant (Khalil and Sulaiman 2010; Viuda-Martos et al. 2008; Kimmich and Randles 1978). Acid phosphatase can be used as a parameter for honey characterization, and it mainly originates from nectar and pollen (Murtaza et al. 2014). The geographical region from which the honey is collected affects its phenolic, flavonoid concentrations and its pollen distribution (Candiracci et al. 2012; Kasala et al. 2015). The presence of vitamins, iron, other minerals, and immune enhancing properties has shown that honey bee pollen improves egg quantity, general fertility, and fecundity (Ronnekleiv-Kelly et al. 2016).

3.5.9 Minerals

Honey contains minerals which are classified as major and minor elements (**35,** Bogdanov et al. 2008). The major elements are potassium, chlorine, sulfur, sodium, calcium, phosphorus, magnesium, silicon, iron, zinc, and manganese, and the minor elements are copper, chromium, lithium, nickel, lead, tin, osmium, beryllium, vanadium, zirconium, silver, barium, gallium, bismuth, gold, germanium, and strontium (Solayman et al. 2016; Anderson et al. 1997). The elements like copper and zinc can increase the insulin sensitivity (Sitasawad et al. 2001; Song et al. 2003). These minerals are present in honey in a very low amount (Oh and Yoon 2008; Bogdanov et al. 2008), and a daily consumption of honey may give an adequate concentration of these minerals (Erejuwa et al. 2011). An evidence has shown that after the supplementation of honey, there is an increase in serum concentrations of these minerals (Al-Waili 2003), and these ions also promote the antidiabetic effect of honey (Sitasawad et al. 2001; Oh and Yoon 2008). In light and dark honey, the mineral content varies (Alqarni et al. 2012). Minerals in the soil transported to the flowers and get into honey by the honeydew or nectar (Anklam 1998), and they also come from anthropogenic sources or by beekeeping practices and honey processing methods (Pohl 2009). The mineral content in honey can be analyzed by acid digestion followed by the spectral analysis such as flame atomic absorption (FAAS), graphite furnace atomic absorption (GF-AAS), electro thermal atomic absorption (ET-AAS), inductively coupled plasma optical emission (ICP-OES), and inductively coupled plasma mass spectrometry (ICP-MS) (Pohl et al. 2012). Minerals are indestructible (Damodaran et al. 2010) and play an important role in body function (Pohl et al. 2012).

3.6 Conclusion

In conclusion, honeybee phytochemistry seems to be an interesting field of research with the prospects to explore new environmental relations between plants and bees, new chemical moieties, and new pharmacologically active molecules.

References

Aazza S, Lyoussi B, Antunes D, Miguel MG (2013) Physico-chemical characterization and antioxidant activity of commercial Portuguese honeys. J Food Sci 78:1159–1165

Adebiyi FM, Akpan I, Obiajunwa EL, Olaniyi HB (2004) Chemical physical characterization of Nigeria honey. Pak J Nutr 3:278–281

Alissandrakis D, Daferera PA, Tarantilis PM, Harizanis PC (2003) Ultrasound-assisted extraction of volatile compounds from citrus flowers and citrus honey. Food Chem 82:575–582

Alissandrakis E, Tarantilis PA, Harizanis PC, Polissiou M (2007) Aroma investigation of unifloral Greek citrus honey using solid-phase microextraction coupled to gas chromatographic mass spectrometric analysis. Food Chem 100:396–404

Aljadi AM, Kamaruddin MY (2004) Evaluation of the phenolic contents and antioxidant capacities of two Malaysian floral honeys. Food Chem 85:513–518

Alonso-Torre SR, Cavia MM, Fernandez-Muiño MA, Moreno G, Huidobro JF, Sancho MT (2006) Evolution of acid phosphatase activity of honeys from different climates. Food Chem 97:750–755

Alqarni AS, Owayss AA, Mahmoud AA (2012) Mineral content and physical properties of local and imported honeys in Saudi Arabia. J Saudi Chem Soc 5:618–625

Alvarez-Suarez JM, Tulipani S, Romandini S, Vidal A, Battino M (2009) Methodological aspects about determination of phenolic compounds and in vitro evaluation of antioxidant capacity in the honey: a review. Curr Anal Chem 5:293–302

Alvarez-Suarez JM, Giampieri F, Gonzalez-Paramas AM, Damiani E, Astolfi P, Martinez-Sanchez G et al (2012) Phenolics from mono floral honeys protect human erythrocyte membranes against oxidative damage. Food Chem Toxicol 50:1508–1516

Alvarez-Suarez JM, Giampier F, Battino M (2013) Honey as a source of dietary antioxidants: structures, bioavailability and evidence of protective effects against human chronic diseases. Curr Med Chem 20:621–638

Alvarez-Suarez JM, Gasparrini M, Forbes-Hernández TY, Mazzoni L, Giampieri F (2014) The composition and biological activity of honey: a focus on Manuka honey. Foods 3:420–432

Al-Waili NS (2003) Effects of daily consumption of honey solution on hematological indices and blood levels of minerals and enzymes in normal individuals. J Med Food 6:135–140

Amiot MJ, Aubert S, Gonnet M, Tacchini M (1989) The phenolic compounds in honeys: preliminary study upon identification and family quantification. Apidologie 20:115–125

Anand S, Pang E, Livanos G, Mantri N (2018) Characterization of Physico chemical properties and antioxidant capacities of bioactive honey produced from Australian grown Agastache rugosa and its correlation with colour and poly-phenol content. Molecules 23:108

Ananias KR, De-Melo AAM, Moura CJ (2013) Analysis of moisture content, acidity and contamination by yeast and molds in *Apis mellifera* L. honey from Central Brazil. Braz J Microbiol 44:679–683

Anderson GH, Woodend D (2003) Effect of glycemic carbohydrates on short-term satiety and food intake. Nutr Rev 61:S17–S26

Anderson RA, Cheng N, Bryden NA et al (1997) Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes 46:1786–1791

Anklam E (1998) A review of the analytical methods to determine the geographical and botanical origin of honey. Food Chem 63:549–562

Arias MC, Sheppard WS (2005) Phylogenetic relationships of honey bees (hymenoptera:Apinae:Apini) inferred from nuclear and mitochondrial DNA sequence data. Mol Phylogenet Evol 37(1):25–35

Belitz HD, Grosch W, Schieberle P (2009) Food chemistry, 4th edn. Springer, Berlin

Beretta G, Orioli M, Facino RM (2007) Antioxidant and radical scavenging activity of honey in endothelial cell cultures (EA. hy926). Planta Med 73:1182–1189

Bertoncelj J, Dobersek U, Jamnik M, Golob T (2007) Evaluation of the phenolic content, antioxidant activity and colour of Slovenian honey. Food Chem 105(2):822–828

Biino L (1971) Looking for some amino acids in two varieties of honey. Rivista Italiana delle Essenze e Profumi 53:80–84

Bishop H (2005) Robbing the bees: a biography of honey, the sweet liquid gold that seduced the world. Free Press, New York, NY

Bocarsly ME, Powell ES, Avena NM et al (2010) High-fructose corn syrup causes characteristics of obesity in rats: increased body weight, body fat and triglyceride levels. Pharmacol Bio Chem Behav 97:101–106

Bogdanov S (2008) Honey as nutrient and functional food. http://www.bee-hexagon.net

Bogdanov S (2011a) Honey technology. In Bogdanov S (ed) The honey book,15–18

Bogdanov S (2011b) Physical properties. In Bogdanov S (ed) The honey book, 19–27

Bogdanov S (2011c) Honey composition. In Bogdanov S (ed) The honey book, 27–36

Bogdanov S, Jurendic T, Sieber R, Gallmann P (2008) Honey for nutrition and health: a review. J Am Coll Nutr, 27(6):677–689

Bogdanov S, Lullman C, Martin P et al (1999) Honey quality and international regulatory standards: review by the international honey commission. Bee World 80:61–69

Bogdanov S, Ruoff K, Persano Oddo L (2004) Determination of honey botanical origin: problems and issues. Apidologie 35:4–17

Bowry VW, Ingold KU, Stocker R (1992) Vitamin E in human low-density lipoprotein. When and how this antioxidant becomes a pro-oxidant. Bio Chem J 288(Pt 2):341–344

Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism and nutritional significance. Nutr Rev 56:317–333

Busserolles J, Gueux E, Rock E, Mazur A, Rayssiguier Y (2002) Substituting honey for refined carbohydrates protects rats from hypertriglyceridemic and prooxidative effects of fructose. J Nutr 132:3379–3382

Candiracci E, Piatti M, Dominguez-Barragan M et al (2012) Anti-inflammatory activity of a honey flavonoid extract on lipopolysaccharide-activated N13 microglial cells. J Agric Food Chem 60(50):12304–12311

Cani PD, Neyrinck AM, Fava F et al (2007) Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia 50:2374–2383

Celestino Santos B, González-Paramás AM (2017) Chemical composition of honey, bee products—chemical and biological properties, pp 43–65

Ceriello A, Giugliano D, Quatraro A, Donzella C, Dipalo G, Lefebvre PJ (1991) Vitamin E reduction of protein glycosylation in diabetes. New prospect for prevention of diabetic complications? Diabetes Care 14:68–72

Chick H, Shin HS, Ustunol Z (2001) Growth and acid production by lactic acid bacteria and bifidobacteria grown in skim milk containing honey. J Food Sci 66:478–481

Ciulu M, Solinas S, Floris I, Panzanelli A, Pilo MI, Piu PC, Spano N, Sanna G (2011) RP-HPLC determination of water-soluble vitamins in honey. Talanta 83:924–929

Ciulu M, Spano N, Pilo MI, Sanna G (2016) Recent advances in the analysis of phenolic compounds in unifloral honeys. Molecules 24:451

Crane EE (1980) A book of honey. Oxford University Press, Oxford. ISBN 9780192860101
Cuevas-Glory JA, Pino LS, Santiago E, Sauri D (2007) Food Chem 103:1032–1043
Damodaran S, Parkin KL, Fennema OR (2010) Química de Alimentos de Fennema, 4th edn. Artmed, Porto Alegre
Dang Q, Song W, Xu D, Ma Y, Li F, Zeng J, Zhu G, Wang X, Chang LS, He D, Li L (2015) Kaempferol suppresses bladder cancer tumor growth by inhibiting cell proliferation and inducing apoptosis. Mol Carcinog 54:831–840
Dash RK (1972) Charaka Samhita, vol 1. Chowkhamba Sanskrit Series Office, Varanasi, India
Deibert P, König D, Kloock B, Groenefeld M, Berg A (2010) Glycaemic and insulinaemic properties of some German honey varieties. Eur J Clin Nutr 64:762
Dewick PM (2009) Medicinal natural products: a biosynthetic approach, vol 3. Wiley, Chichester, pp 89–100
Dilworth LL, Riley CK, Stennett DK (2017) Chapter 5—plant constituents: carbohydrates, oils, resins, balsams, and plant hormones. In: Pharmacognosy: fundamentals, applications and strategies, pp 61–80
Doner LW (2003) Honey. In: Caballero B, Finglas PM, Trugo LC (eds) Encyclopedia of food sciences and nutrition, vol 2, pp 3125–3130
Eraslan G, Kanbur M, Silici S, Karabacak M (2010) Beneficial effect of pine honey on trichlorfon induced some biochemical alterations in mice. Ecotoxicol Environ Saf 73:1084–1091
Erejuwa OO, Sulaiman SA, Wahab MS et al (2011) Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. Int J Biol Sci 7:244–252
Erejuwa OO, Sulaiman SA, Wahab MS (2012) Oligosaccharides might contribute to the antidiabetic effect of honey: a review of the literature. Molecules 17:248–266
Escriche I, Kadar M, Juan-Borras M, Domenech E (2014) Suitability of antioxidant capacity, flavonoids and phenolic acids for floral authentication of honey. Impact of industrial thermal treatment. Food Chem 142:135–143
Estevinho L, Pereira AP, Moreira LG, Dias L, Pereira E (2008) Antioxidant and antimicrobial effects of phenolic compounds extracts of Northeast Portugal honey. Food Chem Toxicol 46:3774–3779
Eteraf-Oskouei T, Najafi M (2013) Traditional and modern uses of natural honey in human diseases: a review. Iran J Basic Med Sci 16:731–742
Ferreres F, Garcia-Viguera C, Tomas-Lorente F, Tomas-Barberan FA (1993) Hesperitin: a marker of the floral origin of citrus honey. J Sci Food Agr 61:121–123
Fujisawa T, Riby J, Kretchmer N (1991) Intestinal absorption of fructose in the rat. Gastroenterology 101:360–367
Gomes S, Dias LG, Moreira LL, Rodrigues P, Estevinho L (2010) Physicochemical, microbiological and antimicrobial properties of commercial honeys from Portugal. Food Chem Toxicol 48:544–548
Gonzalez MM (2002) El Origin, quality and freshness of honey: the interpretation of an analysis. In: De Lorenzo C (ed) La miel de Madrid, 1st edn, pp 27–45
Gonzalez-Paramas AM, Gomez-Barez JA, Cordon-Marcos C, Garcıa-Villanova RJ, Sanchez J (2006) HPLC-fluorimetric method for analysis of amino acids in products of the hive (honey and bee-pollen). Food Chem 95:148–156
Grassi D, Desideri G, Ferri C (2010) Flavonoids: antioxidants against atherosclerosis. Nutrients 2:889–902
Gregory PC, Mc Fadyen M, Rayner DV (1989) Relation between gastric emptying and short-term regulation of food intake in the pig. Physiol Behav 45:677–683
Halliwell B (1996) Vitamin C: antioxidant or pro-oxidant in vivo? Free Radic Res 25:439–454
Havsteen BH (2002) The biochemistry and medical significance of the flavonoids. Pharmacol Ther 96:67–202
Hemadi M, Saki G, Rajabzadeh A, Khodadadi A, Sarkaki A (2013) The effects of honey and vitamin E administration on apoptosis in testes of rat exposed to noise stress. J Hum Reprod Sci 6(1):54–58

Henry RR, Crapo PA, Thorburn AW (1991) Current issues in fructose metabolism. Annu Rev Nutr 11:21–39
Hermosın I, Chicon RM, Cabezudo MD (2003) Free amino acid composition and botanical origin of honey. Food Chem 83:263–268
Huang C, Wei YX, Shen MC, Tu YH, Wang CC, Huang HC (2016) Chrysin abundant in Morinda citrifolia fruit water-EtOAc extracts, combined with Apigenin synergistically induced apoptosis and inhibited migration in human breast and liver Cancer cells. J Agric Food Chem 64:4235–4245
Huidobro JF, Sanchez MP, Muniategui S, Sancho MT (2005) Precise method for the measurement of catalase activity in honey. J AOAC Int 88:800–804
Hussein SZ, Yusoff KM, Makpol S, Yusof YA (2011) Antioxidant capacities and total phenolic contents increase with gamma irradiation in two types of Malaysian honey. Molecules 16:6378–6395
Jaganathan SK, Mandal SM, Jana SK, Das S, Mandal M (2010) Studies on the phenolic profiling, antioxidant and cytotoxic activity of Indian honey: in vitro evaluation. Nat Prod Res 24:1295–1306
Jerkovic J, Mastelic Z, Marijanovic Z, Klein MJ (2007) Comparison of hydrodistillation and ultrasonic solvent extraction for the isolation of volatile compounds from two unifloral honeys of Robinia pseudoacacia L. and Castanea sativa L. Ultrason Sonochem 14:750–756
Jerkovic CIG, Tuberoso Z, Marijanovic M, Jelic KA (2009) Headspace, volatile and semi-volatile patterns of Paliurus spina-christi unifloral honey as markers of botanical origin. Food Chem 112:239–245
Jerkovic MO, Kus PM, Sarolic M (2013) Bioorganic diversity of rare Coriandrum sativum L. honey: unusual chromatographic profiles containing derivatives of linalool/oxygenated methoxybenzene. Chem Biodivers 10:1549–1558
Jones HF, Butler RN, Brooks DA (2011) Intestinal fructose transport and malabsorption in humans. Am J Physiol Gastrointest Liver Physiol 300:202–206
Kasala ER, Bodduluru LN, Madana RM, Athira KV, Gogoi R, Barua CC (2015) Chemopreventive and therapeutic potential of chrysin in cancer: mechanistic perspectives. Toxicol Lett 233:214–225
Kashimura J, Nagai Y (2007) Inhibitory effect of palatinose on glucose absorption in everted rat gut. J Nutr Sci Vitaminol (Tokyo) 53:87–89
Kaskoniene V, Venskutonis PR (2010) Floral markers in honey of various botanical and geographic origins: a review. Compr Rev Food Sci Food Saf 9:620–634
Kassim M, Achoui M, Mustafa MR, Mohd MA, Yusuf KM (2010) Ellagic acid, phenolic acids and flavonoids in Malaysian honey extracts demonstrate in vitro anti-inflammatory activity. Nutr Res 30:650–659
Khalil MI, Sulaiman SA (2010) The potential role of honey and its polyphenols in preventing heart diseases: a review. Afr J Tradit Complement Altern Med 7:315–321
Khalil MI, Alam N, Moniruzzaman M, Sulaiman SA, Gan SH (2011) Phenolic acid composition and antioxidant properties of Malaysian honeys. J Food Sci 76:921–928
Kimmich GA, Randles J (1978) Phloretin-like action of bioflavonoids on sugar accumulation capability of isolated intestinal cells. Membr Biochem 1:221–237
Kucuk M, Kolayl S, Karaoglu S, Ulusoy E, Baltac C, Candan F (2007) Biological activities and chemical composition of three honeys of different types from Anatolia. Food Chem 100:526–534
Kwon S, Kim YJ, Kim MK (2008) Effect of fructose or sucrose feeding with different levels on oral glucose tolerance test in normal and type 2 diabetic rats. Nutr Res Pract 2:252–258
Labropoulos A, Anestis S (2012) Honey. In: Varzakas T, Labropoulos A, Anestis S (eds) Sweeteners: nutritional aspects, applications, and production technology. CRC, Boca Raton, pp 119–146
Lampe JW (1999) Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. Am J Clin Nutr 70:475–490

Lavin JH, Wittert GA, Andrews J et al (1998) Interaction of insulin, glucagon-like peptide 1, gastric inhibitory polypeptide, and appetite in response to intraduodenal carbohydrate. Am J Clin Nutr 68:591–598

Lee A (2007) Digestion and absorption of carbohydrates, proteins and lipids. In: xPharm: the comprehensive pharmacology, pp 1–12

Lee HS, Cho HJ, Yu R, Lee KW, Chun HS, Park JHY (2014) Mechanisms underlying apoptosis-inducing effects of Kaempferol in HT-29 human colon cancer cells. Int J Mol Sci 15:2722–2737

Leon-Ruiz V, Vera S, Gonzalez-Porto AV, Andres MPS (2013) Analysis of water- soluble vitamins in honey by isocratic RP-HPLC. Food Anal Methods 6:488–496

Li X, Wang JN, Huang JM, Xiong XK, Chen MF, Ong CN, Shen HM, Yang XF (2011) Chrysin promotes tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induced apoptosis in human cancer cell lines. Toxicol In Vitro 25:630–635

Lina BA, Jonker D, Kozianowski G (2002) Isomaltulose (Palatinose): a review of biological and toxicological studies. Food Chem Toxicol 40:1375–1378

Liu RH (2013) Health-promoting components of fruits and vegetables in the diet. Adv Nutr 4:384–392

Madero M, Arriaga JC, Jalal D et al (2011) The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. Metabolism 60:1551–1559

Maffei J, Gertsch G, Appendino G (2011) Plant volatiles: production, function and pharmacology. Nat Prod Rep 28:1359–1380

Manyi-Loh CE, Ndip RN, Clarke AM (2011) Volatile compounds in honey: a review on their involvement in aroma, botanical origin determination and potential biomedical activities. Int J Mol Sci 12:9514–9532

Mato I, Huidobro JF, Simal-Lozano J, Sancho MT (2003) Significance of nonaromatic organic acids in honey. J Food Prot 66:2371–2376

Megan Ware LD (2015) Honey: health benefits, uses and risks. Medical News Today

Meirelles CJ, Oliveira LA, Jordao AA et al (2011) Metabolic effects of the ingestion of different fructose sources in rats. Exp Clin Endocrinol Diabetes 119:218–220

Mishra S, Vinayak M (2014) Ellagic acid induces novel and atypical PKC isoforms and promotes caspase-3 dependent apoptosis by blocking energy metabolism. Nutr Cancer 66:675–681

Molan PC (1999) Why honey is effective as a medicine. 1. Its use in modern medicine. Bee World 80:8092

Murtaza G, Karim S, Akram MR, Khan SA, Azhar S, Mumtaz A, Bin Asad MH (2014) Caffeic acid phenethyl ester and therapeutic potentials. Bio Med Res Int 9:145342

Murty KR (2001) Ashtangahridayaya Samhita, (Sutrasthana) (English Translation). Krishnadas Academy, Varanasi

Nathan L, Gloag RS, Anderson DL, Oldroyd BP (2009) A molecular phylogeny of the genus Apis suggests that the Giant honey bee of the Philippines, A. breviligula Maa, and the plains honey bee of southern India, A. *indica Fabricius*, are valid species. Syst Entomol 35(2):226–233

Needham AW (2008) Health benefits of honey. http://www.bees-online.com/HealthBenefitsOfHoney.htm

Oh HM, Yoon JS (2008) Glycemic control of type 2 diabetic patients after short-term zinc supplementation. Nutr Res Pract 2:283–288

Olaitan PB, Adeleke EO, Ola OI (2007) Honey: a reservoir for microorganisms and an inhibitory agent for microbes. Afr Health Sci 7:159–165

Ortiz-Valbuena A, Silva-Losada MC (1991) HMF content in honey from La Alcarria. Cuadernos de Apicultura 10:8–10

Pandey KB, Rizvi SI (2009) Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev 2(5):270–278

Petrus K, Schwartz H, Sontag G (2011) Analysis of flavonoids in honey by HPLC coupled with coulometric electrode array detection and electrospray ionization mass spectrometry. Anal Bioanal Chem 400:2555–2563

Piasenzotto L, Gracco L, Conte L (2003) Solid phase microextraction (SPME) applied to honey quality control. J Sci Food Agric 83:1037–1044
Pohl P (2009) Determination of metal content in honey by atomic absorption and emission spectrometries. Trends Anal Chem 28:117–128
Pohl P, Stecka H, Sergiel I, Jamroz P (2012) Different aspects of the elemental analysis of honey by flame atomic absorption and emission spectrometry: a review. Food Anal Methods 5:737–751
Pontis JA, Da Costa LAMA, Da Silva SJR, Flach A (2014) Color, phenolic and flavonoid content, and antioxidant activity of honey from Roraima, Brazil. Food Sci Technol Campinas 34(1):69–73
Rahman MM, Gan SH, Khalil MI (2014) Neurological effects of honey: current and future prospects. Evid Based Complement Alternat Med 13:958721
Rakha MK, Nabil ZI, Hussein AA (2008) Cardioactive and vasoactive effects of natural wild honey against cardiac malperformance induced by hyperadrenergic activity. J Med Food 11:91–98
Ranganathan S, Halagowder D, Sivasithambaram ND (2015) Quercetin suppresses twist to induce apoptosis in MCF-7 breast cancer cells. PLoS One 10:e0141370
Razquin C, Martinez JA, Martinez-Gonzalez MA, Mitjavila MT, Estruch R, Marti A (2009) A 3 years' follow-up of a Mediterranean diet rich in virgin olive oil is associated with high plasma antioxidant capacity and reduced body weight gain. Eur J Clin Nutr 63:1387–1393
Ronnekleiv-Kelly S, Nukaya M, Diaz-Diaz C, Megna B, Carney P, Geiger P, Kennedy GD (2016) Aryl hydrocarbon receptor-dependent apoptotic cell death induced by the flavonoid chrysin in human colorectal cancer cells. Cancer Lett 370:91–99
Rueppell O, Bachelier C, Fondrk MKREJ (2007) Regulation of life history determines lifespan of worker honey bees (*Apis mellifera* L.). Exp Gerontol 42(10):1020–1032
Sajid M, Azim M (2012) Characterization of the nematicidal activity of natural honey. J Agric Food Chem 60:7428–7434
Samarghandian S, Afshari JT, Davoodi S (2011) Chrysin reduces proliferation and induces apoptosis in the human prostate cancer cell line pc-3. Clinics (São Paulo) 66:1073–1079
Sancho MT, Muniategui S, Huidobro JF, Simal J (1991) Honey Basque Country, X: tendency to granulation. Anales de Bromatologı'a 43:283–292
Sarfraz SAS, Atif AB et al (2018) Honey as a potential natural antioxidant medicine: an insight into its molecular mechanisms of action. Oxid Med Cell Longev 8367846:1–19
Saxena S, Gautam S, Sharma A (2010) Physical, biochemical and antioxidant properties of some Indian honeys. Food Chem 118:391–397
Selvaraj N, Bobby Z, Sathiyapriya V (2006) Effect of lipid peroxides and antioxidants on glycation of hemoglobin: an in vitro study on human erythrocytes. Clin Chim Acta 366:190–195
Shamala TR, Shri Jyothi Y, Saibaba P (2000) Stimulatory effect of honey on multiplication of lactic acid bacteria under in vitro and in vivo conditions. Lett Appl Microbiol 30:453–455
Shirpoor A, Ansari MH, Salami S, Pakdel FG, Rasmi Y (2007) Effect of vitamin E on oxidative stress status in small intestine of diabetic rat. World J Gastroenterol 13:4340–4344
Silici S, Sagdic O, Ekici L (2010) Total phenolic content, antiradical, antioxidant and antimicrobial activities of Rhododendron honeys. Food Chem 121:238–243
Sitasawad S, Deshpande M, Katdare M et al (2001) Beneficial effect of supplementation with copper sulfate on STZ-diabetic mice (IDDM). Diabetes Res Clin Pract 52:77–84
Solayman M, Islam MA, Paul S, Ali Y, Khalil MI, Alam N, Gan SH (2016) Physicochemical properties, minerals, trace elements, and heavy metals in honey of different origins: a comprehensive review. Compr Rev Food Sci Food Saf 15:219–233
Song MK, Hwang IK, Rosenthal MJ et al (2003) Antidiabetic actions of arachidonic acid and zinc in genetically diabetic Goto-Kakizaki rats. Metabolism 52:7–12
Su Q, Peng M, Zhang Y, Xu W, Darko KO, Tao T, Huang Y, Tao X, Yang X (2016) Quercetin induces bladder cancer cells apoptosis by activation of AMPK signaling pathway. Am J Cancer Res 6:498–508
Thibault L (1997) Dietary carbohydrates: effects on selfselection, plasma glucose and insulin, and brain indoleaminergic systems in rat. Appetite 23(3):275–286.

Tomás-Barberán FA, Martos I, Ferreres F, Radovic BS, Anklam E (2001) HPLC flavonoid profiles as markers for the botanical origin of European unifloral honeys. J Sci Food Agric 81:485–496
Trautvetter S, Koelling-Speer I, Speer K (2009) Confirmation of phenolic acids and flavonoids in honeys by UPLC-MS. Apidologie 40:140–150
Turkmen N, Sari F, Poyrazoglu ES, Velioglu YS (2005) Effects of prolonged heating on antioxidant activity and colour of honey. Food Chem 95:653–657
Umesalma S, Nagendraprabhu P, Sudhandiran G (2015) Ellagic acid inhibits proliferation and induced apoptosis via the Akt signaling pathway in HCT-15 colon adenocarcinoma cells. Mol Cell Biochem 399:303–313
Vaidya JTA, Samhita S, Sutrasthana (2002) Dravadravyavidhi. Adhyaya MadhuVarga 45(7):132–142
Vaisman N, Niv E, Izkhakov Y (2006) Catalytic amounts of fructose may improve glucose tolerance in subjects with uncontrolled non-insulin-dependent diabetes. Clin Nutr 25:617–621
Vinson JA, Howard TB (1996) Inhibition of protein glycation and advanced glycation end products by ascorbic acid and other vitamins and nutrients. J Nutr Biochem 7:659–663
Vinson JA, Hao Y, Su X, Zubik L (1998) Phenol antioxidant quantity and quality in foods: vegetables. J Agric Food Chem 46:3630–3634
Viuda-Martos M, Navajas Y, Fernandez-Lopez J, Perez-Alvarez JA (2008) Functional properties of honey, propolis, and royal jelly. J Food Sci 73:117–124
White JW Jr (1978) Honey. Adv Food Res 24:287–374
White JW Jr (1979) Composition of honey. In: Crane EE (ed) Honey: a comprehensive survey, vol 2, pp 157–206
White JW Jr, Maher J (1953) Transglucosidation by honey invertase. Arch Biochem Biophys 42:360–367
White JW Jr, Subers MH, Schepartz AJ (1963) The identification of inhibition, the antibacterial factor in honey, as hydrogen peroxide and its origin in a honey glucose-oxidase system. Biochim Biophys Acta 73:57–70
Wong CH, Bryan MC (2003) Sugar arrays in microtiter plates. Methods Enzymol 362:218–225
Wongsiri S (1997) Comparative biology of Apis andreniformis and Apis florea in Thailand. Bee World 78(1):23–35
Woo KJ, Jeong YJ, Park JW, Kwon TK (2004) Chrysin-induced apoptosis is mediated through caspase activation and Akt inactivation in U937 leukemia cells. Biochem Biophys Res Commun 325:1215–1222
Xie F, Su M, Qiu W, Zhang M, Guo Z, Su B, Liu J, Li X, Zhou L (2013) Kaempferol promotes apoptosis in human bladder cancer cells by inducing the tumor suppressor, PTEN. Int J Mol Sci 14:21215–21226
Yao L, Datta N, Tomas-Barberan FA, Ferreres F, Martos I, Singanusong R (2003) Flavonoids, phenolic acids and abscisic acid in Australian and New Zealand Leptospermum honeys. Food Chem 81:159–168
Zhang Q, Ma S, Liu B, Liu J, Zhu R, Li M (2016) Chrysin induces cell apoptosis via activation of the p53/Bcl-2/caspase-9 pathway in hepatocellular carcinoma cells. Exp Ther Med 12:469–474
Zumla A, Lulat A (1989) Honey–a remedy rediscovered. J R Soc Med 82:384–385