Honey and Its Molecular Pharmacology: An Essay

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Summya Rashid, Andleeb Khan, Aimen Firdous, Yusra Al Dhaheri, Adil Farooq Wali, and Rehan Khan

Abstract

Honey is a sugary, viscous fluid being used nearly 5500 years ago, since prehistoric times. In Sumerian tablet, the first inscribed evidence of honey was found in 2100–2000 B.C. Most olden civilizations like Greeks, Chinese, Egyptians, Romans, Mayans, and Babylonians, used honey mutually aimed at nutrition as well as for medicinal purposes. It exhibits numerous health- benefits which include anti-oxidant, anti-inflammatory, anti-bacterial, anti-diabetic, and protective effects in respiration, gastrointestinal system, cardiovascular, and nervous system. Based on origin, or its way of harvest and processing, honey can be categorized as blossom honey, honeydew or forest honey, monofloral, multifloral honey, raw honey, granulated honey, strained honey, ultra-filtered

S. Rashid (✉)
Department of Pharmacology and Toxicology, College of Pharmacy Girls Section, Prince Sattam Bin AbdulAziz University, Al-Kharj, Saudi Arabia
e-mail: s.abdulrashid@psau.edu.sa

A. Khan
Department of Pharmacology and Toxicology, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

A. Firdous
Department of Processing Technology, Kerala University of Fisheries and Ocean Studies (KUFOS), Panangad, Kerala, India

Y. Al Dhaheri
Department of Biology, College of Science, United Arab Emirates University, Al Ain, United Arab Emirates

A. F. Wali
Department of Pharmaceutical Chemistry, RAKCOPS, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates

R. Khan
Institute of Nano Science and Technology, Habitat Centre, Mohali, Punjab, India

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honey, ultrasonicated honey, chunk honey, comb honey, dried honey, whipped or creamed honey. The methods of extraction, processing, packaging, and preservation of honey alter the physical appearance of honey. Nevertheless, some elementary properties allied with honey contribute to it, regardless of the protocols used in the formation like content of H_2O, matter configuration, and retention of water. Other physical structures and features of honey include taste, odor, color, heat, and crystallization. Depending on honey's source, oldness, and storage/packing conditions, liquid honey may be either clear or no color, yellow, amber to dark amber, or black in color. Honey consists of pollen grains, water, waxes, vitamins, sugars, essential minerals, amino acids, proteins, enzymes, pigments, and pollen grains, and numerous phytochemicals with other 180 types of diverse complexes. Chemically, it consists of enzymes, organic acids, and phenolic acids with gluconic acid being the most abundant organic acid. Phenolic acids include non-flavonoids and flavonoids like isoflavones, flavones, anthocyanidins, flavanones, flavonols, chalcones, and enzymes include glucose oxidase, saccharase, catalase, and diastase and others, respectively. The effect of different constituents of honey obtained have been found to inhibit inflammation, oxidative stress, proliferation, metastasis, angiogenesis, and induce apoptosis. Also, honey has been found to regulate diabetes, cardiovascular and neuropharmacological diseases. However, more mechanism- based research needs to be done to promote the consumption of this healthy food in the general population, to promote a healthy lifestyle, and to regulate normal processes of life.

Keywords

Honey · Polyphenols · Cancer · Cardiovascular pharmacology · Neuropharmacology

10.1 Introduction

Honey is a sugary, viscous fluid as defined through the European Union as naturally formed by honeybees (*Apis mellifera*) from the sap of flowers, defecations of plant-sucking insects or plants parts collected by bees, or from emissions of any plant parts which bees gather, alter in joining per explicit constituents of themselves, deposits, desiccate, stock, then place in honeycombs to grow and ripen. Humans have been using honey nearly 5500 years ago, since prehistoric times. In Sumerian tablet, first inscribed evidence of honey was found in 2100–2000 B.C. Most olden civilizations, like Greeks, Chinese, Egyptians, Romans, Mayans, and Babylonians, used honey mutually aimed at nutrition as well as for medicinal purposes (Samarghandian et al. 2017). It has nutritive, cosmetologic, healing, and industrial properties and is the only naturally derived from insects. It serves as a balanced diet and correspondingly beneficial for both men and women in any population. It is not spoiled by high temperature, can be stored in a dry place unopened at room temperature, so does not need refrigeration. At present time, data on the honey usage for curing of various

natural ailments are present in magazines, research papers, and awareness books. Literature reports demonstrate that honey exhibits numerous health benefits which include antioxidant, anti-inflammatory, antibacterial, antidiabetic, and protective effects in respiration, gastrointestinal system, cardiovascular, and nervous system (Carlos et al. 2011; Ediriweera and Premarathna 2012).

10.2 Classification of Honey

Based on origin, or its way of harvest and processing, honey can be categorized. Depending upon its derivation, it is classified into blossom, honeydew, monofloral, and multifloral honeys. *Blossom honey* comes from the juice of flowers mainly.

Honeydew or forest honey is obtained by bees after collecting honeydew from plant juices.

Monofloral honey is principally obtained from a solo plant source having total pollen content of more than 45% from the identical plants and called as per plant-like citrus, manuka, and acacia honey are obtained (Nyuk and Kandhasamy 2020).

Multifloral honey is identified as polyfloral honey having different plant origins where not any is major like meadow blossom honey and forest honey (Alvarez-Suarez et al. 2010). Based on packaging, mode of production, or presentation, honey is categorized separately and characterized differently like raw, ultra-filtered, granulated, chunk, pasteurized, dried, strained, ultrasonicated, comb and whipped (Zielinski et al. 2014).

Raw honey may be obtained by negligible processing with no heat treatment, attained by extraction, settling, or straining of beehive contents (Decaix 1976). Modern beehives can be visualized in Fig. 10.1a.

10.2.1 Granulated Honey

When the glucose content of honey has naturally crystallized/formed granules in a mixture like monohydrate or granulated honey is produced. This granulated or crystallized honey is moved in a vessel kept at 49 °C in warm water to convert it to a liquid state. However, honey is pasteurized by heating to 161 °F (71.7 °C) to destroy fungal cells and melt tiny crystals in the honey, hence delaying the commencement of discernible crystal formation (Bogdanov et al. 2008).

10.2.2 Strained Honey

Strained honey undergoes straining process to get rid of dirt, waxes, exudates from plants, and propolis and not eliminating minerals, pollen, or enzymes from the mixture of honey obtained.

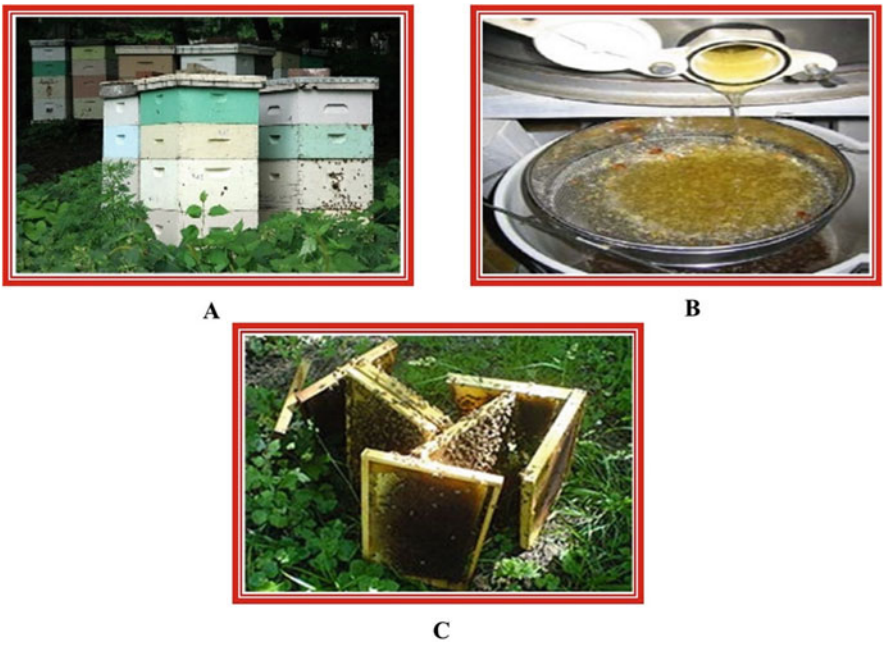

Fig. 10.1 (**a**) Modern beehives, (**b**) filtration of raw honey, and (**c**) typical wood frames

Ultra-filtered honey is achieved by applying 65–77 °C, as it effortlessly melts and passes via fine filter under high pressure in order to get rid of superfluous solids and pollen grains, as shown in Fig. 10.1b (Bogdanov et al. 2008).

10.2.3 Ultrasonicated honey

Ultrasonicated honey attained via non-heating procedure by supposedly kills fungal growth and inhibits crystallization.

Chunk honey filled in large-mouthed bottles having pieces of comb honey engrossed in removed molten honey.

Comb honey is in wax comb of honeybees', conventionally obtained through honey supers before packaging in which the comb is cut in chunks via means of typical wooden frames. Figure 10.1c represents wooden frames (Ajibola 2016).

Dried honey is devoid of moistness to produce entirely compact, nonsticky granules done by aeration and anticaking agents.

Whipped or creamed honey consists of a huge amount of small crystals to produce honey with an even and easily spreadable uniformity.

According to European Union Council Directive which states there is also baker's honey meant for industrial purpose or as a constituent in food industry (Ajibola 2016).

10.3 Physical Properties

The methods of extraction, processing, packaging, and preservation of honey alter the physical appearance of honey (González-Paramas et al. 2000). Nevertheless, some elementary properties allied with honey contribute to it, regardless of the protocols used in the formation-like content of H_2O, matter configuration, and retention of water. It consists of water (16%) and suspended elements (80%) (Ajibola 2016). Viscosity of honey depends on several honey ingredients mainly its water content which is defined as hygroscopicity. Surface tension is dependent on colloidal substances in the honey which is directly proportional to honey's botanical origin serves as additional property influencing the appearance physically. Other physical structures and features of honey include taste, odor, color, heat, and crystallization (White and Doner 1980). Honey is used as a sweetener because of fructose glucose naturally, which contributes to sweetness and has a sweet smell too. Depending on honey's source, oldness, and storage/packing conditions liquid honey may be either clear or no color, yellow, amber to dark amber, or black in color. Nonetheless, pollen or dirt can interfere with transparency or clarity (Olaitan et al. 2007). Honey is also available in bright yellow (sunflower), reddish undertones (chestnut), grayish (eucalyptus), and greenish (honeydew) colors as per its sources. Likewise, external features of honey-like color, crystallization, taste, and fragrance are affected by heat. As a matter of fact, heat converts honey into darker color. Honey crystallization occurs by the development of monohydrate glucose crystals of varying quantity, form, measurement, and excellence with configuration, conservation, and packing procedures of honey (González-Paramas et al. 2000; Decaix 1976). Though regardless of storage conditions over time honey crystallizes.

10.3.1 Crystallization of Honey

Crystallization of honey affects texture and color but would not change the taste, superiority, or nutritive status. Crystallization turns honey lighter in color due to the formation of glucose crystals. The quantity of water also affects rate of crystallization; the lesser water content, the more content of glucose fastens the process (Olaitan et al. 2007). Storage conditions, explicit blend of sugars, and trace components in the honey also influence the rate of crystallization. Tupelo and acacia type honeys extraordinarily crystallize slowly, whereas goldenrod crystallizes in the comb itself often. Heat influences physical characteristics of honey as crystallization, which has been mentioned above. Consequently, at a lower temperature 10 and 21 °C, honey can be crystallized, while as fluidly honey is obtained by heating honey to a higher temperature like 49 °C indirectly to cause the dissolution of the crystals.

Honey is food sweetener, used industrially with no previous processing, and its manufacture is increasing at a global level (Ajibola 2016; Crane 1975).

10.4 Honey: Its Composition and Physicochemical Properties

Honey consists of pollen grains, water, waxes, vitamins, sugars, essential minerals, amino acids, proteins, enzymes, pigments, and pollen grains (PGs) (White and Doner 1980), numerous phytochemicals with other 180 types of diverse complexes. Honey contains a mixture of glucose and fructose in a strenuous aqueous solution but also has various amino and organic acids, at least 22 other intricate carbohydrates, proteins, inhibine containing antibiotics, enzymes, phenol antioxidants, aroma compounds, vitamins, minerals, pigments, etc. (White and Doner 1980). Honey's pH ranges from 3.2 to 4.5, hence is acidic. Sugars which are found in honey are generally monosaccharides like fructose and glucose constituting 75%. Other carbohydrates constituting 10–15% are disaccharides which constitute maltose, maltulose, sucrose, turanose, isomaltose, and trisaccharides (Da Silva et al. 2016). Typically, most predominant sugar in the honey is fructose like in acacia plants, but there are exceptions like dandelion and rape plants which have higher proportion of glucose than fructose (Persano and Piro 2004). Therefore, carbohydrates can help in the recognition of plant-based and/or location-based sources of floral honeys, as well as hydration capacity and other characteristics (Eteraf-Oskouei and Najafi 2013). Apart from percentages of glucose and fructose, its proportion also helps to classify floral honeys and percentages of some trivial oligosaccharides and blended concentrations (Kaškonienė and Venskutonis 2010). Proteins also form part of honey including enzymes like invertase, α-glucosidase, catalase, diastase, sucrase, amylase, and glucose oxidase. Amino acids are present with proline being the maximally present along with other 20 or more amino acids (Da Silva et al. 2016). Table 10.1 consists of the physicochemical composition collected globally around 1000 honey samples. It also contains differing quantity of essential minerals depending upon plant source, location, geographical factors, and processing techniques. Calcium, phosphorus, copper, magnesium, potassium, sodium, zinc, iron, manganese, and selenium are the most abundantly found (Miguel et al. 2017).

Honey consists of small amounts of vitamins which include ascorbic acid (C), riboflavin (B2), niacin (B3), pantothenic acid (B5), and pyridoxine (B6) (Alvarez-Suarez et al. 2013). B complex vitamins are derived mostly from pollen, along with vitamin C which can influence commercial and industrial processes like filtration and oxidation reactions carried out by glucose oxidase (Ciulu et al. 2011). Table 10.2 details about the presence of vitamins/100 g of honey.

Based on plant source and physical location, honey contains minerals and elements of different percentages (Vincēviča-Gaile 2010). Minerals come into existence naturally by decomposition of plant and animal remains via geological processes which occur as inanimate compact elements in the environment (Belitz et al. 2009; Nickel 1995), which happen to be indispensable in controlling metabolism in the living organisms (Gopalan et al. 1989). They are grouped into three categories based on requirements of body as major, trace, and ultra-trace elements. Minerals that are needed in amounts of more than 50 mg/day are major minerals, whereas ones which are required $<$50 mg/day are trace elements and others even less

Table 10.1 Represents the physicochemical composition collected globally around thousand honey samples

Elements	Mean value
Moisture (%)	17.90
pH	3.96
Fructose (%)	39.44
Sucrose (%)	3.19
Glucose (%)	28.15
Reducing sugar (%)	68.31
Minerals (%)	0.36
Total protein (%)	1.13
Lipid amount (mg/g)	215.00
HMFb (mg/kg)	15.49
Vit-C (mg/g)	13.19
Lactone (meq/kg)	8.57
Proline amount (mg/kg)	873.00
Diastase activity (DN)	14.27
Electrical conductance (ms/cm)	0.64
ABS450c (mAU; 50 w/v)	834.00
Acidity (meq/kg)	35.32
Total solids soluble (Brix)	128.00
Refractive index	1.49
Water-insoluble portion (%, w/w)	16.00

Table 10.2 Describes the presence of vitamins/100 g of honey

Vitamins present	Value/100 g
B2	0.038 mg
B3	0.21 mg
B5	0.068 mg
B6	0.024 mg
B9	2 μg
Vit C	0.5 mg
Mixed groups	–

than 1 μg/g and frequently found at <50 ng/g in diet are called as ultra-trace elements (Nielsen 1984; Belitz et al. 2009). Those initiating from natural source in particular micro- or trace minerals are useful for good strength. Instead, having five times specific gravity of H_2O develop toxicity if the source is inorganic or metallic constitute heavy metals (Ajibola et al. 2012). Heavy metals are lethal or noxious at less proportions since they get accrued in the living system (Zugravu et al. 2009). Based on plant source and physical location, honey contains minerals and elements of different percentages (Vincēviča-Gaile 2010).

The volatile compounds include esters, ketones, monoterpenes, sesquiterpenes, benzene derivatives, C13-norisoprenoid and superior alcohols, fatty acids, aldehydes to a lower content (Da Silva et al. 2016). Plant origins and physical location for obtaining honeys can be determined by the presence of some volatile compounds in it like sinensal isomers, etc., which are recognized only in citrus (Alissandrakis et al.

Table 10.3 Depicts about macro, micro, and ultra-trace elements present in honey

Element/units (mg/kg)	Mean
Na	96.48
Cl	302.63
P	84.10
Mg	74.31
Ca	84.36
S	35.27
K	742.43
Trace elements/heavy elements (mg/kg)	Mean
Fe	30.34
Ti	43.40
Si	23.52
Zn	9.33
Al	5.12
Mn	1.42
Ni	1.24
As	0.05
Si	23.52
B	5.36
Mo	0.23
Sr	1.63
V	0.03
Se	0.01
Cd (μg/kg)	89.69
Pb (μg/kg)	424.57
Co (μg/kg)	171.78
Hg (μg/kg)	5.09
Cr (μg/kg)	152.84
Ag (μg/kg)	299.61
Be (μg/kg)	9.93

2007 and Castro-Vázquez et al. 2007) and compound nonanol, etc. are found in acacia honey only (Petretto et al. 2016). Honey from different sources like eucalyptus and chestnut, etc. from varied areas were collected to study the volatile profile and the results were variable, even in the same region. Nevertheless, physicochemical characteristics, major components analysis, clustering analysis, and others are some of the methods to find out plant source and physical location from which honey was obtained by analyzing volatile components of honey samples and it is this method which gives 80% efficacy to classify honey as reported by Oroian et al. (2015) (Table 10.3).

10.5 Chemical Composition

10.5.1 Enzymes and Organic Acids

Organic acids constitute about 0.57% with gluconic acid being the most abundant. Glucose oxidase, saccharase, catalase, and diastase are the enzymes present in honey which are significant in honey formation as well as an efficient food (Cianciosi et al. 2018). Glucose gets converted to δ-gluconolactone by glucose oxidase, which upon hydrolysis converts to gluconic acid, the primary acid, and H_2O_2 having antimicrobial potential. Sucrose is converted to fructose and glucose by invertase. Amylase, an enzyme which acts on long starch chains, makes dextrin and maltose, and hence contributes to honey's quality. Catalase is another enzyme which produces O_2 and H_2O from H_2O_2. Acidity of honey, stability, and its particular taste are due to organic acids present in it (Molan 1999, 2001). Other organic acids found in honey are malic, lactic, formic, fumaric, malonic, aspartic acid, methylmalonic, succinic, citric, oxalic, butyric, acetic, formic, fumaric, glutaric, malonic, formic, acetoglutaric, gluconic, glutamic, galacturonic, butyric, shikimic, isocitric, lactic, malic, quinic, etc. (white and Doner 1980; Mato et al. 2006).

10.5.2 Phenolic Compounds

Polyphenols constitute diverse category of organic substances classified into flavonoids and non-flavonoids (Fig. 10.2). Phenolic acids are non-flavonoids and flavonoids include isoflavones, flavones, anthocyanidins, flavanones, flavonols, and chalcones. They are a by-product of secondary metabolites of plants, which are categorized by numerous phenolic groups present with diverse structural intricacies. The secondary metabolism products have significant ecological functions, yet they are involved in adaptation, respiratory, transporter, and differentiating processes unlike primary metabolites like chlorophyll, amino acids, and simple carbohydrates (Kennedy and Wightman 2011). The phenolic composition may help in classifying and authenticating process like in unifloral varieties, depending mainly on its plant source. The most common phenolic compounds and flavonoids in honey are shown in Fig. 10.3.

These compounds scavenge free radicals by making stable and least harmful molecules, hence having antioxidative activity. The stability of phenolic compounds depends on amount of their hydroxyl groups and they stabilize free radicals by giving away H from OH group (Rice-Evans and Miller 1996).

Flavonoids are generally water-soluble chemicals, bearing low molecular weight and are shaped by combination of benzene rings with alternate straight three carbon chain of atoms (C6–C3–C6); rearrangement repeatedly itself leads to the formation of three rings having 15 carbon atoms called A, B, and C. Largely, these complexes are frequently connected with sugars like glucose with galactose, arabinose, xylose, glucorhamnose, and rhamnose; having two phenolic groups (OH) at least. Aglycones are the compounds when flavonoids are not connected with sugars.

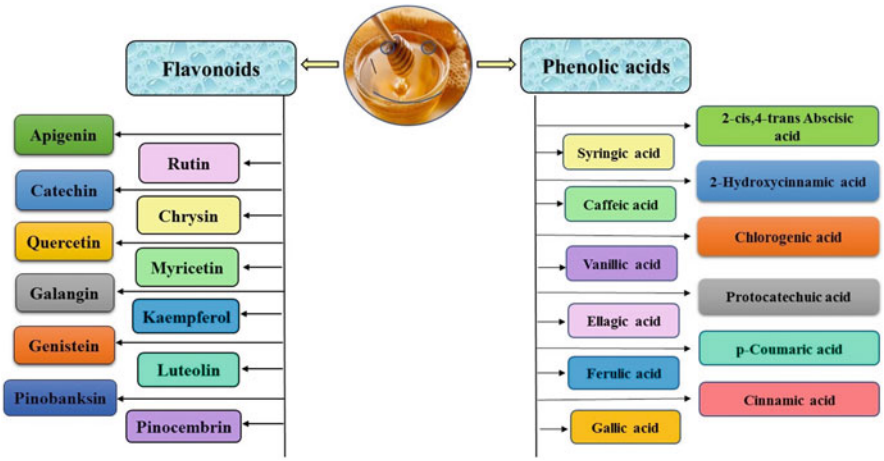

Fig. 10.2 Depicts classification of phytochemicals present in honey

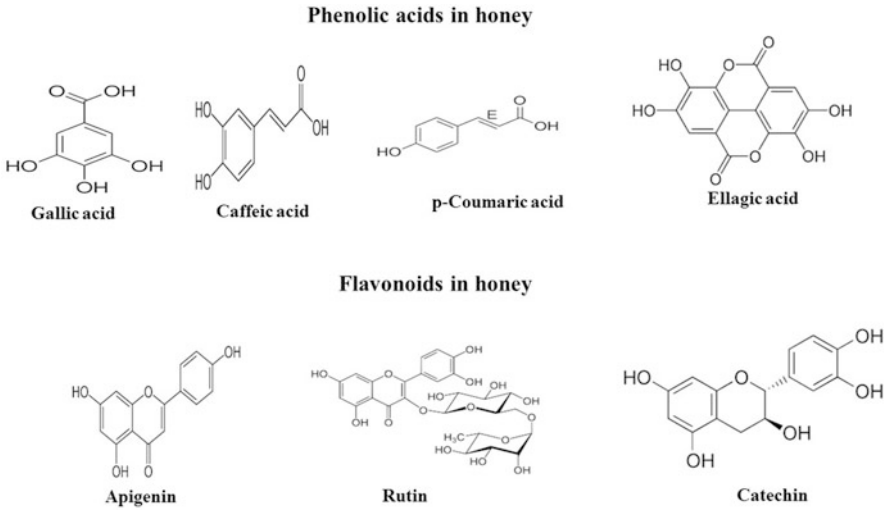

Fig. 10.3 Depicts structure of some compounds present in honey

Therefore, flavonoids are categorized depending on oxidizing of C ring in which we already described above as found in flavanones, flavonols, anthocyanidins, flavanols, flavones, isoflavones, anthocyanins and flavones, flavanols, and flavonols being most copious (Moniruzzaman et al. 2014).

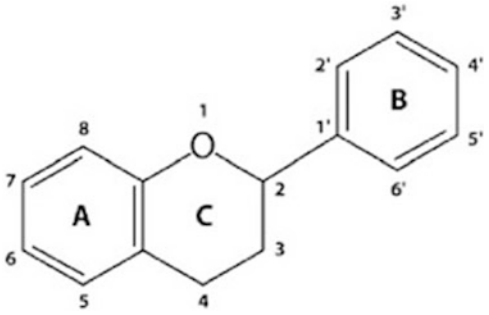

Fig. 10.4 Basic structure of flavonoids

10.5.3 Basic Structure of Flavonoid

Phenolic acids basically comprise of one organic carboxylic acid and a phenolic ring which can further be grouped as per their structure: C6–C3 like ferulic acid and caffeic acid, C6–C2 which include acetophenones and phenylacetic acids and C6–C1 structures which include vanillic and gallic acids. Phenolic compounds or other secondary metabolite structures are typically attached with the structural machineries of the plant-like cellulose, organic compounds like glucose, sugars, or flavonoids (Padayachee et al. 2012; Cianciosi et al. 2018) (Fig. 10.4).

Polyphenols and flavonoids form the most crucial bioactive molecules present in honey. Reports suggest that there may be nearly 30 diverse polyphenols present (Padayachee et al. 2012; D'Archivio et al. 2010) which differ from 50 to 850 mg/kg and have varied flavonoid composition between 36 and 150 mg/kg (Walle 2004), which again depends upon the geographic, climatic, environmental settings as well as floral source. Galangin, quercetin, luteolin, and kaempferol are the kinds of bioactive compounds present in it usually, while hesperetin and naringenin are other constituents found only in explicit types (Spencer et al. 1999; Peternelj and Coombes 2011). However, ellagic acid, quercetin, luteolin, catechin, naringenin, gallic acid, kaempferol, syringic acid, coumaric acid, caffeic acid, benzoic acid, chlorogenic acid, cinnamic acid, myricetin, ferulic acids, apigenin, chrysin, catechin, hesperetin, isorhamnetin, and galangin are generally the most frequently described phenolic acid components and flavonoids present in it (Carlos et al. 2011; Khalil et al. 2011; Erejuwa et al. 2012a, b; Mijanur et al. 2014).

Floral type, physical location, environment around, various bee species around, and then the post collection processing and storage conditions define the elemental, phytochemical constituents, taste, and color of honey (Puscas et al. 2013).

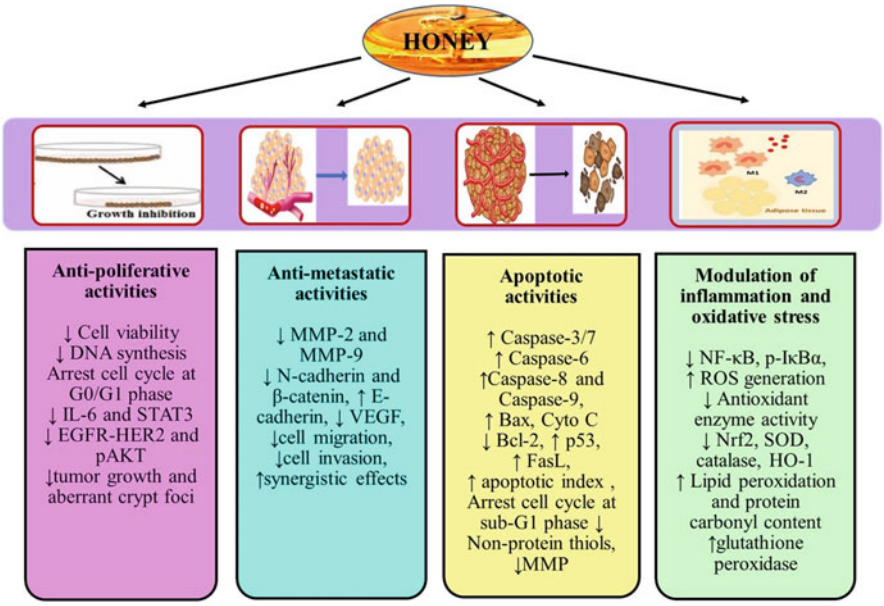

Fig. 10.5 Depicts the possible mechanisms of anticancer effects of honey

10.6 Cancer-Related Mechanistic Studies on Honey

Cancer is a complicated phenomenon commencing with variation at genetic level in healthy cells resulting in uncontrolled propagation, failure to apoptose, leading to development of tumors if the repair pathway does not work (Allan and Travis 2005). Several measures conspire to form cancer-like instigation of oncogenes, suppression of tumor suppressor genes, uncontrolled cell signaling pathways, growth factors and hormones, and other interrelated complex processes (Hanahan and Weinberg 2011). The heterogeneous nature of cellular genotypes and phenotypes and several pathways activate the pathological process of development of cancer. Conventional therapies do not work much because they target one pathway and the cancer cell takes another. The effect of different constituents of honey-like flavonoid or phenolic extracts or fractionated or whole honey extracts from various regions with different dosages on diverse cancer types (Swellam et al. 2003a, b; Khoo et al. 2010; Salucci et al. 2002; Nair et al. 2004; Elattar and Virji 2000) by targeting anti-proliferation, apoptosis initiation process; inhibition of inflammation, oxidative stress, anti-metastasis, and antiangiogenesis (Fig. 10.5) in accordance with type, dose of honey studied in various in vitro and in vivo models. However, it is not limited only to these mechanisms.

Polish honeys with the highest phenolic content decreased MMP-2 and MMP-9 expression, which are the markers of metastasis, in the glioblastoma cell line

Table 10.4 Different kinds of Honey having inhibitory effects on cancer cell lines (anti-proliferation, anti-oxidative, anti-inflammatory, proapoptotic, antimetastatic, and antiangiogenesis pathways)

Honeys	Effects on cancer	In vitro	Dose/ intervention and duration	References
Polish honey	Decrease in cell viability, DNA synthesis, MMP-2 and MMP-9	U87MG glioblastoma cell line	0.5–7.5% polish honey (24–72 h)	Moskwa et al. (2014)
Manuka honey	Decrease NF-κB, p-IκBα	HCT116 and LoVo colorectal cancer cell lines	0–20 and 0–60 mg/mL (48 h)	Afrin et al. (2018a)
	Decreases cell viability, STAT3 phosphorylation, and IL-6 production with decrease in Bcl-2, cell migration, and cell invasion. Caspase-3/ 7, -6, -8, -9, Bax, and Cyto C were elevated	MDA-MB-231 and MCF-7 breast cancer cell lines	0.25–2% (w/v) (24–72 h)	Aryappalli et al. (2017)
	Decrease cell viability and tumor growth in vivo. Increase in apoptosis and coaction with paclitaxel	CT26 colon carcinoma cell line, MCF-7 breast cancer cell line, and B16F1 skin melanoma cell line	0·6–5% for (24, 48, and 72 h)	Fernandez-Cabezudo et al. (2013)
	Decrease in NF-κB, p-IκBα, MMP-2, MMP-9, and cell migration with N-cadherin and β-catenin decrease. Elevation in E-cadherin and synergistic effects	HCT116 and LoVo colorectal cancer cell lines	10–20 and 30–40 mg/mL (48 h) and 5–15 and 20–30 mg/mL (48 h)	Afrin et al. (2018a, b)
Strawberry tree honey	Elevation in p53, caspase-3, -8, -9, c-PARP1, Bax, Cyto C, FasL, and E-cadherin. Decrease in Bcl, cell migration, MMP-2 and MMP-9, N-cadherin, and β-catenin	HCT116 and LoVo colorectal cancer cell lines	3–12 mg/mL (48 h) 10–40 mg/mL (48 h)	Afrin et al. (2019a, b)
	Increased ROS generation, lipid peroxidation, and protein carbonyl content with decrease	HCT116 and LoVo colorectal cancer cell lines	3–12 mg/mL (48 h) 10–40 mg/mL (48 h)	Afrin et al. (2017, 2019b)

(continued)

Table 10.4 (continued)

Honeys	Effects on cancer	In vitro	Dose/ intervention and duration	References
	in antioxidant enzyme activity, Nrf2, HO-1			
Indian honey	Cell cycle arrest, decrease in Bcl-2, nonprotein thiols and MMP with elevation in ROS, p53, caspase-3, PARP cleavage, Bax	HCT15 and HT29 colon cancer cell lines	1–20% (12–48 h)	Jaganathan and Mandal (2010)
Acacia honey	Decrease in cell viability, Bcl-2, p53 arrest cell cycle at G0/G1 phase	NCI-H460 non-small lung cancer cell line	0.5–8% (48 h)	Aliyu et al. (2013)
	Decrease cell viability and arrest cell cycle at G0/G1 phase	A375 and B16-F1 melanoma cell line	0.01–0.2 g/mL (24–72 h)	Pichichero et al. (2010)
	Arrest cell cycle at G0/G1 phase with decrease TNF-α, IL-1β	PC-3 prostate cancer cell line	2–10% (v/v) (48 h)	Aliyu et al. (2012)
	Decrease cell viability with apoptotic cell death	MCF-7 breast cancer cell line	3.12–100% (v/v) (24–72 h)	Salleh et al. (2017)

U87MG (Song et al. 2017). Moreover, the authors suggest a correlation between the quantity of lead and cadmium and found honey having large amount of cadmium to have more potency to inhibit metastasis. It diminished cell viability by decreasing the synthesis of DNA in U87MG glioblastoma cells (Moskwa et al. 2014) (Table 10.4).

Acacia honey (AC) suppresses the development of MCF-7, human breast adenocarcinoma cells, and triggered apoptosis (5.5% v/v) via arrest of the cell cycle at the G0/G1 phase which was revealed through TUNEL assay and live cell view imaging depending upon dose and time (Hegazi and Abd El-Hady 2007) in NCI-H460 (non-small lung) (Aliyu et al. 2013), PC-3 (prostate) (Aliyu et al. 2013) cancer cells. In PC-3 cells, it also upregulated production of cytokines like TNF-α, IL-1β thereby inducing the release of Ca ion from the endoplasmic reticulum (Aliyu et al. 2012, 2013). AC resulted in downregulation of proliferation as well as arresting cell cycle at G0/G1 phase in numerous cell lines (Aliyu et al. 2012; Pichichero et al. 2010) (Table 10.4).

Manuka honey (MH) was found to have antiproliferative effect in time and dose-dependent manner on different cancer cell lines including CT-26, HCT-116, and LoVo (colon), MDA-MB-231 and MCF-7 (breast), and B16-F1 (melanoma) (Aryappalli et al. 2017; Fernandez-Cabezudo et al. 2013; Afrin et al. 2018c),

which were linked with S and G2/M phases cell cycle arrest by modifications in cell cycle–mediated genes. Besides, MH was reported to upregulate phosphorylated p38 mitogen-activated protein kinase (p-p38MAPK) and phosphorylated extracellular signal-regulated kinase 1/2 (p-Erk1/2) pathways and suppress oncogenic signaling pathways like epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER2), phosphorylated protein kinase B (p-Akt), and IL-6/signal transducer and activator of transcription (IL-6/STAT3), which results in regulated signaling (Afrin et al. 2018c; Aryappalli et al. 2017). MH and strawberry tree honey (STH) also upregulated molecules associated with intrinsic and extrinsic apoptotic pathways like caspase-8, caspase-9, Bcl-2-associated X protein (Bax), fatty acid synthetase (Fas) ligand (FasL), and cytochrome C (Cyto C) at mRNA level (Afrin et al. 2018c, 2019a). MH was reported to increase caspase-3/7 and caspase-9 enzyme, c-PARP, DNA fragmentation, and inhibited Bcl-2 in mitochondria-dependent apoptotic pathway in a murine melanoma B16-F1 cells (Fernandez-Cabezudo et al. 2013). It also diminished migratory and invasive pathway molecules like MMP-2, MMP-9, N-cadherin, and E-cadherin HCT-116 and LoVo human colon (Afrin et al. 2019b, a), and MDA-MB-231 and MCF-7 breast cancer (Aryappalli et al. 2017) along with inflammatory mediators like NF-κB, p-IκBα resulting in antimetastatic, anti-invasion, and anti-inflammatory effect in HCT-116 and LoVo colon cancer cells (Pichichero et al. 2010) (Table 10.4).

Strawberry tree honey (STH) decreases cell viability in HCT-116 (colon adenocarcinoma cells) and metastatic LoVo cells in a dose- and time-dependent manner (Pichichero et al. 2010) and augments reactive oxygen species production (ROS) (Afrin et al. 2017, 2018a). Apart from increasing oxidative stress allied with apoptosis by diminishing antioxidant armories like glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD), and catalase; in congruent with inhibiting nuclear-related factor 2 (Nrf2), SOD, catalase, and heme oxygenase 1 (HO-1) pathway leading to antioxidant response, upregulating the injury of cellular biomolecules (lipid, protein, and DNA); and mitochondrial respiration and glycolysis disruption which may be attributed to larger amount of polyphenols present in it (Yaacob et al. 2013; Jaganathan et al. 2010a, b; Morales and Haza 2013; Afrin et al. 2018a) (Table 10.4).

Jaganathan and Mandal (2010) showed that the treatment of Indian honey in HCT-15, HT-29 colon, and MCF-7 breast cancer cells induced apoptosis by freezing cell cycle at sub-G1 phase. It also downregulated intracellular nonprotein thiols in congruence with MMP by oxidative stress, improved p53, caspase-3, c-PARP, and Bax, along with downregulation of expression of Bcl-2 protein (Jaganathan and Mandal 2010; Jaganathan et al. 2010a) (Table 10.4).

Jungle honey boosted immunity in mice against tumor inoculated with Lewis lung carcinoma/2 cells. There was a correlation with an enlarged neutrophil-mediated chemotactic response and ROS generation with declined in tumor rate in honey-treated mice (Fukuda et al. 2011) (Table 10.5).

Indian Honey significantly reduced tumor progression (Jaganathan et al. 2010b) in a murine Ehrlich ascites carcinoma model, which may be attributed to its phenolic

Table 10.5 Inhibitory mechanistic effects of honey on in vivo cancer models

Honeys	Effects/mechanism of action on cancer	In vivo	Treatment regimen	References
Jungle honey	Chemotaxis ↑ ROS production	Lewis lung carcinoma	1 mg/day intraperitoneally for 7 days before tumor inoculation	Fukuda et al. (2011)
Indian honey	↓ Tumor growth	Ehrlich ascites carcinoma	25% (v/v) intraperitoneally for 12 days	Jaganathan et al. (2010b)
Bee honey	↓ Lung nodule formation	Spontaneous mammary carcinoma Anaplastic colon adenocarcinoma	2 g/kg (oral), daily for 10 days 1 g/kg (oral), daily for 10 days	Orsolić et al. (2003)
	↓ PCNA ↓ p53 levels	Diethylnitrosamine-induced liver carcinogenesis	2 g/day (oral) for 6 months	El-kott et al. (2012)
	↓ Tumor volume (93)	MBT-2 bladder cancer	6–12% (intralesional), twice weekly; 3 weeks 50% in drinking water, alternate days; 3 weeks	Swellam et al. (2003)
Manuka	Increases Apaf-1, Caspase-9, IFN-γ, IFNGR1, and p53. Decreasing TNF-α, COX-2, and Bcl-xL 1	Female Sprague–Dawley (SD) breast cancer rats	1-methyl-1-nitrosourea (80) mg/kg. 1.0 g/kg body weight/day of TH and MH, respectively, for 120 days	Porcza et al. (2016)
Tualang	↓ Tumor cell growth, ↓ cell proliferation, ↑ Apaf-1, and caspase-9	(DMBA-induced breast cancer	0.2, 1.0, or 2.0 g/kg bodyweight/day of TH, respectively, for 150 days	Fernandez-Cabezudo et al. (2013)

ingredient, whereas it did not show any effect in leukemia cancer (Jaganathan et al. 2014) (Table 10.5).

Bee honey was given orally to rats for 6 months as 2 g honey/day starting 1 week after diethylnitrosamine (DEN) administration had a beneficial result against inflammation, decreased proliferation, and induced apoptosis (El-kott et al. 2012). Because of carbohydrates and sugar intake to rats by administering honey at such dose for a long period may have confounded the findings as they did not take appropriate controlled sugar to rats. Ehrlich ascites carcinoma growth was inhibited by treatment of 25% (v/v) bee honey intraperitoneally 1 day after tumor inoculation significantly inhibited in mice and this tumor inhibitory efficacy was ascribed to the phenolic content and its antioxidant status (Jaganathan et al. 2010b). Lastly, bee honey was explored for its anti-tumor efficacy in MBT-2 bladder cancer model in C3H/He

mice. Tumor volume was diminished by injecting 6 and 12% solutions of honey inside the lesions of tumor. Furthermore, tumor growth was blocked by treating mice with 50% solution of bee honey orally (Swellam et al. 2003a, b). Although the mechanism of action is unknown. Macrophage phagocytic activity and T-Cell activation are generally attributed to Bee honey and may be responsible to activate immune system (Table 10.5).

Manuka honey was administered a week earlier the initiation of breast cancer with N-methyl-N-nitrosourea to rats at a dose of 1 g/kg body weight blocked tumorigenesis (Samarghandian et al. 2011). It upregulated Apaf-1, Caspase-9, IFN-γ, IFNGR1, and p53 leading to induction of apoptosis and diminished TNF-α, COX-2, and Bcl-xL decreasing inflammation. Manuka honey induced strong proapoptotic activity dose and time dependent upon intravenous administration in mice having murine melanoma tumor cells (B16F1) implanted leading to shrinkage of final tumor volume (Fernandez-Cabezudo et al. 2013).

Tualang honey was administered to rats orally after 7,12-dimethyl benzene anthracene (DMBA) for 150 days deferred tumor progress, multiplication, weights, and volumes compared with control animals, thereby preventing 7,12-dimethylbenzeneanthracene (DMBA)-induced mammary tumors in Sprague–Dawley rats. Tualang honey induced proapoptotic proteins like Caspase 9 and p53, reduction of vascular endothelial growth factor (VEGF), marker of angiogenesis, and modulated inflammatory mediators like TNF-α and COX-2 (Kadir et al. 2013) (Table 10.5).

10.7 Cancer-Related Clinical Studies on Honey

Honey improves the quality of life of cancer patients and has been used in alternative medicine. Nevertheless, not much testing/clinical trials in cancer patients have been done to study the potency of honey. Different types of honey manuka and thyme administered orally have been found to alleviate mucositis as an adverse effect of radiation therapy for head and neck cancer patients, which is one of the rare areas which provides evidence (Rao et al. 2017; Cho et al. 2015; Hawley et al. 2014; Charalambous et al. 2018). Notably, but reports did not mention about its effect on cancer promotion. Honey efficiently ameliorated the sternness of mucositis induced by chemotherapy in meta-analysis of randomized trial (Xu et al. 2016). On the other hand, manuka honey was tested against esophagitis induced by radiation in a randomized clinical trial deciphered that it was not better than the standard supportive care (Fogh et al. 2017). Cancer patients who were given 5 mL processed honey and royal jelly honey for 4 weeks, twice daily had reduced fatigue related to cancer in double-blind randomized trial of 52 patients (Mofid et al. 2014). Administration of honey and ardeh (sesame paste) in another 107 patients getting chemotherapy for acute myeloid leukemia amended gastrointestinal problems, neutropenia and declines fever in another double-blind, randomized, placebo-controlled study (Attia et al. 2008). In another study, 40 children of ages 2.5–10 years having acute lymphoblastic leukemia upon treatment with raw clover honey were found to have

reduction in febrile neutropenia and increase in Hb levels in randomized crossover clinical trial (Mabrouk et al. 2002). Generally, honey has been found to have beneficial effect in decreasing adverse side effects associated with chemotherapy/radiotherapy which includes lethargy, mucositis, neutrophil loss, and gastrointestinal toxicity. Additionally, patients of hormone receptor-positive breast cancer when given adjuvant endocrine therapy with anastrozole, aromatase inhibitor along with tualang honey (42% compared with 10% reduction) showed inhibition of breast cancer growth, cancer remission, more efficiently than anastrozole alone treatment in a randomized controlled trial (Hizan et al. 2018). Therefore, well-controlled trials must be designed due to the above mentioned interesting and positive results to directly gauge the potency of honey as an adjuvant treatment in different types of cancer.

10.8 Honey and Its Antidiabetic Properties

Diabetes mellitus is a multifaceted metabolic disease in which either body does not produce sufficient insulin or has insulin resistance wherein enough insulin is produced, but insulin receptors do not respond (Matteucci and Giampietro 2000). It involves differences in lipoprotein and carbohydrate metabolism shooting up glucose in body along with ketoacidosis which may be lethal (Brownlee 1995; Elgawish et al. 1996). Antidiabetic activity of honey has been observed in animal models to clinical trials (Al-Waili 2003; Erejuwa et al. 2010); therefore, it is a potent antidiabetic agent. Studies show that 0.2, 1.2, and 2.4 g/kg/day of honey exerted hypoglycemia in streptozotocin-induced diabetic rats by improving oxidative stress (Erejuwa et al. 2010). Another study shows reduction in glucose level by inhalation of honey as 60% (W/V) in type-2 diabetes mellitus (Al-Waili 2003), which in both studies is associated with the presence of fructose in honey (Erejuwa et al. 2012a, b). Fructose regulates insulin-response system which results in appropriate and normal blood glucose level. Glucose level is decreased by the delay of digestion and absorption by palatinose, an oligosaccharide sucrose as depicted by another hypothesis (Kashimura and Nagai 2007). Fructose ingestion depresses food intake besides delaying absorption, also associated with deferred gastric emptying. Slow fructose absorption in the intestine may lengthen the period of contact and interface between fructose and intestinal receptors resulting in satiety and in more macronutrients to be passed into the large intestine leading to limited intestinal absorption. Additionally, fructose is shown to decrease food intake which may help in the reduction of weight gain as per evidence (Erejuwa et al. 2012a, b). Hydrolysis of carbohydrates preceding to their absorption gives rise to monosaccharides like glucose, fructose, and galactose (Wright et al. 2003). Fructose is taken up by protein and energy-mediated diffusion via GLUT5 and GLUT2 receptors (Schürmann 2008). Glucose and fructose have been shown to increase GLUT2 mRNA expression. But fructose solely increases GLUT5 mRNA expression resulting in its fast absorption (Stelmańska 2008; Henry et al. 1991; Douard and Ferraris 2008). Research shows that mice induced with diabetes fed with fructose leads to hypoglycemic effect (Kwon et al.

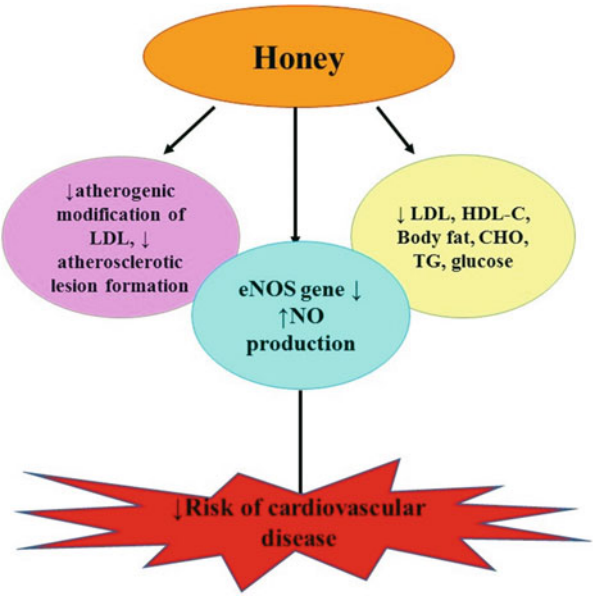

Fig. 10.6 Depicts the possible mechanisms of cardiovascular effects of honey

2008) and also regulates glucose level in the liver by stimulating the phosphorylation enzymes like glucokinase-activating hepatic glucose phosphorylation (Van Schaftingen and Davies 1991). The suppression of these enzymes results in suppression of glycogenolysis. Therefore, fructose regulates whole metabolism of glycogen and glucose depicting its essential vital role to govern hyperglycemia (Youn et al. 1987; Regan et al. 1980). Honey's hypoglycemic effect may be via mediating the insulin signaling pathway is another proposed mechanism (Erejuwa et al. 2010; Batumalaie et al. 2013) having PI3K/Akt as a key component (Carnero et al. 2008) by modulating cell cycle progression, cell survival, and cellular growth. The effect of honey extracts in pancreatic cells under hyperglycemic condition on Akt-activated insulin signaling pathway was recently investigated. Insulin resistance was associated with augmented levels of NF-κB, MAPK, insulin receptor substrate 1 (IRS-1), serine phosphorylation, and decreased Akt expression and insulin contents. Prophylactic treatment with honey and quercetin extract improves expression of Akt and decreased IRS-1 serine phosphorylation, NF-κB, and MAPK (Erejuwa et al. 2012a, b; Vincent et al. 2013; Carnero et al. 2008; Batumalaie et al. 2013) oxidative stress and hyperglycemia. In addition, it was found to alleviate triglycerides, hepatic transaminases, glycosylated hemoglobin (HbA1c), and enhanced HDL cholesterol (Erejuwa 2014). Figure 10.6 is showing the possible mechanisms of antidiabetic effects of honey. Further studies are necessary to explore the exact mechanisms involved in antidiabetic activity of honey.

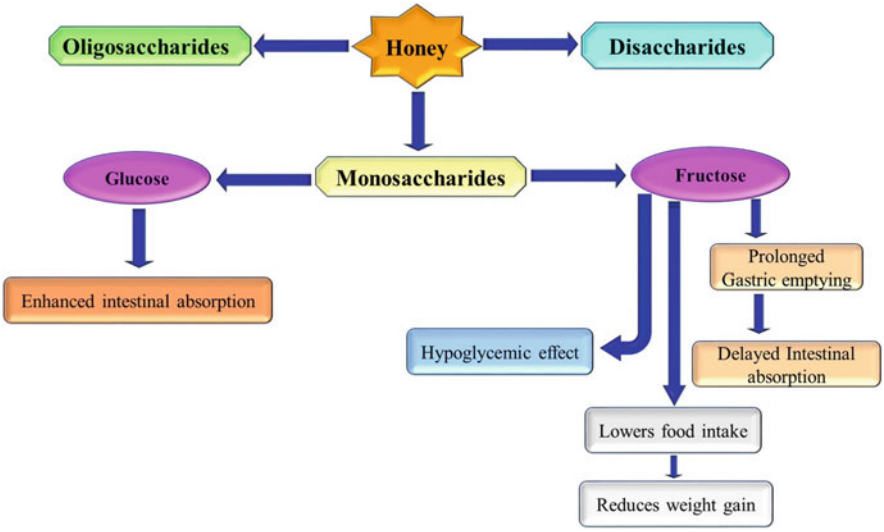

Fig. 10.7 Shows the possible mechanisms of antidiabetic effects of honey

10.9 Cardiovascular Effects of Honey

Some cardiovascular risk factors like blood glucose, cholesterol, CRP (C-reactive proteins), and body weight may be regulated by honey (Yaghoobi et al. 2008) constituents like glucose, fructose, and trace elements including copper and zinc. It was shown that 70 g of honey for 30 days given to cardiac patients and healthy human subjects had decreased LDL (low-density lipoprotein), high-density lipoprotein cholesterol (HDL-C), triacylglycerole, body fat, glucose, and cholesterol levels. Also, reduced CRP level activates nitric oxide production and therefore results in oxidative stress (Yaghoobi et al. 2008). Nitric oxide controls blood pressure, vascular tone, suppresses platelet accumulation, leukocyte accrual, and preclusion of cell proliferation in smooth muscles thereby showing cardioprotection (Naseem 2005). NO is a vital molecule for vasodilation in blood vessels and is initiated by factors which include acetylcholine, shear stress, and cytokines via eNOS synthesis. NO phosphorylates various proteins which cause relaxation of smooth muscles playing a critical role in renal regulation of extracellular fluid homeostasis controlling blood pressure and flow (Naseem 2005; Yoon et al. 2000). Honey modulates cardiovascular risks through some flavonoids by alleviating oxidative stress and augmenting NO bioavailability. Likewise, NO production by rutin increases eNOS gene expression and its activity. Another molecule of honey, Naringin, impedes intercellular adhesion molecule-1 (ICAM-1) expression induced by hypercholesterolemia on endothelial cells. Other major honey flavonoids like catechin and quercetin inhibit aortic atherosclerotic lesions development and atherogenic alteration of LDL (Afroz et al.

2016a). Prophylactic treatment with honey against isoproterenol-induced myocardial infarction in Wistar rats replenished antioxidant armory-like superoxide dismutase, glutathione peroxidase, and glutathione reductase and cardiotoxicity serum toxicity enzymes like creatine kinase-MB, lactate dehydrogenase, aspartate transaminase, and alanine transaminase (Afroz et al. 2016b), thereby providing defense from deleterious effects by free lethal radicals (Khalil et al. 2015). Honey-ameliorated cardiac troponin I (cTnI), triglycerides (TG), total cholesterol (TC), and lipid peroxidation (LPO) and increased antioxidant armory in rat myocardial infraction model (Khalil et al. 2015). Some of the probable mechanisms of cardiovascular effects of honey have been illustrated in Fig. 10.7.

To summarize the cardioprotective mechanism of flavonoids is either by lessening blood platelets activity, preclusion of oxidation of LDLs, and enhancing coronary vasodilatation (Khalil and Sulaiman 2010). Ahmed et al. demonstrated reduction of blood platelets activity in vitro on platelet accumulation and clotting (Ahmed et al. 2011). As honey inhibits all three coagulation cascades and decreases fibrinogen levels. Hence, considered exceptional for thwarting atherosclerotic plaques process resulting in cardiac disorders. However, lipid peroxidation has been found to play an essential role in pathology of atherosclerotic plaques (Ahmed et al. 2011). Therefore, phenolic compounds in honey have prophylactic and mitigating role by counteracting lipid peroxidation (Makedou et al. 2012; Cianciosi et al. 2018).

10.10 Neuropharmacological Effects of Honey

Research demonstrates honey as a mysterious gel having protective effects against gastrointestinal tract, liver, heart, reproductive system as well as anticancer, antidiabetic, antioxidant, antihypertensive, antimicrobial, anti-inflammation, immune mediating, wound healing, cardioprotective, and antineoplastic activities (Manyi-Loh et al. 2011; Cantarelli et al. 2008a, b; Amy and Carlos 1996; Mandal and Jaganathan 2009). However, research on the nootropic and pharmacological effects of honey on brain is rare. Nonetheless, ethno traditional and ancient belief is that honey is a memory-boosting food like Brahma rasayan, an Ayurvedic preparation believed to improve the life span and enhance remembrance, intelligence, attentiveness, and physical strength (Mishra 2011). Honey is found to build and develop complete central nervous system, predominantly among newborns and preschool age children leading to the enhancement of retention and growth, lessening nervousness, and improving intellectual performance later in life (Cantarelli et al. 2008a, b). Besides, human brain also undergoes maturation and restructuring of some edifices like hippocampus and cerebral cortex. Neurogenesis happens after postnatal development occurring principally during childhood, but can encompass puberty through adulthood as per reports (Oyefuga et al. 2012). There was a striking evidence seen in postmenopausal women receiving honey-enhanced instant memory but not after meddling in immediate memory comparatively (Othman et al. 2011). Other report shows normal diet supplemented with honey fed to 2-month-old rats

were examined for their brain function over 1-year period. It was shown honey-fed rats had better spatial memory which was assessed by object recognition tasks and were less anxious during all stages and significantly greater during 9 and 12 months compared to control rats (i.e., 9 and 12) (Chepulis et al. 2009). There was concomitant growth of superoxide dismutase (SOD) and glutathione reductase activity reduction of lipid peroxidation in brain tissue of rats supplemented for short- and long term with honey at a dose of 250 mg/kg body weight as reported previously deciphering role of honey as an anti-oxidative agent (Oyefuga et al. 2012). Additionally, hippocampal CA1 region is susceptible to oxidative stress by diminishing the amount of degenerated neuronal cells, which is prevented due to honey consumption (Cai et al. 2011). Neurodegenerative diseases like Alzheimer's disease (AD), mild cognitive impairment, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) have been accompanied by oxidative stress (Oyekunle et al. 2010). Oyekunle et al. conducted study for the first time that honey has neuropharmacological effect and is used as a nutraceutical in which rats were fed with diverse concentrations of honey (10, 20, and 40%) at a dose of 0.5 mL/100 g was found to significantly increase exploratory activities in a hole board test and locomotion, rearing, and grooming activities in an open-field test dose-dependently as compared to control group rats. The above-mentioned results demonstrate that honey consumption alleviates anxiety and causes excitation on the central nervous system even at largely nonsedative dose (Oyekunle et al. 2010). Another study reports the assessment of neurological activities of honey by measuring three-dimensional working memory either by Y-maze test or hypnosis induced by pentobarbital and its evaluation or using hole board and elevated plus maze tests to check anti-anxiolytic activities, or picrotoxin induced seizure model to calculate its convulsant potential or using hot plate and tail-flick tests to check nociceptive effect and forced swimming test is done to evaluate antidepressant effect. It was found out that honey has anti-anxiolytic, antinociceptive, anticonvulsant, and antidepressant potential and is used as a functional food (Akanmu et al. 2011). Neuropharmacological effects of honey provide insights to highlight the neurological features that are modulated by honey treatment. Excitatory neural systems like cholinergic and dopaminergic neurons are responsible for exploratory behaviors, while inhibitory neurons like γ-aminobutyric acid (GABA) are involved in anxious behavior (Ballenger 1999; Lamprea et al. 2003; Patel et al. 2012). Dopaminergic and nonopioid receptor binding involves voltage-gated sodium channel inhibition, instigation of the noradrenergic inhibitory system and/or serotonergic systems, and the GABAergic systems are some neuropharmacological mechanisms which are mediated by honey as experimental evidence supports (Oyekunle et al. 2010; Akanmu et al. 2011; Ballenger 1999; Lamprea et al. 2003; Patel et al. 2012; Young and Gauthier 1981). Besides neural effects, honey also shows neuroprotective effect in the cerebral focal ischemia model in rats through glial cells (Zárraga-Galindo et al. 2011). Likewise, ischemia-induced neuroinflammation was attenuated by honey via triggering microglia, and neuroinflammation is responsible for the growth of neurodegenerative diseases and neuronal injury linked with stroke (Frank-Cannon et al. 2009; Carson et al. 2006). Remarkably, cognitive losses

induced by ischemia due to neuroinflammation induced by microglia and/or astrocyte were downregulated by honey therapy (Akanmu et al. 2009).

10.11 Conclusion

Honey is an organic compound having proteins, enzymes, carbohydrates, amino acids, essential minerals, vitamins, and phytochemicals like phenolic acids and flavonoids that hold exciting pharmacological activities at in vitro and in vivo. Depending on geographical location, floral type, physical location, environment around, various bee species around, and then post collection processing and storage conditions define the elemental, phytochemical constituents, taste, and color of honey. So different types of honey are effective to inhibit malignant cell transformation via mitigating numerous signaling pathways, which include induction of apoptosis, anti-inflammatory pathway, redox signaling pathway, metastasis, and many more. It also diminishes the plasma level of fructosamine, glycosylated hemoglobin, and glucose in diabetes mellitus patients and attenuates numerous risk factors of cardiovascular disease, and benefits the nervous system as well. On the other hand, it is important to consider that it may contain some toxic compounds that should be avoided mainly in childhood. A deeper understanding of the factors and the mechanisms of honey effect will be of crucial importance to promote the consumption of this healthy food in the general population, to promote a healthy lifestyle, and to prevent the most common pathologies.

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