Polyphenols and Flavonoids from Honey: A Special Focus on Diabetes

Visweswara Rao Pasupuleti and Chandra Sekhar Arigela

Abstract Honey is a matrix of vegetal origin processed by various types of bees. Besides physical properties honey constitutes of several minor chemical constituents such as polyphenols and flavonoids. Phenolic compounds or polyphenols are basically products of the secondary metabolism of plants and so a major group of compounds occurring in honey. The colour intensity of honey defines the percentage of polyphenols present in it. The polyphenols are classified into different types of groups due to the presence of a number of phenol rings and their binding capacity to the structural elements. Phenolic acids and flavonoids are the main classes of the polyphenols. Flavonoids may be categorized into several types including flavonols, flavanones, flavones, anthocyanidins and isoflavones due to their dietary significance. The phenolic compounds show a great extent of biological activities such as antioxidant, antimicrobial, anti-diabetic, anticancer and so on. Honey is one of the natural products which helps in decreasing oxidative stress by cleaning up the oxygen free radicals and also decreases blood sugar level. The rise in reactive oxygen species production depends on various factors. One of the factors is the glucose absorption by muscle cells and adipose tissue which contributes to oxidative stress and, thereby, rise in glycogen synthesis and glucose uptake by cells. Insulin resistance is also one of the important aspects that occur through oxidative stress by disturbing the insulin pathway. The honey found to have the mechanistic properties that ameliorate the damages occurred in diabetic condition and thereby provide benefits to the human beings. This chapter clearly sheds light on the action of polyphenols and flavonoids of honey for the human wellness especially on diabetes.

Keywords Honey · Polyphenols · Flavonoids · Anti-diabetic · Cancer · Biological activity

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1 Introduction

The prevalence of chronic diseases including atherosclerosis, cancer, diabetes mellitus, hypertension and oxidative stress-related Alzheimer's is increasing and has become the main cause of death worldwide (Erejuwa et al. 2014). Oxidative stress is an imbalance between the production of extremely reactive molecules and antioxidant defences and causes structural and functional alterations to the proteins, lipids and nucleic acids which again lead to various types of biological problems including carcinogenesis, aging and atherosclerosis (Droge 2002; Beckman and Ames 1998). Therefore, exogenous antioxidants from diet can counteract the toxic effects of free radicals, reducing oxidative damage (Bach-Faig et al. 2011). Indeed, many epidemiological studies indicate that a polyphenol-rich diet is often associated with a reduced prevalence of several chronic pathologies, such as obesity, infections, cardiovascular and neurological illnesses and cancer (Chu et al. 2002). Honey has been used in the long human tradition not only as an alternative natural sugar but also as a drug for its medicinal properties; it has been used in many cultures, including as a remedy for burns, cataracts, ulcers and wound healing (Bogdanov et al. 2008). Only recently, scientific research focused on its attention on the therapeutic effects of honey particularly on its capacity to protect against cardiovascular diseases (Yaghoobi et al. 2008), cancer (Jaganathan and Mandal 2009) and microbial infections (Kwakman and Zaat 2012).

Honey is widely classified as nectar honey or blossom honey (those acquired from plant nectars) and honeydew honey (mainly insect Hemiptera sucking plant exudations from living plant components) (Bogdanov 1997). Furthermore, honeydew honey can also be described as a type of honey generated by crop sap-sucking insects as flower nectar aphids. Honey can also be grouped as mono- or multifloral honey that relies on pollen types. Pollen quantification is based on four methods such as the first one is Dominants pollen types (obtained from total pollen grains greater than 45%, %); the second one is major Secondary pollen types (16–45%); the third one is Minor pollen types (3–15%); and the fourth method is Minor pollen types (<3%). The honey is regarded as monofloral honey if it possessed a dominant type. If the honey is made up of other pollen types, it is grouped as multifloral honey (Feás et al. 2010). Honey includes enzymes like peroxidase, diastase, glucose oxidase, catalase and invertases. Honey also consists of other enzymes bioactive constituents such as ascorbic acid, vitamins, organic acids, amino acids, trace elements of proteins and Maillard reaction products (Song et al. 2012).

The flavour and fragrance just as the constituents of nectar relies upon the plant sources and climatic conditions. The primary part of nectar is dry load as sugars with fructose having most extreme constituent around 32–38% and then glucose in addition to other disaccharides and oligosaccharides; different constituents of nectar incorporate minerals, organic acids, various nutrients and proteins (Bogdanov et al. 2008; Rao et al. 2016; Solayman et al. 2016; Saba et al. 2013). There is also a fluctuating amount of basic minerals which are approximately 0.2% of its dry weight, which changes as indicated by its plant source, condition and preparing strategies.

The significant minerals in the honeys are calcium, magnesium, copper, manganese, potassium, phosphorus, iron, sodium, selenium and zinc. Honey is made out of little amounts of nutrients such as ascorbic acid (vitamin C), thiamine (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic corrosive (vitamin B5) and pyridoxine (vitamin B6) (Alvarez-Suarez et al. 2013). Most of complex B is chiefly from pollen and together with ascorbic acid. Different processes including filtration and oxidation processes may influence the honey carried out by glucose oxidase (Ciulu et al. 2011). The proteins of honey are mainly made up of enzymes which are derived from the pollen, nectar and bees. The major enzymes present are diastases, glucose oxidases and invertases. Diastases which are also considered as amylolytic enzymes include α-amylases that are liable for the hydrolysis of the starch chains. The hydrolysis of the starch chains leads to the production of β-amylases and dextrin which are responsible for maltose formation, which is one of the vital factors of honey quality. The second important enzyme present in honey is glucose oxidase which breaks down the glucose into two different products which are gluconic acid and also hydrogen peroxide (H2O2), which is accountable for honey's antimicrobial activity. The invertase can hydrolyse sucrose in glucose and fructose (White 1980). As per the recent predictions, by 2022 the global honey market will reach 2.4 million tons (White and Doner 1980). Turkey, Mexico, the United States, Argentina and China are the main makers of honey.

Phenolic Compounds: Polyphenols are a specific class of chemical compounds which are divided into (a) flavonoids and (b) phenolic acids.

These are secondary plant metabolites which differ from primary and these compounds are characterized by the presence of multiple phenolic groups which are represented by complex structures. Floral origin generally describes the structure of phenols and this can be used as authentication and also classification instrument, particularly in the event of unifloral varieties. Table 1 shows the most prevalent flavonoids and phenolic compounds available in honey (Chan et al. 2013; Kečkeš et al. 2013; Campone et al. 2014; Ranneh et al. 2018; Petretto et al. 2015; Hamdy et al. 2009; Kuś et al. 2016; Ferreres et al. 1994; Campillo et al. 2015; Arráez-Román et al. 2006; Akalın et al. 2017).

Flavonoids are low molecular weight water-soluble natural chemical compounds. These compounds usually indicate at least two phenolic groups (OH), associated with sugars (glycosides), primarily xylose, galactose, rhamnose, arabinose, rutinoside and glucorhamnose; flavonoids are defined as aflycones when they are not associated with sugars. The flavonoids are then classified according to the degree of oxidation of the C ring in flavanols, flavones, flavanonols, flavonols, flavanones, isoflavones, anthocyanins and anthocyanidins. Flavones, flavanols and flavonols are the most abundant in honey (Moniruzzaman et al. 2014). Phenolic acids (phenol carboxylic acids) have a phenolic ring and at least one organic carboxylic acid function; they can be split by composition: C6-C3 (e.g. p-coumaric, ferulic and caffeic acid), C6-C2 (e.g. acetophenones and phenylacetic acids) and C6-C1 (e.g. syringic, vanillic and gallic acids). Most of these compounds are usually associated with the plant's structural elements (cellulose, lignin), but also with other kinds of organic molecules such as glucose, other sugars or flavonoids (Padayachee et al. 2012).

Table 1 The common flavonoids and phenolic compounds in honey (Cianciosi et al. 2018)

Flavonoids		
Apigenin	$C_{15}H_{10}O_5$	AH, TH, STH
Catechin	$C_{15}H_{14}O_6$	TH, PH
Chrysin	$C_{15}H_{10}O_4$	MH, AH, TH, HH, THH, RH H
Galangin	$C_{15}H_{10}O_5$	MH, AH, STH, H
Genistein	$C_{15}H_{10}O_5$	AH
Isorhamnetin	$C_{16}H_{12}O_7$	MH
Kaempferol	$C_{15}H_{10}O_6$	MH, AH, TH, STH, THH, RH
Luteolin	$C_{15}H_{10}O_6$	MH, AH, TH, STH, THH, RH
Myricetin	$C_{15}H_{10}O_8$	AH, HH, THH
Pinobanksin	$C_{15}H_{12}O_5$	MH, AH, STH, RH
Pinocembrin	$C_{15}H_{12}O_4$	MH, AH, STH, RH
Quercetin	$C1_5H_{10}O_7$	MH, AH, CH, THH
Rutin	$C_{27}H_{30}O_{16}$	STH
Phenolic acids		
2-*cis*,4-*trans*-Abscisic acid	$C_{15}H_{20}O_4$	STH
2-Hydroxycinnamic acid	$C_9H_8O_3$	TH
Caffeic acid	$C_9H_8O_4$	MH, AH, TH, THH
Chlorogenic acid	$C_{16}H_{18}O_9$	AH, HH, THH
Cinnamic acid	$C_9H_8O_2$	TH, STH, CH, HH, THH
Ellagic acid	$C_{14}H_6O_8$	HH
Ferulic acid	$C_{10}H_{10}O_4$	MH, AH, HH, THH
Gallic acid	$C_7H_6O_5$	MH, AH, TH, HH, THH, PH
p-Coumaric acid	$C_9H_8O_3$	MH, AH, TH, HH, THH, RH, PH
p-Hydroxybenzoic acid	$C_7H_6O_3$	CH, HH
Protocatechuic acid	$C_7H_6O_4$	HH, PH
Sinapic acid	$C_{11}H_{12}O_5$	HH
Syringic acid	$C_9H_{10}O_5$	MH, AH, TH, STH, HH, THH
Vanillic acid	$C_8H_8O_4$	AH, HH

MH Manuka honey, *AH* acacia honey, *TH* tualang honey, *STH* strawberry tree honey, *CH* clover honey, *HH* heather honey, *THH* thyme honey, *RH* rosemary honey, *PH* pine honey

1.1 Bioavailability and Metabolism of Honey Polyphenols

Polyphenols in honey play an important role in health beneficiary effects. Currently there are very few studies on bioavailability of honey polyphenols in humans and hence the mechanism of action of honeys has become vital.

A research revealed that after consumption of 1.5 g of honey/kg body weight of two kinds of honey in 40 tropics, the total phenolic plasma content ($P < 0.05$) similar to antioxidant and reduced plasma capacity ($P < 0.05$) (Schramm et al. 2003) endorsed the idea that phenolic honey antioxidants are bioavailable and boost plasma antioxidant activity by enhancing the defence against oxidant stress. While

the honey used in this study is supplied with 4-hydroxybenzoic and 4-hydroxycinnamic acids per kg of body weight, HPLC assessment could not verify the plasma concentration of these acids. According to the authors, this could be due to (i) the absorption of less than one-third of these compounds, (ii) the rapid distribution of these compounds into non-plasma body compartments or (iii) the first pass metabolism of the monophenols in the human body.

The absorption of flavonoids, however, appears to be much more complicated, mainly owing to their chemical properties. The existing literature indicates that not only the bacterial enzymes in the intestine (Day et al. 1998) are accountable for beta-hydrolysis of sugar molecules in the flavonoids of O-glycosides. Two endoglycosidases are capable of flavonoid glycoside hydrolysis were also defined in the small intestine of humans, namely, lactase-phlorizin hydrolase (LPH) acting as an alternative hydrolysis step within the epithelial cells of the small intestine (Spencer et al. 1999) and cytosolic glucosidase (CBG) as an alternative hydrolysis in the epithelial cells (Sugihara et al. 1999). LPH has a wide substrate specificity for flavonoid-O-D-glucosides and the released aglycone can then enter the epithelial cells due to its enhanced lipophilicity and closeness to the cell membrane (Day et al. 2000). It was also suggested that for the occurrence of CBG-catalysed hydrolysis, the polar glycosides should be transferred to the epithelial cells, potentially with the participation of the active sodium-dependent glucose transporter 1 (SGLT1) (Gee et al. 2000). Bioavailability and pharmacokinetics studies have shown that some flavonoids can inhibit non-Na + −dependent monosaccharide diffusion in intestinal epithelial cells (Kimmich and Randles 1978). This benefits for monosaccharaides the parallel concentrative Na + −dependent ATPase transport (Sharma et al. 1981). Therefore, the two possible routes by which the glycoside conjugates are hydrolysed and the resultant aglycones cross into enterocytes are LPH/diffusion and transport/CBG (Del Rio et al. 2013). Therefore, LPH/diffusion and transport/CBG are the two possible paths through which the glycoside conjugates are hydrolysed and the resulting aglycones pass into enterocytes (Del Rio et al. 2013). In the case of honey, the presence of the glycosidase enzyme in the bee salivary glands (Sabatier et al. 1992) should also be added producing a hydrolysis of the glycosylated flavonoids and releasing the aglycon form. This partly illustrates the fact that, unlike other phenolics found in foods or drinks, flavonoids in honey were recognized mostly as aglycons and not in their glycosylated form. Phenolic aglycons are more readily absorbed through the gut barrier than their corresponding glycosides by passive diffusion (Scalbert and Williamson 2000) and, therefore, flavonoids present in honey may be more readily bioavailable.

Established Biological Roles of Polyphenols: Oxidative stress from reactive oxygen and nitrogen species has been a cause of many diseases. Antioxidant activities of fruits are due to the phytochemicals such as polyphenols rather than vitamin c and also flavanol constituents with highly conjugated systems in phytochemicals and their hydroxylation products such as the 3-hydroxy groups in flavanols are considered important to exhibit the antioxidant activities either as free radical scavengers or metal chelators (Wang et al. 1996).

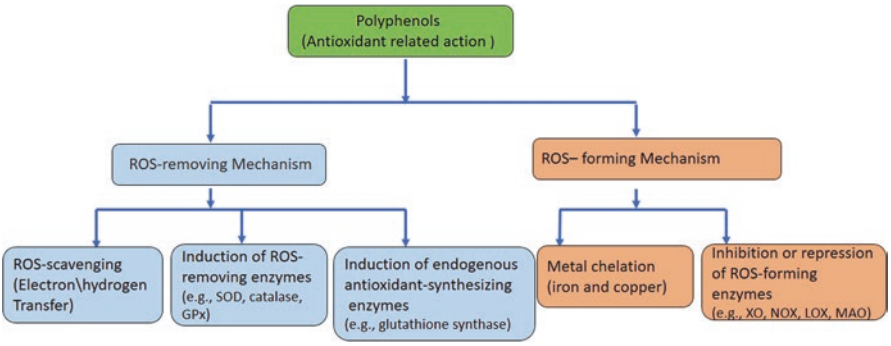

Fig. 1 Antioxidant action of polyphenols from honey (ROS removing and ROS forming mechanisms)

Polyphenols can act as antioxidants via two major modes of action:

(a) ROS removing stage (Fig. 1) consists of a ROS scavenging system, primarily owing to the existence of benzene ring-bound hydroxyl groups capable of donating either one hydrogen atom or one electron to the ROS, thus stabilizing the reactive species (Bors et al. 1990). This mechanism also helps with free radicals like hydroxyl (HO-), superoxide (02-), nitric oxide (NO-) and alkoxyl and peroxyl radicals and non-radicals like peroxynitrite (OONO-) and hypochlorite (ClO-) (Bors et al. 1990). As a result, a polyphenol radical phenoxyl is produced and a stable quinone structure is created after reaction with a second radical (Amic et al. 2007).
(b) ROS formation mechanism: The ROS formation mechanism usually inhibits the production of free radicals which are metal dependant such as superoxide and hydroxyl as well as enzymes producing ROS owing to their direct inhibitory action of polyphenols. It is a systematic process starting with the superoxide dismutase.

ROS-removing enzymes including superoxide dismutase (SOD), catalase (reduction of hydrogen peroxide), glutathione peroxidase (reduction of hydrogen peroxide and lipid hydroperoxide) and endogenous regenerating enzymes such as glutathione reductase (reduction of oxidized glutathione) and also the thioredoxin reductase (reduction of oxidized thioredoxin) play an important role in the antioxidant activity. A well-known mechanism by which polyphenols could be applied to in vitro antioxidant action relates to the capacity of some of these compounds to up-regulate the signalling pathway through activation of Keap1/Nrf2/ARE (Kelch ECH-associated protein 1/NF-E2-associated factor 2/antioxidant reaction elements). Similarly, some polyphenols can stimulate certain stage I and phase II enzymes through the Nrf2 pathway that are involved in the detoxification of xenobiotics (possibly pro-oxidant) (Tsuji et al. 2013). The increase in the activity of all these enzymes follows an NRf2-mediated increase in the expression of their respective coding genes. Cells comprise an amount of endogenously synthesized antioxidant

molecules, such as glutathione (GSH) dihydrolipoic acid and ubiquinol, in addition to the above-mentioned ROS-removing enzymes. Among these, the capacity of polyphenols such as quercetin, kaempferol or apigenin to improve the transcription of the gene coding for glutamate cysteine ligase through the Keap1/Nrf2/ARE pathway for elevating the intracellular levels of this thiol has been documented (Sandoval-Acuna et al. 2014).

2 Actions Promoted at the ROS Formation Level Metal Chelation

In addition to the significant known enzymatic sources of superoxide generation (e.g. membrane-bound NOX, cytosolic xanthine oxidase (XO) and I, II and III mitochondrial complexes), redox-active transition metals such as copper and iron can catalyse to form hydroxyl radicals. The free response of iron in mitochondria may happen under circumstances that lead to increased superoxide output. For example, neurotoxins used to generate experimental PD models during the mitochondrial dysfunction of dopaminergic neurons in Parkinson's illness (PD) or those caused by MPP+ or rotenone. In specific the [4Fe–4S] cluster-containing enzymes aconitase (one cluster) and NADH-ubiquinone dehydrogenase (eight clusters) are affected by an intramitochondrial release of iron mediated by superoxide. Some flavonoids (e.g. baicalein, quercetin, myricetin) and some non-flavonoids (e.g. gallic, 2,3-dydroxybenzoic and protocatechuic acids) are particularly involved in chelating iron and copper ions, making them inactive to engage in free radical reactions. The SAR tests of iron-related polyphenols were usually produced for compounds containing catechol and pyrogallol. In the case of flavonoids in specific, it has been suggested that some molecular elements are prevalent and significant to their metal-chelating properties (Serrano et al. 2016) despite the big variations in the metal-chelating ability of various congeners. However, the metal-chelating property of a specified polyphenol becomes important in terms of its antioxidant capacity only if the latter becomes redox inactive in addition to the sequestration of a specified metal. Otherwise, the shaped metal-flavonoid complex could catalyse the development of free radicals, thus acting as a pro-oxidant.

Total evaluation of antioxidant activities of polyphenols is an outcome of the experimental model system. They have helped to comprehend how polyphenols work as antioxidants and play a crucial part in the human system with confined techniques according to studies. Both the advantages and disadvantages of the experimental in vitro chemical antioxidant animal models were discussed evidently and compared for suitability (Prior et al. 2005).

Future polyphenol study is moving in the same direction. Polyphenols are thought to be powerful antioxidants and defences against oxidative stress induced by excessive reactive oxygen species (ROS) produced in vitro after a progressive disease with antioxidant vitamins and enzymes.

3 Anti-diabetic Properties of Honey and Their Molecular Functions

Diabetes mellitus is one of the complex syndromes that has affected around 424.9 million world population in 2017 (https://www.escardio.org/Sub-specialty-communities/European-Association-of-Preventive-Cardiology-(EAPC)/News/global-statistics-on-diabetes). It is characterized by insulin insensitivity causing rise in the blood glucose level. This chronic non-communicable disease also affects the other organs of the body such as heart, eyes, kidneys and majorly the tissue repair process contributing to 10% of adult mortality (Hillage 2010). Acute complications in this disorder may include hyperosmolar, diabetic ketoacidosis and hyperglycaemic state, which may lead to death (Kitabchi et al. 2009). Many studies have supported the anti-diabetic and the hypoglycaemic capacity of honey because of its antioxidant ability. Oxidative stress is closely related to pathogenesis of diabetes developing ROS in various organs and tissues (Folli et al. 2011). The reason is increase of glucose absorption by adipose tissue and muscles resulting in ROS and hence oxidative stress mechanism that affects the synthesis of glycogen and glucose uptake (Fig. 2). Insulin resistance is due to alteration in the insulin signalling pathway caused due to oxidative stress. Honey helps in restoring the glycogen pathway and increases the pancreatic oxidative stress (Erejuwa et al. 2010a).

Research has reported that the honey is a potential diabetic agent due to certain clinical trials on animal models. The range of concentrations tested (0.2, 1.2 and 2.4 g/kg/day body weight) resulted in improved antioxidant effect exerting a hypoglycaemic in streptozotocin-induced diabetic rats (Omotayo et al. 2010). Similarly, glucose level in type 2 diabetes mellitus was also seen reduced when 60% (W/V)

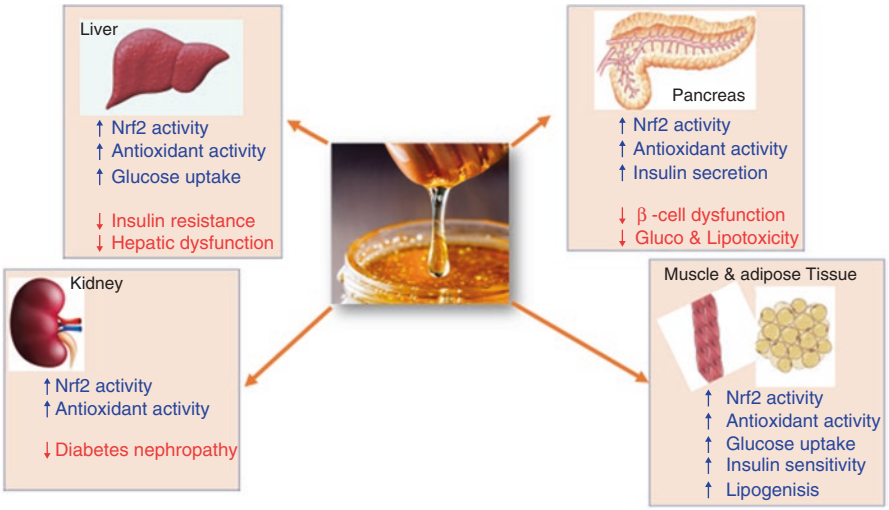

Fig. 2 Effects of honey on various types of tissues including liver, pancreas, kidney, muscle and adipose tissues

honey was administered by inhalation (Al-Waili 2003). The presence of fructose describes the anti-diabetic or hypoglycaemic effect of honey (Erejuwa et al. 2012). Fructose assists to regulate the insulin-response system, resulting in controlled blood glucose level; the main sugars present in honey responsible for glycaemic control are glucose and fructose. Fructose as also shown decreases in the level of hyperglycaemia when tried on various models in diabetic research (Vaisman et al. 2006; Kwon et al. 2008). Evidence suggests that fructose controls blood sugar levels by slowing digestion (Moran and McHugh 1981), prolonging gastric emptying and slowing down the rate of intestinal absorption (Kellett et al. 2008). Glucose is the second major sugar constituent in honey after fructose. Intestinal absorption of fructose is improved in the presence of glucose (Jones et al. 2010) due to a significant collaboration between these molecules which actively influence their absorption. Fructose and glucose have different transporters, GLUT5 (and/or GLUT2) and SGLT1, respectively (Wright et al. 2007). The recruitment of GLUT2 carrier to the brush border membrane caused by increased intestinal fructose may contribute to the synergistic effect of glucose on the absorption of fructose (Jones et al. 2010).

The transport of two sodium ions and one glucose molecule takes place in the brush border membrane of the enterocyte which is responsible for absorption of glucose and fructose. The energy produced by sodium electrochemical potential gradient across the brush border membrane is used to facilitate the glucose accumulation inside of enterocyte against its concentration gradient. Na/K pump in the basolateral membrane helps in the transportation of sodium ion along with glucose, hence maintaining the driving force of glucose transport.

A driving force to transport glucose from cells into the blood via GLUT2 is the accumulation of sugar into enterocytes. A part of the intracellular glucose seems to be taken up into endosomes, as glucose-6-phosphate, and then released into the blood by exocytosis through the basolateral membrane (Uldry and Thorens 2004). Otherwise, after ingestion of fructose, unlike glucose, an increase in the expression levels of GLUT5 mRNA was found (Miyamoto et al. 1993); studies have also stated that there may be a disaccharide-related transport system which considers both fructose and glucose production from the enzymatic hydrolysis of sucrose (Riby et al. 1993). Other evidence suggests that fructose is absorbed via a carrier in the absence of glucose, while in the presence of glucose, fructose is absorbed via a disaccharide-related transport system (Riby et al. 1993). Besides this, passive diffusion across the intestinal epithelium has also been proposed as a possible mechanism (Riby et al. 1993). Studies have shown that glucose improves the transportation and absorption of fructose but not vice versa, increasing the amounts of fructose that reach the liver. According to the results of the investigations exposed above, the potential role of honey against diabetes mellitus is at an early stage, where more specific researches are needed to understand the mechanisms by which it can exert its hypoglycaemic action. Even if these studies are still scarce, they have shown that honey is preferable to the most common sugars or sweeteners, because it is more tolerable both in healthy subjects and in patients with diabetes mellitus.

A particular hypoglycaemic function of the fructose in the liver can also regulate glucose levels. Fructose stimulates phosphorylation enzymes, such as glucokinase,

hepatic glucose phosphorylation (Van Schaftingen and Davies 1991). Glycogenolysis is inhibited by the inhibition of these enzymes. Therefore, fructose is regulated throughout the whole metabolism of glycogen and glucose, which show its essential regulatory function for the control of hyperglycaemia (Youn et al. 1987). Another suggested mechanism illustrates that the impact of honey on hypoglycaemic effect can be caused by the role of honey in modulating the pathway for insulin signalling pathway (Batumalaie et al. 2013). The PI3 K/Akt (Ferreres et al. 1994) is a major element in the signals of insulin. It is renowned for its role in multiple substrates modulating features that control cell cycle development, cell survival and cell development. Honey extracts have been recently explored in the pancreas under the hyperglycaemic condition for Akt-activated insulin signalling pathway. Increased levels of NF-kB, MAPK and the serine acid receptor substrate 1 (IRS-1) were found to characterize the development of insulin resistance (Fig. 3). The expression of the Akt and the contents of insulin have been significantly decreased. This research has shown that honey and quercetin extract pretreatment increases insulin resistance and insulin levels. Honey treatments enhance Akt expression and decreased IRS-1 phosphorylation, NF-kB and MAPK expression (Vincent et al. 2013).

Stingless bee honey (SLBH) showed hypoglycaemic effect in partial insulin deficiency rats caused by the combined administration of STZ-nicotinamide, was reported by Aziz et al. (2017). Rats treated 1.0 and 2.0 g/kg bw/day with SLBH for 28 days have shown a significant reduction of fasting blood sugars (FBS) in the amount of the untreated diabetic rats due to a substantial increase in serum insulin level. In the immunohistochemical assessment analysis also considerably improves the expression of catalase antioxidant enzyme (CAT), reducing oxidative stress in pancreas and promoting pancreatic healing (Arráez-Román et al. 2006). SLBH assessment by means of liquid chromatographic mass spectrometry, which was shown to be accountable for stimulating insulin release and improving glucose tolerance in diabetic rats, showed L-phenylalanine in honey (Aziz et al. 2017).

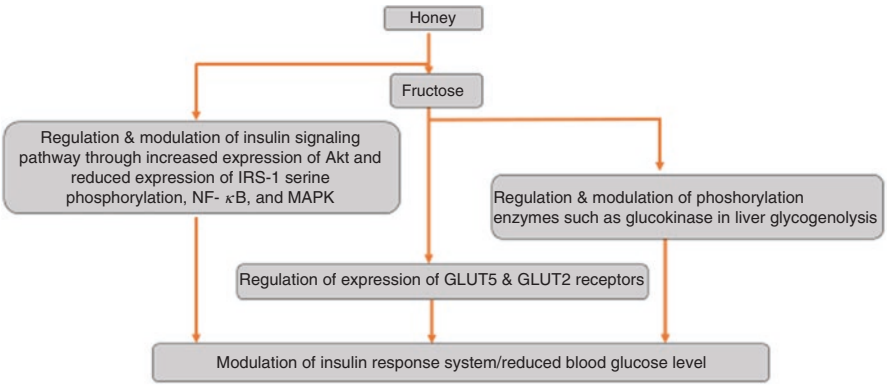

Fig. 3 Mechanisms of anti-diabetic effects of honey. MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor kappa B; Akt = altered PI3 kinase; IRS-1 = insulin receptor substrate 1

Tualang honey (TH) is Malaysian multifloral jungle honey made from *Apis* (or rocky bees), found mainly in the tropical rainforest in hives built in the high branches of *Koompassia excelsa* (known locally as tualang tree) (Ahmed and Othman 2013). The impact of TH on the pancreas of diabetic rats induced by the STZ has been researched. An important down-regulation of pancreas superoxide dismutase (SOD) and MDA ($p > 0.01$) with high pancreas CAT activity ($p < 0.04$) in comparison to diabetic controlling rats was observed with TH (1.0 g/kg/day) provided in diabetic rats over 28 days. The antioxidant effects of TH shielded oxidative damage in the pancreas of diabetic rats, resulting in a substantial enhancement of FBS in diabetic rats compared to diabetic (median (IQR) control: 8.8 (5.8) and 17.9 (2.6) mmol/L) (Erejuwa et al. 2010b). Other types of honey, such as Nigerian honey, also exert a similar hypoglycaemic effect. When given to alloxan-induced diabetic rats for 21 days with a dose of 1.0 and 2.0 g/kg/day, diabetic rats fed with honey had significantly reduced FBS compared with the diabetic control ($p < 0.05$) (Erejuwa et al. 2016). Shorter duration of honey supplementation for a period of 7 days to alloxan-induced diabetic rats also reported a similar trend although the results were not statistically significant (alloxan + honey vs. alloxan alone; FBS mean ± SD; 8.44 ± 1.66 vs. 11.05 ± 2.11 mmol/L, respectively; 2-h postprandial glucose level: 11.57 ± 2.22 vs. 16.45 ± 3.11 mmol/L, respectively) (Bilkisu et al. 2011).

Due to the inherently small expressions and operations of free radical enzymes, the pancreas β-cells are extremely susceptible to oxidative stress (Grankvist et al. 1981). It is well known that antioxidants have a positive impact in defending the pancreas against oxidative stress and harm (Palsamy and Subramanian 2010). We have demonstrated that honey can safeguard the pancreas from oxidative stress and damage. Honey add-ons considerably lowered high MDA concentrations and restored SOD and CAT operations in diabetic rat pancreas (Erejuwa et al. 2010b). The impact on oxidative stress in diabetic rat pancreas was explored and contrasted with that of glibenclamide and honey alone (Erejuwa et al. 2011). The information show that the oxidative stress in the pancreas of diabetic rats was not improved by glibenclamide. In comparison, glibenclamide-honey combined pancreas of diabetic rats has improved CAT activity and restored (Erejuwa et al. 2011) the high concentrations of plasma glucose, and glycosylated haemoglobin was shown to be decreased by antioxidants (Palsamy and Subramanian 2010). Honey supplementation decreased hyperglycaemia in STZ-induced diabetic Sprague-Dawley rats (Erejuwa et al. 2009).

3.1 Anti-diabetic Properties of Flavonoid Compounds and Their Molecular Functions

Honey flavonoids and their action into various biological activities are represented in Fig. 4. The significant bioactive flavonoid in berry is expected to be quercetin and its derivatives to activate MPPA and promote glucose uptake in muscle cells.

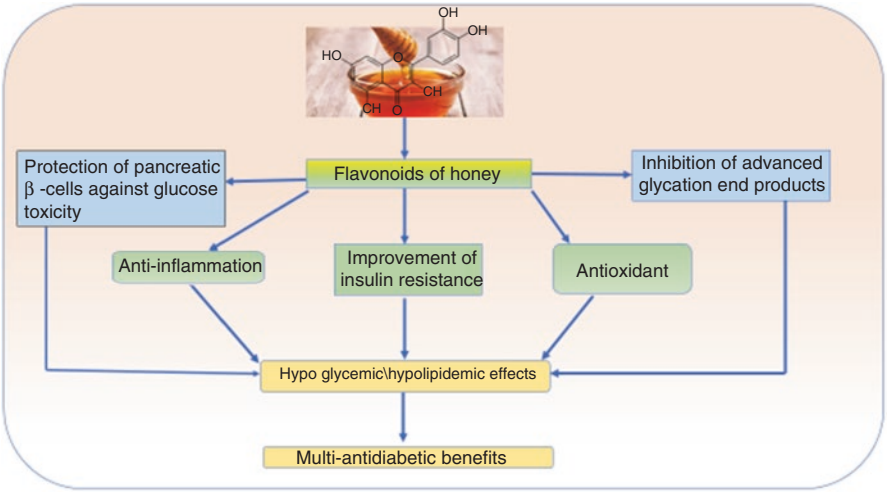

Fig. 4 Schematic representation of anti-diabetic properties of honey flavonoids

Quercetin's anti-diabetic impact has been studied also in streptozotocin (STZ)-caused diabetic mice. Quercetin drug treatment has reduced GLUT 4 and glucokinase stimulation, enhanced liver glucose absorption and reduced gluconeogenesis and hepatic glycogenolysis (Xu et al. 2014). Quercetin injection in STZ-induced diabetic rats resulted to lower hyperglycaemia and increased glucose tolerance, increased activity in hepatic glucokinase activity and reduced plasma cholesterol and triglycerides (Vessal et al. 2003). Both quercetin and the derivative glycoside enhanced glucose-stimulated insulin secretion by controlling NF-kB and ERK 1/2 to protect cells and clonal pancreatic β-cells from oxidative stress. Combined, quercetin is a biomolecule which is efficient to inhibit the digestion of intestinal starch and liver glucose by increasing the absorption of glucose in the skeletal muscle and protecting the islet from pancreatic damage.

Quercetin, apigenin and luteolin inhibited pancreatic β-cell damage caused by cytokine by inhibiting the activation of the nuclear factor kappa B in RINmF5 cells (Kim et al. 2007). Quercetin showed protective impacts by reducing oxidative stress with the protection of streptozotocin (STZ)-induced pancreatic β-cell integrity in rats (Coskun et al. 2005). Isolated rat islets subjected to epicatechin (0.8 mmol/L) or quercetin (0.01 mmol/L) showed increased insulin secretion in the presence of 20 mmol/L glucose by roughly 44%–70% (Hii and Howell 1985).

Through phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3 K) and mitogen-activated protein kinase (MAPK) pathways, rutin was shown to impact glucose uptake in the rat soleus muscle (Kappel et al. 2013). Plasma glucose, haemoglobin A1C (HbA1c, a glycated (beta-N-1-deoxy fructosyl) haemoglobin) and cytokines, including IL-6 and TNF-α, were also reported to decrease rutin. In the STZ-treated diabetic rats fed high-fat diet (HFD/STZ) the flavonoid also resulted in the reestablishment of antioxidant and serum lipid profile (Niture et al. 2014).

In another research, oral isorhamnetin administration did not only substantially inhibit the levels of serum glucose but also decreased the accumulation of sorbitol in STZ-induced red blood cells, lenses and sciatic nerves (Lee et al. 2005). Recent research shows that isorhamnetin glycosides have anti-diabetic action to reduce endoplasmic reticular stress markers and lipid metabolism (An et al. 2011).

Kaempferol obtained from the leaves of *Bauhinia forficata* lowered hyperglycaemia and increased glucose absorption in the rat soleus muscle similar to insulin (Jorge et al. 2004). In vitro outcomes show that kaempferol treatment (10 μM) promotes continued cell viability in β-cells and human islets subjected to hyperglycaemic circumstances, repressed cell apoptosis and decreased caspase 3 activities. These defensive impacts were linked to improved anti-apoptotic AKT expressions (also called protein kinase B (PKB) or Bcl-2), enhanced cAMP signalling and improved insulin secretion and synthesis in ß-cells (Zhang et al. 2011). In addition, the PI3 K and protein kinase C (PKC) pathways and the fresh glucose transducer synthesis in rat soleus muscles stimulated kaempferol. In addition, kaempferol also decreased both TNF-α and IL-1β expression and lipid peroxidation, leading to improved body weight and antioxidation of diabetic rats (Al-Numair et al. 2015). Blood glucose and serum HbA1c concentrations reduced significantly and an enhanced insulin resistance (Coskun et al. 2005) was administered orally with kaempferol. An assessment of the gene expression showed that in liver cells kaempferol reduced the expression of PPAR-β and SREBP-1c. Kaempferol was controlled by SREBP-1c and PPAR-β modulation through AMPK activation for anti-obese and anti-diabetic characteristics (Zhang and Liu 2011).

The glucose-insulin index was decreased by myricetin injected intravenously into genetically obese diabetic rats. Myricetin therapy resulted in an enhanced expression to GLUT4 (Erejuwa et al. 2012; Vaisman et al. 2006) and reduced AKT and insulin receptor substrate phosphorylation 1 (IRS1) (Tzeng et al. 2011). The activity of the synthase I hepatic glucose glycogen and 6-phosphate has also been stimulated by myricetin and adipocytic glucose uptake in rats and an enhanced lipogenesis influenced by elevated insulin levels (Ong and Khoo 1996).

3.2 Anti-diabetic Properties of Phenolic Compounds and Their Molecular Functions

Non-flavonoid phenolics comprise constitutive carbon frameworks, including hydroxycinnamic (C6C3) and hydroxybenzoic (C6C1). Phenolics are well-known compounds with potential antimicrobial activity and, however, their dietary values and anti-diabetic effectiveness have also been examined. Anti-inflammatory activities in various T2DM models were discovered to be associated with decreasing production of IL-1β, IL-8, MCP-1 and COX-2 or iNOS. Some phenolics, like retinopathy, cardiopathy and nephropathy, were also reported to prevent secondary T2DM complication.

Phenolic Acids This class of compounds includes the derivatives of benzoic acid. Hydroxybenzoic acid, cinnamic acid, gallic acid, ellagic acids, caffeic acid, ferulic acid and p- coumaric acids are major compounds of this class. 4-Hydroxybenzoic acid was found to increase peripheral consumption and, therefore, decreased the plasma glucose levels without affecting serum insulin and liver glycogen contents. Hydroxycinnamic acid derivatives, i.e. cinnamic acid (PubChem CID: 637542), p-coumaric acid (PubChem CID: 637542), caffeic acid (PubChem CID: 689043), ferulic acid (PubChem CID: 445858), chlorogenic acid (PubChem CID: 1794427) and rosmarinic acid (PubChem CID: 5281792), possess potent antioxidant and anti-inflammatory properties. These derivatives have been reported to inhibit infiltration of macrophage and activation of NF-μB, reducing expression of type-1 (PAI-1) TNFα, MCP-1 and plasminogen activator inhibitor. These derivatives also prevent differentiation of adipocytes in experimental animals and decrease the lipid profile. Therefore, in diabetes, hyperlipidaemia and obesity, these derivatives are useful (Lau et al. 2013).

Cinnamic acid was also reported to inhibit HMG-CoA reductase and ACA T activities in high cholesterol-fed rats and, hence, reduced the TG and cholesterol levels. It was reported to stimulate the adiponectin secretion and AMPK phosphorylation and, therefore, improved the insulin sensitivity (Tedong et al. 2010). Cinnamic acid also reported to normalize the lipase and angiotensin-converting enzyme (ACE) in high-fat diet rats and increase the diameter of aorta and aortic arch and avoid vasoconstriction comparable to standard drug glibenclamide. Cinnamic acid derivative, i.e. hydroxycinnamic acid, was also reported to inhibit the PTP1B, a major negative regulator of insulin signalling pathway (Alam et al. 2016). Therefore, it exhibits anti-diabetic, anti-obesity and anti-hypertension properties.

Gallic acid (PubChem CID: 370) was reported to increase the expression and secretion of adiponectin by increasing the adipocyte differentiation. It was found to increase the expression of PPAR-γ target proteins and fatty acid binding protein-4. Gallic acid and its derivatives have been discovered to considerably decrease symptoms of depression and oxidative stress.

These findings suggest that gallic acid exerts anti-diabetic effects through adipocyte differentiation and scavenging the free radicals and peroxynitrite (Nayeem et al. 2016). Caffeic acid has been observed to modulate the expression of Nrf2 and thus cause the nuclear translocation of NF-kB and the downstream expression of endothelial adhesion molecule 1 and restore antioxidant concentrations by up-regulating Nrf2/EpRE in human endothelial cells subjected to glucose. It was also observed that caffeic acid affects the apoptosis pathway by down-regulating the expression of caspase enzymes and increasing the Bcl-2 phosphorylation in high glucose-treated cells (Oboh et al. 2015). Caffeic, chlorogenic, ferulic, p-coumaric and cinnamic acids were reported to inhibit triglyceride accumulation in Hepg2 cells and, therefore, useful to treat non-alcoholic fatty liver disease (Oboh et al. 2015). It has also been recorded that ferulic acid acts in the same way as caffeic acid and up-regulates the expression of Nrf2 and inhibits the expression of TNF-α and

IL-1β by inhibiting dose-dependent activation of NF-μB and preventing cell apoptosis and reducing oxidative stress. Ferulic acid treatment also increases the glucose uptake, insulin sensitivity and tolerance in T2DM animal models. It was found to decrease the activity of GS and GK and increase the activity of PEPCK and G-6Pase and restore the glucose levels in a similar fashion of metformin. Moreover, ferulic acid and feruloylated arabinoxylan mono−/oligosaccharides were reported to inhibit GLUT-2 expression by impairing the interaction between SREBP1c, HNF1α, HNF3β and GLUT2 gene promoter and modulate GLUT-4 activity. Ferulic acid was reported to have anti-diabetic properties and significantly reduced the glycated haemoglobin (HbA1c) and lipid peroxidation. It was reported to increase Na+/K + -ATPase levels in high glucose-treated rats and, hence, prevents T2DM. It was also reported to reduce oxidative stress by inhibiting protein carbonylation in GSH-depleted hepatocytes and can be used to inhibit or decrease glyoxal and methylglyoxal-induced hepatotoxicity (Ghosh et al. 2017). Overall, ferulic acid improves the sensitivity of insulin and hepatic glycogenesis and inhibits gluconeogenesis and oxidative stress to maintain homeostasis of glucose in T2DM.

P-Coumaric acid (PubChem CID: 637542) has been discovered to inhibit adipogenesis, GPDH activity and the expression of PPARγ, C/EBPα and leptin and upregulated the expression of adiponectin in 3 T3-L1 adipocytes. At the same time, it was reported to decrease the cholesterol and triglyceride levels in plasma. It was also reported to inhibit TNF-α-mediated increase in MCP-1, PAI-1 and ROS in adipocytes. Therefore, it increased the secretion of adiponectin and expression of SOD, GSH, GPx and GST in TNF-α-treated adipocytes. Moreover, LD50 was very high and therefore, an increased dose may increase the biological activates. However, its low intestinal absorption is a disadvantage in its utilization (Pei et al. 2016). Chlorogenic acid (PubChem CID: 1794427) had adverse connections with fasting blood glucose, haemoglobin glycated and C-reactive protein. As with other phenolics, it also decreases the activity of HMG-CoA reductase and improves plasma LPL activity, thus reducing plasma cholesterol and triglyceride levels. It was noted that by enhancing GLUT 4 translocation and AMPK and Akt phosphorylation (Meng et al. 2013), glucose transport in the skeletal muscle was stimulated similar to the anti-diabetic drug rosiglitazone.

4 Conclusion

Honey acts as a natural source of cure to many diseases. The medicinal features of polyphenols in honey also lead to antimicrobial, antioxidant and anti-diabetic properties and it stimulates the release of cytokines that help repair tissues in wound healing. Honey plays important part in food industry right from being as a natural sweetener to the food and preservation. Various scientific evidences suggest that the use of honey in disease management and more diversified research to discover innovative medicinal properties as well as its underlying mechanisms of honey.

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