REVIEW ARTICLE

Honey and Cardiovascular Risk Factors in Normal Individuals, and in Patients with Diabetes Mellitus or Dyslipidemia

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ABSTRACT   Diabetes mellitus, hypercholesteremia, hypertension (HTN), and obesity are well-known risk factors for cardiovascular diseases (CVD). Various medications are currently in use for management of these comorbidities. Undesirable side effects are unavoidable and the ultimate and ideal goal is hardly achieved. Honey and other bee products are widely used in traditional medicine for management of many diseases. Others and the authors have found potent biological activities of these products. Honey is now reintroduced in modern medicine as part of wound and burn management. Honey has anti-oxidant, anti-inflammatory, and antimicrobial activities. More studies are exploring other aspects of honey activity such as its effect on blood sugar, body weight, lipid profile, C-reactive protein, nitric oxide, proinflammatory prostaglandins, and homocysteine. Growing evidence and scientific data support the use of honey in patients with diabetes, HTN, dyslipidemia, obesity, and CVD. This review discusses clinical and preclinical studies on potential influence of honey on diabetes mellitus and cardiovascular risk factors, and emphasizes the importance of conducting more clinical and controlled studies.

KEY WORDS: ● *cholesterol* ● *C-reactive protein* ● *glucose* ● *honey* ● *insulin* ● *obesity* ● *triacylglycerol*

INTRODUCTION

CARDIOVASCULAR DISEASES (CVD) are associated with hypercholesterolemia, hypertension (HTN) and diabetes mellitus (DM). Atherosclerosis, which is due to endothelial dysfunction, is the main cause of CVD. Cardiovascular disorders remain the leading cause of death worldwide.[1] Obese and diabetic patients have a high risk of dying from complications associated with CVD.

In addition to normal BMI and blood pressure, maintaining normal levels of serum homocysteine, C-reactive protein (CRP), lipids, and insulin are essential to maintain a healthy cardiovascular system. Normal biological activities of the vasoactive factors, nitric oxide (NO) and prostaglandins are important to maintain a healthy heart and blood vessels.

Humans have used bee products in folk medicine since ancient times. Ancient religious texts mentioned honey as a popular remedy. In this regard, the Talmud, the Old and New Testaments of the Bible, and the Holy Quran (1400 years ago) mentioned honey as a cure for diseases. A large chapter (SORA) appears in the Holy Quran named BEE (Al Nahl) and part of it says; (And thy LORD taught the bee to build its cells in hills, on trees and in men's habitations, then to eat of all the produce of the earth and find with skill the spacious paths of its LORD, there issues from within their bodies a drink of varying colors, wherein is healing for men, verily in this is a sign for those who give thought).

The health benefits attributed to bee products are based on anecdotes or public observations with limited scientific data. ◀ AU3
However, during the last few decades, these products have been subjected for analysis and testing. Others and the authors have published numerous scientific data showing the medicinal and nutritional values of bee products.[2–6] The literature shows that honey has antibacterial, antifungal, antiviral, anti-inflammatory, antihypertensive, antioxidant, antitumor, cardioprotective, hepatoprotective, and hypoglycemic properties.[3,4,6–15] A recent review showed that the polyphenol content of various types of honey might prevent CVD by improving coronary vasodilatation, decreasing the ability of platelets in the blood to clot, and preventing low-density lipoproteins (LDL) from oxidizing.[16] Therefore, honey has received renewed interest as an important natural substance that can be used in new therapies almost free from side effects that are encountered with the use of synthetic and chemical medicines.

HONEY COMPOSITION

Honey is a carbohydrate-rich syrup produced by bees, from floral nectars. Color, flavor, and aroma depend on its

TABLE 1. THE MAIN SOLID CONTENTS OF HONEY

Groups	Members	References
Carbohydrates	Dextrose and fructose account for about 85% of the solids in honey. Ten disaccharides present in honey: sucrose, maltose, isomaltose, maltulose, nigerose, turanose, kojibiose, laminaribiose, a, B-trehalose, and gentiobiose. Ten trisaccharides are present: melezitose, 3-a-isomaltosylglucose, maltotriose, l-kestose, panose, isomaltotriose, erlose, theanderose, centose, and isopanose. Two more complex sugars, isomaltotetraose and isomaltopentaose, have been determined	25,28,39
Nonaromatic organic acids	Butyric, malic, maleic, citric, succinic, fumaric, oxalic, pyroglutamic acids, and gluconic acid	24,31,32,43
Trace elements and minerals	Aluminum, lead, arsenic, lithium, barium, molybdenum, boron, nickel, bromine, rubidium, cadmium, silicon, chlorine, strontium, sulfur, florid, vanadium, iodide, zirconium, cobalt, sodium, calcium, potassium, magnesium, phosphorus, zinc, copper, iron, manganese, chromium, and selenium	25,27,32,40,42
Vitamins	Thiamin, riboflavin, pyridoxin, vitamin A, niacin, panthothenic acid, phyllochinon, vitamin E, and ascorbic acid	24,25,27
Amino acids	Eighteen essential and nonessential amino acids; proline, glutamic acid, alanine, phenylalanine, tyrosine, leucine, and isoleucine are the most common	24,27,28
Enzymes	Glucose oxidase, invertase, amylase, catalase, and acid phosphatase	30,33
Polyphenols	Phenolic acids, flavonoids, and phenolic acid derivatives; quercetin, chrysin, galangin, luteolin, kaempferol, and apigenin are the main flavonoids in honey	20,21,22,23,34–36
NO	NO end products	42,74,75

NO, nitric oxide.

floral origin. Aberrantly, honey composition is tightly associated to its botanical origin, which is closely related to the geographical area in which it is originated. In this regard, soil and climate characteristics determine melliferous flora, in addition to the presence of different minerals in soil.[17] The organoleptic characteristics of honey are strongly dependent on its botanical origin and to some extent on its geographical origin.[18]

Composition of different honeys from many regions of the world has been studied, including the United Arab Emirates (UAE), the United States, Algeria, India, Slovenia, Bangladesh, and Malaysia.[19–25] Honey contains 181 bioactive substances.[26] More than 500 different volatile compounds were identified in various types of honey.[27] Fructose and glucose are the major components while disaccharides, trisaccharides, and oligosaccharides are present in small quantities. In addition, honey contains protein, enzymes, amins acids, vitamins, and minerals.[25,27–29] (Table 1).

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The physical chemistry characteristics of honey are directly related to floral origin.[30,31] Approximately 30 nonaromatic organic acids have been identified.[32] Gluconic acid is the major organic acid produced by enzymatic glucose oxidase reaction. The glucose oxidase reaction in honey produces glutamic acid and hydrogen peroxide from glucose. Invertase converts sucrose to fructose and glucose.[33] Amylase splits starch chains yielding dextrins and maltose.[30] Polyphenols are an important group of compounds present in honey.[34–36]

An analytical survey of U.S. honey was reported.[28] This includes analyses of 490 samples of U.S. floral honey and 14 samples of honeydew honey gathered from 47 of the 50 States and representing 82 single floral types and 93 blends of known composition. Floral honey is higher in fructose and dextrose, lower in disaccharides and higher sugars, and contains much less acid. The water content of honey varies greatly, ranging between 13% and 25%. We have analyzed honey collected from the UAE; the composition includes fructose 38 g%, glucose 30 g%, acidity 13%, moisture 29%, vitamin C 2.3 mg%, copper 0.098 mg%, zinc 0.6 mg%, vitamin E 0.74 mg%, vitamin A 0.49 mg%, selenium 0.44 mg%, chromium 0.007 mg%, iron 0.2 mg%, cobalt 0.016 mg%, calcium 17 mg%, and glutathione reductase 0.52 mg%.[25]

Electric conductivity, acidity, amino acids, mineral content, carbohydrate content, and pollen proteins are used to assess provenience of honey.[37–41] Seventeen minerals in Spanish honey have been determined, reporting a relationship between mineral contents and geographical origin.[40] The authenticity of Galician-labeled honey has been confirmed by analyzing elemental composition of honey combined with chemometrics modeling techniques.[41] Further, it was found that $NO(3)(-)$ is a potential reliable marker of a honey's origin and quality.[42] The acids have been used as factors for the characterization of both botanical and geographical origins of honeys.[43]

HONEY AND GLYCEMIC RESPONSE

Many studies showed that honey from various origins has almost similar activity on blood sugar (Table 2). Glycemic ◄ T2

TABLE 2. EFFECTS OF HONEY ON BLOOD SUGAR IN NORMAL INDIVIDUALS

Study	Origin of honey	Number of individuals	Results
Robert et al. (2009)[44]	Malaysia and Australia	8	Mean AUC/glycemic index of both honeys were significantly less than that after glucose
Deibert et al. (2010)[45]	Eight samples of honey-Germany	10	5/8 samples of honey show a low glycemic index
Münstedt et al. (2008)[46]	Basswood honey-Germany	12	Serum insulin, C-peptide, and glucose values at 60 min were significantly lower for honey. AUC for glucose response was lower for the honey than the honey-comparable glucose-fructose solution
Ischayek and Kern. (2006)[47]	Clover, buckwheat, cotton, and tupelo honey-USA	12	No significant differences in glycemic index between the honey samples
Shambaugh et al. (1990)[48]	USA	33	Sucrose gave higher PGL readings than honey, producing significantly greater glucose intolerance
Ahmad et al. (2008)[49]	Pakistan	26	Glycemic responses were significantly lower in subjects who consumed natural honey than those who consumed glucose or artificial honey
Yaghoobi et al. (2008)[50]	Iran	38	Honey reduces fasting PGL (4.2%) compared with sucrose
AL-Waili (2008)[25]	UAE	10	Honey reduced fasting blood sugar by 5%
Al-Waili (2003)[14]	UAE	24	Honey inhalation lowers PGL and elevates plasma insulin and C-peptide
Al-Waili (2004)[51]	UAE	16	In glucose tolerance test, dextrose raised PGL at 1 h (53%) and 2 h (3%), and lowered PGL after 3 h by 20%. Honey elevated PGL after 1 h by 14% and decreased it after 3 h by 10%. Elevation of insulin and C-peptide was significantly higher after dextrose than after honey. Daily consumption of 75 g of honey for 15 days reduced fasting PGL by 6%

AUC; PGL, plasma glucose level.

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index of Malaysian honey and Australian honey was studied in eight healthy volunteers. The patients received 50 g carbohydrate; two varieties of honey or the reference food. The results showed that the mean AUC and glycemic index of the Malaysian and Australian honeys did not differ from each other but were significantly less than that after glucose.[44] In Germany, eight various German honeys differing in their floral source and carbohydrate composition were tested. Ten healthy fasting individuals received isoglucidic test meals (25 g carbohydrate) and a 25 g glucose reference. Five of the eight tested samples of honey showed a low glycemic index below 55. In addition, the glycemic index and insulinemic index significantly correlated with the fructose content of honey varieties.[45] Another study compared the effects of Basswood honey, an identical sugar solution (containing 75 g of glucose), and oral glucose tolerance test solution on serum glucose, insulin, and C-peptide values in 12 healthy subjects.[46] Serum insulin, C-peptide, and glucose values at 60 min were significantly lower for honey. The area under the concentration-time profile for glucose response was lower for honey than the honey-comparable glucose-fructose solution. Honey had less effect on serum glucose, C-peptide, and insulin values than the honey-comparable glucose-fructose solution.[46]

In the United States, the glycemic index of a 250 mL solution serving of clover, buckwheat, cotton, and tupelo honey providing 50 g carbohydrate were assessed in 12 healthy adults, relative to triplicate feedings of 50 g carbohydrate as a glucose solution.[47] No significant differences in glycemic index between these varieties of honey were found, and there was no relationship between glycemic index and the fructose-to-glucose ratio. Therefore, small differences in fructose-to-glucose ratios do not substantially affect honey glycemic index.[47]

In another U.S. study, oral glucose tolerance testing comparing sucrose, fructose, and honey was conducted in 33 individuals. Fructose showed minimal changes in plasma glucose level (PGL) while sucrose gave higher PGL readings than honey, producing significantly greater glucose intolerance.[48]

In Pakistan, oral glucose tolerance test was conducted in 26 healthy individuals with use of natural honey, simulated honey, or D-glucose (1 g/kg body weight). Glucose response was significantly lower in the natural honey group compared with the artificial honey and D-glucose groups.[49] At 60 min, individuals in D-glucose and simulated honey group exhibited 20% increments in PGL compared with natural honey group. However, at 180 min, 20% decrease in PGL was

observed in the D-glucose group compared with 9.75% reduction in the honey group. Therefore, glycemic responses were significantly lower in subjects who consumed natural honey than those who consumed glucose or artificial honey.[49]

Another study from Iran has shown that a regimen of a 30-day natural honey intake (70 g) in 38 overweight individuals slightly reduced fasting PGL (4.2%) compared with 70 g of sucrose.[50]

In the UAE, 10 normal individuals received a normal diet supplemented with daily consumption of 1.2 g/kg body weight honey dissolved in 250 mL of water during a 2-week test period. Honey reduced fasting blood sugar by 5% after 2 weeks.[25] In 24 normal individuals, 10% dextrose inhalation caused mild reduction of plasma insulin and C-peptide and unremarkable changes in PGL. Honey inhalation caused lowering of PGL and elevation of plasma insulin and C-peptide.[14] In eight healthy subjects, effects of dextrose solution (250 mL of water containing 75 g of dextrose) or honey solution (250 mL of water containing 75 g of natural honey) on PGL was studied in the UAE. Further, in eight other normal individuals, effects of honey solution, administered for 15 days, on PGL was studied. It was found that dextrose raised PGL at 1 h (53%) and 2 h (3%), and lowered PGL after 3 h by 20%. Honey elevated PGL after 1 h by 14% and decreased it after 3 h by 10%. Elevation of insulin and C-peptide was significantly higher after dextrose than after honey. In addition, daily consumption of 75 g of honey for 15 days reduced fasting PGL by 6%.[51]

In the UAE, food restriction with 50% honey feeding in rats caused greater reduction in fasting blood sugar compared with total food restriction with 50% dextrose feeding. Similar results were obtained after acute blood loss in rats on total food restriction with 50% honey feeding compared with the other groups.[52] In addition, the authors assessed the effects of four diets on blood variables in rats: a commercial regular diet as control, total food restriction with honey, a commercial regular diet with dextrose, or total food restriction with dextrose after administrating carbon tetrachloride. Honey feeding ameliorated reduction in PGL observed after carbon tetrachloride toxicity.[53]

Intravenous infusion of 40 g of honey collected in the UAE in healthy sheep caused elevation of PGL for 90 min postinfusion, whereas it decreased PGL at 2 and 3 h postinfusion compared with fasting blood sugar. Dextrose caused significant elevation of PGL at all time intervals. Similar results were obtained with the use of 10% dextrose compared to 80 g of honey. Inhalation of honey caused significant lowering of PGL during and after inhalation compared with water inhalation.[54]

In the United Kingdom (U.K.), hyperglycemic effects of glucose, sucrose, and honey equivalent to 20 g in 12 normal volunteers were studied. Honey attenuated the postprandial glycemic response in normal volunteers.[55]

HONEY AND DIABETES

Animal experimentation

In Malaysia, honey (0.2, 1.2, and 2.4 g/kg/day) given by oral gavage for 4 weeks significantly increased body weight, total antioxidant status, activities of catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, and superoxide dismutase activity in diabetic rats. In addition, honey ameliorated side effects of DM on kidney rats and significantly reduced fasting blood sugar.[8] Tualang honey significantly reduced elevated malondialdehyde levels in streptozotocin-induced diabetic rats and restored superoxide dismutase and catalase activities. These results suggest that hypoglycemic effect of tualang honey might be attributed to its antioxidative effect on the pancreas.[13] In streptozotocin-induced diabetic rats, it was found that the combination of glibenclamide or metformin with honey improved glycemic control. Glibenclamide or metformin combined with honey significantly reduced the elevated levels of creatinine, bilirubin, triacylglycerol, and VLDL.[56]

In Pakistan, oral administration of Apis florea (Small-Bee) and Apis dorsata (Large-Bee) in a dose of 5 mL/kg did not produce a significant increase in PGL in normal and alloxan-diabetic rabbits, whereas the adulterated honey significantly raised the PGL in normal and hyperglycemic rabbits.[57] In higher doses of 10 mL/kg and 15 mL/kg body weight, all the three honeys produced a significant rise in PGL of normal and alloxan-diabetic rabbits.[57] In this study, the animals received very high doses of the interventions and that may be why PGL increased in all groups.

In New Zealand, a study conducted on rats showed that HbA1c levels were significantly reduced in 10% honey-fed compared with rats fed 7.9% sucrose or a sugar-free diet.[58]

Human experimentation

In the U.K., hyperglycaemic effects of glucose, sucrose, and honey equivalent to 20 g in eight patients with type 1 DM, and six patients with type 2 DM were studied. Honey attenuated postprandial glycaemic response in the patients with DM.[55] In Italy, honey, compared to an isoglucidic amount of bread, had no additional hyperglycemic effect in 21 type 2 diabetic individuals when consumed for breakfast.[59] In Greece, the metabolic effects of honey (alone or combined with other foods) were investigated in 31 type 2 diabetics. Honey caused a hyperglycemia similar to that produced by consuming bread in individuals with type 2 diabetes.[60]

In India, 30 individuals with a proven parental history of type 2 DM were subjected to an oral glucose tolerance test with the use of either honey or glucose. The subjects with impaired glucose tolerance showed significantly lower PGL after consumption of honey in comparison with the glucose tolerance test. In diabetic patients, high degree of tolerance to honey was recorded too.[61]

In Egypt, a case–control cross-sectional study was conducted on 20 children and adolescents with type 1 DM and 10 healthy children and adolescents. Oral glucose tolerance tests using glucose, sucrose, or honey were conducted measuring fasting and postprandial serum C-peptide levels. Honey, compared with sucrose, had a lower glycemic index and incremental index in both diabetic patients and control.[62]

In the UAE, the effects of 70 g of dextrose or 90 g of honey on PGL in seven patients with type 2 DM and the

effects of 30 g of sucrose or 30 g of honey on PGL, plasma insulin, and plasma C-peptide in five diabetic patients were studied.[51] Honey compared with dextrose caused a significantly lower rise of PGL. Elevation of PGL was greater after honey than after sucrose at 30 min, and was lower after honey than it was after sucrose at 60, 120, and 180 min. Honey caused a greater elevation of insulin than sucrose did after 30, 120, and 180 min in diabetics.

Sixteen patients with type 2 DM were treated with intrapulmonary inhalation of honey. Fasting PGL was estimated in each patient and was re-estimated during 3 h after honey inhalation, at 30 min intervals. Glucose tolerance tests were performed in another eight patients with type 2 DM and after 1 week, the procedure was repeated with inhalation of honey after ingestion of glucose. Honey inhalation caused lowering of PGL and elevation of plasma insulin and C-peptide, and significantly reduced random PGL after 30 min. Fasting PGL was reduced after honey inhalation at hour three postinhalation, which was significant at hour three. Honey inhalation was effective in reducing PGL, suggesting it could improve glucose tolerance and elevate plasma insulin and C-peptide in diabetic patients.[14]

The blood glucose and plasma insulin responses to some simple carbohydrates (glucose, fructose, and lactose) and honey were studied in 32 Type 2 DM patients. Ingestion of 25 g glucose, fructose, or lactose, or 30 g honey was tested. Sixty minutes after ingestion of each meal, the increases in PGL and in plasma insulin were significantly higher after glucose, fructose, and lactose than after honey.[63]

The above studies showed that honey collected from different regions had almost similar glycemic effect. Honey compared with dextrose reduced PGL and insulin in normal subjects. This is important since hyperinsulinemia is a single independent determinant for coronary artery diseases and it increases homocysteine in healthy normal weight, overweight, and obese premenopausal women.[64] Hyperglycemia increases circulatory cytokine concentrations by an oxidative mechanism, particularly in subjects with impaired glucose tolerance.[65]

Mechanism of action

Honey contains fructose, oligosaccharides, minerals, and antioxidants.[19–25] In normal individuals, a daily consumption of 1.2 g/kg body weight honey during a 2-week test increased blood vitamin C concentration by 47%, β-carotene by 3%, uric acid by 12%, and glutathione reductase by 7%. Honey increased serum copper by 33%.[25]

Many studies have shown that flavonoids exert diverse normoglycemic effects and lead to a lower incidence of complications associated with DM.[66–68] Antioxidants such as myricetin, fisetin, quercetin, and their glycoside precursor (isoquercitrin) showed a strong inhibition of the fructose and glucose transport mediated by GLUT2.[69] These compounds are all present in beehive products.[70]

Zinc lowers PGL by improvement of insulin sensitivity and copper sulfate significantly decreases PGL.[71,72] Zinc

and copper are important for insulin and glucose metabolism; both minerals were increased with consumption of honey.[25]

We have found that honey reduces prostaglandin levels and elevates NO.[73–75] It has been shown that prostaglandin E2 is one of the main physiological inhibitors of insulin.[76] Higher levels of NO and various NO donors stimulate insulin secretion.[77] Glycemic carbohydrates present in natural honey decrease saccharide absorption.[78–79] It has been found that hydrogen peroxide can effectively mimic the function of insulin.[80] Oligosaccharides may play a role in the antidiabetic effect of honey.[81–83] Oligosaccharides delayed gastric emptying, slowed rate of digestion, and delayed intestinal absorption.[84–87]

Infusion of small amounts of fructose induced amplification of the counter regulatory response to mild hypoglycemia in normal individuals.[88] It has been proposed that due to presence of fructose in addition to glucose, the augmentation of hormonal response to hypoglycemia by using honey might have a place in the prevention of hypoglycemia frequently encountered with use of insulin in patients with diabetes.[25] Fructose could increase hepatic glucose uptake and glycogen storage, and reduce peripheral glycemia and insulin levels; this could be beneficial in diabetic patients.[89] This suggests that honey might be a suitable food for diabetics and nondiabetics. However, fructose consumption causes undesirable effects such as hyperinsulinemia, induction of insulin resistance, hypertriglyceridemia, increased weight gain, hepatic *de novo* lipogenesis, and HTN in animal models.[90–94]

Honey contains more than 181 bioactive constituents including free radical scavenging and antioxidant compounds.[27,95] In addition, honey contains arginine and NO metabolites and it increases NO production in animals and human.[74,75] L-Arginine is able to prevent fructose-induced HTN and hyperinsulinemia.[96] Therefore, we have proposed that NO might inhibit fructose-induced hyperinsulinemia after ingestion of honey.[25] Honey compared with dextrose or sucrose decreased insulin levels in normal subjects. The mild effect of honey on PGL and plasma insulin and C-peptide in normal subjects might be due to fructose content, as fructose does not stimulate insulin secretion from pancreatic β cells.[97]

Fructose reduces hyperglycemia in rodent models of diabetes, healthy subjects, and diabetic patients.[98–100] Fructose prolongs gastric emptying and it lowers food intake.[101–103] A low or moderate fructose diet resulted in weight loss in obese subjects.[103] Obese subjects on the moderate fructose diet lost more weight than those on the low fructose diet.[104] However, some studies have found that fructose feeding or consumption at high doses is associated with increased weight gain.[91,94] Fructose increases hepatic glucose phosphorylation via activation of glucokinase, and inhibits glycogenolysis via suppression of phosphorylase.[105,106] Fructose increased hepatic glycogen synthesis in diabetic and nondiabetic rats.[105,107]

Honey tastes sweeter than sucrose, so it was suggested that a pure natural honey in low doses might be

recommended as sources of carbohydrates and even as sweetening agents in place of sucrose to diabetic patients.[25] The effects of honey or its constituents on gastric emptying, insulin secretion, rate of intestinal absorption, prostaglandin inhibition, NO production, fructose transporter, antioxidants level, hepatic glucose uptake, zinc and copper levels, and food intake, and perhaps the synergistic effect of glucose on fructose may contribute to the lowering of glucose levels.[85,101,103,108–109]

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HONEY AND LIPIDS

In Iran, 48 patients with type 2 DM received oral natural honey intake for eight weeks; honey decreased total cholesterol, LDL-cholesterol, and triacylglycerol, and increased HDL-cholesterol.[110] Another study showed that 70 g of natural honey collected in Iran decreased total cholesterol (3%), LDL-C (5.8%), and triacylglycerol (11%), and increased HDL-C (3.3%) in subjects with normal values and in patients who were overweight or obese.[50]

In New Zealand, rats fed 10% honey increased the HDL cholesterol significantly compared with rats fed 7.9% sucrose or a sugar-free diet.[58] In Germany, among patients who had high cholesterol, LDL-cholesterol values did not significantly reduce in males after ingesting a 75-g honey solution for 14 days. However, in women, these values increased in the sugar solution group, but not in that fed honey.[111] It was suggested that although ingesting honey did not reduce LDL cholesterol values, women might benefit from substituting honey for sugar in their diet.[111]

In the United States, a study conducted in rats showed that honey lowered serum concentrations of triacylglycerol compared with diets of equal energy densities. However, there were no significant differences in serum total cholesterol, or HDL- cholesterol.[112] In Nigeria, a recent study showed that consumption of unrefined Nigerian honey significantly improved lipid profiles and the computed CVD predictive index in male albino rats.[113]

The authors found that a single dose of glucose or artificial honey (consisting of 40 g fructose + 35 g glucose in 250 mL water) increased cholesterol and triacylglycerol; this effect was not observed with natural honey collected in the UAE.[51] In this regard, daily consumption of 75 g honey for 15 days decreased total cholesterol (8%), LDL-C (11%), and CRP (75%) in normal and hyperlipidemic subjects.

Natural honey decreased total cholesterol and LDL-C in healthy and hyperlipidemic subjects while artificial honey increased lipids because of the presence of fructose. It was proposed that the difference between the effects of artificial and natural honeys on lipids might be due to the presence of certain substances in natural honey that are able to reduce blood lipids in healthy and hyperlipidemic subjects.[51] Fructose potentiates postprandial lipidemia in both diabetic and nondiabetic subjects and very high intake of sucrose or fructose increased fasting triacylglycerol.[114,115]

In patients with hypercholesterolemia, the formation of the F2-isoprostane 8-epi-PGF2α is enhanced, which is suppressed by vitamin E supplementation.[116] It has been reported that high doses of B complex vitamin may be useful in lowering blood cholesterol and triacylglycerole levels. Vitamin E reduces atherosclerosis plaque, coronary artery diseases, and myocardial infarction.[117] Many studies showed that ascorbic acid deficiency involved in the development of hypercholesterolemia and atherosclerosis.[118] Antioxidants can modulate the activity and/or the protein levels of 3-hydroxy-3-methylglutaryl coenzyme A reductase (the rate-limiting enzyme of cholesterol biosynthetic pathway).[119] Polyphenols derived from tea were shown to have antioxidative, antithrombogenic, anti-inflammatory, hypotensive, and hypocholesterolemic properties.[120] Further, polyphenols have vasodilating effects, and they can improve the lipid profile and lessen the oxidation of LDL.[121] The effects of honey on lipid profile might be related to NO, antioxidants, vitamin E, prostaglandins, and antioxidant properties.[116–123] However, the exact mechanisms through which honey exerts its effect on lipid values are not well identified.

HONEY AND BLOOD PRESSURE

It is well known that HTN is one of the major risk factors for cardiovascular and renal diseases. Most of patients fail to maintain goal blood pressure despite using various antihypertensive modalities.

Administration of Malaysian tualang honey for 3 weeks in streptozitocine-induced diabetic spontaneously hypertensive rats resulted in reduction in systolic blood pressure.[124] This effect was mediated via amelioration of oxidative stress in the kidney.[125] The authors found that systolic and diastolic blood pressure was reduced by honey inhalation in hypertensive patients; significant changes were obtained at 60 and 120 min after inhalation.[14]

Oxidative stress and free radicals are involved in the pathogenesis and/or maintenance of elevated blood pressure in HTN.[126–129] In addition, there is strong evidence of a close relationship between NO deficiency and development of HTN.[130] Further, chronic NO inhibition with L-Nitro-Arginine Methyl Ester, an antagonist for L-arginine, causes salt-sensitive HTN and the development of renal injury.[131] Therefore, honey might mitigate HTN by its antioxidant constituents and its ability to increase NO. Further studies are needed to explore the exact mechanism of action.

HONEY AND CRP

CRP is an acute phase protein that is produced by hepatocytes in response to inflammatory cytokines in the body. CRP serves as a biomarker of CVD risk and inflammation. Increased levels of CRP are correlated with cardiac risk factors such as type 2 diabetes mellitus, obesity, and smoking.[132,133] CRP functions as a pro-atherosclerotic factor too.[134] In the previous study, oral ingestion of honey reduced CRP.[51] Further, daily ingestion of 70 g of natural honey caused 3.2% reduction in CRP in subjects with normal values and in patients with elevated variables in obese and overweight individuals.[50] However, in the United States, a study conducted in rats showed that there were no

significant differences in CRP in rats fed honey or diets of equal energy densities.[113]

It has been shown that antioxidants and vitamin E reduce the concentration of CRP.[135,136] An increased intake of foods rich in polyphenolic compounds is inversely associated with CRP concentrations.[132,133,137–138] Honey contains many antioxidants. Therefore, honey might reduce CRP by its antioxidant properties.

HONEY AND NO

NO is a gaseous signaling molecule, which plays an important role in a variety of human biological processes. It is synthesized by NO synthase; neuronal, inducible and endothelial. NO plays an important role in vasodilation via the relaxation of vascular smooth muscle, in increasing circulation in the body and in the protection against the onset and progression of CVD. The cardioprotective roles of NO include regulation of blood pressure and vascular tone, vasodilatation, prevention of smooth muscle cell proliferation, inhibition of platelet aggregation, and leukocyte activation.[139–141] Patients with atherosclerosis, DM, or HTN show impaired NO pathways.[142]

We have found that honey contains NO end products.[74] In addition, honey increases NO end products in various biological fluids such as urine, saliva, and plasma.[75] Intravenous honey increased NO end product in plasma and urine.[75]

Tualang honey inhibited UVB-induced inflammatory cytokines and inducible NO synthase protein expression. Intravenous honey reduced cytokine (tumor necrosis factor-α, interleukins 1β, and 10) and NO levels and increased heme oxygenase-1 levels in rats with LPS-induced endotoxemia.[143]

In inflammatory processes, it was found that honey inhibits NO and prostaglandins.[143–146] In this situation, honey might inhibit inducible harmful NO. Inhibition of inducible nitric oxide synthase (iNOS) activity produces a marked anti-inflammatory effect in acute and chronic inflammation.[147] Further, the anti-inflammatory effect of honey might be due to the presence of polyphenolic compounds.[148,149] Polyphenolic compounds have potent antioxidative activities that might scavenge iNO.[150]

In this regard, it has been demonstrated that many plant polyphenolic compounds could modulate NO levels and/or actions.[151,152] Therefore, honey could prevent or ameliorate CVD with upregulation of NO. More studies are required to explore this important field.

HONEY AND PROSTAGLANDINS

It is well documented that prostaglandins are mediators of inflammation and pain. Prostaglandins reduce immunity and play a critical role in cancer development.[153,154]

The main vasoactive factors released by endothelial cells are NO and prostaglandins.[155,156] PGI2 and PGD2 are vasodilators, whereas PGH2, PGF2α, and thromboxane A2 are vasoconstrictors and platelet aggregation inducers.[157–159] PGE2 can induce vasodilation or vasoconstriction.[160,161]

Interaction between PGF2α and its receptor triggers potent vasoconstriction.[162,163] PGF2α promotes cardiac hypertrophy.[164] Studies have shown that serum levels of 8-iso-PGF2-α increased in obesity, DM, arthritis, and CVD.[165,166] Thromboxane A2 elicits platelet aggregation and vascular smooth muscle contraction.[167] The production of thromboxane A2 is increased in patients with unstable angina, infarction, cerebral vasospasm, and pregnancy-induced HTN.[168,169]

Gelam honey was also shown to depress production of PGE2 and NO on exudates of rat's paw induced with carrageenan and lipopolysaccharide.[145] It was found that tualang honey inhibited UVB-induced COX-2 expression and PGE2 production.[146]

The authors have reported for the first time that oral honey could reduce plasma and urinary PGE2, PGF2-α, and thromboxane B2.[73] Its inhibitory effect was increased with time. The site of actions could be either at COX-1 or COX-2, or both. In addition, it was found that artificial honey made of glucose and fructose, increased prostaglandin concentrations.[170]

Hydrogen peroxide induces PGE2 production by forming ROS that oxidizes phospholipids in the membrane.[171] Gelam and Nenas monofloral honeys showed significant anti-inflammatory effects on inflammation induced-HT29 cells by decreasing the level of PGE2 of cells as effective as indomethacin.[172] Polyphenols can reduce serum 8-Iso PGF2α.[173] Therefore, natural honey might contain raw materials that are capable of inhibiting prostaglandin synthesis.[73] Obviously, it appears that honey has anti-inflammatory properties that make it a suitable nutrient to be used in acute or chronic inflammatory conditions.[73]

HONEY AND HOMOCYSTEINE

Homocysteine, an amino acid that is produced in the human body, impairs the generation and decreases bioavailability of NO. Individuals with lower homocysteine have lower rate of CVD.[174] Homocysteine is an important risk factor for cancer and CVD and increases in its concentrations are associated with an increased risk for nephropathy and proliferative retinopathy.[175,176] Honey decreases homocysteine level by 8% in normal subjects after 15 days of consumption. Vitamin C protects LDH-cholesterol from homocysteine-mediated oxidation.[177] In healthy and diabetic subjects homocysteine inhibited platelet NO production.[178] We found that honey increased the NO concentration and antioxidant levels in humans.[24,73–75,174] This might explain, in part, the hypohomocysteinemic effects of honey.

HONEY AND OBESITY

Obesity is a global epidemic.[179] It is associated with CVD, type 2 DM, HTN, cancer, and sleep apnea. Obesity is an independent risk factor for CVD.[180] Abnormal endothelial function as a results of decreased NO is found in obesity.[181] HTN is more common in obese than in lean individuals.[182] A strong correlation was demonstrated

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TABLE 3. EFFECT OF VARIOUS SAMPLES OF HONEY ON BLOOD SUGAR IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS   ◀AU11

Study	Origin of honey/method of administration	Number of patients	Results
Samanta et al. (1985)[55]	UK, PO	8-type 1 DM 6-type 2 D	Honey attenuated postprandial glycemic response
Bornet et al. (1985)[59]	Italy, PO	21 type 2 DM	Honey, compared to an isoglucidic amount of bread, has no additional hyperglycemic effect in 21 type 2 diabetic individuals when consumed for breakfast
Katsilambros et al. (1988)[60]	Greece, PO	31 type 2 DM	Hyperglycemia similar to that produced by consuming bread
Agrawal et al. (2007)[61]	India, PO	30 with impaired glucose tolerance test or type 2 DM	Significantly lower PGL after consumption of honey in comparison to the glucose tolerance test. In diabetic patients, the high degree of tolerance to honey was recorded too
Abdulrhman et al. (2011)[62]	Egypt, PO	20 children and adolescents with type 1 DM and 10 healthy children and adolescents	Honey, compared to sucrose, had lower glycemic index and incremental index in both diabetic patients and control
Al-Waili (2004)[51]	UAE, PO	12 type 2 DM	Honey compared with dextrose caused a significantly lower rise of PGL after GTT. Honey caused greater elevation of insulin than sucrose did after 30, 120, and 180 min in diabetics
Al-Waili (2003)[14]	UAE-inhalation	24 type 2 DM	Honey inhalation was effective in reducing PGL; it could improve glucose tolerance test and elevate plasma insulin and C-peptide in diabetic patients

DM, diabetes mellitus; GTT; PO, per oral.   ◀AU10

between obesity and IL-6 and CRP levels. In general, obesity is a low-grade systemic inflammation. Diet modulation, physical activity, pharmacotherapy, and surgery are recommended as part of the management of obesity.[183] Weight loss improves or prevents many of the obesity-related risk factors for CVD.[183]

In the United States, a study conducted in rats showed that honey lowered serum concentrations of leptin and reduced weight gain and adiposity compared with diets of equal energy densities.[112] In New Zealand, a study was conducted in rats to determine whether 10% honey and 7.9% sucrose would have differential effects on weight gain during 52 weeks feeding. Overall weight gain and body fat levels were significantly higher in sucrose-fed rats than those fed honey or a sugar-free diet.[58] In New Zealand, despite a similar food intake, the percentage weight gain was significantly lower in honey-fed rats than those fed sucrose or mixed sugars.[184]

In the University of Wyoming, Laramie, a double-blind, randomly assigned study evaluated whether the meal-induced responses of ghrelin and peptide YY (3–36) and/or

meal-induced thermogenesis differ following a honey-versus a sucrose-containing meal. It was found that honey delayed the postprandial ghrelin response, enhanced the total PYY response, and blunted the glucose response   ◀AU4 compared with consumption of the sucrose-containing meal.[185] In Iran, daily ingestion of 70 g of natural honey caused reduction in body weight (1.3%), body fat (1.1%) in overweight and obese individuals.[50]

Honey does not cause a significant reduction in PGL 3 h after consumption compared with sucrose or D-glucose.[49,51] This might reduce hunger and food intake.

ANTIOXIDATIVE AGENTS

In animal models and clinical studies, DM, hypercholesterolemia, or HTN are associated with increased vascular free radicals generation.[186–190] CVD is a disease of oxidative damage and inflammation, which results in elevation of proinflammatory mediators and low NO bioavailability. Increased free radicals cause a functional inactivation NO

TABLE 4. EFFECTS OF HONEY ON COMMON CARDIOVASCULAR RISK FACTORS

Variables	Effect of honey	Possible mechanism of action
Blood sugar	Reduces blood sugar in normal individuals and in patients with diabetes.	Flavonoids and antioxidants[66–69] Increases copper and zinc[71,72] Inhibition of prostaglandin[73,76] Elevation of NO[74,75] Glycemic carbohydrates[78,79] Hydrogen peroxide[80] Oligosaccharides[81–83] Fructose[98–107]
HTN	Lowers blood pressure	Antioxidant constituents and increment of NO[24,110]
Lipid profile	Decreases total cholesterol, LDL-cholesterol, and triacylglycerol, and increases HDL-cholesterol in healthy and hyperlipidemic subjects	Antioxidants, polyphenols, and vitamins contents, elevation of NO, and suppression of prostaglandins[124–131]
CRP	Decreases CRP	Antioxidants, polyphenols, and vitamin E contents[132,133,135–139]
Homocysteine	Decreases homocysteine	Vitamin C content.[177] NO production.[178]
Body weight	Decreases body weight in normal, overweight and obese individuals.	Honey delays the postprandial ghrelin response, enhances the total PYY response, and blunts the glucose response.[184] Honey reduces hunger and food intake.[49,51]

CRP, C-reactive protein; HTN, hypertension; LDL, low-density lipoproteins; PYY. ◀AU10

due to the reaction with superoxide anion. A cross-sectional study performed on 71 patients clinically diagnosed with CVD showed a significant reduction in antioxidant status (enzymatic and nonenzymatic) with a concomitant increase in the concentrations of lipid peroxidation products.[191]

Polyphenols and flavonoids inhibit LDL oxidation and platelet aggregation; reduce atherosclerotic lesion formation; reduce blood pressure; improve endothelial function; and decrease vascular cell adhesion molecule expression, iNO generation, and inflammatory responses.[192–204] Flavonoid intake reduces risk of CVD.[205] Flavonoids have antithrombotic, anti-ischemic, antioxidant, and vasorelaxant properties.[206] They are scavengers of superoxide anions, singlet oxygen, and lipid peroxy-radicals and they prevent LDL cholesterol oxidation.[190,207,208] The beneficial effect of polyphenols on CVD is attributed to modulation of NO bioavailability to the endothelium.[209,210]

β-carotenoids have anti-inflammatory activity in the vasculature and this might explain the protective effects of carotenoid-rich diets against CVD risk.[211] β-carotene affect endothelial response to TNF-α and reduce nitro-oxidative stress.[211]

Improvement of endothelial function and the antihypertensive effects of quercetin might be mediated by enhanced eNOS activity and decreased NADPH oxidase-mediated superoxide anion generation associated with reduced p47 expression.[212]

Various types of honey contain many antioxidants and antioxidant enzymes including vitamin E and C, ascorbic acid, phenolic acids, flavonoids, carotenoid derivatives, organic acids, Maillard reaction products, glucose oxidase, catalase, and glutathione perioxidase.[213–216]

The polyphenols in honey are caffeic acid, caffeic acid phenyl ester, chrysin, galangin, quercetin, acacetin, kaempferol, pinocembrin, pinobanksin, and apigenin.[217] Natural honey protects normal rats from the incidence of epinephrine-induced cardiac disorders and vasomotor dysfunction.[218]

The beneficial effect of honey on CVD might be attributed to its antioxidative and anti-inflammatory properties, increment of NO production, and improvement of blood sugar and blood pressure Table 4. ◀T4

CONCLUSION

Natural honey has many biological activities besides its antimicrobial activity Figure 1. Honey ingestion increases blood vitamin C level, β-carotene, uric acid, glutathione reductase, copper, zinc, NO end products, and decreases PGL, CRP, homocysteine, and plasma prostaglandin E2, F2-α, and thromboxane B2 concentrations. Moreover, honey improves lipid profiles and modulates C-peptide and insulin ◀F1
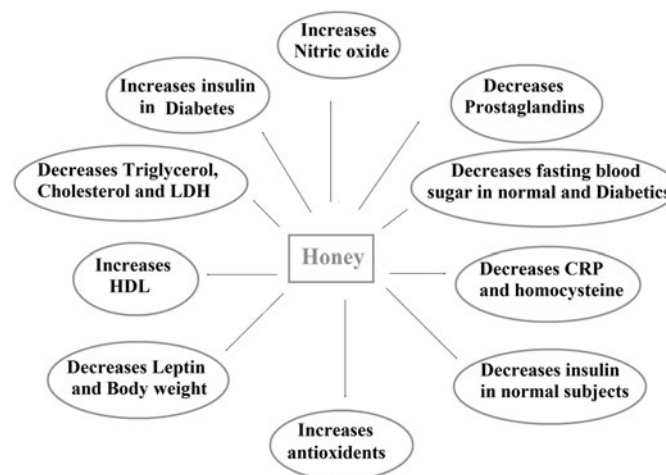

FIG. 1. ◀AU12

secretion. Honey has powerful antioxidative activity and its ingestion increases antioxidative materials. Honey appears to have many effects on various metabolic parameters. Its contents and effects on metabolic parameters might result in beneficial effects seen in patients with DM, HTN, and CVD. From studies reviews, honey appears to be a powerful natural biological syrup that may be recommended to be used in healthy individuals, and in patients with DM, HTN, and CVD.

AUTHOR DISCLOSURE STATEMENT

The authors declared that there is no conflict of interest regarding the publication of this article.

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