Honey Intake and Risk of CVDs: A Mechanistic Disclosure

12

Sadaf Ali, Sabhiya Majid, Shiekh Amir, Rafiqa Eachkoti, Shafat Ali, and Muneeb U. Rehman

Abstract

Honey is a naturally occurring sweet substance with gummy consistency produced by honey bees. It is also formed by nectar-producing plants and trees. Honey is well known for its usefulness which is mainly attributed to its flavonoid components. Cardiovascular diseases are the single largest cause of early mortality, especially in developed countries but are also emerging in developing countries at an alarming rate. In most of the cases, atherosclerosis has remained as its main underlying pathological cause. The basic pathology behind atherosclerosis is due to a chronic inflammatory process in the endothelium of arteries. Oxidation of the neo-intimal lipids that releases oxidized molecular species

S. Ali (✉) · R. Eachkoti
Department of Biochemistry, Government Medical College, Karan Nagar, Srinagar, Jammu & Kashmir, India

S. Majid
Department of Biochemistry, Government Medical College, Karan Nagar, Srinagar, Jammu & Kashmir, India

Nodal Officer Multidisciplinary Research Unit (MRU-ICMR), Government Medical College, Srinagar, Jammu & Kashmir, India

S. Amir
Department of Forensic Medicine and Toxicology, Government Medical College, Karan Nagar, Srinagar, Jammu & Kashmir, India

S. Ali
Department of Biochemistry, Government Medical College, Karan Nagar, Srinagar, Jammu & Kashmir, India

Cytogenetics and Molecular Biology Laboratory, Centre of Research for Development, University of Kashmir, Hazratbal, Srinagar, Jammu & Kashmir, India

M. U. Rehman
Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

© Springer Nature Singapore Pte Ltd. 2020

M. U. Rehman, S. Majid (eds.), *Therapeutic Applications of Honey and its Phytochemicals*, https://doi.org/10.1007/978-981-15-7305-7_12

eventually leads to vascular atherosclerotic changes. Formation of reactive oxygen species (ROS) in excess amounts due to oxidation of DNA, proteins, carbohydrates, lipids and other bio molecules adds on to these vascular changes. Antioxidant defence mechanisms of our body fail to balance this surplus ROS production, hence producing oxidative stress. Oxidative stress is associated with various metabolic disorders like cardiovascular diseases, systemic hypertension, diabetes mellitus, etc. Honey plays a protective role in a number of metabolic disorders as well as in cardiovascular health mainly due to its rich flavonoid and antioxidant content. Honey is believed to decrease the risk of developing elevated blood pressure. Intake of honey has the capability to decrease systolic blood pressure in healthy subjects. Honey also balances the lipid profile by increasing high-density lipoprotein (HDL) levels and reducing the levels of triglycerides and very low-density lipoproteins (VLDL). In this chapter, we have discussed how honey intake can help in prevention of cardiovascular disorders that has significant mortality and morbidity. A balance between the antioxidant intake and free radical injuries can help our body's defence mechanism to overcome different forms of oxidative stress. Honey may prove as a useful substance that can help in the improvement of biochemical imbalances in the human body.

Keywords

Honey · Flavanoids · Oxidative stress · Atherosclerosis

12.1 Introduction

Honey is a naturally occurring sweet substance with gummy consistency produced by honey bees. It is secreted by all types of honey bees but is formed particularly by the species Apis mellifera (Cortes et al. 2011). It is also produced from nectar or otherwise from exudates of nectar-producing plants and trees (Alvarez-Suarez et al. 2010). Honey is well known for its usefulness attributed mainly to its flavonoid components. Honey samples of various types contain a good quantity of flavonoids such as catechin, kaempferol, rutin, chrysin, acacetin, luteolin, quercetin, etc. (Khalil and Sulaiman 2010). Flavonoids are the compounds with strong biological properties that are beneficial for avoidance of many chronic diseases like atherosclerosis and other forms of cardiovascular diseases (Gross 2004). Most of these flavonoids have therapeutic benefits due to their beneficial properties and may be used as pharmacological agents (Khalil and Sulaiman 2010). According to the recent research, it was established that catechin and quercetin are the two major flavonoids present in honey (Afroz et al. 2016). Aortic atherosclerotic lesion formation is inhibited by the consumption of these flavonoids. These also had an inhibitory outcome on the development of various atherogenic variations of LDLs (Hayek et al. 1997). In addition to the preventive properties against atherosclerosis, honey flavonoids also tend to have anti inflammatory, antioxidant, antiproliferative and even antiplatelet actions. These are believed to lower both cholesterol and blood

pressure levels (Gross 2004). Nitric oxide is present in the vascular endothelium and is produced by nitric oxide synthase. It has good vasodilator properties and prevents atherosclerosis. According to the oxidation hypothesis the main mechanism for atherosclerosis is the oxidative modification of LDLs producing immunogenic stimulus which further results in migration of monocytes to various vessel walls. This is followed by phagocytic uptake of oxidized LDL molecules by macrophages (Nigro et al. 2006). Widespread oxidation of LDLs leads to their accumulation and formation of aggregates (Hoff and O'Neil 1991; Maor et al. 1997; Hayek et al. 1997). In a vascular atherosclerotic injury, both of these modified forms of LDLs have been seen.

Oxidative stress plays a vital role in the pathogenesis of cardiovascular diseases including the initial process of atherosclerosis. Progression of endothelial dysfunction is hindered by nitric oxide. Its deficiency results in the development of atherosclerosis and CVDs. Certain flavonoids like rutin that are present in honey of stingless bees promotes NO production. The mechanism for the production of nitric oxide by rutin is via induction of eNOS gene expression, eNOS protein synthesis and eNOS activity. Increased gene and protein expression of basic fibroblast growth factor (bFGF) is also made possible by giving rutin as treatment (Hayek et al. 1997).

12.2 Brief Idea About Composition of Honey (Al-Waili 2005)

Honey is a nutritive compound as it is composed of numerous contents (Fig. 12.1).

- Carbohydrates: 85% of the solids in honey are mainly contributed by dextrose and fructose. Many disaccharides and trisaccharides are present in honey.
  - Examples of disaccharides: Maltose, maltulose, isomaltose, turanose, kojibiose, B-trehalose, etc.
  - Examples of trisaccharides: Maltotriose, melezitose, panose, isomaltotriose, centose, isopanose, etc.
- Non-aromatic organic acids: Butyric, citric, succinic, fumaric, malic, maleic, oxalic acids, etc. (Anklam 1998).
- Trace elements and minerals: Honey has a good mineral component.
- Examples: Sodium, potassium, calcium, copper, iron, aluminum, sulfur, fluoride, iodide, lead, cobalt, arsenic, lithium, barium, etc. are present in honey (Bogdanov et al. 2008).
- Vitamins: different vitamins like vitamin A, vitamin E, and vitamin C, niacin, thiamine, riboflavin and pyridoxine are found in honey.
- Amino acids: Various essential and non-essential amino acids are present in honey. Some of the examples are proline, glutamic acid, alanine, phenylalanine, tyrosine, etc.
- Enzymes: Honey has good quality of enzymes also. Examples: Glucose oxidase, amylase, acid phosphatase, invertase, catalase, etc. (Baroni et al. 2002).

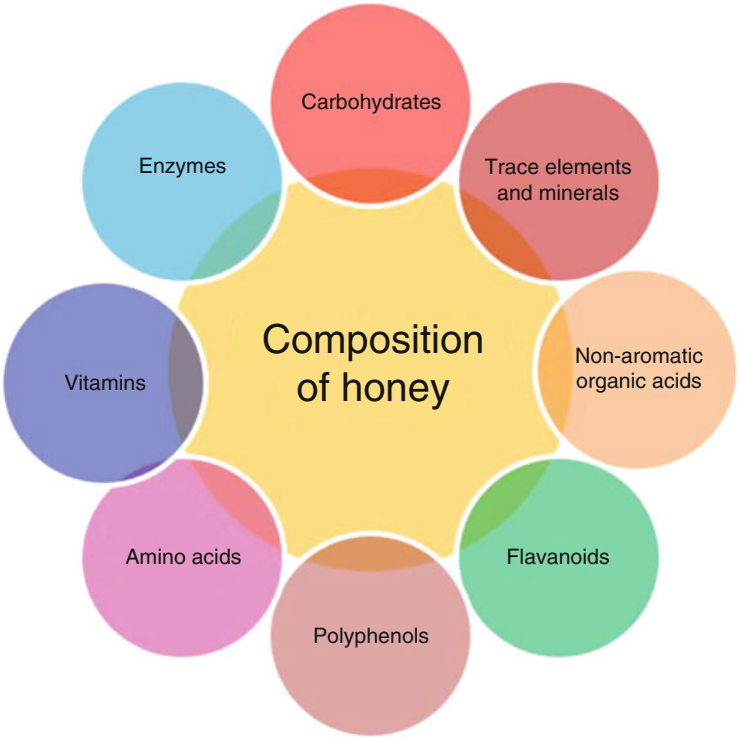

Fig. 12.1 An illustration showing some important phyto-constituents of honey

- Polyphenols: Various polyphenols and their derivatives are present in honey. Examples: quercetin, luteolin, kaempferol, chrysin, etc. (Bertoncelj et al. 2007; Aljadi and Kamaruddin 2004; Islam et al. 2012).
- Nitric oxide: Nitric oxide and its end products are also there in honey.

12.3 Role of Flavanoids in CVDs

The major sources of antioxidants in the diet consist of fruits, leafy vegetables, dark chocolate and green tea. These dietary components have proven protective effects against CVDs (Steinberg et al. 2003). The potential of lowering CVD risks has been revealed by such foods rich in antioxidants and flavonoids. Cocoa products are believed to have greater antioxidant power than most of the teas and red wines. It is imperative to explore the possible beneficial properties of chocolate on CVDs (Lee et al. 2003). Honey has a protective role on a wide range of diseases. The benefits of honey consumption on cardiovascular health are remarkable due to its flavonoid content. Biological and pharmacological activities of honey flavonoids in the prevention and treatment of atherosclerosis and CVDs have been considered in many

studies. In this study, the action of honey on CVDs will be disclosed with a mechanistic approach.

12.4 Cardiovascular Diseases

Cardiovascular diseases (CVDs) are described as a group of disorders of the blood vessels and heart. CVDs are the leading cause of mortality and morbidity worldwide (Gordon et al. 1989; Musselman et al. 1998). In developed countries CVD is the single largest cause of early mortality. In most cases atherosclerosis has remained as its main underlying pathological cause (Little et al. 2011). Untreated CVD can further develop into myocardial infarction and ischemic heart disease. Myocardial infarction being another fatal end point of cardiac diseases is manifested as angina pectoris and other clinical signs and symptoms. CVDs if left untreated can lead to financial and social burden for an individual and eventually to the whole society (Roger et al. 2012). Chronic inflammatory progression in the vascular wall of artery takes place due to oxidation of the neo-intimal lipids that releases oxidized molecular species, eventually leading to vascular atherosclerotic changes. Low density lipoproteins are transported into vascular endothelium and trigger the development of atherosclerosis (Grassi et al. 2009). Lipids present in tunica intima are trapped by proteoglycans that are modified and have hyper elongated glycosaminoglycan chains (Dadlani et al. 2008). Most significant risk factors for cardiac diseases are smoking followed by elevated blood cholesterol, obesity and diabetes mellitus. These all are related to inappropriate eating habits (Kivimäki et al. 2006). Among these, modifiable by dietary changes are elevated blood pressure and high fasting blood glucose (Bostom and Lathrop 1997).

As per various reports it has been established that intake of flavonoids is helpful in the prevention of cardiovascular diseases. This is mainly accomplished by declining oxidative stress and increasing the rising bioavailability of nitric oxide causing vasodilation. Different types of foods that are rich in flavonoids have been identified. Certain polyphenolic compounds like flavonoids work at molecular levels by modulating gene expression linked with human body metabolism, enzymes for the metabolism of drugs and xenobiotics, stress resistance and other detoxification reactions (Grassi et al. 2008). The integrated effect of different flavonoids is protective and overcomes the deleterious effects of cardiovascular risk factors. Therefore, the overall effect is delayed in the onset of atherosclerosis (Grassi et al. 2010).

12.4.1 Prevalence

Cardiovascular disease (CVD) is a group of disorders and a leading cause of death worldwide and in the United States of America (American Heart Association 2004). In India, the CVD death rate is 272 per 100,000 and is higher than the global average of 235 per 100,000 (Prabhakaran et al. 2016). Cardiovascular diseases caused over 16.7 million deaths globally in the year 2002. CVD disease burden is proposed to

rise to 143,000,000 disability-adjusted life-years by the year 2020 (Mackay and Mensah 2004).

12.4.2 Types of CVDs

Cardiovascular diseases are also known as vascular diseases and are of the following types:

1. Coronary artery disease/ischemic heart disease
2. Hypertensive heart diseases
3. Congestive cardiac failure
4. Arrhythmia
5. Peripheral artery disease
6. Cerebrovascular disease-stroke
7. Valvular heart diseases
8. Congenital heart disease
9. Rheumatic heart disease
10. Cardiomyopathy
11. Renal artery stenosis
12. Aortic aneurysm
13. Pulmonary heart disease
14. Inflammatory heart diseases: endocarditis, myocarditis, inflammatory cardiomyopathy and eosinophillic myocarditis (Mendis et al. 2011; Naghavi et al. 2015).

12.4.3 Signs and Symptoms

1. Angina pectoris or chest pain
2. Dyspnoea or breathlessness
3. Pedal oedema (swelling in feet)
4. Puffy face
5. Irregular pulse

12.4.4 Aetiology and Contributing Factors

1. Smoking
2. Systemic hypertension
3. Diabetes mellitus
4. Dyslipidemias progressing into atherosclerosis
5. Excessive alcohol consumption
6. Unhealthy lifestyle
7. Excessive weight gain and obesity
8. Sedentary lifestyle
9. Intake of junk food (Yusuf et al. 2004; Eckel 1997)

12.4.5 Diagnostic Tests

- Biochemistry: KFT, LFT, lipid profile, blood sugar fasting and post parandial, troponin-T, troponin-I, HbA1C in case of diabetic patients (Saenger 2012).
- Haematological and microbiological: CBC, CRP, hsCRP.
- Radiographic: ECG, echocardiography, Holter, etc. (Curry et al. 2018).

12.4.6 Treatment Options

- Diet and lifestyle modification: According to research, lifestyle modifications such as regular exercise and healthy nutrition may prevent cardiovascular diseases (Hu and Willett 2002). American Heart Association, American Diabetes Association, and the U.S. Preventive Services Task Force (Eyre et al. 2004) have established the significance of a healthy diet for the avoidance of CVDs.
- Medical treatment: Commonly, anticoagulants such as aspirin, streptokinase and tissue plasminogen activators are given in medical treatment. Intake of antihypertensives like atenolol comes under conservative management. Further steps include management of myocardial infarction and stroke.

12.5 Molecular Mechanism of Cardiovascular Injury

Oxidative stress and free radicals: A group of molecules that include molecular oxygen and its derived forms in all aerobic cells are called as reactive oxygen species (Herbst et al. 1999). Oxidation of the genetic material i.e. DNA and also other bio-molecules like proteins, carbohydrates and lipids directs excessive formation of reactive oxygen species. This excess production is not balanced by the antioxidant defence mechanisms of our body and is referred to as oxidative stress (Gimbrone 1995). According to research oxidative stress is related to various cardiac diseases, hypertension, diabetes and heart failure (Schachinger et al. 2000). It is also supposed to contribute to the in development of atherosclerosis, dyslipidemias, and hypercholesterolemia. Oxidative stress is believed to alter the normal endothelium functioning (Fig. 12.2) and affect the vascular tone also. This has been referred to a conventional risk that predisposes to atherosclerosis. Nitric oxide, a potent vasodilator, is inactivated by superoxide and other reactive oxygen species. This occurs commonly in systemic hypertension, dyslipidemias, diabetes mellitus and cigarette smoking. Many enzymatic systems are capable of producing reactive oxygen species however; extensive studies have been done on mechanisms like xanthine oxidase, uncoupled endothelial nitric oxide synthase and NADH/NADPH oxidase in vascular cells (Fig. 12.3). Therefore, research on the function of various enzymatic sources of ROS is becoming clearer. This possibly will lead to the improvement of therapies in order to prevent the formation of ROS and ultimate correction of endothelial dysfunction (Cai and Harrison 2000).

Fig. 12.2 An illustration showing some common precursors for oxidative stress and resultant endothelial dysfunction

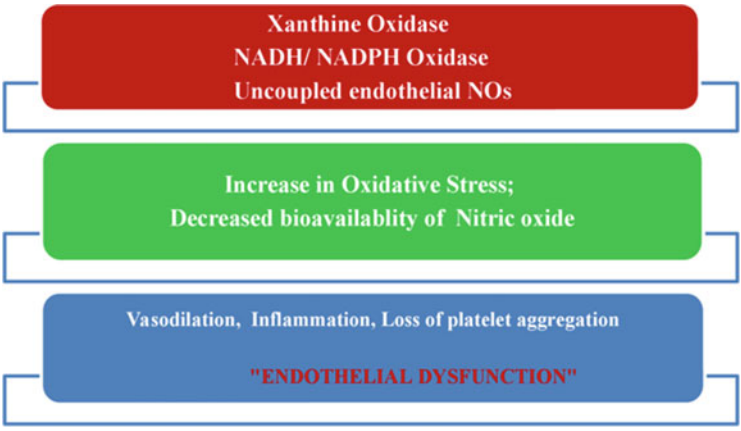

Fig. 12.3 Diagrammatic representation of molecular mechanism of oxidative stress induced endothelial dysfunction

12.6 Protective Action of Honey in CVD

Diet provides fuel to our body. A balanced diet provides nutrition to our body and is beneficial; however unhealthy diet is unfavourable to health. Studies have revealed that drinking beverages and sugar-sweetened drinks is related to the rise in blood pressure levels (Nguyen et al. 2009). Interestingly, honey which is a composite form of sugars is known to have a number of therapeutic and healthy advantages (Alvarez-Suarez et al. 2010). Although consumption of honey on a regular basis can decrease blood pressure, more research work is mandatory to assess the long-term effects of

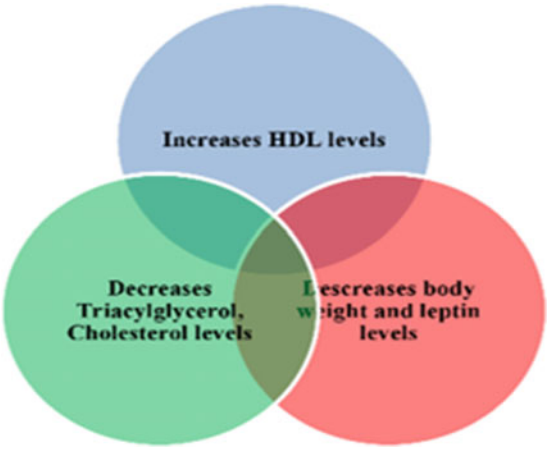

Fig. 12.4 A graphical representation of effect of honey intake on lipid profile

honey on healthy male subjects. Honey has many useful properties such as low pH, flavonoid content, hydrogen peroxide, phenols and sugar concentration that make it a good antimicrobial and antibacterial agent (Molan 1992). The risk of developing hypertension is related to gender because males have a higher risk than their female counterparts (Reckelhoff 2001). According to this study it is understood that honey has the ability to decrease blood pressure (both systolic and diastolic) and also the heart rate in healthy male subjects. Kaempferol is a flavanoid present in honey that shows effects by gene modulation and protein expression of inflammatory molecules (Zeng et al. 2015). Another honey flavonoid chrysin has numerous pharmacological actions and has a protective role in atherosclerosis. Chrysin inhibits the formation of foam cells some of which stimulate cholesterol flow (Kong et al. 2013).

Hypertension is linked to diet. Unhealthy diet being one of the modifiable risk factors linked to high BP. High salty diets have been documented as a cause for high blood pressure (Sacks et al. 2001). Increased cholesterol levels in the blood lead to atherosclerosis. Therefore, foods rich in saturated fats and trans fats are injurious to the heart (Assmann and Schulte 1992). Diets rich in carbohydrate content are harmful for health and lead to diseases of the cardiovascular system (Meena et al. 2007). Honey, though a composite sugar mixture, is described as cardio protective (Maureen 2004) as it improves the lipid profile (Fig. 12.4). According to a study, honey consumption in hypertensive patients decreased both systolic and diastolic blood pressure (Al-Waili 2003). According to a report, honey decreased the blood pressures levels that were raised in rats fed on a carbohydrate diet to induce obesity (Romero-Silva et al. 2011). This was supported by another study that concluded decreased systolic blood pressure in hypertensive rats by honey intake (Erejuwa et al. 2012). The effects that honey intake exert on hypertensive and diabetic patients are summed up in Fig. 12.5.

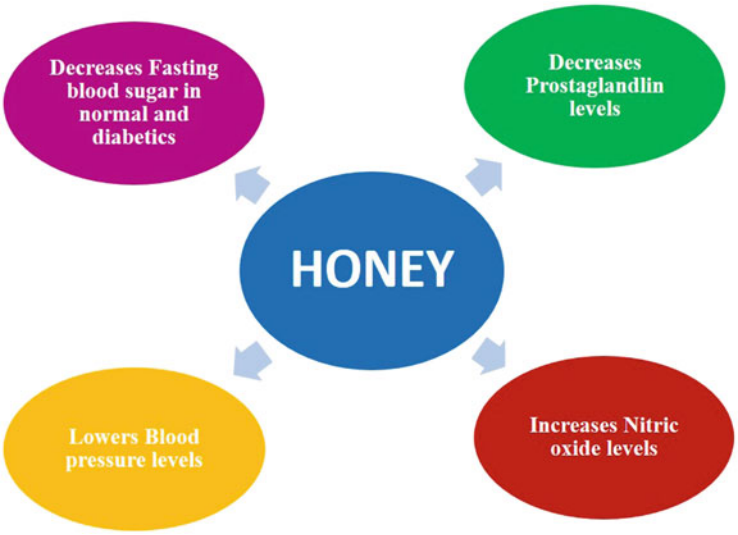

Fig. 12.5 Protective effect of honey on blood sugar and blood pressure

12.7 Other Applications of Honey

1. Prevents gastric ulcers (Ali et al. 1991)
2. Honey is useful as a therapy for diarrhoea (Jeddar et al. 1985)
3. Wound healing (Dumronglert 1983)
4. Used as skin disinfectant (French et al. 2005)
5. Immune inducer (Al-Waili and Haq 2004)
6. Anti-diabetic agent (Akhtar and Khan 1989)
7. Antibacterial agent (Jeddar et al. 1985)
8. Antioxidant (Raloff 1998) and
9. Antimutagenic and antitumour activity (Orsolic 2004).

12.8 Conclusion

Natural honey has many biological functions. The potential of lowering CVD risks is commonly found in foods like honey, green tea, fruits, etc. due to their antioxidant and flavonoid content. A number of flavonoids such as catechin, quercetin etc. that are present in honey are beneficial for CVDs with proven protective effects against metabolic disorders. Honey ingestion increases the levels of vitamin C, beta carotene, glutathione reductase, copper, zinc, NO and its end products. It is also believed to decrease the levels of different prostaglandins like PG E2 and PG F2, thromboxane B2 levels, CRP and homocysteine. Honey consumption improves lipid profiles

and transforms C-peptide levels and insulin secretion. Consumption of honey on a regular basis increases HDL levels and decreases triglycerides and VLDL levels. Honey has dominant antioxidant capacity and its intake prevents oxidative stress, thereby helps in promotion of good health. The flavanoid and polyphenolic content of honey helps to prevent complications in patients with diabetes mellitus, hypertension and cardiac diseases.

Therefore, honey plays a beneficial role in various cardiovascular diseases.

References

Afroz R, Tanvir EM, Paul S, Bhoumik NC, Gan SH, Khalil MI (2016) DNA damage inhibition properties of sundarban honey and its phenolic composition. J Food Biochem 40:436–445

Akhtar MS, Khan MS (1989) Glycaemic responses to three different honeys given to normal and alloxan-diabetic rabbits. J Pak Med Assoc 39:107–113

Ali AT, Chowdhury MN, Al-Humayyd MS (1991) Inhibitory effect of natural honey on Helicobacter pylori. Trop Gastroenterol 12:139–143

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

Alvarez-Suarez JM, Tulipani S, Romandini S, Bertoli E, Battino M (2010) Contribution of honey in nutrition and human health: a review. Mediter J Nutr Metabol 3:15–23

Al-Waili NS (2003) Intrapulmonary administration of natural honey solution, hyperosmolar dextrose or hypoosmolar distill water to normal individuals and to patients with type-2 diabetes mellitus or hypertension: their effects on blood glucose level, plasma insulin and C-peptide, blood pressure and peaked expiratory flow rate. Eur J Med Res 8:295–303

Al-Waili NS (2005) Mixture of honey, beeswax and olive oil inhibits growth of Staphylococcus aureus and Candida albicans. Arch Med Res 36:10–13

Al-Waili NS, Haq A (2004) Effect of honey on antibody production against thymus-dependent and thymus independent antigens in primary and secondary immune responses. J Med Food 7:491–494

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

Assmann G, Schulte H (1992) Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Am J Cardiol 70:733–737

American Heart Association (2004) Heart Disease and Stroke Statistics: 2004 Update. American Heart Association, Dallas, TX, p 2003

Baroni V, Chiabrando A, Costa C, Wunderlin A (2002) Assessment of the floral origin of honey by SDS–PAGE immunoblot techniques. J Agric Food Chem 50:1362–1367

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

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

Bostom AG, Lathrop L (1997) Hyperhomocysteinemia in end-stage renal disease: prevalence, etiology, and potential relationship to arteriosclerotic outcomes. Kidney Int 52:10–20

Cai H, Harrison DG (2000) Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 87:840–844

Cortes ME, Vigil P, Montenegro G (2011) The medicinal value of honey: a review on its benefits to human health, with a special focus on its effects on glycemic regulation. Cien Inv Agr 38:303–317

Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW et al (2018) Screening for cardiovascular disease risk with electrocardiography: US preventive services task force recommendation statement. JAMA 319(22):2308–2314

Dadlani H, Ballinger ML, Osman N, Getachew R, Little PJ (2008) Smad and p38 MAP kinase-mediated signaling of proteoglycan synthesis in vascular smooth muscle. J Biol Chem 283:7844–7852

Dumronglert EA (1983) Follow-up study of chronic wound healing. Dressing with pure natural honey. J Nat Res Counc Thail 15:39–66

Eckel RH (1997) Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. Circulation 96:3248–3250

Erejuwa OO, Sulaiman SA, Abwahab MS, Kuttulebbai NS, Salzihan S, Gurtu S (2012) Honey supplementation in spontaneously hypertensive rats elicits antihypertensive effect via amelioration of renal oxidative stress. Oxid Med Cell Longev 2012:1–14

Eyre H, Kahn R, Robertson RM, ACS/ADA/AHA Collaborative Writing Committee, ACS/ADA/AHA Collaborative Writing Committee Members, Clark NG, Doyle C, Hong Y, Gansler T, Glynn T, Smith RA (2004) Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Circulation 109:3244–3255

French VM, Cooper RA, Molan PC (2005) The antibacterial activity of honey against coagulase-negative staphylococci. J Antimicrob Chemother 56:228–231

Gimbrone MA (1995) Vascular endothelium: an integrator of pathophysiologic stimuli in atherosclerosis. Am J Cardiol 75:67B–70B

Grassi D, Aggio A, Onori L, Croce G, Tiberti S, Ferri C et al (2008) Tea, flavonoids, and nitric oxide-mediated vascular reactivity. J Nutrit 138:1554S–1560S

Grassi D, Desideri G, Tiberti S, Ferri C et al (2009) Oxidative stress, endothelial dysfunction and prevention of cardiovascular diseases. Agro Food Ind Hi Tech 20:8–11

Grassi D, Desideri G, Ferri C (2010) Flavonoids: antioxidants against atherosclerosis. Nutrients 2:889–902

Gross M (2004) Flavonoids and cardiovascular disease. Pharm Biotechnol 42:21–35

Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD et al (1989) High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 79:8–15

Hayek T et al (1997) Reduced progression of atherosclerosis in apolipoprotein E-deficient mice following consumption of red wine, or its polyphenols quercetin or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation. Arterioscl Thromb Vascul Biol 17:2744–2752

Herbst U, Toborek M, Kaiser S, Mattson MP, Hennig B (1999) 4-Hydroxynonenal induces dysfunction and apoptosis of cultured endothelial cells. J Cell Physiol 181:295–303

Hoff HF, O'Neil J (1991) Lesion-derived low density lipoprotein and oxidized low density lipoprotein share a lability for aggregation, leading to enhanced macrophage degradation. Arterioscl Thromb Vascul Biol 11:1209–1222

Hu FB, Willett WC (2002) Optimal diets for prevention of coronary heart disease. JAMA 288:2569–2578

Islam A, Islam N, Moniruzzaman M (2012) Physicochemical and antioxidant properties of Bangladeshi honeys stored for more than one year. BMC Complement Altern Med 12:177

Jeddar A, Kharsany A, Ramsaroop UG, Bhamjee A, Haffejee IE, Moosa A (1985) The antibacterial action of honey: an in vitro study. S Afr Med J 67:257–258

Khalil M, Sulaiman S (2010) The potential role of honey and its polyphenols in preventing heart disease: a review. Afr J Tradit Complement Altern Med 7:315–321

Kivimäki M, Virtanen M, Elovainio M, Kouvonen A, Väänänen A, Vahtera J (2006) Work stress in the etiology of coronary heart disease—a meta-analysis. Scand J Work Environ Health 32:431–442

Kong L, Luo C, Li X, Zhou Y, He H (2013) The anti-inflammatory effect kaempferol on early atherosclerosis in high cholesterol fed rabbits. Lipids Health Dis 12:115

Lee KW, Kim YJ, Lee HJ, Lee CY (2003) Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. J Agric Food Chem 51:7292–7295
Little PJ, Chait A, Bobik A (2011) Cellular and cytokine-based inflammatory processes as novel therapeutic targets for the prevention and treatment of atherosclerosis. Pharmacol Ther 131:255–268
Mackay J, Mensah G (2004) The atlas of heart disease and stroke. The World Health Organization. http://www.who.int/cardiovasculardiseases/resources/atlas/en/
Maor I, Hayek T, Coleman R, Aviram M (1997) Plasma LDL oxidation leads to its aggregation in the atherosclerotic apolipoprotein E-deficient mice. Arterioscl Thromb Vascul Biol 17:2995–3005
Maureen W (2004) Eating honey can lower the risk of heart disease. J Med Food 1:100–107
Meena S, Beverley A, Abhimanyu G (2007) Effect of high-carbohydrate or high-cis-monounsaturated fat diets on blood pressure: a meta-analysis of intervention trials. Am J Clin Nutr 85:1251–1256
Mendis S, Puska P, Norrving B (2011). Global Atlas on Cardiovascular Disease Prevention and Control (PDF). World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp 3–18. ISBN 978-92-4-156437-3. Archived (PDF) from the original on 2014-08-17
Molan PC (1992) The antibacterial activity of honey. The nature of antibacterial activity. Bee World 73:5–28
Musselman DL, Evans DL, Nemeroff CB (1998) The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psych 55:580–592
Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M (2015) GBD 2013 Mortality and causes of Death collaborators. "Global, regional and national age sex specific all cause specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the global Burden of Disease Study 2013". Lancet 385:117-171
Nguyen S, Choi HK, Lustig RH, Hsu CY (2009) Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. J Pediatr 154:807–813
Nigro J, Osman N, Dart AM, Little PJ (2006) Insulin resistance and atherosclerosis. Endoc Rev 27:242–259
Orsolic N (2004) Basic I. Honey as a cancer-preventive agent. Period Biol 106:397–401
Prabhakaran D, Jeemon P, Roy A (2016) Cardiovascular diseases in India: current epidemiology and future directions. Circulation 133:1605–1620
Raloff J (1998) Honey a source of antioxidants. J Apic Res 37:221–225
Reckelhoff JF (2001) Gender differences in the regulation of blood pressure. Hypertension 37:1199–1208
Roger VL et al (2012) Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 125:e2
Romero-Silva S et al (2011) Effects of Honey against the accumulation of adipose tissue and the increased blood pressure on carbohydrate-induced obesity in rat. Lett Drug Des Discov 8:69–75
Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D et al (2001) Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. N Engl J Med 344:3–10
Saenger AK (2012) Universal lipid screening in children and adolescents: a baby step toward primordial prevention? Clin Chem 58:1179–1181
Schachinger V, Britten MB, Zeiher AM (2000) Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 101:1899–1906
Steinberg FM, Bearden MM, Keen CL (2003) Cocoa and chocolate flavonoids: implications for cardiovascular health. J Am Diet Assoc 103:215–223
Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the interheart study): case-control study. Lancet 364:937–952
Zeng P, Liu B, Wang Q, Fan Q, Diao JX, Tang J et al (2015) Apigenin attenuates atherogenesis through inducing macrophage apoptosis via inhibition of AKT Ser473 phosphorylation and downregulation of plasminogen activator inhibitor-2. Oxidative Med Cell Longev:2015