Potential benefits of honey in type 2 diabetes mellitus: A review

Amudha Kadirvelu [1*], Sunil Gurtu [2]

[1] MBBS, PhD; School of Medicine & Health Sciences, Monash University Sunway Campus, Malaysia
[2] MBBS, MD; School of Medicine & Health Sciences, Monash University Sunway Campus, Malaysia

**** Corresponding Author:*** Dr. Amudha Kadirvelu
School of Medicine & Health Sciences, Monash University Sunway Campus
Jalan Lagoon Selatan, 46150, Bandar Sunway, Selangor DE, Malaysia
Tel: ++(603) 55146316 Fax: ++(603) 55146323 | Email: amudha.kadirvelu@monash.edu

Abstract

Honey, besides being a nutrient has been a subject of renewed research interest in the last few years for its multiple medicinal values. Evidence indicates that honey can exert several health-beneficial effects such as gastroprotective, hepatoprotective, reproductive, hypoglycemic, antioxidant, antihypertensive, antibacterial, anti-fungal and anti-inflammatory effects. Several different surveys have been compiled on the nutritional and health aspects of honey. However, the nutritional value and medicinal properties of natural honey are too numerous to be comprehensively documented by these manuscripts. This review presents a synopsis of experimental studies performed in the recent years, which support honey as a novel antioxidant and anti-diabetic agent that might be of potential significance for the management of diabetes and its complications.

Key words: Natural honey, oxidative stress, type 2 diabetes mellitus

Introduction

Natural honey (NH) has been used as food and medicine by mankind since ancient times. It has been reported that raw honey is the most ancient sweetener, and has been in use throughout the world since several million years ago.[1] Natural honey (NH) is a sweet liquid food of high nutritional value, and immense health benefits.[2,3] NH is produced by honey-bees as blossom honey by secreting nectars of flowers, and honeydew honey (forest honey) by secreting the exudates of plant sucking insects (Aphids). The use of honey is even encouraged for all ages and embraced by all religious and cultural beliefs.

Honey is spoken of by all religious books, and accepted by all generations, traditions and civilizations, both ancient and modern. The religion of Islam recommended the use of honey as food and medicine, and an entire chapter called Surah al-Nahl meaning chapter of the Honey Bee was dedicated in the Holy Qur'an.[4,5] In the book of hadith, Prophet Muhammad encouraged the use of honey for curative and healing purposes.[6] In Christendom, there are

references made to the importance of bees and honey in the Bible, and these include the Books of Exodus, Judges, Mathew and Proverbs.[7-10] Honey has been used in Ayurveda medicine in India for at least 4000 years. The other traditions and civilizations that have long embraced honey include Budhists and Jews.[1,11]

For a long time in human history honey was an important source of carbohydrate and the only largely available sweetener until after 1800 when it was replaced by industrial sugar.[1] In the long human tradition honey has been used not only as a nutrient but also a medicine[11].

The composition of honey is mainly sugars and water. In addition, it also contains several vitamins and minerals, including B vitamins. The other constituents of honey are amino acids, antibiotic-rich inhibine, proteins, phenol antioxidants, and micronutrients.[2] The sugars in honey are sweeter and give more energy than artificial sweeteners, and the most abundant sugar in honey is fructose.[2,3,12] The high nutritional profile of honey with wide range of nutrients encourages its use as food. Recent studies have reported enhanced body weight gain, bone growth and mineralisation indicating growth stimulating property of honey.[13,14] Histological studies on wounds seem to suggest that stimulation of cell growth by honey could also enhance healing properties of honey.[14]

Type 2 diabetes mellitus (T2DM), one of the fastest-growing and the most alarming of chronic illnesses, is characterized by hyperglycemia, relative lack of insulin action, insulin resistance, and the development of diabetes specific complications in the retina, renal glomerulus, and peripheral nerve. Diabetes is also associated with accelerated atherosclerotic disease affecting arteries that supply the heart, brain, and lower extremities. In addition, diabetic cardiomyopathy is a major diabetic complication. Rapidly increasing prevalence of type 2 diabetes mellitus (T2DM) is a major cause of concomitant increase in the incidence of cardiovascular disease in the industrialized world. According to International Diabetes Federation if current trends continue, it is estimated that the number of individuals with diabetes will increase to over 300 million by 2025.[15]

Chronic hyperglycemia, which is the primary manifestation of diabetes, is responsible for the microvascular complications which ultimately result in damage to several target organs such as the eyes, kidneys and nerves.[16] While the focus of current management of DM - whether non-pharmacological, such as dietary modifications, exercise and weight loss or with drugs - is aimed at achieving optimal control of the hyperglycemic state and thus preventing or delaying the onset of complications, this is often difficult to achieve even with the use of multiple drugs.[17,18] There is therefore, an unmet need for supplemental, alternative therapeutic modalities which might provide additional positive outcomes. In this regard, several studies have focused on the potentially beneficial effects that honey might provide in the long term management of diabetes mellitus.

Oxidative stress and diabetes-associated complications

Although the origin of diabetic complications is multifactorial, oxidative stress is considered to be a vital link between metabolic abnormalities, hyperglycaemia and cardiovascular complications. Oxidative stress is defined as an “imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage”.[19] The increased oxidative stress observed in patients with diabetes most likely results from the overproduction

of mitochondrial ROS induced by hyperglycaemia. ROS are a heterogeneous population of molecules that include free radicals, such as superoxide (O2-), hydroxyl (OH), peroxyl (RO2), and hydroperoxyl (HRO2-), as well as nonradical species, as hydrogen peroxide (H2O2) and hydrochloric acid (HCl).[20,21]

A direct relationship is known to exist between glycemic control and the severity of micro- and macrovascular complications, among subjects with T2DM[22].Several studies have shown that oxidative stress is an important determinant of vascular injury in subjects withT2DM and that hyperglycemia is the causal link between DM and oxidative stress.[23,24] Interestingly, studies performed in diabetic rodents found increased concentrations of superoxide (O2-) and hydrogen peroxide (H2O2) in the aortic wall.

The ability of cells to scavenge excess reactive species is largely dependent on the efficiency of the overall antioxidant defense system.[25,26] This antioxidant defense network consists of endogenous and exogenous antioxidants. The endogenous antioxidants comprise the enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and non-enzymatic antioxidants including glutathione (GSH), vitamins C and E as well as small molecules.[27] The exogenous antioxidants comprise the micronutrients and other exogenously administered antioxidants.[19,25] Evidence indicates that individuals with chronic or degenerative diseases are more susceptible to oxidative stress due to the imbalance between oxidants and antioxidants.[28, 29]

Molecular Mechanisms of Hyperglycemia-Induced Oxidative Stress

The increased oxidative stress in patients with poorly controlled DM is predominantly due to hyperglycemia, which occurs through five metabolic pathways:[30] increased flux of glucose through the polyol pathway;[23] increased formation of advanced glycation end products (AGEs) and their receptors;[31] activation of protein kinase C isoforms- β, δ, and α;[32] overactivity of hexosamine pathways,[33] and a decrease of antioxidant defenses.[23] The increased polyol flux results from the increased enzymatic conversion of glucose to polyalcohol sorbitol, which in turn, reduces intracellular NADPH and glutathione concentrations. Besides, sorbitol dehydrogenase metabolizes sorbitol to fructose, increasing the intracellular ratio of NADH/NAD+, that inhibits glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which increases the concentration of triose phosphate. Increased concentrations of triose phosphate drive the formation of both methylglyoxal, a precursor of AGEs, and diacylglycerol (DAG) (through α-glycerol-3- phosphate), thereby activating Protein Kinase C (PKC).[23]

Chronic hyperglycemia also increases the circulating concentrations of cytokines, growth factors, and hormones, such as endothelin-1 and angiotensin II, which activate PKC isoforms β and δ by binding to their cell surface receptors.[34-36] PKC activation in turn, inhibits insulin-stimulated endothelial Nitric Oxide Synthase (eNOS) expression in endothelial cells and decreases nitric oxide production in smooth muscle cells.[37] In vascular smooth muscle cells, PKC also has been shown to induce the over expression of the fibrinolytic inhibitor, plasminogen activator inhibitor (PAI)-1, and the activation of NF-κβ.[38] Over expression of PKC contributes to the accumulation of a microvascular matrix protein by inducing the expression of transforming growth factors (TGF)-β, fibronectin, and type IV collagen in both cultured mesangial cells and in glomeruli of diabetic rats.[39] By a similar mechanism, PKC

contributes to cardiac fibrosis through upregulation of the expression of fibrosis-promoting factors, such as TGF-β and connective tissue growth factor.[40] PKC also enhances vascular permeability by increasing the expression of vascular endothelial growth factor (VEGF).[41]

The production of ROS in subjects with DM is mediated by the binding of AGEs to their receptors (RAGE). AGEs are formed by the excessive intracellular glucose concentration that occurs with hyperglycemia. Binding of AGEs to RAGE induces the generation of intracellular ROS and the subsequent activation of the redox sensitive transcription factor NF-κβ, which in turn promotes the expression of a variety of genes associated with atherosclerosis, including intracellular adhesion molecule-1 (ICAM-1), vascular adhesion cell molecule-1 (VCAM-1), monocyte chemotactic protein-1 (MCP-1), PAI-1, tissue factor, and VEGF.[42,43] Moreover, AGEs that are present in the extracellular matrix decrease elasticity and quench nitric oxide, reducing endothelium dependent vasodilatation.[44] Since nitric oxide is a mediator of the angiogenic signal of VEGF, the AGE-RAGE axis may impair the formation of collateral arteries after myocardial infarction.[45] RAGE induction and activation of PKC both augment oxidative stress, which induces low-grade chronic inflammation, a common feature of T2DM, altering anti-oxidant defences and inducing apoptosis of circulating endothelial progenitor cells, thereby impeding vascular repair.[46]

Hyperglycemia causes added damage to blood vessels by also inducing the hexosamine pathway. Under hyperglycemic conditions, increased nutrient availability is shunted into the hexosamine pathway. The end product of this pathway, UDP-N-acetyl glucosamine, is utilized as a substrate for the enzymatic glycosylation of transcription factors *via* O-GlcNActransferase (OGT), which in turn regulate the expression of genes, such as PAI-1, TGF-α, TGF-β1, each of which is implicated in the pathogenesis of vascular complications. In addition, hyperglycemia, through the hexosamine pathway, impairs activation of the IR substrate (IRS)/phosphatidylinositol 3-kinase (PI3-K)/Aktpathway, resulting in deregulation of eNOS activity.[47-50]

Excess superoxide also directly inhibits critical anti-atherosclerosis endothelial enzymes independent of activating the 5 damaging pathways implicated in metabolite-induced diabetic complications. Both of these enzymes (eNOS and prostacyclin synthase) are inhibited in diabetic patients and diabetic animals.[51] Treatment of the diabetic animals with an SOD/catalase mimetic has been shown to prevent diabetes-induced oxidative inactivation of aortic prostacyclin synthase.[51] Inhibition of hyperglycemia-induced ROS production in diabetic mice using either transgenic antioxidant enzyme expression or combinations of antioxidant compounds reportedly prevents the development of experimental diabetic retinopathy, nephropathy, neuropathy and cardiomyopathy.[52-57]

Thus, the metabolic abnormalities of diabetes play a pivotal role in the development of diabetes related complications, both microvascular and cardiovascular by causing mitochondrial superoxide over production in endothelial cells of large and small vessels, as well as in the myocardium. (Figure 1).

Animal models of diabetes mellitus

Animal models of DM have been used extensively for screening natural and synthetic compounds for anti-diabetic activity as well as for investigating the pathophysiological

mechanisms involved in the development of diabetes and its complications. The most widely used experimental tool for this purpose is streptozotocin (STZ), which can induce either type 1 or type 2 DM with appropriate dose selection.[58-61] Other experimental models include the alloxan-induced-diabetes model, [58,62,63] high-fat-diet model[60,64] and genetic models.[65,66]

Potential effects of honey on diabetes and its complications

Honey has been shown to exert beneficial effects on experimentally induced diabetes and its complications in animal models. Potentially beneficial effects have been demonstrated on three major components *viz*. a) glycemic control and lipid metabolism b) increased oxidative stress which could contribute to c) organ damage. Evidence for these, from experimental studies in animals, is discussed below.

Effect of honey on glycemic control and lipid metabolism

Pure natural honey has been reported to produce a lower glycemic response in rabbits as compared to sucrose or commercial honey, possibly due to added sugar in the latter.[67] Chepulis and Starkey reported a significant decrease in HbA1c levels in Sprague-Dawley rats fed with honey over several weeks.[14] They also found a significant increase in HDL cholesterol in the honey fed group as compared to the sucrose-fed or sugar free diet-fed groups. No other differences were observed in the levels of other lipids. The weight gain in the honey-fed rats was similar to the sugar free-diet group and significantly less as compared to the sucrose-fed group. On the other hand, Erejuwa et al, reported insignificant differences in fasting blood glucose or body weight in honey-fed rats.[68] Busserolles et al, reported reduced serum triglyceride levels in honey fed rats.[69] Yet another study reported a reduction in ependymal fat and triglycerides but an increase in other (non-HDL) lipids with honey administration in rats.[70]

While reports on the effects of honey on resting levels of blood glucose and lipids in normal animals appear to be equivocal, there is relatively more consistent evidence for a beneficial effect of honey treatment on the biochemical parameters in experimentally-induced diabetic animals.[13,67,71] Fasanmade and Alabi reported that honey elicited significant anti-hyperglycemic effects in alloxan-induced diabetic rats while Erejuwa et.al found similar effects in STZ induced diabetic rats.[71-73] Furthermore, honey supplementation appears to augment the anti-hyperglycemic effect of standard anti-diabetic drugs in STZ-induced diabetic rats.[74,75] Increase in HDL cholesterol and a decrease in triglycerides and VLDL has been reported in STZ-induced diabetic rats following administration of honey alone or in combination with metformin.[76]

The exact mechanism by which honey might elicit these positive effects on blood glucose and lipid levels is not clear. However based on several studies the following possibilities merit consideration:

Effects of fructose content in honey

One of the potential mechanisms for the antidiabetic effects of honey could be related to the fructose content in honey. There is evidence that fructose tends to lower blood glucose levels in rodent models of diabetes.[77,78] Mechanisms responsible for this may include a prolongation of gastric emptying time,[79,80] reduced rate of intestinal absorption[81] and reduced food intake.[82,83] Additionally, fructose has also been shown to stimulate glucokinase in hepatocytes which plays a significant role in the uptake and storage of glucose (as glycogen) by the liver.[84] Watford demonstrated that infusion of small amounts of fructose into the duodenum increased hepatic uptake and storage and reduced peripheral glucose and insulin levels in dogs.[85] Interestingly, glucose which is present along with fructose in honeys has been shown to synergistically enhance the absorption of fructose and may thus promote its hepatic actions through its enhanced delivery to the liver.[86,87]

Effects of honey on liver

The liver has been termed as one of the 'Three Musketeers' in the control of glycemia; the other two being the pancreas and skeletal muscle.[88] Fructose which is present in significant proportions in most honeys has been shown to enhance glucokinase and glycogen synthase activities and inhibit phosphorylase activity in the liver.[91,84,89,90] The net effects of these actions would tend to result in increased hepatic glucose phosphorylation, increased synthesis and decreased breakdown of glycogen in the liver. The presence of glucose and fructose together in honey have been suggested to provide a complimentary effect on glucose and glycogen in the liver.[92,93] However, only low concentrations of fructose have been found to improve glucose tolerance and hepatic glucose metabolism while higher concentrations have an opposite effect.[94] Although, there is considerable evidence to suggest that consumption of high amounts of fructose may result in weight gain and other adverse metabolic consequences such as impaired lipid metabolism, insulin resistance and increased visceral fat deposition,[83,95-98] this concern is more in relation to its excessive consumption associated with high-fructose drinks and foods which are likely to yield higher concentrations of fructose delivered to the liver. [99,100]

Effects of honey on hormones regulating satiety, food intake and body weight

A few experimental studies have documented the effects of honey on hormones that regulate satiety and calorie intake and expenditure. Honey fed rats have been reported to exhibit lower levels of leptin compared to sucrose fed rats.[70] Like so many of the effects described above, a role of fructose has also been suggested for the reduction of leptin secretion and an attenuation of postprandial suppression of ghrelin.[101,102] However the effects of honey administration on body weight are equivocal with some studies reporting reduced weight gain.[13, 70,103]

Honey, contains several other constituents, [3,104,105] in addition to glucose and fructose and these bioactive constituents might also contribute to its overall effects on glycemic control which has been reported in several experimental studies in both non-diabetic and diabetic animals.[3,13,67,71-73]

Effects of honey on diabetic complications

The metabolic derangement in diabetes mellitus is not confined to hyperglycemia and impaired utilization of glucose by the tissues but it also sets in motion a train of other metabolic abnormalities which result in progressive complications including abnormalities of microcirculation, atherosclerosis and end organ damage such as retinopathy, nephropathy and neuropathy. While some of these damaging consequences can be minimized with anti-diabetic medication others continue to progress despite restoration of glycemic control.[106-108] Several mechanisms have been proposed, however mitochondrial oxidative stress appears to be the primary determinant for the deleterious effects of hyperglycemia which result in tissue and organ damage.[51,109] Further, oxidative stress has also been shown to reduce glucose uptake and storage and to promote insulin resistance.[110-114] Hyperglycemia itself exerts toxic effects on pancreatic β-cells through increased oxidative stress leading to increased apoptosis and reduced insulin content.[115-118] There is evidence to suggest that honey might provide protection against diabetic complications via its antioxidant and organ protective effects.

Anti-oxidant and organ protective-effects of honey

Antioxidants have been shown to improve insulin levels and reduce insulin resistance in diabetes mellitus.[119-123] There are a number of reports which show that honey possesses free radical scavenging properties.[117,124-126] Since oxidative stress is believed to impact the health and insulin producing ability of pancreatic β cells as also to promote insulin resistance (see above) it is reasonable to expect that honey supplementation will provide a rescue for the stressed insulin producing pancreatic cells and also combat insulin resistance.

Oxidative and non-oxidative metabolic stress generated in the hyperglycemic state might also play a potential role in damaging other organs like the kidneys, heart, nerves and liver.[106,107,127-130] There is experimental evidence to support an organ protective effect of honey against injuries induced by chemical insults which are presumed to result as a consequence of increased oxidative stress.[131-134] The fact that honey supplementation has also been found to ameliorate oxidative stress and exert a protective effect against organ damage in experimentally induced diabetes in animals[68,72-75,135,136] would tend to indicate that it could potentially ameliorate the progressive end-organ damage that results from of sustained hyperglycemia in diabetes mellitus. Moreover, since this protective effect was also apparent in the pancreatic β cells,[68,74,136] it might also slow down the progress of the diabetic state itself.

Clinical studies

In contrast to the ample evidence from experimental studies which suggests potentially beneficial effects that honey supplementation might offer for the control of diabetes mellitus and its complications, the data available from studies in normal human subjects or diabetic patients is rather sparse. There are some sporadic reports of effects (Table 1) which tend to indicate a potential positive impact of honey supplementation on glycemic control and progression of diabetes mellitus. The favourable effects are reported in both diabetic and non-diabetic subjects.[137-146] Besides, honey is also reported to reduce body weight ameliorate lipid

metabolism in diabetic and non-diabetic subjects.[138,144,147,149,150] In addition, Gheldof et al have shown an increase in serum antioxidant capacity with honey consumption in healthy men.[152] Since oxidative stress has been implicated both in the development of diabetes as well as its complications, the antioxidant effects of the constituents of honey might also afford an organ-protective effect which could limit the progression of diabetes and reduce complications.

Conclusion

There is considerable evidence from experimental studies that honey may provide benefits in the management of diabetes mellitus. These potential benefits could be both in terms of better control of the hyperglycemic state *per se*, as well as for limiting other metabolic derangements and reduction of deleterious effects on organs which produce diabetic complications. However, most of the studies on experimental animal models of diabetes have employed chemically (Streptozotocin or Alloxan) induced diabetes which may not truly reflect the development of diabetes in humans specially Type 2. It is therefore necessary that studies are carried out in other animal models e.g. high-fat diet fed obese animals or genetically prone animals which might correlate more closely with the human type 2 diabetes. Also, the promising effects seen in experimental studies need to be further investigated in well designed, controlled clinical studies to determine whether these can be duplicated in actual clinical situations. Additionally, it must also be considered that the major constituents of honey are sugars and consumption of high doses on a regular basis could possibly nullify or even reverse any beneficial effects. Thus optimal doses would have to be determined. Based on the experimental data from several sources, it may be concluded that honey has potential benefits in the management of diabetes and its complications and there is a strong case for pursuing this further.

Conflict of interest: None declared.

References

1. Crane E: History of honey. In Honey, A Comprehensive Survey. Edited by Crane E. London: William Heinemann; 1975:439–488.
2. Ajibola A, Chamunorwa JP, Kennedy HE. Nutraceutical values of natural honey and its contribution to human health and wealth. Nutrition & Metabolism, 2012, 9: 61.
3. Bogdanov S, Jurendic T, Sieber R. et al. Honey for nutrition and health: a review. J Am CollNutr. 2008;27:677–89.
4. An-Nahl (The Bee) 16, 1 – 128: The Holy Qur'an, English translation of the meanings and Commentary. The Presidency of Islamic Researches, IFTA, Call and Guidance.
5. Al-Madinah Al-Munawarah: Kingdom of Saudi Arabia: King Fahd Holy Qur'an Printing Complex; 1990:753. 1410 A.H.
6. Al-Bukhari M: SahihBukhari Nazi Publications. 3 Rev Editionthedition. Chicago LISA: 740A.D; 1976.

7. Exodus 33, 3: The Holy Bible. Authorised King James Version. New York: Oxford University Press; 1972.
8. Judges 14, 8: The Holy Bible. Authorised King James Version. New York: Oxford University Press; 1972.
9. Mathew 3, 4: The Holy Bible. Authorised King James Version. New York: Oxford University Press; 1972.
10. Proverb 24, 13: The Holy Bible. Authorised King James Version. New York: Oxford University Press; 1972.
11. Jones R: Honey and healing through the ages. In Munn P, Jones R (eds): Honey and Healing." Cardiff: International bee research association IBRA, pp. 1-4, 2001.
12. Ajibola A, Idowu GO, Amballi AA, Oyefuga OH, Iquot IS: Improvement of some haematological parameters in albino rats with pure natural honey. *J Biol Sci Res* 2007, 2:67–69.
13. Chepulis L, Starkey N. The Long-Term Effects of Feeding Honey Compared with Sucrose and a Sugar-Free Diet on Weight Gain, Lipid Profiles, and DEXA Measurements in Rats. *Journal of Food Science*, 2008, 73 (1): H1–H7
14. Molan P: Why honey is effective as a medicine. 2. The scientific explanation of its effects. Bee World 2001, 82:22-40.
15. Diabetes and Cardiovascular Disease: Time to act. IDF 2001. Available from http://www.idf.org/webdata/docs/Diabetes%20and%20CVD.pdf
16. Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: The "metabolic memory": is more than just tight glucose control necessary to prevent diabetic complications? *J Clin Endocrinol Metab*, 2009, 94(2):410-5.
17. vanRaalte DH, Diamant M. Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? *Diabetes Res Clin Pract*, 2011, 93 (Suppl 1):S37-46.
18. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care*, 2004, 27(7): 1535-40.
19. Sies, H. Oxidative stress: Introduction. In Oxidative Stress: Oxidants and Antioxidants; Academic Press: London, UK, 1991.
20. Pieper GM, Langenstroer P,Siebeneich W. Diabetic-induced endothelial dysfunction in rat aorta: role of hydroxyl radicals. *Cardiovasc Res* 1997; 34(1): 145-56.
21. Chang KC, Chung SY, Chong WS, et al. Possible superoxide radical-induced alteration of vascular reactivity in aortas from streptozotocin-treated rats. *J Pharmacol Exp Ther* 1993; 266(2): 992-1000.
22. Baldeweg SE, Yudkin JS. Implications of the United Kingdom prospective diabetes study. *Prim Care* 1999; 26(4): 809-27.
23. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; 414(6865): 813-20.
24. Giardino I, Edelstein D, Brownlee M. BCL-2 expression or antioxidants prevent hyperglycemia-induced formation of intracellular advanced glycationendproducts in bovine endothelial cells. *J Clin Invest* 1996; 97(6): 1422-8.
25. Halliwell B, Gutteridge J.M.C. Free Radicals in Biology and Medicine; Clarendon Press:Oxford, UK, 2007.
26. Halliwell B. Free radicals and antioxidants-quo vadis? *Trends Pharmacol. Sci*. 2011, 32,125–130.
27. Niture sk, Kasper JW, SHen J, Jaiswal AK. Nrf2 signaling and cell survival. *Toxicol Appl Pharmacol*. 2010; 244(1):37-42.

28. Shibata N, Kobayashi, M. The role for oxidative stress in neurodegenerative diseases. *Brain Nerve* 2008, 60, 157–170.
29. Kadenbach B, Ramzan R, Vogt S. Degenerative diseases, oxidative stress and cytochrome c oxidase function. *Trends Mol. Med*. 2009, 15, 139–147.
30. Narayan KM, Boyle JP, Geiss LS, et al. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. *Diabetes Care* 2006; 29(9): 2114-6.
31. Schreck R, Rieber P, Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NFkappa B transcritption factor and HIV-1. *EMBO J* 1991; 10(8): 2247-58.
32. Nathan DM, Lachin J, Cleary P, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003; 348(23): 2294-303.
33. Nathan DM, Cleary PA, Backlund J-YC, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353(25): 2643-53.
34. Robin P, Boulven I, Desmyter C, et al. ET-1 stimulates ERK signaling pathway through sequential activation of PKC and Src in rat myometrial cells. *Am J Physiol Cell Physiol* 2002; 283(1): C251-60.
35. Malhotra A, Kang BP, Cheung S, et al. Angiotensin II promotes glucose-induced activation of cardiac protein kinase C isozymes and phosphorylation of troponin I. *Diabetes* 2001; 50(8): 1918-26.
36. Koya D, Jirousek MR, Lin YW, et al. Characterization of protein kinase C beta isoform activation on the gene expression of transforming growth factor-beta, extracellular matrix components, and prostanoids in the glomeruli of diabetic rats. *J Clin Invest* 1997; 100(1): 115-26.
37. Kuboki K, Jiang ZY, Takahara N, et al. Regulation of endothelial constitutive nitric oxide synthase gene expression in endothelial cells and in vivo : a specific vascular action of insulin. *Circulation* 2000; 101(6): 676-81.
38. Yerneni KK, Bai W, Khan BV, et al. Hyperglycemia-induced activation of nuclear transcription factor kappa B in vascular smooth muscle cells. *Diabetes* 1999; 48(4): 855-64.
39. Struder RK ,Negrete H, Craven PA, et al. Protein kinase C signals thromboxane induced increases in fibronectin synthesis and TGFbeta bioactivity in mesangial cells. *Kidney Int* 1995; 48(2): 422-30.
40. Way KJ, Isshiki K, Suzuma K, et al. Expression of connective tissue growth factor is increased in injured myocardium associated with protein kinase C beta2 activation and diabetes. *Diabetes* 2002; 51(9): 2709-18.
41. Harhaj NS, Felinski EA, Wolpert EB, et al. VEGF activation of protein kinase C stimulates occludin phosphorylation and contributes to endothelial permeability. Invest Ophthalmol Vis Sci 2006; 47(11): 5106-15.
42. Yamagishi Si, Yonekura H, Yamamoto Y, et al. Advanced glycation end products-driven angiogenesis in vitro. Induction of the growth and tube formation of human microvascular endothelial cells through autocrine vascular endothelial growth factor. *J BiolChem* 1997; 272(13): 8723-30.
43. Bierhaus A, Schiekofer S, Schwaninger M, et al. Diabetesassociated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 2001; 50(12): 2792-808.

44. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest* 1991; 87(2): 432-8.
45. Murohara T, Asahara T, Silver M, et al. Nitric oxide synthase modulates angiogenesis in response to tissue ischemia. *J Clin Invest* 1998; 101(11): 2567-78.
46. Chen J, Huang L, Song M, et al. C-reactive protein upregulates receptor for advanced glycation end products expression and alters antioxidant defenses in rat endothelial progenitor cells. *J CardiovascPharmacol* 2009; 53(5): 359-67.
47. Gabriely I, Yang XM, Cases JA, et al. Hyperglycemia induces PAI-1 gene expression in adipose tissue by activation of the hexosamine biosynthetic pathway. *Atherosclerosis* 2002; 160(1): 115-22.
48. Kolm-Litty V, Sauer U, Nerlich A, et al. High glucose-induced transforming growth factor beta1 production is mediated by the hexosamine pathway in porcine glomerular mesangial cells. *J Clin Invest* 1998; 101(1): 160-9.
49. Du XL, Edelstein D, Rossetti L, et al. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci* USA 2000;97(22): 12222-6.
50. Federici M, Menghini R, Mauriello A, et al. Insulin-dependent activation of endothelial nitric oxide synthase is impaired by Olinked glycosylation modification of signaling proteins in human coronary endothelial cells. *Circulation* 2002; 106(4): 466-72.
51. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54:1615–25.
52. Shen X, Zheng S, Metreveli NS, Epstein PN. Protection of cardiac mitochondria by overexpression of MnSOD reduces diabetic cardiomyopathy. *Diabetes*. 2006;55:798–805.
53. Vincent AM, Russell JW, Sullivan KA, Backus C, Hayes JM, McLean LL, Feldman EL. SOD2 protects neurons from injury in cell culture and animal models of diabetic neuropathy. *Exp Neurol*. 2007;208:216 –227.
54. Otero P, Bonet B, Herrera E, Rabano A. Development of atherosclerosis in the diabetic BALB/c mice. Prevention with vitamin E administration. *Atherosclerosis*. 2005;182:259 –265.
55. Zhang Y, Wada J, Hashimoto I, Eguchi J, Yasuhara A, Kanwar YS, Shikata K, Makino H. Therapeutic approach for diabetic nephropathy using gene delivery of translocase of inner mitochondrial membrane 44 by reducing mitochondrial superoxide production. *J Am Soc Nephrol*. 2006;17:1090 –1101.
56. Kowluru RA, Kowluru V, Xiong Y, Ho YS. Overexpression of mitochondrial superoxide dismutase in mice protects the retina from diabetes-induced oxidative stress. *Free Radic Biol Med*. 2006;41: 1191–1196.
57. DeRubertis FR, Craven PA, Melhem MF. Acceleration of diabetic renal injury in the superoxide dismutase knockout mouse: effects of tempol. *Metabolism*. 2007;56:1256 – 1264.
58. Mohanam S, Bose SM. Influence of streptozotocin- and alloxan-induced diabetes in the rat on collagenase and certain lysosomal enzymes in relation to the degradation of connective tissue proteins. *Diabetologia*, 1983 Jul;25(1):66-70.
59. Szkudelski T. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. PhysiolRes 2001, 50(6):637-46.

60. Srinivasan ,Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: A model for type 2 diabetes and pharmacological screening. *Pharmacological Research* , 2005, 52(4) 313–320
61. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia*,2008, 51(2):216-26.
62. Hoftiezer V, CarpenterAM . Comparison of streptozotocin and alloxan-induced diabetes in the rat, including volumetric quantitation of the pancreatic islets. *Diabetologia*, 1973;9(3): 178-184.
63. Carvalho EN, Carvalho NAS, Ferreira LM. Experimental model of induction of diabetes mellitus in rats. Acta Cir Bras [serial online] 2003 Vol18 Special Edition. Available on URL:http://www.scielo.br/acb.
64. Matveyenko AV, Gurlo T, Daval M, Butler AE, Butler PC. Successful Versus Failed Adaptation to High-Fat Diet–Induced Insulin Resistance. The Role of IAPP-Induced β-Cell Endoplasmic Reticulum Stress. *Diabetes* 2009;58(4):906-916.
65. Luo J, Quan J, Tsai J, Hobensack CK, Sullivan C, Hector R, et al. Nongenetic mouse models of non-insulin-dependent diabetes mellitus. *Metabolism* 1998;47:663–8.
66. Shafrir E. Diabetes in animals: Contribution to the understanding of diabetes by study of its etiopathology in animal models. In: Porte D, Sherwin RS, Baron A, editors. Diabetes mellitus. NewYork: McGraw-Hill; 2003. p. 231–55
67. Akhtar MS, Khan MS. Glycemic responses to to three different types of honeys given to normal and alloxan-diabetic rabbits. *J Pak Med Assoc* 39 (4), 107-13
68. Erejuwa OO, Sulaiman SA, Wahab MSA, Sirajudeen KNS, Salleh MSM, Gurtu S. Antioxidant protection of Malaysian tualang honey in pancreas of normal and streptozotocin-induced diabetic rats. *Ann Endocrinol* 2010 a, 71(4): 291-296.
69. Busserolles j, Gueux E, Rock E, Mazur A, rayssiguier Y. Substituting honey for refined carbohydrates protects rats from hypertriglyceridemic and prooxidative effects of fructose. *J Nutr*,2002;132(11):3379-82
70. Nemoseck TM, Carmody EG, Furchner-Evanson A, Gleason M, Li A, Potter H, Rezende LM, Lane KJ, Kern M. Honey promotes lower weight gain, adiposity and triglycerides than sucrose in rats. *Nutr Res*, 2011, 31(1):55-60.
71. Fasanmade AA, Alabi OT. Differential effects of honey on selected variables in alloxan-indiced and fructose-induced diabetic rats. *Afr J Biomed Res*, 2008, 11(20): 191-6.
72. Erejuwa OO, Sulaiman SA, Wahab MS. et al. Effects of Malaysian tualang honey supplementation on glycemia, free radical scavenging enzymes and markers of oxidative stress in kidneys of normal and streptozotocin-induced diabetic rats. *Int J Cardiol*. 2009;137:S45.
73. Erejuwa OO, Gurtu S, Sulaiman SA. et al. Hypoglycemic and antioxidant effects of honey supplementation in streptozotocin-induced diabetic rats. *Int J Vitam Nutr Res*. 2010b;80:74–82.
74. Erejuwa OO, Sulaiman SA, Wahab MS. et al. Antioxidant protective effect of glibenclamide and metformin in combination with honey in pancreas of streptozotocin-induced diabetic rats. *Int J Mol Sci*. 2010c;11:2056–66.
75. Erejuwa OO, Sulaiman SA, Wahab MS. et al. Comparison of antioxidant effects of honey, glibenclamide, metformin, and their combinations in the kidneys of streptozotocin-induced diabetic rats. *Int J Mol Sci*. 2011a;12:829–43

76. Erejuwa OO, Sulaiman SA, Wahab MS. et al. Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. *Int J Biol Sci*. 2011b;7:244–52.
77. Kwon S, Kim YJ, Kim MK. Effect of fructose or sucrose feeding with different levels on oral glucose tolerance test in normal and type 2 diabetic rats. *Nutr Res Pract*. 2008;2:252–8.
78. Erejuwa OO, Sulaiman SA, Wahab MS. Fructose might contribute to the hypoglycemic effect of honey. *Molecule*s. 2012;17:1900–15.
79. Moran TH, McHugh PR. Distinctions among three sugars in their effects on gastric emptying and satiety. *Am J Physiol*. 1981;241:R25–30.
80. Gregory PC, McFadyen M, Rayner DV. Relation between gastric emptying and short-term regulation of food intake in the pig. *Physiol Behav*. 1989;45:677–83.
81. Kellett GL, Brot-Laroche E, Mace OJ. et al. Sugar absorption in the intestine: the role of GLUT2. *Annu Rev Nutr*. 2008;28:35–54
82. Thibault L. Dietary carbohydrates: effects on self-selection, plasma glucose and insulin, and brain indoleaminergic systems in rat. *Appetite*. 1994;23:275–86.
83. Meirelles CJ, Oliveira LA, Jordao AA. et al. Metabolic effects of the ingestion of different fructose sources in rats. *Exp Clin Endocrinol Diabetes*. 2011;119:218–20.
84. Van Schaftingen E, Vandercammen A. Stimulation of glucose phosphorylation by fructose in isolated rat hepatocytes. *Eur J Biochem*. 1989 Jan 15;179(1):173-7
85. Watford M. Small amounts of dietary fructose dramatically increase hepatic glucose uptake through a novel mechanism of glucokinase activation. *Nutr Rev* 2002; 60(8):253-7
86. Fujisawa T, Riby J, Kretchmer N. Intestinal absorption of fructose in the rat. *Gastroenterology*. 1991;101:360–7.
87. Ushijima K, Riby JE, Fujisawa T. et al. Absorption of fructose by isolated small intestine of rats is via a specific saturable carrier in the absence of glucose and by the disaccharidase-related transport system in the presence of glucose. *J Nutr*. 1995;125:2156–64.
88. Klip A, Vranic M. Muscle, liver, and pancreas: Three Musketeers fighting to control glycemia. *Am J Physiol Endocrinol Metab*. 2006;291:E1141–3.
89. Van Schaftingen E, Davies DR. Fructose administration stimulates glucose phosphorylation in the livers of anesthetized rats. *FASEB J*. 1991;5:326–30.
90. Ciudad CJ, Carabaza A, Guinovart JJ. Glycogen synthesis from glucose and fructose in hepatocytes from diabetic rats. *Arch Biochem Biophys*. 1988;267:437–47.
91. Youn JH, Kaslow HR, Bergman RN. Fructose effect to suppress hepatic glycogen degradation. *J Biol Chem*. 1987;262:11470–7.
92. Regan JJ Jr, Doorneweerd DD, Gilboe DP. et al. Influence of fructose on the glycogen synthase and phosphorylase systems in rat liver. *Metabolism*. 1980;29:965–9.
93. Shiota M, Galassetti P, Igawa K. et al. Inclusion of low amounts of fructose with an intraportal glucose load increases net hepatic glucose uptake in the presence of relative insulin deficiency in dog. *Am J Physiol Endocrinol Metab*. 2005;288:E1160–7.
94. Wei Y, Bizeau ME, Pagliassotti MJ. An acute increase in fructose concentration increases hepatic glucose-6-phosphatase mRNA via mechanisms that are independent of glycogen synthase kinase-3 in rats. *J Nutr*. 2004;134:545–51.
95. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr*. 2006;84:274–88.

96. Huynh M, Luiken JJ, Coumans W. et al. Dietary fructose during the suckling period increases body weight and fatty acid uptake into skeletal muscle in adult rats. *Obesity* (Silver Spring) 2008;16:1755–62.
97. Stanhope KL, Schwarz JM, Keim NL. et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119:1322–34.
98. Tappy L, Le KA. Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev*. 2010;90:23–46.
99. Bocarsly M, Powell ES,Avena NM, Hoebel BG. High-fructose corn syrup causes characteristics of obesity in rats: Increased body weight, body fat and triglyceride levels, *Pharmacol Biochem Behav* (2010), doi:10.1016/j.pbb.2010.02.012
100. Lê KA, Faeh D, Stettler R, Ith M, Kreis R, Vermathen P, Boesch C, Ravussin E, Tappy L. A 4-wk high-fructose diet alters lipid metabolism without affecting insulin sensitivity or ectopic lipids in healthy humans. *Am J Clin Nutr*. 2006;84(6):1374-9.
101. Teff KL, Elliott SS, Tschop M. et al. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. *J Clin Endocrinol Metab*. 2004;89:2963–72
102. Erejuwa OO, Sulaiman SA, Wahab MS. Fructose might contribute to the hypoglycemic effect of honey. *Molecules*. 2012;17:1900–15
103. Chepulis LM. Chepulis LM. The effect of honey compared to sucrose, mixed sugars, and a sugar-free diet on weight gain in young rats. *J Food Sci*. 2007;72:S224–9.
104. Gheldof N, Wang XH, Engeseth NJ. Identification and quantification of antioxidant components of honeys from various floral sources. *J Agric Food Chem*. 2002;50:5870–7.
105. Bogdanov S. Honey in medicine. Published online http://www.bee-hexagon.net Jan 15, 2012, 1- 19.
106. Nishikawa T, Edelstein D, Brownlee M. The missing link: a single unifying mechanism for diabetic complications. *Kidney Int Suppl*. 2000;77:S26–30.
107. Kowluru RA, Kanwar M, Kennedy A. Metabolic memory phenomenon and accumulation of peroxynitrite in retinal capillaries. *Exp Diabetes Res.* 2007;2007:1–7.
108. Seghrouchni I, Drai J, Bannier E. et al. Oxidative stress parameters in type I, type II and insulin-treated type 2 diabetes mellitus; insulin treatment efficiency. *Clin Chim Acta*. 2002;321:89–96.
109. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res*. 2010;107:1058–70.
110. Kim JS, Saengsirisuwan V, Sloniger JA. et al. Oxidant stress and skeletal muscle glucose transport: roles of insulin signaling and p38 MAPK. *Free RadicBiol Med*. 2006;41:818–24
111. Talior I, Yarkoni M, Bashan N. et al. Increased glucose uptake promotes oxidative stress and PKC-delta activation in adipocytes of obese, insulin-resistant mice. *Am J Physiol Endocrinol Metab*. 2003;285:E295–302.
112. Rudich A, Tirosh A, Potashnik R. et al. Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes. *Diabetes*. 1998;47:1562–9.
113. Dokken BB, Saengsirisuwan V, Kim JS. et al. Oxidative stress-induced insulin resistance in rat skeletal muscle: role of glycogen synthase kinase-3. *Am J Physiol Endocrinol Metab.* 2008;294:E615–21.
114. Henriksen EJ. Dysregulation of glycogen synthase kinase-3 in skeletal muscle and the etiology of insulin resistance and type 2 diabetes. *Curr Diabetes Rev*. 2010;6:285–93.

115. Drews G, Krippeit-Drews P, Dufer M. Oxidative stress and beta-cell dysfunction. *Pflugers Arch*. 2010;460:703–18.
116. Miwa I, Ichimura N, Sugiura M. et al. Inhibition of glucose-induced insulin secretion by 4-hydroxy-2-nonenal and other lipid peroxidation products. *Endocrinology*. 2000;141:2767–72.
117. Tanaka Y, Gleason CE, Tran PO. et al. Prevention of glucose toxicity in HIT-T15 cells and Zucker diabetic fatty rats by antioxidants. *Proc Natl Acad Sci* U S A. 1999;96:10857–62.
118. Marchetti P, Dotta F, Lauro D. et al. An overview of pancreatic beta-cell defects in human type 2 diabetes: implications for treatment. *Regul Pept*. 2008;146:4–11.
119. Rahimi R, Nikfar S, Larijani B. et al. A review on the role of antioxidants in the management of diabetes and its complications. *Biomed Pharmacother*. 2005;59:365–73.
120. Lai MH. Antioxidant effects and insulin resistance improvement of chromium combined with vitamin C and E supplementation for type 2 diabetes mellitus. *J Clin Biochem Nutr*. 2008;43:191–8.
121. Lautt WW, Ming Z, Legare DJ. Attenuation of age- and sucrose-induced insulin resistance and syndrome X by a synergistic antioxidant cocktail: the AMIS syndrome and HISS hypothesis. *Can J Physiol Pharmacol*. 2010;88:313–23.
122. Tong X, Dong J, Wu Z. et al. [Whey protein improves insulin resistance via the increase of antioxidant capacity in model rats] *Wei Sheng Yan Jiu*. 2011;40:617–9.
123. Wright D, Sutherland L. Antioxidant supplemention in the treatment of skeletal muscle insulin resistance: potential mechanisms and clinical relevance. *Appl Physiol Nutr Metab*. 2008;33:21–31.
124. Beretta G, Granata P, Ferrero M. et al. Standardization of antioxidant properties of honey by a combination of spectrophotometric/fluorimetric assays and chemometrics. *Anal Chim Acta*. 2005;533:185–91.
125. Beretta G, Orioli M, Facino RM. Antioxidant and radical scavenging activity of honey in endothelial cell cultures (EA.hy926) *Planta Med*. 2007;73:1182–9. [PubMed]
126. Erejuwa OO, Sulaiman SA, Wahab MS. Honey: a novel antioxidant. *Molecules*. 2012;17:4400–23.
127. Kowluru RA. Effect of reinstitution of good glycemic control on retinal oxidative stress and nitrative stress in diabetic rats. *Diabetes*. 2003;52:818–23.
128. Ceriello A. Hypothesis: the "metabolic memory", the new challenge of diabetes. *Diabetes Res Clin Pract*. 2009;86(Suppl 1):S2–6.
129. Ihnat MA, Thorpe JE, Kamat CD. et al. Reactive oxygen species mediate a cellular 'memory' of high glucose stress signalling. *Diabetologia*. 2007;50:1523–31.
130. Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: The "metabolic memory": is more than just tight glucose control necessary to prevent diabetic complications? *J Clin Endocrinol Metab*. 2009;94:410–5
131. Chilwant KS, Muglikar AG. Effect of honey on gentamicin induced nephrotoxicity in albino rats. Int. *J. Pharma and Bio Sc* 2012; 3(1) 459-464
132. Ramadan BK, Schaalan MF. The Renoprotective Effect of Honey on Paracetamol - Induced Nephrotoxicity in Adult Male Albino Rats. *Life Science Journal*, 2011;8(3) 589-596
133. Garba, AM, Mohammed B, Garba SH, Numan AI, Dalori BM. The effects of Honey and Aloe Vera extract on Ibuprofen Induced Liver Damage in rats. IOSR *Journal of Pharmacy and Biological Sciences* (IOSR-JPBS)2012; 3(2) 06-10.

134. Galal RM, Zaki HF, Seif El-Nasr MM, Agha AM. Potential Protective Effect of Honey Against Paracetamol-induced Hepatotoxicity. *Arch Iran Med.* 2012 ;15(11):674-80
135. Erejuwa OO, Sulaiman SA, Wahab MS. et al. Honey supplementation in spontaneously hypertensive rats elicits antihypertensive effect via amelioration of renal oxidative stress. *Oxid Med Cell Longev*. 2012;2012:1–14.
136. Erejuwa OO, Sulaiman SA, Wahab MS. et al. Effect of glibenclamide alone versus glibenclamide and honey on oxidative stress in pancreas of streptozotocin-induced diabetic rats. *Int J Appl Res Nat Prod*. 2011;4:1–10.
137. Sanz ML, Gonzalez M, Lorenzo C. et al. Carbohydrate composition and physicochemical properties of artisanal honeys from Madrid (Spain): occurrence of Echium sp. honey. *J Sci Food Agric*. 2004;84:1577–84.
138. Yaghoobi N, Al-Waili N, Ghayour-Mobarhan M. et al. Natural honey and cardiovascular risk factors; effects on blood glucose, cholesterol, triacylglycerole, CRP, and body weight compared with sucrose. *Scientific World Journal*. 2008;8:463–9.
139. Shambaugh P, Worthington V, Herbert JH. Differential effects of honey, sucrose, and fructose on blood sugar levels. *J Manipulative Physiol Ther*. 1990;13:322–5.
140. Ahmad A, Azim MK, Mesaik MA. et al. Natural honey modulates physiological glycemic response compared to simulated honey and D-glucose. *J Food Sci*. 2008;73:H165–7
141. Abdulrahman M, El-Hefnawy M, Hussein R. et al. The glycemic and peak incremental indices of honey, sucrose and glucose in patients with type 1 diabetes mellitus: effects on C-peptide level-a pilot study. *Acta Diabetol*. 2011;48:89–94.
142. Samanta A, Burden AC, Jones GR. Plasma glucose responses to glucose, sucrose, and honey in patients with diabetes mellitus: an analysis of glycaemic and peak incremental indices. *Diabet Med*. 1985;2:371–3.
143. Al-Waili N. 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*. 2003;8:295–303.
144. Bahrami M, Ataie-Jafari A, Hosseini S, Foruzanfar MH, Rahmani M, Pajouhi M. Effects of natural honey consumption in diabetic patients: an 8-week randomized clinical trial. *Int J Food Sci Nutr*. 2009;60:618–26.
145. Agrawal OP, Pachauri A, Yadav H. et al. Subjects with impaired glucose tolerance exhibit a high degree of tolerance to honey. *J Med Food*. 2007;10:473–8.
146. Abdulrahman M, El-Hefnawy M, Ali R, et al. Honey and type 1 diabetes mellitus. In: Liu CP, editor. Type 1 diabetes - complications, pathogenesis, and alternative treatments. Croatia: InTech; 2011. pp. 228–33.
147. Al-Waili NS. Natural honey lowers plasma glucose, C-reactive protein, homocysteine, and blood lipids in healthy, diabetic, and hyperlipidemic subjects: comparison with dextrose and sucrose. *J Med Food*. 2004;7:100–7.
148. Munstedt K, Sheybani B, Hauenschild A. et al. Effects of basswood honey, honey-comparable glucose-fructose solution, and oral glucose tolerance test solution on serum insulin, glucose, and C-peptide concentrations in healthy subjects. *J Med Food*. 2008;11:424-8
149. Katsilambros NL, Philippides P, Touliatou A. et al. Metabolic effects of honey (alone or combined with other foods) in type II diabetics. *Acta Diabetol Lat*. 1988;25:197–203.

150. Munstedt K, Hoffmann S, Hauenschild A. et al. Effect of honey on serum cholesterol and lipid values. *J Med Food*. 2009;12:624–8.
151. Larson-Meyer DE, Willis KS, Willis LM. et al. Effect of honey versus sucrose on appetite, appetite-regulating hormones, and postmeal thermogenesis. *J Am Coll Nutr.* 2010;29:482–93.
152. Gheldof N, Wang XH, Engeseth NJ. Buckwheat honey increases serum antioxidant capacity in humans. *J Agric Food Chem*. 2003;51:1500–5.

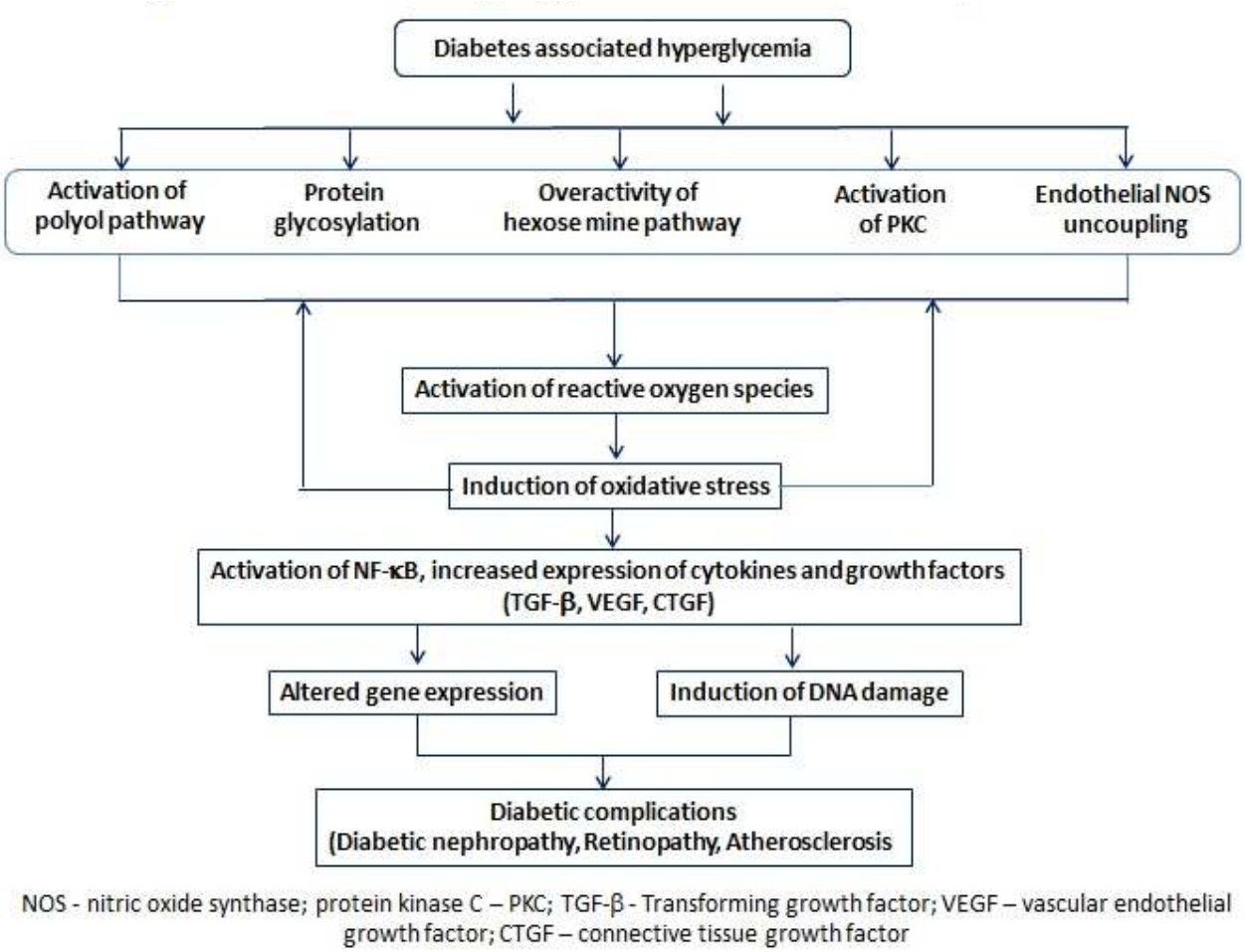

Figure 1: Mechanism of hyperglycemia induced diabetic complications

Table 1: Beneficial effects of honey in human subjects

Effect on	In non-diabetic subjects	In diabetic subjects
Glycemia Post-prandial glycemic response	Reduced [137-141]	Reduced [139,141,142]
Blood sugar level		Decrease in type 2[143-145] and type 1 diabetes[146]
Body weight and fat	Reduced in overweight /obese subjects[138]	Reduced in type 2 diabetic patients[144]
Insulin levels	Lower increase with honey compared to glucose-sucrose[147,148]	Greater increase with honey compared to sucrose[147] Decreased insulin resistance [149]
Lipid metabolism	Decrease in TC, LDL and CRP; increase in HDL[138,147] Decrease in elevated levels of TGs[138,150]	Decrease in TGs[144,149]
Appetite regulating hormones	Delayed post-prandial ghrelin release and increase in peptide YY response in normal subjects[151]	
Oxidative stress	Increased serum antioxidant capacity[152]	