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

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## 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.

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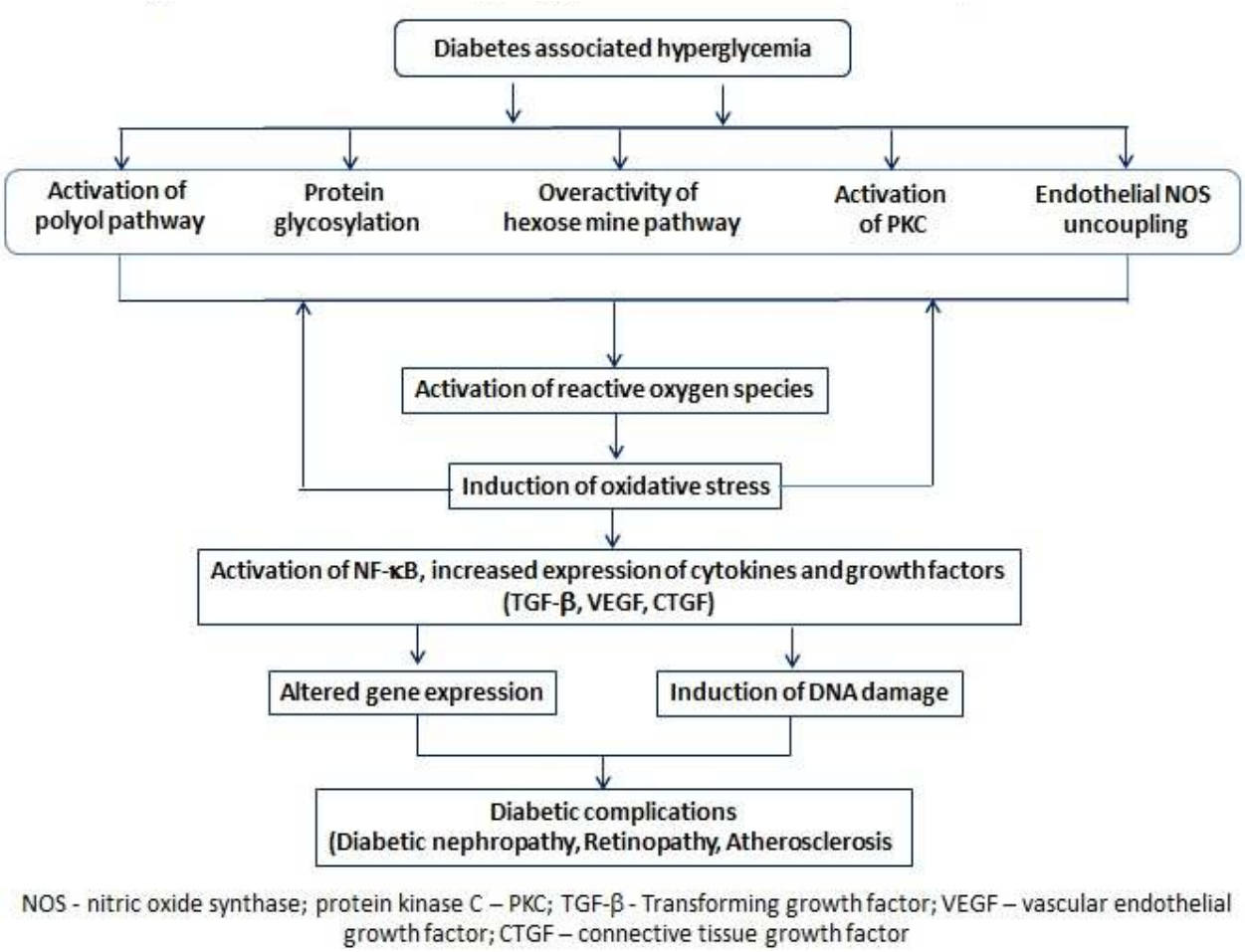


**Figure 1:** Mechanism of hyperglycemia induced diabetic complications

**Table 1:** Beneficial effects of honey in human subjects

| Effect on | In non-diabetic subjects | In diabetic subjects |
|---|---|---|
| Glycemia<br>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]<br>Decreased insulin resistance [149] |
| Lipid metabolism | Decrease in TC, LDL and CRP; increase in HDL[138,147]<br>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] | |