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Review Article

The role of honey in the treatment of type 2 diabetes mellitus: a review of literature

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ABSTRACT

The use of honey in the control of hyperglycemia in patients with type 2 diabetes mellitus is a current option being explored globally. Honey bees which are named in Latin as Apis, use the collected nectar from plants to produce honey after regurgitation and digestion of nectar. Carbohydrate constitutes about 80% of the components of honey. It includes monosaccharides [fructose (37.5%) and glucose (30.6%), disaccharides (sucrose (1.6%) and maltose (2.7%)] and oligosaccharides. Natural honey also contains water (17.2%), proteins, vitamins, minerals, enzymes, acids such as flavonoids, phenolic acids and other components. Honey is rich in antioxidant content and these antioxidant compounds function as endogenous cellular antioxidant defences against free radicals in diabetes mellitus. Antioxidants have also been shown to exert a beneficial effects on blood glucose. Fructose and other bioactive constituents of honey have also been linked with amelioration of hyperglycemia. Besides the beneficial effects of honey on blood glucose, honey is widely used in the management of diabetic foot ulcers, an important complication of diabetes mellitus. The wound-healing benefits of honey are attributed to its antioxidant constituents and broad-spectrum antimicrobial activity. Though additional studies are needed, the use of honey in the management of diabetes mellitus holds much promise.

Keywords: Diabetes mellitus, Honey, Antioxidants, Carbohydrates, Hyperglycemia

INTRODUCTION

Diabetes mellitus (DM) is a pathologic metabolic state characterized by hyperglycemia due to either insulin deficiency or impaired insulin response. It is an incurable disorder which is associated with poor quality of life, cardiovascular complications, increased mortality and morbidity.[1] There are two types of DM: type 1 DM, which is caused by a severe deficiency in insulin synthesis or production and type 2 DM which results from insulin resistance or decreased insulin production by the beta cells of the pancreas.[1] In 2014, it was estimated that there were about 387 million diabetic patients worldwide.[2] The latest statistics show that the global prevalence of diabetes mellitus has risen to 536.6 million people in 2021 and this estimate is predicted to increase to 783.2 million people by 2045.[3] These recent figures showing the astronomical rise in the worldwide incidence of DM are frightening because it shows DM is fast becoming an epidemic. This is of public health concern due to its social and economic burdens.[3] Even though DM is linked with insulin deficiency and/or insulin resistance, a complex interplay of several factors including genetic, social and environmental factors is implicated in its aetiology.[4]

Currently, the management of this disorder involves increased physical activity, healthy eating or diet and the use of anti-diabetic agents or insulin.[5] Despite the availability of diverse classes of agents, high mortality and/or morbidity in patients with DM continue unabatedly

globally. Besides, these agents are expensive and therefore, not easily affordable to the majority of patients especially those from the lower economic class. This has compelled many diabetic patients to seek an alternative and cheaper remedies which may contribute to increased mortality and morbidity.[6]

The use of honey in the control of hyperglycemia in type 2 DM patients is a current option being explored globally. Honey is produced by honey bees which are named in Latin Apis. Honey bees use nectars collected from plants to produce honey after regurgitation and digestion of nectar.[7] Currently, two types of honey are produced worldwide: the *Apis mellifera* honey and the stingless bee honey. Honey is documented to contain more than 200 substances including sugars, phenolic acids, flavonoids, amino acids, proteins, vitamins and enzymes.[7] Phenolic compounds are considered among the main constituents contributing to the antioxidants and other beneficial properties of honey.[8] The botanical origin of honey is one of its main quality parameters. It has been reported that the composition and antioxidant capacity of honey depends on the floral source of the nectar, seasonal and environmental factors, as well as the method used in processing the honey.[9, 10] Honey is known to exert some health benefits which include antioxidant, antibacterial, antiproliferative and anti-inflammatory effects.[11-13] Latest findings have also attributed the anti-diabetic effect to honey.[14,15]

The aim of the review was to highlight recent studies that have been done on the benefits of natural honey in the treatment of DM and its associated complications especially diabetic foot ulcers.

CHEMICAL COMPOSITION OF NATURAL HONEY

Honey contains both macro and micronutrients which depend basically on various factors such as bee type, floral source, environmental and processing factors.

In general, more than 200 compounds have been identified in honey. These include sugars, proteins, enzymes, minerals, vitamins, amino acids and a wide range of other bioactive substances such as polyphenols.[7,9]

The variety ratio of these compounds results in a different colour, taste, viscosity, and biological activities of each honey. In this sense, these compounds interact synergistically in different aspects of the application. Most of the honey all over the world share 80% of the physical properties and chemical composition.[16]

MACRONUTRIENTS IN NATURAL HONEY

Carbohydrate constitutes about 80% of the components of honey. It includes monosaccharides, disaccharides and oligosaccharides. These include fructose (37.5%) and glucose (30.6%) which are monosaccharides as well as sucrose (1.6%) and maltose (2.7%) which are disaccharides. Water constitutes about 17.2%. Honey also contains proteins, vitamins, minerals, enzymes, acids such as flavonoids, phenolic acids and other components.[17,18] Other carbohydrate constituents in honey include oligosaccharides such as turanose, nigerose, melibiose, panose, maltotriose, melezitose. More than 20 types of carbohydrates have been identified in honey samples from different parts of the world.[19] The sugar proportion of honey is an important signature used in differentiating natural honey from adulterated honey.[20]

The protein content of honey ranges from 0.2 to 0.5% in the form of enzymes and free amino acids. The free amino acid in honey is approximately between 10 to 200 mg/100 g of honey and proline contributes 50% of the total amino acid in natural honey. Other amino acids include gamma amino butyric acid (GABA), ornithine, b-alanine and a-alanine. The lipid content of most honey samples is negligible (about 0.002%). They include palmitic, oleic, meristic and linoleic acid.[21]

MICRONUTRIENTS IN NATURAL HONEY

Micronutrients in honey include minerals and vitamins. They constitute 0.2 to 0.5% of honey dry weight. Potassium and sodium constitute 80% of the minerals while iron, copper and manganese are insignificant in quantity.[22] Barium and lead are specific components of rape honey. Thiamine, riboflavin, pyridoxine, niacin and ascorbic acid are common vitamins found in many honey samples. This macro and micronutrients in honey usually interact and combine synergistically s to contribute to the therapeutic effects of natural honey in the treatment of type 2 DM and its complications.[22]

ANTIOXIDANTS IN NATURAL HONEY

The *in vitro* antioxidant properties of natural or synthetic agents are measured in the form of antiradical activity using the 1,1-diphenyl-1-2-picrylhydrazyl (DPPH) scavenging assay, oxygen radical absorbance capacity (ORAC) assay and ferric reducing antioxidant power (FRAP) assay.[23] Several *in vitro* antioxidant properties have been documented for kinds of honey from various geographical regions. These studies have shown that there is a direct relationship between antioxidant activity and some honey bioactive substances such as phenolic compounds and flavonoids.[24,25] The main phenolic and flavonoid compounds in honey include ellagic acid, syringic acid, benzoic acid, cinnamic acid, ferulic acid, myricetin-chlorogenic acid, caffeic acid, hesperetin, coumaric acid, isorhamnetin, chrysin, quercetin, galangin, luteolin and kaemferol.[26]

While some of these bioactive compounds such as alanine, kaemferol, quercetin, isorhamnetin and luteolin are found in most honey samples, others such as hesperetin and naringenin are found in few honey varieties.[26] By and large, compelling evidence shows that honey is not only an antioxidant but also rich in numerous antioxidant

compounds. These antioxidant compounds can function as cellular antioxidant defences against free radicals in the body.[27]

Chronic diseases like diabetes mellitus, hypertension, cancer, and Alzheimer's disease are major causes of mortality and morbidity globally.[28] The role of oxidative stress is implicated in the pathogenesis and complications of these diseases.[29] Oxidative stress is defined as an imbalance between oxidants and antioxidants in favour of the oxidants, potentially leading to damage. It is caused by increased production and/or reduced removal of reactive species by the antioxidant defences. Reactive species can be reactive oxygen species (ROS) or reactive nitrogen species (RNS).[30] Reactive oxygen species include superoxide (O_2), hydroxyl ($OH\cdot$) and hydrogen peroxide (H_2O_2) while RNS are nitric oxide (NO), nitrogen dioxide (NO_2) and peroxynitrite ($OONO^-$).

These reactive species are produced by aerobic organisms as byproducts of metabolism such as during mitochondrial electron chain transport or as a result of accidents of chemistry such as the autoxidation of unstable biomolecules (dopamine).[30] Reactive species may also be produced in response to inflammation during which phagocytes release ROS to kill invading bacterial.[30]

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. The exogenous antioxidants comprise the micronutrients and other exogenously administered antioxidants.[30]

Since diabetes mellitus is a chronic disease associated with oxidative stress, natural and unadulterated honey is highly recommended as part of the management because of its abundant antioxidant property.[5] Various studies have also demonstrated that honey (1.2 g/kg) elevated the amount and activity of antioxidant agents such as beta-carotene, vitamin C, glutathione reductase and uric acid in healthy human subjects.

MECHANISMS OF ANTIDIABETIC EFFECT OF NATURAL HONEY

Effects of the antioxidant components of natural honey on glycaemic control

There are abundant evidence-based reports that implicate the role of oxidative stress in the pathogenesis and/or progression of diabetic Mellitus in terms of glycemic control.[31] Increased glucose uptake in both skeletal muscle and adipose tissues enhances ROS generation and oxidative stress which in turn impairs glucose uptake and glycogen synthesis.

Oxidative stress causes insulin resistance through impaired insulin signalling pathways such as interference with insulin receptors, insulin receptors substrate-1 and protein kinase B/AKT.[32] Honey, therefore, through its antioxidant activity may enhance insulin sensitivity in the liver and muscle thereby increasing glucose uptake and resulting in reduced blood glucose levels.

The pancreas expresses a low levels of antioxidant enzymes, which makes it very vulnerable to oxidative stress. The toxic effect of hyperglycemia on the β-cells, a condition referred to as glucotoxicity, is mediated via oxidative stress.[33] Several studies have demonstrated that ROS or oxidative products impair insulin secretion in pancreatic β-cells, inhibit glucose-induced insulin secretion and biosynthesis, deplete insulin content of the pancreatic β-cells and increase β-cell apoptosis.[34] Honey administration has been shown to increase insulin secretion and protect the pancreas against oxidative stress and damage.[15,33]

Effects of fructose component of natural honey on glycaemic control

The fructose content of honey varies from 21 to 43% and the fructose/glucose is ratio from 0.4 to 1.6 or even higher. Although fructose is the sweetest naturally-occurring sweetener, it has a glycaemic index of 19, compared to glucose which has 100 or sucrose (refined sugar) with 60.[35]

There is evidence that fructose tends to lower blood glucose in animal models of diabetes.[5] Hence, fructose is postulated to contribute to the antidiabetic effect of honey. This is believed to involve mechanisms such as reduced rate of intestinal absorption, prolongation of gastric emptying time and reduced food intake.[5] However, some of these effects of fructose have also been demonstrated with glucose in recent studies.[36]

Fructose also stimulates glucokinase in hepatocytes, which plays an important role in the uptake and storage of glucose as glycogen by the liver.[37]

Oligofructose supplementation in rats increased caecal GLP-1 content and serum GIP concentration. The proximal mucosa of the colon of rats fed fructans had increased concentrations of GLP-1 and pro-glucagon mRNA in the caecum compared to those of control rats.[34]

Although honey contains several types of polyphenols, only a few such as kaemferol, catechin, quercetin, luteolin, rutin and apigenin have been shown to decrease blood glucose levels through various mechanisms.[16] Some of the mechanisms include inhibition of enzymes such as α-glucosidase and α-amylase,[11] improved pancreatic beta cell protection by reducing oxidative stress, and increased secretion and activity of insulin.[38]

Other mechanisms include greater absorption of glucose and production of insulin receptors and GLUT-4, inhibition of gluconeogenic enzymes and inhibition of the enzyme aldose reductase.

CONCLUSION

Natural honey is rich in both macro and micronutrients which invariably aid the physiological functions of the body. Fructose and various bioactive substances present in honey play important roles in the regulation of blood sugar levels in diabetic patients. Honey also possesses significant anti-inflammatory and anti-oxidant properties and therefore, aids the immunological response of the body system. Though additional studies are needed, the use of honey in the management of diabetes mellitus holds much promise.

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