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Review Article

ANTIOXIDANT POTENTIAL OF HONEY IN TYPE 2 DIABETES MELLITUS

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Abstract:

Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Oxidative stress plays important role in the onset of diabetes and many other disorders. In oxidative stress generation of free radicals increases. The main source of oxidative stress is a cascade of reactive oxygen species. Antioxidants protect the human body by scavenging the free radicals and also inhibit chelate metals which catalyze the oxidation process. Antioxidant capacity of honey contributes to the prevention of diabetes mellitus and oxidative stress. Various constituents of honey such as Phenolic acids, flavonoids, sugars show antioxidant effect and may help honey to enhance its antidiabetic properties. In this review we are highlighting the different mechanisms, how honey is acting as an antidiabetic agent.

Keywords: Antioxidant, hyperglycaemia, Oxidative stress.

INTRODUCTION

The prevalence of type 2 diabetes among adults aged 20-70 years is expected to rise from 285 million in 2010 to 438 million by the year 2030. Estimates of diabetes are high for all Asian countries and are expected to increase further in the next two decades [1]. According to the data collected by (WHO, 2011) the main complications associated with diabetes is renal failure and cardiovascular disease. Genetic factors and life-style factors also play important role to increase the risk of diabetes [2]. Diabetes mellitus is the chronic disease which continues to increase in numbers and significance, due to changing lifestyles which lead to reduced physical activity, and increased obesity. It results from a defect in insulin secretion, insulin action, or both. Insulin deficiency leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism [3]. Type 2 diabetes is a progressive disorder that begins with peripheral insulin resistance and ends with failure of pancreatic β-cells [4].

Oxidative stress occurs in a cellular system when excess formation of free radical exceeds the antioxidant capacity of the system. If cellular antioxidants do not remove free radicals, radicals

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attack and damage proteins, lipids, and nucleic acids of the body [5]. Highly reactive molecules such as Reactive oxygen species (ROS) and Reactive nitrogen species (RNS) are formed during oxidative stress [6]. Superoxide (O_2) and Nitric oxide (NO) are most widely studied (ROS) and (RNS) species. Both these species play very important role in diabetic complications [7]. Honey is a sweet substance made by honey bees when the nectar from plants are collected, processed and stored in the honey combs. It has been used as a nutrient and as a medicine in the long human tradition. There is a separate branch of science which is known as apitherapy which offers treatments based upon honey and other bee products [8]. Main composition of honey is sugars, glucose, water and fructose. The water content of honey ranges from 15% to 20% and sugars account for about 85% [9]. Honey contains large amount of flavonoids which reduce oxidative stress and are excellent radical scavengers, therefore it acts as good antioxidant and protects heart diseases by inhibiting cyclooxygenase and lipoxygenase activities in platelets and macrophages [10].

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes begins in adulthood accompanied by high blood pressure, obesity and disturbance in levels of lipids in blood. When body mass index increases risk of type 2 diabetes also increases [11]. Insulin is a potent hormone which helps in the metabolism of glucose and leading to a decline in the plasma level of free fatty acid and carbohydrate is the main dietary component responsible for fluctuations in blood glucose level [12]. Main Pathophysiological conditions which contribute to type 2 diabetes are impaired insulin secretion and insulin resistance in muscle, liver and adipocytes [13]. Insulin is synthesized constantly in body from pancreatic β-cells and is stored inside the vacuoles and released when there is elevation in blood glucose level [14]. It also converts glucose to glycogen for internal storage in liver and skeletal muscle cells. During insulin resistance delayed or suppressed response to insulin is there and the cells that respond to insulin or produce insulin do not perform their function properly. β-cells destruction is also a leading cause of type 2 diabetes occurs in two circumstances when insulin resistance is delayed or when suppressed response to insulin is there, and the cells that respond to insulin or produce insulin do not perform their function properly [15].

ROLE OF OXIDATIVE STRESS IN DIABETES

Oxidative stress plays an important role in the pathogenesis of diabetes. Hyperglycemia results in overproduction of oxygen free radicals, which plays an important role in the progression of type 2 diabetes. Different types of complications are also caused by oxidative stress during type 2 diabetes. The cardiovascular complications and cerebrovascular diseases are very closely related to oxidative damage [16]. Abnormally high levels of free radicals and the simultaneous decline of antioxidant defence mechanisms can lead to damage of cellular organelles and enzymes, increased lipid peroxidation, and development of insulin resistance. A number of external agents

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can trigger ROS production. A sophisticated enzymatic and nonenzymatic antioxidant defence system including catalase (CAT), superoxide dismutase (SOD) and reduced glutathione (GSH) counteracts and regulates overall ROS levels to maintain physiological homeostatis [17]. Lowering ROS levels below the homeostatic set point may interrupt the physiological role of oxidants in cellular proliferation and host defence.

Under hyperglycemic conditions, the generation of active oxygen is increased and antioxidant defence is impaired, which leads to the activation of redox-sensitive transcriptional factor including necrotic factor-B and activator protein-1, resulting in promoted synthesis of basement membrane proteins, decreased vasodilatation, glomerular hyper filtration, as well as the activation of endothelial cells, platelets, and leukocytes that accompanies increased cell-cell interaction [18]. Insulin resistance is a condition characterized by hyperinsulinemia is frequent in the majority of the individuals with type 2 diabetic mellitus [19]. Insulin induces the release of H_2O_2 when activating its receptors. Even though H_2O_2 is a non-free radical; it is membrane permeable and can diffuse to other sites, and different from its site of production. Chronic hyperinsulinemia together with the impaired antioxidant defences in diabetes will lead to inefficient scavenging of H_2O_2. In the presence of transition metals such as copper and iron, H_2O_2 undergoes Fenton reaction to generate OH which is implicated in the initiation and propagation of lipid peroxidation [20]. Substances indicating oxidative damage to DNA (oxidized DNA bases), proteins (protein carbonyls) and lipids can be measured. The results of in vitro, animal and human studies suggest that oxidative stress through an increased formation of free radicals might be involved in the development of complications [21].

Due to metabolism of excessive glucose, increased generation of reactive oxygen species occur which causes destruction of pancreatic β-cells. Due to this, oxidative stress plays an important role in destruction of β-cells and causes type2 diabetes [22]. Scientific data indicates that hyperglycemia and increased free fatty acid (FFA) level causes formation of ROS through glycation reaction [23]. Due to hyperglycemia and dyslipidemia inflammatory-immune responses and oxidative stress reactions are generated. During ROS formation nitric oxide act as signaling molecule and activate various determinants of gene expression [24]. ROS is used as secondary messengers by cytokines, growth factors, hormones and various neurotransmitters in intracellular signal transduction. It directly oxidizes and damage lipid, proteins and DNA and play important role in the pathogenesis of diabetes and diabetic complications [25]. Antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase are very low in islet cells when compared with other tissues and cells [26].

ANTIOXIDANTS:

Antioxidants protect the human body by scavenging the free radicals [27], and also inhibit chelate metals which catalyze the oxidation process, inhibition of certain enzymes [28]. They appear to inhibit some of the pathology of chronic inflammation. The antioxidant enzymes are catalase, glutathione peroxidase and superoxide

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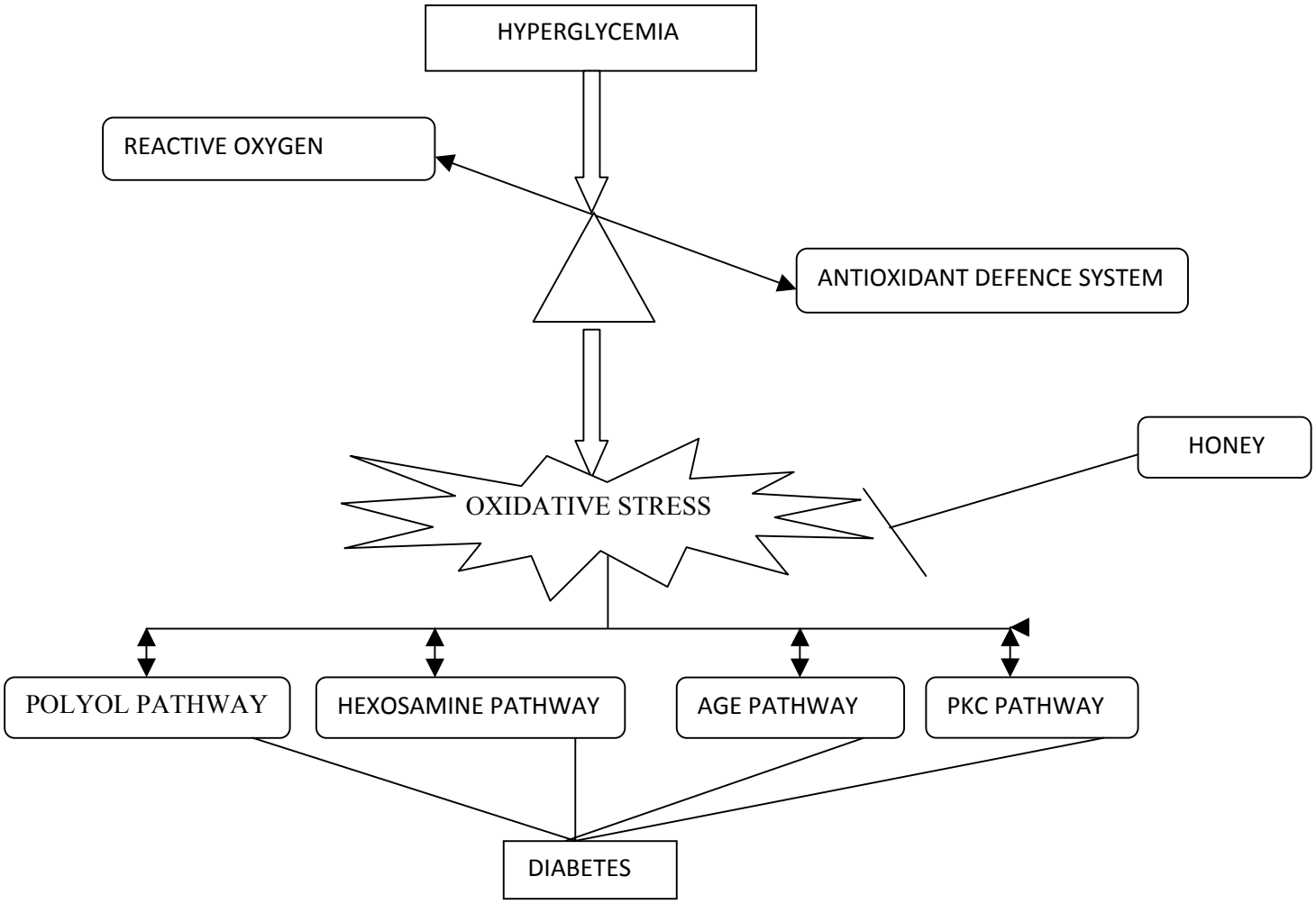

Figure1: Role of honey to reduce oxidative stress in diabetes.

dismutase, these all metabolize the oxidative toxic intermediates and required micronutrient cofactors such as iron, copper, zinc and manganese for optimum catalytic activity. Glutathione is highly present in the cytosol and mitochondria and is the major soluble antioxidant in cell compartments. Production of superoxide also occurs mostly in mitochondria of the cell.

The mitochondrial electron transport chain is the main source of ATP in the mammalian cell and thus is essential for life. Non-enzymatic antioxidants are also present in body such as ascorbic acid, tocopherol and carotenoids. Balance between both these antioxidants are important for the survival of organisms and their health [29].

Main categories of antioxidants are

1. Vitamins: Examples include vitamins A, C, E and super fruit juices (rich in antioxidants, polyphenols,
alpha-lipoic acid, punicalagins, resveratrol, and phyto-nutrients).

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2. Enzymes:Glutathione peroxidase (GPx), Catalase and superoxide dismutase (SOD) are produced by the body, with the properdiet.They stays in the body and protects cells 24 hours a day.
3. Minerals:Manganese, selenium, copper are antioxidants which can be used to treat oxidative stress, and diseases relevant to generation of reactive oxygen species (ROS) [30].

BENEFICIAL EFFECTS OF ANTIOXIDANTS IN TYPE2 DIABETES:

Adequate amount of antioxidants is very important to for the prevention of chronic diseases such as diabetes, cardiovascular disorders and cancer. Antioxidant therapy play important role in type 2 diabetes and show beneficial effects in diabetic complications and cardiovascular disorders. Antioxidants improve insulin sensitivity and prevent diabetes because of its distinctive biological activity and low toxicity [31]. The administration of antioxidants shows beneficial effects during trials to balance antioxidants and pro-oxidants. Available data shown that antioxidants also improve glycemic control in patients of type 2 diabetes [32]. They control free radical production and increases intracellular antioxidant defence system. There are two main types of antioxidants enzymatic and non-enzymatic. Enzymatic antioxidants include catalase, glutathione peroxidase, glutathione reductase and non-enzymatic antioxidants include glutathione, copper, zinc, vitamins, co enzymes etc. Glutathione is a direct scavenger and also acts as a co substrate for GSH peroxidase. Vitamin E prevents lipid peroxidation and may help to reduce oxidative stress in diabetes [33]. Antioxidants affect signal transduction, regulation of proliferation and the immune response through normal physiological processes. Flavonoids and carotinoids are present in honey and show maximum contribution in antioxidant effect of honey. If level of these constituents is high in honey than antioxidant effect of honey is also high. Recent studies on honey shows relationship between color and antioxidant effect of honey. Dark color honey has more antioxidant property than light colored honey [34].

HONEY AS ANTIOXIDANT IN DIABETES

Honey formed by honeybees from the nectar of flowers, is the interesting subject for various types of research studies. It forms part of traditional medicine in many cultures although it is widely used as sweetener [35]. It is used by ancient Egyptians in embalming and to make salves with it to treat diseases related with eye and skin. Honey was used as a drug more than a nutrient. Honey was also mentioned in Holy Quran1, 400 years ago [36]. Honey is most widely used as sweetener. There are 181 components in honey of those the major components are fructose (38%), glucose (31%), moisture content (17.7%) and the minor components are phenolic acids, flavenoids, antioxidant enzymes (catalase, glucose oxidase), organic acids, aminoacids, proteins etc. However the exact composition of honey depends upon various factors such as environmental conditions, climate and

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pollen source [37]. Antioxidant capacity of honey contributes to the prevention of diabetes mellitus and oxidative stress. Glycemic index of honey is lower than other carbohydrates. Honey contains fructooligosaccharide and this provides prebiotic effect to the intestinal microflora. Honey may show its mechanism of action by improving gut health in diabetes and by management of glucose production [38]. Honey contains different constituents such as copper, antioxidant enzymes, calcium, potassium, water etc. Many of these constituents may help honey to be antidiabetic by maintaining normal glucose tolerance and improves insulin secretion from the pancreatic *β*-cells. Zinc and copper also help in the metabolism of glucose and insulin. Studies also shown that when diabetic animals are treated with honey their insulin secretion is improved [39]. Gelam honey supplementation increases activity of antioxidant enzymes in erythrocytes.

VARIOUS MECHANISMS OF HONEY WHICH IS ACTING AS ANTIOXIDANT

Honey contains Mineral elements such as chromium, calcium, potassium, copper; manganese, zinc, selenium etc are present in honey [40]. Chromium is important antidiabetic constituent of honey and is recognized for its role in reduction of elevated blood glucose and insulin secretion from the pancreatic β-cells [41]. Zinc and copper might contribute to antidiabetic effect of honey. Different types of sugars are also present in honey such as fructose, oligosaccharides, polysaccharides etc. Oligosaccharides and polysaccharides, found in honey, are not easily digested and absorbed in small intestine but they can be absorbed in large intestine [42]. Oligosaccharides are considered "Prebiotics". Prebiotics are non-digestible dietary ingredients that positively affect the host by helping the growth and activity of one or many bacteria in the colon. Certain chronic diseases such as diabetes mellitus and insulin resistance have been reported to be decreased by oligosaccharides [43]. Gut microbiota in the pathopysiology of insulin resistance and diabetes mellitus are possible to play an important role. Oligosaccharides contribute to the antidiabetic effect via modulation of gut microbiota [44]. It is also proven that oligosaccharides administration can lower glucose stimulated insulin secretion, improved glucose tolerance, reduce hyperglycemia and insulin sensitive hepatic glucose production [45]. By analyzing various studies it was deduced that oligosaccharides show their positive effect by increase glucagon like polypeptide1 secretion and reduce increased blood glucose [46]. Clinical trials shown that patients who were suffering from type 2 diabetes and obesity had significantly reduced blood glucose concentration when they were introduced to oligofructose [47]. Honey ingestion in diabetic patients resulted in decrease in fasting glycosylated hemoglobin as well as post prandial concentration [48]. Combination of polydextrose and oligofructose increases insulin and C-peptide level in type 2 diabetic patients. By using convincing findings with those of honey it can be understood that

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oligosaccharides may contribute to antidiabetic and other beneficial effects of honey. This will help modern science to understand the benefits of honey as antidiabetic and will add to our knowledge of benefits of honey to diabetic patients. Fructose is also an important constituent of honey which may act as antidiabetic. Fructose helps the diabetic patients by protecting pancreas from oxidative stress. Fructose is the sweetest naturally produced sweetener [49]. Its quantity can be 21% or as high 43.5% in honey, its ratio from glucose ranges from 0.46 to 1.62 [50]. The reasons for these variations are mainly floral sources different geographical origins and changing climatic factors. Fructose content of honey is also correlates with glycemic index [51]. Fructose on decomposition gives Hydroxymethylfurfuraldehyde (HMF). Amount of HMF increases in honey by storage and prolonged heating. Fructose does not increase the blood glucose level as discussed earlier that it has a low glycemic index. Due to this property fructose is used as energy source in diabetic patients. There is no active absorption mechanism of fructose in the intestinal mucosa but absorbed incompletely by facilitated diffusion. Blood glucose level in case of fructose increases slowly as compared to other carbohydrates [52]. When combination of glucose and fructose is used both of them compete for Glucose transporter 2 (GLUT2) which exist in the apical and fructose suppress the absorption of glucose. Mechanism by which fructose help diabetic patients, it increases hepatic glucose uptake by activating glucokinase and promoting synthesis of glycogen by activating glycogen synthase in the liver. This indicates that glucose and fructose might exert a holistic effect in pancreas and intestine. The result is potential enhancement in intestinal fructose absorption in the intestine and stimulation of insulin secretion in the pancreas. Hence fructose might improve glycemic control independent of its insulinotropic effect. Glucose is a major regulator of biosynthesis and secretion of insulin [53]. Animal studies shown that fructose improve glucose homeostasis and insulin response when compared to those rats which got only glucose dosage when fructose is taken in low or moderate doses it increases glycogen synthase flux, glycogen synthesis and endogenous lactate. Levels of circulating glucose suggest the ability of fructose to stimulate insulin secretion [54]. A study in which effects of honey are compared with glucose-fructose solution shows that honey significantly decreases serum concentrations of glucose, insulin and C-peptide in comparison to other glucose –fructose solution.

Flavonoids, Phenolic acids, lignans, tannins and oxidized polyphenols are various types of Phenolic compounds which are present in honey. In high oxidative stress conditions honey has potential antioxidant effect. The oxidative stress can be mitigated by the antidiabetic Phenolic compounds such as xanthone C-glucoside and mangiferin [55]. Honey has strong correlation between the content of Phenolic compounds with their antioxidant capacity and beneficial effects. Depending

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upon the basic structure of Phenolic compounds, they can be divided into 10 types and flavonoids are the most important member of this group with 5000 compounds [56]. Flavonoids are natural antioxidants, exihibit various biological effects such as anti-inflammatory, antibacterial and vasodilatory actions. Chemical structure of Phenolic compounds has an important impact on radical scavenging activity. Antioxidant capacity is directly related to hydroxyl moieties. Phenolic compounds also help to keep cell membranes in normal state by decreasing lipid peroxidation and free radical scavenging. They also enhance membrane integrity to protect from chemical and physical stress conditions. Free radicals were scavenged by Phenolic compounds of honey by thwarting production of malondialdehyde which is a biomarker of oxidative damage. Maximum Phenolic content is found in Gelam honey. Animal studies revealed that Phenolic compounds exhibit antidiabetic effect when they are administered in higher doses and moderate antidiabetic response in lower doses by regerative changes in islet cells of the pancreas [57].

CONCLUSION

Increased body's antioxidant content may help protect against cellular damage and the development of chronic diseases such as diabetes, cardiovascular disorders etc. In diabetes oxidative stress also play important role and by curing oxidative stress of diabetes we can give pallaitive effect to diabetic patients. Honey is an important nutrition since man's earliest days. In honey there is a mixture of substances such as glucose, fructose, oligosaccharides, antioxidant enzymes, Phenolic compounds and so on, all these components of honey shows the antioxidant effect which reduces the oxidative stress in diabetes and thereby helps in controlling diabetes. Scientists have sought to understand the health benefits of honey in diabetes mellitus. Composition of various components of honey depends upon the floral sources, season and geographic factors as well as the action of the bees that collect the primary nectar. Processing and storage of honey also play important role in ensuring health benefits of honey. Data from different floral and regional origins are needed before we can fully assess and compare specific health impacts. The review tells us about the abnormalities which are linked with type diabetes and its disorders, also it outlines the useful effects of oligosaccharides on diabetes.

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Table 1: Showing evidences for the antioxidant effect of honey.

SOURCE	TITLE	FINDINGS
Hazan .A. Alzahrani *et al* 2012	Evaluation of antioxidant activity of three varieties of honey from different botanical and geographical origin.	Antioxidant effect of honey depends upon Phenolic content of honey. Manuka >Acacia>Wild carrot honey
Vilma Baltrusaityte *et al* 2007	Radical scavenging activity of different floral origin honey and beebread Phenolic extracts.	Radical scavenging activity of Lithuanian honey and beebread samples revealed the antioxidant properties of these useful products.
Omotayo owomofoyon Erejuwa *et al* 2011.	Comparison of antioxidant effects of honey, glibenclamide, metformin and their combinations in the kidneys of streptozotocin induced diabetic.	Beneficial role of tualang honey as an adjunct to metformin or glibenclamide in ameliorating oxidative stress in the kidneys of streptozotocin diabetic rats.
Isabel C.F.R Ferreira *et al* 2009.	Antioxidant activity of Portuguese honey samples: different contributions of the entire honey and Phenolic extract.	The increase of the colour intensity seems to be related to an increase in the antioxidant properties and in the Phenolic contents.
Sarvana Kumar jaganathan and Mahitosh Mandal 2009.	Antiproliferative effects of honey and of its polyphenols: A review.	Honey polyphenols tested in laboratorial setups showed to be a promising pharmacological agent for inhibiting cancer cell proliferation.
Lee ke yao *et al* 2011	Malaysian gelam honey reduces oxidative damage and modulates antioxidant enzyme activities in young and middle aged rats.	Gelam honey supplementation reduced the DNA damage and MDA level of young and middle aged rats.
M.I khalil *et al* 2010	Antioxidant properties of honey and its role in preventing health disorder.	Antioxidant properties of honey are due to the presence of some antioxidant compounds such as vitamin c, monophenolics, flavonoids and polyphenolics.
Beatriz A. Rodrigue *et al* 2012	Quality parameters of antioxidant and antibacterial properties of some Mexican honeys.	High variability was found in the evaluated biological activities of monofloral honey samples from orange blossoms and eucalyptus flowers demonstrated to be good sources of antioxidant and antimicrobial compounds.

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