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Role of antioxidant in the regulation of blood glucose level

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Abstract
Antioxidants play important role in the prevention of free radical formation and helps in reducing various disorders such as cancer, aging, cardiovascular disease, cataracts, immune system decline, and brain dysfunction. There are several foods such as fruits, green leafy vegetables, tea, coffee, nuts and oilseeds which have been found to have good antioxidants potential. These dietary antioxidants such as vitamin A, vitamin C, vitamin E, carotenoids, phytochemicals etc. are found to have various disease preventive capacities. These antioxidants play an important role in protection against photo oxidative processes by acting as oxygen and peroxyl radical scavengers. These have the capacities of preventing cardiovascular diseases include atherosclerosis, coronary heart disease, arterial hypertension, and heart failure. Antioxidants stimulate the immune system by enhancing T-lymphocyte proliferation in response to infection increasing cytokine production and synthesis of immunoglobulin and protect membrane stability, including quenching or scavenging Reactive Oxygen Species. The present review highlights the health benefits of antioxidants with supporting evidence from animal studies and humans.

Keywords: Antioxidants, diabetes mellitus, free radicals, oxidative stress, medicinal plants

Introduction
Antioxidants are defined as "The substance that delays, prevents or removes oxidative damage to a target molecule". In the same year defined antioxidants as "substance that directly scavenges ROS (Reactive Oxygen Species) or indirectly acts as inhibitor of ROS production". Compounds which have the ability, after scavenging the radical, to form a new radical that is stable through intramolecular hydrogen bonding on further oxidation are called as antioxidants. "Antioxidants" are substances that neutralize the actions of free radicals. Every cell in nature is endowed naturally with several protective mechanisms against any harmful effects of free radicals: superoxide dismutase (SOD), glutathione reductase, glutathione peroxidases are the enzymatic antioxidants. α-Tocopherol (vitamin E) is an essential nutrient which acts as a chain breaking antioxidant preventing the propagation of free radical reactions in all cell membranes in the human body. Ascorbic acid (vitamin C) is also an antioxidant which protects against free radicals. Carotenoids, flavonoids and polyphenols, α-lipoic acid, glutathione etc are the other non-enzymatic antioxidants. These antioxidants plays diverse physiological role in body by inhibiting the process of oxidation, even at relatively small concentration (Verma and Mishra, 2014) [7].

The prevalence of diabetes among adults has been increased significantly worldwide. It has been predicted that the number of adults with diabetes will increase from 135 million in 1995 to 30 million in 2025. The age range of diabetic patients in developing and developed countries is between 45–64 and 63–65 years, respectively. Diabetes is the fourth leading cause of death globally and every 1 min 6 persons die from the complications of diabetes (Mohammad *et al.*, 2016) [4].

Diabetic causes arterial diseases in conjunction with neuropathy which accounts for more than 60 percent of all non-traumatic amputations in the United States. Diabetes mellitus and impaired glucose tolerance increase cardiovascular disease risk up to 8-fold. Furthermore, new blood vessel growth is impaired in response to ischemia in diabetic patients, resulting in decreased collateral vessel formation in ischemic hearts and in non-healing foot

ulcers (Madiseh *et al.,* 2016) [4]. Type 2 or non-insulin-dependent diabetes mellitus (NIDDM) accounts for about 90–95 of all diagnosed cases of diabetes. Hyperglycaemia alone does not cause diabetic complications. It is rather the detrimental effect of glucose toxicity due to chronic hyperglycaemia mediated and complicated through augmented oxidative stress. Hyperglycaemia increases the production of reactive oxygen species (ROS) inside the aortic endothelial cells. ROS-induced activation of protein kinase-C isoforms, increased formation of glucose-derived advanced glycation end products, increased glucose flux through aldose reductase pathways and activation of cytokines are some of the known biochemical mechanisms of hyperglycaemia-induced tissue and cell damage. Thus, antioxidant therapy in diabetes may be helpful in relieving symptoms and complications observed in diabetes patients. Many traditional medicinal plants that possess substantial quantity of antioxidant components have been found to be useful against diabetes and its related complications. Hence, there is a huge prospect of development of potential hypoglycaemic agent coupled with antioxidant activity from traditional medicinal plants to combat diabetes and its complications (Dewanjee *et al.*, 2011) [6]

Free Radicals

Free radicals are a molecule with one or more single pair of the electron that can quickly react with the constituents such as proteins, nucleic acid and lipids. The reactive molecule comprises the reactive oxygen species (ROS) and reactive nitrogen species was derived from oxygen and nitrogen, respectively. These reactive particles are generated in cellular membrane, mitochondria, nucleus, lysosome, peroxisome, endoplasmic reticulum, and cytoplasm. The enhanced generation of the reactive species associated with hyperglycemia (Rajendiran *et al.,* 2018).

Oxidative Stress and Diabetes

Oxidative stress plays a key role in the development of wide range of diseases including cancer, cardiovascular disease, diabetes, aging, liver, and lung diseases. Oxidative stress due to an imbalance between radical engendering and radical scavenging systems. Previous experimental studies have been reported overproduction of free radicals and defect of antioxidants protection involved pathogenesis of diabetes. The mechanism behind the prooxidant-antioxidant imbalance in diabetes mellitus is auto-oxidation of glucose, increased the formation of advanced glycation end products (AGEs), polyol pathway, hexosamine pathway, and mitochondrial respiratory chain. The enzymatic source of free radical generation includes nitric oxide synthase, NADPH oxidase, and xanthine oxidase (Rajendiran *et al.,* 2018).

Role of Antioxidants in Diabetes and Controlling the Sugar Level

The antioxidants therapy defends the beta-cell against oxidative stress induced apoptosis and preserves the function of the beta-cell. Data from earlier studies show the antioxidants diminish diabetic-related complication and recover insulin sensitivity. Epidemiological studies revealed a strong association between the dietary antioxidants intake and protection against diabetes (Rajendiran *et al.,* 2018).

Vitamin E

It is naturally occurring lipophilic antioxidant exists as tocopherol and tocotrienol. It defends the cell against oxidative damage. It is believed Vitamin E playing a key role in controlling hyperglycemia, and the combined antioxidants therapy also considered for control and prevention of diabetic complication. The studies in an animal model have shown supplementation of Vitamin E decreases the hepatic lipid peroxide level in streptozotocin-induced diabetes. However, the increased level of lipid peroxide due to change of antioxidant status in the diabetic rat. Dietary vitamin and administration of Vitamin E positively associated with glucose concentration. The level of glucose significantly decreased and the OGGT improved in diabetic condition by supplementation of Vitamin E.

Vitamin E has been shown to controls hyperglycemia and lowering the HbA1c by inhibiting the sequence of oxidative stress in diabetic rats. The mechanism by which antioxidants reduced the glucose levels not yet clear, but the plasma glucose level decreased by increasing the glucose metabolism in peripheral tissues. Supplementation of Vitamin E (1800IU/day) showed that the serum level of Vitamin E increases in Type 1 diabetes and control rats, whereas the retinal blood flow significantly increased and elevated baseline creatinine clearance normalized, but the HbA1C level not affected in the same experiment,

In synergy with β-carotene and Vitamin C, it is reduced the risk of diabetes and cancer. The antioxidant property of Vitamin E associated with the prevention of hyperglycemia and minimizes the macrovascular and microvascular complications in individuals with diabetes (Rajendiran *et al.,* 2018).

Vitamin C

It is powerful antioxidants scavenging free radicals in aqueous compartment. It is essential to convert Vitamin E free radicals to Vitamin E, as a cofactor required for hydroxylation reaction in human. The most important function of Vitamin C is key chain-breaking antioxidants in the aqueous phase. It provides stability to the cell membrane. The research conducted by Yazd Diabetes Research Center, Iran, has been reported that totally 84 diabetic patients received 500 mg or 1000 mg of ascorbic acid daily for 6 weeks. The daily consumption of 1000 mg of Vitamin C may be beneficial in reducing blood glucose level and lipids, whereas 500 mg not significantly made any change during the parameter studied.

Eriksson and Kohvakka studied the effect of Vitamin C supplementation (2 g/day for 90 days) in 56 diabetic patients; the result has shown the high-dose supplementation reduced the level of fasting blood glucose, HbA1c and improve glycaemic control. Frequent intake of Vitamin C dietary source was found to decrease the risk of Type 2 diabetes in a population-based study.

Some of the studies have been reported that diabetes may result in decreased plasma Vitamin C and E due to increased oxidative stress (Rajendiran *et al.,* 2018)

Alpha-lipoic acid

A potent antioxidant, it is also known as 1, 2-dithiolane-3-pentanoic acid or thioctic acid. Alpha-lipoic acid fights cellular injuries triggered by free radicals, those unstable, highly reactive molecules that are derivatives of both normal and frazzled cell activity. It has a capability to restore endogenous antioxidants such as glutathione, Vitamin E, and Vitamin C. It is effective in many pathological conditions such as cardiovascular disease, diabetes mellitus, and liver disease. Alpha-lipoic acid has been reported to progress glucose metabolism in Type 2 diabetes mellitus patient by

directly activate lipid, tyrosine, and serine/threonine kinases in target cells, due to these mechanisms which stimulate glucose uptake and glycogenesis. In vitro studies have reported that the alpha-lipoic acid increases the translocation of GLUT1 and GLUT4 to the plasmatic membrane of adipocytes and skeletal muscle. It is related to an improved activity of proteins of insulin signalling pathway (Rajendiran *et al.*, 2018).

Budin *et al*., (2007) [1] had reported that the intake of ALA reduced the glucose level and total cholesterol in STZ-induced diabetes in rats. It also regenerates the other antioxidants such as Vitamin C, Vitamin E, and SOD in diabetic condition. The same results have been previously reported in experimental animals.

Jacob *et al.*, (1996) [3] have been reported that the administration of 500 mg of ALA in Type 2 diabetes patients for 10 days shown a significant increase of insulin-stimulated glucose disposal (30%) and no changes observed in fasting plasma glucose level or insulin. In the clinical study, 20 patients received 500 mg, it able to improve insulin resistance in NIDDM. Same results were obtained by chronic administration (100 mg/kg) of antioxidant in type 2 diabetes mellitus.

Selenium

It is important trace element, naturally present in many foods. It exists in organic and inorganic forms. Selenomethionine and selenocysteine belong to organic form; selenate and selenite are inorganic forms. Mostly the inorganic selenite presents in the soil. Selenium plays a major role in thyroid hormone metabolism and immune functions. Based on previous experimental and clinical studies, selenium focused on the prevention of many diseases due to their antioxidant activity. Previously, selenium was found as a toxic component due to Selenium poisoning in animals and humans, thereafter, it was recognized as essential element since selenium deficiency considered a major problem in animal and human. The supplementation of selenium with low doses has a beneficial effect on glucose metabolism, which mimics insulin-like actions in the animal experimental model. While the mechanism behind the mimicking insulin is not clear, however, the previous report showed that Se activates the key protein responsible for insulin signal cascade.

In another study stated the above-mentioned insulin-like activity of selenium due to increased glucose tolerance and alteration in the activity of gluconeogenic and glycolytic maker enzyme. In the same way, selenomethionine also studied their antioxidant activity in a diabetic animal, supplementation of selenomethionine, Vitamin E plus selenomethionine in type I diabetic rat for 24 weeks effectively decreased the glucose and glycosylated haemoglobin level (Rajendiran *et al.*, 2018).

Medicinal Plants in Diabetes

Medicinal plants are tremendous in the treatment of numerous diseases due to their antioxidant activity. All parts of medicinal plants are effective in the treatment of disease and help to discover new kind of drug. The plants contribute a potential source of hypoglycemic drugs due to their phytoconstituents. The active constituents responsible for hypoglycemic activity may include polysaccharides, sterol, triterpenoid, alkaloids, flavonoids, fat, coumarins, phenolics, and peptides. It stimulates the beta-cell to restore the function of pancreatic tissue. The insulin secretion in beta-cell increased and the uptake of glucose increased by adipose tissue and muscle in plant treated rat, at same the time the absorption of glucose decreased and hepatic glucose production decreased by inhibiting the enzymes. Some of the antidiabetic plants possess antioxidants activity include *Nerium oleander* Linn. (Nerium), *Annona squamosa* (Custard Apple), *Cynodon dactylon* (Bermuda grass, Dūrvā grass), *Padina boergesenii* (leafy rolled-blade alga) and *Tectona grandis* Linn... (Teak) Medicinal plants have a long history in the treatment of diseases majorly in diabetes; therefore, it focused mainly due to its curative property with fewer side effects.

Conclusion

Among the antioxidants, the diet-derived antioxidants are important in the prevention and management of various diseases. Over the past decades, antioxidant-based experimental research emerged in the production of a new drug. However, many drugs are in clinical trials which possess antioxidants activity. Based on the review, supplementation of antioxidants such as Vitamin E, C, alpha-lipoic acid, and selenium shows their hypoglycemic and hepatoprotective effect, but some of the studies have been reported that vitamin supplementation does not affect glucose level. In diabetic condition, the low level of vitamin reported in the previous study. The mechanism behind the antioxidant is undefined, most of the study reported it prevent and minimize the complication of diabetes. Diabetes mellitus can damage the eyes, kidneys, nerves and heart. Microvascular and macrovascular disorders are the leading causes of morbidity and mortality in diabetic patients. Hyperglycemia increases oxidative stress in which ROS has the main role in the pathogenesis of these complications. Therefore, antioxidants which combat oxidative stress should be able to prevent and repair ROS induced damages. It seems that antioxidants in vegetables, fruits and grains help preventing diabetes complications; however, there is little evidence that taking single antioxidants such as vitamin E or vitamin C protect against these complications.

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