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REVIEW ON: "ROLE OF ANTIOXIDANTS IN DIABETES MELLITUS"

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Abstract:

Diabetes is a prevalent systemic disease affecting a vast proportion of the population worldwide. The effects of diabetes are devastating and well-documented. There is increasing evidence that chronic diseases, the increased production and/or ineffective scavenging of reactive oxygen species (ROS) may play a critical role. The high reactivity of Reactive Oxygen Species determines chemical changes in virtually all cellular components, leading to lipid peroxidation. Production of reactive oxygen species and disturbed capacity of antioxidant defence in diabetic subjects have been reported. It has been suggested that enhanced production of free radicals and oxidative stress is central to the development of diabetic complications. This suggestion has been supported by the demonstration of increased levels of indicators of oxidative stress in diabetic individuals suffering from complications. There are many reports on the effects of antioxidants in the management of diabetes. In this paper, after completing the biography and criticizing all relevant articles, the relationships between diabetes and oxidative stress and the use of antioxidants in the management of diabetes and its complications have been well reviewed. This review will indicate that antioxidants are involved in the pathogenesis of diabetes and its complications. The use of antioxidants reduces oxidative stress and alleviates diabetic complications.

Key words : Diabetes, endogenous oxidant, oxidative stress, ROS, etc

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INTRODUCTION:

Diabetes mellitus is a most common chronic disorder of carbohydrates, fats and protein metabolism. A deficient insulin secretary response, which translates into impaired carbohydrates (glucose) use, is a characteristic feature of diabetes mellitus, as is the result of hyperglycemias. Diabetes mellitus (DM) is commonly referred to as a "sugar" and it is the most common endocrine disorder and usually occurs when there is deficiency of insulin, impairment of insulin activity and insulin resistance. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025 Insulin and glucagon hormones both are secreted by the pancreas. Insulin is secreted by the beta (ß) cells and glucagon is secreted by the alpha (α) cells both are located in the islets of Langerhan's. Insulin decreases the blood glucose level by the glycogenesis and transport glucose into the muscles, liver and adipose tissue. Neural tissue and erythrocytes do not required insulin for glucose utilization whereas alpha (α) cells plays an important role in controlling blood glucose by producing the glucagon and it increases the blood glucose level by accelerating the glycogenolysis. In addition to increased risk of obesity, metabolic and cardiovascular disorders, and malignancy in future life of fetus after delivery. Type II diabetes mellitus comprises 80% to 90% of all cases of diabetes mellitus. Geographical variation can contribute in the magnitude of the problems and to overall morbidity and mortality.[1][2] Moreover, people with diabetes who undertake moderate amounts of physical activity are at inappreciably lower risk of death than inactive persons. It is now well established that a specific genetic constitution is required for such an event to cause. The growing burden of diabetes and other non-communicable diseases is one of the major health challenges to economic developments bedeviling WHO African Region states.[3]

In diabetes, there is an aberration either in the synthesis or secretion of insulin as seen in Type 1 diabetes mellitus (T1DM) and stenosis in the pancreatic duct, or the development of resistance to insulin or its subnormal production as in the case of Type 2 diabetes (T2DM) and certain secondary diabetes.[4]

1.1 TYPES OF DIABETES

1.1.1 Type 1 diabetes (T1D)/ Juvenile diabetes/ Insulin dependent diabetes:

T1D affects both adults and children at any age and occurs when the person's pancreas stop producing insulin due to destruction of the pancreatic beta cells or by inactivity of these insulin-producing cells. Affected individuals depend on daily injections of insulin to maintain normal blood glucose levels. The causes of T1D are not entirely understood however; scientists believe that both genetic and environmental factors are involved.

1.1.2 Type 2 diabetes/ non-insulin dependent diabetes mellitus (T2D or NIDDM):

This is the most common form of diabetes that most often occurs in adulthood. However, because of increased obesity rates and sedentary lifestyles, teens and young adults are also being diagnosed with T2D or the precursor, prediabetes. In T2D, fat, muscle and liver cells do not respond correctly to insulin. This is called insulin resistance

1.1.3 Gestational diabetes:

This refers to diabetes that is first diagnosed during pregnancy. As many as eight out of 100 pregnant women in the U.S develop gestational diabetes. Weight gain and changing hormones that occur during pregnancy can impair insulin function, resulting in high blood sugar. This form of diabetes usually disappears after pregnancy, however, women who have had gestational diabetes have a 40-60% chance of developing T2D within 5 to 10 years.[5]

1.2 PATHOPHYSIOLOGY

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1Therefore, deficiency of insulin or the insensitivity ofits receptors play a central role in all forms of diabetes mellitus.[6]

The body obtains glucose from three main sources: the intestinal absorption of food; the breakdown of glycogen (glycogenolysis), the storage form of glucose found in the liver; and gluconeogenesis, the generation of glucose from non-carbohydrate substrates inthe body.[7] Insulin plays a critical role in regulating glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.[8]

The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich versus a starch-rich meal is

highlighted .Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose.

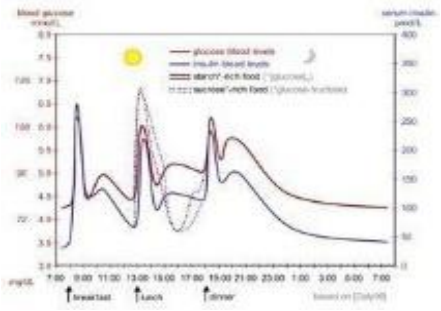
The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich starch-rich meal is highlighted. Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.

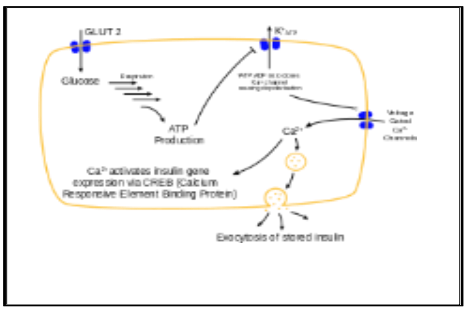
If the amount of insulin available is insufficient, or if cells respond poorly to the effects of insulin (insulin resistance), or if the insulin itself is defective, then glucose is not absorbed properly by the body cells that require it, and is not stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as metabolic acidosis in cases of complete insulin deficiency.[9]

When glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss.[10]

Lost blood volume is replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). In addition, intracellular glucose deficiency stimulates appetite leading to excessive food intake (polyphagia).[8]

The etiology of oxidative stress in diabetes arises from a variety of mechanisms such as excessive oxygen radical production from auto-oxidation of glucose, glycated proteins, and glycation of antioxidative enzymes, which limit their capacity to detoxify oxygen radicals. In addition to these mechanisms, two others have been suggested as being responsible for the generation of oxygen radicals in diabetes. First, Jain demonstrated that high glucose levels could stimulate cytochrome P450-like activity by excessive nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) produced by glucose metabolism. Second, ketosis, a hallmark of T1DM in particular, could increase oxygen radical production in diabetic patients.





2.1 ROLE OF OXIDATIVE STRESSIN DIABETIC COMPLICATIONS

The balance between the rate of free radical generation and elimination is important. Excess cellular radical generation can be harmful;[11] however, if there is a significant increase in radical generation, or a decrease in radical elimination from the cell, oxidative cellular stress ensues[12].There is convincing experimental and clinical evidence that the generation of reactive oxygen species (ROS) increases in both types of diabetes and that the onset of diabetes is closely associated with oxidative stress.

Oxidative stress results from increased ROS and/or reactive nitrogen species (RNS).[13] Examples of ROS include charged species such as superoxide and the hydroxyl radical, and uncharged species such as hydrogen peroxide and singlet oxygen. The possible sources of oxidative stress in diabetes might include auto-oxidation of glucose, shifts in redox balances, decreased tissue concentrations of low molecular weight antioxidants, such as reduced reduced glutathione (GSH) and vitamin E, and impaired activities of antioxidant defence enzymes such as superoxide dismutase (SOD) and catalase (CAT). ROS generated by high glucose is causally linked to elevated glucose and other metabolic abnormalities important to the development of diabetic complications. However, the exact mechanism by which oxidative stress may contribute to the development of diabetic complications is undetermined.

In the past few decades, increasing evidence has connected oxidative stress to a variety of pathological conditions, including cancer, cardiovascular diseases (CVDs), chronic inflammatory disease, post-ischaemic organ injury, diabetes mellitus, xenobiotic/drug toxicity, and rheumatoid arthritis.[14][15] Over time, convincing evidence has established the role of free radicals and oxidative stress in the pathogenesis and development of complications from DM[16], including retinopathy, nephropathy, neuropathy, and accelerated coronary artery disease[17]. Several studies have shown that elevated extra - and intra- cellular glucose concentrations result in oxidative stress which was reported both in experimental diabetes in animals and in diabetic patients. The source of oxidative stress is a cascade of ROS leaking from the mitochondria. This process has been associated with the onset of type 1 diabetes (T1DM) via the apoptosis of pancreatic beta-cells, and the onset of type 2 diabetes (T2DM) via insulin resistance.

The underlying mechanisms in the onset of diabetes are complex because hyperglycemia could also be due to the cause-effect relationship of increased oxidative stress. Biomarkers of increased oxidative stress, as measured by indices of lipid peroxidation and protein oxidation, increase in both T1DM, and T2DM.

Nowadays, diabetic micro- and macro-angiopathy are considered to be poly aetiological multifactorial diseases. A number of studies have evaluated the role of oxidative stress in the aetiology of micro-vascular and macro-vascular complications of diabetes in the fasting state. Furthermore, there is growing evidence suggesting the role of hyperglycemia, hyper insulinemia and dyslipidaemia in diabetic patients, all of which have been implicated in the development of macro-angiopathies, which possibly act upon their ability to induce oxidative stress, leading to endothelial dysfunction and atherosclerosis. Many studies have suggested that oxidative stress is a common pathogenic factor for the dysfunction of beta and endothelial cells. Beta cell dysfunction results from prolonged exposure to high glucose, elevated free fatty acid (FFA) levels, or a combination of both Beta cells are particularly sensitive to ROS because they are low in free-radical quenching (antioxidant) enzymes such as catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD). Therefore, the ability of oxidative stress to damage mitochondria and markedly blunt insulin secretion is not surprising. For example, it has been demonstrated that oxidative stress generated by short exposure of beta cell preparations to hydrogen peroxide (H_2O_2) increases the production of protein cyclin-dependent kinase inhibitor 1 (p21) and decreases insulin messenger ribonucleic acid (mRNA), cytosolic adenosine triphosphate (ATP), and calcium flux in cytosol and mitochondria. In other studies, much experimental evidence has been accumulated to show that various types of vascular cells are able to produce ROS under hyperglycemic conditions.

The pathogenesis of diabetic nephropathy remains far from clear. An important role of oxidative stress for the development of nephropathy and neurological complications is suggested by experimental and clinical studies. These studies establish a causal relationship between oxidative stress and diabetic nephropathy by observations that

1.lipid peroxides and 8-hydroxydeoxyguanosine, indices of oxidative tissue injury, increase in the kidneys of diabetic rats with albuminuria.

2. high glucose directly increases oxidative stress in glomerular cells and target cells of diabetic nephropathy;
3.oxidative stress induces mRNA expression of transforming growth factor beta 1 (TGF-β1) and fibronectin, which are the genes implicated in diabetic glomerular injury, and
4. inhibition of oxidative stress ameliorates all the manifestations associated with diabeticnephropathy.

Preview studies demonstrated that there is a close relationship between endothelial dysfunction and the development and progression of renal and cardiovascular pathology in patients with T1DM.The combined development of renal and cardiovascular complications is referred to as cardio-renal syndrome. The causes of the development of cardiorenal syndrome in T1DM are poorly understood. Previous studies suggest that endothelial dysfunction and the concomitant atherosclerotic process may lead to simultaneous development and progression of renal and cardiac pathology, since endothelial dysfunction is already present at the early stages of T1DM.[18]

2.1 Pathophysiology of oxidative stress in diabetes

Nowadays, evidences have been reported that support the role of oxidative stress in the pathogenesis of both type 1 and type 2 diabetes. Free radical formation in diabetes by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation leads to damage of enzymes, cellular machinery and also increased insulin resistance due to oxidative stress (Maritim et al., 2003). According to latest research, lipid is not only but also the lipoprotein component of LDL that forms insoluble aggregates oxidatively due to hydroxyl radical-induced cross-linkage between apo-B monomers that is responsible for oxidative damage in diabetic complications (Pham-Huy, 2008)

In diabetes mellitus, main sources of oxidative stress are mitochondria. During oxidative metabolism in mitochondria, a component of the utilized oxygen is reduced to water, and the remaining oxygen is transformed to oxygen free radical (O) which is an important ROS that is converted to other RS such as ONOO, OH and H2O2 (Moussa, 2008). Insulin signaling is modulated byROS/RNS by two ways. On one side, in response to insulin, the ROS/RNS are produced to exert its full physiological function and on the other side, the ROS and RNS have got negative regulation on insulin signaling, interpreting them to develop insulin resistance whichis a risk factor for diabetes type 2.[19]

3.1 ANTIOXIDANTS

Antioxidants are substances able to slow or inhibit the oxidation of other molecules. Recently, the medicinal field focused the antioxidants therapy in the management of numerous diseases, especially diabetes. Preceding experimental studies and clinical trials have suggested the efficacy of antioxidants in preventing diabetes complication. The therapeutic strategy uses the antioxidants as a substrate, combined drug, synthetic antioxidants, and drug with antioxidants activity. Medicinal plants with antioxidants activity are considered for the treatment of diabetes mellitus.

4.1 ROLE OF ANTIOXIDANTS IN DIABETES

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 antioxidant's intake and protection against diabetes. [19]

3.1NATURALLY OCCURING ANTIOXIDANT

3.1.1 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[20] . 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[21]. During diabetic condition, the antioxidant enzymes SOD, CAT, and GPX decreased. However, the oral administration of Vitamin E (440 mg/kg of body weight, once a week for 30 days) significantly increased SOD and GSH-Px activity and decreased the hydroperoxide level due to an improvement of glycemia [6]. During diabetic condition, the excess glucose attached to hemoglobin to produce glycosylated hemoglobin. It is an important marker for diabetes which is prevented Vitamin E treated rat in diabetic condition.

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. It is achieved by unchanged glycemic control and normalization of DAG/PKC pathway through activation of DAG kinase in diabetic patients. 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 macro-vascular and micro-vascular complications in individuals with diabetes.

3.1.2 Vitamin C

It is powerful antioxidants scavenging free radicals in aqueous compartment. It is essential to convert Vitamin E free radicals to Vitamin E, 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 [17].

Eriksson and Kohvakka studied the effect of Vitamin C supplementation (2g/day for 90days) in 56 diabetic patients; the result has shown the high-dose supplementation reduced the level of fasting blood glucose, HbA1c and improve glycemic control . Frequent intake of Vitamin C dietary source was found to decrease the risk of Type 2 diabetes in a population-based study. Administration of Vitamin C and E (100 mg/kg of body weight of rat) significantly reduced the blood glucose level However, lowered level of ascorbic acid and SOD observed in the diabetic subject when compared to the non-diabetic person. The increased level of Vitamin C in diabetes may due to increased utilization in trapping theoxy radicals. Some of the studies have been reported that diabetes may result in decreased plasma Vitamin C and E due to increased oxidative stress . The mechanism behind the treatment of diabetes is not clear. However, it diminishes the micro albumin uria, erythrocyte sorbitol levels and plays a chief role in ameliorating insulin resistance of diabetic patients due to its antioxidant function .

3.1.3 3.1.3 **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 signaling pathway . Budin-et-al 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. 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 [22]

In another study, the oral supplementation ALA (600 mg twice daily for 4 weeks) treatment which increases the plasma insulin sensitivity . According to Packer et al., ALA is capable to scavenge ROS produced during the lipid peroxidation and guards the cell structure against damage. The continued supplementations of the LA in diabetic rats were associated with diminution of both hyperglycemia and diabetic nephropathy.

Selenium

It is important trace element, naturally present in many foods. It exists in organic and inorganic forms. Seleno-methionine and seleno-cysteine 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 [23]. Previously, selenium was found as a toxic component due to Se poisoning in animals and humans, thereafter, it was recognized as essential element since selenium deficiency considered a major problem in animal and human [24]. 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. [25]

3.2 Antioxidant efficacy of vitamins and supplements in diabetes

ANTIOXIDANTS	DOSAGE	DIABETOGEN	EFFICACY	REFERENCE
Vitamin E	500 mg/kg on the day 1, 4, 7, 11, 14.21, 24, 27	Streptozotocin (single dose 60 mg/kg body weight)	Lowered lipid peroxide level inthe liver of the diabetic rat	Seven et al.
Vitamin C	500 mg twice a day	Type 1 and 2 diabetic patients	Supplementationof Vitamin C with metformin reduces FBS, PMBG and improves HbA1c.	Ganesh et al.
Vitamin E + Vitamin C	Vitamin C 60 mg daily and Vitamin E 200mg twice a week for 5 weeks	STZ (single dose 75 mg/Kgbody weight)	Reduced hepatic lipid peroxide, normalized Vitamin C, and raised Vitamin Eabove the normal level	Madhu et al.
Alpha-lipoic acid	300 mg daily	Type 2 diabetic patients	Decreased FBS and IR	Hasti et al.
Selenium (sodium selenite)	0.5 µg/day	STZ (55 mg/kg body weight)	Selenium reduced oxidative stress associated diabetes	Mukherjee et al.

3.3 Antidiabetic plants which possess antioxidants activity

PLANT NAME	EXTRACT	DOSE	EFFICASY	REFERENCE
Allium sativumL.	Ethanolic extract of the bulb	500 mg/kg body weightof rat	Significantly decreased the bloodsugar level	. Shakya et al.
Aloe vera (L.)	Aqueous extract of leaves	500 mg/kg body weightof mice	Hypoglycemic and hepatoprotective effect	Sharma et al.
Syzygium cumini Walp.(Eugenia jambolana)	Seed powder	500 and 1000 mg/kg body weight of rat	Hypoglycemic activity	Sridhar et al.
Mimosa pudica	Thottal vadi choornam (Leaves and roots)	100 and 200 mg/kg body weight of rat	Hypoglycemic activity	Vishwanathan etal.
Momordica charantia	Alcoholic extract of bittermelon	0.5-1.5 g/kg body weightof rabbits.	Hypoglycemic activity	Vangoori et al.
Psidium guajava	Ethanolic extract of leaf	250 mg/kg of body weight of rat	Hypoglycemic activity	Mukhtar et al.
Mangifera indica	Ethanolic extract of seed kernels	300 mg/kg of body weightof rat	Hypoglycemic activity	Gupta and Gupta
Andrographis paniculata	Ethanolic extract. (Aerial part)	0.1, 0.2, and 0.4 g/body weight of rat.	Hypoglycemic and hypotriglyceridemic effect	Zhang et al.

[26]

4.1 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.

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