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REVIEW ARTICLE

Antioxidants And Their Potential Role In Diabetes.

SU Mohamed Afreeth^{1*}, M Dheepthi¹, S Suba Dhanisha¹, C Sowmya², and R Kaleeswari³.

¹Pharm D, Department of Pharmacy Practice, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil - 626126, Tamil Nadu, India.

²Professor, Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil - 626126, Tamil Nadu, India.

³Assistant Professor, Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil - 626126, Tamil Nadu, India.

ABSTRACT

Diabetes is one of the most common disorders affecting about 450 million people around the world and is rapidly increasing every year. Uncontrolled diabetes leads to variety of acute and chronic complications which are the major burden of healthcare system. Oxidative stress and free radical are generally detrimental to people and contribute to many chronic health issues. The formation of oxidative stress depends on the intensity of impact of the stress factor and pathology of individual. It is formed by imbalance between production and accumulation of reactive species in the body. Oxidative stress is the vital component in worsening of diabetic condition including resistance to insulin. Antioxidants are compounds that counteract oxidation thus helping in management of oxidative stress. A balance between reactive oxygen species and antioxidants availability in the body is demanded for well physiologic functioning. Naturally available antioxidants are adopted due to enormous availability and their least toxic effects in the ministration of diabetes mellitus since antioxidants have improved insulin sensitivity. Flavonoids, flavones, catechins, polyphenols, phytoestrogens are some of the plants and food based antioxidants that are intended to be consumed regularly in addition to vitamin C and vitamin E to inhibit the progress of oxidative stress. In this article, the significance of antioxidants in management of hyperglycemic condition and prevention of further consequences are discussed.

Keywords: Antioxidants, Diabetes, Free radical, Oxidative stress, Vitamin C and E, Flavonoids.

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**Corresponding author*

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INTRODUCTION

Diabetes is a chronic condition which is defined as a metabolic disorder characterized by destruction of beta cells of pancreas leading to rise of blood glucose level [1]. Diabetes plays a main threat to health of human beings and it is considered as disease of minor significance in world health [2] and it is the most common non-communicable diseases in world wide. It also associated with disturbances of carbohydrate, protein and fat metabolism. As a result various complications are developed due to these consequences of metabolic de arrangement and those complications of diabetes are collectively grouped into micro vascular complications and macro vascular complications.

Free radicals are short lived reactive chemical entities. These are the molecules with lone pair of electron which can easily react with constituents such as proteins, nucleic acids and lipids. The reactive molecule comprises of both reactive oxygen species (ROS) from oxygen and reactive nitrogen species from nitrogen get generated from cellular membrane and various other cellular constituents. Oxygen is one of the important components of life but in some circumstances these oxygen may be a killer of cells when it generate reactive species that causes necrosis and organ damage and ultimately to cell death [3]. This enhanced generation of these reactive species associated with hyperglycemia [4]. Oxidative stress is the key factor in progress of endothelial dysfunction that leads to complications in diabetic population [5]. It is accepted that oxidative stress results due to imbalance between generation of oxygen derived radicals and the organism antioxidant potential [6]. Various study shown that the diabetic condition is due to increased formation of free radical and decreases in anti-oxidant potential contributing to oxidative damage of cell components such as proteins, lipid, nucleic acids [7].

Mechanisms involved in oxidative stress [8]

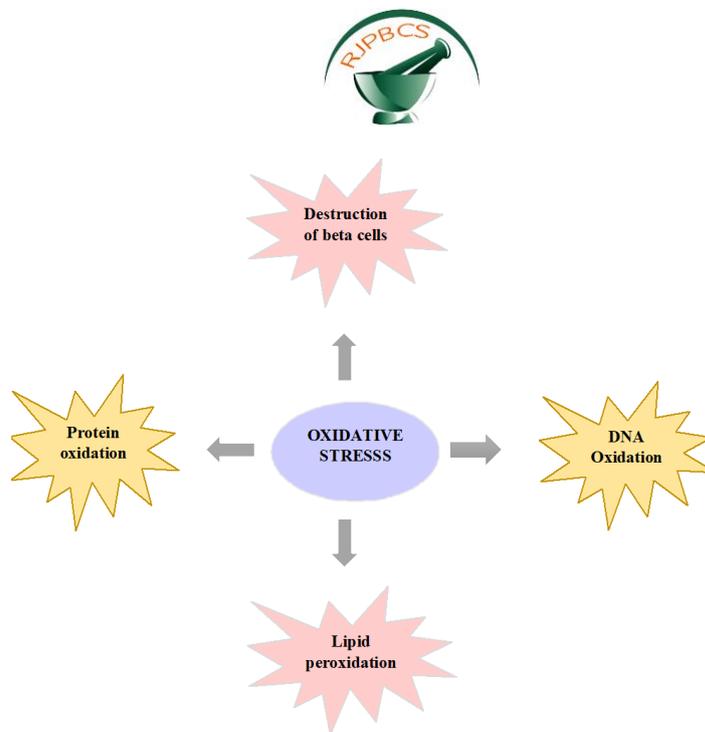
1. Auto-oxidation of glucose
2. Polyol pathway
3. Hexosamine pathway
4. Mitochondrial respiratory chain
5. Advanced glycation end product (AGEs)

Mechanism of free radicals

In diabetes oxidative stress is increased due to various factors. Among those factors glucose autooxidation is dominant factor leads to production of free radicals. Other factor includes cellular oxidation/ reduction imbalance and decrease of antioxidant defence including decreased cellular antioxidant levels and a reduction in activity of antioxidant enzyme that dispose free radicals. In diabetes there is also elevation of some pro-oxidants levels such as ferritin and homocysteine. Other important mechanisms are interaction of advanced glycation end product (AGEs) with specific cellular receptors called (RAGE). Elevated level of advanced glycation end product are formed under hyperglycemic condition. Their formation begins when glucose interact with specific amino acid on protein forming compound that undergo further chemical reactions. Alteration of protein and cellular function and also a binding of ages to their receptors is due to the process of glycation of protein. This process can further lead to modification in cell signaling and further production of free radicals [9]. In type 2 diabetes oxidative stress play a vital role in development of vascular complications [10] which is the burden to healthcare system as it increases the mortality in diabetic population [11].

Types of free radicals:

- Reactive oxygen species (ROS)
- Reactive nitrogen species (RNS)
- Reactive chlorine species (RCS)



Antioxidants and their efficacy in diabetes

Antioxidants are the substances able to slow or inhibit the oxidation of molecules and prevent cell damage [12]. These antioxidants preserve the function of beta cells by defending the beta cell against oxidative stress induced apoptosis and help to recover insulin sensitivity. Due to metabolic changes, antioxidant defense reduces in diabetes [13] and worsens the condition. In general, medicinal plants with antioxidant activity are considered as for treatment of diabetes mellitus. These antioxidants counter the action of free radicals by several mechanisms including,

- Enzymes that degrade free radicals
- Protein such as transferrin that can bind metal which stimulate the production of free radicals
- Anti-oxidants such as vitamin C and vitamin E that act as free radical scavenger

The capacity of total antioxidant in plasma of diabetic patient is 16% which is much lower than non-diabetic people [14]. Some study states that increase level of antioxidants in individual particularly serum tocopherol there will be lower risk of type 2 diabetes [15]. However there were also an study which states that there is no significant difference in antioxidant status between diabetic patient & normal individual [16, 17]. Antioxidants includes vitamin C and E, reduced glutathione (gsh) and glutathione peroxidases (gsh-px) that act as a primary defense against oxidative stress in the cell [18].

Vitamins as antioxidants

Numerous studies have demonstrated that this vitamin & its supplements play a vital role in reducing oxidative stress & lipid peroxidation in diabetic patients and also animals. And also it reports that there is a deficiency of vitamin C and E, beta carotene in diabetic patient & animals [19].

Vitamin E

It' s a naturally available lipophilic antioxidants and it exist as tocopherol & tocotrienol. It prevents the cell damage against oxidative stress and also plays a key role in controlling hyperglycemia. In diabetic condition the supplement of vitamin E decrease the glucose level significantly. However oral administration of vitamin E [440mg/kg once a week for 30 days] significantly increase glutathione peroxidases activity and decreased hydro peroxide level due to improvement of glycemic condition [20]. Vitamin E inhibit the sequence of oxidative stress which results in control of hyperglycemia and decreasing of HbA1C level [21]. The plasma control of hyperglycemia is by increasing glucose metabolism in peripheral tissue [22]. The antioxidant property of vitamin E results in reduction in progress of the macro and micro vascular complication in chronic diabetic patients [23].



Vitamin C

It act as a powerful antioxidant by its role as converting vitamin E free radicals into vitamin E and washing out all the free radicals in aqueous compartment by key chain breaking antioxidants. In a population based study there was low risk of type 2 diabetes in patients who frequently took vitamin c as dietary source [24]. Vitamin C provides stability to cell membrane. Utilization of more oxyradicals results in increasing level of vitamin c in diabetic patient some study states that this decreased plasma vitamin C and E levels are due to oxidative stress [25, 26] the mechanism of vitamin C behind the treatment of diabetes involves decreasing level of microalbuminuria & prevention of insulin resistance by its role of antioxidant in diabetic patient [27].

Alpha lipoic acid

It is also called as thioctic acid or 1, 2-dithiolane-3-pentanoic acid which is derived from octononic acid is a potent antioxidant. Its mechanism involves scavenging of free radicals, recycling of antioxidant and also a chelation of metal ion. Endogenous antioxidants such as glutathione, vitamin E and vitamin C are restored by this alpha lipoic acid. Its plays a major role in management of diabetes and associated cardiovascular disease and liver disorder [28]. It is observed that oral supplementation of alpha lipoic acid results in increasing the plasma insulin sensitivity [29]. It directly activate lipid, tyrosine and serine kinase in target cells which results in progress of glucose metabolism in type 2 diabetes patients by stimulation of glucose uptake and glycogenesis. It also improves neural blood flow helping in prevention of neuropathy [30].

Table 1: Antioxidants efficiency of vitamins & supplement in diabetes [31-33]

ANTIOXIDANTS	DOSAGE	EFFICACY
Vitamin E	500mg on the day 1,4,7,11,14,21,24,27	Lowered lipid peroxide level in liver
Vitamin C	500mg BD	Supplementation of vitamin C with metformin reduces FBS & Improves HbA1C
Alpha lipoic acid	300mg daily	Decreases FBS & increase insulin sensitivity

Medicinal plants as Anti oxidants

All the parts of plants are effective in treatment of various kinds of diseases due to their antioxidant activity. Higher plants consumes more number of antioxidant property in its all parts (wood, bark, stem, flower, fruit, roots, pollens, seeds, pods) [34]. Hypoglycaemic activity of plants is due to presence of phytoconstituents [35]. Some of those are polysaccharides, sterol, triterpenoid, alkaloids, flavonoids, coumarins and peptides. These active constituents restore function of pancreatic tissue by stimulation of beta cells [36]. Some of the plants that have the characteristics of antioxidant activity are useful in management of diabetes mellitus and includes the following [37-41].

- *Lerium oleander linn*
- *Annona squamosa*
- *Cynodan dactylon*
- *Padina boergesenii*
- *Tectona grandis linn*

Table 2: Plants which possess antioxidant activity used in diabetes mellitus [42]

<i>IMAGE</i>	<i>PLANT NAME</i>	<i>PART OF PLANT</i>	<i>EFFICACY</i>
	<i>Allium sativum</i>	Ethanollic extract of bulb	Significantly reduce the blood glucose level
	<i>Aloe vera</i>	Aqueous extract of leaves	Hepatoprotective & reduce blood glucose
	<i>Mimosa pudica</i>	Leaves & roots	Reduce blood glucose level
	<i>Mangifera indica</i>	Ethanollic extract of seeds	Reduce blood glucose level
	<i>Psidum guajova</i>	Ethanollic extract of leaves	Reduce blood glucose level
	<i>Andrographis paniculata</i>	Ethanollic extract of aerial parts	Reduces both blood glucose level & triglycerides

	<i>Momordica charantia</i>	Ethanollic extract of bitter melon	Reduce blood glucose level
	<i>Syzgium cumini walp</i>	Powder of seeds	Reduce blood glucose level

Drugs as antioxidants

Drugs used for treatment of hyperglycaemia have an antioxidant property which acts as scavengers of ROS & modulators of antioxidant enzymes. Some of them have beneficial effects on diabetic complications such as neuropathy- angiotensin converting enzyme inhibitor (ACEI), Angiotensin receptor blockade (ARB) & Melatonin, & retinopathy & neuropathy- melatonin and alpha lipoic acid. Most of them are beneficial against cardiovascular disease: caffeic acid, carvedilol and metformin [43]. In fact, metformin, the currently used biguanide antihyperglycemic agent, can decrease xanthine oxidase activity & TNF alpha production, chelates metal ions and inhibits advanced glycation end product formation [44]. With intracellular modulation of free radical production, metformin is the only conventional drug from herbal source and *Galega officinalis* mostly used in treatment of non- insulin dependent diabetes [45, 46]. Melatonin also shows a significant effect in treatment of diabetic neuropathy [47]. Rapaglinide act as insulin releaser and shows antioxidant property by inhibiting protein peroxidation by upregulating glutathione reductase [48].

Table 3: Drugs showing antioxidant mechanism used in treating diabetes mellitus [49].

DRUGS	MECHANISM	INDICATION
ACE Inhibitor & angiotensin block receptor	Blocking of angiotensin II & NADPH oxidase	Nephropathy
Melatonin	Scavenging of free radicals	Nephropathy & neuropathy
Alpha lipoic acid	Scavenging of free radicals, metal ion chelation, antioxidant recycling	Retinopathy & neuropathy
Glibenclamide	Scavenging of free radicals	Nephropathy & neuropathy
Allopurinol	Inhibition of xanthine oxidase	Nephropathy & neuropathy
Rapaglinide	Glutathione reductase & glutathione levels	Nephropathy & neuropathy
Phosphodiesterase inhibitors	Inhibition of phosphodiesterase, increase cAMP & cGMP	Nephropathy & neuropathy
Caffeic acid phenethyl ester	Scavenging of free radicals	Cardiovascular disease
Metformin	Decrease xanthine oxidase activity, inhibition of advanced glycation end product formation.	Cardiovascular disease
Carvedilol	Inhibition of electron addition, inhibition of lipid peroxidation in myocardial cell membranes, scavenging of free radicals	Cardiovascular disease



Dietary foods as antioxidants

Dietary antioxidants or some part of food have beneficial effects on glucose metabolism, includes prevention of diabetes. Increased physical activity and dietary management be a fundamental initial treatment for type 2 diabetes and has been recommended for long term by international consequences [50]. In a patient with newly diagnosed type 2 diabetes mellitus consumption of Mediterranean diet (fresh fruit, vegetables, breads, seeds, cereals etc.,) result in greater reduction of HbA1C level, higher rate of diabetic remission & delayed need for diabetic medication [51]. Consumption of fruits and vegetable rich diets (apple, cherry, onion, garlic, green bean) may not have benefit against diabetes but decrease the risk of developing diabetes [52, 53]. Tea (*camellia sinensis L*) is most widely consumable beverage in the world next to water. It contains catechins, the antioxidant property of catechins were well documented [54, 55]. Catechins also increases body endogenous antioxidants to reduce oxidative damage & lipid peroxidation biomarkers [56]. Cinnamon used extensively in food which has cinnamic acid in its bark. Cinnamic acid exhibit antioxidant and antidiabetic property and helps in management of early diabetes [57-59]. Watermelons, pawpaw, pink grape fruit, tomatoes contains a carotenoid called lycopene that has potent antioxidant property and tend to inactivate hydrogen peroxide and nitrogen dioxide thus inhibiting further damages [60].

CONCLUSION

The progress of diabetes can be controlled by inhibiting free radicle formation which provides strategy to prevent oxidative stress. In case of diabetic complications antioxidant therapy in addition to first line pharmacological management is much beneficial. Though many hypoglycaemic agents are in use in treatment of diabetes they are subjected to produce toxic effects in due time. Naturally, available antioxidants hence now emerged as better alternative in management of hyperglycaemic condition with minimal side effects. The easily available natural foods rich in antioxidants can be consumed by every individual regularly to maintain glucose level at standard as well as minimise the risk of developing diabetic complications. Combination therapy of oral hypoglycaemic agents with natural antioxidants have positive outcome of therapy which in turn improves quality of life.

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