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Review Paper

The Role of Natural Antioxidants in Oxidative Stress Induced Diabetes Mellitus

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Abstract

Diabetes mellitus is a group of metabolic disorder disturbing around 1.5% of the entire population that persisting to present a global health trouble. It is characterized by abnormally elevated levels of blood glucose due to complete or relative insufficiency in insulin secretion and /or insulin action together with chronic hyperglycemia as well as disturbances in carbohydrate, fat and protein metabolism. Diabetes mellitus is coupled with an imbalance among generation of oxygen free radicals and endogenous antioxidant defense that leads to the development of oxidative stress which is partially responsible for diabetes as well as its complications. Several studies have recommended that oxidative stress play a major role in reduced secretion of pancreatic β cells, systemic inflammation, endothelial damage and impaired glucose consumption in peripheral tissues, where absolute treatment with insulin as well as oral hypoglycemic agents with no side effect has been difficult. On the other hand, use of antioxidants can be an apparent substitute in patients with diabetes mellitus. Antioxidants obtained from nature helps in neutralization of reactive oxygen species and significantly reduce the probability of progression of diabetic complications. A variety of nutritionally important vitamins, supplements and some constituents of natural food sources including cappers, broccoli, tomatoes, berries, grapes, spinach, carrots, nuts, etc. naturally reduce the injury caused by oxidative stress in diabetes mellitus. Natural products are better known for their traditional use; moreover pharmacy professionals having a sufficient knowledge of such natural products are in a better position to guide patients on their proper use. This review describes the importance of naturally occurring antioxidant in management of diabetes mellitus and its complications.

Keywords: Diabetes mellitus, insulin, antioxidant, oxidative stress.

Introduction

Diabetes mellitus is a persistent metabolic disorder characterize by abnormally elevated level of blood glucose because of deficiency in insulin secretion by the β cells of pancreas and /or resistance toward the action of antidiabetic hormone insulin associated with disturbances in the carbohydrates, lipids, and proteins metabolism which leads to macro and micro vascular dysfunction and long term health complications[1]. The common symptoms of diabetes mellitus are polydipsia (i.e. increased thirst), polyuria (i.e. frequent urination) and polyphagia (i.e. increased hunger). In diabetic patient, long lasting damage, dysfunction, and/or chronic malfunctioning of various organs, particularly the eyes (especially diabetic retinopathy), nerves (diabetic neuropathy), heart (mainly myocardial infarction), kidneys (diabetic nephropathy) as well as blood vessels (atherosclerosis) are linked with uncontrolled hyperglycemia[2,3]. However, tendency to the development of diabetic complications vary person to person and depends mainly on patient's diet[4]. The genetic theory of diabetes proposed that complications of diabetes are genetically predetermined, while the metabolic theory of diabetes proposed that complications such as cellular and endothelial damage are belongs to the long term hyperglycemia. The Diabetes Control and Complications Trial, a chief clinical study carried out between 1983 to 1993 practically illustrated that complications of diabetes mellitus can be delayed and diminished by maintaining blood glucose levels as normal as possible [5]. Diabetes mellitus is commonly known as one of the main reason of death and impairment in the world. The global analysis states that diabetes mellitus affecting approximately 190 million population belonging to all age groups (approximately 3% of the global population) which persistently presenting a universal health problem. In India there are about 11 million diabetic victims are diagnosed and probably around 26 million are those who are undiagnosed and they are suffering without knowing[6].

Role of oxidative stress in human health

Oxidative stress is defined as a state of overload due to imbalanced formation and elimination of highly reactive micro molecules including reactive oxygen species (ROS) as well as reactive nitrogen species (RNS)[7]. Reactive oxygen species include free radical species for example superoxide molecule, hydroxyl molecule, peroxyl and hydroperoxyl molecule as well as non-radical species for example hydrogen peroxide molecule

and hydrochlorous acid. Reactive nitrogen species consist of free radicals like nitric oxide and nitrogen dioxide, in addition to non-radicals like peroxynitrite and peroxynitrates molecules[7]. Among these vastly reactive radicals, superoxide molecules, nitric oxide and peroxy-nitrite molecules are the leading extensive deliberate species and play essential roles in the tissue injury through physical, chemical and psychological factors that result in a variety of disorders including diabetes mellitus. Human body works against oxidative induced by free radical through a variety of defense mechanisms such as anticipatory mechanism, tissue repair, physical resistance and antioxidant defenses. Reactive oxygen species derived reactions of various free radicals are involved in the development of numerous human illness including[8], i. Neurodegenerative disorders (e.g. Alzheimer's disease, Parkinsonism, disseminated sclerosis, amnesia and depression). ii. Cardiovascular diseases (e.g. atherosclerosis, ischemia, Cardiomyopathy, high blood pressure, shock and injury). iii. Respiratory diseases (e.g. inflammatory lung diseases, chronic obstructive pulmonary disease and bronchial asthma). iv. Renal disorders (e.g. glomerulonephritis, chronic renal failure, proteinuria, and uremia). v. Autoimmune disease (e.g. rheumatoid arthritis). vi. Peptic ulcer, an inflammation of the inner lining of the colon leading to rectal hemorrhage, diarrhea, abdominal soreness, liver disorders, pancreatitis etc. vii. Lung cancer, malignant neoplasm of blood, cancers of breast, ovary and rectum etc. viii. Cataract, retinopathy, Diabetic maculopathy and ageing. ix. Diabetes mellitus, Skin lesions etc.

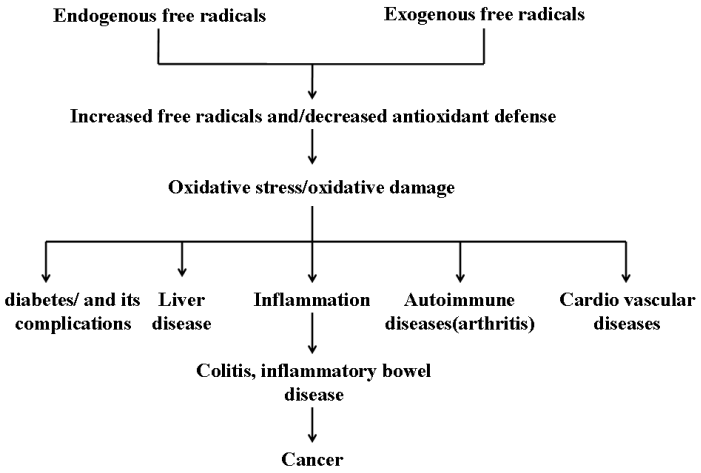

Figure-1
Organization of free radicals and their impact on human health

Diabetes Mellitus and Oxidative Stress

The main sources of oxidative stress in diabetes mellitus comprise various enzymatic pathways, non-enzymatic pathways and mitochondrial pathways. The most leading factor behind the development of prooxidant-antioxidant imbalance in diabetes mellitus is auto-oxidation of glucose that leads to generation of high-energy particles. The relation between diabetes mellitus and oxidative stress is also explained by the fact that oxidative stress result of an imbalance between the formations of oxygen derived free radicals and the person's endogenous antioxidant defense potential and diabetes mellitus is linked with augmented generation of free radicals and diminished antioxidant capacity. The equilibrium usually exists in cells among free radical development and their elimination by cellular antioxidants is disturbed. Such oxidative breakdown of cell constituent such as proteins, lipoid molecules, and nucleic acids results in the induction of type 1 and type 2 diabetes and its complications[9].

Apart from the auto-oxidation of glucose, cellular oxidation/reduction process, decreased cellular antioxidants, like reduced glutathione (GSH) and vitamin E, as well as impaired actions of antioxidant defense enzymes like superoxide dismutase (SOD) and catalase (CAT), elevated levels of some pro-oxidants such as ferritin a protein containing 20% iron that is found in the intestines and homocysteine are the probable sources of oxidative stress in diabetes mellitus. Reactive oxygen molecules formed by high glucose is unexpectedly associated with metabolic abnormalities which play an essential role in the improvement of diabetic complications. The prostaglandin like compounds known as F2-isoprostanes are formed from peroxidation of arachidonic acid mediated by free radical are came into view as precise measurement of oxidative stress. It was reported that the levels of F2-isoprostane have been augmented in the plasma of patient with type 2 diabetes mellitus as well as in the urine of type 1and type 2 diabetic patients. The association between impaired glucose level and improved lipid peroxidation has also been reported in diabetic patients[10].

In the oxidative stress initiated by non-enzymatic sources, initially hyperglycemia directly causes increased free radicals/reactive oxygen species generation. Glucose undergoes auto-oxidation and generates hydroxyl radicals. Besides these glucose also reacts with proteins in a non-enzymatic way leading to the improvement of advanced glycation end products which alters protein and cellular/immune function, and binding of advanced glycation end products to their receptors may leads to modification in cell signaling pathways and additional production of reactive oxygen species at multiple steps during this biological process[11]. The enhanced metabolism of glucose through the polyol (sorbitol) pathway in hyperglycemia also leads to improved production of superoxide radicals[11]. Nitric Oxide synthases, NAD(P)H oxidase and xanthine oxidase are membrane associated enzymes and play the vital role as enzymatic source of production of reactive oxygen species in diabetes mellitus[12].

Another resource for generation of reactive species through non-enzymatic mechanism includes the mitochondrial respiratory chain. The process involves electron transfer from electron carriers NADH and FADH2, during the oxidative phosphorylation through complex formation in the inner

mitochondrial membrane. Under usual situation, superoxide molecules are immediately removed by endogenous defense mechanisms. Scientific studies also demonstrated that generation of superoxide on the mitochondrial stage is the beginning of oxidative stress in diabetes during hyperglycemic conditions[13]. When endothelial cells experience hyperglycemic condition, it triggers improved production of reactive oxygen species, especially superoxide, which lead the commencement of key pathways concerned with the development of diabetic complications.

Antioxidants: Antioxidants are the compounds that protect cells against the injury originated by unstable molecules, such as singlet oxygen molecule, superoxide molecule, peroxyl radicals, hydroxyl radicals and peroxynitrite radicals. Antioxidants are the molecules able to slow or avoid the oxidation process of other micro molecules. Oxidation is a reaction that direct chemical shift of electron from a substance to an oxidizing agent which can create toxic metabolite together with free radicals which damage tissues/cells by sequence of chain reactions. Antioxidants are the chemical stuff that terminate these chain reactions through the elimination of free radical intermediates and impede other oxidation reactions by being oxidized themselves and thus protect cells against the destructive effects of oxygen species. Although oxidation reactions play an important role in human everyday life, they can also be harmful; hence, plants as well as animals preserves the diverse systems of various antioxidants, such as glutathione, lycopene, beta-carotene, carotenoids, selenium, flavonoids and natural vitamins together with vitamin C, vitamin A, and vitamin E, antioxidant enzymes including glutathione S. transferase, superoxide dismutase, catalase, peroxidase, in addition to Proteins that diminish the accessibility of peroxidase such as iron, copper ions and heme protein etc. Endothelial damage or cellular damage is the result of a discrepancy among antioxidant molecules and reactive oxygen species. Recently oxidative stress originated from reactive oxygen species is emerged as an important element of many human disorders/diseases[14]. Thus antioxidants are intensively studied in the field of medicine, predominantly as management for inflammation related metabolic disorder and its complications like diabetes mellitus, cardiac arrest, cancer and neurodegenerative diseases.

Classification of antioxidants: Antioxidants are categorized as follows, (a) **Natural antioxidants:** They are also called as the chain breaking antioxidants which act in response with lipid free radicals and change them into highly stable end products. They are mainly following[15]. i. Vitamins: These vitamins are the vital components essential for metabolic activities, for example ascorbic acid, alpha-tocopherol, vitamin B and its subtype. ii. Mineral antioxidants: These minerals are act as co-factors of important enzymatic antioxidants and paly dynamic role in metabolism of several macromolecules, for instance carbohydrates, nucleic acids etc. E.g. selenium, copper, iron, zinc and manganese. iii. Phytochemicals: These include; Flavonoids: are the phenolic complexes that give colors to the vegetables, fruits, grains, seeds, leaves, flowers and bark. Catechins: are the major bio-active antioxidants occurring in green and black tea and sesamol. Carotenoids: a fat soluble pigment occurs in fruits and vegetables. Beta carotene: present abundantly in carrot and transforms to vitamin A in case of nutritional deficiency of vitamin A. Lycopene: A red pigment is an important phyto-constituent of certain vegetables and fruits including tomatoes and in known for its cancer fighting ability. (b) **Synthetic antioxidants:** This belongs to phenolic group of compounds and performs the important function of arresting free radicals, diminishing oxidative stress and impeding the chain reactions through various biological actions. Examples includes; i. Butylated hydroxyl anisole (BHA) ii. Butylated hydroxyl toluene (BHT), iii. Tertiary butyl hydroquinone (TBHQ), iv. Esters of Gallic Acid (Propyl gallate) and Ethylenediaminetetraacetic acid, v. Nordihydroguaretic acid (NDGA).

Sources and origin of antioxidants

Antioxidants are abundantly present in leaf vegetables, fruits and natural food source especially lemon, Amla, Ashwagandha and Shatavari, in addition to nuts, grains, meats, chicken and fish. The common biologically active antioxidants such as Beta-carotene is found in various colored fruits including orange, sweet potatoes, carrots, squash, apricots, pumpkin and mangoes. Few green leafy vegetables, including collard greens, spinach, and kale, are too the abundant source of beta-carotene. Lutein, best recognized as vital for healthy eyes, is rich in green leafy vegetables[16,17].

Rice and wheat are the chief dietary sources of selenium, a mineral component of antioxidant enzymes in most developing and developed countries. The recent studies reported that animals that grown in the soil abundance of selenium have high amount of selenium in their body muscle. Brazil nuts, meats and bread are usual sources of dietary selenium in the United States. Sweet potatoes, carrots, milk, egg yolks and mozzarella cheese etc. are the main source of retinol (Vitamin A1), 3,4-didehydroretinol (Vitamin A2), and 3-hydroxyretinol (Vitamin A3). Vitamin C is abundantly present in many fruits, vegetables, cereals, beef, poultry, and fish. Vitamin E, also known as alpha-tocopherol, is rich in almonds, wheat germ oil, safflower oil, corn oil, soybean oil, in mangoes, nuts, broccoli, and other nutrient foods. Phytoconstituents with antioxidant potential include some cinnamic acids, coumarin derivetives, diterpenes, flavonoids, monoterpenes, phenylpropanoids, tannins and triterpenes. Natural antioxidants are present in all parts of higher plants like wood, bark, stems, pods, leaves, fruit, roots, flowers, pollen, and seeds[18]. Injury to plant cells, and mammalian cells, is linked with the activation of lipoxygenases pathway. The occurrence of such oxidative mechanisms in plants clarifies why an plenty of antioxidant compounds have been recognized in plant tissue. Plants mostly those with elevated levels of powerful antioxidant compounds

have an essential role in cure and treatment of illness concerning oxidative stress including diabetes mellitus[19].

Role of antioxidants in diabetes mellitus

Since oxidative stress could be a significant component of many disorders/diseases in human beings, antioxidants are commonly used in dietary supplements in the desire of maintaining health as well as improving immune defense systems.

Various enzymatic and non- enzymatic antioxidant defense mechanisms play an essential role in eliminating reactive oxygen species. In enzymatic antioxidant system, SOD directly converts superoxide to hydrogen peroxide, followed by detoxification to water either through catalase in the lysosomes or through glutathione peroxidase within the mitochondria. Glutathione reductase is another essential enzyme, which regenerates glutathione which can be used as a hydrogen donor by glutathione peroxidase throughout the elimination of hydrogen peroxide. In diabetic patients with chronic cardiac complications, all these crucial enzymes are turn down in the smooth muscle[20]. Thus, adjusting the proportion of such enzymes in target organs which are susceptible to diabetic complications such as heart and kidney can prove advantageous in the prevention and treatment of dysfunctions related to heart and kidney. Non-enzymatic antioxidant system include retinol, ascorbic acid and tocopherol, glutathione, carotenoids, trace elements like copper, zinc and selenium, α-lipoic acid, coenzyme Q10, and several cofactors like folic acid, uric acid, albumin, and vitamins like thiamine, riboflavin, pyridoxine and cyanocobalamin. Glutathione acts as a scavenger as well as a substrate for glutathione peroxidase. Vitamin E is a fat-soluble vitamin responsible for prevention of lipid peroxidation. Vitamin E exists in eight different fat-soluble forms, of which α-tocopherol found most abundantly in wheat germ oil, sunflower, and safflower oils is the most biologically active in humans. Hydroxyl radical when reacts with tocopherol, forms a stabilized phenolic radical which is again reduced to phenol by ascorbate and NAD(P)H dependent enzymes reductase. Coenzyme Q10 which functions as an electron carrier from enzyme complex is a lipid soluble antioxidant, and in elevated concentrations, it scavenges superoxide in the mitochondrial electron transport chain which is recognized as the site of superoxide generation under elevated glycemic conditions and thus improves endothelial dysfunction in diabetes[21]. Recent studies suggest that vitamin C increases Nitric oxide production within endothelial cells by means of stabilization of NOS cofactor BH4. A-Lipoic acid is a hydrophilic antioxidant which can exert favorable effects in aqueous and lipid environments. Dihydrolipoate, a reduced product of α -lipoic acid is capable of fortify other antioxidants such as vitamin C, alpha-tocopherol and reduced glutathione through redox cycling[22].

Antioxidants contradict a variety of actions of free radicals by numerous molecular mechanisms. These mechanisms comprise, inhibition of enzymes that humiliate free radicals reactions, degradation of proteins including transferrin that can bind metals which eventually stimulate the production of free radicals, and free radical scavenging activity. To battle oxidative stress, various clinical trials are in pipeline investigating the administration of exogenous antioxidants to balance antioxidants and pro-oxidants status. The actual hypothetical structures arrive from numerous clinical studies which have established that persons with decreased plasma antioxidant level are at higher risk for the development of diabetic complication particularly cardiovascular events[23]. Besides these individuals with type 2 diabetes found to be at lower levels of antioxidants than control patients. This indicates the application of antioxidant-based therapy in the treatment of diabetes and its various complications.

Nature consist of diverse natural antioxidants that hold assurance to be a novel approaches for the management of insulin resistance diabetes mellitus, including N-acetyl cysteine, and α-lipoic acid (LA), as well as flavonols. A variety of researches using experimental animal models of diabetes pointed out that the antioxidants α-lipoic acid, alpha-tocopherol, and vitamin C augment insulin sensitivity in patients having insulin resistance type 2 diabetes, and cardiovascular disease. N-acetylcysteine (NAC), a thiol-containing antioxidant which raises intracellular glutathione concentrations, is in receipt of increasing interest for budding therapeutic use in experimental animal models in which there is indications of increased oxidative stress[24]. Several studies have demonstrated that the antioxidant vitamins and nutritional supplements can assist in lowering the markers of oxidative stress and lipid peroxidation in diabetic patients as well as experimental animals.

Chain reaction in the process of lipid peroxidation can inhibit in presence vitamin E, a lipophilic antioxidant. It is likely that vitamins C and vitamin E act in a potentiation with each other, where vitamin E is mostly being oxidized to the tocopheroxyl radical and subsequently reduced to tocopherol in presence of vitamin C and glutathione. Vitamin C is emerging as the strongest physiological antioxidant targeting the aqueous environment of the organism and also found to be a significant natural antioxidant, to restore vitamin E through redox cycling, and to elevate intracellular glutathione levels. Thus, vitamin C plays a vital role of preserving protein thiol group during oxidation reactions. Antioxidants especially Flavonoids are also extensively come across in the plants tested as the most active free radical scavengers and it is not surprising that most flavonoids comprise strong free radical scavenging properties[25,26].

Newer therapeutic/preventive approaches through natural antioxidants

The management of diabetes mellitus with no side effects is

still a challenge to the biomedical ground of diabetes. The use of Herbal drugs in the treatment of diabetes mellitus is increased significantly because of their efficiency, less side effects as well as fairly low cost and thus variety of active principles derived from plant source has established as novel anti-diabetic therapy. The major active Phytoconstituents of these plants include alkaloids, glycosides, carbohydrates, gums, peptidoglycan, polysaccharides, hypoglycans, guanidine, terpenoids, steroids, glycopeptides, various amino acids and inorganic ions. Such Phytoconstituents influence various metabolic activities, which directly or indirectly affect glucose level in the human body. The World Health Organization report shows that approximately 80 percent of the global population depends principally on traditional medicines as resource for their primary health care[24].

Over the past three decades the utilization of antioxidant based formulations for management of multifarious diseases like cardiac arrest, atherosclerosis, stroke, diabetes mellitus, Parkinson's disease, Alzheimer's disease, cancer, etc. is augmented globally. Free radical scavengers has significantly stimulated awareness about the role of nutritional antioxidants in preventing numerous human ailments, including cancer, atherosclerosis, stroke, rheumatoid arthritis, neuro-degenerative disorders and diabetes mellitus. Dietary antioxidants might be the promising therapeutic approach in impeding the onset as well as in reducing diabetic population and its related complications[27].

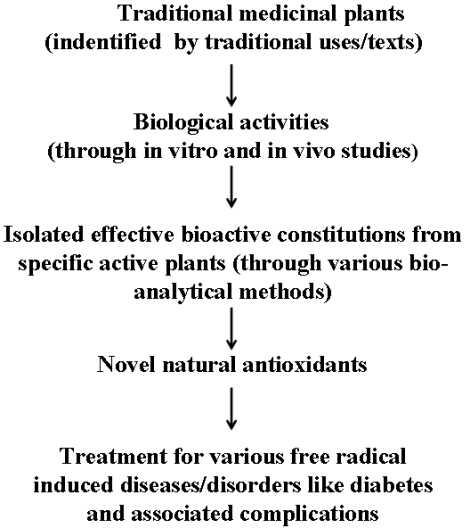

Figure-2
Natural products drug discovery process against different ailments

Conclusion

The review summaries that, induction of oxidative stress is a main process in the commencement of diabetic complications and various antioxidants have been developed recently to manage oxidative stress in diabetes mellitus. The exact mechanisms by which oxidative stress may hasten the development of diabetic complications are still fairly known. Indication for the protective effect of antioxidants in various human aliments has been demonstrated in various experimental, clinical, and epidemiological studies, and established that antioxidants might be useful in the management of diabetes mellitus and its complications. Traditional system of medicines like Ayurveda and Siddha, if united with modern science, India can produce outstanding products. Recognition of natural resources full of antioxidants, preparing molecular fingerprints of bioactive constituents of such antioxidants and studying the several therapeutic properties may help making us independent in antioxidant based drug discovery process in future.

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