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ROLE OF ANTIOXIDANT IN DIABETES MANAGEMENT

Vandna Dewangan[1]*, Himanshu Pandey, Trilochan Satpathy[1]

Department of Pharmacology, Columbia Institute of Pharmacy, Tekari, Near Vidhansabha, Raipur-493111(C.G.) India.

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***Corresponding Author**
Vandna Dewangan
Department of Pharmacology, Columbia Institute of Pharmacy, Tekari, Near Vidhansabha, Raipur-493111(C.G.) India.

ABSTRACT

Diabetes mellitus is a group of metabolic disorder of endocrine system and is characterized by rise in blood sugar level, through there are various factor which are responsible for diabetes mellitus one of which is oxidative stress which is consider as major factor for inducing diabetes. oxidative stress result in production of reactive oxygen species(ROS) which cause alteration in cellular component by taking its electron and become unstable which ultimately cause many disorder including diabetes. This article focusing on the use of antioxidant obtained from different plant source to interact with free radical and prevent cellular components from getting unstable. Plant and dietary source which are rich in vitamin C and contain polyphenols have been reported to show antioxidant properties and have ability to donate a pair of electron and prevent cell from getting unstable, amount of antioxidant help to cure diabetes like symptoms. The review describes the oxidative stress, antioxidant and their role in diabetes mellitus.

KEYWORDS: Diabetes mellitus, oxidative stress, free radical, Antioxidant, polyphenols,

1) INTRODUCTION

Diabetes mellitus is consider as metabolic disorder generally characterized by rise in blood sugar level that result from either deficiency in insulin production, or its action on beta cell. **Zimmet Pet. al 2001 Dec.** when beta cell of pancreases are fail to produce sufficient amount of insulin it is called type -1 diabetes and when the cell resist the insulin and prevent its action it is called as type-2 diabetes. type -1 diabetes is also known as insulin dependent diabetes mellitus and type-2 diabetes is called insulin resistance diabetes, if diabetes are untreated it may show several symptoms like are weight loss, increased urination, increased

thirst, and increased hunger . In type-1 diabetes this symptoms may observe rapidly while in type-2 diabetes mellitus it occur after long time. Waring W et. al 2014 Jun.

2) PATHOPHYSIOLOGY OF DIABETES MELLITUS

2.1) TYPE -1 DIABETES

Destruction of beta cell as a result of auto immune attack by T-cell is the major factor responsible for type 1 diabetes mellitus, which in turn result in insulin deficiency and inadequate production of insulin. Other factorswhich triggered the autoimmune destruction of beta cell are environmental factor, genetic factor.Van Belle TL et. al2011 Jan. Type-1 diabetes is generally occurring before age of 30 years. In type 1 diabetes patient's body can no longer produce insulin and cause insulin deficiency thus insulin injection has to be given to his/her body. Polychronakos C et. al 2011 nov.In Type -1 diabetes level of ketone increase due to less insulin glucose could not enter into cell and thus remain into blood vessel , through biolysis body fat is broke and convert into glycerol and free fatty acid, this free fatty acid further converted into ketone and which lead to decrease concentration of hydrogen ion and also decrease level of electrolyte thus dehydration and frequent urination are generally occur in type -1 diabetes ,untreated ketoacidosis may result in death**.** Vehik K, Dabelea D et. al 2011 Jan.

2.2) TYPE-2 DIABETES

Type 1 diabetes is due to auto immune destruction of beta cell and thus insufficient production of insulin, but in Type -2 diabetes insulin is sufficiently produce by beta cell but that insulin is not utilized by cell thus it is also called insulin resistance diabetes mellitusand is characterized by 3 disorder (1) excess glucose production by liver (2) dysfunction in production of insulin by pancreases (3) peripheral resistance of insulin.Obesity is consider as major factor contributing insulin resistance, about 80% of people who suffered from type -2 diabetes have obesity problem, in type -2 diabetes ketolysis is not observed because there is enough production of insulin to prevent ketone formation. **Inzucchi SE et. al 2011.**

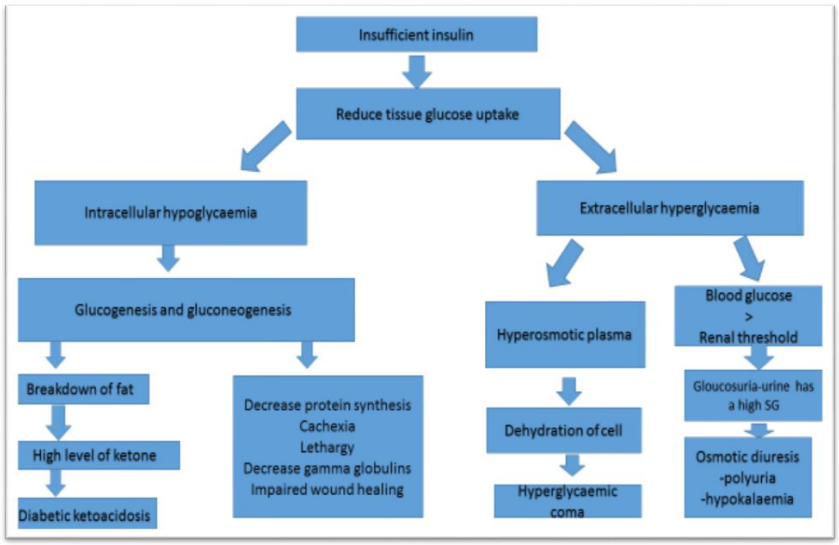

Fig-1: Various steps involved in the occurrence of Diabetes

3) Oxidative stress and Free radicals

Oxidative stress is an imbalance between the systemic production of free radicals and the ability of biological system to detoxify it, by neutralized reactive species with antioxidant and prevent its harmful effect. Free radical is very highly reactive molecule that contains oxygen with usually one or more unpaired of electron**. El HA et. al 2012.** Free radicals are harmful for body because they can chemically interact with components of cell and take their electron and become stable but it makes DNA, protein or lipid unstable. The byproduct of oxygen is usually unreactive but some of them interact with biological system and produce reactive oxidant. But some of them and not harmful for body and help in killing pathogens and microbes.**Apel K et. al 2004 jun.**

4) ROLE OF OXIDATIVE STRESS IN DIABETES

Researchers from past few years working on diabetes found that oxidative stress play a major role in development of diabetes .Though exact mechanism by which oxidative stress tend to induce diabetes is still a matter of discussion, but according to a hypothesis it was believe that due to production of Reactive oxygen species (ROS) cellular component become unstable because it can take oxygen form intracellular component to become stable. **Macdougall IC et. al 2009 Jan.**To prevent such condition antioxidants are use which is either obtained from plants source or prepared in laboratories. From different studies time to time it has been found that (ROS) induced diabetes pathogenesis by change in various physiological pathways like alteration in lipid peroxide and enzymatic system, by impairment of metabolism of glutathione and also by decrease vitamin c level in body. Complications which may arise due

to oxidative stress induced diabetes are retinopathy, stroke, and neuropathy.**Eckardt KU et. al 2009 jun.**

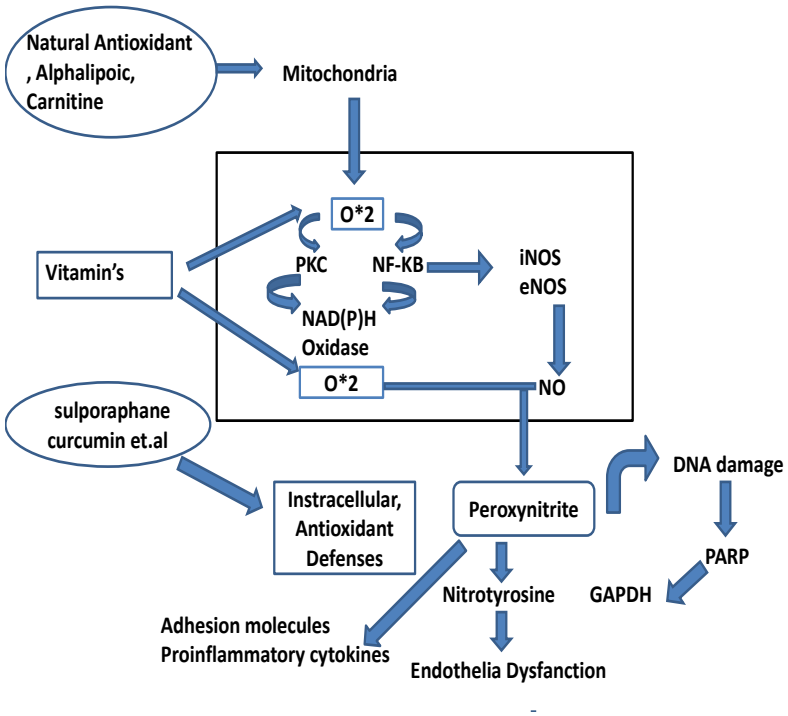

FIG: -Mechanism of Action of Antioxidant in Diabetes Mellitus.

5) ANTIOXIDANTS

An antioxidant is a molecule that prevents other molecules to get oxidized. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells. Blomhoff R et. al 2005 feb. Antioxidants such as ascorbic acid (vitamin C) can prevent formation of these chain reactions. In studies that have been done in past few years, strong relation found between oxidative stress and reactive oxygen species for human disorders/diseases. Blois MS et. al1 958 Apr. So the study of antioxidants and free radicals are very important in today's research for understanding the relationships of diseases such as cancer, neurodegenerative diseases, diabetes mellitus and cardiac arrest. Antioxidants canbe classifiesinto Synthetic or Natural type. Synthetic Antioxidants are phenolic group compounds are included in synthetic antioxidants and these finish the oxidative stress, free radicals and various biological reactions associated with the free radical negative effect. e.g.; Nordihydroguaiaretic acid (NDGA), esters of Gallic acid (propyl gallate), tertiary butyl hydroquinone (TBHQ), butylated hydroxyl anisole (BHA) and butylated hydroxyl toluene (BHT). Natural Antioxidants These act on lipid free radicals and break the chain. e.g.: Mineral antioxidants, Vitamins, Phytochemicals. Rice-Evans C et. al 1997 Apr 30.

	ANTIOXIDANTS	ROLES
ENZYME	Superoxidate dismutase (sod) Mitochondrial cytoplasmic Extracellular	Dismutates $O2^{-}$ to H2O2
	Catalase	Dismutates H202 to H20
VITAMINS	Alpha tocophero	Breaks lipid peroxidations Lipid peroxide and 02 and OH scavenge
	Beta carotene	Prevent oxidation of vitamin A Binds to transition metal
	Ascorbic acid	Direct scavenges O2 ,OH and H2O2 Neutralize oxidant from stimulated neutrophils Contribute to regeneration of vitamin E

6) PLANT POLYPHENOLS AS A SOURCE OF ANTIOXIDANT

Polyphenols are naturally occurring secondary metabolites obtain from different plants, many fruits like grapes, apple, orange which are in food, polyphenols may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability. Pandey KB, et. Al In many countries wheat and rice are the main dietary sources that havecontent major antioxidant enzymes. Carrots, milk, sweet potatoes, mozzarella and egg yolks consist retinol, 3 hydroxyretinol and didehydroretinol. Poultry, beef, cereals and fish contains vitamin C. Flavonoids, diterpenes, cinnamic acid, phenylpropanoids contains phytoconstituents with antioxidants. In wheat germ oil, corn oil, mangoes, almonds, nuts contains vitamin E. Higher plants contain natural antioxidants in leaves, roots, seeds, pollen, wood and bark. Treatment of severe diseases with oxidative stress is possibly cured by plants antioxidants including diabetic mellitus. Khan AN,et. al . 2015**.** It is well known that phenolic compounds exist in both free and bound forms in plant cells, and that the free phenolic compounds are solvent extractable. In contrast, the bound phenolic compounds, which are covalently bound to the plant matrix, cannot be extracted into water or aqueous/organic solvents mixtures these studies only considered the solvent extractable free phenolic compounds present in the pulp. Arulselvan P et. al Reported that about 4– 57% of the phenolic compounds present in fruits existed in their bound forms. With this in mind, the phenolic contents and antioxidant activities of different fruits could well be underestimated, to a large extent, if the bound fractions are not considered in some way.Alamgir AN et. al 2017.

7) PLASMA ANTIOXIDANT MEASUREMENT

Measures of in vivo antioxidant status can be helpful in understanding the role of oxidative events in the initiation of various diseases, including cancer, atherosclerosis, and diabetes. By measuring plasma or tissue levels of antioxidants such as vitamin C, vitamin E, invivo measurement of level of antioxidant can be done. While it is difficult for various other compounds, including flavonoids and polyphenol-like compounds that may influence in vivo antioxidant status. Valko M et. al 2007 dec. Antioxidant status can be determined by measuring antioxidant capacity AOC which provide tool for measuring antioxidant status. Numerous techniques, often utilizing quite different free radical sources, are used to assess AOC in plasma. Low-molecular-weight antioxidants in plasma or tissues express the evaluation of AOC. However, AOC assays do not provide information about the role of various antioxidant enzymes in protecting against free radical action. IN AOC method analysis of each individual antioxidant component is not necessary so it has an advantage over other method and an estimate of the total AOC can be obtained. Bhattacharyya A et. al 2014 Apr.

8) ROLE OF ANTIOXIDANT AGAINST DIABETES MELLITUS

Per oxidation of lipid is cause by cellular damage due to imbalance between free radical and antioxidant which lead to development of insulin resistance. Therapeutic approach can be achhive by inhibiting free radical and prevent development of oxidative stress. Orrenius S, et. al Feb 2007antioxidant act by inhibiting formation of free radical at different levels and increase enzyme capacity to defence free radical. Generally, the antioxidant pharmacotherapy can be divided in the use of antioxidant enzyme and substrates, biogenic elements, combined drugs, synthetic antioxidants, and drugs with antioxidant activity. body has naturall cellular defence mechanism and act as natural antioxidant component which have capability to neutralized damage caused by free radical,. ROS may remove by enzymatic antioxidant systems, such as copper, zinc, manganese superoxide dismutase, gluthatione peroxidase, gluthathione reductase, and catalase and help in, preventing excessive accumulation of free radical and its adverse effects. Non-enzymatic antioxidant systems include molecules that are produce endogenously such as glutathione, ubichinol, and uric acid and vitamins C and E, carotenoids, lipoic acid, selenium,which are derivative of diet. Exercise training can increase the defense mechanism of body against free radical and increase susceptibility of antioxidant Flora SJ et. al dec 2013.

9) OXIDATIVE STRESS-INDUCED CELLULAR DAMAGEIN DIABETES COMPLICATION

Nowadays, many evidences have been reported that support the role of oxidative stress in the pathogenesis of both type 1 and type 2 diabetes. formation of Free radical in diabetes by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation which leads to damage of enzymes, cellular machinery and also increased insulin resistance due to oxidative stress.The target of ROS damage induced all major group of bimolecular can be described as following:

9.1) PROTIENS

Since ROS can target almost all cellular compounds, several studies report that ROS can react with several amino acids residues in vitro, when ROS reacts with some amino acid in vitro, it may modified denatured and non-functioning proteins which produce chemical species that in further may be responsible for oxidative stress .Diabetic hyperglycemia, production of free radical, causes protein glycation and oxidative degeneration. Biomarkers such as glycated hemoglobin and fructosamine levels are used to determine degree of such protein glycation. Alteration in function and structure of antioxidant protein enzymes may also be due to nonenzymatic glycation such that detoxification of free radicals is effected enhancing oxi3dative stress in diabetes According to in vitro studies myeloperoxidase catalyzes the conversion of L-tyrosine to 3, 3-dityrosine which serves as a crosslink between polypeptide chains of the same or different proteins making it a convenient biomarker for protein oxidation. Matough FA,et. al Feb 2012.

9.2) LIPIDS

The cells become more susceptible to lipid peroxidation and cause disturbance in body lipid profile which cause Lipids Diabetes mellitus.Due to the presence of multiple bonds polyunsaturated fatty acids in cell membrane are extremely liable to suffer from attack by free radicals. Very reactive and toxic lipid radical generated from fattyacid throughintermediate radical reaction. A critical biomarker of oxidative stress is Lipid peroxidation which is the most explored area of research when it comes to ROS. Malondialdehyde (MDA) is formed as a result of lipid peroxidation that can be used to measure lipid perox ides after reacting it with thiobarbituric acid Asmat U et. al sep 2016.

9.3) Glutathione

Diabetes induces alterations in activity of enzymes glutathione peroxidase and glutathione reductase. These enzymes are found in cell that metabolizes peroxide to water and converting glutathione disulfide back into glutathione. **Maritim et al. 2003**. Any alteration in their levels will make the cells prone to oxidative stress and hence cell injury. **Ullah A et. al 2015.**

9.4) Catalase (CAT)

Catalase is regulator of hydrogen peroxide metabolism that can, in excess, cause serious damage to lipids, RNA and DNA. CAT converts H2O2 catalytically into water and oxygen and thus neutralizes it. In case of catalase deficiency, beta cell of pancreas that contain large amount of mitochondria, undergoes oxidative stress by producing excess ROS that leads to b-cells dysfunction and ultimately diabetes (Dana Jamieson, 1986). While investigating hyperglycemia-induced functional Diabetes mellitus and oxidative stress 551 changes, hydrogen peroxide production, superoxide, mitochondrial membrane polarization, and gene expression fingerprints of related enzymes in endothelial cells suggest that hyperglycemia increased hydrogen peroxide production and down-regulated CAT gene expression **Ullah A et. al 2015.**

CONCLUSION

Many studies have been suggested that oxidative stress have e play major role in progression of diabetic complication which, including impairment of insulin secretion and its action. antioxidant available from different plant source have been reported to minimized the effect of oxidative stress. lipid per oxidation, non-enzymatic glycation of proteins and oxidation of glucose are associated with Increase in the levels of oxygen and nitrogen free radicals (ROS/RNS) which contributes toward diabetes mellitus and its complications. Free radical can affect normal cellular function and cause diabetes complication, but polyphenols available in different plant having antioxidant properties can help in preventing such conditions.

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