CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4394137

Avalable online at: http://www.iajps.com *Review Article*

# REVIEW ON ROLE OF ANTIOXIDANT IN DIABETES

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**Abstract:**
*Diabetes Mellitus(DM) is a metabolic disorder characterized with insulin deficiency or due to insulin resistance. Macrovascular and microvascular complications are the major causes of mortality and morbidity in diabetes patient. During Hyperglycemia condition, oxidative stress and increase lipid peroxidation are due to free radical's formation which have a main role in diabetic complications. Therefore, antioxidants act against an oxidative stress that can prevent tissue or cell damage induced by free radicals. Antioxidants in fruits, vegetables, and grains helps to prevent the diabetes complications. There is some evidence regarding prevention of cell or tissue damage is that taking antioxidants substance can protect diabetes complications. The main objective of given review is regarding a role of antioxidants for the prevention and treatment of diabetes complication.*
***Keywords:*** *oxidative stress, antioxidant, diabetes mellitus, hyperglycemia, free radical.*

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*Please cite this article in press Christal C et al,* ***Review On Role Of Antioxidant In Diabetes.,*** *Indo Am. J. P. Sci, 2020; 07(12).*

## INTRODUCTION:

Diabetes mellitus is a metabolic disease caused by insufficient insulin production or do not respond properly to insulin or both, which leads to hyperglycemic condition [1]. The pathogenesis processes of Diabetes mellitus reveals that autoimmune destruction of beta cells of pancreas produce insulin deficiency to abnormalities that results in resistance to insulin action. Abnormalities in carbohydrates, fat and protein metabolism in diabetes affects the action of insulin on target tissues that results as inadequate insulin secretion [2]. Oxidative stress produces reactive oxygen species which generated by hyperglycemia and increased free fatty acid. Oxidative stress occurs due to imbalance between production of reactive oxygen species and breakdown by endogenous antioxidants, which is closely associated with diabetes mellitus [3]. Antioxidants are molecules which prevent cellular damage caused by oxidation of other molecules. During oxidation reaction that produce free radicals which are highly reactive species with one or more unpaired electron in outer most shell and starts chain reaction. Antioxidant reacts with free radicals and terminate chain reaction and inhibit oxidation reaction [4].

### Types of diabetes mellitus

Diabetes mellitus has two broad categories they are type1 - insulin dependent diabetes mellitus and type2 - noninsulin dependent diabetes mellitus. Type 1 diabetes (insulin dependent) divided two subunits. The first subunit is immunologic type, Type 1 DM, which is characterized pathologically by destruction of pancreatic beta cells, and the second subunit is named idiopathic, Type 1 Diabetes is characterized with insulin deficiency, and in this type destruction of pancreatic beta cell is occurred. Type 1diabetes is also known as juvenile onset diabetes that results from cellular mediated autoimmune destruction of beta cells in pancreas that includes islet cell autoantibodies – insulin; autoantibodies – glutamic acid decarboxylase, tyrosine phosphatases IA2 and IA 2b [2]. Type II diabetes (Non-Insulin dependent) is caused due to insulin secretory defect and insulin resistance. Approximately around 90% of all cases of diabetes worldwide are type 2 diabetes. It is a progressive disease. Overweight and obese people are higher risk of developing type 2 diabetes compared to healthy body weight[1]. Ketoacidosis occur in type 2 diabetes usually arises with stress of another illness such as infection. If type 2 diabetes is not frequently diagnosed for many years, then at earlier stage produce hyperglycemic condition and later produce higher risk of developing macrovascular and microvascular complication. Macrovascular complications such as atherosclerosis, myocardial infarction and gangrene. In general, complications of diabetes mellitus can be categorized into metabolic acute and systemic late complications[2].

### Oxidative stress and antioxidants

Reactive nitrogen and carbon species cause oxidation by the generation of certain mechanism that interferes with the normal physiological processes inside the cell[5]. Oxidative stress is defined as a disturbance in between oxidants and antioxidants which caused due to different factors such as drug actions and toxicity, and/or addiction[6]. This occur in general due to excess formation or/and insufficient removal of highly reactive molecules. Oxygen is highly reactive species that has the ability to become part of potentially harmful and damaging molecules; free radicals. Oxidative stress causes healthy cells of the body to lose their function and structure by attacking them[7]. Antioxidants are natural substances that would prevent or delay many types of cell damage. Many antioxidants are found in so many foods, fruits and vegetables. There are so many nutrients in food that contain antioxidants. Vitamin C, vitamin E, and beta carotene are commonly used dietary antioxidants. There are so many species or molecules, endogenous (internally synthesized) or exogenous (consumed), which may play a role in antioxidant defence and may acts as biomarkers of oxidative stress. Antioxidants can divided as chain breaking antioxidants or preventive antioxidants, depend upon their mechanism of action. Different types of biological antioxidants include glutathione, vitamin C and E, cysteine, and many others. Plant-derived substances are known as phytonutrients or phytochemicals that possess antioxidant properties Phenolic compounds such as flavonoids are found in several fruits, vegetables and green tea extracts[8,9].

### Mechanisms of diabetes induced tissue damage

In Diabetes condition, Macrovascular complication and intracellular Hyperglycemia, have been shown to cause tissue damage through 5 major mechanisms:

1. Increase in expression of the receptor for advanced glycation end products (AGEs) and its activating ligands.
2. Increase in intracellular formation AGEs
3. Increase in flux of glucose and other sugars through the polyol pathway
4. Activation of protein kinase C isoforms
5. Overactivity of the hexosamine pathway.

All five mechanisms have been shown to be activated by mitochondrial over production of reactive oxygen species (ROS). In Diabetes patient macrovascular complication and heart damage, are resulted from increased oxidation of fatty acids, resulting from pathway-specific insulin resistance. Many cellular pathways which cause insulin resistance and diabetic complications which have a link for the production of free radicals and oxidative

stress. Early effects of elevated glucose may increase the presence of potentially protective pathways but prolonged exposure of elevated glucose can cause formation of ROS and can be determine even after glucose control. Excess levels of free radicals that cause damage to lipid membranes, cell proteins and nucleic acids, which finally may cause cell death. Hyperglycaemia condition is caused due to increased production of ROS in different cell types. For example, with increase in age in type 2 DM in rat models, elevated levels of 8-hydroxydeoxy guanosine (8-OHdG) and hydroxynonenal (HNE)-modified proteins in pancreatic beta-cells have been reported. Oxidative stress and apoptotic cell death during this disorder such as diabetes mellitus are associated with impairment in cellular energy maintenance and mitochondrial function. ROS exposure can lead to the opening of the mitochondrial membrane permeability transition pore, reduction of mitochondrial b-nicotinamide adenine dinucleotide (NAD+) stores, and thereby apoptotic cell injury. Free fatty acids also can lead to ROS release, mitochondrial DNA damage, and impaired pancreatic beta-cell function. ROS can oxidize the DNA, protein and lipid and have an important role in chronic diseases like diabetes. Microvascular complication such as predicate loss and meningeal expansion, which may contribute to diabetic retinopathy and nephropathy, respectively. Thus, an increase in oxidative stress induced by free fatty acids, lipids, or other processes is not sufficient to cause microvascular complications of diabetes. Microvascular complications of diabetes are initiated by oxidative stress. Lastly, the damage caused by oxidative stress is likely to be tissue specific because hyperglycemia appears to increase oxidant production in many cell types and tissues that do not manifest significant pathologies [10].

**METHODS FOR EVALUATING ANTIOXIDANT ACTIVITY:**

**1.DPPH (2,2 diphenyl 1 picryl hydrazyl) radical scavenging activity [11]:**

The DPPH methanol solution was prepared by of 0.6 mM concentration. A volume of 200 µL of DPPH solution was added to 100 µL extract solution. The solution was mixed and reacted at room temperature in dark. After 30 min, the absorbance of the solution was measured by a microplate reader at 517 nm. The analysis was in triplicate. Ascorbic acid was used as a positive control. DPPH radical scavenging activity was calculated by

DPPH radical scavenging rate (%) = 1 − (As − Ao) /Ab × 100

Where,

As is the absorbance of the sample solution

Ao are the absorbance of the sample solution without DPPH.

Ab is the absorbance of DPPH solution.

2.**OH scavenging method[12]:**

OH radical scavenging activity was determined by the salicylic acid method. In this method A volume of 500 µL sample solution was taken into a test tube. In this 500 µL of 6 mM FeSO4 solution, 500 µL of 6 mM salicylic acid ethanol solution, 2 mL distilled water, and 500 µL of 2.4 mM H2O2 were added into the test tube. After incubation for 15 min at 37 ◦C in the water bath, the absorbance of the mixture solution was measured at 510 nm. Ascorbic acid was used as the positive control. Each sample was done for three times. Hydroxyl radical clearance rate was calculated by.

OH radical clearance rate (%) = Ao − (As − A)/ Ao × 100

where

Ao is the absorbance of distilled water - blank control,

As is the absorbance value of sample solution.

A is the absorbance of sample solution without adding H2O2.

3.**ABTS radical scavenging activity[13]:**

The ABTS radical scavenging activity was evaluated by ABTS radical cation decolorization assay with modifications. ABTS+ was prepared by mixing 7 mM ABTS+ solution with 2.45 mM K2S2O8 solution (1:1, v/v) at room temperature in dark for 16 h. The ABTS+ solution was diluted with purified water to an absorbance of 0.070 ± 0.02 at 734 nm. In total, 50 µL sample solution was reacted with 200 µL of ABTS+ at room temperature for 10 min in dark. The absorbance of the mixture solution was measured at 734 nm.

Trolox is used as a positive control.

The scavenging rate was calculated by.

ABTS radical scavenging rate (%) = 1 – As/ Ab × 100

Where

As is the absorbance of the sample

Ab is the absorbance value of the blank.

**Antioxidant vitamins:**

The main principal involved in antioxidant vitamins for tissue defence against free-radical damage includes vitamins E, C and β-carotene. Selenium act as mineral most specifically related to antioxidant function. There are several antioxidants such as Selenium proteins and include selenoprotein P, five glutathione peroxidases and three thioredoxin reductases (TrXR1). TrXR1 reduces harmful ROS and facilitates the gene expression of other cytoprotective antioxidants. Vitamin E mainly functions as a membrane-bound antioxidant, trapping lipid peroxyl free radicals that produced from unsaturated fatty acids under conditions of 'oxidative stress'.

Vitamins and minerals in antioxidant systems.[14]

| Nutrients | Components (location in the cell) | Function |
|---|---|---|
| Vitamin C | Ascorbic acid (cytosol) | Reacts with many types of ROS/RNS |
| Vitamin E | Alpha tocopherol (membrane) | It breaks fatty acid peroxidation chain reactions |
| Beta carotene | Beta carotene (membrane) | It Prevent initiation of fatty acids peroxidation chain reaction |
| Selenium | Glutathione peroxidase (cytosol) | An enzyme which converts superoxide to water. |
| Copper and Zinc | Superoxide dismutase (cytosol) | An enzyme which converts superoxide to hydrogen peroxide. |
| Manganese and zinc | Superoxide dismutase (mitochondria) | An enzyme which converts superoxide to hydrogen peroxide. |
| Iron | Catalase (cytosol) | An enzyme (in liver) which converts hydrogen peroxide to water. |

**Experimental parameters measured in vitamins:**

The vitamin supplementation that produces antioxidant effect and prevent cell and tissue damage in diabetes patients. The effect of antioxidant is given below;

| Sl.no | | Antioxidant | Effect | Measured parameters | Authors |
|---|---|---|---|---|---|
| 1 | Animals | Vitamin A and E | Decrease oxidative stress | Lipid level, plasma TNF, IL6, protein level[15] | Javed Y. et.al |
| 2 | | Vitamins A, C and E, glutathione, α-lipoic acid, carotenoids, | Increase antioxidant effect | Superoxide dismutase, catalase, glutathione peroxidase[16] | Purabi Sarkar. et.al |
| 3 | | Vitamin C, E | Decrease oxidative stress | Serum Nitric oxide, Serum SOD, Erythrocyte GSH[17] | Sarita.et.al |
| 4 | | Baicalein | Protect liver cell from oxidative damage | SOD, CAT, and GSH enzyme[18] | Sarkar.et.al |
| 5 | Humans | Vitamin C, E, Carotenoids. | Protect free Radical damage | Erythrocyte GSH[19] | Srivatsan.et.al |
| 6 | | Vitamin E | Decrease oxidative damage | Blood glucose level, Reduce MDA and TBARS level[20] | Balbi.et.al |
| 7 | | Vitamin C, E, Carotenoids | Decrease oxidative stress | Blood glucose level[21] | Khanam.et.al |
| 8 | | Vitamin C, E supplements | Reduce oxidative damage | Blood glucose level, Glutathione peroxidase, Superoxide dismutase.[22] | Zahra Rafighi.et.al. |

## CONCLUSION:

In this review, it is concluded that, Oxidative stress play an important role in diabetes condition, including impairment of insulin action and elevation of the diabetes complication incidence. The increase in levels of oxygen and nitrogen free radicals is closely related to lipid peroxidation, non-enzymatic glycation of proteins and oxidation of glucose which

may contributes against diabetes mellitus. Plants contain a large variety of substances that possess antioxidant activity. Therefore, antioxidant vitamins act as a potential natural therapy to reduce oxidative stress and diabetic complications.

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