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**Review Article:**

# OXIDATIVE STRESS AND ANTIOXIDANTS: AN OVERVIEW

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## ABSTRACT

Oxidative stress refers to the imbalance between free radicals and their stabilizing agent's antioxidant enzymes in the body. Reactive oxygen species or free radicals can be produced by normal cellular metabolism and react with biomolecules like protein, lipid, and DNA to cause cellular damage and responsible for degenerative changes. At low concentration free radicals play a vital role in the physiological regulation and cellular signaling processes but the high level can cause deleterious changes in the cell. Contrary to these antioxidants lowers the oxidants by donating its own electron to stabilize free radical and make it not reactive compound so as to minimize the harmful effects generated by these radicals in the cell. Human life is meant for the realization of scientific knowledge, and then tries to distribute it throughout the world. The materialistic civilization stressing our body, therefore our cell age faster and suffer from deleterious changes which arise in the body. Aging, the word is not new for decades and recently, it has become a new approach of being live healthy and long life till death with the progress in the medical sciences. The aging can be defined as the deleterious changes occur in the cell due to oxidative metabolism in mitochondria. The overburden of oxidative burst is the cause of conquering cell's capability of surviving and to meet the challenges of change in the environment with respect to time. Various theories regarding aging have been proposed by various scientists to improve our knowledge about how we age. Aging not only presiding with that of the human but other vertebrates also reproached.

**Key words:** Oxidative stress, Antioxidant, ROS, Aging.

## 1. INTRODUCTION

Aging is gradual changes in the body of a human being. These changes occur due to reactive oxygen species (ROS) that cause protein unfolding, collagen disintegration, lipid breakdown, DNA damage and fragmentation (Said and Aiman, 2014). This will ultimately lead to cell death by apoptosis and cause aging that is the reason we look older as we age. Free radicals (Oxygen-derived) are reasonable for the age-related destructive effects at the tissue and cellular levels. The findings of reactions of free radical as promoters of the aging process imply that action is taken to improve and is aimed at limiting them which should be capable to decrease the rate of production of aging changes with a continuous diminishing rate of the aging rate and age related disease (Fusco et al., 2007). Free radicals are the free electrons which are highly reactive in nature and cause deleterious changes in our body. The main sources of ROS generation are

environmental pollution, harmful ultraviolet rays, and metabolism, phagocyte cells etc (Lobo et al., 2010).These sources generate free oxygen radicals and further the oxidative stress in the human body. The theory of oxidative stress suggests that the stress leads to cellular degradation which causes a cascade of apoptotic events and finally to the cell death. Oxidative damage caused by free radicals induce the generation of superoxide radical, peroxynitrite and many more radicals that are the major cause how we age and also age related disorders like Alzheimer's, Parkinson's, neurodegenerative diseases and other related disorders.

Human aging entails the deleterious accumulation in the cell over time (Uttara et al., 2009). The deteriorating changes integrate physiological, psychological, and social changes. Current theories of aging describe the collection of damage in genetic material like DNA mutation or oxidative damage to DNA may cause perturbed cellular responses.

Oxygen is very crucial for the survival of living organism and form the basis of cellular respiration which brings about aerobic respiration. But oxygen in the form of free radical acts as a substance or molecule which causes oxidative stress (Stamatti et al., 2011). An uneven stage of the making and removal of free radicals which generate stress, it's called oxidative stress. When free radicals generated as the large amount in the human body these conditions caused oxidative stress which gives disease able effects on the life cycle of living cells (Bhattacharya, 2015). So these oxidative stresses cause many impactful-age related diseases like- cancer, neurodegeneration, and aging. Harmful effects of ROS which cause biological damage are known as oxidative stress. Oxidative stress produced when there is an increased production of ROS and decreased a level of antioxidants in the body. Reactive oxygen species include Singlet oxygen, Superoxide, hydroxyl radical, hydrogen peroxide, hydroperoxyl radical, ozone etc (Halliwall and Cross, 1994). If the ratio of oxidative stress generators like free radicals and the antioxidants get disturbs, then cell undergoes oxidative cellular stress.

It contributes to many pathophysiological conditions to the cell that is the cause of many degenerative changes. Oxidative cellular damage affects the biomolecules thus leads to fragile structures in the cell (Fanjul moles and Lopez-Riquelme, 2016). Alcohol-induced oxidative stress is connecting to the metabolism of ethanol involving mitochondrial energy producing system. Free radicals and Reactive oxygen species (ROS) are formats during ethanol metabolism process, causing oxidative stress. Ethanol metabolism is directly included in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

These forms of oxygen species create a convenient environment to oxidative stress. Ethanol administration caused mtDNA depletion and replacement of its coiled form to simple linear form. This condition occurred in heart, skeletal muscle and liver when ethanol administrates for 2 h but in the brain after 10h (Mansouri, 2001).

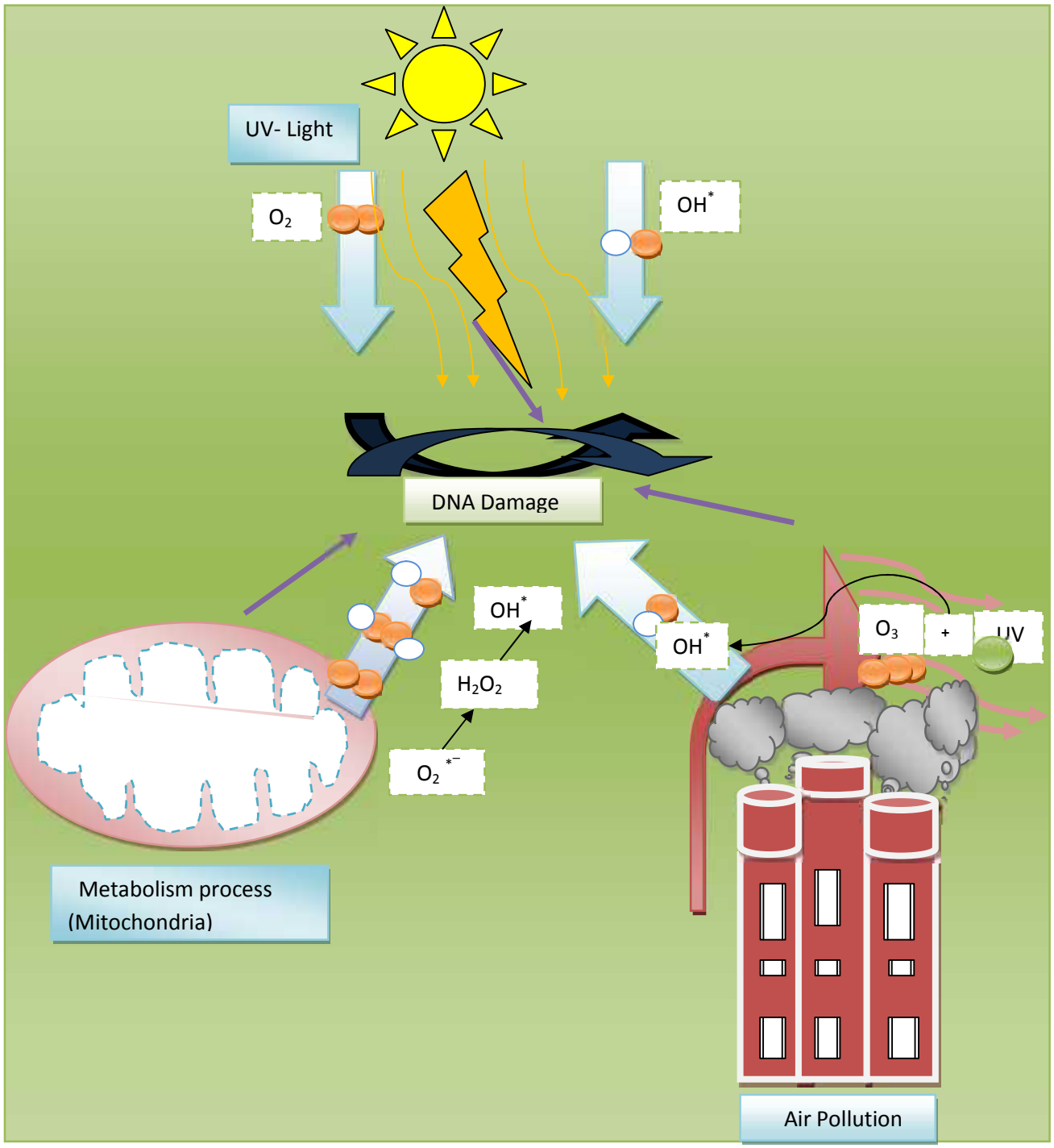


**Figure -1. ROS Production through UV-radiation, mitochondrial metabolism and air pollution which cause DNA damage of the cells.**

## 2. TOXICITY OF REACTIVE OXYGEN SPECIES

Oxygen is used in metabolic reactions. Sometimes it reacts with the metabolic compound to form a free radical which causes biological damage (Rahman, 2007). Oxygen is a stable product but when there is gain or loss of an electron in oxygen molecule or its compound it becomes reactive

oxygen species. Toxicity of oxygen refers to the toxic endpoints of the oxygen formation. Oxidative stress refers to the distorted balance between the transformation of the reactive oxygen species from one form to another indulging beneficial component of cell or biomolecules (Alvarado and Acre, 2016). Reactive oxygen species (ROS) play a most important role in various biological processes, like as the oxidative burst reaction which is necessary for phagocytes, and are taking part in a variety of cell signaling pathways. In the cytosol, IκB is a sequester and inhibitory factor of NF-κB. ROS are also participating in moderating the action of specific transcription factors, containing activator protein–1 and NF-κB. So ROS can play a very important role in inflammation modulating (Giordano, 2005). Perturbed reduction state of cell produces lipid peroxides, protein carbonyls and other adducts in the cell. These adducts in cell deposits in clumps to inactivate the normal cell functioning processes of the cell that lead DNA damage, strand breaks etc.

## 3. REACTIVE OXYGEN SPECIES (ROS)

| Radicals | Non radicals |
|---|---|
| $OH^{\cdot}$ (Hydroxyl radical) | $O_2$ (Singlet oxygen) |
| $O_2^{-\cdot}$ (Superoxide radical) | $H_2O_2$ (Hydrogen peroxide) |
| $RO_2^{\cdot}$ (Peroxyl radical) | HOCl (Hypochlorous acid) |
| $RS^{\cdot}$ ( Thyl radical) | O3 (Ozone) |
| $RO^{\cdot}$ (Alkoxyl radical) | LOOH ( Lipid peroxide) |
| $LOO^{\cdot}$ (Lipid peroxyl) | |

**Table-1: List of radicals and non-radicals molecules.**

## 4.DISEASES / DISORDER LINKED TO ROS

The reactive oxygen species are the product of cellular metabolism in also normal condition and readily they are important for cellular signaling pathways. But in some extreme condition, the accumulation of ROS up to a limit can cause pathological condition responsible for various diseases (Fanjul-moles, 2016).The reactive oxygen species generated through the process of oxidative stress are superoxide radical, hydroxyl radical and hydrogen peroxide. Oxidative DNA damage is mostly indirect and adduction of radicals to the DNA can cause mutation so that the cell may become cancerous. Mitochondrial ETC is one of the types of internal source factor for the formation of free radicals in internal cellular metabolism (Shinde et al., 2012). Further many of these reactive oxygen intermediates, some may act secondary messengers of redox signaling. This can cause the disruption of normal cellular signaling pathways.ROS production increased by the inhibition of complex 1 of mitochondrial electron transport chain (ETC) by the effects of some pesticides like rotenone which increase the chances of brain related disease in the human being (Swarnkar et al.,2010). Ethanol metabolism is directly related to the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These both kinds of oxygen species make an environment favorable for oxidative stress (Das and Vasudevan, 2007). Ethanol metabolism also causes oxidative degradation of the mitochondrial genome in the brain, heart, and skeletal muscles. These effects of ethanol could be contributing to the development of muscles-myopathy and brain injury. Alcohol intake can develop not only liver lesions but also brain damage, peripheral neuropathy, cardio-myopathy and skeletal muscle myopathy. Mitochondria are major targets for ethanol toxicity in liver, brain, heart and skeletal muscles. Chronic ethanol intoxication causes oxidative damage to mitochondrial proteins, cardiolipin (phospholipids), and mitochondrial DNA (mtDNA) (Mansouri et al., 2001).

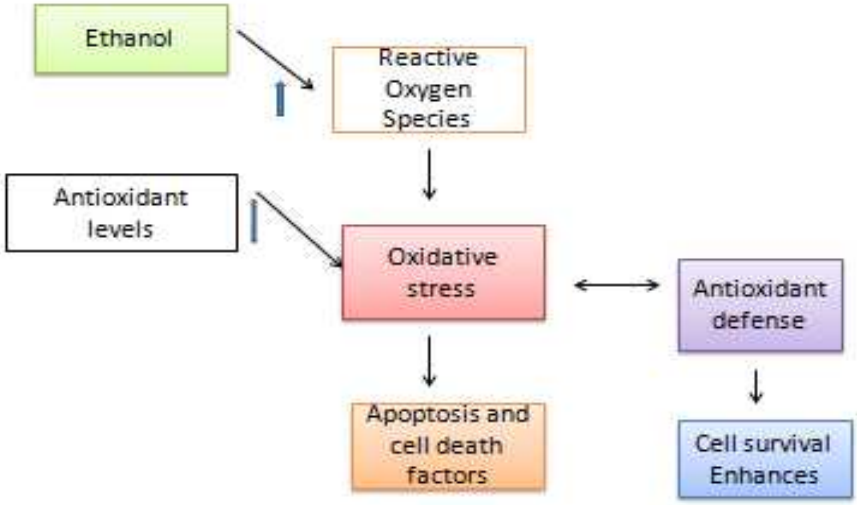


Figure 2: alcohol exert effect on cell as seen with the increased oxidative stress and decreased antioxidant levels

### 4.1. ALZHEIMER'S DISEASE

It is a kind of memory loss disease which shatters the memory and other main mental functions. In this disease, brain cells lose connections, degenerate and finally cells die which cause slowly memory loss. Recent studies reveal the neuron mitochondria from aging in the rats, are more susceptible to produce reactive oxygen species that cause neurodegenerative dementia like Alzheimer's disease (Parihar and Brewer, 2007). One of the common forms of dementia that affect our older population characterized by degeneration of neurons within the brain. It affects hippocampus region of the brain which is the responsible part of the brain for memory formation so it causes loss of memory and premature aging.

### 4.2.PARKINSON'S DISEASE

It is a kind of movement disorder which affects the central nervous system, responsible for body movement so in this disease, patient's loss body balance and movements. Over expression of α-synuclein and oxidative stress has been implicated in the neuronal cell death in the Parkinson's disease (Parihar et al., 2009). In Parkinson's disease, selective degeneration of dopaminergic stimuli of neurons occurs (Garrett, 2004). After Alzheimer's, this is the most degrading neurogenic disorder. Parkinson's disease is a common neurodegenerative disease induced by some stressors from the endoplasmic reticulum and oxidative damage (Xiaotian et al., 2013).

### 4.3.AMYOTROPHIC LATERAL SCLEROSIS

It is a nervous system related disease which causes muscle weakness and loses the movement control by the motor neurons degeneration. ALS probably leads to a new disease, skeletal muscle dystrophy in the infected patients of ALS disease because of motor neuron loss (Kong and Xu, 1998). The brain has two types of receptors glutamate and GABA receptors. Glutamate is a chemical mediator which stimulates motor neurons so its excess formation, is possibly

responsible for motor neuron destruction in ALS. The GABA receptor acts to lessen the effects of glutamate. Gabapentin and Baclofen named medicines act as a GABA modulators which increase GABA activity, are the probable cure for ALS (Amyotrophic lateral sclerosis) (Diana et al., 2017).

### 4.4.CARDIAC DISEASE

Oxidative stress and ROS are most factors of cardiac diseases like congestive heart failure, hypertension, and atherosclerosis (Sugamura and Keaney, 2011). Smooth muscles and cardiac muscles on the regulation of metabolic process release free oxygen radicals in the form of the byproducts of the process. This leads to the myocardial infarction to the heart. Some phagocytes cells utilize the LDL cholesterol and oxidize LDL that lead to the formation of artery clogging plaque and thus responsible for the stroke (Esterbauer et al., 1991). ROS have been involving in the important processes which have notable effects on cardiac functions like as hypertrophy, ion flux (calcium), extracellular matrix (ECM) configuration, metabolism, signaling of various growth factors, cytokines and gene expression. Thioredoxin and thioredoxin reductase (enzymatic pathways of formation of ROS) together form an additional enzymatic antioxidant and redox regulatory system that has been implicated in a wide variety of ROS-related processes. Thioredoxin and thioredoxin reductase can catalyze the regeneration of many antioxidant molecules, including ubiquinone, lipoic acid, and ascorbic acid, and as such constitute an important antioxidant defense against ROS. Deletion of thioredoxin reductase results in developmental heart abnormalities and in cardiac death secondary to a severe dilated cardiomyopathy (Giordano, 2005).

### 4.5.CANCER

Free radicals play an important role as the carcinogenic molecule for DNA damage which inhibits DNA repair. Attack of free radicals on the hydroxyl group of nucleic acids makes mutation fragmentation of nucleic acid thus give rise to cancer. ROS cause DNA damage and leads to DNA strand break or fragmentation of the bases. Oxidative products of DNA induce activation of some transcription factor like NF-κ B (nuclear factor κ B) that causes abnormal cell growth. Post-transcriptional modification by phosphorylation nitration by free radicals also induces cancer risk (Simone et al., 2010). Endogenous and exogenous stimuli participate in cancer developmental process. Formation of Oxygen-free-radicals (OFR), which attacks not only on the bases but also the deoxyribosyl backbone of DNA, is the one kind of endogenous damage stimuli which is format through the intermediate oxygen reduction. OFR is a class of important carcinogens for DNA-damage (Valko et al., 2004).

### 4.6. AGEING BONES

Remodeling of bone is a natural phenomenon where the bone absorption and formation takes place during entire life. The less formation of bones and more breaks down will cause deteriorating bone health in aging people. With the aging of human, could occur the deficiencies of both primary and secondary Vitamin D which may be participated in the pathogenesis process of senile osteoporosis and also take part in the development of osteomalacia in an adult human being. Although a mild deficiency could lead to a stage of secondary hyperparathyroidism, with the result as the development of osteoporosis (Lau and Adarchi, 2011). Decreased mineral content and fragility are the symptoms of aging bones. Loss of bone density may be related to osteoporosis where the bones are more prone to fractures. In the bones, the Rate of repair and regain their mechanical adeptness (power) after fracture, the rate of revascularization, cell

proliferation & differentiation of the cells and bones healing process, decreases with aging (Boskey and Coleman, 2010).

## 5.PATHOPHYSIOLOGICAL SIGNIFICANCE OF FREE OXYGEN RADICALS

Free radical plays significant role in controlling the blood pressure and also fight for the cures of infection. Formation of reactive oxygen species is a physiological process, which increases the production of free radicals and also its lead to the dysbalance between the production of radicals and antioxidants which could lead to oxidative stress with the changes of various biological functions and structural changes in the cells (Halliwell, 1991). Immune cells participate in defense system by destroying foreign molecules such as virus or bacteria by producing oxidants or free radicals. Some phagocytic cells like macrophages, eosinophils, neutrophils as well as T and B lymphocyte contain NADH oxidase which forms superoxide free radicals responsible for damaging the micro-organisms. The process is known as the oxidative or respiratory burst. It is defense mechanism used by the immune cells of the body (Abheri et al., 2010).

## 6.ANTIOXIDANTS AND THEIR MECHANISM OF ACTION

Antioxidants are the compounds that can stabilize ROS. These molecules are the scavengers of free radicals and get easily oxidized. Vitamins are the most important class of non-enzymatic antioxidants. There is two classes water soluble like vitamin C and fat soluble vitamin A (retinoic acid or retinol) and vitamin E. Vitamin E ( α-tocopherol ) is a predominant scavenger that has its significant activity in the protection of biomolecules of biomembranes, which are attacked by free radicals(Irshad and Choudhary,2002). Supplement of vitamin E, and probably vitamin C, being able to significantly lower lipid oxidative damage in both smokers and nonsmokers, so we can conclude that antioxidants vitamins supplementation reduces oxidative damage in humans [McCall and Frei, 1998].

Antioxidants donate their electron to stabilize free radical and make it a stable compound so as to minimize the harmful effect of free radicals. Antioxidants have been classified into:-

**I. On the basis of their location**

- Plasma antioxidants; uric acid, ascorbic acid, bilirubin, transferrin, caeruloplasmin.
- Cell membrane antioxidants; α- tocopherol (membranous chain breaking antioxidant)
- Intracellular antioxidants; SOD (superoxide dismutase), catalase, glutathione peroxidase, glutathione reductase.
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**II. On the basis of their nature and action**

- Enzymatic antioxidants; SOD, catalase, glutathione peroxidase and glutathione reductase.
- Non-enzymatic antioxidants and Nutrient antioxidants; Beta- carotene, α-tocopherol, ascorbic acid.
- Metabolic antioxidants; GSH, bilirubin, uric acid, transferrin, caeruloplasmin, albumin, haptoglobin.

| Oxidant | Enumerations |
|---|---|
| $O_2$ Superoxide anion | One electron reduction state of $O_2$ produced perpetually in many auto-oxidation reactions and by the ETC, presiding nonreactive but can release $Fe^{2+}$ from iron sulphur protein and vanquish ferrition to dismutate and form $H_2O_2$. |
| $H_2O_2$ Hydrogen peroxide | Two electron reduction state, surmount dis-mutation of $O_2$ or directly reduce $O_2$. Retain lipid solubility and ability to move across the lipid bilayer. |
| OH Hydroxyl radical | Three electron reduction state, recited by Fenton reaction and decomposition of peroxynitrite. Utmost reactive and annihilate several cellular components. |

**Table.2- Name's of oxidants and their resources of formation.**

Superoxide dismutase is the cytosolic copper dependent enzyme whereas the mitochondrial superoxide dismutase is the manganese dependent enzymes, stabilize superoxide molecule (Sheng et al., 2014). Glutathione peroxidase is a selenium dependent enzyme stabilizes the peroxide molecule (Lobos et al., 2011). Selenium is a cofactor one of the enzymes for glutathione peroxidase, is considered the major detoxification enzyme for H2O2. In this process, the disulfide (GSSG) format by the oxidation of reduced glutathione (GSH). This enzyme is found in both the mitochondria and cytosol. The reduced plasma selenium and depressed glutathione peroxidase activities have a correlation between each other (Preedy et al., 1999).Catalase enzyme from peroxisome converts the acidic hydrogen peroxide to water and molecular oxygen (Lobo et al., 2010 and Gaetani et al., 1996).

## 7. CONCLUSION

Not a single cell in the animal world is eternal and the cells are experiencing mortality. Mortality of a cell is a natural phenomenon that is conceived by the cell via the process of aging. Generation of reactive oxygen species due to oxidative stress is responsible for many pathological conditions within the cell. Oxygen in the form of reactive oxygen species acts as a molecule that generates oxidative stress in the body or cell. Accumulation of ROS up to a certain limit causes degenerative conditions in the cell that lead to cellular damage and disease conditions. Oxidative stress is the cellular phenomenon that in a particular extent can be stabilized by antioxidants enzymes. Various antioxidants like glutathione peroxidase, catalase and non-enzymatic antioxidants like vitamin E, C and metabolic antioxidants like bilirubin and uric acid decrease the level of free radicals in the tissue by their self-repairing mechanisms in the cell. We know that Thiamine, also known as vitamin B1, is an essential nutrient which required by all tissues, including the brain. Thiamine deficiency and muscle looseness are a common disease occurrence in people because of high rate formation of the free radicals. In this study, we are investigating the neuro-modulatory effects of nutrients/ antioxidants on the living beings for neurodegenerative response and mitochondrial Myo-pathological changes that arise due to the excess amount formation of free radicals and oxidative stress.

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