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Neurodegenerative Disorders and Antioxidants; A Review

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A B S T R A C T

This study aims to review the association between nutrient metabolism and the development of degenerative diseases. Over the years, the rate of degenerative diseases has increased along with other issues. Degenerative diseases can be defined as diseases that develop when the ability of the tissues and cells to function optimally is dysfunctional or lost. The causes of degenerative diseases can be complex and multi-factorial and may include genetics, lifestyle factors, environmental factors, aging and chronic health conditions. The most common factors include inflammation and oxidative stress that leads to the development and growth of degenerative diseases. The high quantities of ROS in the environment have prompted the evolution of several protective systems in animals. Dietary recommendations need to be strictly considered to increase the antioxidants in the diet. These antioxidants will work as a preventive measure against degenerative diseases. Reactive Oxygen Species are mostly neutralized by Vitamin C which is acting as a reducing agent. Conclusively, the progression of degenerative disorders affects nutrient metabolism and likewise, intake of healthy nutrients prevents the development of degenerative ailments.

Keywords: Degenerative Diseases, Diabetes Mellitus, Parkinson's disease, Alzheimer's disease, Nutrition Metabolism.

Introduction

Over the years, the rate of degenerative diseases has increased along with other issues. Elderly people are at a greater risk of acquiring degenerative diseases. Degenerative diseases can be defined as diseases that develop when the ability of the tissues and cells to function optimally is dysfunctional or lost.[1] Several health problems are linked to these diseases including, Cancer, Alzheimer's, Type 2 diabetes mellitus, Rheumatoid Arthritis, Osteoporosis and Parkinson's, these diseases are often developed due to the damage caused to the cells and molecules over time.[2,1] The World Health Organization (WHO) recognizes degenerative diseases, also known as non-communicable diseases (NCDs), as a major world health challenge. NCDs include conditions such as chronic respiratory diseases, cardiovascular diseases, diabetes and cancers which are leading causes disability and death worldwide (WHO, 2023). The WHO works to raise awareness and support actions to prevent and control NCDs through global health initiatives, research and development, and evidence-based policies.[3]

The causes of degenerative diseases can be complex and multi-factorial and may include genetics, lifestyle factors, environmental factors, aging and chronic health conditions.[4,2,1] Some NCDs have a strong genetic component, meaning that certain individuals may be more susceptible to the disease due to their genetic makeup. Besides genetics, many lifestyle factors lead to the development of degenerative diseases.[5,4] Excessive consumption of alcohol, physically inactive, tobacco use and unhealthy diet are the major risk factors of developing the NCDs. Similarly, there are also environmental factors including the toxic substances and the environmental hazards increase the risk of the NCDs.[6] Furthermore, as the body ages, it may become more susceptible to certain NCDs, as the risk of developing them increases with age. There are also certain chronic health conditions, like high blood pressure and obesity that can increase the risk of NCDs.[7;6] The most common factors include inflammation and oxidative stress that contributes to the development and growth of degenerative diseases. Many cellular macromolecules and activities are vulnerable to these reactive oxygen and nitrogen species.[8] The brain is the most delegate organ of the body which uses most of the oxygen inhaled, therefore the production of free radicles is also higher in brain cells which ultimately leads to progression of neurodegenerative disorders. Hydrogen peroxide, extremely

reactive hydroxyl radical and superoxide anion are examples of reactive oxygen species (ROS) that contribute to neurodegeneration.[9]

This paper aims to review the association between nutrient metabolism and the development of degenerative diseases. This paper has recorded the observations presented on the oxidative stress that acts as a key modulator for degenerative diseases. This paper covers the different degenerative diseases along with their pathophysiology and mechanism of action. The effect of antioxidants has also been covered.

Oxidative stress: a key modulator of degeneration

Oxidative stress [7] is a condition when an inadequate balance between the antioxidants and free radicles exists in a biological system.[9,10] Excessive reactive oxygen species or inefficient antioxidant defenses cause the imbalance. By altering the activity of biomolecules, ROS considerably contribute to the decline of neuronal cells.[11] Many cellular macromolecules and activities are vulnerable to these reactive oxygen and nitrogen species. Due to excessive usage of oxygen, brain is more vulnerable to the damages associated with oxidative stress.[12] Hydrogen peroxide, extremely reactive hydroxyl radical and superoxide anion are examples of reactive oxygen species that contribute to neurodegeneration. Also proven to be harmful to neurons are reactive nitrogen species (RNS) like nitric oxide.[13] Moreover, several other factors such as environmental pollutants, chemicals, & radiations contribute to the progression of oxidative stress. (Figure 1).

The alterations and modifications to biomolecules such as lipids, proteins, DNA/RNA and enzymes that occur under stress circumstances might serve as indicators for OS because of how susceptible they are to free radicals.[9,14] Different ROS can change the way lipids and proteins work that ultimately lead to neurodegenerative diseases (Table I). Alzheimer's brain has a higher level of protein carbonylation and nitration. Because of their importance to neuronal function, lipids are concentrated in the brain's plasma membrane, where they serve as a physical barrier between the cell's internal and external environment. This makes them more susceptible to lipid peroxidation, which occurs when free radicals damage lipids.[15] Proteins in membranes, enzymes, and receptors are all vulnerable to damage from a variety of chemicals. Since polyunsaturated fatty acids (PUFA) are abundant in neuronal membrane lipids, the side chains in these lipids are especially susceptible to oxidative damage from reactive nitrogen and oxygen species.[9,14] The decline of these biomolecules has great potential as OS biomarkers.

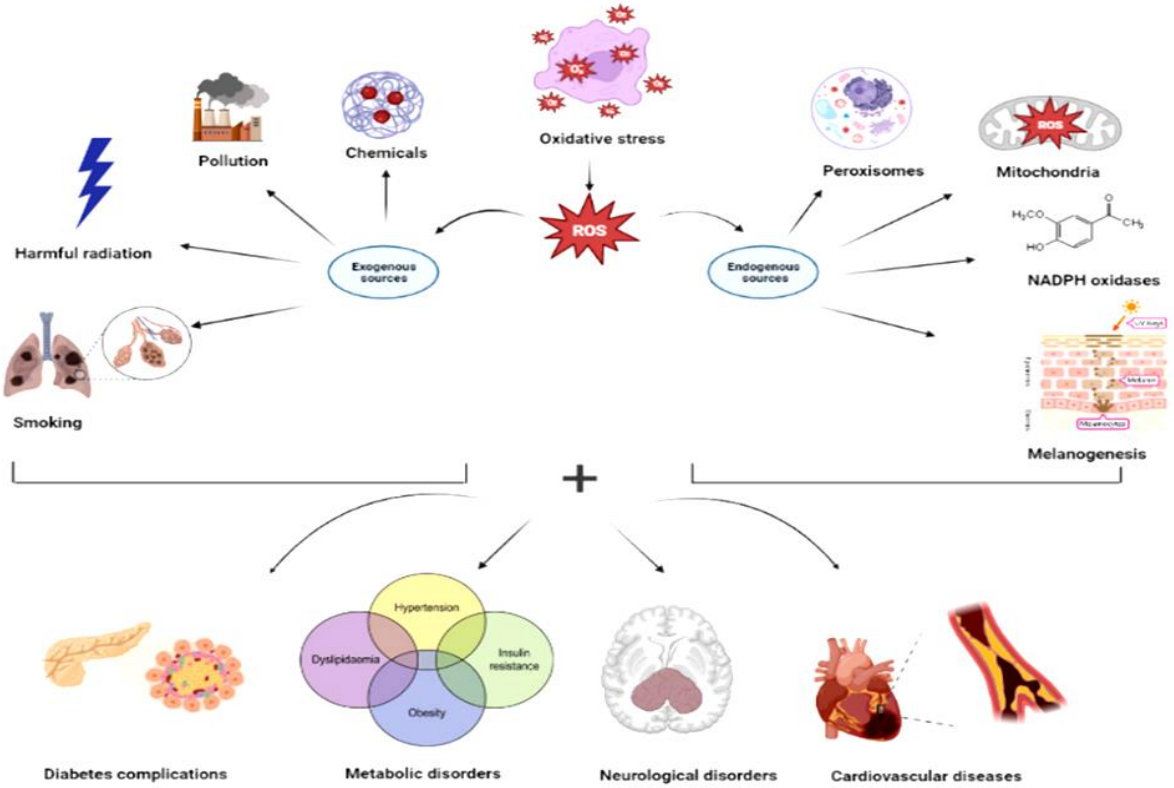

Figure 1. Exogenous and endogenous factors contributing to occurrence of various disorders on oxidative

Role of mitochondria in oxidative stress

ATP is widely acknowledged as the cellular energy currency due to its key role in cellular function, signaling, and activity.[16] Through the processes of oxidative phosphorylation and the electron transport chain, mitochondria generate ATP. In addition to aiding in cell respiration and programmed cell death, they also have a role in the production of chemicals that can combat oxidative stress.[17] ROS production in the cellular environment is thought to be caused by mitochondrial malfunction and different redox enzymes.[18] Biomolecules such as lipids, proteins, and DNA are known to be oxidative damage indicators of ageing and other neurological illnesses. Lipid peroxidation to malondialdehyde, the oxidation of guanine to 8,oxo-deoxyguanosine in DNA and protein carbonyls are all processes in which reactive oxygen species are implicated and all have been shown to have a negative effect on lipids.[9,14] There is a phospholipid called cardiolipin inside the mitochondrial membrane, and also has a role in the electron transport chain. Adenine nucleotide translocase, an inner membrane transporter, requires it on a basis. Cardiolipin is an important target for reactive oxygen species because it is enriched with polyunsaturated fatty acids like linoleic acid and is located near the sites of ROS formation in the mitochondrial electron transport chain. This oxidation of CL is thought to contribute to mitochondrial ETC malfunction and the subsequent release of proapoptotic proteins.[9,14,19]

Neurodegenerative Disorders

Type 2 Diabetes Mellitus: The most prevalent metabolic illness involves the type 2 diabetes mellitus (T2DM). Occurrence of this disease is due to the following two factors: pancreatic cells produce deficient or defective insulin or the non-responsive insulin sensitive tissues in response to the insulin.[20] Different molecular mechanisms are involved in the production and secretion of insulin are strictly controlled because of their importance in maintaining glucose homeostasis. Any disruption in these mechanisms might cause a metabolic imbalance, which can cause sickness.[21] High blood sugar levels are caused by a breakdown in the feedback loops between insulin activity and insulin production that causes diabetes. [22] When β-cells aren't working as they should, the body can't secrete as much insulin, which makes it difficult for the body to keep glucose levels within normal range. However, due to IR liver produces more glucose and causes muscle and adipose tissue to take less glucose inside the cells. Dysfunction of cells is typically more severe than IR, even though both processes occur at the start of pathophysiology and play a role in the development of diabetes. Hyperglycemia and the development of T2DM only occur more frequently in the presence of both cell dysfunction and insulin resistance. [23]

Cellular integrity needs to be maintained, and the processes and pathways involved in cell physiology must be strictly managed to protect cell function. [21] Pre-proinsulin, the precursor to insulin, is produced by cells. [24] Several proteins in the endoplasmic reticulum aid in the conformational change that pre-proinsulin must go through to become proinsulin. Cleavage of proinsulin into C-peptide and insulin occurs after it has been transported from the endoplasmic reticulum to the Golgi-apparatus.[21,25] Once insulin matured, it is kept in granules until it is time for release. The production of insulin is predominantly a metabolic reaction to elevated blood glucose levels.[26] Dysfunctioning of β-cells leads to cell death. However, new research shows that highly complicated interaction between both the environment and multiple molecular pathways in cellular biology may be responsible for the malfunctioning of cells in T2DM. Hyperglycemia and hyperlipidemia are common in an excessive state of diet such that seen in obesity, and both of these conditions support IR and chronic inflammation.[27] Toxic stresses such as inflammatory stress, inflammation, oxidative stress, ER stress, metabolic stress and amyloid-stress might act on cells differently depending on their genetic sensitivity, potentially resulting in a loss of islet integrity.[27] Dysfunction of insulin secretion is the fundamental driver of cell failure and mechanism of type 2 diabetes and can be caused by defects in the synthesis of insulin, insulin precursors or by disturbing the secretion pathway. [28]

Cancer: Cell division is a key mechanism in the process of mutagenesis. A mutation might arise from unrepaired DNA damage during cell division. [29] Cell reproduction rate in tumor-initiating cells is thus a significant element in mutagenesis that leads to carcinogenesis. Since stem cells are not discarded, they play a vital role as precursor cells in cancer. A rise in their cell division rate would lead to an increase in mutation. [30] Predictably, no dividing cells are less likely to become cancerous. Increased cell division increases the risk for cancer, and a wide variety of stimuli, from infection to high levels of certain hormones to chemicals at amounts that trigger cell death, contribute to it. [31] Alterations to genes responsible for cell proliferation and differentiation are required for normal cells to develop into cancer. Gain or loss of a whole chromosome, or a mutation affecting a single nucleotide in DNA, are only two examples of the various types of genetic alterations that may occur. These modifications impact two major classes of genes.[32] Oncogenes can be either modified genes with novel features or normally occurring genes that are expressed in excessive quantities. Cancer cells expressing these genes are

more likely to exhibit malignant characteristics. Genes known as tumor suppressors work to prevent cancer by affecting cell growth, survival, and/or other aspects of cancer cell biology. Gene mutations that promote cancer are frequently responsible for the inactivation of tumor suppressor genes. Changing a normal cell into a cancer cell often involves alterations to numerous genes. [33]

Regulation of gene expression by chemical, non-mutagenic changes in DNA structure is the focus of epigenetics. Non-genetic modifications to DNA can also result in changes of gene expression, according to the epigenetics theory of cancer causation. [34] DNA methylation is one mechanism through which oncogenes remain dormant under normal conditions. Cancer etiology can be triggered by the loss of this methylation, which can cause the abnormal production of oncogenes.[35] Methylation of DNA and acetylation or methylation of histone proteins attached to chromosome DNA at some sites are two known processes of epigenetic modification. The epigenetic signals in cancer cells can be re-regulated by pharmaceutical classes known as histone deacetylase inhibitors and DNA methyl-transferase inhibitors. [32]

Oncogenes stimulate cell expansion in several ways. Hormones are produced by many organisms and act as a "chemical messenger" between cells to promote mitosis; the response of the receiving tissue or cells is determined by the strength of the sent signal. That is to say, when a hormone receptor is activated on a recipient cell, a signal is sent from the surface of the cell to the cell nucleus, where it is used to alter the control of gene transcription. [36] To regulate their targets' responsiveness to hormones, certain oncogenes are part of the signal transduction system or also work as signal receptors in tissues and cells. [37] The proteins and enzymes that make biochemicals or the products that cells utilize and interact with are created by oncogenes, and they are often engaged in the transcription of DNA in protein synthesis. [38]

Alzheimer's Disease

A progressive degenerative abnormality or disorder is Alzheimer's disease. It is also the major cause of dementia. Its symptoms include the loss of memory and dome how people face problems with languages and thinking skills.[39] It also affects the problem-solving abilities of the person. According to the WHO, the number of people facing Alzheimer's disease are nearly 35.6 million in 2010 which can become three times more than this ratio in 2050. This data has been calculated by epidemiologists. [40] It has been demonstrated by the hypothesis that there are plaques deposited in the brain i.e. Aβ-plaques. These are foreign material that initiates the inflammatory response in the brain and the immune system response which is activated by the cytokines stimulation and the microglia. This process eventually causes cell death and the degeneration of the neurons. [41] Moreover, there are microtubule neural proteins that are known as the Tau proteins. These proteins have a special binding domain with the microtubules. This can be involved in the stabilization and somehow polymerization of the microtubules. So the integrity of the cytoskeleton will be maintained by this. Neurofibrillary tangles are mostly caused by the CDK5.[42] So this deposition of the plaques causes abnormality in the axon's transportation, the transmission of the synapses, signal transduction and the degeneration of the cell slowly [43]. This is caused by the gene mutation in the genes of the tau or kinases dysregulation and the hyper phosphorylation.[43]

In the process of cognition, a system of cholinergic is involved. Dementia is caused by the dysfunction of the cholinergic systems. Alzheimer's disease is also a part of it. Neurofibril tubules and the amyloid plaque deposited in the nucleus basal are of the cholinergic neurons. On the other hand, there is the initiation of the proinflammatory process which causes degeneration. This process further deteriorates the cognition level.[44] The major reason involved in the pathogenesis of Alzheimer's disease is the inflammation of the neurons. Brain injuries like Aβ-plaque can be protected by acute inflammation. It shows the protective role against the disease. [45] Antimicrobial properties have been observed in the Aβ-plaque. It has been demonstrated that many pathogens including Spirochetes and Chlamydia have an increasing number of NFTs and the deposition of the AB. Alzheimer's disease is also caused by different types of infections. [46]

Parkinson's Disease

It is a serious and complex neurodegenerative disorder that shows the symptom of unconsciousness and uncontrollable movements. It also causes difficulty in coordination and balance. These symptoms slowly progress and start worse with time. It also causes shaking and stiffness in the body. [47] A study has been conducted that showed that there are some genetic factors that play an important role in causing Parkinsonism disease in patients of Parkinson's disease. An alpha-synculin gene mutation is identified in some patients who have been running in the family's genes. These are autosomal dominant genes. [48] Autosomal recessive Parkinson's disease is caused by a mutation in the genes of PARKIN and PINK1 genes. [49,50] These are both involved in the deterioration of the lysozymes of the mitochondria, the process is known as mitophagy. So, it leads to the functional loss of the genes eventually, leading to mitochondrial dysfunctioning. [51]

Rheumatoid Arthritis

Rheumatoid arthritis is a bone degenerative disease that the inflammation in your joint. As the result, joints become swollen in the different parts of the body. [52] It is an autoimmune disease so our immune system destroys the healthy cells which leads to the inflammation of the joints and pain. It attacks more than one joint at the same time. [53,54] Several hypotheses have been identified regarding the mechanism of the action and the pathophysiology of rheumatoid arthritis. It caused the pre-rheumatoid process which triggers the immune system many years before the joint inflammation. It has been seen that there are changes in the environmental factors and the gene structure which further cause the changes in the self-antigens.[54] This also causes the modification of the IgG, collagen type 2 and other structures. Peptidyl arginine deiminases are the enzymes that are used to convert these proteins along the arginine into citrulline. This whole modification process is known as citrullination. It causes joint inflammation by the cytokines which further causes joint disorders and also changes the self-antigens. [55]

Osteoporosis

The rate of osteoporosis is progressing with time. It becomes prevalent mostly in women. It affects women mostly after menopause and the age after 65 years. [48,56] With the advancement in age, people are more suffering from osteoporosis. This needs extensive care and long-term medication. It includes the porous bone which is the softening of the bones. It is a skeletal degenerative disorder with a bone mineral density of the bones and strength. This loss of strength increases the risk of fractures. [57] Many factors affect the bones and it results causes osteoporosis. The main factors involved are genetics, environment, lifestyle and medications. There are some endo and exogenous factors which cause osteoporosis. [56,58] Some other factors which influence bone mineral density are estrogen-mediated, hyperparathyroidism, and the deficiency of the estrogen hormone. It may be due to poor dietary habits including reduced calcium intake and other lifestyle factors. Vitamin D deficiency is also the cause of calcium deficiency. [59]

Table I: Oxidative stress-based development of Degenerative Diseases.

Degenerative Diseases	Mechanism of Action	References
Diabetes	Beta cell dysfunction Insulin resistance Hyperglycemia	[21]
Cancer	Inactivation of tumour suppressor gene Cell proliferation and inactivation of DNA gene repair Formation of oncogenes	[33,35].
Alzheimer's disease	Neurodegeneration associated with the AB plaque Inflammation of the neurons Imbalance of the neurotransmitter and synaptic dysfunction Degeneration of the neurofibrils.	[41,43].
Parkinson's disease	Mutation in the genes of PARKIN and PINK1 genes	[50]
Rheumatoid Arthritis	Modification of the IgG, collagen type 2 Citrullination	[54]
Osteoporosis	Genetics, environment, lifestyle and the medications	[58]

Antioxidants

The high quantities of reactive oxygen species in the environment have prompted the evolution of several protective systems in animals. Endogenous (NADPH oxidase, mitochondria, etc.) and exogenous (chemicals, radiation, etc.) sources of oxygen and other free radicals are continually introduced to the cellular environment that may cause different diseases (Figure 2). Antioxidants, a part of the body's defensive mechanism neutralizes ROS's harmful effects. In response to reactive oxygen species, cells create antioxidants such as creatine, glutathione, zinc, taurine, vitamins E, C, A and polyphenols. Antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dis-mutase are important to boost the effect of antioxidants. [16,60]

Oxidized DNA is repaired by excision repair enzymes, which may or may not be specific to the oxidized base that they are repairing, and by a sequence of glycosylases that target individual oxidized bases. Without cell division, the mutation rate is maintained low by the efficient removal of oxidative damage from DNA.[9] Proteases catalyze the breakdown of oxidized proteins. Glutathione peroxidase is responsible for the elimination of lipid hydroperoxides. As with the vast many other forms of protection, it appears that the levels of these defenses may be induced (increased) in response to harm. An abundance of research shows that exposure to even modest doses of radiation, an oxidative mutagen, causes cells to develop antioxidant defenses that make them more resistant to mutation when exposed to even more radiation. Taking in antioxidants through food appears to be just as important as the body's enzymatic antioxidant defenses. [9,60]

Dietary recommendations need to be strictly considered to increase the antioxidants in the diet. These antioxidants will work as a preventive measure against degenerative diseases. Several recommendations need to be considered. Vitamin C, or ascorbic acid, is a reducing agent that

may be used to neutralize reactive oxygen species (ROS) like hydrogen peroxide. At least two fruits and three vegetables, which together contain several micronutrients and antioxidants, are recommended by the National Cancer Institute and the Research Council of the Academy of Science. Vitamin C, or ascorbic acid, is a monosaccharide antioxidant that is present in both animals and plants.[61] Reduction to its reduced state is maintained in cells by a reaction with glutathione, performed by protein disulphide isomerase and glutaredoxins. In addition to its direct antioxidant effects, ascorbic acid is also a substrate for the antioxidant enzyme ascorbate peroxidase, a function in plants that is particularly important for stress resistance.[62]

Fat-soluble vitamins having antioxidant capabilities are known together as vitamin E, a designation given to a group of eight closely related tocopherols and tocotrienols. Since the body absorbs and metabolises tocopherol more efficiently. Tocopherol (in its tocopherol form) has been argued to be the most crucial lipid-soluble antioxidant, protecting membranes from oxidation via interaction with lipid radicals generated during the lipid peroxidation chain reaction.[63] The free radical intermediates are eliminated, and the chain reaction is stopped in its tracks. Reduced by other antioxidants such as ascorbate, retinol, or ubiquinol, the oxidised-tocopheroxyl radicals produced in this process can be reused.[62,64]

More than 700 naturally occurring carotenoids have been reported to date, and new carotenoids are published annually. Carotenoids are one of the most widely dispersed pigment families in nature. The 40 carbon atoms in carotenoids come from 4 terpenes.[61] Mammals lack the ability to synthesize carotenoids, however, these pigments are produced by nature in cyanobacteria, algae, plants, certain fungi, and some bacteria. The antioxidant properties, activation of certain genes involved in cell-to-cell communication, provitamin A activity, modulation of lipoxygenase activity, and carotenoid pigmentation of lutein, zeaxanthin, -cryptoxanthin, astaxanthin, and fucoxanthin have all been linked to a reduction in the risk of cancer, cardiovascular disease, and eye disease. [65]

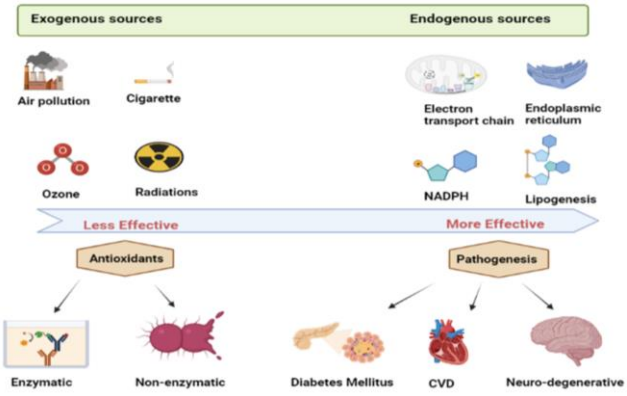

Figure 2: Diseases caused by the types of Free Radicals.

Conclusion

In conclusion, the major causative factors behind the progression of degenerative diseases is oxidative stress and inflammation. This review highlighted the escalating burden of degenerative disorders including diabetes, cancer, Alzheimer's, Parkinson's, Rheumatoid arthritis and osteoporosis. These disorders not only affecting the human health but overall imposing the social and economic burden. It has become evident that reactive oxygen/nitrogen species plays major in development of various illnesses however, antioxidants acts as promising remedial agents. Natural antioxidants like Vitamin C & E, Zn and many countless bioactive components protects brain cells by reducing oxidative stress and inflammation. Nevertheless, antioxidants not only have been observed to reduce the free radicles but also protects against the insulin resistance, uncontrolled cell division, accumulation of proteins and bone remodeling etc. National Cancer Institute and the Research Council of the Academy of Science has emphasized the importance of fruits and vegetables servings in the diet as they contain abundant amount of micronutrients and antioxidants.

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