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ANTIOXIDANTS AND FREE RADICALS IN HUMAN DISEASES: CURRENT STATUS AND FUTURE PROSPECTIVES

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ABSTRACT

Reactive oxygen species are highly reactive species, formed inside a cell thus of ordinary metabolic actions and certain environmental factors such as pollutants, smoke, drugs, illness and even extreme exercise can cause increase in free radicals exposure. ROS that includes superoxide, hydrogen peroxide, hypochlrous acid, hydroxyl, and single oxygen radicals, are intricate in discrepancy, development, growth and decease of cell. They are able to respond with cellular nucleic acids, tissue lipids, proteins, and sometimes with certain carbohydrates. ROS protect cells from pathogens but higher concentration of ROS can induce numerous diseases for example malignancy, diabetes, arthritis, atherosclerosis, cardiac disease and enhance aging process. Antioxidants can be natural or synthetic substances, likely act as protective guard that delay the formation of ROS plus assist cell in abolition of ROS. The objective of this review is to emphasize on progresses in comprehension of ROS, antioxidants, moreover to review the comprehensive influence and contribution of antioxidant compounds in particular human ailments.

KEY WORDS: antioxidants, reactive-oxygen-species, mechanism, molecular damage, human diseases.

INTRODUCTION

In aerobic organisms, oxygen not only plays an important role in energy manufacture but unexpectedly it also yields toxic species which cause enduring poisonous tension in the cells. There must be a defensive mechanism for elimination of poisonous oxygen related byproducts. Various self-protective mechanism have developed to assist the cell to adapt this oxidative atmosphere. These protective antioxidant schemes are basic for survival of both prokaryotic organisms and eukaryotic cells.

Oxidative stress (OS) upshots at a point when assembly of reactive oxidants species (ROS) surpasses the capability of antioxidants fortifications to eradicate these lethal species. Epidemiological as well as medical studies have related ecological factors for example nutrition, and living style (e.g., contact to ionizing irradiation, toxic heavy metals, insecticides, biological lethal tenacious complexes, air particles, and various pharmaceuticals preparations) to melanoma, diabetes, heart, and brain ailments.[1]

Antioxidants

Antioxidants are defined as the substances which protect cells from reactive oxygen species, when present in low concentration inhibit the oxidative stress, by oxidizing themselves. Latest studies propose that numerous exogenous and endogenous antioxi-agents are utilized to defend body from reactive radicals by nullifying them as well as by maintaining balance in redox potential.[2,3] Singh *et al*. (2010) argues that the antioxidants are the "Physiological Molecules" which perform a vibrant part in cellular pathways.[4] They also defend cell. Nevertheless current contradictory suggestion has enforced researchers to dive further keeping in mind the end goal to find the role of compounds: antioxidants plus pro-oxidants, meanwhile free radical responses have also been involved in human obsessive disorders which comprises brain related maladies like Alzheimer's disease, Parkinson's disease, multiple sclerosis, memory loss, anxiety and heart diseases such as atherosclerosis, cardiac hypertrophy, hypertension, shock and strain. Moreover, it also associated with respiratory ailments which include inflammatory lung diseases, inflammatory bowel disease and colitis, diabetes, tumors and cancers".[5,6]

Reactive oxygen species (ROS)

Free radicals or species are characterized as particles or else molecular particles which have free revolving electrons in their orbits.[7] The presence of free electrons in the outer most shell give these free radicals a degree of reactivity. The most important class of free radicals produced within living organism are the radicals derived from the oxygen species.[8] Molecular oxygen also act as a radical due to its exclusive electronic configuration. The accumulation of one free electron to the molecular oxygen comes about into the establishment of "superoxide anion radical" ($O_2^{\bullet-}$) (8). Superoxide

produced by means of cellular metabolim's courses or through direct triggering by the corporeal irradiations, is viewed as "primary" ROS and if additionally react with other molecular particles to produce "secondary" ROS either specifically or by enzyme or metal-catalyzed procedures.[9]

The assembly of superoxide frequently take place within mitochondrial organelle of the cell.[10] Mitochondria is an important organelle within the cell as it contains electron transport chain (ETS) for the creation of ATP thus it is vital for lifetime. In the course of energy generation some electrons "escape" to oxygen impulsively, from electron transport chain and end in formation of free reactive superoxide that has been associated with pathological conditions of various syndromes.[11,12] Superoxide negative ion is mainly formed from both of the complexes I & III exist in mitochondrial electron transport chain, as soon as it is produced, due to presence of strong charge on it, it readily escape from inner mitochondrial membrane.[13]

The hydroxyl radical, $^{\bullet}OH$, is actually neutral kind of hydroxide ion. Hydroxyl radical is very impulsive radical with very minute half lifetime of 10^{-9}s, this property makes it very dangerous radical.[14] Thus hydroxyl radical reacts adjacent to the spot of its creation. Cell's redox condition is highly linked to cupper and iron redox pair and is sustained inside severe physiological limit. Regulation of iron confirms that there should be no freely available iron within the cell, so that it would not be available to form free radicals, but in vivo in stress conditions, superoxide anions release "free" Fe from iron binding molecules. The atoms of iron released via superoxide validated for [4Fe_4S] assembling biological catalysts of dehydratase-lyase family.[15] The unconfined Fe^{2+} contribute in "Fenton reaction" (as shown below) and release free radicals of hydroxyl ions.

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^{-}$$

Consequently, superoxide underneath stress situation act as oxidizing agent for "[4Fe-4S]" clustering enzymes also assists $^{\bullet}OH$ production from H_2O_2 hence making iron ions (Fe^{2+}) freely accessible for Fenton's reaction.[16] Thus according to the Fenton reaction, iron ion plays important role in hydroxyl ion radicals formation, so the organism which contain higher "free iron" amount (as in b-thalassemia, hemodialysis), it can have lethal effect on health.[17]

ROS can strike vibrant constituents of cell such as poly and oligo unsaturated fatty acids and nucleic acid, lipids, and proteins, sometime ROS can also damage carbohydrates but up to a lesser extent. These metabolic reactions are able to change core membrane possessions such as ion transport, fluidity, loss of activity of enzyme, synthesis of protein, DNA damage, and signal transduction; eventually resulting in cell death (Figure 01).[18,19]

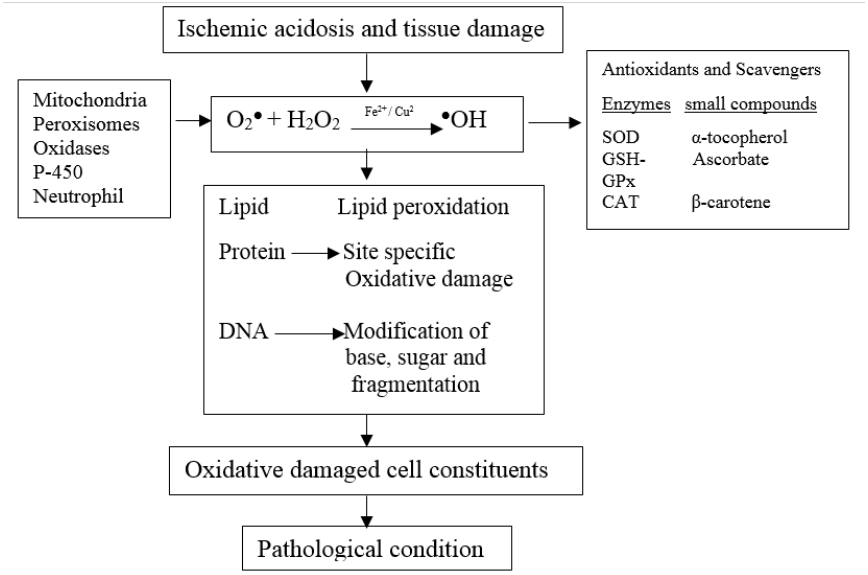


Figure 1: Effect of ROS on Biological molecules

Other reactive species generated by oxygen in organism are "peroxyl radicals" ($ROO^{\bullet}$). Among peroxyl radicals, $HOO^{\bullet}$ is the simplest one, which is formed by superoxide protonation, it is usually term as "hydroperoxyl" or "perhydroxyl" radical. De Grey, (2002) suggests that 0.3% superoxide exists in protonated form in cytosol in a cell.[20] The hydroperoxyl ions initiates peroxidation of fatty acid in two analogous paths: fatty acids hydroperoxides (LOOH)-dependent and (LOOH)-independent.[21] The LOOH-dependent of theses radicals which began fatty acid peroxidation is very much related to lipids peroxidation mechanism in vivo. Xanthine oxidoreductase (XOR) has two interconvertible form "Xanthine dehydrogenase" XD and "Xanthine Oxidase" XO.[22,23] Uric acid produces from oxidation of Xanthine which previously produces from

oxidative hydroxylation of hypoxanthine, this reaction is catalyzed by XOR during purine catabolism. Therefore XOR shows a significant role in cellular protection system as it acts as oxidative stress in contrast to enzyme. Both XD and XO are involved in synthesis of various reactive oxygen species ROS and reactive nitrogen species RNS.[23] Thus, together antioxidants and several free radicals synthesis mark XOR a significant defensive regulator of cellular redox potential.[3]

Peroxisomes are known to generate H_2O_2, but not superoxide in the cell, under physiological conditions.[11] Peroxisomes participate as a site for several oxygen consuming functions in a typical cell. This oxygen consumption heads towards the production of H_2O_2 in peroxisomes, which is then used to produce various oxidized molecules and molecular fragments. Peroxisome although contains catalase enzyme which decomposes H_2O_2 and most probably inhibits the accretion of this poisonous compound. Consequently, peroxisome maintains a subtle balance between relative concentration of catalase enzyme and reactive oxygen species. The mechanism of maintenance of delicate balance by peroxisome is still vague. While peroxisomes gets damaged, its hydrogen peroxide regulating enzyme decreases, as a result of which H_2O_2 discharges into the cytosol, thus subsidize to progress of oxidative stress.[3]

Supplier of cellular ROS

Numerous systems are there in the cell which are involved in producing ROS. Mitochondrial organelles are one of the foremost sites for Reactive Oxygen Species generation, especially mitochondrial complex I and complex III are specific sites for ROS production.[24,25] Besides mitochondria, several enzymes are also present inside a cell which are able to produce ROS. These enzymes include; xanthine oxidase [26,25], α-ketoglutarate dehydrogenase complex [27], d-amino acid oxidase[28], NADPH oxidase[29,25] and dihydrolipoamide dehydrogenase.[30,31]

Relationship between antioxidants and ROS

Low concentrations of ROS are needed in processes like cellular signaling and protection from micro-organisms. Greater aggregates of ROS cause aging, human disease states, including cancer, metabolic failures and destruction to biotic macromolecules. So against ROS, we have several Antioxidant defense mechanisms. Protective antioxidant mechanisms- comprise of enzymes related and non-enzymes related antioxidant fortifications. . Stability between the activities and the intracellular intensities of these antioxidants is obligatory for diligence and vigor of organisms.

Types of antioxidants

Antioxidants are majorly classified by Guttering and Halliwell into three main categories such as; primary antioxidants, secondary antioxidants and tertiary antioxidants.[32] Primary are those that prevent the formation of oxidant species, secondary scavenge the ROS, and tertiary antioxidants are dietary antioxidants that repair these oxidants.

Antioxidants can also be divided in to enzymatic and non-enzymatic antioxidants as shown in figure 2.

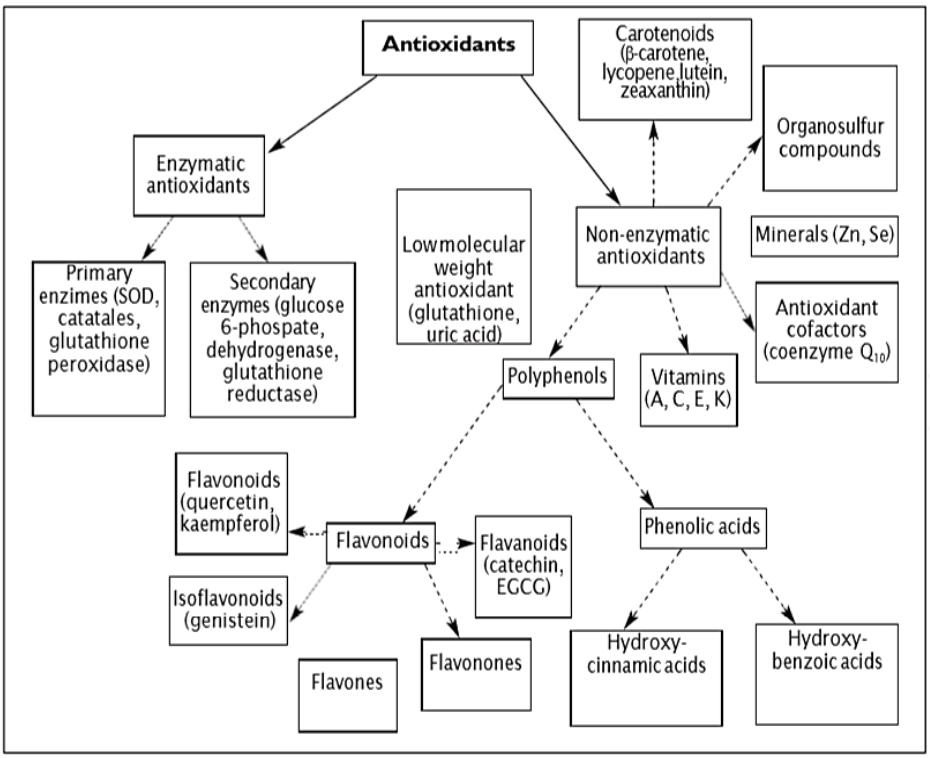


Figure 2 Antioxidants: Classification

Enzymatic antioxidants

These antioxidants system directly or indirectly provide protection against ROS. This system includes Catalase, glutathione reductase, superoxide dismutase etc. These enzymes require some cofctora to perform their functions efficiently.

Superoxide dismutases are involved in the dismutation of superoxides into hydrogen peroxide. This end product then neutralizes by other enzymes which are the part of this enzymatic protection system. A mammalian tissue have three types of superoxide dismutases that are present at various subcellular locations such as cupper or zinc superoxide dismutases that have particularly active zinc and copper atoms and are located in the cell cytoplasm or organelles. Manganese superoxide dismutase are consist of four protein subunits each having an active manganese atom and they are located in mitochondria of nearly all cells.[33] The third category is extracellular superoxide dismutases which also have copper and zinc cofactors but they are somewhat different from above mentioned SODs. They are secreted by endothelial cells and fibroblast cells where they are attached with heparin sulfates on cell surface.[34]

Catalase removes H_2O_2 i.e., the final product of dismutation reaction. To catalyze hydrogen peroxide into water and oxygen it uses iron or manganese as cofactors. Glutathione enzyme system have many enzymes such as glutathione reductase, s transferases, and peroxidases. These enzymes scavenge hydrogen peroxide as well as organic peroxides very efficiently.[35] They utilize selenium as cofactors and are mostly found in peroxisomes. Plasma type of glutathione is synthesized by kidney so to neutralize its substrates, they are mainly present in these subcellular sections.[36]

Non-enzymatic antioxidants

There re variety of non-enzymatic antioxidants: nitrogen compounds such as uric acids, organosulfur compounds, minerals, vitamins A, ascorbic acid, E and K, enzyme cofactors, peptides and polypeptides.

Vitamin A has beneficial effect not only on skin, but also on eyes and interior organs. It supposed to combine with peroxyl radicals and neutralize their damaging effect.[37] Coenzyme Q10 scavenges lipid peroxyl species and minimizes their effect after their formation, also involves in the reformation of vitamin E. It is present in all cells and ply important role in cell metabolism i.e., electron transport chain processes.[38] Uric acid is the end product of purine nucleotide metabolism. About 90% of uric acid produced through kidneys is reabsorbed by the body as it plays important role in reacting with singlet oxygen species and hydroxyl radicals. It also known to prevent the over generation of "oxy-heme" oxidants that produced from the peroxides reaction with hemoglobin.[39] Other non-enzymatic antioxidants are shown in table 1.

Table 1 Major enzymatic and non-enzymatic antioxidants

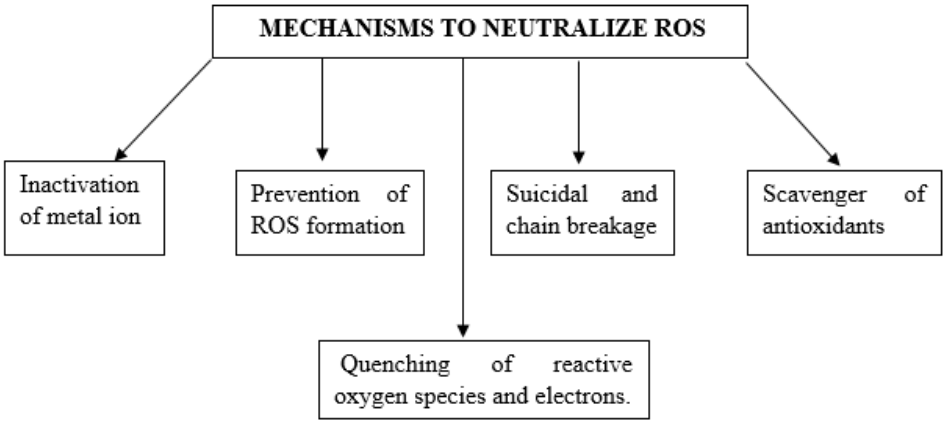
Enzymatic antioxidants	**Location**	**Properties**
Superoxide dismutase (SOD)	Mitochondria and cytosol	Dismutation of superoxide radicals
Catalase (CAT)	Mitochondria and cytosol	Removes hydrogen peroxide
Glutathione peroxidase (GSH))	Mitochondria and cytosol	Removes hydrogen peroxide and organic hydroperoxide
Non-enzymatic antioxidants	**Location**	**Properties**
Vitamin C	Aqueous phase of cell	Acts as a free radical scavenger and recycles vitamin E
Vitamin E	Cell membrane	Major chain-breaking antioxidant in cell membrane
Uric acid	Product of purine metabolism	Scavenger of OH radicals
Carotenoids	Membrane tissue	Scavengers of ROS and singlet oxygen quencher
Glutathione	Non-protein thiol in cell	Serves multiple roles in the cellular antioxidant defense
Lipoic acid	Endogenous thiol	Effectual in recycling vitamin C, and also a functional glutathione substitute
Metals ions sequestration: transferrin, ferritin, lactoferrin	Mitochondria and cytosol	Scavenger of free radical and inhibitor of lipid peroxidation
Nitric oxide	Mitochondria and cytosol	Chelating of metal ions, and responsible for Fenton reactions
Ubiquinones	Mitochondria	Reduced form serve as functional antioxidants
Bilirubin	Product of heme metabolism in blood	Extracellular antioxidant

Mechanism of antioxidant activity

Oxidation is a process in which the normal cells also destroyed due to formation of free radicals. Sometime these free radicals have deleterious effect on structure and functions of DNA, Protein, and lipids. These free radicals are involved in oxidative stress. Best remedy to prevent the cell from oxidative stress is the use of antioxidants. Function of antioxidant is to delay or prevent action of $FR^{\bullet}$.

Antioxidants have wide applications at the level of prevention, interception and repair. Maintenance of healthy biological system balance between oxidation and ant oxidation is critical but it is observed that antioxidants are required in small amount for efficient working as its high quantity can disturb the biological system.[6]

There are also other mechanism shown by antioxidants such as classical and modern method as shown in the scheme 1 which includes binding or inactivation of metal ions, stop the formation of reactive ROS, suicidal and chain breaking, scavenger of antioxidants, quenching of reactive oxygen.[40]



Scheme 1 Different mechanisms to neutralize ROS

Classical method

In the classical method antioxidants are combined with free radicals and neutralize their effect by donating electron or hydrogen atoms this reaction is considered as base of classical method of antioxidant activity.

$AH + FR^{\bullet} \longrightarrow A + FRH$

AH = antioxidant, FR= free radical

This process inhibits the damage of proteins, DNA, and lipids from free radicals. There are some other factors that affect the activity of antioxidants such as reactivity, lip solubility, secondary reactions etc.

Reactivity

Rate of above reaction is:

$R= k1[AH][FR^{\bullet}]$.

According to kinetics point of view compound whose K1 is high is a good antioxidant but in the case of antioxidant good antioxidant is that which has faster or comparable rate of reaction with radicals than that of the endogenous antioxidants reacting with free radicals.[41]

Liposolubility

Free radicals are sometime present in the compartmentalized systems of membranes so it is necessary for antioxidants to reach at that site of membrane to inhibit the peroxidation of membrane lipids. For this purpose antioxidant should be sufficient liposoluble. For example α tocopherol is liposoluble it work well with the ascorbic acid to prevent peroxidation of lipids.[41]

Secondary reactions

It is observed that during the reaction[1] the secondary free radicals also generated that has deleterious effect on biological targets

$A^{\bullet} + BTH \longrightarrow AH + BT^{\bullet}$

Secondary peroxyl radical is formed on reaction of oxygen with free radicals.

$A^{\bullet} + O_2 \longrightarrow AOO^{\bullet}$

These secondary free radicals are implicated in oxidative alteration of proteins, DNA and lipids.

Modern method

Modern method of antioxidant activity is based on redox signaling. The concept of oxidative stress proposed by Helmut Sieus in 1985 has been unacceptable by introduction of new reactive species such as RNS (a biologically produced reactive free specie from the nitric oxide).[42] Its discovery convince that reactive species produced by enzyme systems are not only involved in chemical defense but has crucial role in cell signaling. On the basis of redox signaling pathway, in 2006 Dean Jones gave a new definition of oxidative stress "that was an interruption in redox signaling and control".[43] This shows that mechanism of antioxidant is complex one. Free radicals have useful effects along with damaging effect such as they are involved in gene expression, cellular growth. Regulation of perturbation of redox cellular network provoke oxidative stress.[41]

Compartmentalized redox signaling pathway

Some redox signaling pathways are reported which are controlled by transcriptional factors NRF-2 and Nfk-b compartmentalized in cytosol and in nucleus. Oxidative signal in cytoplasm activates the NRF-2 which is a transcriptional factor sensitive to redox signaling. This signals forced NRF- 2 to move from cytoplasm to nucleus here it binds with DNA ARE- region. This region has cytoprotective enzymes such as GST, SOD, NADPH quinine oxidase(ARE regulated gene). In cytoplasm NRF-2 is present along with another protein keap 1 that help in its degradation and in result level of NRF-2 lower down. ARE inducer activate NRF-2 and dissociation of NRF-2/ Keap 1 take place due to this NRF-2 accumulate in nucleus and transcription of gene carried out under control of ARE. Under oxidative stress cysteine residues of keap 1 are modified but NRF-2 also require reduce cysteine to bind to DNA.[41]

In the end much result is still needed in this area to discover other mechanisms of antioxidants to control the oxidative stress.

Free radicals induce molecular damage

Proteins, lipids and DNA are biological molecules present in the body. Due to oxidation these molecules can be at risk of attack by the free radicals due to this structure and function of biological molecules can disturb and eventually death of the cell can happen leading to disease state.

Lipid and lipid peroxidation

In eukaryotes every organelle is surrounded by the membrane. Mammalian membrane is composed of lipids, proteins and polysaccharides. Free radicals formed as a result of oxidation react with membrane lipids and series of lipid peroxidation chain reactions take place that has direct and indirect effect on cell working.[44] Lipid peroxidation leads to the production of other by- products which may act as secondary messenger (secondary messenger means having action at sites other than their generation point).[44] Peroxidation process take place in series of step. In the preliminary step free radicals assault on the membrane lipids and knock out H from the methylene group and subsequently release a carbon radical. This carbon radical is balanced out by atomic modification to deliver conjugated diene, which additionally counter with an oxygen particle to give a lipid peroxyl radical. Radicals formed has ability to remove hydrogen atoms from other lipids and form lipid hydroperoxides. This process of peroxidation can be terminated by many ways among them one is the use of antioxidants. As the antioxidants has ability to form stable radicals that cannot allow the reaction to further proceed.

$LH + {}^{\bullet}OH \longrightarrow {}^{\bullet}L + H_2O$

$L^{\bullet} + O_2 \longrightarrow LOO^{\bullet}$

$LOO^{\bullet} + LH \longrightarrow L^{\bullet} + LOOH$

$LOO^{\bullet} + \alpha\ TOH \longrightarrow LOOH + \alpha\text{-}\ TO^{\bullet}$

During the process of lipid peroxidation many products are formed which are of toxic nature such as 4 hydroxynonenal (4-HNE) malondialdehyde (MDA), and several 2-alkenals.[44]

Effect of Oxidative stress on DNA

Oxidative stress has significant effect on signal transduction pathway.[45] Oxygen carryings biochemical reactions lead to the formation of toxic and very reactive oxygen species that may cause DNA damage including modifications of bases, production of base-free (apurinic and apyrimidinic) sites, knick development in DNA strand and DNA-protein cross-links.[45] Purines and pyrimidines are highly sensitive to free radicals such that interaction of OH free radicals with pyrimidine generate oxidative pyrimidine damage products, including thymine glycol, uracil glycol, urea residue.[44] Any change in DNA termed as mutation and mutations leads to the development of cancer. Oxidation process generates ROS that can play an important role in development of cancer by inducing the oncogenic phenotypes of cancers.[46]

Effect of oxidative stress on proteins

ROS are involved in oxidation of proteins and can produce reactive products like protein hydroperoxide which on reaction with transition metals further produce reactive radicals. Now there are two destinations for oxidized proteins either they will remove from cell or will accumulate in the cells and cause damage associated with diseases. This can be elaborated with the example of Alzheimer's disease in which lipofusin accumulate in the lysosome of old and brain cells of patients and lipofusin are aggregates of peroxide lipids and proteins.[44]

Oxidative stress has deleterious effect on protein working; it can bring reversible and irreversible oxidative modification in proteins.

Irreversible modifications: In Irreversible modification carbonylation and tyrosine nitration take place in proteins, these modifications cause damage and can be used as biomarker to evaluate the level of oxidative stress in aging and in other diseases.[47] These modifications can have deleterious effect on target proteins but some studies also show that carbonylation and tyrosine nitration can play an important role in cellular functions under stress conditions.

Reversible modification: In the protein structure Cysteine modification take place and these are generally considered as reversible modification. Reversible cysteine oxidation has potential to change the redox condition of the cell and can save the target protein from additional damage. Reversible cysteine oxidation is also involved in redox signaling cascades that can draw out positive stress responses to stop unpredicted shocking events such as stroke and heart attack.

Current status of Antioxidants and human diseases

Oxidative stress damages proteins, lipids and DNA which leads towards the pathogenesis of numerous variety of diseases mainly heart disease, cancer, diabetes, pulmonary dysfunction etc.[48] A developing body of animal and epidemiological and clinical trial and studies reveal that antioxidants play an important role in decelerating or precluding the development of some sorts of cancer and heart diseases.[49]

Antioxidant and cancer

Reactive oxygen species are key elements in developing the process of multigenic cancer. To balance ROS-intervened damage in the body endogenous antioxidant system always present there. DNA is highly susceptible to attack of free radical and it is confirmed that oxidative DNA damage is involved in process of cancer development. During the cancer therapy (radiotherapy or chemotherapy) free radicals generate that are considered to have side effects such as causing nephrotoxicity, cardiotoxicity etc.[50] Free radicals produce chromosomal defects by the production of hydroxylated bases which leads to initiation and proliferation of cancer.[2] For example smoke of tobacco contains asbestos which cause oxidative damage to DNA and leads to the development of lungs cancer. A research was conducted on tongue carcinoma patients its results reveal that cancer was developed due to high level of oxidative stress markers and low level of antioxidants.[50] For example in mice due to downregulation of p53 ROS level increases and and the drugs containing antioxidants efficiently hinder the tumor formation. In another study ROS level in embryonic fibroblast of mouse containing mutant G12V K-Ras was low but antioxidants level was high and this condition leads to the survival of mouse. All these situations clear that whether antioxidants and ROS are good or bad depends on genetic, epigenetic, and microenvironmental variation present.[51]

Another benefit of antioxidant is that they protect normal healthy cells from the effect of radiations and chemotherapeutics during the cancer treatment.[50]

Antioxidant and diabetes

High amount of glucose may cause damage to the cell by the process of oxidative stress. Oxidative stress assumes to have a real part in the pathogenesis of both types of diabetes.[6] The inhibition of intracellular free radical formation would provide a therapeutic strategy to prevent oxidative stress and the related diabetic vascular complications. Antioxidants may act at different levels, inhibiting the formation of ROS or hunt free radicals, or increase the antioxidants defense enzyme capabilities.[52]

The restraint of intracellular free radical arrangement would give a helpful system to counteract oxidative stress and the related diabetic vascular problems. Antioxidants may act at various levels, repressing the development of ROS or, on the other hand look through free radicals, or increment the antioxidant defense enzyme abilities. It is observed that in type II diabetic nephropathy, over expression of Cu+Zn2+ superoxide dismutase (SOD) protects the organ from damage due to high glucose level.[6] Some antioxidants such as vitamins C improve endothelial dysfunction in diabetes.

Antioxidants and Pulmonary disorders and cataracts

Due to high amount of oxygen absorption and large surface area of lungs make it a sensitive target for ROS, it is also believed that pollutants in air are also main source of free radicals.[53] It is also believed that free reactive oxygen radicals can also cause the progression of asthma.[54] Inflammation and cellular damage to bronchia is distinguishing character of this disease may also cause by free radicals. It has been recommended that antioxidants consumption may aid to decrease the expansion of asthmatic signs. β-carotene, vitamin C and K supplementation are related with better pulmonary functions. Some sort of pulmonary damage may also be protected by glutathione itself or its precursors i.e., "N-acetyl cysteine".[53,55]

Other pathologies induce by ROS include cataracts. Development of cataracts is supposed to damage to proteins of eye-lens, prompting the loss of transparency of lens. It is suggested that formation of cataracts can be slow down by intake of additional antioxidants, predominantly vitamin C and E, and carotenoids. It is believed that development of cataracts can be delayed by almost 10 years as a consequence of enhanced antioxidants defense that would decrease the cataracts surgeries' number implemented in U.S by more than half.[56]

Antioxidants and Neurodegenerative diseases

Nervous tissues are extremely prone to oxidative stress due to increase lipid and polyunsaturated fatty acid content. Certain histological and biochemical studies related to "Alzheimer's disease" (AD) provide evidences that there is increased level of membrane lipid peroxidation (LP) and oxidative stress. In increased stress condition it is believed that there is consistent alteration in the enzymatic oxidants such as catalase, CuZn or Mn-SOD in the nervous tissues including brain of AD patient. Not only enzyme alteration but also nitration and oxidation of protein in neurotic tangles and plaques occur. In AD patients LP becomes quite widespread if amount of oxidation products i.e., 4-hydrononenal (4-HNE) becomes high in cerebrospinal fluids, which promotes the neurological damage by four mechanism including loss of function of membrane ATPase ion motive force, transporters of glutamate and glucose.[57]

Antioxidant and Cardiovascular disease

Cardiovascular disease (CVD) is caused by the variety of factors such as hypercholesterolaemia, hypertension, smoking, diabetes, poor diet, stress. In order to cure cardiovascular diseases antioxidants are widely used, among them use of vitamins as antioxidant is promising

area of research to prevent CVD. There is a hypothesis related with vitamins such as they reduce the risk of developing cardiovascular diseases. Antioxidants have ability to prevent the oxidation of low density lipoprotein such as cholesterol that is common cause of CVD. Vitamin E prevents coronary heart disease

NO• in the vascular endothelium is created due to nitric oxide synthase renovating the substrate L-arginine to L-citrulline.

L-Arg + O2 + NADPH $\xrightarrow{\text{NOS}}$ NO• + citrulline

Abundant antioxidant-rich diet use can reduce the rate of coronary heart malady.[58]

CONCLUSION

In normal condition, an appropriate balance is maintained between oxidants an antioxidants. Any disturbance in this balance in favor of oxidants can develop oxidative stress in the body. Oxidative stress is the state that not only damages membranes, biomolecule but also harms the integrity of cell and its functionality. As oxidants may accumulate in the vibrant organs after time to time which may lead towards the progression of several degenerative and chronic ailments, so protection against these radicals is necessary for normal body functioning. The elevated oxidants level also badly effect immune related cells and its defensive mechanism. As a protective mechanism various enzymatic and non-enzymatic antioxidants are produced in the body having ability of scavenging superfluous ROS to make sure the ideal balance between oxidants and antioxidants, thus sustaining proper cellular homeostasis. Besides maintaining this balance, antioxidants also prevent the disorders, and preserve health.

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