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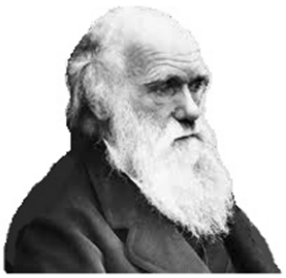

World News of Natural Sciences

An International Scientific Journal

WNOFNS 44 (2022) 150-164 EISSN 2543-5426

Pathogenesis of Reactive Oxygen Species: A Review

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ABSTRACT

Oxidative stress is known top-lay an important role in the development and pathogenesis of several chronic diseases such as diabetes, neurodegenerative diseases, and cancer. Exposure to poisons and toxicants results in the generation of pro-oxidant which eventually cause dysfunction in enzymatic activities and defect in the DNA, resulting to alteration in the expression of genes the induction of oxidative stress is by far associated with modern life styles which include the consumption and exposure to chemicals which are used to preserve and process food. Hence, this review provides insight to the relationship between reactive oxygen species and some chronic disorders. That is the contribution of reactive oxygen species to the pathogenesis of some diseases.

Keywords: Oxidative stress, Chronic diseases, ROS, Pathogenesis

1. INTRODUCTION

Many biological processes in our bodies are known to generate very dangerous compounds called free radicals, which are known to be deleterious to the body. These dangerous compounds can be prevented by the antioxidant system in the body, but when this system is extremely weak, then these compounds end up inducing oxidative stress through the formation of reactive oxygen species [1], which eventually lead to the induction of several acute and chronic diseases like cancer [2]. Although free radicals are known to be deleterious, but researches have shown that it plays some very important role in life process. For example, it helps in the destruction of bacteria through phagocytic process [3] and also functions in several

(Received 15 July 2022; Accepted 07 August 2022; Date of Publication 10 August 2022)

cellular signaling mechanism. It has also been discovered that the resulting factor of free radical, which is the formation of reactive oxygen species, at low concentration is highly beneficial to the body by helping in homeostasis and also in the regulation of several cellular functions [4].

Overproduction of reactive oxygen species is therefore deleterious to the body because it causes alteration in the structure, function and processes of cellular proteins and lipid which eventually result in the damage of DNA. In relations to lipid, Reactive oxygen species causes the breakage of lipid membrane, leading to an increase in the fluidity and permeability of the membrane [5-8].

Due to the dual function of this radical, the body has a lot of processes to reduce the damage being caused by this radical via protection against its overproduction through the advantageous function of antioxidants and chemoprevention. Antioxidant help in the preventing the body against the harmful effect of free radicals and reactive oxygen and nitrogen species [6]. It should be noted that, because of the beneficial effect of free radical and antioxidant, it is very important to maintain a balance between these two. An imbalance between the antioxidant defense system and reactive oxygen species, in favor of reactive oxygen species is termed oxidative stress.

Therefore, the frequent production of free radical but balance with the consumption of antioxidant in the body so as to prevent several disease condition [9]. Looking at autoimmune diseases, the expression of antigen type protein can be changed by free radicals, thereby leading to a spike in the immune response [10-12]. In susceptible people, antioxidants from external sources like allergens can influence the immune response system. Research has shown that several pollens produced by some species of plants contain NADPH oxidase (i.e. nicotinamide adenine dinucleotide phosphate oxidase). This NADPH oxidase is responsible for the induction of inflammatory reaction in the aviation routes together with distinct side effects as a result of penetration with pro-inflammatory cytokines, TNF-alpha and interleukins from epithelial cells.

The advent and gathering of intracellular pro-oxidant elements has a drawn out impact of changing the immune response by modifying the framework and, certainly, the role of enzymes/proteins, for example: TNF-α (tumor necrosis factor-alpha), CD14 (cluster of differentiation antigen 14), and IFN-γ (interferon-gamma) [3-5].

In malignant growths, modification of pyrimidine or purine in the design of DNA cell, which is related with various reactions that create free revolutionaries and oxides, might be the reason for neoplasms. Assuming that the intracellular repair mechanisms of oxidative disorders are deficient or disturbed in turn by the oxidative elements present, there are conclusive outcomes in certain genes or items resulting from these genes expression, which causes mutagenesis and change of the apoptotic component of the cellular structure, which then bring about the cancer cell [8].

At the long run, the modifications unfold and self-preserve with super durable actuation of the autoimmune reaction and the buildup of local pro-inflammatory elements, such as: kinases, TNF-α, and proteases. All these elements are in support of tissue necrosis and speed up the development of tissue with the presence of latest adjusted cells that preserve the immune reaction and proliferate the underlying hereditary imperfections (genetic defects) tumultuous and broad augmentation; additionally, oxidative stress creates primary alterations of cell films with low adhesion, and the movement of modified cancer cells in adjoining tissues or in distant lymph and blood [14].

There are 2 main theories on the mechanisms of cellular aging and these mechanisms are presently acknowledged. These two theories include free radical theory and mitochondrial

theory. These two theories agree with the hypothesis that mitochondria are infected by an expanded degree of intracellular free radicals, which results to the modification in their capability and a reduced cellular regenerative ability. Simultaneously, the ever-evolving buildup of intracellular oxidizing elements which surpass the antioxidant limit is likewise accepted. In this circumstances, the natural retrogression of both tissues and reduction of adaptability to stress begin to show up. Hence, no matter what the system involved, in mitochondrial DNA damage or in the immediate association of pro-oxidant factors in cell components, the cell reaction to stress will create an over-flow of pro-inflammatory genes with expanding degrees of pro-oxidant factors [15].

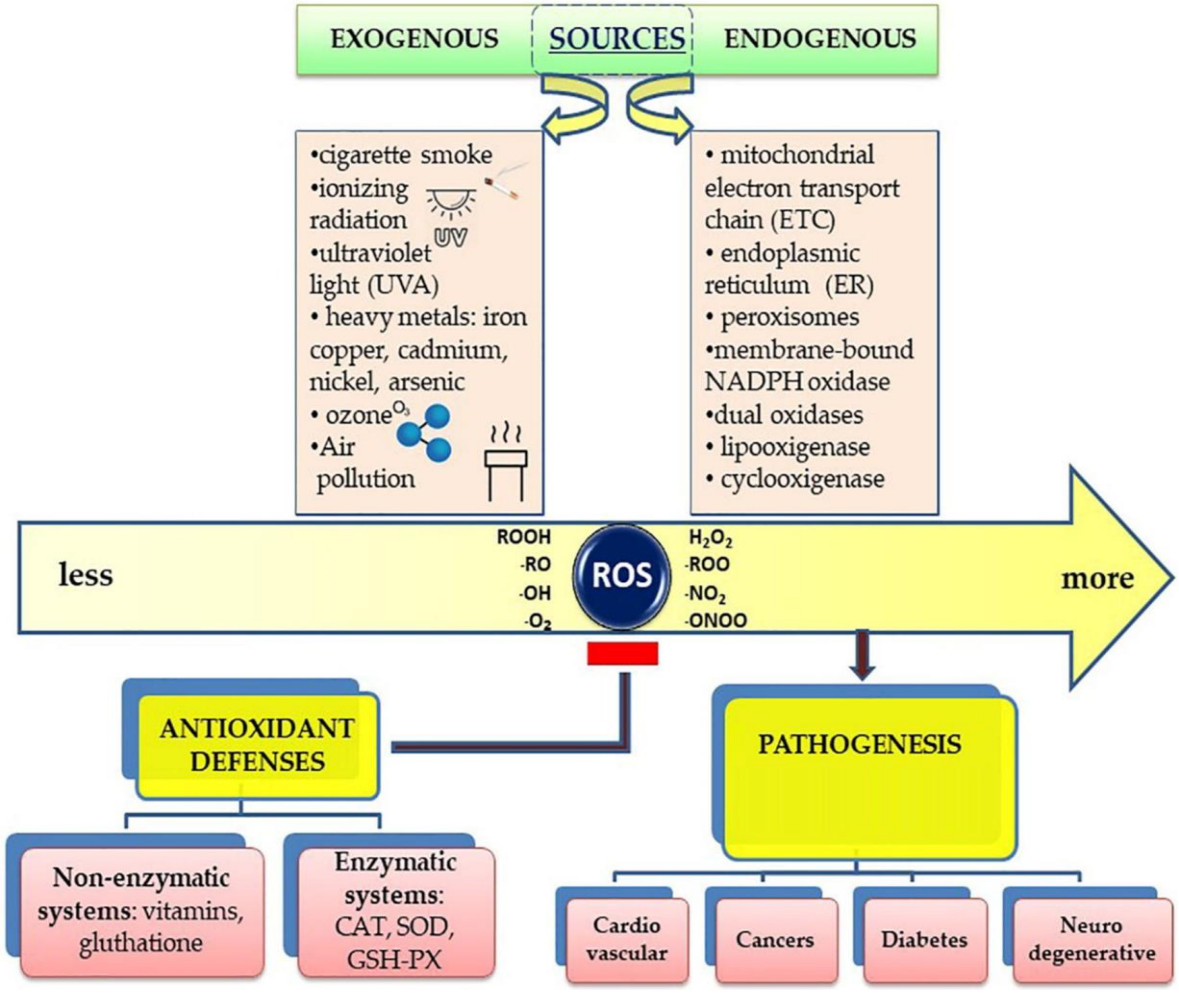

Figure 1. Diagrammatic representation of the origins of free radicals and their impacts on human body system [4].

The immune response can be stimulated by oxidative stress and causes hypersensitive sicknesses, like atopic dermatitis, asthma, food allergies, or allergic rhinitis. This implies that the antioxidant protection system of individuals with allergic illnesses is obsolete contrasted with that of healthy people [16]. Antioxidants supplementation can consequently make up for

the expanded inflammatory and oxidative stress processes in individuals suffering from asthma disease.

The presence of oxidative stress in human being is commonly influenced by absence of physical activity, unhealthy eating routine, and exposure to a blend of synthetic compounds from various pesticides [17], natural pollution, food additives, and heavy metals. It can as well add to the development of a chronic illnesses, as is proposed by a few research experiment and human investigations [2, 3, 5]. This comprehensive review aims to provide strong evidence that antioxidants may contribute to the amelioration of some chronic-degenerative conditions, in addition to being able to promote healthy aging.

1. 1. Chronic Diseases Influenced by ROS-Modalities of Action

1. 1. 1. The ROS Sources

Free radicals are by and large delivered because of the impact of environmental elements, for example, tobacco smoke, pollution, or internal factors, due to intracellular metabolism if the antioxidant mechanisms are overpowered.

1. 1. 2. Exogenous ROS

Increase in the level of ROS in the cell is being associated with environmental toxicants and contaminants like cigarette smoke, UV radiation, heavy metal ions, ozone, allergens, drugs or toxins, pollutants, pesticides, or insecticides, and these may lead to the generation of oxidative stress and damage [18]. Some of these exogenous substances act by either converting hydroxyl radicals, superoxides and organic radicals into organic hydroperoxides and hydrogen peroxide [19-21], stimulating riboflavin, porphyrins and NADPH-oxidase, with the production of 8-oxo-guanine as the main result and the decrease of intracellular glutathione (GSH) level with a return to normal after cessation of exposure [22], or directly inducing free radicals by Fenton or Haber-Weiss type reactions, leading to several disease disorders.

1. 1. 3. Endogenous Reactive Oxygen Species Production

The major endogenous sites of cell redox-reactive species generation-including reactive oxygen species and RNS (reactive nitrogen species) contain dual oxidases (Duox) 1 and 2 complexes, endoplasmic reticulum (ER), nitric oxide synthases isoforms 1–5 (NOS1–3), peroxisomes, mitochondrial electron transport chain (ETC),and membrane-bound NADPH oxidase (NOX) isoforms 1–5. Complex 1 and Complex 3 of mitochondrial electron transport chain creates superoxide anion [22].

The fundamental origin of reactive oxygen species has been suggested to be the mitochondrial electron transport chain, however, the presence of different internal origins are likewise recognized. Other various origins of reactive oxygen species, primarily hydrogen peroxide, are peroxisomes and microsomes. ROS can also be generated by the action of immune cells, like neutrophils and macrophages as a result of their oxygen-dependent mechanisms to defend against antigens based totally on NOX2 isoform [23]. Moreover, abnormally regulated ROS signaling can additionally make a contribution to numerous of illnesses related with oxidative stress [21].

During the process of aerobic metabolism, ROS are also generated in mitochondria [2]. The production of reactive oxygen species in the mitochondria (oxidative metabolism) is related

with the synthesis of adenosine triphosphate (oxidative phosphorylation). The interaction of these reactions is the fundamental energy sources in aerobic microbes [7].

The mitochondria functions as main ROS producer and also as ROS receptor simultaneously. Covalent and enzymatic changes in proteins during or after protein biosynthesis as well as during protein cleavage or degradation promote disease through oxidative damage and mitochondrial dysfunction. Those post-translational alterations take part in the maintenance of the role of mitochondrial via free radical species and other messengers [8].

On the ground that oxidative phosphorylation is a weak process, 0.2 % to 5 % of the electrons flow through electron transport chain in every round of adenosine triphosphate synthesis. This however results into reduction in oxygen production [9].

NADPH oxidases (NOX) are responsible for the production of superoxide radicals. To a minor extent, superoxide radicals are also produced as by-products of an extensive range of metabolic enzymes like lipoxygenase, cytochrome p450, cyclooxygenase (COX) 1/2 and xanthine oxido-reductase (XOR) [25].

Superoxide radicals diffuse through natural lipid membranes at an insignificant level and this is due to the anionic characteristics they possess. They decreased inside the cells in a sequential order to produce H_2O_2 and OH radical [13]. In addition, alkoxyl and peroxyl radicals, and hypochlorite ions, are also produced [12].

Some of these sorts of reactive oxygen species are toxic to the cells; they can even undergo oxidation and then make lots of the roles of cellular components and DNA inactive [25]. Irreversible apoptotic and necrotic cellular death are usually caused by many of these mechanisms.

Numerous researches done imply that human cells also has the potential to initiate the production of reactive oxygen doses in smaller doses. They also participate in signaling pathways, modulating cell growth and development, and protection against antigens. Some distinct enzymatic systems like the NOX family have been specifically developed by cells. These systems are dedicated specifically to the synthesis of superoxide radical with physiological signaling functions [27].

In regular conditions, electrons are transported via mitochondrial electron transport chain for the reduction of O_2 to H_2O, but electrons of ~1 % to 3 % are released from this system and synthesize superoxide [6]. Aside from this, various internally produced origins of reactive oxygen species are found in human beings. They include (i) detoxification of toxic substances (i.e., vigorous exercise, chronic inflammation, and infections); (ii) arachidonate pathways; (iii) oxidative burst from phagocytes (white blood cells) during bacteria and virus killing and foreign proteins denaturation; (iv) peroxisomes metabolism; (iv) xanthine oxidoreductase (XOR) metabolism [7].

Phosphatase activity is usually decreased by reactive oxygen species. ROS does this by halting the catalytic areas which are vulnerable to oxidation, and hence, improve PTP (protein tyrosine phosphatase) phosphorylation and also impacts signal transduction [8]. Reactive oxygen species can likewise enhance the signal transduction pathways which disrupt the activation of the nuclear factor-κB (NF-κB) and translocation of the nuclear factor to the nucleus. There is a significant reduction in the ability of the oxidized NF-κB to bind to DNA. Moreover, redox factor 1 or TR can also reduce the nuclear factor κB [17]. The aforementioned triggers RNS and ROS in order for it have a significant effect on NF-κB-dependent inflammatory signals.

An electrophilic anti-inflammatory prostaglandin known as cyclopentenones coupled with the reactive thiols of ROS-regulated proteins and peptides and for that reason lessens ROS-regulated NF-κB signaling [14]. However, an internal source has been associated with endogenous stress. A lot of researchers have pointed the function of cultural cell conditions, changing the patterns of gene expression various genes and their DNA steadiness. Various kinds of ROS are induced by metabolic processes, which have the ability to oxidize DNA and cause different harm, like the dsDNA deficiencies and breaks, often discovered in human tumors [12]. However, there're reactions which are non-enzymatic in nature, such as the mitochondrial respiratory chain which include XOR, lipoxygenase, cytochrome P450 enzymes, NADPH oxidase, COX and uncoupled endothelial NOS [11]. Cellular oxidative metabolism generates free revolutionaries (or radicals) and natural peroxides as by-products at some point of the cellular mitochondrial electron transfer or via metallic-catalyzed oxidation of metabolites and oxidoreductase [16].

Furthermore, NO (nitric oxide) is generated in a respiratory chain reaction under a hypoxic condition, and RNS can initiate the production of ROS, for example 4-hydroxy-2-non-enal, MDA (malondialdehyde), reactive aldehydes [19]. Reactive oxygen species can also cause a change in the status of the cell redox and, consequently send a signal. An imbalance in this protective process can however results to harm in the cellular structure, for example lipids, proteins and DNA, leading to cell mortality by apoptotic and necrotic processes [15]. Triggered reactive oxygen species was initially shown in the phagocytic cells, which include macrophages and neutrophils, during phagocytosis with a large range of agents via the activation of NADPH oxidase. The name "the respiratory burst" was given to this as a result of the brief consumption of oxygen [14]. The degranulation and respiratory burst of neutrophils give rise to a protective reaction to damage in the host tissue, whether induced by infectious, mechanical (thermal stress, muscle damage during physical exercise) or chemical stimuli [18]. In recent times, the production of ROS has been found in different cells aside from phagocytes, and their consequences in physiologic signal properly documented [13].

1. 2. The Role of Lifestyle in Oxidative Stress Response

Unhealthy lifestyle such as consumption of alcohol, smoking, inadequate and adequate diet, exercise or untrained condition, make substantial contribution to oxidative stress. A few studies has proven the presence of ROS and muscle level as well as their function in modulating muscle activity. Skeletal muscle fibers constantly produce ROS at a low stage, which increases in the course of muscle contraction. They exert numerous oblique and direct impacts on the activities of the muscle such as metabolism, excitability, calcium homeostasis and contractibility and also, they are active in skeletal muscle fatigue at the period of stressful workout [17].

Arduous sporting activities, overtraining syndrome, prolonged exercises, as well as overcoming limits which is a stage of the early onset of overtraining syndrome, trigger a considerable reaction to oxidative strain. Alternatively, slight exercising, reduced stressful exercise, as well as lengthy exercise, enhance the status of endogenous antioxidant.

ROS have a critical function in the signaling of cells and in the regulation of antioxidant genes expression. Physical exercise generates an over-regulation of the nuclear factor kappa B as well as the mitogen-activated protein kinase which actuates the genetic expression of few proteins and enzymes with a crucial function in the regulation of antioxidant/oxidative intracellular homeostasis [3].

Physical exercising is viewed as the fundamental therapy of non-pharmacological treatments alongside lifestyle adjustments for diverse persistent illnesses, particularly cardiovascular illnesses [9]. The consequences of few research have pointed the function of autophagy, a catabolism process for the debasement and recycling of organs and vitamins, in the cardiovascular advantages given by the exercise [21]. Daily workout as an extraordinary type of physiological stress can set of transformation, while autophagy, particularly specific mitochondrial autophagy (which is likewise known as mitophagy), considers such cardiovascular variation [19].

Tobacco smoke involves a progression of oxidants, free revolutionaries, and natural constituent (such as nitric superoxide and nitric oxide) where the lung level enacts the buildup of macrophages and neutrophils, which builds the creation of oxidants locally [13].

2. BIOCHEMICAL/MOLECULAR TARGETS AND CHRONIC DISEASES MECHANISTICALLY LINKED TO ROS

Endogenous reactive oxygen species contains the side-effects of cell digestion in oxygen consuming microorganisms. At low focuses, they're normally engaged with various cell metabolism, like multiplication, separation, and apoptosis, similar to a second courier in cell flagging [16]. Reaction oxygen species creation inside cells under physiological condition is subject to mitochondria breath, NOX, uncoupled NOS and XOR.

The expansion in levels of ROS, its creation in unseemly cell compartments or its creation with deficient structures during oxidative cycles can set off the advancement of various constant degenerative issues, prompting serious harm to bio macromolecules [5]. Oxidative pressure, because of the awkwardness among oxidative and antioxidative cycles in cells, in this way assumes a fundamental part in the pathogenesis of various constant degenerative issues.

2. 1. ROS and Cardiovascular Diseases

The major cardiovascular risk factors, for example, hypercholesterolemia and hypertension add to upgrading ROS production, prompting oxidative stress [7]. From every one of these cardiovascular risk factors, hypertension is a fundamental element in the improvement of cardiovascular sicknesses [8]. Reactive oxygen species plays a double part in cardiovascular physiopathology.

Modest quantities of reactive oxygen species in the cardiovascular framework may give surprising advantages: endogenous cardio-protective, pro-angiogenesis and anti-atherosclerotic, impacts [16]. Enormous quantities of reactive oxygen species actuate the deficiency of cell viability, since oxidative stress is engaged with the improvement of CVD, like cardiovascular breakdown, atherosclerosis, arrhythmias myocardial ischemia/reperfusion harm and endothelial disorder [16].

In cardiovascular disease, gene articulation is changed because of oxidative pressure. Expanded reactive oxygen species levels regulate transcription factor movement, particularly NF-κB, activator protein-1 (AP-1) and the peroxisome proliferators-activated receptor (PPAR) group of transcriptional activators [23].

Because of expanding reactive oxygen species production, perhaps the earliest occasion in atherogenesis, and in other CVDs related with endothelial brokenness, is the oxidative alteration of low-density lipoprotein (LDL) [27]. To be sure, both LDL and cell layers,

improved with phospholipids, are profoundly delicate to oxidative change. Oxidized phospholipids, through receptor-mediated or receptor-independent pathways, can thusly then enact endothelial cells, instigate endothelium bond atoms articulation, draw in monocytes, have endothelium cytotoxic impacts, and increment pro-inflammatory quality movement and cell development factors [8]. These cycles incite endothelial brokenness, platelet accumulation, and metalloproteinase articulation and favor thrombogenesis [8].

In atherosclerotic disease, expanded grid metalloproteinase articulation and action set off by oxidative stress cause its break and resulting thrombosis [3]. The NF-κB movement in atherosclerosis is principally because of oxidized low-density lipoprotein [2]. Simultaneously, upregulated NF-κB is recognized in macrophages, endothelial cells, smooth muscle cells, and T cells of atherosclerotic diseases [1].

In the vein wall, every layer can generate reactive oxygen species under neurotic circumstances, and the majority of them are essentially gotten from NOX. Because of expanded ROS levels, NO bioavailability is diminished, and thus, endothelium-subordinate unwinding is decreased [9]. Heart myocytes have a larger number of mitochondria than different cells and utilize increased oxygen levels for energy creation as adenosine triphosphate. In myocytes, reactive oxygen species provoked cardiovascular injury, both oxidizing fundamental proteins for excitation-compression and diminishing NO bioactivity [14].

The mitochondrial electron transport is not balanced in myocardial ischemia, and this leads to the depletion of adenosine triphosphate, mitochondrial depolarization, acidosis, intracellular Ca^{2+} over-burden and apoptosis [10]. Moreover, oxidative pressure created in mitochondria prompts mitochondrial DNA (mtDNA) harm and results in cardiovascular disease. Re-oxygenation and hypoxia induce an expansion in free radicals' creation in cardiovascular tissue in myocardial ischemia [6]. ROS generated during re-oxygenation lead to direct oxidative harm to cell parts and cause roundabout harm via the activation of localized inflammation [8]. In cardiovascular breakdown, unreasonable reactive oxygen species generation depends on expanded action of NOX and XOR [5]. Expanded reactive oxygen species creation is an outcome of drawn out endoplasmic reticulum stress and mitochondrial-determined oxidative pressure in cardio-metabolic disorders.

The capability of these organelles is corresponded with Ca^{2+} delivery and take-up and, because of oxidative pressure, strange Ca^{2+} taking care of can lead to arrhythmias. Moreover, some aggravation in these organelles actuates flagging pathways which modify heart particle channels capability or articulation, engaged with the age of an activity potential that advances arrhythmogenesis [4]. The organization of cytostatics to people is trailed via cardiotoxicity because of expanded plasma levels of reactive oxygen species and lipid peroxidation items and diminished plasma and tissue levels of cell reinforcements. Myocardial alterations that happen after therapy include: loss of myocyte via necrosis or apoptosis, myofibrils loss, distension of the sarcoplasmic reticulum, and mitochondrial inflammation. Research carried out recently on transgenic mice indicates that in cardiotoxicity prompted by Doxorubicin, free revolutionaries can be checked by liensinine and metallothionein [4].

2. 2. ROS and Cancers

The development of cancer in people id a mind boggling process that incorporates sub-atomic and cellular alterations regulated by different exogenous and endogenous stimuli. One of the critical attributes of carcinogenesis has been traced down to oxidative DNA damage [4]. Malignant growth commencement and advancement are related with chromosomal

imperfections and initiation of oncogenes by free extremists [8]. A typical type of damage is the development of hydroxylated DNA bases, considered a significant occasion in compound carcinogenesis. They impede sound cell development by causing hereditary transformations and changing normal transcription of gene. Oxidative sores additionally create many changes in the DNA structure [16].

ROS contribution in an alternate phase of carcinogenesis has been displayed in different model frameworks. Inordinate measures of these free radicals can prompt to cell harm and apoptosis. Many types of malignant growth are viewed as the consequence of free radicals and DNA responses, prompting changes that can influence the cell cycle and lead to neoplasia [10].

The overproduction of ROS affects the cancer cell expansion, metastatic potential and it's related with intrusiveness and poor prognosis [18]. ROS adds to malignant growth cell movement via different mechanisms: (a) matrix debasement, (b) cell to cell contact, (c) cytoskeleton redesigning, modulation of gene articulation, (d) invadopodia development [19].

For instance, ROS derived from mitochondria affects the early extracellular matrix contact, NOX-determined ROS are engaged with invadopodia development. Simultaneously, ROS expansion in cytosol assumes a huge part in cytoskeleton renovating [11]. The impact of ROS on malignant growths relies upon the kind of organ, and on the grade of infection movement.

Skin carcinogenesis and openness to UVA: the ultraviolet component A sunlight (UV-A with the wavelength 320 nm-400 nm) can possibly create oxidative stress in tissues and cells, so exogenous and endogenous cancer prevention agents unequivocally impact the natural impacts of UVA [1]. The physiological dosages of UVA decide the outflow of certain genes (hem oxygenase-1, atomic oncogenes and collagenase), whose impacts can be altogether expanded by eliminating intracellular GSH or by expanding the duration of sub-atomic oxygen. Frequent openness of human skin to UV rays leads not exclusively to skin carcinogenesis, but likewise to photograph maturing through DNA harm.

Hydroxyl radicals can be connected to DNA and generate 8-OH deoxyguanosine (8-OHdG), which thus builds the risk of transformation. 8-OHdG can likewise trigger disease initiating mutagenesis by changing GC matches to TA matches during the replication of DNA [19]. Thusly, 8-OHdG atoms might be utilized as pointers with the expectation of free radicals' discovery during DNA mutagenesis [22]. Also, expanded malignant growth cell multiplication requires increased ATP levels which result in ROS aggregation, especially at beginning phases of cancer genesis.

In cancerous cells, there is the state of steady oxidative stress actuated by mitochondrial brokenness and metabolic alterations. As a matter of fact, under regular conditions, expanded ROS levels invigorate cell mortality, however malignant growth cells defeat that by enacting various oncogenes, which then, at that point, instigate atomic component erythroid 2-related factor 2 (NRF2) articulation. NRF2 is the essential controller of cell endurance that raises malignant growth movement by shielding disease cells from ROS and DNA harm [17].

ROS are embroiled in the progression of cancer, advancing cyclin D1 articulation, extracellular signal-regulated kinase (ERK) and JUN N-terminal kinase (JNK) phosphorylation, and MAPK actuation [26]. Nonetheless, malignant growth cells empower expansion, staying away from ROS-actuated apoptosis, in spite of high mutagenesis.

In neoplastic disorders, ROS enhance lipid peroxidation and protein oxidation. Besides, ROS trigger poisonous protein carbonyls development which essentially affects different proteins or lipids [25]. Likewise, because of lipid peroxidation, cancer cells aggregate items,

for example, 4-hydroxy-2-non-enal, one of the most studied results of phospholipid peroxidation, inferable from its cytotoxicity and reactivity.

2. 3. ROS and Neurodegenerative Disorders

All neuronal groups in the brain are similarly delicate to oxidative pressure. For example, neurons with longer axons and numerous neurotransmitters need lots of energy for axonal vehicle or long haul versatility [11]. High ATP interest, in blend with damaged mitochondria, cause these neuron groups more delicate to degradation [18]. Accurately, dopaminergic neurons are presented to extra oxidative stress created by the dopamine digestion, producing H_2O_2 and dopamine autoxidation, which produces superoxide [16].

Amyotrophic lateral sclerosis, Alzheimer's, Huntington's, Parkinson's, as well as Friedreich's ataxia include the most well-known neurodegenerative problems. At the period of aging, alterations in mtDNA buildup, cytosolic calcium dysregulates, as well as electron transport chain capability diminishes, which makes aging one of the significant risk factors adding to neurodegeneration [14]. The oxidized atoms of DNA, lipids and proteins discovered in the brain tissue of after death patients with neurodegenerative issues feature the function of oxidative stress in these illnesses [18]. One more reason for neurodegenerative sicknesses is a defective utilization of metals by the brain, by the mediation of mutant proteins, framed because of oxidative stress. On account of Alzheimer illness, a protein called amyloid-β (Aβ), comprising of 40 amino acids deposits, is available in every cell of the body, under ordinary, non-poisonous and, surprisingly, useful circumstances, as it’s an organic antioxidant [16].

It has been observed that in adjusted protein developments Aβ plaques, which are shaped on account of Alzheimer's illness outside the impacted neurons, in regions that control mental capabilities, amounts of three, up to multiple times higher than typical Cu, Zn and Fe are fixed [15].

One clarification is the gathering in the brain of an altered type of the Aβ protein (comprising of 42 amino acid buildups), which neglects to appropriately connect metals, advances oxidative cycles; by responding with good reason, neurons produce cell reinforcements in expanded amounts, including the adjusted type of the Aβ protein, which in this way turns into a cancer prevention agent favorable to oxidant, enhancing oxidative fiascos by starting chain responses [23].

Transformations of the superoxide dismutase 1 (SOD1) protein have been connected to another neurodegenerative infection that influences motility (familial amyotrophic sidelong sclerosis) [22]. In its unaltered structure, SOD1 is a characteristic cell reinforcement that forestalls the development of peroxide anion as a risky receptive type of oxygen [27]. The freak types of this protein focus a lot more modest measure of metals than the typical structure, which brings about the development of an overabundance of peroxynitrite ($ONOO^-$) influencing the engine neurons expected for ordinary working, leading to extreme motor issues [22].

The exorbitant utilization of glucose for the generation of energy makes the brain particularly vulnerable to oxidative stress, and mitochondrial electron transport chain is the fundamental origin of ROS. The greater part of the ROS present in the cerebrum get from mitochondrial electron transport chain complex I and III (ETC I and III), as O_2- results [20].

Monoamine oxidase (MAO) is likewise an extraordinary origin of ROS, particularly in Parkinson's. For sure, the principal focuses for mitochondria-derived ROS are mtDNA, mitochondrial permeability transition pore (MPTP), and poly (ADP-ribose) polymerase

(PARP). Other oxidant origins emerge from NADPH oxidase, present in neurons, microglia, and astrocytes, while NOS inhibition makes shown neuroprotective impacts [21].

2. 4. ROS, Diabetes, and Metabolic Syndrome

Numerous metabolic settings can cause states of oxidative stress. A condition where oxidation is a significant pathogenetic interface is type II diabetes. In this illness, insulin obstruction is the fundamental part, to which a compensatory hypersecretion of insulin is connected. ROS can trigger inactivation of flagging mechanisms between insulin receptors and the glucose transport framework, which results in insulin resistance [23].

Then again, diabetes produces oxidative stress, with atherogenetic outcomes. Hyperglycemia actuates the production of superoxide particles in endothelial cells at the mitochondrial level. In diabetes, the transfer of electron and oxidative phosphorylation are disconnected, bringing about the creation of superoxide anions and ineffective synthesis of ATP. Hence, forestalling the harm brought about by oxidation is a helpful procedure in diabetes. Expanded degrees of free unsaturated fats with successive aggregation of intra-myocellular lipids were believed to be the reason for insulin resistance and β-pancreatic cell mortality.

Research has demonstrated that both glucose and free unsaturated fats can start the arrangement of free revolutionaries through mitochondrial components and NADPH oxidase in beta cells, adipocytes, muscles, and other cell types. Free unsaturated fats enter cell organs, including mitochondria, where elevated degrees of ROS have the potential to lead to damage and peroxidation. Ongoing examinations show that insulin resistance and type II diabetes are related with a decline in mitochondrial oxidative capability in skeletal muscle. Additionally, in this kind of diabetes, the mitochondria are more modest, rounder and bound to deliver superoxide. Issues of the mitochondrial ETC, unnecessary production of ROS and lipoperoxides, and diminishes in cell reinforcement systems have likewise been seen in obesity diabetes.

Diabetes has various intricacies over the long run, of which macrovasculopathy is vital. The expansion in cardiovascular risk in patients with diabetes can be made sense of by the relationship between diabetes hypertension, dyslipidemia and coronary atherosclerotic illness. In any case, different mechanisms are additionally involved, like the impacts of hyperglycemia on endothelial capability, the impacts of glucose and unsaturated fats on myocardial cells, at the primary level but also of gene articulation [21].

Diabetic cardiovascular intricacies are brought about by disabled heart microvascular capability. Notwithstanding the primary and useful changes that happen in diabetic cardiomyopathy, different systems can be focused on pharmacologically. Sodium-glucose co-carrier 2 (SGLT2) inhibitors are the top notch of antidiabetic medicates which have diminished the gamble of cardiovascular breakdown in type II diabetes [25]. Empagliflozin has a sign to decrease cardiovascular death in patients with diabetes and atherosclerotic sickness. A new report exhibited the useful impact of empagliflozin on heart microvascular injury in diabetes and the defensive component against oxidative pressure in mitochondria [22].

Another new review indicated that aminoguanidine helpfully affects diabetes-actuated heart irregularities. Aminoguanidine protects contractile irregularities and diabetes-initiated heart remodeling. This was made sense of by inhibition of endoplasmic reticulum stress and acceptance of autophagy [24].

Abdominal obesity, insulin resistance, endothelial dysunction. Atherogenic dyslipidemia, hypercoagulability, hypertension, hypercoagulability, persistent stress and genetic

predisposition are the primary factors underlying the metabolic disorder. Metabolic disorder is many a time portrayed by oxidative pressure, a condition in which there is an unevenness between the creation and inactivation of ROS. Expanded production of ROS, diminished action of antioxidant frameworks or the two components might be engaged with the event of oxidative stress [27].

2. 5. The role of ROS in ageing process

The process of ageing is incomplete without giving an insight into the 60 years old free radical theory of ageing that explains the role of ROS as the major cause of damage in cells and tissues, most especially connective tissues, which is the major cause of several diseases associated with aging related disorders [21]. Apart from the free radical theory of aging, we have a whole lot of theories of aging, but these theories are all center on the generation and overproduction of oxidative stress and the major organ involved in this process is the mitochondria and NOX.

Accumulation of high molecular weight aggregate protein (which might be oxidized or modified by several reactive metabolites) has been associated with ageing process [19], which also has in combination with lipids [15], which functions in the regulation of homeostasis

Proteasome is not functional during aging, although it is the central place for cell damage protein degradation, which identifies unfolded protein as degradation target [10]. Among several functions of proteasome is the inhibition of newly formed oxidized protein and an increase in its aggregation in the cell, but are always dysfunctional during aging [9]. Activation of proteasome has been shown to decrease the process of aging thereby increase longevity [4]. Although, recent researches have shown that several antioxidant supplements has no effect on aging related disorders [6].

3. CONCLUSION

To study the pathogenesis of several disease conditions in human, it is very important to have a deep insight into the molecular mechanism of reactive oxygen specie and oxidative stress, because this will give a deep insight into the proper therapeutic management of such disease.

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