International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Role of Free Radicals in the Pathogenesis of Some Common Diseases

Dr. Chithra V.

Assistant Professor, Department of Biochemistry, NSS College, Pandalam, Kerala, India
Email: *chitra.vasanthakumari[at]gmail.com*

Abstract: ***Free radicals and other oxidants have gained importance in the field of biology due to their central role in various physiological conditions as well as their implication in a diverse range of diseases. Biological free radicals, notably reactive oxygen species (ROS) and reactive nitrogen species (RNS) are derived from both endogenous sources (mitochondria, peroxisomes, endoplasmic reticulum, phagocytic cells etc.) and exogenous sources (pollution, alcohol, tobacco smoke, heavy metals, transition metals, industrial solvents, pesticides, certain drugs like halothane, paracetamol, and radiation). However, when their production overwhelms the body's antioxidant defences, a state of oxidative stress develops. Antioxidants- both enzymatic (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic (e.g., vitamins C and E, glutathione, polyphenols)- serve as critical protective systems that neutralize free radicals and prevent biomolecular damage. Effective antioxidant defences are crucial in mitigating free radical-induced cellular damage and maintaining biological homeostasis. The free radicals induced oxidative stress can damage critical biomolecules including DNA, lipids, and proteins, has been reported to be involved in several diseased conditions such as diabetes mellitus, neurodegenerative disorders (Parkinson's disease-PD, Alzheimer's disease-AD and Multiple sclerosis-MS), cardiovascular diseases (atherosclerosis and hypertension), respiratory diseases (asthma), cataract development, rheumatoid arthritis and in various cancers (colorectal, prostate, breast, lung, bladder cancers). This review deals with the general aspects of free radicals and antioxidant defence mechanism and the role of free radicals in the development of pathogenesis of some common diseases.***

Keywords: Free radicals, Reactive oxygen species (ROS), Reactive nitrogen species (RNS), Oxidative stress, antioxidants, pathogenesis

1. Introduction

Free radicals are the products of normal cellular metabolism. A free radical can be defined as an atom or molecule containing one or more unpaired electrons in valency shell or outer orbit and is capable of independent existence. The odd number of electron(s) of a free radical makes it unstable, short lived and highly reactive. Because of their high reactivity, they can abstract electrons from other compounds to attain stability.[1] Thus the attacked molecule loses its electron and becomes a free radical itself, beginning a chain reaction cascade which finally damages the living cell[2]. Free radicals or pro-oxidants are classified into two types, namely, reactive oxygen species (ROS) and reactive nitrogen species (RNS).

ROS oxidants are classified into superoxide anions (O2•−), peroxyl radicals (ROO•), hydroxyls (OH•), and hydrogen peroxide (H2O2). Representative RNS oxidants are nitrogen oxide (NO•) and peroxynitrite (NO3•) [3,4] refer Reactive oxygen species and reactive nitrogen species (ROS and RNS) were identified as key players in initiating, mediating, and regulating the cellular and biochemical complexity of oxidative stress either as physiological (acting pro-hormetic) or as pathogenic (causing destructive vicious circles) processes [5,6].

Thus, the ROS/RNS play a twofold job as both beneficial and toxic compounds to the living system. At moderate or low levels ROS/RNS have beneficial effects and involve in various physiological functions such as in immune function (i.e. defense against pathogenic microorganisms), in a number of cellular signaling pathways, in mitogenic response and in redox regulation [7,8]. The dual nature of free radicals plays a crucial role in human physiology and pathology. On the one hand, they are vital for normal cellular functions. For instance, free radicals are involved in cell signaling pathways that regulate vascular tone, immune response, and apoptosis. But at higher concentration, both ROS as well as RNS generate oxidative stress and nitrosative stress, respectively, causing potential damage to the biomolecules. The oxidative stress and nitrosative stress are developed when there is an excess production of ROS/RNS on one side and a deficiency of enzymatic and non enzymatic antioxidants on the other side. Most importantly, the excess ROS can damage the integrity of various biomolecules including lipids[9], proteins[10] and DNA [11] leading to increased oxidative stress in various human diseases such as diabetes mellitus, neurodegenerative diseases, rheumatoid arthritis, cataracts, cardiovascular diseases, respiratory diseases as well as in aging process.. There are some non radical species which include hydrogen peroxide (H2O2), hypochlorous acid (HOCl), hypobromous acid (HOBr), ozone (O3), singlet oxygen (1O2), nitrous acid (HNO2), nitrosyl cation (NO+), nitroxyl anion (NO−), dinitrogen trioxide (N2O3), dinitrogen tetraoxide (N2O4), nitronium (nitryl) cation (NO2+), organic peroxides (ROOH), aldehydes (HCOR) and peroxynitrite (ONOOH) [12,13]. These non radical species are not free radicals but can easily lead to free radical reactions in living organisms [14]

Generation of free radicals in biological system

Formation of free radicals is the result of nonenzymatic and enzymatic reactions in tissues involved in the respiratory chain, prostaglandin production, adrenalin autoxidation, phagocytic cells, riboflavin depletion, ischemia, aging, cancer, infections, and mental stress[15]. However, other sources of free radicals can originate within the human body (endogenous) such as the endoplasmic reticulum, mitochondria, and peroxisomes.

Mitochondria are the major organelles in the production of adenosine triphosphate (ATP). The major end product of ROS generation in mitochondria is the superoxide anion radical. Both carbohydrate and fatty acid oxidation pathways are in mitochondria[16]. The process of ATP or energy formation in mitochondria involves the process of electron transport with the help of four enzyme complexes, consisting of complex I, complex II, complex III, and complex IV. Complex III (cytochrome c reductase or ubiquinone) and complex I (NADH dehydrogenase) are the major sites in the electron transport chain where superoxide radical is generated.[17,18,19],The antimycin inhibitor A can be used to detect most of the ROS production in complex III. Reduced ubiquinone is generated by electron transfer from NADH dehydrogenase to coenzyme Q. Consequently, the reduced ubiquinone regenerates coenzyme Q with the semiquinone anion as an intermediate to generate the superoxide anion radical[20]. MAO, cytochrome b5 reductase, NADPH oxidase 4, and dihydroorotate dehydrogenase are part of the mitochondria that may contribute to ROS generation. ROS can lead to the formation of other highly reactive radicals such as singlet oxygen, nitrogen species, and carbonate radicals[21,22] The main factor contributing to ROS production in mitochondria lies in the respiratory process [23]

The circulatory pathway on the peroxisome utilizes electron transfer to generate H2O2. H2O2, O2•−, OH•, and NO• are some of the additional free radicals generated in peroxisomes (Figure 1). The main metabolic mechanism of peroxisomes to produce H2O2 is produced by the oxidation of fatty acids. Several peroxisomal enzymes have been shown to create ROS, including acyl CoA oxidases, D-amino acid oxidases, L-hydroxy oxidases, urate oxidases, xanthine oxidases, and D-aspartate oxidases.[24] Endoplasmic reticulum enzymes such as diamine oxidase, cytochrome p-450, and b5 enzymes enhance ROS generation[25]. Erop1p is a key thiol oxidase enzyme that catalyzes the electron exchange from a dithiol to molecular oxygen to produce H_2O_2 [26].

2. Mechanism of Free Radicals Reactions

Free radical reactions have the following three main stages: initiation, propagation, and termination. In the initiation stage, molecules start a chain reaction and undergo homolysis to form free radical molecules. Free radicals are formed from neutral molecules by the energy from UV light, heating, or free radical initiators[27] . In the propagation stage, free radical molecules react with other neutral molecules to form new free radical molecules[28]. The free radical reaction ends in a termination stage in which two free radicals combine into a neutral molecule[29].

Effect on Biomolecules

Free radicals target essential macromolecules in the body, primarily lipids, nucleic acids, and proteins, causing cellular damage and disrupting homeostasis. This damage can lead to a range of health issues, including accelerated aging and various diseases. The mechanisms by which free radicals exert their effects involve several pathways[30]

Action on lipids

The primary mechanism involved is lipid peroxidation, where free radicals attack polyunsaturated fatty acids in cell membranes [31]. This process begins with the abstraction of a hydrogen atom from the fatty acid, forming a lipid radical. The lipid radical reacts with molecular oxygen to form a lipid peroxyl radical, which can further propagate the chain reaction by abstracting hydrogen atoms from neighbouring fatty acids, leading to a cascade of lipid peroxidation[31]. The end products of lipid peroxidation, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), are highly reactive and can form adducts with proteins and DNA, impairing their function[32]. MDA, a stable end product of polyunsaturated fatty acid (PUFA) decomposition, is measured as an indicator of lipid peroxidation. Elevated levels of MDA have been linked to diseases like cardiovascular conditions, cancer, and neurodegenerative disorders[33]. Similarly, 4-HNE, a highly reactive aldehyde formed during lipid peroxidation, has been implicated in inflammation and aging.

Action on proteins

Protein oxidation is another critical mechanism where free radicals modify amino acid side chains, form protein-protein cross-links, and fragment peptide chains. Such modifications can result in loss of enzymatic activity, altered cellular signalling, and degradation of structural proteins, contributing to cellular dysfunction and death [34,35]. Specific amino acids, such as cysteine and methionine, are particularly susceptible to oxidation, which can disrupt the redox-sensitive signalling pathways and protein function [36].

Action on Nucleic acids

ROS can damage DNA by inducing base modifications, deletions, strand breakage, cross-linking. chromosomal rearrangements and hyper- and hypo-methylation of DNA [37] The hydroxyl radical is especially notorious for causing DNA damage. It can abstract hydrogen atoms from the deoxyribose sugar backbone, leading to strand breaks, or add to the double bonds of DNA bases, resulting in base modifications such as 8-hydroxydeoxyguanosine (8-OHdG) [38]. These modifications can lead to mutations, genomic instability, and if not adequately repaired, contribute to carcinogenesis and other genetic disorders [39].

Free radicals – Role in the pathogenesis of diseases

Free radicals, despite their essential roles in various physiological processes, can cause significant harm when their levels are not properly regulated [40]. An imbalance between free radical production and the body's antioxidant defences leads to oxidative stress, which is implicated in the pathogenesis of numerous diseases [41]. Excessive free radicals can damage cellular components such as lipids, proteins, and DNA, contributing to chronic conditions like cardiovascular diseases, neurodegenerative disorders, cancer, and inflammatory diseases[41,42]. Conversely, insufficient free radical activity can impair the immune response and disrupt cellular signalling.[43]

Cancer

The role of free radicals, particularly ROS and RNS, in the initiation, promotion, and progression of cancer is well-documented. These reactive species can damage DNA, proteins, and lipids, thereby contributing to genomic

instability and tumour development[44].Free radicals cause different types of chemical changes in DNA, thus they could be mutagenic and involved in the etiology of cancer [45,46]. Cancer cells in particular, in comparison to normal cells, have higher levels of ROS and are more susceptible to mitochondrial dysfunction due to their higher metabolic rate[47]. Oxygen and nitrogen reactive species produce damage in the DNA and other biomolecules and play a major role in genetic instability, affecting progression through the cell cycle, cell repair, and the type of cell death (apoptosis, senescence, or autophagy). Free radicals are also important in cell transformation, differentiation, and cell proliferation processes and may be useful for evaluating the tissue inflammatory response. Finally, with respect to carcinogenesis, these radicals have been implicated in tumor progression, angiogenesis, the immune response, and the invasive and metastatic potential of tumor cells [48].

Mutation to genes in the DNA can cause them to make ineffective proteins. A key area where mutation can cause problems is in tumor suppressor genes.[49]

Cancer cells display elevated levels of oxidative stress due to activation of oncogenes and loss of tumor suppressors[50] These series of mutations in tumor suppressor genes and other genes that lead a cancer cell to form. ROS by altering the growth signals and gene expression cause continuous proliferation of cancer cells[51]

The ROS produced are responsible for the cellular proliferation of prostate cancer cells [52]. Prostrate Tumors have considerably higher levels of ROS and Nox1 levels [53]. The superoxide produced (by NOX) in prostate cancer cells facilitates cellular immortality through resistance to programmed cell death which results in cancer-promoting effect [54]

Damage to the breast epithelium by ROS can lead to fibroblasts proliferation, hyperplasia of epithelium, cellular atypia and breast cancer[55]. In majority of breast carcinomas the oxidative stress can be induced by the over expression of thymidine phosphorylase enzyme which catabolizes thymidine to thymine and 2-deoxy-D-ribose-1-phosphate; the latter is a powerful reducing sugar that rapidly glycates proteins, generating oxygen radicals within the carcinoma cell [56]. Different members of the Bcl-2 and Bcl-xL family function as antagonists of ROS production in apoptosis, protecting cells from apoptotic induction by exogenous oxidants. One example of the capacity of ROS to induce apoptosis is the action of surfactin, a lipopeptide produced by B.subtilisc which has antitumor, antimicrobial, and anti-mycoplasma activity that phosphorylates JNK in breast cancer cells (MCF-7). This capacity was demonstrated by using N-acetylcysteine/catalase (antioxidant action) to block ROS, which led to the inhibition of apoptosis in the MCF-7 cells [57]

In colorectal cancer the gastrointestinal tract, particularly the colon and rectum, is continuously exposed to ROS originating from both endogenous and exogenous sources [58] Since the intestinal mucosa is constantly confronting with diet and bacterial-derived oxidants and carcinogens, an unrestrained production of free radicals, redox imbalance, and DNA damage occurs, finally leads to an altered intestinal metabolic homeostasis with cancer as an endpoint [59].

The ROS produced are responsible for the cellular proliferation of prostate cancer cells[60]. Prostrate Tumors have considerably higher levels of ROS and Nox1 levels[53]. The superoxide produced (by NOX) in prostate cancer cells facilitates cellular immortality through resistance to programmed cell death which results in cancer-promoting effect [54]. Oxidative stress plays an important role in lung inflammation and lung cancer [61].

Lungs are the main organ for gaseous exchange in the body, which makes them more vulnerable to ROS exposures. Factors like lifestyle, disease conditions, and medications are known to influence the ROS levels in the lungs. Lifestyle factors regulate ROS levels in different ways, for example, cigarette smoking and occupational hazards introduce exogenous ROS into the body. Reactive oxygen species are known factors of lung carcinogenesis resulting from the xenobiotics and their mechanistic paths are under critical investigation. Air pollution, inhalable agents, and tobacco smoking are a few of the critical factors that determine lung cancer incidence and mortality worldwide. It is estimated that smoking accounts for ~80 % of global lung cancer burden in males and 50 % in females[62]. The ROS can damage the tissues resulting in progressive transformation of cells into the malignant form, which leads to increased frequency of mutations by the oxidative damage to DNA and, eventually leading to lung cancer[63].

The most common risk factors for bladder cancer are cigarette smoking, exposure to industrial carcinogens (aromatic amines), high levels of arsenic intake and diet[64]. Oxidative stress critically contributes to the development of bladder cancer[65]. Increased NO levels have been reported in bladder cancer patients[66]. This NO stimulates matrix metalloproteinases (MMPs), especially prolidase activity, which is involved in the terminal step of collagen degradation. Significantly higher serum prolidase activities were reported in patients with bladder cancer than healthy controls[67]. Therefore, increased prolidase activity may, in part, play a role in the pathogenesis of bladder cancer.

Cardiovascular diseases

In recent years, a multitude of studies provide comprehensive evidence that increased production of reactive oxygen species (ROS) are involved in the development and progression of cardiovascular diseases. Over the last decades, it has become significantly evident that oxidative stress presents a significant role in the pathogenesis of coronary atherosclerosis and its complications[68,69]. Reactive oxygen species are the most likely agents inducing DNA damage in atherosclerosis[70]. ROS generally exist in all aerobic cells in balance with biochemical antioxidants[71]. Recently, increased oxidative stress and impaired antioxidant defence have been suggested as contributory factors for initiation and progression of complications in coronary artery diseases[72]. The ROS are common by- products of many oxidative biochemical and physiological processes. They can be released by mitochondrial respiration, NADH/NADPH oxidase,

xanthine oxido-reductase or the uncoupling of nitric oxide synthase (NOS) in vascular cells. ROS mediate various signalling pathways that underlie cardiovascular pathophysiology. In a number of cardiovascular disease conditions, the delicate equilibrium between free-radical generation and antioxidant defence is altered in favor of the former, thus leading to redox imbalance i.e. escalating oxidative stress and increased tissue injury[73].

A constant supply of oxygen is indispensable for cardiac viability and function. As oxygen is a major determinant of cardiac gene expression and a critical participant in the formation of free radicals commonly known as reactive oxygen species (ROS) which plays a major role in the pathogenesis of cardiac dysfunction[74].In the vascular system, the formation of ROS from endothelial cells, smooth muscle cells and macrophages may be of major relevance in atherogenesis. This oxidative stress is recognised as a key mechanism for atherogenesis and in the development of atherosclerosis[75]. Under normal conditions, numerous cellular antioxidant systems exist to defend against oxidant stress and maintain the redox balance of the cell.

Endothelial cells produce nitric oxide (NO•), a free radical that acts as a vasodilator and inhibits platelet aggregation and adhesion[76]..However, under conditions of oxidative stress, superoxide radicals ($O_2^{\bullet -}$) react with NO• to form $ONOO^-$, reducing the bioavailability of NO• and leading to endothelial dysfunction [77] .This imbalance impairs vasodilation, promotes vasoconstriction, and increases vascular permeability, creating a conducive environment for the infiltration of lipoproteins and immune cells into the arterial wall. The oxidative modification of low-density lipoprotein (LDL) is another critical event in the development of atherosclerosis[78]. Free radicals can oxidize LDL particles, resulting in the formation of oxidized LDL (oxLDL)[79]. OxLDL is taken up by macrophages through scavenger receptors, leading to the formation of foam cells. These foam cells accumulate within the arterial intima, forming fatty streaks—the earliest visible lesions of atherosclerosis[80].

Several studies showed that CAD intensity is closely linked to increased lipid peroxidation and decreased antioxidant status when compared to normal healthy subjects [81,82,83]

Diabetes mellitus

Type I diabetes is caused by destruction of the pancreatic beta cells responsible for producing insulin. In humans, the diabetogenic process appears to be caused by immune destruction of the beta cells; part of this process is apparently mediated by white cell production of active oxygen species[84]. The interplay between hyperglycemia and oxidative stress contributes to the pathogenesis of diabetic complications, including neuropathy, nephropathy, retinopathy, and cardiovascular diseases[85] . Hyperglycemia-induced oxidative stress begins with the excessive production of ROS due to elevated glucose levels. Glucose undergoes autoxidation, producing ROS as by-products.[86.] Furthermore, high glucose levels increase the formation of advanced glycation end products (AGEs) through the non-enzymatic reaction between reducing sugars and cellular proteins, lipids, or nucleic acids. AGEs, in turn, generate ROS through various mechanisms, including metal-catalyzed oxidation reactions. This cascade of oxidative stress can lead to cellular dysfunction and damage, significantly impacting various tissues and organs[87,88].

Mitochondrial dysfunction is another critical aspect of oxidative stress in diabetes. Mitochondria are central to cellular energy production, and their function is intimately linked with ROS generation. In the context of diabetes, chronic hyperglycemia overwhelms the mitochondrial electron transport chain, leading to increased ROS production[89].

Free radicals – An underlying cause for complications in Diabetes

The impact of oxidative stress in diabetes is particularly evident in its complications. Free radical and oxidative stress induced complications from DM include coronary artery disease, Neuropathy, nephropathy, retinopathy and stroke[90]

Oxidative stress is a potent causative factor of diabetic neuropathy[91.92] .It modulates functions of nerve cells through many molecular signalling pathways[92,93].In Diabetic neuropathy, a common complication, is characterized by nerve damage, particularly in the peripheral nervous system. Elevated ROS levels lead to lipid peroxidation, resulting in the formation of toxic aldehydes that damage neuronal membranes[94]. Impaired glucose metabolism in diabetes is a critical mechanism to induce oxidative stress as a result of shunting excess glucose to other metabolic or nonmetabolic pathways[95,96]. This causes accumulation of the toxic metabolites and overconsumption of nicotinic acid adenine dinucleotide phosphate (NADPH)[97] .These converge to increase intracellular redox stress and abnormal modifications on protein [98] lipid [99], and DNA [100] thereby adding mitochondrial injury and causing overproduction of ROS. This damages the peripheral nervous system, as indicated by loss of Schwann cells, myelinated axons, and sensory neurons located in the dorsal root ganglia[92,101,102]

Diabetic nephropathy, another major complication, involves progressive kidney damage that can lead to proteinuria, decreased glomerular filtration rate (GFR), and eventually end-stage renal disease.[103] High glucose upregulates transforming growth factor-β1 (TGF-β1) and angiotensin II (Ang II) in renal cells and high glucose, TGF-β1, and Ang II all generate and signal through ROS. ROS mediate high glucose-induced activation of protein kinase C and nuclear factor-κB in renal cells. Intensive glycemic control and inhibition of Ang II delay the onset and progression of diabetic nephropathy[104] .Increased ROS also activate nuclear factor kappa B (NF-κB), which drives the expression of pro-inflammatory cytokines and adhesion molecules, contributing to renal dysfunction[105] fibrosis

ROS is maintained in equilibrium; however, its overproduction can lead to biological process called oxidative stress and this is considered the main pathogenesis of diabetic retinopathy. The retina is susceptible to ROS because of high-energy demands and exposure to light. When the balance is broken, ROS produces retinal cell injury by interacting with the cellular components. High glucose level and diabetically induced activation of retinal

vascularization is linked with elevation in the enzymatic activity of arginase as well as in the reduction of bioavailability of NO[106.] The over activity of arginase plays an important role in the development of DR through its reducing effect on NO and increase of oxidative stress[107]

In diabetic retinopathy, a major microvascular complication affecting the retina, oxidative stress leads to damage of retinal endothelial cells. Elevated ROS levels increase vascular permeability and leakage of plasma components, contributing to the development of retinopathy[108]. AGEs accumulate in the retina and interact with their receptor, RAGE, triggering inflammatory responses and exacerbating oxidative damage[109]. Additionally, ROS activate the hypoxia-inducible factor-1 alpha (HIF-1α) pathway, leading to increased expression of vascular endothelial growth factor (VEGF) and the formation of retinal neovascularization[110].

Free radicals impact on Ageing process

Ageing is defined as progressive loss of tissue and organ function over time[111.]. The aging process is a complex phenomenon influenced by various factors, including genetic predisposition and environmental influence Aging is marked by a decline in maximum function and the gradual accumulation of mitochondrial DNA mutations, particularly notable in organs with post-mitotic cells, such as the brain. Oxygen radicals are widely believed to contribute to these aging processes. During normal aging, the brain suffers both morphological and functional modifications affecting dendritic trees and synapses, neurotransmitters, brain circulation and metabolism, motor and sensory systems, sleep, memory and learning, and lipofuscin accumulation[112]

According to the free radical theory of aging, the progressive build-up of oxidative radicals plays a pivotal role in cellular aging by inducing damage to cellular components[113] Almost every investigation in this area has shown that the rate of ROS production of mitochondria which have been isolated from post-mitotic tissues including brain is indeed lower in long-lived than in short-lived species[114].The detrimental effects of free radicals include DNA damage, protein cross-linking, and other alterations within the body. An important area where damage can cause problems is in tumour suppressor genes[115]. As time passes, this cumulative damage ultimately leads to the experience of aging[116]. External factors that can elevate ROS include poor diet, alcoholism, smoking and some prescription medication[117]

Free radicals and cataract

A cataract is a clouding of the lens of the eye, which is ordinarily clea [118] Seeing through hazy lenses is similar to gazing through fogged-up or frosted glass for those who have cataracts. Cataract-related visual impairments can make it harder to read, drive (particularly at night), or read a friend's expression. Retinal illnesses such as cataract, age-related macular degeneration (AMD), glaucoma, diabetic retinopathy (DR), and retinal vein occlusion (RVO) are all significantly accelerated by oxidative stress. Overproduction of reactive oxygen species (ROS) can cause abnormalities in the morphology and function of endothelial cells, retinal ganglion cells (RGCs), and retinal pigment epithelium[119].

Free radicals and Neurodegenerative diseases

Free radicals cause oxidative stress, damaging brain cells (neurons) by attacking lipids, proteins, and DNA, which is central to neurodegenerative diseases like Alzheimer's (AD) and Parkinson's (PD). This imbalance between free radicals and the brain's defenses leads to neuronal dysfunction, cell death (apoptosis), inflammation, and the accumulation of damaged proteins, accelerating disease progression and symptoms like cognitive decline or motor impairmen.[120]

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), are characterized by the progressive loss of structure and function of neurons, leading to cognitive and motor impairments[121].

Mitochondrial dysfunction is a central feature of neurodegenerative diseases Mitochondria are both a major source and target of ROS. In these diseases mitochondrial abnormalities, including impaired electron transport chain function and reduced mitochondrial biogenesis, lead to increased ROS production and diminished ATP generation. The resulting energy deficit and oxidative damage to mitochondrial DNA (mtDNA) and proteins further compromise neuronal function and survival[122].

Alzheimer's disease (AD)AD is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein[123].

In Parkinson's disease (PD), oxidative stress is closely associated with the degeneration of dopaminergic neurons in the substantia nigra. Oxidative stress contributes to PD pathogenesis through multiple mechanisms, including mitochondrial dysfunction, protein misfolding, and neuroinflammation[124].· Additionally, the metabolism of dopamine by monoamine oxidase (MAO) produces hydrogen peroxide (H_2O_2), which can be converted to highly reactive hydroxyl radicals via Fenton reactions in the presence of transition metals[125].

In Huntington's disease (HD), oxidative stress plays a significant role in the neurodegenerative process. HD is caused by an expanded CAG repeat in the huntingtin (HTT) gene, leading to the production of a mutant huntingtin protein with toxic gain-of-function properties. The mutant huntingtin protein can disrupt mitochondrial function and increase ROS production[126].

Amyotrophic lateral sclerosis (ALS) is another neurodegenerative disease where oxidative stress plays a central role. ALS is characterized by the progressive loss of motor neurons, leading to muscle weakness and paralysis. Mutations in the superoxide dismutase 1 (SOD1) gene are associated with familial forms of ALS[127].SOD1 is an enzyme that catalyzes the dismutation of superoxide radicals into hydrogen peroxide and oxygen, providing a crucial antioxidant defense. Mutant SOD1 proteins can form toxic aggregates and lose their enzymatic activity, leading to increased oxidative stress [128]. Elevated levels of oxidative damage markers, such as 8-OHdG and protein carbonyls, have been detected in ALS patients.. Additionally, the

activation of microglia and astrocytes in ALS leads to the production of ROS and pro-inflammatory cytokines, further exacerbating oxidative damage and motor neuron degeneration [129]

Autoimmune diseases

Autoimmune diseases arise when the body's immune system mistakenly attacks its own tissues, recognizing them as foreign. Free radicals, especially Reactive Oxygen Species (ROS), significantly worsen autoimmune diseases by causing oxidative stress, which damages cells, modifies proteins into foreign-like "neo-antigens" that trigger immune attacks, promotes chronic inflammation, and disrupts immune cell function, contributing to conditions like Rheumatoid Arthritis and Lupus by creating a vicious cycle of damage and auto-reactivity[130] .The role of ROS in autoimmune response remains complex and they have been implicated in the initiation, generation, and amplification of novel epitopes [131].

One of the key mechanisms by which free radicals contribute to autoimmune diseases is through the modification of self-antigens[132]. Oxidative stress can induce structural changes in proteins and other molecules, creating neo-antigens that are recognized as foreign by the immune system [133].

In addition to modifying self-antigens, free radicals can directly damage tissues, triggering inflammation and immune activation[134]. Oxidative stress can lead to lipid peroxidation, a process in which ROS react with lipids in cell membranes, resulting in the formation of lipid peroxides and aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [135]. These reactive aldehydes can form adducts with proteins, further contributing to neo-antigen formation and immune activation. The resulting inflammation and tissue damage can perpetuate the autoimmune response, creating a vicious cycle of oxidative stress and immune-mediated tissue injury [136]. Elevated levels of ROS and oxidative damage markers, such as 8-OHdG and MDA, have been detected in the synovial fluid and tissues of Rheumatoid Arthritis [RA] patients[137].

In autoimmune diseases such as systemic lupus erythematosus (SLE), mitochondrial damage and the release of mitochondrial DNA (mtDNA) into the cytoplasm and extracellular space have been observed[138] .Extracellular mtDNA can act as a damage-associated molecular pattern (DAMP), triggering the activation of innate immune receptors such as toll-like receptors (TLRs) and inducing the production of type I interferons (IFNs)[139] .The chronic activation of the type I IFN pathway is a hallmark of SLE and contributes to the dysregulation of immune responses in this disease[140].

The role of oxidative stress in the activation and function of immune cells is also critical in autoimmune diseases [133].[141] ROS can modulate the activity of various transcription factors and signalling pathways involved in immune cell activation, differentiation, and function. For example, ROS can activate nuclear factor kappa B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules[142] .Chronic activation of NF-κB by oxidative stress can lead to sustained inflammation and the perpetuation of autoimmune responses[143] .Additionally, ROS can influence the differentiation and function of T cells, promoting the polarization of T helper 17 (Th17) cells, which are known to play a pathogenic role in autoimmune diseases such as multiple sclerosis (MS) and psoriasis[144] .Oxidative stress is integral in driving Th17 cell differentiation by modulating key transcription factors, such as RORγt, and cytokines like IL-6, IL-23, and TGF-β[145]. Additionally, ROS can impair the function of Tregs, reducing their ability to suppress autoreactive T cells and control immune responses. This disruption of immune tolerance contributes to the development and progression of autoimmune diseases[146].

Chronic inflammation, often driven by oxidative stress, is a common feature of autoimmune diseases. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) are elevated in many autoimmune diseases and contribute to the inflammatory milieu [147] .ROS can enhance the production of these cytokines by activating transcription factors like NF-κB and AP-1, creating a feed-forward loop that amplifies inflammation and tissue damage. The persistent inflammatory environment not only exacerbates oxidative stress but also promotes the recruitment and activation of additional immune cells, further perpetuating the autoimmune response[134].

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system, characterized by demyelination and neurodegeneration. Oxidative stress plays a critical role in MS by promoting inflammation, mitochondrial dysfunction, and neurodegeneration.[148]. Elevated levels of ROS and oxidative damage markers have been detected in the brains and cerebrospinal fluid of MS patients[149]. ROS can damage myelin and oligodendrocytes, the cells responsible for myelin production, leading to demyelination. Additionally, oxidative stress can activate microglia and astrocytes, contributing to neuroinflammation and further neuronal damage[144,150].

Lung Diseases

Free radicals cause significant lung damage by overwhelming antioxidant defences, leading to oxidative stress, which damages cell membranes, proteins, and DNA, contributing to chronic diseases like COPD, emphysema, asthma, and lung cancer. They are generated by smoking, pollution, and infection, triggering inflammation and cellular destruction, especially damaging elastin in emphysema, and acting as carcinogens in cancer development, with imbalances leading to serious respiratory illness.[151].

In the respiratory system, ROS may be either exogenous from more or less exhalative gaseous or particulate agents such as air pollutants, cigarette smoke, ambient high-altitude hypoxia, and some occupational dusts, or endogenously generated in the context of defense mechanisms against such infectious pathogens as bacteria, viruses, or fungi. ROS may also damage body tissues depending on the amount and duration of exposure and may further act as triggers for

enzymatically generated ROS released from respiratory, immune, and inflammatory cells. [151].

The increased oxidative burden in COPD may contribute to a range of pathogenic processes starting with inactivation of antiproteases; enhancing bronchial inflammation by activating redox-sensitive transcription factors; mucus gland hyperplasia and hypersecretion; corticosteroid resistance; enhanced senescence; activation of neutrophils, macrophages, and fibroblasts; abnormal airway T-cell population; and small airway fibrosis culminating in direct damage to respiratory cells (apoptosis) with defective regeneration[152,153].

Role of antioxidants in managing these diseases

Antioxidants like B-carotene or vitamin E play a vital role in the prevention of various cardiovascular diseases[154].

Antioxidants can decrease oxidative stress induced carcinogenesis by a direct scavenging of ROS and/or by inhibiting cell proliferation secondary to the protein phosphorylation. B-carotene may be protective against cancer through its antioxidant function, because oxidative products can cause genetic damage. Thus, the photo protective properties of B-carotene may protect against ultraviolet light induced carcinogenesis. Immunoenhancement of B-carotene may contribute to cancer protection. B-carotene may also have anticarcinogenic effect by altering the liver metabolism effects of carcinogens[155].Vitamin C may be helpful in preventing cancer[156]. The possible mechanisms by which vitamin C may affect carcinogenesis include antioxidant effects, blocking of formation of nitrosamines, enhancement of the immune response, and acceleration of detoxification of liver enzymes. Vitamin E, an important antioxidant, plays a role in immunocompetence by increasing humoral antibody protection, resistance to bacterial infections, cell-mediated immunity, the T-lymphocytes tumor necrosis factor production, inhibition of mutagen formation, repair of membranes in DNA, and blocking micro cell line formation[157.] Hence vitamin E may be useful in cancer prevention and inhibit carcinogenesis by the stimulation of the immune system.

Reduction of free radicals or decreasing their rate of production may delay aging. Some of the nutritional antioxidants will retard the aging process and prevent disease. Based on these studies, it appears that increased oxidative stress commonly occurs during the aging process, and antioxidant status may significantly influence the effects of oxidative damage associated with advancing age. Research suggests that free radicals have a significant influence on aging, that free radical damage can be controlled with adequate antioxidant defense, and that optimal intake of antioxidant nutrient may contribute to enhanced quality of life. Recent research indicates that antioxidant may even positively influence life span.[158]

Many antioxidant compounds, naturally occurring in plant sources have been identified as free radical or active oxygen scavengers[159]. Attempts have been made to study the antioxidant potential of a wide variety of vegetables like potato, spinach, tomatoes, and legumes[160]. There are several reports showing antioxidant potential of fruits.[161]. Strong antioxidants activities have been found in berries, cherries, citrus, prunes, and olives. Green and black teas have been extensively studied in the recent past for antioxidant properties since they contain up to 30% of the dry weight as phenolic compounds[162].

3. Conclusion

Free radicals are highly reactive molecules with unpaired electrons that play a dual role in human health. While essential for some physiological processes, an imbalance between free radical production and the body's ability to manage these reactive species leads to oxidative stress. This condition is implicated in various chronic diseases, including cardiovascular disorders, cancer, diabetes mellitus, aging, cataract, neurodegenerative diseases, autoimmune conditions, and lung diseases.

The impact of oxidative stress is profound, causing damage to lipids, proteins, and DNA, which disrupts cellular function and contributes to disease progression. In cardiovascular diseases, oxidative stress exacerbates endothelial dysfunction and atherosclerosis. In neurodegenerative conditions, it leads to neuronal damage and cognitive decline. Cancer is often driven by oxidative DNA damage, and autoimmune diseases can result from chronic oxidative stress-induced inflammation. Diabetes mellitus complications, such as neuropathy and retinopathy, are also linked to oxidative stress. An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage. Antioxidants act as radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal-chelating agents. Both enzymatic and nonenzymatic antioxidants exist in the intracellular and extracellular environment to detoxify ROS

References

[1] Alugoju Phaniendra , Dinesh Babu Jestad, Latha Periyasamy.Free Radicals: Properties, Sources, Targets, and Their Implication in Various Diseases. Indian J Clin Biochem. 2014. Jul 15;30(1) p :11–26.
[2] Phaniendra A., Jestadi D. B., and Periyasamy L.. Free radicals: properties, sources, targets, and their implication in various diseases. Indian Journal of Clinical Biochemistry.2015 ;30(1) p: 11–26.
[3] Apak R., Calokerinos A., Gorinstein S., Segundo M., Hibbert D., Gülçin İ., Demirci Çekiç S., Güçlü K., Özyürek M., Çelik S., Magalhães L., and Arancibia-Avila P., Methods to evaluate the scavenging activity of antioxidants toward reactive oxygen and nitrogen species (IUPAC Technical Report). Pure and Applied Chemistry.2022; 94(1)p: 87–144.
[4] Sies H., Belousov V. V., Chandel N. S., Davies M. J., Jones D. P., Mann G. E., Murphy M. P., Yamamoto M., and Winterbourn C. Defining roles of specific reactive oxygen species (ROS) in cell biology and physiology. Nature Reviews Molecular Cell Biology. 2022; 23(7) p: 499–515,

[5] Neven Zarkovic . Roles and Functions of ROS and RNS in Cellular Physiology and Pathology. Cells. 2020 ;;9(3) p:767.
[6] Gomberg M. An Incidence of Trivalent Carbon Trimethylphenyl. J Am Chem Soc. 1900; 22 p:757–771.
[7] Valko M, Leibfritz D, Moncola J, Cronin MT, Mazura M, Telser J. Review Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39 (1) p :44–84.
[8] Nordberg J, Arner EJ. Reactive oxygen species, antioxidants, and the mammalian Thioredoxin system. Free Radical Biol Med. 2001;31(11) p:1287–1312
[9] Yla-Herttuala S. Oxidized LDL and atherogenesis. Ann N Y Acad Sci. 1999;874 p:134–137
[10] Stadtman ER, Levine RL. Protein oxidation. Ann N Y Acad Sci. 2000; 899 p :191–208.
[11] Marnett LJ. Oxyradicals and DNA damage. Carcinogenesis. 2000;21(3) p:361–370.
[12] Kohen R, Nyska A. Invited review Oxidation of Biological Systems: Oxidative Stress Phenomena, Antioxidants, Redox Reactions, and Methods for Their Quantification. Toxicol Pathol. 2002;30(6) p:620–650.
[13] Halliwell B. Free Radicals and other reactive species in disease. Nature Encyclopedia of life sciences. 2001; p: 1–7.
[14] Genestra M. Oxyl radicals, redox-sensitive signalling cascades and antioxidants. Review Cell Signal. 2007;19(9) p:1807–1819.
[15] Phaniendra A., Jestadi D. B., and Periyasamy L., Free radicals: properties, sources, targets, and their implication in various diseases, Indian Journal of Clinical Biochemistry. 2015; 30, no. 1, p:11–26,
[16] Morant-Ferrando B., Jimenez-Blasco D., Alonso-Batan P., Agulla J., Lapresa R., Garcia-Rodriguez D., Yunta-Sanchez S., Lopez-Fabuel I., Fernandez E., Carmeliet P., Almeida A., Garcia-Macia M., and Bolaños J. Fatty acid oxidation organizes mitochondrial supercomplexes to sustain astrocytic ROS and cognition. Nature Metabolism. 2023; 5(8),p: 1290–1302.
[17] Wong H., Dighe P. A., Mezera V., Monternier P., and Brand M. D. Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions Journal of Biological Chemistry.2017; 292(41) p: 16804–16809
[18] Kausar S., Wang F., and Cui H., The role of mitochondria in reactive oxygen species generation and its implications for neurodegenerative diseases. Cells. 2018; 7(12), p: 274–319
[19] Duong Q., Levitsky Y., Dessinger M., Strubbe-Rivera J. O., and Bazil J. N. Identifying site-specific superoxide and hydrogen peroxide production rates from the mitochondrial electron transport system using a computational strategy. Function. 2021; 2(6)
[20] Ohnishi T., Ohnishi S., and Salerno J. C., Five decades of research on mitochondrial NADH-quinone oxidoreductase (complex I), Biological Chemistry. 2018; 399(11) p: 1249–1264.
[21] Ahmadinejad F., Geir Møller S., Hashemzadeh-Chaleshtori M., Bidkhori G., and Jami M.-S. Molecular mechanisms behind free radical scavengers' function against oxidative stress. Antioxidants.2017; 6(3) p: 51–15,
[22] Zeb A. Ellagic acid in suppressing in vivo and in vitro oxidative stresses, Molecular and Cellular Biochemistry.2018; 448(1-2) p: 27–41
[23] Nisansala Chandimali, Seon Gyeong Bak, Eun Hyun Park, Hyung-Jin Lim, Yeong-Seon Won, Eun-Kyung Kim, Sang-Ik Park & Seung Jae Lee. Free radicals and their impact on health and antioxidant defenses: a review Cell Death Discovery 2025.
[24] Mukherji SM, Singh SP. Reaction mechanism in organic chemistry. Madras: Macmillan IndiaPress; 1986.
[25] Giuseppina Barrera, Stefania Pizzimenti, Martina Daga, Chiara Dianzani, Alessia Arcaro, Giovanni Paolo Cetrangolo, Giulio Giordano, Marie Angele Cucci, Maria Graf, Fabrizio Gentile Lipid Peroxidation-Derived Aldehydes, 4-Hydroxynonenal and Malondialdehyde in Aging-Related Disorders.Antioxidants (Basel). 2018 ;7(8) p:102
[26] Nisansala Chandimali, Seon Gyeong Bak, Eun Hyun Park, Hyung-Jin Lim, Yeong-Seon Won, Eun-Kyung Kim, Sang-Ik Park, Seung Jae Lee. Free radicals and their impact on health and antioxidant defenses: a review. Cell Death Discov. 2025.
[27] Domínguez R, Pateiro M, Munekata PES, Zhang W, Garcia-Oliveira P, Carpena M, et al. Protein oxidation in muscle foods: a comprehensive review. Antioxid (Basel). 2021.
[28] Höhn A, König J, Grune T. Protein oxidation in aging and the removal of oxidized proteins. J Proteom. 2013;92 p:132–59.
[29] Gu SX, Stevens JW, Lentz SR. Regulation of thrombosis and vascular function by protein methionine oxidation. Blood. 2015;125 p:3851–9.
[30] Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. Role of oxygen radicals in DNA damage and cancer incidence. Mol Cell Biochem. 2004;266(1–2) p:37–56.
[31] Nowell PC. The clonal evolution of tumor cell populations. Science 1976; 194, p:23–8
[32] Jung Joo Moon 1, Alexander Lu 1, Chulso Moon 1,2, Role of genomic instability in human carcinogenesis Exp Biol Med (Maywood). 2019 Feb 13;244(3) p:227–240.
[33] Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem. 2015;30, p:11–26
[34] Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010;4, p:118–26
[35] Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci. 2008; (4) p:89–96.
[36] Lynne Eldridge . Free Radicals: Definition, Cause, and Role in Cancer, MD Updated on March 21, 2025.
[37] Zhao Y, Ye X, Xiong Z, Ihsan A, Ares I, Martínez M, et al. Cancer metabolism: the role of ROS in DNA damage and induction of apoptosis in cancer cells. Metabolites. 2023;13. p:796.

[38] Goldstein BD, Witz G. Free radicals and carcinogenesis. Free Radic Res Commum. 1990;11(1–3)p:3–10
[39] Dreher D, Junod AF. Role of oxygen free radicals in cancer development. Eur J Cancer. 1996;32 (1) p:30–38.
[40] Acuna UM, Wittwer J, Ayers S, Pearce CJ, Oberlies NH, De Blanco EJ. Effects of (5Z)-7-Oxozeaenol on the Oxidative pathway of cancer cells. Anticancer Res. 2012;32(7) p:2665–2671
[41] Sandra Ríos-Arrabal, Francisco Artacho-Cordón, Josefa León, Elisa Román-Marinetto, María del Mar Salinas-Asensio, Irene Calvente, Maria Isabel Núñez. Involvement of free radicals in breast cancer Springerplus. 2013 ;2, p:404
[42] Jiang D, Rusling JF. Oxidation Chemistry of DNA and p53 Tumor Suppressor Gene. Chemistry Open. 2019;8(3) p:252-265
[43] Cairns RA, Harris I, McCracken S, Mak TW. Cancer cell metabolism. Cold Spring Harb Symp Quant Biol. 2011;76, p:299–311.
[44] Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal hitological functions and human disease. Int J Biochem Cell Biol. 2007;39(1) p:44–84.
[45] Arnold RS, He J, Remo A, Ritsick D, Yin-Goen Q, Lambeth JD, et al. Nox1 expression determines cellular reactive oxygen and modulates c-fos-induced growth factor, interleukin-8, and Cav-1. Am J Pathol. 2007;171(6) p:2021–2032
[46] Lim SD, Sun C, Lambeth JD, Marshall F, Amin M, Chung L, et al. Increased Nox1 and hydrogen peroxide in prostate cancer. Prostate. 2005;62(2) p:200–207.
[47] Brar SS, Corbin Z, Kennedy TP, Hemendinger R, Thornton L, Bommarius B, et al. NOX5 NAD(P)H oxidase regulates growth and apoptosis in DU 145 prostate cancer cells. Am J Physiol Cell Physiol. 2003;285(2) p:C353–C369
[48] Murrell TG. Epidemiological and biochemical support for a theory on the cause and prevention of breast cancer. Med Hypotheses. 1991;36(4) p:389–396.
[49] Brown NS, Jones A, Fujiyama C, Harris AL, Bicknell R. Thymidine phosphorylase induces carcinoma cell oxidative stress and promotes secretion of angiogenic factors. Cancer Res. 2000;60(22) p:6298–6302.
[50] Cao X-h, Wang A-h, Wang C-l, Mao D-z, Lu M-f, Cui Y-q, Jiao R-z. Surfactin induces apoptosis in human breast cancer MCF-7 cells through a ROS/JNK-mediated mitochondrial/caspase pathway. Chemico-biological interactions. 2010;183(3) p:357–362.
[51] Blau S, Rubinstein A, Bass P, Singaram C, Kohen R. Differences in the reducing power along the rat GI tract: lower antioxidant capacity of the colon. Mol Cell Biochem. 1999;194(1–2) p:185–191.
[52] Guz J, Foksinski M, Siomek A, Gackowski D, Rozalski R, Dziaman T, et al. The relationship between 8-oxo-7,8-dihydro-2-deoxyguanosine level and extent of cytosine methylation in leukocytes DNA of healthy subjects and in patients with colon adenomas and carcinomas. Mutat Res. 2008;640(1–2) p :170–173.
[53] Azad N, Rojanasakul Y, Vallyathan V. Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. J Toxicol Environ Health. 2008;11(1) p:1–15.
[54] K N ArulJothi , K Kumaran 1, Sowmya Senthil, A B Nidhu, Nashita Munaff V B Janitri Rangasamy Kirubakaran, Sachin Kumar Singh, Gaurav Gupt , Kamal Dua , Anand Krishnan Implications of reactive oxygen species in lung cancer and exploiting it for therapeutic interventions. Med Oncol. 2022;40(1) p:43.
[55] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2) p:69–90.
[56] Hoagland LF 4th, Campa MJ, Gottlin EB, Herndon 2nd JE, Patz Jr EF. Haptoglobin and posttranslational glycan-modified derivatives as serum biomarkers for the diagnosis of non-small cell lung cancer. Cancer. 2007;110(10) p:2260–2268.
[57] Wynder EL, Goldsmith R. The epidemiology of bladder cancer: a second look. Cancer. 1977;40, p:1246–1268
[58] Opanuraks J, Boonla C, Saelim C, Kittikowit W, Sumpatanukul P, Honglertsakula C, et al. Elevated urinary total sialic acid and increased oxidative stress in patients with bladder cancer. Asian Biomedicine. 2010;4(5) p:703–710.
[59] Eijan AM, Piccardo I, Riveros MD, Sandes EO, Porcella H, Jasnis MA, et al. Nitric oxide in patients with transitional bladder cancer. J Surg Oncol. 2002;81,p:203–208.
[60] Gecit I, Aslan M, Gunes M, Pirincci N, Esen R, Demir H, et al. Serum prolidase activity, oxidative stress, and nitric oxide levels in patients with bladder cancer. J Cancer Res Clin Oncol. 2012;138(5) p:739–743.
[61] Supriya Simon, V Chithra, Anoop Vijayan, Roy D Dinesh and T Vijayakumar. Altered DNA repair, oxidative stress and antioxidant status in coronary artery disease . J. Biosci. 2013;38(2) p: 385–389
[62] Cervantes Gracia K, Llanas-Cornejo D, Husi H. CVD and oxidative stress. J Clin Med. 2017;6, p:22.
[63] Mahmoudi M, Mercer J and Bennett M. DNA damage and repair in atherosclerosis. Cardiovasc. Res. 2006; 71, p: 259–268.
[64] A Supriya Simon, T Vijayakumar. Molecular Studies on Coronary Artery Disease—A Review.Indian J Clin Biochem. 2013;28(3) p:215–226.
[65] Akila D, Souza B, Prashant V and D'Souza V Oxidative injury and antioxidants in coronary artery bypass graft surgery:Off pump CABG significantly reduces oxidative stress. Clin.Chem. Acta 2007;375, p: 147–152
[66] Sanjib Bhattacharya 1 .K. Mueen Ahmed 2 Subhankar Chakraborty 3 Free Radicals Cardiovascular Diseases: An Update. Free Radicals and Antioxidants 20111;(1) p: 17-2].
[67] Frank J Giordano. Oxygen, oxidative stress, hypoxia, and heart failure. J Clan Invest. 2005 ;115(3) p:500–508.
[68] Matthew Batty, Martin R Bennett, Emma Yu. The Role of Oxidative Stress in Atherosclerosis. Cells 2022 ;11(23) p:3843.

[69] Cyr AR, Huckaby LV, Shiva SS, Zuckerbraun BS. Nitric oxide and endothelial dysfunction. Crit Care Clin. 2020;36, p:307–21.
[70] Janaszak-Jasiecka A, Płoska A, Wierońska JM, Dobrucki LW, Kalinowski L. Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. Cell Mol Biol Lett. 2023;28,p:21.
[71] Maiolino G, Rossitto G, Caielli P, Bisogni V, Rossi GP, Calò LA. The role of oxidized low-density lipoproteins in atherosclerosis: the myths and the facts. Mediators Inflamm. 2013;2013, p:714653.
[72] Poznyak AV, Nikiforov NG, Markin AM, Kashirskikh DA, Myasoedova VA, Gerasimova EV, et al. Overview of OxLDL and its impact on cardiovascular health: focus on atherosclerosis. Front Pharm. 2020;11, p:613780.
[73] Mushenkova NV, Bezsonov EE, Orekhova VA, Popkova TV, Starodubova AV, Orekhov AN. Recognition of oxidized lipids by macrophages and its role in atherosclerosis development. Biomedicines. 2021;9 p:915.
[74] Supriya Simon, Anoop Vijayan, V. Chithra, T. Vijayakumar, Evaluation of Oxidativestress and Antioxidant status in Coronary artery disease patients with smoking and/or alcoholism, Pushpagiri Med. J. 2011; 3,p:25–28.
[75] V. Chithra, A. Supriya Simon, Anoop Vijayan, Rajan Joseph Manjuran, A study toevaluate the severity of coronary artery disease (CAD) in relation to oxidative stressand antioxidant status, Int. J. Health Sci. 2015; 2, p :242–247.
[76] Anoop Vijayan , V. Chithra , C. Sandhya . The relationship of lipid peroxidation and antioxidant status to selected modifiable risk factors in coronary artery disease patients. International Journal of Healthcare Sciences 2015 ; 2(2), p: 242-247.
[77] L W Oberley. Free radicals and diabetes. Free Radic Biol Med. 1988;5(2) p:113-24.
[78] Caturano A, D'Angelo M, Mormone A, Russo V, Mollica MP, Salvatore T, et al. Oxidative stress in type 2 diabetes: impacts from pathogenesis to lifestyle modifications. Curr Issues Mol Biol..2023;45, p:6651–66.
[79] González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. Int J Mol Sci. 2023;24, p:9352.
[80] Khalid M, Petroianu G, Adem A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. Biomolecules. 2022;12, p:542.
[81] Uceda AB, Mariño L, Casasnovas R, Adrover M. An overview on glycation: molecular mechanisms, impact on proteins, pathogenesis, and inhibition. Biophys Rev. 2024;16, p:189–218.
[82] Zhang Z, Huang Q, Zhao D, Lian F, Li X, Qi W. The impact of oxidative stress-induced mitochondrial dysfunction on diabetic microvascular complications. Front Endocrinol (Lausanne). 2023;14, p:1112363
[83] Ullah Asmat a, Khan Abad a, Khan Ismail b. Diabetes mellitus and oxidative stress—A concise review. Saudi Pharm J. 2015;24(5) p:547–553.
[84] Feldman E. L., Callaghan B. C., Pop-Busui R., et al. Diabetic neuropathy. Nature Reviews Disease Primers. 2019;5(1)
[85] Feldman E. L., Nave K. A., Jensen T. S., Bennett D. L. H. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. Neuron. 2017;93(6) p:1296–1313.
[86] Fernyhough P., McGavock J. Mechanisms of disease: mitochondrial dysfunction in sensory neuropathy and other complications in diabetes. Handbook of Clinical Neurology. 2014;126, p:353–377.
[87] Pang L, Lian X, Liu H, Zhang Y, Li Q, Cai Y, et al. Understanding diabetic neuropathy: focus on oxidative stress. Oxid Med Cell Longev. 2020;2020, p:9524635.
[88] Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865) p:813–820.
[89] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–1625. doi: 10.2337/diabetes.54.6.1615. [DOI] [PubMed] [Google Scholar
[90] Lei Pang 1, Xin Lian 2, Huanqiu Liu 1, Yuan Zhang 1, Qian Li 3, Yin Cai 4, Haichun Ma 1,✉, Xin Yu Understanding Diabetic Neuropathy: Focus on Oxidative Stress,. Oxid Med Cell Longev. 2020 Jul 31;2020:9524635. doi: 10.1155/2020/9524635]T
[91] Ott M., Gogvadze V., Orrenius S., Zhivotovsky B. Mitochondria, oxidative stress and cell death. Apoptosis. 2007;12(5) p:913–922.
[92] Vincent A. M., Hayes J. M., McLean L. L., Vivekanandan-Giri A., Pennathur S., Feldman E. L. Dyslipidemia-induced neuropathy in mice: the role of oxLDL/LOX-1. Diabetes. 2009;58(10) p :2376–2385.
[93] Guo K., Elzinga S., Eid S., et al. Genome-wide DNA methylation profiling of human diabetic peripheral neuropathy in subjects with type 2 diabetes mellitus. Epigenetics. 2019;14(8) p:766–779.
[94] Chowdhury S. K. R., Smith D. R., Fernyhough P. The role of aberrant mitochondrial bioenergetics in diabetic neuropathy. Neurobiology of Disease. 2013;51 p :56–65.
[95] Fernyhough P. Mitochondrial dysfunction in diabetic neuropathy: a series of unfortunate metabolic events. Current Diabetes Reports. 2015;15(11)
[96] Natesan V, Kim SJ. Diabetic nephropathy - a review of risk factors, progression, mechanism, and dietary management. Biomol Ther (Seoul). 2021;29 p:365–72.
[97] B. Lee, J.Y. Seo, M.R. Yu, S.-T. Uh, H. Ha. Radical approach to diabetic nephropathy. Kidney 2007; 72(106) p: S67-S70
[98] Na Ren, Wen-Feng Wang, Liang Zou, Yan-Long Zhao , Hua Miao , Ying-Yong Zhao The nuclear factor kappa B signaling pathway is a master regulator of renal fibrosis .Front Pharmacol. 2024;;14, p:1335094.
[99] Patel C, Rojas M, Narayanan SP, Zhang W, Xu Z, Lemtalsi T et al. Arginase as a mediator of diabetic retinopathy. Front Immunol 2013; 4 p: 173.
[100] G D Calderon, O H Juarez, G E Hernandez, S M Punzo, Z D De la Cruz . Oxidative stress and diabetic

retinopathy: development and treatment . Eye (Lond). 2017 ;31(8) p:1122–1130.
[101] Haydinger CD, Oliver GF, Ashander LM, Smith JR. Oxidative stress and its regulation in diabetic retinopathy. Antioxid (Basel). 2023;12, p:1649.
[102] Dong H, Zhang Y, Huang Y, Deng H. Pathophysiology of RAGE in inflammatory diseases. Front Immunol. 2022;13, p :931473.
[103] Garber D, Zhu S. Implications of caspase 1/ interleukin-1 beta (IL-1β) signaling and hypoxia-inducible factor 1-alpha (HIF-1α) on diabetic retinopathy pathology. Cureus. 2023;15, p : 42479
[104] Singh Sunita D, Choudhury Manashwini, Singh Devanshi, Singh Daulat,, Gogoi Javin,Bishnu. Effect of Free Radicals on Ageing Process in Human Health. International Journal of Pharmaceutical and Clinical Research 2024; 16(1) p; 1612-1629]
[105] Timiras PS. Physiological basis of aging and geriatrics. CRC Press; 2007.
[106] Barja G. Free radicals and aging. Trends in Neurosciences. 2004;27(10) p :595–600.
[107] Barja G. Aging in vertebrates, and the effect of caloric restriction: a mitochondrial free radical production–DNA damage mechanism?. Biological Reviews. 2004 May; 79(2):235-51.
[108] Jiang D, Rusling JF. Oxidation Chemistry of DNA and p53 Tumor Suppressor Gene. ChemistryOpen. 2019 ; 8(3) p:252–65.
[109] Stibich M. The Free Radical Theory of Aging [Internet]. Verywell Health. Verywell Health; 2007.
[110] Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative stress: harms and benefits for human health. Oxidative medicine and cellular longevity. 2017.
[111] Rao GN, Khanna R, Payal A. The global burden of cataract. Curr Opin Ophthalmol. 2011;22(1) p :4-9.
[112] Nsonwu, Ozims S and Nnodim JK. Perspective of Cataract and Oxidative Stress. Series of Clinical and Biomedical Research. Open Access 2024; Vol 1(1)
[113] B Halliwell Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment Drugs Aging. 2001;18(9) p :685-716.
[114] Hui-Ming Gao, Jau-Shyong Hong. Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression .Trends Immunol. 2008; 29(8) p:357–365.
[115] Misrani A, Tabassum S, Yang L. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. Front Aging Neurosci. 2021;13, p:617588.
[116] Rajmohan R, Reddy PH. Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. J Alzheimers Dis. 2017;57, p :975–99.
[117] Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS, Karunakaran R, et al. Alpha-synuclein aggregation in Parkinson's disease. Front Med (Lausanne). 2021;8, p :736978.
[118] Leathem A, Ortiz-Cerda T, Dennis JM, Witting PK. Evidence for oxidative pathways in the pathogenesis of PD: are antioxidants candidate drugs to ameliorate disease progression. Int J Mol Sci. 2022;23, p:6923.
[119] D'Egidio F, Castelli V, Cimini A, d'Angelo M. Cell rearrangement and oxidant/antioxidant imbalance in Huntington's disease. Antioxid (Basel). 2023;12, p:571.
[120] Wenz T. Mitochondria and PGC-1α in aging and age-associated diseases. J Aging Res. 2011; 2011, p:810619.
[121] Terrell E Brotherton 1, Yingjie Li 1, Jonathan D Glass 1 Cellular toxicity of mutant SOD1 protein is linked to an easily soluble, non-aggregated form in vitro Neurobiol Dis. 2012;0, p :49–56.
[122] Calafatti M, Cocozza G, Limatola C, Garofalo S. Microglial crosstalk with astrocytes and immune cells in amyotrophic lateral sclerosis. Front Immunol. 2023;14, p:1223096.
[123] nnas D, Loi E, Serra M, Firinu D, Valera P, Zavattari P. Relevance of essential trace elements in nutrition and drinking water for human health and autoimmune disease risk. Nutrients. 2020;12, p:2074.
[124] Haseeb Ahsan a,Mohammad Yusuf Hasan b, Rizwan Ahmad [Chapter 16 - Role of free radicals in autoimmune diseases Translational Autoimmunity, Etiology of Autoimmune Diseases , Translational Immunology. 2022;1,P: 317-32
[125] Kurien BT, Scofield RH. Autoimmunity and oxidatively modified autoantigens. Autoimmun Rev. 2008;7,p:567–73.
[126] G, Gevezova M, Sarafian V, Maes M. Redox regulation of the immune response. Cell Mol Immunol. 2022; 19, p:1079–101.
[127] Tian T, Wang Z, Zhang J. Pathomechanisms of oxidative stress in inflammatory bowel disease and potential antioxidant therapies. Oxid Med Cell Longev. 2017;2017, p:4535194.
[128] Antonio Ayala , Mario F Muñoz, Sandro Argüelles. Lipid Peroxidation: Production, Metabolism, and Signaling Mechanisms of Malondialdehyde and 4-Hydroxy-2-Nonenal Oxid Med Cell Longev. 2014 ;2014, p:360438.
[129] Pizzimenti S, Ciamporcero E, Daga M, Pettazzoni P, Arcaro A, Cetrangolo G, et al. Interaction of aldehydes derived from lipid peroxidation and membrane proteins. Front Physiol. 2013;4, p:242.
[130] Wang X, Fan D, Cao X, Ye Q, Wang Q, Zhang M, et al. The role of reactive oxygen species in the rheumatoid arthritis-associated synovial microenvironment. Antioxid (Basel). 2022;11, p:1153.
[131] Zhao L, Hu X, Xiao F, Zhang X, Zhao L, Wang M. Mitochondrial impairment and repair in the pathogenesis of systemic lupus erythematosus. Front Immunol. 2022;13, p:929520.
[132] Grazioli S, Pugin J. Mitochondrial damage-associated molecular patterns: from inflammatory signaling to human diseases. Front Immunol. 2018;9, p:832.
[133] Sim TM, Ong SJ, Mak A, Tay SH. Type I interferons in systemic lupus erythematosus: a journey from bench to bedside. Int J Mol Sci. 2022;23, p:2505.
[134] Wójcik P, Gęgotek A, Žarković N, Skrzydlewska E. Oxidative stress and lipid mediators modulate immune cell functions in autoimmune diseases. Int J Mol Sci. 2021;22, p:723.

[135] Checa J, Aran JM. Reactive oxygen species: drivers of physiological and pathological processes. J Inflamm Res. 2020;13, p:1057–73.
[136] Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduct Target Ther. 2024;9, p:53.
[137] Ohl K, Tenbrock K, Kipp M. Oxidative stress in multiple sclerosis: central and peripheral mode of action. Exp Neurol. 2016;277, p:58–67.
[138] Liu Y, Tang X, Tian J, Zhu C, Peng H, Rui K, et al. Th17/Treg cells imbalance and GITRL profile in patients with Hashimoto's thyroiditis. Int J Mol Sci. 2014;15, p:21674–86.
[139] Hatzioannou A, Boumpas A, Papadopoulou M, Papafragkos I, Varveri A, Alissafi T, et al. Regulatory T cells in autoimmunity and cancer: a duplicitous lifestyle. Front Immunol. 2021;12, p :731947.
[140] Hirano T. IL-6 in inflammation, autoimmunity and cancer. Int Immunol. 2021;33, p :127–48.
[141] Pegoretti V, Swanson KA, Bethea JR, Probert L, Eisel ULM, Fischer R. Inflammation and oxidative stress in multiple sclerosis: consequences for therapy development. Oxid Med Cell Longev. 2020; 2020, p :7191080.
[142] Burgetova A, Dusek P, Uher T, Vaneckova M, Vejrazka M, Burgetova R, et al. Oxidative stress markers in cerebrospinal fluid of newly diagnosed multiple sclerosis patients and their link to iron deposition and atrophy. Diagnostics (Basel). 2022; 12, p:1365.
[143] López-Muguruza E, Matute C. Alterations of oligodendrocyte and myelin energy metabolism in multiple sclerosis. Int J Mol Sci. 2023;24, p:12912.
[144] Domej, Karl Oettl, Wilfried Renner..Oxidative stress and free radicals in COPD – implications and relevance for treatment Wolfgang Obstruct. Int J Chron Pulmon Dis. 2014 ;9, p:1207–1224 6
[145] Ebadi M. Antioxidants and free radicals in health and disease: An introduction to reactive oxygen species, oxidative injury, neuronal cell death and therapy in neurodegenerative diseases. Arizona: Prominent Press; 2001.
[146] Lea AJ. Dietary factors associated with death rates from certain neoplasms in man. Lancet. 1966;2, p :332–3.
[147] V Lobo, A Patil, A Phatak, N Chandra. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010;;(8) p :118–126
[148] Poppel GV, Golddbohm RA. Epidemiologic evidence for β – carotene and cancer prevention. Am J Clin Nutr. 1995;62, p:1393–5.
[149] Glatthaar BE, Horing DH, Moser U. The role of ascorbic acid in carcinogenesis. Adv Exp Med Biol. 1986;206, p:357–77.
[150] Sokol RJ. Vitamin E deficiency and neurologic diseses. Annu Rev Nutr. 1988;8, p:351–73.
[151] V Lobo, A Patil, A Phatak, N Chandra.Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010; 4(8) p :118–126
[152] Nurhayat Atasoy and Ufuk Mercan Yücel. Antioxidants from Plant Sources and Free Radicals Open access peer-reviewed chapter of Reactive Oxygen Species 2021
[153] Krishnaswamy K. Indian functional food: Role in prevention of cancer. Nutr Rev. 1996;54, p:127–31.
[154] Ana Arias, Gumersindo Feijoo, Maria Teresa Moreira. Exploring the potential of antioxidants from fruits and vegetables and strategies for their recovery. Innovative Food Science & Emerging Technologies 2022; 7, p: 102974
[155] Jyoti V. Vastrad, Pratikhya Badanayak and Giridhar Goudar. Phenolic Compounds in Tea: Phytochemical, Biological, and Therapeutic Applications Open access peer-reviewed chapter in Phenolic Compounds - Chemistry, Synthesis, Diversity, Non-Conventional Industrial, Pharmaceutical and Therapeutic Applications 2021.