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Human Diseases Caused By Oxidative Stress: Targeting Free Radicals

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Abstract

Under situations of oxidative stress, biological systems' ability to remove reactive oxygen species (ROS) from cells and tissues falls out of balance, resulting in cell and tissue damage. ROS, which is normally produced as a consequence of a range of metabolic processes, may perform a variety of physiological tasks (such as cell signalling).However, environmental stressors (i.e., ultraviolet, ionising radiation, pollutants, and heavy metals), xenobiotics (i.e., antiblastic drugs), and xenobiotics (i.e., antibacterial drugs) all contribute significantly to ROS production, resulting in the imbalance that results in ROS-induced cell damage to endanger cells and tissues (oxidative stress). Antioxidants such as vitamin E, flavonoids, and polyphenols have witnessed an increase in popularity in recent years due to their alleged therapeutic benefits on oxidative stress. Apart from being detrimental to the human body, oxidative stress is also employed therapeutically to treat clinical illnesses such as cancer, with some effectiveness. We will summarise the most recent studies on oxidative stress in this section, emphasising both its negative and positive consequences on human health.

Keywords: oxidative stress, health, cancer, neurodegenerative disease

1. Introduction

A ROS is defined as a "reactive oxygen species" that is produced as a consequence of biological systems' metabolic activities. This category contains radicals such as superoxide, hydrogen peroxide, hydroxyl radicals (•OH), and singlet oxygen (1O2). The formation and presence of reactive oxygen species (ROS) in cells are required for a variety of activities, including protein phosphorylation, activation of several transcription factors, death, immunity, and differentiation. When the creation of critical biological structures such as proteins, lipids, and nucleic acids increases, ROS have a deleterious effect on them. Numerous studies indicate that oxidative stress may have a role in the onset and/or development of a broad variety of diseases (i.e.,cancer, diabetes, metabolic disorders, atherosclerosis, and cardiovascular

diseases)(1-3). Endothelial and inflammatory cells, as well as lipoxygenases (LOX) and cyclo oxygenases (COX) involved in arachidonic acid metabolism, all contribute to the creation of reactive oxygen species (ROS), which are created largely by mitochondria in normal and pathological conditions. Despite this, these organelles' ROS scavenging capacities are insufficient to eliminate the amount of ROS created by mitochondria. Cells are protected against ROS-induced cellular damage by antioxidant defences such as SOD, CAT, and GPx(4, 5).

2. Free Radical Production and Oxidants

Enzymatic and non-enzymatic mechanisms both contribute significantly to the creation of ROS. ROS are produced during prostaglandin synthesis, phagocytosis, cytochrome P450, and respiratory chain enzymatic activities. The superoxide radical (O2•-) is produced by NADPH oxidase, xanthine oxidase, and peroxidases. Hydrogen peroxide is produced chemically by several reactions, including the generation of hydroxyl radicals (OH•), peroxynitrites (ONOO-), and hypochlorous acids (HOCl). This nonradical is produced by enzymes that convert amino acids and xanthine to nonradical H2O2. In vivo, the most reactive free radical species, the hydroxyl radical (OH•), is formed when O2•- reacts with H2O2 and a reaction catalyst such as Fe2+ or Cu+ (Fenton reaction). Nitric oxide synthase catalyses the oxidation of arginine to citrulline to produce the nitric oxide radical (NO•), which serves a range of physiological activities (NOS). Even nonenzymatic reactions, such as the reaction of oxygen with organic molecules or the exposure of cells to ionising radiation, may result in the formation of free radicals(6, 7). Nonenzymatic free radical production may also occur during mitochondrial respiration. Free radicals are produced by both endogenous and external activities. Internal free radical production may be ascribed to a variety of events, including immune system activation, increased inflammation, or increased blood flow to a region contaminated with an infection, cancer, or just ageing. Exogenous free radical generation may occur as a result of exposure to environmental contaminants such as heavy metals (Cd, Hg, and Pb), as well as certain medications (cyclosporine, tacrolimus, gentamycin, and bleomycin), chemical solvents, cooking (smoked meat, used oil and fat), cigarette smoke, and radiation. They are broken down or metabolised in the body, and as a result, free radicals are generated(8-10).

3. Physiological Effects of Free Radicals

When maintained at low or moderate levels, free radicals have a variety of beneficial impacts on the body. For instance, cellular architecture and host defence mechanisms need the presence of these enzymes. However, phagocytes make and store free radicals to unleash them when hazardous germs enter. Patients with granulomatous disease reveal the critical role of reactive oxygen species (ROS) in the immune system. Individuals with a deficient NADPH oxidase system are unable to produce O2•-, rendering them more vulnerable to both acute and chronic infections. Additionally, free radicals contribute to the formation of free radicals in several cellular signalling pathways. For instance, nonphagocytic NADPH oxidase isoforms may generate free radicals that are required for intracellular signalling cascades in endothelial cells and vascular smooth muscle. Perhaps the most well-known free radical signalling molecule is nitric oxide (NO)(11-13). It is a crucial cell-to-cell messenger involved in a variety of processes, including blood flow control, thrombosis, and proper brain function. Another role of NO is non-specific host defence, which is critical for eradicating pathogens and tumour cells inside the

cell. A mitogenic response is another physiological function caused by free radicals. In a nutshell, free radicals in small to moderate concentrations are necessary for human health(14, 15).

4. Free radicals have a detrimental influence on human health

As previously stated, free radicals and oxidants may produce oxidative stress, which can cause damage to a variety of cellular components, including membranes, lipids, proteins, lipoproteins, and deoxyribonucleic acid. This is a detrimental procedure (DNA). Oxidative stress develops when there is an imbalance between the generation of free radicals and the ability of cells to eliminate them. Lipid peroxidation may be induced by an overabundance of hydroxyl radicals and peroxynitrite, which damage cell membranes and lipoproteins. As a consequence, malondialdehyde (MDA) and conjugated diene compounds are created, which are both cytotoxic and mutagenic. Lipid peroxidation spreads swiftly because it is a chain process involving several lipidic molecules. Additionally, oxidative stress may alter the structure of proteins, resulting in the loss or decrease of enzyme performance(16, 17). As Nishida et al. point out, the creation of 8-oxo-2'-deoxyguanosine (8-OHG) is a particularly damaging DNA lesion that may be responsible for both mutagenesis and mutation. Additionally, epigenetic information may be lost as a consequence, maybe as a result of a decrease in the CpG island methylation asset in gene promoters. As Valavanidis and colleagues highlight, the concentration of 8-OHdG in tissues was traditionally considered a biomarker of oxidative stress. DNA damage may induce a range of defence responses in cells, including base excision repair (BER) and antioxidants. If oxidative stress is not carefully managed, it may result in the development of a variety of chronic and degenerative diseases, as well as a quicker ageing process and acute pathologies (i.e., trauma and stroke)(18-20).

a. Cancer and Oxidative stress

It is a complex process requiring both cellular and molecular changes induced by endogenous and exogenous stimuli. It has long been recognised that oxidative DNA damage plays a role in the development of cancer. Oxidative stress may result in chromosomal aberrations and oncogene activation, which both contribute to the development of cancer. As a byproduct of oxidation, hydrolyzed DNA bases are produced, which is considered to be one of the most important steps in chemical carcinogenesis. Gene mutations arise as a result of the changed physiological transcriptome profile generated by various sorts of adducts, which complicates proper cell growth. Crosslinks between DNA and proteins, DNA strand breakage, and base-free regions are all examples of DNA structural changes caused by oxidative stress(21, 22). The oxidative DNA damage that may result in the creation of tumours can be induced by several causes, including tobacco use, environmental pollutants, and chronic inflammation. Given the strong correlation between dietary fat consumption and cancer mortality rates, lipid peroxidation may play a critical role in the development of cancer as a result of oxidative stress caused by lifestyle variables(23-25).

4.2 Cardiovascular Disease and Atherosclerosis

Cardiovascular disease (CVD) is associated with a broad variety of risk factors in the general population, including hypercholesterolemia, hypertension, smoking, diabetes, an unbalanced diet, stress, and a sedentary lifestyle. In recent years, oxidative stress has emerged as a primary or secondary cause of a variety of cardiovascular illnesses (CVDs). In the majority of instances, oxidative stress initiates

atherosclerosis. The formation of atheromatous plaques is commonly accepted to be induced by early endothelial inflammation, which results in ROS generation by recruited macrophages. Reactive oxygen species oxidise circulating LDL cholesterol, leading to the formation of foam cells and lipid accumulation. As a result of these events, atherosclerotic plaque forms. In both in vivo and ex vivo studies, oxidative stress has been associated with atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy, and congestive heart failure(26-28).

4.3 The Relationship Between Oxidative Stress and Neurological Disease

Numerous neurological disorders, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, depression, and memory loss, have been linked to oxidative stress. Numerous investigations in Alzheimer's disease (AD), both experimental and clinical, have shown a critical role in oxidative damage in the loss of neurons and the development of dementia. -amyloid, one of the toxic peptides identified in the brains of Alzheimer's disease (AD) patients, is generated by free radical activity and is assumed to be responsible for at least some of the neurodegeneration seen throughout the illness's development and progression(29, 30).

4.4 Respiratory disorders and oxidative stress

Oxidative stress has been linked to a variety of lung illnesses, including asthma and chronic obstructive pulmonary disease (COPD), both of which are characterised by persistent inflammation. Increased inflammation is connected with the activation of numerous oxidant-activated pathways and transcription factors, such as NF-kappa B and AP-1(31, 32).

4.5 Rheumatoid arthritis and oxidative stress

In rheumatoid arthritis, a chronic inflammatory illness, macrophages and activated T cells enter the joints and surrounding tissues. The increased levels of isoprostane and prostaglandin in affected persons' synovial fluid demonstrate that free radicals at the site of inflammation play a significant role in both the onset and progression of this illness(33, 34).

5. An Overview of the Exogenous Antioxidant Effects on Human Health

Antioxidant molecules inherent in the human body, such as SOD, CAT, and GPx, as well as lipoic acid, glutathione, -arginine, and coenzyme Q10, have been produced to battle free radicals and oxidative stress. This is only a sampling of the many exogenous antioxidant chemicals that may be found in food or obtained via supplementation. This section will discuss the most significant dietary antioxidants and how they protect human health(35, 36).

a. **Vitamin E** is composed of four lipophilic molecules: α-tocopherol; tocotrienol. In

In vitro, RRR—tocopherol, the most active form of vitamin E, inhibited the proliferation of vascular smooth muscle cells through PKC regulation, even when stimulated by low-density lipoproteins (LDLs) (LDL). These results were confirmed in vivo using both mouse and rabbit models of atherosclerosis. The transition of macrophages into foam cells is one of the earliest and most crucial stages in the development of atherosclerotic lesions, and the CD36 receptor, a scavenger receptor, plays a vital role in this process. Vitamin E may limit foam cell growth since it has been found to suppress CD36 mRNA

expression in response to cholesterol in multiple investigations. Additionally, vitamin E supplementation increased PPAR, LXR, and ABCA1 expression in ApoE knockout mice, resulting in a reduction of early (but not advanced) atherosclerotic lesions. Vitamin E inhibits c-Jun phosphorylation (thereby reducing inflammation and monocyte invasion) and matrix metalloprotease (MMP) synthesis, which is both stimulated by oxidative stress and the NF-kB pathway(37-39).

b. **Flavonoids** are a group of polyphenolic compounds with a benzo—pyrone structurethat are abundant in plants. They are involved in a variety of pharmacological actions. These compounds have been examined for their potential health benefits as antioxidants due to their functional hydroxyl groups' capacity to scavenge free radicals and/or bind metal ions. The arrangement of functional groups, their substitution, and the overall quantity of hydroxyl groups all contribute significantly to the determination of antioxidant processes such as ROS/RNS scavenging and metal chelation. Their antioxidant activity is conditional on the structural arrangement of their functional groups. As a consequence, flavonoids affect I the suppression of ROS formation; (ii) the promotion of ROS scavenging and defence mechanisms; and (iv) the augmentation of antioxidant defences. Genistein is undoubtedly the most intriguing and well-studied flavonoid molecule in terms of pharmacological properties. The antioxidant genistein has been extensively studied, demonstrating its capacity to scavenge ROS and RNS. This flavonoid molecule may increase a cell's antioxidant defences by regulating genes and proteins, therefore reducing apoptosis. In nonhuman primates and rabbits, dietary genistein supplementation delayed atherosclerosis(40, 41). Additionally, another study observed a substantial increase in LDL antioxidant protection and an anti-atherosclerotic effect. Is of lavones found in soy are widely believed to lessen postmenopausal women's risk of lipoprotein and DNA damage. Genistein has several potential applications for reducing inflammation and oxidative stress in the vascular intima layer. Genistein inhibits both NF-kB activation and gene expression regulation triggered by oxidative stress. Genistein protects antioxidant enzymes from oxidative DNA damage and increases their expression in human prostate cancer cells(42, 43).

6. Antioxidant Agents' Therapeutic Applications

Additionally, despite their well-known deleterious effects on human health, prooxidant chemicals have been researched and used as medicinal agents, primarily for cancer therapy. This section will explain ascorbic acid (AA), polyphenols, and ionising radiation in short, as well as the most often employed prooxidant in therapy, ionising radiation.

a. Vitamin C (Ascorbic Acid)

In nature, ascorbic acid, the water-soluble form of vitamin C, acts as an antioxidant. To lower the risk of cancer, ascorbate reacts with reactive oxygen species (ROS), quenching them and accelerating their conversion to semi hydroascorte radicals, a less reactive chemical species.Along with reducing metal ions such as Fe3+ and Cu3, ascorbate stimulates the Fenton reaction, which produces a highly reactive free radical that has been demonstrated to induce cytotoxicity through DNA backbone breaking and base changes(44-46).

b. Polyphenolic compounds

Under specific conditions, such as high concentrations, high pH, and the presence of redox-active metals such as peroxyl radicals or labile complexes with metal cations, phenolic compounds may become prooxidants. An aryl radical may generate O2•- or a ternary compound including DNA, copper, and flavonoids. Caffeic acid, ferulic acid, and apigenin are all examples of polyphenols that may serve as prooxidants by boosting the production of reactive oxygen species (ROS) within cells through NOX. Fenton and Fenton-like reactions may also enhance the generation of hydroxyl radicals through transition metal ions; it is critical to emphasise that cancer cells have a higher concentration of transition metal ions than normal cells(47-49).

Polyphenols seem to cause damage via several methods, including apoptosis and cell cycle arrest. Anthocyanin pigments, which are present in red wine and berries, cause apoptosis in cancer cells by increasing intracellular ROS generation (Aronia melanocarpa, Rosaceae, Vaccinium myrtillus, and Ericaceae)(50, 51).

Conclusions

Both free radicals and oxidative stress are detrimental to human health. Numerous studies indicate that the presence of free radicals in the circulation may contribute to the development and progression of a broad variety of disorders, ranging from cardiovascular disease to cancer. These compounds, which are capable of combating oxidative stress and mitigating its detrimental effects on human health and well-being, have garnered considerable attention from the biomedical research community due to their efficacy in disease prevention and/or treatment, as well as a widespread perception of their lack of significant side effects. Regardless matter how important antioxidants are in preventing and managing the human illness, they are not immune to causing adverse consequences. On the other hand, some prooxidant chemicals or agents may be advantageous to human health, particularly in cancer therapy. We may employ oxidative stress as a therapeutic tool if we can fine-tune it inside the human body, even though it is one of the most detrimental elements to people's health.

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