



Oxidative Stress, Tissue Damage, and Carcinogenesis: A Comprehensive Review

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Abstract

This review highlights the role of oxidative stress caused by excessive reactive oxygen species (ROS) in inducing tissue damage through lipid peroxidation, protein oxidation, and DNA damage. An imbalance between ROS and antioxidant defense systems leads to chronic inflammation and dysregulated cellular signaling. Accumulated oxidative damage promotes genomic instability and impairs DNA repair mechanisms. These processes enhance abnormal cell proliferation, resistance to apoptosis, angiogenesis, and tumor microenvironment remodeling. Collectively, oxidative stress-mediated alterations play a central role in carcinogenesis, influencing cancer initiation, progression, and therapeutic response.

Key words :- Oxidative Stress; Reactive Oxygen Species (ROS); Tissue Damage; DNA Damage; Genomic Instability; Antioxidant Defense; Tumor Microenvironment

Introduction :

Oxidative stress disrupts physiological processes and leads to tissue damage in the form of the disruption of the equilibrium between the generation of reactive oxygen species and antioxidant defense mechanisms (1). This balance is disturbed by nutritional or metabolically factors and promotes the formation of reactive oxygen species which can cause damage to nucleic acids, lipids and proteins and create further changes in metabolic condition of the tissue. The factual connection between oxidative stress and tissue damage entails the generation of products that are typical of the damaged molecules. Of greater significance are the indirect associations because oxidative stress can cause mutations and change various signaling pathways. Therefore, oxidative stress has been identified as a significant activity in the pathogenesis and pathophysiology of chronic-degenerative diseases including cancer because it facilitates various cellular activities including cell death to cell proliferation(2). One of the major risk factors of cancer is tissue damage. Epidemiology investigations have revealed strong links between environmental or work-associated exposure, oxidative-stress-induced tissue injury, and a higher rate of cancer in many types of

organs such as the breast, lung, liver, colon, prostate, ovary, and the brain. Preventative measures to reduce the risk of cancer by monitoring and reducing tissue damage and oxidative stress are therefore suggested (3).

Definition and Mechanisms:

Oxidative stress has become a key concept in the research of tissue damage and carcinogenesis. It has been defined variably, though a generally accepted way of defining it has to do with a surplus of either reactive oxygen species (ROS) or other oxidants relative to antioxidants within an organism or an organ system. Living things are kept in a dynamic state between the pro-oxidant and the antioxidant species. This disproportion, which leads to unregulated generation of reactive species and / or ineffective detoxification, is the basis of the definition of oxidative stress (4). The exposome is projected to be exponentially growing with regards to human societies in terms of exposure to exposome nodes in the next decades. The exposome toxicological agents engage off-pathway cellular signaling pathways that derail transient reactive signaling pathways. The uncontrolled nature of cellular pathways and outflows towards significant processes within cells that cause risks to vegetative and reproductive functions is a major threat to the health of human beings. The processes of lethality and stress agents that enter the homeostatic reality create effective disruption, which may shock in various organizational stages of life and may end up in diseases, including cancer. It seems that a considerable number of stressors with multiple pathways of action disrupt physiological homeostatic signaling sites by stimulating adaptive regulatory processes that convert physiological events into poisonous and aberrant behaviors. The horizontal transfer of signals that promote oxidative and chemical stress may be helped by cellular vesicles, including exosomes. Exogenous small interfering RNA (siRNA) and microRNA (miRNA) are found to have a role in regulation of gene expression as part of cell response to some toxic insult. This has significant but mostly immeasurable toxicological and medical consequences relating to the early genesis and pathogenesis of significantly chronic disorders, as well as neurodegenerative diseases and cancer (5).

The sources of Reactive Oxygen Species:

Examples of reactive oxygen species (ROS) are superoxide anions, hydroxyl radicals, singlet oxygen, hydrogen peroxide, and hypochlorous acid. They are produced within the cellular environment because of normal metabolism, e.g. the depletion of dioxygen and are exogenous, e.g. cigarette smoke and radiation. ROS play physiologic roles that go as far as cell growth, differentiation, proliferation, apoptosis, and tissue hypoxia.

Therefore, the aim was to identify which AIWs are the most important in the early stages of acquiring new languages. Consequently, the purpose was to determine the most significant AIWs during the initial phases of learning new languages. Air pollution is one of the major causes of particulate matter that will contribute to respiratory illnesses like asthma and chronic obstructive pulmonary disease, not to mention long-term risk of cancer as showed in figure 1. The short-term outcome of the exposure to particulate matter is the formation of ROS that led to the oxidative stress, the latter being a key determinant in the development of cancer (6).

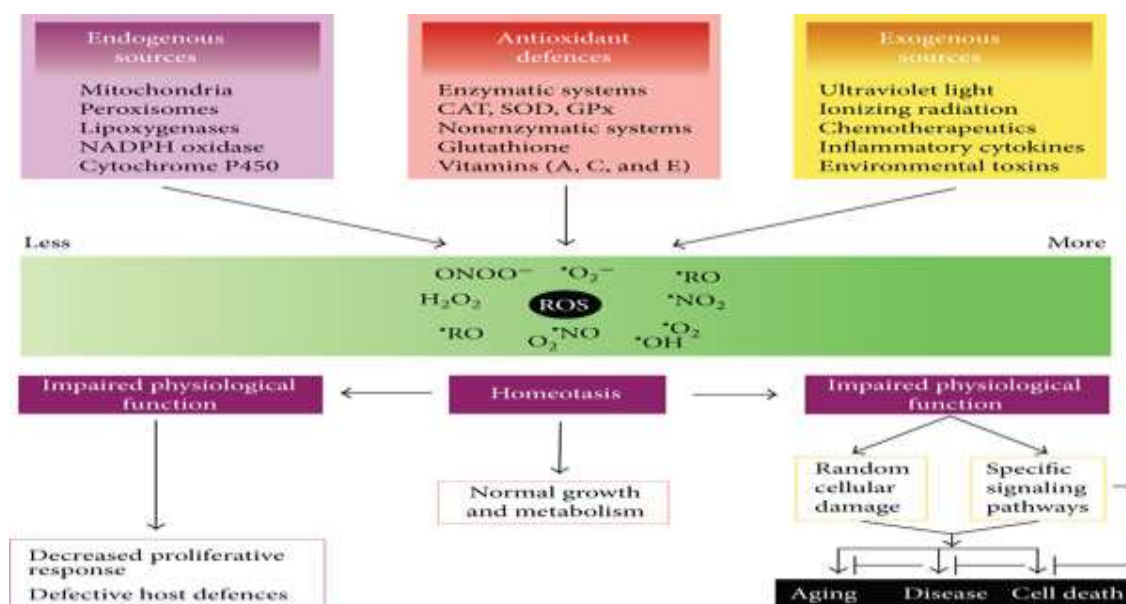


Figure 1: The sources and cellular responses to reactive oxygen species (ROS) (7).

Antioxidant Defense mechanisms:

Antioxidant defense is an ordered system that regulates redox circulation within the cell, and the enzymes and non-enzymatic molecules are all involved. The highly reactive species are transformed into less-reactive species by the help of antioxidant enzymes. Catalase is one of these enzymes and it is used in the reduction of hydrogen peroxide to water and oxygen. Research has shown that catalase overexpression could positively regulate murine melanoma and is a predictor of a better prognosis in case of breast cancer. Superoxide dismutase is used to catalyze the neutralization of superoxide anion to oxygen and hydrogen peroxide; catalase neutralizes the product. The reduction of glutathione peroxidase is a reaction that is mediated by glutathione and catalyzed by the enzyme glutathione peroxidase. It has been found to be lower in a variety of cancers like the bladder, colorectal cancer and gastric cancer (8). The glutathione-S-transferase prefers conjugation of glutathione to reactive electrophiles, the goal of which is to generate less reactive species, which play an important part in cellular detoxification. Different antioxidants are categorized as non-enzymatic molecules and these are further divided into natural and non-natural antioxidants; natural counterparts include mostly vitamins and natural metabolites including polyphenols. Of the polyphenols, allyl isothiocyanate, which is present in mustard, cabbage, and horseradish, is of importance in carcinogenesis by causing antioxidant enzymes. In selecting an antioxidant, one should consider that some are attracted to association with the cell membrane, whereas others are free to move in the cytosol. The most recognized of the lipophilic four isoprenoids are four tocopherols (vitamin E) and four tocotrienols, whose properties are attributed to their antioxidant properties (9).

Damage of Tissues by Oxidative Stress:

Oxidative stress, which is an imbalance between the production of free radicals and antioxidant defenses, is a key contributor in the destruction of tissues. Because of their reactivity, the oxidative compounds interfere with the membranes, proteins and DNA. Leaky membranes allow ionic changes that reduce cell viability, and membrane proteins that bind to receptors or the extracellular matrix could be changed or inactivated. Cytosolic enzymes of glycolysis or antioxidative defense (thiol peroxidase, thioredoxin reductase or manganese superoxide dismutase) are also prone to attack (10). Single or multiple strand breaks, non-bulky base damages, adducts, DNA damage resulting in the actions of oxidative stress can

also cause epigenetic changes, such as methylation and chromatin modifications. The process of inflammation increases oxidative stress, thus increasing the degree of tissue injury(11).

Cellular Damage Targets Oxidative Damage:

Oxidative stress leads to tissue damage by changing the different cellular components which are mostly lipids, proteins and DNA as they are important in the physiological functioning of the body. Membrane lipids especially phospholipids, are susceptible to oxidation that forms hydroperoxides which deteriorate membrane functioning and elevate permeability. Chickens fed high diets of copper chloride exhibited lipid peroxidation, tissue destruction, and related mitochondrial malfunction. By-products of lipid oxidation inhibit electron transport chain enzymes, which cause the accumulation of reactive oxygen species (ROS), mitochondrial swelling, chromatin condensation, DNA fragmentation, and a DNA strand breakage in vitro.

Proteins, which regulate most of the cellular functions, as well as form a significant fraction of the cell mass, become critical targets of oxidative stress. Direct and indirect attacks cause oxidative stress to amino acid residues and dissect protein backbones. Protein carbonyl formation is an indicator of intense protein oxidation, and lipid peroxidation products such as 4-hydroxynonenal and malondialdehyde have the ability to alter proteins. Cross-linking of proteins and carbonyl groups by ROS causes permanent damage and causes oxidized and cross-linked proteins with defective biological functioning.

Prone to different types of damage, catalysis, or oxidation, DNA molecules are subjected to oxidative alterations caused by ROS in addition to alkylation and hydrolysis and other chemically and physically induced damages. Some of the consequences of accumulated oxidative and other DNA damage include lipid dysregulation and additional disruption of cellular homeostasis. The most common lesions, which are best characterized, are oxidized DNA bases, specifically, 8-oxoguanine (8-oxoG). Oxidative damage of DNA is often associated with mutagenesis that is caused by the replicative bypass of 8-oxoG by the DNA polymerases (12).

Effects on Lipids, proteins and DNA:

Cellular antioxidant systems are not sufficient to counter the damage of oxidative stress on biomolecules when the level of ROS surpasses them. These biomolecules are lipids, proteins and DNA. Lipids react with ROS via chain reactions of secondary reactive agents, and thus, lipid hydroperoxides are formed, which readily change to highly reactive aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). The latter molecules damage DNA, as well as modify protein structure and activity. Peroxidation of lipids is done on lipoproteins and lipid membranes and plays a role in the depletion of membrane fluidity and permeability.

(13). The proteins and secretory proteins are likely to undergo oxidative changes such as formation of carbonyls, formation of disulphide bonds, protein backbone fragmentation besides oxidative changes of the side-chain. In vitro experiments indicate that protein unfolding and misfold when under oxidative conditions occur in most studies, although they are not directly supported in vivo. Proteins with modified oxidation states are also prone to cross linking with several reactive intermediates that can proceed to form protein aggregates. ROS also react with DNA bases that may produce various alterations at the level of sugars and bases and cause the strand breaks. The bulk of the cellular response mechanisms in response to oxidative stress is focused on the knowledge and repair of the damage incurred to the DNA(14).

Part of Inflammation in the Tissue destruction:

Inflammatory cells are essential in tissue injury caused by oxidative stress intensifying the damage in different ways. Inflammation is a local reaction to pathogens, damaged cells or irritants which are associated with molecular and cellular mediators. It involves the recruitment of leukocytes into the injured site (mainly neutrophils and monocytes) in minutes followed by their differentiation into macrophages and the activation of T lymphocytes. These immune cells release a lot of oxidants such as superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^\cdot$), hypochlorous acid ($HOCl$), omega-3 and omega-6 polyunsaturated fatty acids, cytokines, cytotoxic enzymes and inflammatory mediators like prostaglandins and leukotrienes. They can be released with collateral damage on the healthy cells around the site of inflammation (15).

Oxidative Stress and carcinogenesis:

Oxidative stress is a vital component of tissue damage and carcinogenesis. Genomic integrity is disrupted by persistent exposure of cells to high levels of reactive oxygen species (ROS) thus leading to cell transformation. In this regard, ROS have been regarded as the important variables that transform normal cells into malignant cells. Epidemiological evidence has reinforced the connection between oxidative stress and cancer by relating risk of disease to poor antioxidant defense systems, or the occurrence of oxidized DNA, lipids and proteins in human cancers (16). Malignant transformation is characterized by multistep development which starts with the growth of a single cell. The direct effect of ROS is the damage to DNA, mutagenesis, and the instability of the genome, which are the initial stages of carcinogenesis. (17). In addition, air pollution crude particle content can cause oxidative DNA damage reactions by binding p53 to gene promoters and potentially reprogramming gene expression and putting cancer at risk.

Pathways of association of Oxidative Stress to Cancer:

Oxidative stress occurs when the reactive oxygen species (ROS) surpass the ability of antioxidant defense mechanisms. The physiological significance of low levels of ROS is significant and the overproduction of ROS with respect to time and concentration cause morphological tissue damage. The destruction of cellular elements leads to the turn on of the immune response and additional production of proinflammatory mediators, which, along with ROS, lead to the preservation of inflammation. Unchecked inflammation long-term, unless countered, could jeopardize the cells to transformation, is now more commonly known to be a hallmark of cancer.

(18). Excessive production of ROS and subsequent oxidative stress with the breakdown of antioxidant system has been associated with the occurrence and development of cancer of various forms including breast cancer, lung cancer, colorectal, and prostate cancer (19).

The Role of Mutagenesis:

The cell can also repair the damage after having been exposed to mutagens, or the cell can use mechanisms that involve using template DNA, like translesion DNA synthesis. In case of these failures, DNA synthesis is arrested and the degenerative chain of events aimed at repairing the integrity of the genome is initiated. Unrepaired DNA mismatches, deaminated residues, and abasic sites, which typically occur as a result of attack on deoxyribose and bases, can persist as a result of exposure. Unrepaired such lesions put more chances of mutations during replication.

(20). DNA damage is created by oxidation which is involved in the initiation, progression and development of tumors.

wherein mutations can be oncogenes or tumor suppressor genes, and thus, stimulate carcinogenesis. The importance of mutagenesis in the carcinogenic process is stressed in past data (21).

Epigenetic Changes caused by Oxidative Stress:

Epigenetic changes form a wide spectrum of reversible and hereditary DNA expression changes which do not alter the DNA sequence. This is especially vulnerable to oxidative stress.

(22). The activity and detoxification of reactive oxygen species (ROS) are coordinated by redox metabolism and promote the homeostasis of cells and the regulation of oxidative damage to macromolecules. Exogenous and endogenous reactive species participate in the role of activating major signaling pathways that mediate oxidative stress. The increase of the ROS levels, in turn, alters the epigenetic regulation, which has a mechanism of metabolic changes to regulate gene expression. The various stress responses that occur during oxidative, reductive, and nitrosative stresses involve the various reactions that have been empirically reported to result in epigenetic modifications: carbonylation, glycation, glutathionylation, sulfhydrylation, nitration, and nitrosylation. On the DNA level, the ROS lead to damage which include strand breaks and formation of 8-oxo-d guanosine. They also alter the actions of histone methyltransferases, acetyltransferases, and deacetylases. Moreover, the oxidative stress also changes DNA repair enzymes using posttranslational modifications and modulates intracellular enzymes in metabolic and signaling pathways using posttranslational modifications. All these responses can create new epigenetic marks which affect gene expression.

Oxidative Stress of Particular Cancers:

Many cancers such as breast, lung, colorectal, and prostate cancer have been reported to be caused by oxidative stress.

(23). The causal role of oxidative stress in such cancers is aligned with the fact that either of the affected tissues is the major locations of body fluid excretion locations or locations of descent of asbestos fibers. In cancer of the breast, increased tissue and circulating concentrations of antioxidants enzymes have been reported and have been ascribed to stress response to high levels of oxidative stress. Oxidative stress is also increased in lung tumors. Exogenous factors like tobacco smoke also raise the risk of lung cancer by generating free radical species that leads to oxidative damage of the pulmonary parenchyma and also, oxidize the elements of cigarette smoke into other carcinogens. The second cancer causing high mortality rates and sporadic colon tumors are colorectal cancer and high oxidative stress, respectively. The factors that cause oxidative stress in the colon include the high rate of proliferation in which the mitochondria generate a lot of free radicals, and inflammation. It has also been postulated that 70 percent of all exposure of man to carcinogenic agents is realised by the gastrointestinal tract and oxidative damage has been extensively established as a key precipitating influence of the adenomacarcinoma transition in sporadic colorectal cancer carcinogenesis. The concentrations of tissue and circulating antioxidants in prostate tumors are reduced considerably, likely due to the fact that the prostate gland does not normally have very large concentrations of antioxidant enzymes, and hence experiences a higher level of oxidative stress.

(24). Nevertheless, despite the significant role of oxidative stress in carcinogenesis, the role of reactive oxygen species in tumor genesis and progression appears to be cancer type-specific and, thus, has not been fully addressed yet.

Breast Cancer:

Increased levels of ROS cause tumorigenesis and deepen the malignant development of breast cancer. The generation of ROS in the initial phases of the carcinogenic process is associated with the enhanced rigidity of the extracellular matrix (ECM), as a result of which the tumor invasion and metastasis become possible. Neoplastic cells are reprogrammed based on metabolism, which leads to an increase in the level of superoxide in order to promote proliferation, invasion, and metastasis. The second level of tumor progression is characterized by altered mitochondrial metabolism and increased superoxide production that allows cells to remain metabolically plastic during hypoxic conditions.

Lung Cancer:

Lung cancer is the biggest cause of cancer related deaths globally, and it is ranked as one of the major malignancies in the world. Deaths are 1.6 million annually, which is 20 percent of the deaths that are cancer-related. There are two major histopathological groups of lung cancer, namely, non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The most important risk factor is tobacco smoke as it causes about 85 percent of cases. (25).

There are many free supplementary therapies used in relieving symptoms of lung cancer. Phytomedicine is an ancient form of medical practice and has been rejuvenated in the lung cancer patients as an adjuvant to improve pain, appetite and side effects of cytotoxic drugs. (26).

Among other theories that interrelate oxidative stress to carcinogenesis is the production of free radicals by activated macrophage in locations of chronic inflammation. It may disrupt DNA synthesis and repair, which promotes oncogenic conversion. Posttranslational alterations in tumor-suppressor proteins, including p53, can also be triggered by reactive oxygen species, which are alterations in their activity, and, consequently, enhanced the likelihood of malignant transformation.

Colorectal Cancer:

Colorectal cancer (CRC) is one of the most significant health problems globally because it is the third most diagnosed malignancy in the world. The mounting evidence is associated with oxidative stress (OS) in the pathogenesis of CRC.

(27). Specifically, local and systemic oxidative damage occurs because of the formation of superoxide radicals (O_2^-) in the tumour microenvironment. (28). OS causes protein glyco- and lipoxidation, DNA damage, nitrosative stress. Additional deposition of mutations and epigenetic alterations facilitate malignant transformation. Due to the similarity of O_2^- generation in systemic antioxidant pathways, the patients with CRC have continuously elevated blood levels of oxidised glutathione, 4-hydroxynonenal-proteins conjugation and malondialdehyde. Considering the established correlation between microenvironmental OS and disease stage and histological grading, redox biomarkers can be potentially informative about the prognosis. OS therefore, is a key pathologic central mechanism of precancerous phenotype and a prime target of preventative and curative therapeutics.

Prostate Cancer:

Prostate cancer is a hormone-dependent malignancy and it is the second most common and the fifth leading cause of mortality among men across the globe. (29). The risk determinants identified are aging, race/ethnicity, genetic predisposition, and lifestyle factors. Oxidant/ antioxidant balance investigations indicate that oxidative stress is a causative factor in prostate carcinogenesis. (30). Reactive oxygen species increase with age causes lipid peroxidation and DNA damage, which are both age-associated and

implicated in cancer. Oxidative stress is increased by excess reactive oxygen species crushing antioxidant defenses. In the literature comparing oxidative damage and antioxidant status of high-risk individuals, the results show a decreased erythrocyte glutathione, increased leukocyte 8-hydroxydeoxyguanosine and plasma catalase, glutathione peroxidase, glutathione reductase, glutathione S-transferase, superoxide dismutase, and lipid peroxide products. High-risk individuals have more markers of oxidative damage suggesting an early contribution of oxidative insult to prostate carcinogenesis.

Prevention and Therapeutic Strategies:

Oxidative stress has been identified as a significant cause of the pathogenesis of human diseases such as cancer. The agents contributing to increased oxidative stress increase the incidence of cancer and promote the development of the malignant phenotype. Oxidative stress leads to the excess production of reactive oxygen species (ROS), which changes various signaling pathways in a manner associated with cancer initiation, progression, and resistance to therapy. Arsenic, cadmium, chromium, and nickel are carcinogenic metals that produce ROS through direct or indirect mechanisms that mediate the development of cancers caused by metals. (31). The damage of the end-organs caused by the individual metals does not always appear in the same way- arsenic and chromium lead to lung and bladder cancer respectively, and arsenic does not only lead to lung cancer but also to bladder cancer. The possible mechanisms of action of ROS in carcinogenicity of these metals, however, include genotoxic and aberrant transcription factor activation as well as genetic and epigenetic changes that control tumor development. (32). Since oxidative stress is an important factor in cancer genesis and progression, antioxidants could be appropriate chemopreventive factors in malignancy. The replenishment of antioxidants that are necessary to promote proper nutrition like ascorbic acid, α -tocopherol, β -carotene among other compounds may significantly decrease the effects of oxidative stress and provide immunity against tumorigenesis. In the given conditions, the reasonable consumption of dietary antioxidants, medication, and changing of life-style are the successful methods of cancer prevention.

Dietary Antioxidants:

The dietary components can modulate the antioxidant defenses to impact oxidative cell/tissue injury, procarcinogen bioactivation and tumor initiation, promotion, or progression. Food constituents may regulate the operation and expression of enzymes of xenobiotic-metabolizing, the metabolism of carcinogens, and the pathways of DNA damage response and repair. Understanding has shown that cancer is connected to nutrition and dietary practices, a connection that happens through oxidative stress, which is the mediator of the relationship, at least partially. (33). Antioxidants consist of inert molecules that are used to feed the oxidation reactions. Diet, especially fruits and vegetables is the greatest exogenous supply of antioxidants to human beings. Many plant parts serve as antioxidants in vitro, and it is not yet clear which of them are the most important in humans. Antioxidants are potentially dangerous, so some are prescribed on a regular basis in pharmacology and dietetics to regulate oxidative stress. The roles of antioxidants in human body, as physiological determinants of oxidation processes as well as pharmacological, are one of the biggest challenges to comprehend. (34)

Pharmacological Approaches:

Even with the current knowledge levels on the molecular and cellular basis of the disease, cancer patients are still paying a high price in terms of death, and even the treatment of cancer cells is more likely to contribute to or maintain the process of carcinogenesis. These two therapies, as well as a few carcinogens of the environment, produce reactive oxygen species (ROS) as a by-product which results in oxidative

stress causing pre-cancerous and other forms of genomic instability. A key endogenous source of ROS is the mitochondria which are involved in most energy production in an organism by oxidative phosphorylation. Defensive mechanisms against ROS are built into the cells and include glutathione-S-transferases, NADP(H) quinone oxidoreductase, glutathione peroxidases, catalase, superoxide dismutases and others; these defense mechanisms protect the macromolecules against oxidative damage and prevent oxidative-mediated mutagenesis. Other chronic diseases also involve oxidative stress such as aging, atherosclerosis, diabetes, arthritis and neurodegenerative diseases. (35).

Lifestyle Modifications:

Good life practices have been associated with reduced oxidative stress. Exercise and healthy nutrition seem to be safe in cancer patients and can alleviate the severity of the symptoms. Adiposity is associated with increased survival, resistance to therapy, and risk of recurrence in selected cancers, probably because it increases pathways associated with cancer. Plant-based diets that are high in antioxidant-containing phytochemical sources can be used to induce oxidative homeostasis. Exercise lowers the generation of ROS and increases antioxidant activities by inducing mitochondrial biogenesis and activity in patients with some comorbidities. Therefore, avoiding oxidative stress and sustaining cellular antioxidant defense are important factors to be considered in the improvement of longevity and the prevention of cancer (36).

Prospects of the Research:

The biomarker development of oxidative stress has been guided by evidence of the evaluation of the production of ROS in the affected tissues. ROS-reactive fluorescent probes produce signal when reacting with the ROS and are very sensitive but have issues such as lack of quantitative capability and limitations in tissue penetration because of their need to be generated at optical wavelengths in the visible or near-infrared spectrum.

(37). NF-E2-related factor 2 (Nrf2), hypoxia-inducible factor-1 alpha (HIF-1alpha), peroxisome proliferator-activated receptor -gamma (PPARgamma), AP-1, NF-kB and p53 are examples of transcription factors correlated with oxidative stress. (Acharya et al., 2010). Nrf2 is especially remarkable in its control over the expression of antioxidant proteins in the reaction to oxidative stress. Specifically, theragnostic nanoparticles that are able to detect the presence of ROS have been introduced, which is a new direction of research. Selective degradation of Thioketal nanoparticles under the effect of ROS allows site-specific delivery of drugs, indicating an integrative approach to the diagnostic and therapeutic requirements.

New Biomarkers of Oxidative Stress:

Accurate evidence shows that oxidative stress has been involved in the pathogenesis and progression of various diseases including cancer. However, COX-2 inhibition did not inhibit pancreatitis and the related pancreatic cancer implying that a more potent action would be achieved by a single-targeted agent that acts on both mitogenic and apoptotic signaling biomarkers of oxidative stress may help to estimate the probability of the occurrence of a particular pathophysiological condition, track the development of a diagnosed disease, and forecast the probability of successful treatment (38). The analysis of the variation in the number of targeted biomarkers with the short-term exposure to antioxidant molecules in intervention trials can be significant in terms of supporting the mitigation of the harmful effect of oxidative/nitrosative stress (biomarker modulation). Numerous natural antioxidants reduce oxidative damage in an in vitro environment, although the accumulation of animal and human studies is still minimal. The long-term effects are yet to be understood since several papers have revealed the short-term protective effects of

antioxidants against molecules damaged in protein, DNA, and lipid components. Other intervention trials have yielded controversial or adverse outcomes, including the lack of effect of vitamin E on cardiovascular events, the augmented occurrence of lung cancer after the intake of supplements of vitamin E and vitamin A in smokers, as well as the uncertainty of the capability of vitamin C to decrease oxidative damage of proteins in patients on haemodialysis. Some studies on antioxidants and damaged DNA are constrained by the methodology and /or high baseline of damaged DNA damage that prohibits meta-analysis. Great advances in the preparation of biomarkers of oxidative/nitrosative stress have occurred and the biomarkers may be used extensively in the prevention of diseases. The key issues in the future include verification of currently existing biomarkers with reference to their specificity, stability, and relevance to a specific disease, cautious research around what is the minimal level of damage in healthy individuals, and confirmation of expected protective action of antioxidant modulation in long-term intervention studies of well-defined groups of subjects. As it is supposed, appropriately validated markers will offer the equipment to identify disease in its initial stages and to check the efficacy of treatment.

Novel Therapeutic Targets:

Several new therapeutic targets that control the oxidative stress and cancer development have been discovered. Attacking the redox imbalance of cancerous cells is one of the possible ways of designing nutritional prevention and therapeutic solutions. The redox control has a dual effect on cancer due to its association with tumour growth promotion and inhibition. To prevent the occurrence of the programmed cell death, cancer cells retain high levels of antioxidant enzymes and molecules to neutralize excessive levels of oxygen radicals. (39).

Complementary and Alternative Therapy in Cancer:

Oxidative stress is the state of disruption of the pro-oxidant/antioxidant balance causing a threat of destruction. New information associates oxidative stress with many disease conditions, such as cancer. Hence, cancer treatment is positive with the development of the drugs and therapies, which address the oxidative stress. Oxidative Stress is a response of surplus of reactive oxygen species (ROS) and antioxidant factors. The over-stimulation of ROS triggers oxidative tissue injury of lipids, proteins, and DNA, which cause the dysfunction of key biomolecules and various chronic diseases, including cancer. The cells of cancer have high metabolism and remain in a higher level of ROS than the normal cells. Furthermore, antioxidant enzyme and antioxidant molecule expressions are very high in cancer cells to endure in an oxidative stress condition. A strict amount of ROS in cancer cells is critical to tumor growth and progression. HO thus, the control of the ROS concentration in chemotherapy is of importance in preserving the sensitivity of cancer cells to oxidative stress and in enhancing the action of anticancer agents (40).

Conclusion:

The linkage of oxidative stress (OS), tissue injury and carcinogenesis still forms the main concern of redox research. The molecules that can manifest OS are involved in the initiation of cancer in an indirect way (through the loss of gene stability, DNA oxidation, and changes in protein expression); they also play the leading role in the deregulation of cellular processes. It has been shown that OS-induced prevalence exists in a number of tumor types, such as breast, lung, colorectal, and prostate cancers. There is now vigorous research being put into the assessment of the effects of natural molecules and pharmacological agents in countering OS. The directions of research take into consideration particular intracellular OS functions that

induce cancer and are to include late-stage research to provide therapeutic interventions against malignancies in advanced clinical stages.

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