IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 14, Issue 2 Ser. II (Mar – Apr 2019), PP 57-64
www.Iosrjournals.Org

Free Radicals as Mediators of oxidative Damage and Disease

Abiodun Olusoji Owoade [1]*, Adewale Adetutu[1], and
Olubukola Sinbad Olorunnisola[1]

[1] *Department of Biochemistry, Ladoke Akintola University of Technology, Ogbomosho, Nigeria*
**Corresponding Author:Abiodun Olusoji Owoade*
Department of Biochemistry,
Ladoke Akintola University of Technology,Ogbomosho,Nigeria

Abstract:*Reactive oxygen species (ROS) and reactive nitrogen species (RNS) areknown to play a dual role in biological systems, since they can be either harmful or beneficial to living systems.The cumulative production of ROS/RNS through either endogenous or exogenousinsults is termed oxidative stress. Oxidative stress determines structure modifications and function modulation in nucleic acids,lipidsand proteins which has been found to be present in various disease cells when compared with normal cells. This reviewexamines the evidence for involvement of the oxidative stress in disease process. Attention is focused on endogenous and exogenous sources of free radicals generation, the metal (iron,copper)-mediated formation of free radicals (e.g. Fenton chemistry), theDNA damage, the damage to lipids and proteins by free radicals. Theoxidative damage in the cell resulted in over-expression of oncogene genes, generation ofmutagen compounds, promotion of atherogenic activity, senile plaque occurrence or inflammation. Thisleads to cardiovascular diseases, carcinogenesis, neuronal diseases, diabetes and inflammatory diseases.*

Keywords:*Reactive oxygen species, free radicals, oxidative stress, fenton chemistry, DNA damage*

Date of Submission: 07-04-2019Date of acceptance: 23-04-2019

I. Reactive Oxygen And Nitrogen Species

There has been an 'explosive' interest in the biological role of free radicals, more generally known as "reactive oxygen species," (ROS) and of "reactive nitrogen species" (RNS) in experimental and clinical medicine in the last two decades(Halliwell and Gutteridge, 1999). ROS and RNS are generated *in vivo* from incomplete reaction of oxygen during aerobic metabolism, stimulated host phagocytes, or from exposure to environmental agents such as radiation and redox cycling agents(Park et al., 2003). ROS include free radicals (which are defined as molecules or molecular fragments containing one or more unpaired electrons) such as superoxide ($O_2^{\bullet-}$), hydroxyl ($OH^{\bullet}$), peroxyl ($ROO^{\bullet}$), hydroperoxyl ($HROO^{\bullet}$) as well as non-radical species such as hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl)(Evans et al., 2002; Turko and Murad, 2002). RNS include free radicals like nitric oxide ($NO^{\bullet}$) and nitrogen dioxide ($NO^{\bullet}_2$), as well as nonradicals such as peroxynitrite ($ONOO^{-}$), nitrous oxide (HNO_2) and alkyl peroxynitrates (RONOO)(Evans et al., 2002; Turko and Murad, 2002). Reactive oxygen and nitrogen species are products of normal cellular metabolism and they are known to play a dual role in biological systems, since they can be either harmful or beneficial to living systems(Valko et al., 2006). Beneficial effects of ROS which occur at low/moderate concentrations include (a) physiological roles in cellular responses to stress, as for example in defence against infectious agents and in the function of a number of cellular signalling systems and (b) the induction of a mitogenic response(Valko et al., 2006). The harmful effect of ROS includes widespread damage to macromolecules leading to lipid peroxidation, protein oxidation and DNA base modification and strand breaks(Poli et al., 2004; Stocker et al., 2004). This damage effect is termed oxidative and nitrosative stress(Kovacic and Jacintho, 2001; Ridnour, et. al., 2005)

II. Oxidative And Nitrosative Stress

Oxidative and nitrosative stress is defined in general as excess formation and/or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS)(Turko et al., 2001; Maritim et al., 2003). This occurs in biological systems when there is an overproduction of ROS/RNS on one side and a deficiency of enzymatic and non-enzymatic antioxidants on the other(Valko et al., 2007). The excess ROS are harmful because they can damage cellular lipids, proteins, and DNA which are the most important biomolecules in the human body(Orhan et al., 2006). Because of this, oxidative stress has been implicated in the development of many ageing-related diseases, like cancer, cataract and heart diseases (Dalle-Donne et al., 2006). The delicate balance between beneficial and harmful effects of free radicals is a very important aspect of living organisms and is achieved by mechanisms called "redox regulation". The process of

"redox regulation" protects living organisms from various oxidative stresses and maintains "redox homeostasis" by controlling the redox status *in vivo*. (Dröge, 2002).

2.1 Hypochlorous (HOCl) – Induced Oxidative Stress

The heme enzyme myeloperoxidase (MPO; EC 1.11.1.7), which is released from activated polymorphonuclear leukocytes and monocytes at sites of inflammation, plays a key role in the generation of oxidants by the human immune system(Klebanoff et al., 2005).

$$H_2O_2 + Cl^- \xrightarrow{MPO} HOCl + OH^-$$

The HOCI generated is thought to play an important role in defence against micro-organisms(Klebanoff et al., 2005). However, the properties that make it such a useful antimicrobial agent also places the host at considerable risk, because HOCl has the potential to damage host tissue through the same processes used in the destruction of invading microorganisms(Klebanoff et al., 2005). Clinical studies have shown that a myeloperoxidase deficiency, or a low level of blood myeloperoxidase, had beneficial effects against cardiovascular damage in patients presenting with this deficiency(Kutter et al., 2000; Zhang et al., 2001). The oxidation of LDL by myeloperoxidase mainly leads to modifications of apolipoproteins with the formation of chlorotyrosine, dityrosine, and nitrotyrosine(Heinecke, 2003), 3-chlorotyrosine is therefore use as a marker of HOCl generation, and it has been found to be elevated in human atherosclerotic intima(Imran et al., 2006). Therefore, HOCl produced by neutrophils and other phagocytic cells *in vivo*could form significant oxidative stress on host cells and tissues.

2.2. Metal-Induced Oxidative Stress

Many studies have focused on metal-induced toxicity emphasising their role in the generation of reactive oxygen and nitrogen species in biological systems, and the significance of this therein(Chen et al., 2001; Leonard et al., 2004; Valko et al., 2005). Metal-mediated formation of free radicals may cause various modifications to DNA bases, enhanced lipid peroxidation, and changes in calcium and sulphydryl homeostasis(Valko et al., 2006).

2.2.1. *Iron*

Iron, in virtue of its ability to participate directly as a donor or acceptor in electron transfer reactions, is an essential trace element for cell function. This property makes iron the most common cofactor within the oxygen handling biological machinery(Beard, 2003; Aracena et al., 2006). However, if iron is not handled properly by the cell, it interacts with molecular oxygen, generating reactive oxygen species (ROS) through Haber-Weiss and Fenton reactions(Halliwell and Gutteridge, 1999). Uncontrolled ROS production leads to oxidative damage of cellular components, a condition termed 'oxidative stress'(Droge, 2003). Both animal and human studies, have established the links between increased levels of iron in the body and an enhanced risk of a variety of diseases including vascular disease, cancer and certain neurological conditions(Berg et al., 2001; Siah et al., 2005). Iron-induced free radical damage to DNA appears to be important for the development of cancer and cancer cells are known to grow rapidly in response to iron(Petersen et al., 2005). These effects are more pronounced in metal overloading conditions (Kontoghiorghes et al., 2005). Correspondingly, pre-menopausal women and children are believed to have a lower risk of common diseases because amounts of iron in the body are unlikely to be excessive at these times(Nelson, 2001). Occupational exposure to asbestos containing about 30% (weight) of iron is related to an increased risk of asbestosis — the second most important cause of lung cancer after smoking(O'Reilly et al., 2007). It is generally accepted that asbestos-induced carcinogenesis is linked with formation of free radicals.

2.2.2. *Copper*

Several mechanisms have been proposed to explain Cu-induced cellular toxicity. Free Cu ions participate in the formation of reactive oxygen species (ROS). Cu^{2+} in the presence of superoxide ($O_2^{\bullet -}$) or reducing agents such as ascorbic acid or GSH, can be reduced to Cu^-, which is capable of catalysing the formation of hydroxyl radicals ($OH^\bullet$) from hydrogen peroxide (H_2O_2) via the Haber-Weiss reaction(Dikalov et al., 2004; Nakamura et al., 2007). The hydroxyl radical is a powerful oxidizing radical and can initiate oxidative damage by abstracting the hydrogen from an amino-bearing carbon to form a carbon centred protein radical and from an unsaturated fatty acid to form a lipid radical(Powell, 2000). The weight of evidence from *in vitro* and *in vivo* studies indicates that copper is capable of producing ROS and inducing DNA strand breaks and oxidation of bases(Keyhani et al., 2006; Hadi et al., 2007). It is also a powerful catalyst of LDL oxidation and may be involved with oxidative modification of LDL to an atherogenic form(Xu et al., 2007). Copper has been

implicated in the pathogenesis of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis(Choi et al., 2005; Boll et al., 2008). Also, it has been implicated in the process of carcinogenesis(Daniel et al., 2004) *in vitro* studies have shown that cancer cells in a high copper environment find it easy to proliferate into tumours(Wu et al., 2004; Hayashi et al., 2007). Therefore, it has been proposed that copper-lowering drug may stabilize advanced cancer.

III. Oxidative Damage To Biomolecules

3.1. DNA Damage

It was estimated that approximately 2% of inhaled oxygen was converted to reactive oxygen by various biological reactions with the potential to induce protein and DNA damage(Campa et al., 2004). It has also been estimated that one human cell is exposed to approximately 1.5×10^5 oxidative hits a day from hydroxyl radicals and other such reactive species (Beckman and Ames, 1997). Permanent modification of genetic material resulting from these "oxidative damage" incidents represents the first step involved in mutagenesis, carcinogenesis and ageing. ROS can induce a number of covalent modifications to DNA, which encompass single-nucleobase lesions, strand breaks, inter and intrastrand cross-links, along with protein-DNA cross-links(Evans et al., 2004). DNA damage can result either in arrest or induction of transcription, induction of signal transduction pathways, replication errors and genomic instability, all of which are associated with carcinogenesis (Marnett, 2000; Cooke et al., 2003). In addition to ROS, reactive nitrogen species (RNS), such as peroxynitrites and nitrogen oxides, have also been implicated in DNA damage (Azad et al., 2008). Both peroxynitrites and nitrogen oxides can induce guanine nitration, producing G:C to T:A transversions, and thus are involved in inflammation-induced carcinogenesis(Ohshima et al., 2005; Terasaki et al., 2006). While the stability of this lesion in DNA is low, in RNA, however, this nitrogen adduct is stable.

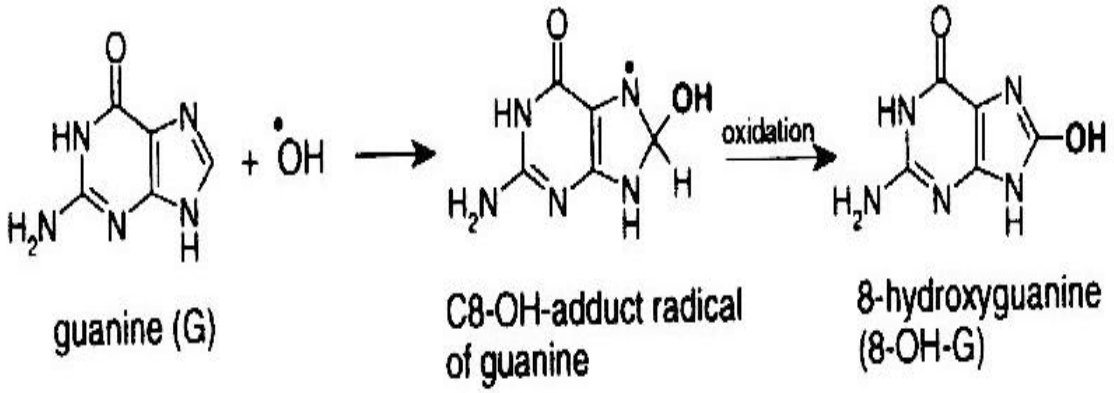

Figure 1. Guanine oxidation by hydroxyl radical. Modified from Valko et al., (2006)

3.2. Lipid Damage

Stress-induced lipid peroxidation could play a role in the development of atherosclerosis, neurodegeneration, cancer, and other disorders(Halliwell and Gutteridge, 1999). Lipid damage can be triggered by reactive oxygen species (ROS) such as hydroxyl radical ($OH^{\bullet}$), hydroperoxyl radical ($HROO^{\bullet}$), and singlet molecular oxygen ($^1O_2$), or by reactive nitrogen oxide species such as peroxynitrite ($ONOO^-$) and nitrogen dioxide (NO_2)(Halliwell and Gutteridge, 1999). The overall process of lipid peroxidation consists of three stages: initiation, propagation and termination. Both ($OH^{\bullet}$), and ($ONOO^-$) can trigger free-radical-mediated (chain) lipid peroxidation via abstraction of an allylic hydrogen from an unsaturated lipid (LH). The resulting lipid radical ($L^{\bullet}$) with free electron delocalized over several carbons reacts rapidly with O_2 to give a peroxyl radical ($LOO^{\bullet}$). Once formed, peroxyl radicals ($LOO^{\bullet}$) can be rearranged via a cyclisation reaction to endoperoxides (precursors of malondialdehyde) with the final product of the peroxidation process being malondialdehyde (MDA)(Marnett, 1999). The major aldehyde product of lipid peroxidation other than malondialdehyde is 4-hydroxy-2-nonenal (HNE). Peroxidation of lipids is an autocatalytic process which can be terminated by the recombination of radicals ($L^{\bullet} + L^{\bullet} \rightarrow$ non-radical product) or depletion of the substrate(Valko, 2006).

Table 1. Elementary Reactions of Lipid Peroxidation

Initiation:	$LH + X^{\bullet}$	→	$L^{\bullet} + XH$
Oxygen Addition	$L^{\bullet} + O_2$	→	$LOO^{\bullet}$
Chain Propagation	$LOO^{\bullet} + LH$	→	$LOOH + L^{\bullet}$
Inhibition by antioxidants	$LOO^{\bullet} + AH$	→	$LOOH + A^{\bullet}$

LH: lipid containing a PUFA; $L^{\bullet}$: Carbon centred PUFA radical; $X^{\bullet}$: initiating free radical; $LOO^{\bullet}$: lipid peroxyl radical; LOOH: lipid hydroperoxide; AH: antioxidant
Modified from Klatt and Esterbauer, 1996

3.3. Proteins Damage

Radical-mediated oxidation of proteins leads to fragmentation of the polypeptide chain, oxidation of amino acid side chains, and generation of protein–protein cross linkages(Stadtman, 2004). Unlike other types of modification (except cysteine oxidation), oxidation of methionine residues to methionine sulfoxide is reversible; thus, cyclic oxidation and reduction of methionine residues leads to consumption of ROS and thereby increases the resistance of proteins to oxidation.

Table 2. Oxidation of methionine residues

Met	+ ROS	→	Met O	+	IRS
Met O	+ Th $(SH)_2$	→	Met	+	ThS- S
Ths- S	+ $NADPH + H^+$	→	Th $(SH)_2$	+	$NADP^+$
ROS	+ $NADPH + H^+$	→	IRS	+	$NADP^+$

Met: Methionine; Met O: oxidized Methionine; ROS: reactive oxygen species; IRS; inactive form of ROS; Th $(SH)_2$: Thioredoxin; Ths-S: oxidized thioredoxin. Modified from Stadtman, 2004

The side chains of all amino acid residues of proteins are susceptible to oxidation by ionising radiation and by the action of ROS/RNS(Stadtman, 2004). The products formed by most vulnerable amino acid are presented in Table 1.1. Oxidation of proteins is associated with a number of age-related diseases and ageing(Stadtman, 2001; Levine and Stadtman, 2001). The importance of protein oxidation in aging is supported by the observation that levels of oxidized proteins increase with animal age. The age-related accumulation of oxidized proteins may reflect age-related increases in rates of ROS generation, decreases in antioxidant activities, or losses in the capacity to degrade oxidized proteins(Stadtman, 2004)

Table 3. Products of oxidation of various amino acids. Modified from Stadtman, 2004

Amino Acid	Products
Arginine	Glutamic semialdehyde
Cysteine	CyS–SCy; CyS–SG; CySOH; CySOOH; CysO2H
Glutamic acid	Oxalic acid; pyruvate adducts
Histidine	2-Oxohistidine; 4-OH-glutamate
Leucine	3-OH-leucine; 4-OH-leucine; 5-OH-leucine
Lysine	α-aminoadipicsemialdehyde; N_c-(carboxymethyl)lysine
Methionine	Methionine sulfoxide; methionine sulfone
Phenylalanine	2-, 3-, and 4-Hydroxyphenylalanine; 2,3-Dihydroxyphenylalanine
Proline	Glutamylsemialdehyde; 2-pyrrolidone, 4- and 5-OH-proline;
Threonine	2-Amino-3-keto-butyric acid
Tryptophan	2-, 4-, 5-, 6-, 7-Hydroxy tryptophan; formylkynurenine; 3-OH-kynurenine; nitrotryptophan
Tyrosine	3,4-Dihydroxyphenylalanine; tyr–tyr crosslinks; 3-nitrotyrosine; 3-chlorotyrosine; 3,5-dichlorotyroxine

IV. Oxidative Damage and Disease Implications

Oxidative stress has been implicated in various pathological conditions involving cardiovascular disease, cancer, neurological disorders, diabetes, ischemia/reperfusion, other diseases and ageing(Dhalla et al., 2000; Sayre et al., 2001; Jenner, 2003; Dalle-Donne et al., 2006). Oxidative damage to important biomolecules is a deleterious pathway, but also influences of ROS on gene regulation or the immune system might impair bodily functions. There is increasing evidence that antioxidants might prevent or delay the development of disease states.

4.1. Cardiovascular Disease

The primary cause for most cardiovascular diseases is thought to be atherosclerosis, a multifactorial disease of the artery wall. Arteriosclerosis is characterized with deposition of lipid, otherwise called fatty streaks in the subendothelial space(Davidson, 2007). ROS-induced oxidative stress plays a role in various cardiovascular diseases such as atherosclerosis, ischemic heart disease, hypertension, cardiomyopathies, cardiac hypertrophy and congestive heart failure(Madamanchi et al., 2005). ROS have particularly been implicated in

the oxidation of LDL(Touyz, 2004). LDL oxidation is due to a lipid peroxidation reaction initiated by free radicals. Oxidative stress is associated with increased formation of ROS that modifies phospholipids and proteins leading to peroxidation and oxidation of thiol groups (Molavi and Mehta, 2004). ROS such as superoxide $O_2^{\bullet-}$, and peroxynitrite are known to initiate lipid peroxidation and lipoproteins oxidation, both important events in the incidence of atherosclerosis(Valko et al., 2007). Also, metal ion (Ca^{2+} and Fe^{2+}) have been demonstrated to play critical role in the development of atherosclerosis. Yuan and Li,(2003) observed significant amounts of iron pool in atherosclerotic lesions which indicate that the iron-catalysed formation of free radicals (e.g. Fenton chemistry) may take place in the process development of atherosclerosis. Increased levels of intracellular level of Ca^{2+} were observed in human endothelial cells, suggesting that Ca^{2+}-overload induced oxidative stress is another factor participating in atherosclerosis(Podrez et al., 2000). Increased amounts of superoxide radical and hydrogen peroxide have been reported in hypertensive patients, indicating that ROS-induced oxidative stress play a vital role in the pathogenesis of hypertension(Touyz, 2004). ROS-induced oxidative stress in hypertensive patients is accompanied by decreased levels of antioxidants such as Vitamin E, GSH, and SOD, all good scavengers of free radicals.

4.2. Carcinogenesis

Carcinogenesis is a complex multistep process including initiation, promotion and progression. The generation of ROS is thought to be linked to tumorigenesis at different levels. ROS-induced DNA damage involves single- or double-stranded DNA breaks, purine, pyrimidine, or deoxyribose modifications, and DNA cross-links. DNA damage can result in arrest or induction of transcription, induction of signal transduction pathways, replication errors, and genomic instability, all of which are associated with carcinogenesis(Marnett, 2000; Valko et al., 2006). Also, reactive nitrogen species (RNS), such as peroxynitrites and nitrogen oxides, have been implicated in DNA damage(Hehner et al., 2000). In addition to ROS/RNS, various redox metals, due to their ability to generate free radicals, or non-redox metals, due to their ability to bind to critical thiols, have been implicated in the mechanisms of carcinogenesis and ageing(Leonard et al., 2004; Waalkes et al., 2004; Santos et al., 2005; Valko et al., 2005). Iron-induced oxidative stress is considered to be a principal determinant of human colorectal cancer(Valko et al., 2001). Further, ROS are capable of deactivating detoxifying enzymes responsible for the scavenging of potent carcinogens. Data from epidemiological studies support the idea that antioxidants are preventive in carcinogenesis by scavenging ROS(Karihtala and Soini, 2007).

4.3. Neuronal Diseases

The brain is particularly vulnerable to oxidative damage because of its high oxygen utilisation, its high content of oxidizable polyunsaturated fatty acids, and the presence of redox-active metals (Cu, Fe)(Valko et al., 2007). Growing data from experimental models and human brain studies add evidence that oxidative stress plays a role in the development of neuronal degeneration related to diseases such as Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease(Loh et al., 2006). ROS are capable of inducing both necrosis and apoptosis. As a consequence of lipid peroxidation membrane rupture might occur or ion gradients, operative over compartments which are separated by membranes, might be disturbed. Neurons might undergo necrotic cell death as has been demonstrated in cell culture following depletion of intracellular GSH, the major endogenous antioxidant thiol NO has been hypothesized to be an important mediator of neuronal death under pathological conditions. The ultimate species responsible for NO toxicity may be peroxynitrite which is formed by the reaction of the NO-radical with the superoxide radical(Calabrese et al, 2004)

4.4 Diabetes

Cell damage caused by enhanced oxidative stress mayaffect the pancreatic b cell function, which, given the impairedexpression of antioxidant enzymes, is outstandingly sensitive toreactive oxygen and nitrogen species (Bandeira et al., 2012; Valko et al., 2007).The reactive oxygenated species are able to interact with thesubstrates involved in the insulin intracellular signalling (Evans et al., 2005). It has been suggested that under deficient glycaemic control, thatcan arise in spite of the use of pharmaceuticals, oxidative stress maybe promoted via NADPH oxidase activity enhancement, with subsequentsuperoxide radical anion production. Studies assessingenzymatic and non-enzymatic markers of oxidative stress in diabetesmellitus condition showed that total superoxide dismutaseactivity and the lipid peroxidation were higher in diabetics whencompared to healthy controls. Moreover, the total superoxide dismutaseactivity differed for the hypertensive diabetics in comparisonwith the prediabetics and normotensive controls. Lipidperoxidation was considerably increased in both groups of diabetics(hypertensive and normotensive) as compared with prediabeticgroups and hypertensive and normotensive controls (Bandeira et al., 2012).

4.5. Inflammatory diseases

The imbalance between the oxidativespecies' activity, and the antioxidantdefence, is involved in asthma and allergic rhinitis (Sequeira et al., 2012; Marple, 2010; Ercan et al., 2006). Theenhanced occurrence of hydroxyl radicals, superoxide radical anionsand peroxides, may initiate a series of alterations in nasal andairway mucusas: lipid peroxidation, marked airway reactivity, nasalmucosal sensitivity and secretions, as well as generation of chemoattractantmolecules and high vascular permeability (Sequeira et al., 2012). Basically, it has been noticed that reactive species and antioxidantsinfluence the immune system. Oxidative stress causesdisruption in cell signalling and impairs arachidonic acid metabolism,enhances airway and systemic inflammation (Moreno-Macias and Romieu, 2014).The involvement of oxidative stress in allergic rhinitis isbelieved to be identical to that manifested in asthma (Russel and James, 2002). Themarker of lipid peroxidation as average thiobarbituricreactivesubstances level evaluated in allergic rhinitis patients was higher,with respect to healthy controls. The susceptibility to undergoenhanced lipid peroxidation (as result of the oxidative damage) andthe mean superoxide dismutase enzyme activity were significantlyincreased in the erythrocytes of patients with allergic rhinitis (Aguirre et al., 1998; Sequeira et al., 2012). The increase inceruloplasmin levels noted in allergic rhinitis was considered areaction to the inflammation of airways, as well a component of theincreased antioxidant response occurring after cell injury (Sequeira et al., 2012).Oxygen metabolism and increased ROS production causingtissue damage, and associated with inflammation, have animportant role in the pathogenesis of rheumatoid arthritis (Mirshafiey andMohsenzadegan, 2008).

V. Conclusions

Oxidative stress results from an excessive reactive oxygen speciesgeneration, and consists in an imbalance of oxidative toreducing species, being also better defined as a perturbation ofredox signalling. The action of reactive oxygenated/nitrogenatedspecies (superoxide anion radical, hydroxyl, alkoxyl, lipid peroxylradicals, nitric oxide and peroxynitrite) results in alterations andfunction modulations of key biomolecules.The marker of DNA damage is represented by 8-hydroxydeoxyguanosine. The oxidative attack on lipids also resultsin reactive aldehydes, such as malondialdehyde and 4-hydroxynonenal. Oxidation of thiol groupstakes mainly account on protein oxidative damage, along withcarbonylation that leads to advanced glycation end products. Sidechainoxidation, backbone fragmentation, unfolding and misfolding,with activity loss, may also occur in protein structure.The oxidative insults of the components of lipid membranes areinvolved in the mechanism of neurodegeneration, cancer, cardiovascularor inflammatory diseases. It has been confirmed thatexcessive reactive oxygenated species production may lead to overexpressionof oncogene genes or to formation or mutagen compounds,can promote pro-atherogenic activity, and is related tosenile plaque occurrence or inflammation.

Authors' Contributions

This work was carried out in collaboration between all authors. All authors read and approved the finalmanuscript.

Conflict of Interests

Authors have declared that no competing interests exist.

References

[1]. Aguirre F, Martin I, Grinspon D, Ruiz M, Hager A, De T, Paoli J, Ihlo J, Harach HA, Poole CP (1998). Oxidative damage, plasma antioxidant capacity, and glicemic control in elderly NIDDM patients, Free Radic. Biol. Med. 24: 580-585.

[2]. Aracena, P., Aguirre, P., Muñoz, P., Núñez, MT. (2006) Iron and glutathione at the crossroad of redox metabolism in neurons. Biological Research, 39: 157-165, 2006

[3]. Azad, N,, Rojanasakul, Y., Vallyathan, V. (2008) Inflammation and lung cancer: roles of reactive oxygen/nitrogen species. Journal of Toxicology and Environmental Health Part B, 11(1):1-15.

[4]. Bandeira SM, Guedes GS, Da Fonseca LJS, Pires AS, Gelain DP, Moreira JCF, Rabelo LA, Vasconcelos SML, Goulart MOF (2012). Characterization of blood oxidative stress in type 2 diabetes mellitus patients: increase in lipid peroxidation and SOD activity, Oxid. Med. Cell. Longev. 2012, http://dx.doi.org/10.1155/2012/819310.

[5]. Beard, J. (2003) Iron deficiency alters brain development and functioning. Journal of Nutrition 133: 1468S- 1472S

[6]. Beckman, KB., Ames, BN. (1997) Oxidative decay of DNA. Journal of biological chemistry, 272:19633–19636.

[7]. Berg, D., Gerlach, M., Youdim, MBH., Double, KL., Zecca, L., Riederer, P., Becker, G. (2001) Brain iron pathways and their relevance to Parkinson's disease, Journal of neurochemistry, 79:225–236.

[8]. Boll, MC., Alcaraz-Zubeldia, M., Montes, S., Rios, C. (2008) Free Copper, Ferroxidase and SOD1 Activities, Lipid Peroxidation and NO(x) Content in the CSF. A Different Marker Profile in Four Neurodegenerative Diseases. Neurochemical Research.33 (9) : 1717-1723.

[9]. Calabrese, V., Boyd-Kimball, D., Scapagnini, G., Butterfield, DA. (2004) Nitric oxide and cellular stress response in brain aging and neurodegenerative disorders: the role of vitagenes. In Vivo, 18 (3) : 245-267.

[10]. Campa, A., Esposito, G., Belli, M., Simone, G., Tabocchini, MA. (2004) DNA fragmentation in V79 cells irradiated with light ions as measured by pulsed-field gel electrophoresis. II. Simulation with a generalized broken stick model. International journal of radiation biology, 80 (3) : 229-238.

[11]. Chen, F., Ding, M., Castranova, V., Shi, XL. (2001) Carcinogenic metals and NF-kappa B activation. Molecular and cellular biochemistry, 222:159–171.
[12]. Choi, J., Rees, HD., Weintraub, ST., Levey, AI., Chin, LS., Li, L. (2005) Oxidative modifications and aggregation of Cu, Zn-superoxide dismutase associated with Alzheimer and Parkinson diseases. The Journal of biological chemistry, 280 (12) : 11648-55.
[13]. Cooke, MS., Evans, MD., Dizdaroglu, M., Lunec, J. (2003) Oxidative DNA damage: mechanisms, mutation, and disease, FASEB Journal, 17:1195–1214.
[14]. Dalle-Donne, I., Rossi, R., Colombo, R., Giustarini, D., Milzani, A. (2006) Biomarkers of oxidative damage in human disease. Clinical Chemistry, 52:601–623.
[15]. Daniel, KG., Harbach, RH., Guida, WC., Dou, QP. (2004) Copper storage diseases: Menkes, Wilson's, and cancer. Frontiers in bioscience, 9 : 2652–2662.
[16]. Davidson, MH. (2007) Overview of Prevention and Treatment of Atherosclerosis With Lipid-altering Therapy for Pharmacy Directors. The American Journal of Managed Care. Supplement Content, pp. S260-S269.
[17]. Dhalla, NS., Temsah, RM., Netticadan, T. (2000) Role of oxidative stress in cardiovascular diseases. Journal of Hypertension, 18 (6) : 655-673.
[18]. Dikalov, SI., Vitek, MP., Mason, RP. (2004) Cupric-amyloid beta peptide complex stimulates oxidation of ascorbate and generation of hydroxyl radical. Free Radical Biology and Medicine, 36 (3) : 340- 347.
[19]. Droge, W. (2002). Free radicals in the physiological control of cell function. Physiological reviews, 82 : 47–95.
[20]. Droge, W. (2003) Oxidative stress and aging. Advances in experimental medicine and biology, 543: 191-200.
[21]. Ercan H, Birben E, Dizdar EA, Keskin O, Karaaslan C, Soyer OU, Dut R, Sackesen C, Besler T, Kalayc O (2006). Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma, J. Allergy Clin. Immunol. 118: 1097-1110
[22]. Evans JL, Maddux BA, Goldfine ID (2005) The molecular basis for oxidative stress-induced insulin resistance, Antioxid. Redox Signal 7: 1040-1052
[23]. Evans, JI., Goldfine, ID., Maddux, BA., Grodsky, GM. (2002) Oxidative Stress and Stress-Activated Signaling Pathways: A Unifying Hypothesis of Type 2 Diabetes. Endocrine Reviews, 23 (5): 599–622.
[24]. Evans, MD., Dizdaroglu, M., Cooke, MS. (2004) Oxidative DNA damage and disease: induction, repair and significance. Mutation Research, 567: 1–61.
[25]. Hadi, SM, Bhat, SH, Azmi, AS, Hanif, S, Shamim, U, Ullah, MF (2007) Oxidative breakage of cellular DNA by plant polyphenols: a putative mechanism for anticancer properties. Seminars in cancer biology, 17 (5) : 370-376.
[26]. Halliwell, B., Gutteridge, JMC (1999) Oxidative stress: Adaptation, damage, repair and death. In: Free Radicals in Biology and Medicine. 3rd Ed. Oxford, UK: Oxford University Press. Pp: 246-350.
[27]. Hayashi, M., Nishiya, H., Chiba, T., Endoh, D., Kon, Y., Okui, T. (2007) Trientine, a copper-chelating agent, induced apoptosis in murine fibrosarcoma cells in vivo and in vitro. The Journal of Veterinary Medical Science, 69(2):137-142.
[28]. Hehner, SP., Breitkreutz, R., Shubinsky, G., Unsoeld, H., Schulze-Osthoff, K., Schmitz, ML. et al. (2000) Enhancement of T cell receptor signaling by a mild oxidative shift in the intracellular thiol pool. Journal of Immunology, 165: 4319–4328.
[29]. Heinecke, JW. (2003) Oxidative stress: new approaches to diagnosis and prognosis in atherosclerosis.American Journal of Cardiology, 91 (3A) : 12A-16A.
[30]. Imran, MD., Hong Chai, H., Lin, PH., Lumsden, AB. (2006) Nitrotyrosine and Chlorotyrosine: Clinical Significance and Biological Functions in the Vascular System. Journal of surgical research, 133 : 143-149.
[31]. Jenner, P. (2003) Oxidative stress in Parkinson's disease. Annals of neurology, 53: S26-38.
[32]. Karihtala, P., Soini, Y. (2007) Reactive oxygen species and antioxidant mechanisms in human tissues and their relation to malignancies. Acta pathologica, microbiologica, et immunologicaScandinavica, 115 (2) : 81-103.
[33]. Keyhani, E., Abdi-Oskouei, F., Attar, F., Keyhani, J. (2006) DNA strand breaks by metal-induced oxygen radicals in purified Salmonella typhimurium DNA. Annals of the New York Academy of Sciences, 1091 : 52-64.
[34]. Klatt P, Esterbauer H (1996) Oxidative hypothesis of atherogenesis Journal of Cardiovascular Risk, 3: 346–351.
[35]. Klebanoff, SJ. (2005) Myeloperoxidase: friend and foe, Journal of Leukocyte Biology, 77 : 598–625.
[36]. Kontoghiorghes, GJ., Eracleous, E., Economides, C., Kolnagou, A. (2005) Advances in iron overload therapies. prospects for effective use of deferiprone (L1), deferoxamine, the new experimental chelators ICL670, GT56-252, L1NA11 and their combinations.Current medicinal chemistry, 12 (23) : 2663-2681.
[37]. Kovacic, P., Jacintho, JD. (2001) Mechanisms of carcinogenesis: Focus on oxidative stress and electron transfer. Current medicinal chemistry, 8 : 773–796
[38]. Kutter, D., Devaquet, P., Vanderstocken, G., Paulus, JM., Marchal, V., Gothot, A. (2000) Consequences of total and subtotal myeloperoxidase deficiency: risk or benefit ?Acta Haematologica, 104 (1) : 10-5.
[39]. Leonard, SS., Harris, GK., Shi, X. (2004) Metal-induced oxidative stress and signal transduction. Free Radical Biology and Medicine, 37 : 1921–1942.
[40]. Levine, RL., Stadtman, ER. (2001) Oxidative modification of proteins during aging. Experimental Gerontology, 36:1495–1502.
[41]. Loh, KP., Huang, SH., De Silva, R., Tan, BK., Zhu, YZ. (2006) Oxidative stress: apoptosis in neuronal injury. Current Alzheimer Research, 3 (4) : 327-37.
[42]. Madamanchi, NR., Vendrov, A., Runge, MS. (2005) Oxidative stress and vascular disease. Arteriosclerosis, Thrombosis, and Vascular Biology, 25 (1) : 29-38.
[43]. Maritim, AC., Sanders, RA., Watkins, JB., (2003) Diabetes, oxidative stress, and antioxidants: Journal Biochemistry and Molecular Toxicology, 17, 24–38.
[44]. Marnett, LJ. (1999) Lipid peroxidation—DNA damage by malondialdehyde. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 424: 83–95.
[45]. Marnett, LJ. (2000) Oxyradicals and DNA damage. Carcinogenesis, 21: 361–370.
[46]. Marple BF (2010) Allergic rhinitis and inflammatory airway disease: interactions within the unified airspace, Am. J. Rhinol. Allergy 24: 249-254.
[47]. Mirshafiey A, Mohsenzadegan M (2008) The role of reactive oxygen species in immunopathogenesis of rheumatoid arthritis, Iran. J. Allergy Asthma Immunol. 7: 195-202.
[48]. Molavi, B., Mehta, JL. (2004) Oxidative stress in cardiovascular disease: Molecular basis of its deleterious effects, its detection, and therapeutic considerations. Current Opinion in Cardiology, 19 : 488–493
[49]. Moreno-Macias H, Romieu I (2014) Effects of antioxidant supplements and nutrients on patients with asthma and allergies, J. Allergy Clin. Immunol. 133: 1237-1244.
[50]. Nakamura, M., Shishido, N., Nunomura, A., Smith, MA., Perry, G., Hayashi, Y., Nakayama, K., Hayashi, T. (2007) Three histidine residues of amyloid-beta peptide control the redox activity of copper and iron. Biochemistry, 46 (44) : 12737-43.

[51]. Nelson, RL. (2001) Iron and colorectal cancer risk: human studies. Nutrition Reviews, 59 (5) : 140-148.
[52]. Ohshima, H., Tazawa, H., Sylla, BS., Sawa, T. (2005) Prevention of human cancer by modulation of chronic inflammatory processes. Mutation Research, 591 : 110–122.
[53]. O'Reilly, KM., Mclaughlin, AM., Beckett, WS., Sime, PJ. (2007) Asbestos-related lung disease. American Family Physician, 75(5):683-8.
[54]. Orhan, H., Orhan, GH., Vriese, E., Vermeulen, NPE., Meerman, JNN. (2006) Application of lipid peroxidation and protein oxidation biomarkers for oxidative damage in mammalian cells. A comparison with two fluorescent probes. Toxicology in Vitro, 20:1005-1013.
[55]. Park, JE., Yang, JH., Yoon, SJ., Lee, JH., Yang, ES., Park, JW. (2003) Lipid peroxidation – mediated cytotoxicity and DNA damage in U937 cells. Biochimie, 84 : 1198-1204.
[56]. Petersen, DR. (2005) Alcohol, iron-associated oxidative stress, and cancer. Alcohol, 35 : 243–249.
[57]. Podrez, EA., Abu-Soud, HM., Hazen, SL. (2000) Myeloperoxidase-generated oxidants and atherosclerosis. Free Radical Biology and Medicine, 28 : 1717–1725.
[58]. Poli, G., Leonarduzzi, G., Biasi, F., Chiarpotto, E. (2004) Oxidative stress and cell signalling. Current medicinal chemistry, 11: 1163–1182.
[59]. Powell, SR. (2000) The antioxidant properties of zinc. Journal of Nutrition, 130 (5S) : 1447S-1454S.
[60]. Ridnour, LA., Isenberg, JS., Espey, MG., Thomas, DD., Roberts, DD., Wink, DA. (2005) Nitric oxide regulates angiogenesis through a functional switch involving thrombospondin-1. Proceedings of the National Academy of Sciences of the United States of America, 102 : 13147–13152.
[61]. Russel PB, James DC (2002). Oxidative stress in allergic respiratory diseases, J. Allergy Clin. Immunol. 110: 349-335.
[62]. Santos, FW., Zeni, G., Rocha, JBT., Weis, SN., Fachinetto, JM., Favero, AM., et al. (2005). Diphenyl diselenide reverses cadmium-induced oxidative damage on mice tissues. Chemico-biological interactions, 151 : 159–165.
[63]. Sayre, LM., Smith, MA., Perry, G. (2001) Chemistry and biochemistry of oxidative stress in neurodegenerative disease. Current medicinal chemistry, 8 : 721–738.
[64]. Sequeira S, Rao AV, Rao A (2012) Increased oxidative stress and altered antioxidants status in patients with chronic allergic rhinitis, Adv. Biosci. Biotechnol. 3: 951-956.
[65]. Siah, SW., Trinder, D., Olynyk, JK. (2005) Iron overload, Clinicachimica acta, 358 : 24–36.
[66]. Stadtman, ER. (2004) Role of oxidant species in aging. Current medicinal chemistry, 11 : 1105–1112.
[67]. Stadtman, ER., (2001) Protein oxidation in aging and age-related diseases, Annals of New York Academic of Science, 928 : 22–38.
[68]. Stocker, R., Keaney, JF. (2004) Role of oxidative modifications in atherosclerosis. Physiological reviews, 84 : 1381–1478.
[69]. Terasaki, Y., Akuta, T., Terasaki, M., Sawa, T., Mori, T., Okamoto, T., Ozaki, M., Takeya, M., Akaike, T. (2006) Guanine nitration in idiopathic pulmonary fibrosis and its implication for carcinogenesis. American journal of respiratory and critical care medicine, 174 (6) : 665-73.
[70]. Touyz, RM. (2004) Reactive oxygen species, vascular oxidative stress, and redox signaling in hypertension: what is the clinical significance? Hypertension, 44(3) : 248-52.
[71]. Turko, IV., Marcondes, S., Murad, F. (2001) Diabetes-associated nitration of tyrosine and inactivation of succinyl-CoA:3-oxoacid CoA-transferase. American Journal of Physiology, Heart and Circulatory Physiology, 281 (6) : H2289-94.
[72]. Turko, IV., Murad, F. (2002) Protein Nitration in Cardiovascular Diseases. Pharmacology Review, 54 : 619–634.
[73]. Valko, M., Leibfritz, D., Moncola, J., Mark T.D. Cronin, MTD., Mazura, M., Telser, J. (2007) Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry and Cell Biology, 39 : 44–84.
[74]. Valko, M., Morris, H., Cronin, MTD. (2005) Metals, toxicity and oxidative stress. Current medicinal chemistry, 12 : 1161–1208.
[75]. Valko, M., Morris, H., Mazur, M., Rapta, P., Bilton, RF. (2001) Oxygen free radical generating mechanisms in the colon: Do the semiquinones of Vitamin K play a role in the aetiology of colon cancer? Biochimica et Biophysica Acta, 1527 : 161–166.
[76]. Valko, M., Rhodes, CJ., Moncol, J., Izakovic, M., Mazur, M. (2006) Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chemico-Biological Interactions, 6 (10) : 1–40.
[77]. Waalkes, MP., Liu, J., Ward, JM., Diwan, LA. (2004) Mechanisms underlying arsenic carcinogenesis: Hypersensitivity of mice exposed to inorganic arsenic during gestation. Toxicology, 198 : 31–38.
[78]. Wu, TJ., Sempos, CT., Freudenheim, JL., Muti, P., Smith, E. (2004) Serum iron, copper and zinc concentrations and risk of cancer mortality in US adults. Annals of Epidemiology, 14 : 195–201.
[79]. Xu, BJ., Yuan, SH., Chang, SK. (2007) Comparative studies on the antioxidant activities of nine common food legumes against copper-induced human low-density lipoprotein oxidation in vitro. Journal of Food Science, 72(7) : S522-527.
[80]. Yuan, XM., Li, W. (2003) The iron hypothesis of atherosclerosis and its clinical impact. Annals of Medicine, 35 (8) : 578-591.
[81]. Zhang, Z., Huang, CS., Li, JX., Leonard, SS., Lanciotti, R., Butterworth, L., Shi, XL. (2001) Vanadate-induced cell growth regulation and the role of reactive oxygen species, Archives of Biochemistry and Biophysics, 392 : 311–320.

Abiodun Olusoji Owoade " Free Radicals as Mediators of oxidative Damage and Disease" IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 14.2 (2019): 57-64.