

## Review article: Oxidative stress versus antioxidants

Said M. Al-Dalaen<sup>1</sup>, Aiman I. Al-Qtaitat<sup>2</sup>

<sup>1</sup>Department of Pharmacology, Faculty of Medicine, Mu'tah University, Karak, Jordan

<sup>2</sup>Department of Anatomy & Histology, Faculty of Medicine, Mu'tah University, Karak, Jordan

### Email address:

aldalaensm@yahoo.com (S. M. Al-Dalaen), aimanaq2000@yahoo.com (A. I. Al-Qtaitat)

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**Abstract:** Oxidative stress is a phenomenon that reflects an imbalance between the production of reactive oxygen species and so-called oxidants, and their elimination by protective mechanisms. These are referred to as antioxidative systems which can detoxify the reactive intermediates, or repair the resulting damage causing toxic effects through the production of peroxides and free radicals that damage all cell components. Further, some reactive oxidative species act as cellular messengers in redox signaling that can cause disruptions in normal cellular signaling mechanisms. In humans, oxidative stress is thought to be involved in the development of atherosclerosis, neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, cancer, diabetes mellitus, inflammatory diseases, as well as psychological diseases or aging processes. It is presently accepted that the reactive oxygen species can be beneficial. Depending on the type of oxidants, intensity and time of redox imbalance, as well as on the type of cells, oxidative stress can play a role in the regulation of other important processes. This is achieved through modulation of signal pathways, influencing synthesis of antioxidant enzymes, repair processes, inflammation, or via the immune system, as a way to attack and kill pathogens. This limits the potential for apoptosis and cell proliferation, and thus affects malignant processes. Imprudent administration of antioxidants may therefore have a negative impact on the organism.

**Keywords:** Reactive Oxygen Species, Antioxidants, Oxidative Stress, Redox Stress, Signaling

## 1. Summary

Reactive oxygen species (ROS) are chemically reactive molecules produced by living organisms as a result of normal cellular metabolism. At low to moderate concentrations, they function in physiological cell processes. However, when present in high concentrations, they produce adverse modifications to cell components, such as lipids, proteins, and DNA [1-3]. The shift in the oxidant/antioxidant balance in favor of oxidants is termed "oxidative stress." Oxidative stress contributes to many pathological conditions, including cancer, neurological disorders [4] atherosclerosis, hypertension, ischemia/perfusion [5] diabetes, acute respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease [6] and asthma [7-10].

Aerobic organisms have integrated antioxidant systems, which include enzymatic and nonenzymatic antioxidants that are usually effective in blocking harmful effects of ROS. However, in pathological conditions, the antioxidant systems can be overcome [11].

Table 1. Nomenclature of the various O<sub>2</sub> forms [12].

Triplet Oxygen (Ground state)	O-O
Singlet Oxygen	O-O:
Superoxide	O-O:
Perhydroxyl radical	O-O:H
Hydrogen peroxide	H:O-O:H
Hydrogen radical	H:O
Hydrogen ion	H:O:
Water	H:O:H

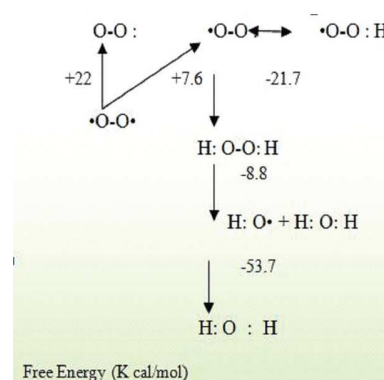


Figure 1. The activation states of oxygen [12].

## 2. Oxidants

### 2.1. Endogenous Sources of Oxidants

ROS (shown in Figure 1 and table 1) are produced from the activation of molecular oxygen, intracellularly through multiple mechanisms, as a result of normal cellular metabolism. Their major sources are mitochondria, peroxisomes, endoplasmic reticulum, and the NADPH oxidase (NOX) complex in cell membranes (Figure 2) [13, 14]. ROS can be classified as either free radicals or nonradicals.

Molecules containing one or more unpaired electrons and thus giving reactivity to the molecule are called free radicals. When two free radicals share their unpaired electrons, nonradical forms are created. The three major ROS that are of physiological significance are superoxide anion ( $O_2^{\cdot-}$ ), hydroxyl radical ( $\cdot OH$ ), and hydrogen peroxide ( $H_2O_2$ ) [11].

Mitochondria convert energy into ATP—a form that can be utilized by the cell. The ATP production process, known as oxidative phosphorylation, involves the transport of protons (hydrogen ions) across the inner mitochondrial membrane by means of the electron transport chain. In the electron transport chain, electrons are passed through a series of proteins via oxidation-reduction reactions, with each acceptor

protein along the chain having a greater reduction potential than the previous one. The final destination for an electron along this chain is an oxygen molecule. In normal conditions, oxygen is reduced to produce water. However, in about 1–3% [11] of electrons passing through the chain, oxygen is prematurely and incompletely reduced, resulting in the superoxide radical ( $\cdot O_2$ ). While superoxide is not particularly reactive, it can inactivate specific enzymes or initiate lipids peroxidation in its protonated form, hydroperoxyl  $HO_2\cdot$  [15],  $O_2^{\cdot-}$  itself can also react with  $H_2O_2$  and generate  $OH^{\cdot}$  [16]. Hydroxyl radical is the most reactive ROS and can damage proteins, lipids, carbohydrates and DNA. It can also initiate lipid peroxidation by taking an electron from polyunsaturated fatty acids. Hydrogen peroxide is also produced by xanthine oxidase, amino acid oxidase, and NADPH oxidase [17] and in peroxisomes by consumption of molecular oxygen in metabolic reactions. In a succession of reactions, called Haber–Weiss and Fenton reactions (Figure 3),  $H_2O_2$  can break down to  $OH^{\cdot}$  in the presence of transition metals, such as  $Fe^{2+}$  or  $Cu^{2+}$  [18].

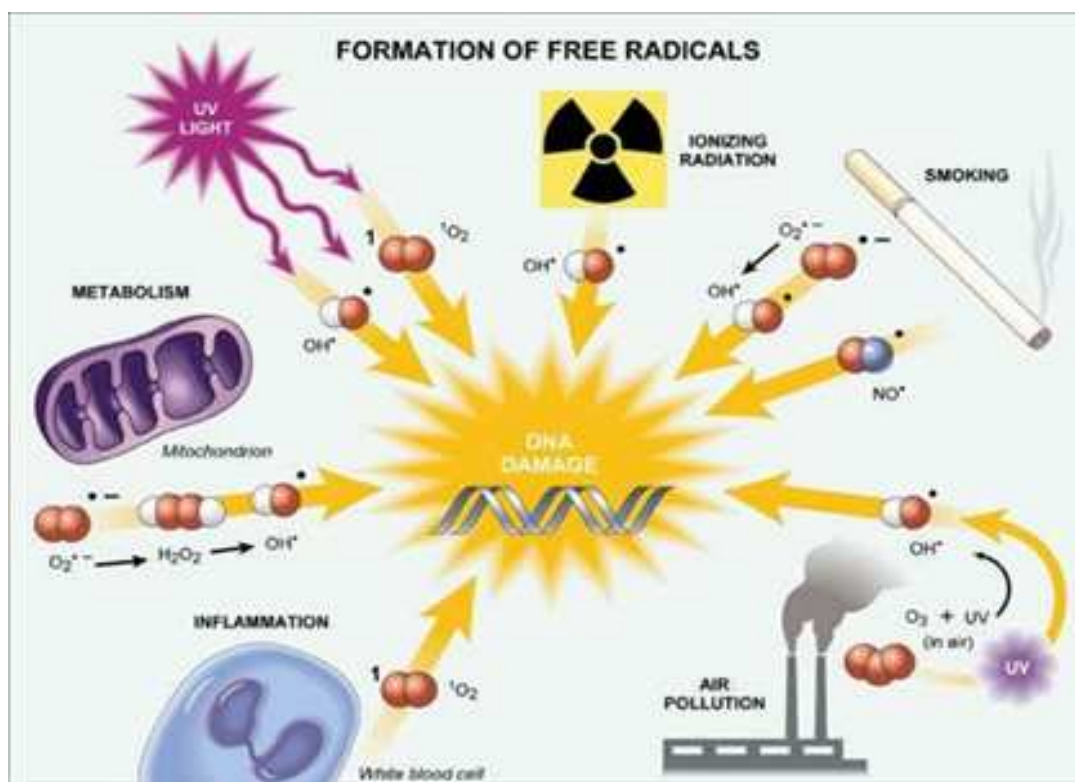
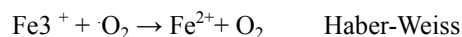


Figure 2. Different ROS sources [13].

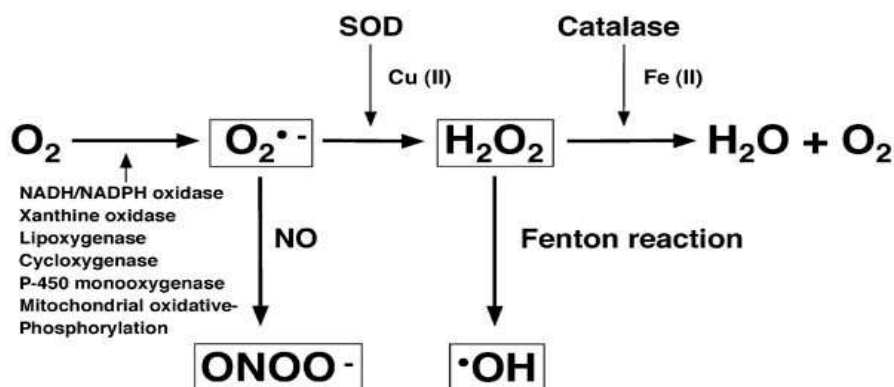


Figure 3. Fenton reaction [18].

Granulocytic enzymes further expand the reactivity of  $H_2O_2$  via eosinophil peroxidase and myeloperoxidase (MPO). In activated neutrophils,  $H_2O_2$  is consumed by MPO. In the presence of chloride ion,  $H_2O_2$  is converted to hypochlorous acid (HOCl), which is highly oxidative and plays an important role in killing of the pathogens in the airways [19]. However, HOCl can also react with DNA, induce DNA-protein interactions, produce pyrimidine oxidation products and add chloride to DNA bases [20]. Eosinophil peroxidase and MPO also contribute to the oxidative stress through modification of proteins by halogenations, nitration, and protein cross-links via tyrosyl radicals [21].

The peroxy radicals ( $ROO\cdot$ ) are another type of oxygen-derived free radicals, the simplest of which is hydroperoxyl radical ( $ROO\cdot$ ) that plays a role in fatty acid peroxidation. Free radicals can trigger lipid peroxidation chain reactions by abstracting a hydrogen atom from a side chain methylene carbon. The lipid radical then reacts with oxygen to produce peroxy radical. Peroxy radical initiates a chain reaction and transforms polyunsaturated fatty acids into lipid hydroperoxides, which are very unstable and easily decompose to secondary products, such as aldehydes and malondialdehydes. Isoprostanes are another group of lipid peroxidation products that are generated via the peroxidation of arachidonic acid and have also been found to be elevated in plasma and breath condensates of asthmatics [22].

## 2.2. Exogenous Sources of Oxidants

Exogenous ROS can be produced as a result of smoking [23] as well as exposure to pollutants, ozone [24], hyperoxia [25], heavy metals [26] or radiation [27]. Cigarette smoke contains many oxidants, free radicals and organic compounds, such as superoxide and nitric oxide [24]. Ozone exposure can cause lipid peroxidation and induce influx of neutrophils into the airway epithelium.

Short-term exposure to ozone also causes the release of inflammatory mediators, such as MPO, eosinophil cationic proteins, lactate dehydrogenase and albumin [28].

Hyperoxia refers to conditions characterized by oxygen levels that are higher than normal partial pressure of oxygen in the lungs or other body tissues. This leads to greater production of reactive oxygen and nitrogen species [29].

Heavy metal ions—such as iron, copper, cadmium,

mercury, nickel, lead, and arsenic—can induce generation of reactive radicals. This can cause cellular damage via depletion of enzyme activities through lipid peroxidation and reaction with nuclear proteins and DNA, where ROS generated by metal-catalyzed reactions can modify DNA bases. Three base substitutions,  $G \rightarrow C$ ,  $G \rightarrow T$ , and  $C \rightarrow T$ , can occur as a result of oxidative damage by metal ions, such as  $Fe^{2+}$ ,  $Cu^{2+}$ , and  $Ni^{2+}$ . Previous studies have shown that  $G \rightarrow C$  can be predominantly produced by  $Fe^{2+}$ , while  $C \rightarrow T$  substitution is typically achieved by  $Cu^{2+}$  and  $Ni^{2+}$  [30].

In the presence of  $O_2$ , ionizing radiation converts hydroxyl radical, superoxide, and organic radicals to hydrogen peroxide and organic hydroperoxide, which can react with redox active metal ions, such as Fe and Cu, via Fenton reactions, and thus induce oxidative stress [31]. In addition, it can generate damaging intermediates through interaction with water, a process termed radiolysis. Since water comprises 55-60% of the human body, the probability of radiolysis is quite high under the presence of ionizing radiation. The outcome is conversion of water into hydroxyl radical ( $\bullet OH$ ), hydrogen peroxide ( $H_2O_2$ ), superoxide radical ( $O_2^-$ ) and ultimately oxygen ( $O_2$ ) [32]. Moreover, according to the findings of extant studies, various signal transduction molecules—such as extracellular signal-regulated kinase 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38—and transcription factors—such as activator protein-1 (AP-1), nuclear factor- $\kappa B$  (NF- $\kappa B$ ), and p53—are activated under effect of ionizing radiation. This results in the expression of radiation response-related genes [33, 34].

## 3. Oxidative Stress-Induced Cellular Damage

The targets of ROS damage include all major biomolecular groups, as discussed below.

### 3.1. Proteins

It is well known that ROS can target almost all cellular compounds. According to the findings of several studies, ROS can react with several amino acid residues *in vitro*, generating a wide range of products—from modified and less active enzymes to denatured, non-functioning proteins [35].

Fragmentation of the peptide chain and aggregation of cross-linked reaction products result in an altered electrical charge and increased susceptibility to proteolysis by degradation by specific proteases. Here, the amino acids in a peptide differ in their susceptibility to attack, while the various forms of activated oxygen differ in their potential reactivity [36].

Cysteine and methionine residues in proteins are particularly susceptible to oxidation [37]. For example, oxidation of sulfhydryl groups or methionine residues of proteins causes conformational changes, protein unfolding, and degradation [38, 39]. Enzymes that have metals at or close to their active sites are especially more sensitive to metal catalyzed oxidation, which can inhibit their activities [40].

### 3.2. Lipids

Oxidative stress can induce lipid peroxidation, causing different arrangement in the membrane lipid bilayer. This results in inactivation of the membrane-bound receptors and enzymes and causes an increase in tissue permeability [41].

Products of lipid peroxidation, such as malodialdehyde and unsaturated aldehydes, are capable of inactivating many cellular proteins by forming protein cross-linkages [42]. This causes depletion of intracellular GSH, induces peroxide production [43] activates epidermal growth factor receptor [44] and induces fibronectin production [45].

### 3.3. DNA

Most of the long-term effects of oxidative stress are inflicted by modifications of DNA [46] which involves degradation of bases, single- or double-stranded DNA breaks, purine, pyrimidine or sugar-bound modifications, mutations, deletions or translocations, and cross-linking with proteins.

Most of these DNA modifications are highly relevant to carcinogenesis, aging, and neurodegenerative, cardiovascular, and autoimmune diseases. DNA damage similar to that induced by oxidative stress can also be induced by ionizing radiation. Promoter regions of genes contain transcription factor-binding sites that have consensus sequences. These contain GC-rich sequences are susceptible for oxidant attacks, which can change the expression of the related gene [47].

Single-base damage by radiation or oxidation, such as 8-oxoguanine and thymine glycol, is well known. However, the research focus has recently shifted to some of the more complex lesions, such as tandem DNA lesions, formed at substantial frequency by ionizing radiation and metal-catalyzed  $H_2O_2$  reactions.

Under anoxic conditions, the predominant double-base lesion is a species in which C8 of guanine is linked to the 5-methyl group of an adjacent 3'-thymine (G [8, 5-Me] T) [48]. Most of these oxygen-derived species are produced at a low level by normal aerobic metabolism. As a result of oxidation, 5-methyl cytosine is converted into 5-hydroxy methyl uracil, due to a deamination/oxidation reaction, affecting DNA organization and repair activity [49]. Normal cellular defense

mechanisms destroy most of these and any damage to the cells is constantly repaired. However, under the severe levels of oxidative stress that cause necrosis, the damage causes ATP depletion, preventing the control of cell death by apoptosis and causing cell disintegration [50].

## 4. Effects of Oxidative Stress on Signal Transduction

Oxidative stress can cause disruption of the GSH/GSSG ratio, leading to activation of redox sensitive transcription factors, such as the nuclear factor of activated T cells (NF- $\kappa$ B) and hypoxia-inducible factor 1 (AP-1). Owing to their involvement in inflammatory responses, these factors can facilitate the transmission of information into the cell. Tyrosine kinase receptors, most of the growth factor receptors—such as epidermal growth factor receptor, vascular endothelial growth factor receptor, and receptor for platelet-derived growth factor—as well as protein tyrosine phosphatases and serine/threonine kinases are targets of ROS [51]. Moreover, oxidants can regulate many of the extracellular signal regulated kinases, such as p38, which are the members of mitogen-activated protein kinase family. As such, they are involved in several processes in the cell, including proliferation, differentiation, and apoptosis. ROS can activate NF- $\kappa$ B by phosphorylating I $\kappa$ Bs at serine residues, which frees NF- $\kappa$ B to enter the nucleus to activate gene transcription [52]. A number of kinases have been reported to phosphorylate I $\kappa$ Bs; these kinases are targets for oxidative signals to activate NF- $\kappa$ B [53]. As a result of NF- $\kappa$ B activation via oxidation, several antioxidant defense-related genes that can participate in immune response are activated. These include IL-1b, IL-6, tumor necrosis factor- $\alpha$ , IL-8, and several adhesion molecules. NF- $\kappa$ B also regulates angiogenesis, proliferation and cell differentiation [54].

## 5. Oxidative Stress and Diseases

### 5.1. Aging

In an attempt to explain the aging process, many theories have been put forward [55, 56]. However, only the “free radical theory of aging” [57] has gained universal acceptance, as it is supported by the fact that the production of free radicals and the free radical damage increases with age [58]. This theory postulates that free radicals in the body cause oxidative damage to cellular components—a process that results in altered cellular function, compromised tissue and organ function, ultimately leading to death. The free radical theory is also supported by the “rate of living” hypothesis, which inversely links metabolic rate with the longevity of the organisms [59]. This is supported by empirical evidence proved by indicating that oxidative damage to proteins, DNA and lipids increases with age [58]. As free radical-mediated oxidative stress increases with age, it may overwhelm the natural repair systems in the elderly [60]. Thus, it is a major contributor to diseases associated with aging [61].

### 5.2. Cardiovascular Disease

Vascular proliferation and inflammation are closely linked [62] and excessive proliferation of vascular cells plays an important role in the pathology of vascular occlusive disease. Free radicals are considered to play a causal role in this process [63]. ROS lead to the oxidation of low density lipoprotein, which accumulates within plaques. It thus contributes to the inflammatory state of atherosclerosis and plays a key role in its pathogenesis [64]. Oxidized-LDL leads to endothelial dysfunction, and can result in either cell growth or apoptotic cell death, causing vasoconstriction. Free radicals have also been implicated in congestive heart failure [65].

### 5.3. Diabetes

Findings of pertinent studies indicate that free radical-induced damage also plays a role in the development of insulin resistance,  $\beta$ -cell dysfunction, impaired glucose tolerance, and type II diabetes mellitus [66]. Hyperglycemia can induce oxidative stress through several mechanisms, including glucose autooxidation, the formation of advanced glycation end-products (AGEs), and activation of the polyol pathway [67]. In diabetics, a significant increase in protein glycation (AGE) has been noted. Moreover, evidence suggests that, owing to their accumulation, prevalence of microvascular lesions increases. These are present in diabetic retinopathy, and are also responsible for cardiovascular complications in diabetic patients [67, 68]. The damage caused by ROS has also been implicated in primary open angle glaucoma (POGA), which is the leading cause of irreversible blindness [69].

### 5.4. Cancer

ROS can activate the initiation, promotion and progression stages of carcinogenesis [70] due to the interaction between free radicals and DNA components. By damaging its bases and the deoxyribose backbone, it causes mutations in crucial genes, thus leading to cancer [71]. In support of this free radical-mediated damage to DNA, either through arrest or induction of transcription, induction of signal transduction pathways, replication errors, and genomic instability occurs. All these phenomena are associated with carcinogenesis [49] which has been found in various cancer tissues. Moreover, there is a direct link between the size of benign tumors and the amount of DNA oxidized product, 8-hydroxyguanine (8-OH-G) adduct formation. Understanding this process may be important in explaining the transformation of benign to malignant tumors [72]. In cancer cells, the high level of oxidative stress can induce apoptosis or even necrosis, while, its low level can stimulate cell division and thus promote tumor growth [73].

### 5.5. Neurodegenerative Diseases

A growing body of evidence indicates that free radicals are involved in the initiation of cellular injury observed in

neurodegenerative diseases [74] which are characterized by loss of specific neuronal populations. This is often accompanied by intraneuronal damage, as well as extracellular accumulation of fibrillary materials.

### 5.6. Parkinson's Disease

This progressive neurodegenerative movement disorder is considered the most common form of motor system degeneration, affecting approximately 1% of the population over the age of 65 [75]. Empirical evidence suggests the involvement of free radicals in the pathogenesis of this disease. It has been observed that that oxidation of dopamine yields potentially toxic semiquinones. Moreover, the accelerated metabolism of dopamine by monoamine-oxidase-B may induce an excessive formation of hydrogen peroxide, superoxide anions, and hydroxyl radicals, which not only maintain the oxidative stress level, but also initiate/propagate apoptosis of the dopaminergic neurons [76]. According to the reports in the pertinent literature, Parkinson's disease is associated with increased oxidative damage to DNA [77], proteins [78] and lipids [79].

### 5.7. Huntington's Disease

This inherited autosomal dominant neurodegenerative disease is characterized by uncontrollable movements, irritability and depression [80]. There is a direct evidence to support the involvement of free radicals in the pathogenesis of Huntington's disease, in that increased levels of F<sub>2</sub>-isoprostanes have been detected in the cerebrospinal fluid of the patients compared to those measured in the healthy persons [81].

### 5.8. Alzheimer's Disease

This neurodegenerative disorder is characterized by cognitive impairment and a gradual loss of memory, language skills, and dementia. It eventually leads to death due to the loss of neurons and synapses [82]. Oxidative damage may play a role in amyloid deposition in Alzheimer's disease, and oxidizing conditions can cause protein cross-linking and aggregation of  $\beta$ -amyloid protein, tau and other cytoskeletal proteins [83]. The accumulated  $\beta$ -amyloid can cause oxidation of the nonsaturated carbohydrate side chains of membrane lipids, which leads to the disintegration of the neural membrane. The outcome of this process is cell lysis due to lipid peroxidation [84] which is associated with DNA damage and oxidative modification of proteins in the frontal cortex of brain affected by Alzheimer's disease [85].

### 5.9. Stroke

In the patients that have suffered stroke, neuronal death is caused by the free radicals arising from various sources, such as xanthine oxidase, cyclooxygenase, inflammatory cells and mitochondria [86]. The mitochondrial electron transport chain is altered during ischemia and reperfusion and is also a likely source of free radicals. This can result in increased formation of superoxide radical anions [87].

The accumulation of blood borne inflammatory cells, such as neutrophils and monocytes/macrophages, which can occur during reperfusion, can also promote further oxidative stress. This can cause lipid peroxidation and oxidative damage to DNA in ischemic stroke patients [88]. In addition; increased ROS levels can make the brain more susceptible to oxidative stress due to a variety of reasons. For example, the brain could consume a significant amount of the body's oxygen supply, or have a relatively poor antioxidant defense system. Alternatively, it could be enriched in pro-oxidant molecules or contain high concentration of readily peroxidizable lipids [89].

## 6. Antioxidants

Humans have evolved complex antioxidants strategies against prooxidant conditions. The antioxidant defensive system has many components, and a deficiency of any of these components can cause destruction in the overall antioxidant status of an individual [90]. Antioxidants are the molecules that have the ability to counterbalance the effects

of oxidants before these attacks the cells (Figure 4). There are highly complex antioxidant systems (enzymatic and nonenzymatic) in human cells, working in collaboration in order to protect the body against free radical damage.

Antioxidants can be endogenous or obtained exogenously, as a part of a diet or through dietary supplements. They can also be consumed as compounds that do not neutralize free radicals, but rather enhance endogenous activity.

An ideal antioxidant should be readily absorbed, quench free radicals, and chelate redox metals. It should also work in both aqueous and/or membrane domains, positively affecting gene expression.

Endogenous antioxidants play a crucial role in maintaining optimal cellular functions. However, under conditions that promote oxidative stress, endogenous antioxidants may not be sufficient. In such cases, dietary antioxidants should be supplied to maintain optimal cellular functions. Some antioxidants can interact with other antioxidants, regenerating their original properties. This process is referred to as the "antioxidant network." [91].

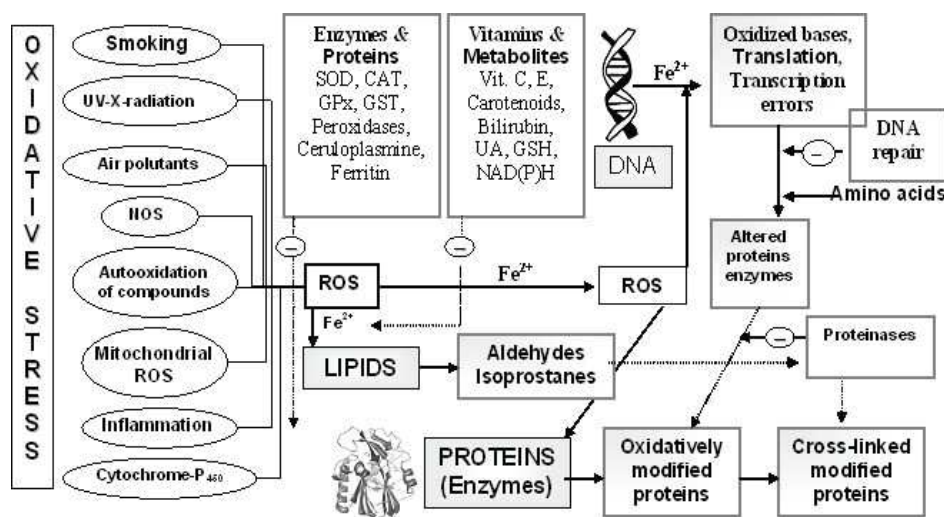


Figure 4. Mutual association between oxidants and antioxidants [92].

### 6.1. Enzymatic Antioxidants

The major enzymatic antioxidants found in the lungs are superoxide dismutases (SODs) (EC 1.15.1.11), catalase (EC 1.11.1.6), glutathione peroxidases (GSH-Pxs) (EC 1.11.1.9) and glutathione-S-transferase (GSTs) (EC 2.5.1.18) [93]. In addition to these major enzymes, other antioxidants, including heme oxygenase-1 (EC 1.14.99.3), and redox proteins, such as thioredoxins (TRXs, EC 1.8.4.10), peroxiredoxins (PRXs, EC 1.11.1.15), and glutaredoxins, have been found to play crucial roles in the pulmonary antioxidant defenses.

Since superoxide is the primary ROS produced in a variety of sources, its dismutation by SOD is of primary importance for each cell. All three forms of SOD—CuZn-SOD, Mn-SOD, and EC-SOD—are widely expressed in human tissues [94]. Mn-SOD is localized in the mitochondria matrix. EC-SOD is primarily localized in the extracellular matrix, especially in

areas containing high amounts of type I collagen fibers and around pulmonary and systemic vessels. It has also been detected in the bronchial epithelium, alveolar epithelium, and alveolar macrophages [95]. Overall, CuZn-SOD and Mn-SOD are generally thought to act as bulk scavengers of superoxide radicals. The relatively high EC-SOD level in the lung with its specific binding to the extracellular matrix components may represent a fundamental component of lung matrix protection [96].

Cu, Zn-SOD has two identical subunits, with a molecular weight of 32 kDa. Each subunit contains a dinuclear metal cluster, comprising of copper and zinc ions as the active site, and it specifically catalyzes the dismutation of the superoxide anion to oxygen and water [97]. The mitochondrial Mn-SOD is a homotetramer with a molecular weight of 96 kDa and contains one manganese atom per subunit. It vacillates from Mn (III) to Mn (II) and back to Mn (III) during the two-step

dismutation of superoxide [97]. Extra-cellular superoxide dismutase contains copper and zinc. It is a tetrameric secretory glycoprotein, characterized by a high affinity for certain glycosaminoglycans, such as heparin and heparin sulphate. However, its regulation in mammalian tissues occurs primarily in a manner coordinated by cytokines, rather than as a response to oxidative stress [97].

$H_2O_2$  produced by the action of SODs or oxidases, such as xanthine oxidase, is reduced to water by catalase and the GSH-Px. Catalase exists as a tetramer composed of four identical monomers, each of which contains a heme group at the active site. Degradation of  $H_2O_2$  is accomplished via the conversion between two conformations of catalase-ferricatalase (iron coordinated to water) and compound I (iron complexed with an oxygen atom). Catalase also binds NADPH as a reducing equivalent to prevent oxidative inactivation of the enzyme (formation of compound II) by  $H_2O_2$  as it is reduced to water [98]. Catalase has one of the highest turnover rates of all enzymes; one molecule of catalase can convert approximately 6 million molecules of hydrogen peroxide to water and oxygen each minute [97]. The GSH-Pxs are a family of tetrameric enzymes that contain the unique amino acid selenocysteine within the active sites and use glutathione (GSH) to reduce  $H_2O_2$  and lipid peroxides to their corresponding alcohols. While four GSH-Pxs have been described, encoded by different genes, GSH-Px-1 (cellular GSH-Px) is ubiquitous. It reduces  $H_2O_2$  and fatty acid peroxides, but not esterified peroxy lipids [99]. Esterified lipids are reduced by membrane-bound GSH-Px-4 using several different thiols as reducing equivalents. GSH-Px-2 (gastrointestinal GSH-Px) is localized in gastrointestinal epithelial cells, where it serves to reduce dietary peroxide levels [100]. GSH-Px-3 (extracellular GSH-Px) is the only member of the GSH-Px family that resides in the extracellular compartment and is believed to be one of the most important extracellular antioxidant enzymes in mammals [101].

GSTs can inactivate secondary metabolites, such as unsaturated aldehydes and hydroperoxides. Presently, three major families of GSTs are recognized—cytosolic GST, mitochondrial GST [102, 103] and membrane-associated microsomal GST that plays a role in eicosanoid and GSH metabolism [104]. During non-stressed conditions, Mu and Pi classes of cytosolic GSTs can interact with kinases Ask1 and JNK, respectively, resulting in their inhibition [105]. The dissociation of GSTP1 from JNK in response to oxidative stress [106] results in the recovery of peroxiredoxin VI (PRX VI) enzyme activity through glutathionylation of the oxidized protein [107].

The enzymatic antioxidants also include six different types of PRXs, each playing a major role in the protection of alveolar epithelium, PRX VI in particular [108]. PRX V has been found to function as a peroxynitrite reductase [109]; according to some authors, it may also function as a potential protective compound in the development of ROS-mediated lung injury [110].

## 6.2. Nonenzymatic Antioxidants

### 6.2.1. Vitamin E ( $\alpha$ -Tocopherol)

This fat-soluble vitamin is considered a major powerful membrane-bound antioxidant, employed by the cell [111] as a protection against lipid peroxidation [112]. During the antioxidant reaction,  $\alpha$ -tocopherol is converted into  $\alpha$ -tocopherol radical by the donation of labile hydrogen to a lipid or lipid peroxy radical. Thus, the  $\alpha$ -tocopherol radical can be reduced to the original  $\alpha$ -tocopherol form by ascorbic acid [113].

### 6.2.2. Vitamin C (Ascorbic Acid)

As it is water-soluble, Vitamin C acts in the aqueous environments of the body, along with the antioxidant enzymes. Vitamin C cooperates with Vitamin E to regenerate  $\alpha$ -tocopherol from  $\alpha$ -tocopherol radicals in membranes and lipoproteins [112] (Figure 5). By raising intracellular glutathione levels, it also plays an important role in protein thiol group protection against oxidation [114]. Yuanyuan et al. (2014) [115] reported that vitamin C decreased ROS and DNA damage of severe CAP PBMC in vitro, and vitamin C decreased TNF- $\alpha$  and IL-6 in whole blood cells from severe CAP.

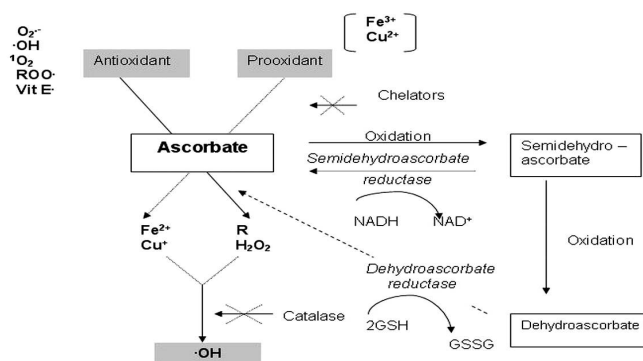


Figure 5. Ascorbic acid – antioxidant and potential prooxidant properties [92].

### 6.2.3. Carotenoids ( $\beta$ -Carotene)

These are mainly colored pigments present in plants and microorganisms. Epidemiological studies have revealed that a diet rich in carotenoids is correlated with a lower risk of age-related diseases [116]. Primarily,  $\beta$ -carotene has been found to react with peroxy ( $ROO^{\cdot}$ ) to prevent damage in lipophilic compartments [117] hydroxyl ( $\cdot OH$ ), and superoxide ( $O_2^{\cdot-}$ ) radicals [118]. The antioxidant activity of carotenoids arises due to their ability to delocalize unpaired electrons, and thus quench singlet oxygen without degradation [119]. The efficacy of carotenoids with respect to physical quenching is related to the number of conjugated double bonds present in the molecule. Both  $\beta$ -Carotene and retinoic acid are capable of regulating different transcription factors [120],  $\beta$ -Carotene inhibits the oxidant-induced NF- $\kappa$ B activation and interleukin (IL)-6 and tumor necrosis factor- $\alpha$  production. On the other hand, retinoic acid can affect cell apoptosis, arrest cell cycle, or both [121, 122].

#### 6.2.4. Thiol Antioxidants

Glutathione (GSH) is the major thiol-disulphide redox intracellular multifunctional soluble antioxidant of the cell. It can be found abundant in cytosol, nuclei, and mitochondria [123]. It can be found in the reduced form, i.e., as GSH, or in the oxidized form, known as GSSG (glutathione disulphide). The antioxidant capacity of thiol compounds is attributed to the presence of sulfur atom, which can easily accommodate the loss of a single electron [124]. As oxidized glutathione (GSSG) is accumulated inside the cells, the GSH/GSSG ratio is a reliable indicator of oxidative stress of an organism [125]. It can act as a co-factor for several detoxifying enzymes, participate in amino acid transport across plasma membrane, scavenge hydroxyl radical and singlet oxygen directly, and regenerate Vitamin C and E back to their active forms [123]. In addition, evidence suggests that GSH protects cells against apoptosis by interacting with proapoptotic and antiapoptotic signaling pathways. It also regulates and activates several transcription factors, such as AP-1, NF- $\kappa$ B, and Sp-1 [123]. Thioredoxin (TRX) is another thiol antioxidant with oxidoreductase and ubiquitous activity in both mammalian and prokaryotic cells. In its reduced form, it contains two adjacent -SH groups that are converted to a disulphide unit in oxidized TRX when it undergoes redox reactions with multiple proteins. TRX and GSH may have overlapping as well as compartmentalized functions in the activation and regulation of transcription factors [1].  $\alpha$ -Lipoic is another thiol disulphide derivative of octanoic acid antioxidant. It is both water- and fat-soluble and is widely distributed in both cellular membranes and the cytosol of eukaryotic and prokaryotic cells [126]. Thus, it is readily absorbed from the diet and is converted rapidly to its reduced form, dihydrolipoic acid, which is a stronger antioxidant than lipoic acid. Both  $\alpha$ -Lipoic and dihydrolipoic acids are powerful antioxidants. They can scavenge free radicals, chelate metal ion, act in recycling antioxidants and repair protein damage due to oxidative stress either in the cytosol or hydrophobic domains [127].

#### 6.2.5. Melatonin

This is a neurohormone that is derived from tryptophan mainly in the pineal gland. One of the major functions of melatonin is scavenging free radicals in oxygen metabolism, thereby potentially protecting against free radical-induced damage to DNA, proteins and membranes. Owing to these properties, it has the potential to play an important role in the reduction of free radical-mediated diseases [128].

## 7. Conclusion

Extant research has led to a universal agreement that oxidative damage to proteins, lipids, and DNA occurs as a result of ROS overproduction. These are highly reactive due to the unpaired electrons in their structure that allow them to react with several biological macromolecules in cell, thus altering their functions. ROS are produced by cellular metabolic reactions that use oxygen and shift the balance in oxidant/antioxidant status in favor of the oxidants. In

addition, a variety of environmental factors, such as air pollutants or cigarette smoke, can result in the production of ROS, which can also affect the expression of several genes by upregulation of redox-sensitive transcription factors and chromatin remodeling through alteration in histone acetylation/deacetylation. The human body deals with the pathological effects of ROS by utilizing the endogenous antioxidant enzymatic system and by the ingestion of exogenous antioxidants in the diet. If the oxidative stress exceeds the protection afforded by antioxidants, the aging process and some of the diseases associated with it—such as cardiovascular diseases, neurodegenerative diseases, diabetes and cancer — can accelerate. Regulation of redox state is critical for cell viability, activation, and proliferation, as well as organ function.

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